Perhaps the greatest advance in outcomes for patients with precancer or cancer has been the realisation that national and indeed international co-operation is necessary to accrue a sizeable number of patients to adequately power randomised trials in as short a time as possible. The breast cancer community was quickest to draw on this concept soon to be followed by gynaecological oncologists, both, of course, being leaders in the field of multidisciplinary care.

The GOG was founded in 1970 and with over 60 participating US institutions quickly established the standard of care in women with cancer. The GCIG was formed in the late 1990s to generate non-US international studies and has since with other key research groups such as ENGOT matched the GOG’s success.

EUROGIN then AOGIN have together ensured best practice for screening, vaccination and treatment in first and low/middle income countries and in particular has established best practice in countries with the highest burden of cervix cancer with the least resources.

International co-operation is not easy and poses its own ethical, scientific and regulatory challenges. These will be addressed and tentative solutions suggested.
Cancer represents over 25% of total deaths in China. The rural areas of the mid-west regions were suffering the high burdens of cervical cancer. Cancer victims return back to poverty even if their life had previously been improved. It creates enormous challenges in health care.

In 2009, China has initiated the cervical cancer screening of rural women between 35 years and 59 years firmly on ambitious health reform plan. Started from 2012, 10 million rural women in 1000 more counties/districts have been able to access free screening for cervical cancer annually.

China authorities finally approved HPV vaccines in mainland China in 2016, despite the first HPV vaccine was licensed in 2006 and WHO recommendations. Because of the high price and lack of supplies, the available HPV vaccine is not yet affordable and accessible for a vast number of Chinese females, especially for those in rural areas. Responding to WHO call for action towards the global elimination of cervical cancer, the current strategy is still enhancing the population based screening program in China.

This presentation will discuss the epidemiological features and genotypes of HPV and reality of the CareHPV™ Test which recently gained WHO prequalification status for cervical cancer screening. It will be a good screening tool in lower resources areas and potential comprehensive cervical cancer prevention in China.
Detection of pre-invasive cervical lesion and proper management can prevent cervical cancer. However different screening methods yielded different abnormal results requiring different management strategy. Subsequent management of pre-invasive lesion depends on grade, age, extent, histology, facilities and expertise. The classical use of cervical cytology has standard protocol that include when to perform colposcopy and biopsy and when and how to treat. The use of VIA +/- treatment has been used in countries with limited resources. Treatment of CIN depends on grade. Low grade CIN has a high chance of spontaneous regression and normally manage conservatively. High grade CIN should be treated unless in special situation. Treatment could be destructive or excisional.

In AOGIN countries, with its diverse economic status and culture background, different strategies have been employed. With all different modalities of detection and treatment methods available, it is possible to control cervical cancer in AOGIN countries.
Cervical cancer is the 3rd most common cancer in Asian women and ranks 2nd among women in the reproductive age group. According to the suggestions of WHO, every woman in the target age group (30-49 years) should at least be screened once. HPV testing, cytology and visual inspection with acetic acid are all recommended screening tests. The most important strategy is to reach the largest proportion of women at risk with quality screening and treatment. Organized screening programmes are preferable to opportunistic screening.

Cervical cytology screening has been effective in prevention of cervical cancer screening in the developed countries but the effect seems to have plateaued. The demand on well trained professionals also limits its application. In the last two decades, various technical platforms have been developed to improve the efficiency of screening. (1) Liquid based cytology to improve the quality of the sample for cyto-morphological evaluation and provide one-stop convenient and reliable material for ancillary tests. (2) High risk human papilloma virus (HR-HPV) DNA / RNA tests to detect the most important risk factor for cervical cancer and increase the sensitivity of screening. (3) Computerized imager for automated detection of abnormal cells and reduce the pressure on cytology evaluation manpower. (4) Molecular markers such as p16INK4A and Ki-67 to enhance the specificity of cancer cell detection.

There is increased application of HR-HPV detection and genotyping tests in screening of cervical cancers as co-testing or primary tool followed by cytology triage. The application will become particularly beneficial in places with high HPV vaccine coverage. HPV molecular tests are also used for triage of atypical squamous cells undetermined significance and evaluation of recurrence of cervical diseases.

Health professionals should be aware of the advantages and limitations of the tests that can be applied. The importance of quality control and laboratory accreditation should be emphasized.
It is important to note that continuation of cervical cancer screening is necessary even in the post HPV vaccine era. There is wide variation in the economic status, health system and availability of screening infra-structures among AOGIN countries. Each country / region / city should find the screening strategy that is most suitable to ensure the success.
High-risk type HPV (hrHPV) is the well known carcinogen of development of cervical cancer from initiation to metastasis. However, while the whole mucosa of female lower genitor tract is vulnerable to HPV infection, cancer only arises at the invariable zone (the transformation zone) at the historical junction between the squamous epithelium of exocervix and the columnar epithelium of endocervix (SCJ), which migrates cephalically by age and is regarded as the tissue-of-origin of cervical cancer. Recently, pathological studies from Christopher Crum’s group further identified the embryonic-originated Krt7+ SCJ cells as he cell-of-origin of cervical cancer. Krt7+ SCJ cells give rise to reserve cells that bi-potentially differentiate to either columnar or squamous epithelium. Infection of these SCJ cells by hrHPV is likely to be responsible for the transformation and gives rise to either squamous cell carcinoma or adenocarcinoma, depending on the epigenetically defined lineage of differentiation.

I propose that the consequence of HPV infection is determined by the predetermined fate of the infected cell. Infection to the progeny of stem/progenitor cells at the exocervix ends with transient infection. Infection to the stem/progenitor cells at the exocervix results in a persistent but non-transforming infection. Infection to the progeny of Krt7+SCJ ends with nontransforming LSIL. It is infection to the Krt7+ SCJ cells undergoing squamous metaplasia that leads to malignant transformation.

Meanwhile, the first tissue change of HPV transformation is atypical squamous metaplasia (ASM) characterized by nuclear atypia, occasional perinuclear halos and a surface layer of mucinous epithelium. Although to be the earliest lesion of HPV transformation, application of ASM as diagnosis entity is impracticable due to poor reproducibility and low agreement of the morphological calling. New biomarkers based on the key mechanism of metaplasia of SCJ cells, i.e. DNA methylation that determines the fate of cell differentiation, are emerging and show promising performance in identifying HPV infections that are really transforming.
The human papillomavirus (HPV) vaccines have been shown to be efficacious in preventing the key HPV types associated with genital warts and cervical, penile and anal cancers.

This presentation summarises the key milestones of HPV vaccines employment and discusses the current global concerns of the HPV vaccines especially in the aspects of:

- Vaccines' Safety
- Controversies and
- Public sentiments

These global concerns have become significant barriers to HPV vaccination program implementation and impeded vaccines uptake in many countries.

Possible ways of overcoming these barriers will also be presented.
For any vaccination program and particularly for one that is new, surveillance is important to measure the impact and effectiveness of it. This is relevant politically and financially for Governments that invest in them. Moreover, for HPV, where disease manifestations take time (neoplasia takes decades), to show vaccination results in disease reduction in the target population, requires accurate age standardised incidence and mortality rates.

In the shorter term reduction of the HPV genotypes causing the disease, followed by earlier onset clinical disease such as genital warts, recurrent respiratory papillomatosis and precursor lesions for cancer [CIN3] are reasonable surrogates.

In countries where vaccination has been embraced and high coverage achieved, already very large reductions in vaccine-HPV genotype infection, genital warts and CIN3 have been seen and there is now an early indication that cancers are being impacted, where detailed surveillance has occurred.

Program monitoring is important to measure vaccine coverage as well as vaccine safety, very pertinent in showing high effectiveness and impact on those vaccinated. This is an exciting time in HPV related disease prevention with the Director General of WHO endorsing elimination of cervical cancer. Good surveillance will be needed to underpin the outcomes of this.
Over the past two years, China Food and Drug Administration (CFDA) has approved 2-valent, 4-valent based on the evidence of clinical trials. And 9-valent prophylactic HPV vaccine got the conditional CFDA approval following a vastly reduced regulatory timeline. International HPV vaccines available in China is a major step towards cervical cancer prevention but challenges lie ahead. The vaccine demand in China extremely exceeds supply. Additionally, the financial issues, particularly pricing for HPV vaccines, is a major consideration for high uptake in China. Up to now, 20 domestic HPV vaccines(including 2-valent, 4-valent, 9-valent, 14-valent, et al) are to be or have been initiated clinical trial with the first one(Cecolin) almost having completed third-phase clinical trial. Based on clinical trial, 3-dose schedule is administrated in China. 2-dose or 1-dose non-inferior study will be conducted in the near future to improve the vaccine coverage, which advances the elimination of cervical cancer in China.
CERVICAL CANCER CONTROL IN BANGLADESH – INTRODUCTION OF VACCINATION AND POPULATION BASED SCREENING

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The Government of Bangladesh (GOB) has introduced a cervical cancer screening programme through Visual Inspection of Cervix with Acetic Acid (VIA). Since 2005, VIA facilities have gradually been scaled up to all 64 districts and half of the sub-districts. Presently 2212 trained service providers of 431 VIA centres are offering VIA to women aged 30 years and above. Among 1816802 screened women, 85079 (4.68%) were VIA positive. Among them, about one-third attended the colposcopy clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU), and of them, 12690 (50.5%) had cervical precancer or cancer. Recently the GOB has approved a strategy to initiate population-based organized cervical cancer screening. The GOB is about to introduce HPV vaccination programme through existing EPI after successful completion the HPV Demonstration Programme (2016-18). A school-based vaccination programme will be implemented for all girls of Grade V every year. The vaccination programme and a population-based cervical screening programme should have visible impact on cervical cancer control.
In Japan, because of the increase of risk factors and changes in young women’s behavior, mortality and incidence have been increasing recently. Public health policy of MHLW on cervical cancer control has not been innovated, although enough resources and evidences. We reported the effectiveness of HPV vaccine against CIN2+. It was investigated in 22,743 women aged 20 to 29 years (Vaccine. 2018 May 21. [Epub]). Vaccinated women had a statistically significant 69% lower risk of CIN2+ as compared to the unvaccinated women; the crude relative risk estimate was 0.31 (95% CI: 0.11–0.83; p-value = 0.013) by normal approximation and 0.31 (95% CI: 0.08–0.80; p-value = 0.009) by the exact Poisson regression. The effect of age was not significant. Japan needs to issue strong recommendations for the HPV vaccine and HPV primary cervical screening based on scientific evidences with an epidemiological monitoring system to break the stigma. Public health governance without right education and appropriate risk communication is likely to continue witnessing increased cervical cancer in the near future. Maintaining public health trust in vaccine safety/effectiveness and cervical cancer screening is key to the success in cancer prevention.
HPV vaccine in mainland China was delayed by nearly 10 years, which is not included in the Chinese Expanded Program on Immunization (EPI) yet. A huge demanding for HPV vaccine exists in China, to date, 5 million doses of HPV vaccines have been released to mainland China since launch. However, HPV vaccine delivery in the context of China's enormous population, expansive geography, and strained healthcare system demands advanced planning and logistics. Additionally, limited supplies, high pricing, and lower awareness towards cervical cancer and HPV vaccine hamper HPV vaccination rollout in China. A great diversity of communication have been conducted even before the HPV vaccine launch, such as speeches by health-care professionals, announcements via newspapers, website. In the near future, series pre-rollout sustainable effort and more effective communication strategy targeting the public, officials, health-providers and medium, will be conducted to raise awareness of the public and ensure political will for HPV vaccine.
Project ROSE is a paradigm shift from the conventional cervical screening programme. Its uniqueness is the application of design thinking principles in the development of a prototype solution for Malaysia and potentially other countries where population-based organized screening remains a challenge. The uptake of conventional Pap smear remains low in Malaysia, despite regular campaigns and easy access to healthcare facilities. Barriers include ‘patient factors’ such as fear, embarrassment, inconvenience, and lack of awareness and ‘health system factors’ such as poor infrastructure and lack of dedicated resources/staff due to competing health priorities in busy clinical settings.

The ‘human centered approach’ towards cervical screening adopted by Project ROSE includes a combination of (i) self-sampling by women instead of a physician acquired specimen requiring an uncomfortable pelvic examination (ii) the adoption and implementation of registry support and (iii) communication by mobile technology, facilitating efficient tracking of women along the screening pathway, and real time, real world program monitoring.

Human Papillomavirus (HPV) testing which has higher sensitivity compared to conventional Pap smear, has been recommended by the World Health Organization (WHO) as the primary test for cervical screening programs. The objective nature of the test and its high negative predictive value allow for an extended screening interval. Furthermore, self-sampling for HPV has been shown to be a convenient and cost-effective method to increase screening participation among hard-to-reach women.

In designing a solution, The Project ROSE team spent significant time understanding the issues / barriers of cervical screening within the Malaysian context. They visited clinics and spoke to the staff on the ground to define their daily challenges in the context of cervical screening. Much planning was dedicated to maximizing the use of existing resources within the local clinic setting. Strategic utilization of existing infrastructure and resources was a key part of the innovation of Pilot Project ROSE. The idea was not to disrupt the daily service provision in these busy clinics or invest in additional infrastructure, but to integrate within the clinic's eco-system to maximize opportunities for cervical screening. As with any new intervention, careful attention was also paid to educating the health providers.
The strategy is now being refined towards the goal of making cervical cancer a rare disease in Malaysia by increasing the uptake of cervical screening among women.
Background: The National Cervical Screening Program in Australia underwent major changes on December 1st, 2017. We surveyed primary care practitioners to understand their level of preparedness to undertake cervical screening under the new guidelines.

Methods: Surveys were conducted between 14th August-30th November 2017 (pre-renewal) and from 9th February-15th August 2018 (post-renewal). Preparedness was assessed in three areas: 1) level of comfort, 2) level of confidence and 3) access to resources. Comparisons were made between the pre- and post-renewal periods.

Results: The proportion of practitioners who felt comfortable and confident with the changes, and could access resources, increased significantly from pre- to post-renewal period. The area where the practitioners expressed most discomfort with the new guidelines was in relation to the option of self-collection for under-screened women, in regard to womens' eligibility, test reliability and waiting period.

Conclusion: There remains a need for more education, information and communication around self-collection.
In December 2017, Australia’s National Cervical Screening Program NCSP transitioned from recommending 2-yearly cytology starting at age 18-20 years, to recommending 5-yearly primary HPV screening starting at age 25. In addition to being one of the first countries internationally to adopt primary HPV screening, Australia has a highly vaccinated population following an extensive catch-up vaccination program for women aged up to 26 years (now aged up to 38). Clinical management explicitly incorporates 16/18 genotyping results.

Early data from the NCSP will be presented, including information on participation, test results in a highly vaccinated population, and colposcopy demand post-transition. In addition some of the other issues that arose before and after the NCSP transitioned will be discussed.
On December 1, 2017 Australia became the first country to have a National Cervical Screening Program based on primary Human Papillomavirus (HPV) testing which allowed multiple different HPV testing platforms and assays to be used. There is a wide variety of data on these different assays (with different viral targets, genotyping outputs, workflows) in the scientific literature but how they perform in the same national program is a question which is being asked by jurisdictions across the world as they consider how best to implement their own programs. A number of different assays suitable for the Australian program are being used in the laboratories at VCS Pathology and the different facets of their performance will be presented.
The key intervention in the prevention of cervical cancer is successful treatment of CIN2/3. Incomplete excision of CIN2/3 is associated with an increased risk of recurrence; therefore EFC defined at least 85% of specimens with clear margins as one quality indicator (QI) for colposcopy. However this is potentially harmful because unnecessary removal of cervical tissue increases obstetrical complications.

COCHRANE included 93 studies reporting risk of recurrence associated with margin status with 25 analysing accuracy of margin status and HPV testing as proof of cure. The rate of margin involvement ranged from 2.8% to 53%. In 53/93 studies the EFC QI was not met. HPV testing and margin status both predicted treatment failure with a better sensitivity for HPV testing (91% vs 55.8%) but similar specificity. The overall risk of treatment failure rose from 6.6% to 17.1% (margin+) and 28.4% (HPV+) while a negative HPV test was a better predictor of cure (0.8% vs 3.7% recurrences)

Apart from special cases there is no need for immediate re-excision in CIN2/3 with margin involvement.
Publishing your work is important; for you, for your career, for science and because it's unethical not to.

I'll explain what helps ‘you’ publish and what hinders ‘you’ publishing. I'll then provide an outline of ‘how’ to publish articles and ‘how’ to manage others in this process, including your supervisors.

Without a publication the study and its data will be lost forever. That means that the risk that the participants took by being in the study - was utterly wasted. If the ‘world’ wants to see that data again then someone else will need to repeat the experiment. They'll use resources and put participants at risk again.

But beyond this ethical view, you need to publish for your own career. Then you need a great supervisor, a great project and lots of energy. You also need to understand the processes that editors for journals go through when considering papers for publication in their journals.
Early career researchers (ECRs) share similar challenges. They want to further their research, and make an impact. They seek funding and recognition, yet this may lag years behind their expertise and efforts. They may be starting or continuing responsibilities as parents or carers. Many ECRs experience precarious employment in highly competitive research funding environments. Others may have more stable employment but be balancing significant teaching or clinical responsibilities. For some, imposter syndrome is a constant companion.

Engaging as early career researchers in the media sphere takes time, energy and confidence. Yet this presentation will argue for its value, suggesting strategies for deciding where and how to strategically engage, with the primary goal being research impact. It will cover social media, mainstream media and specialised online outlets, giving practical examples of how other ECRs have successfully used these. Finally, it will touch on some of the pitfalls and how to avoid them.
In this short presentation, I will briefly describe my journey in becoming a clinician scientist. Having completed my undergraduate, postgraduate clinical training and research degree in high resourced countries, I found myself having to adapt to the healthcare and research environment in Malaysia. In this unique session, I will share some of my personal experience in 'global' health and research.
HIV infection is prevalent worldwide, with ~37 million infected persons. Combination anti-retroviral therapy (ART) has transformed the care of infected persons, many of whom will now live essentially normal lifespans. However, even in ART treated subjects who are aviraemic (undetectable) there remain subtle immunologic, metabolic and tissue abnormalities. Persons with HIV have increased rates of HPV acquisition, persistence, and multiple genotype infections, and increased rates of HPV disease and disease progression, including to invasive cancer. Aviraemic HIV+ve subjects also have defects in memory TFH cell function leading to abnormal B cell responses. Thus, immune responses to vaccination are often sub-optimal in HIV, and vaccine-induced antibody levels may decline more rapidly.

Nevertheless, studies to date show that HPV vaccines are immunogenic in HIV infection, but there is as yet a paucity of studies with efficacy (HPV disease) endpoints. I will review the evidence, and directions for future research.
LATEST ADVANCES IN TREATMENT FOR HPV-RELATED CANCERS: THE MEDICAL ONCOLOGIST’S PERSPECTIVE

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This session will be focused on the current treatment landscape of HPV associated malignancies including the common cancers of head and neck and cervical cancer but also the rare cancers of anal and penile cancer. Recent pivotal literature and ongoing clinical trials will be highlighted.
Among the many impactful vaccines developed over the last century, vaccines against HPV stand out as one of the most remarkable. First licensed in 2006, HPV vaccines developed by the two manufacturers have continued to exceed expectations in their ability to provide safe and durable protection against infections and pre-cancerous lesions wherever deployed. The primary challenge limiting their impact is inadequate deployment, in particular where the burden of HPV-related disease is highest. In countries supported by Gavi financing, introduction planning has positioned local health systems ready to accelerate impact, including support for vaccination of multi-age cohorts of girls aged 9-14 years. Additional suppliers have been hard at work developing new and affordable vaccine supply, including the first demonstration of efficacy in a phase 3 clinical trial with a novel vaccine platform. This talk will review the current trajectory of new vaccine development and opportunities for acceleration of impact of HPV vaccine in countries of highest disease burden.
A GLOBAL CALL FOR CERVICAL CANCER PREVENTION: IMPLICATIONS FOR FUTURE RESEARCH NEEDS

C. Wild

International Agency for Research on Cancer, Director, Lyon, France

The tools for cervical cancer prevention are available. Research establishing human papilloma virus (HPV) as a necessary etiologic agent provided the foundation both for prophylactic vaccine development and HPV-based screening. However, there are many barriers to ensuring these tools are implemented and benefit women equally, everywhere. Research does not stop with implementation: it must precede it, accompany it and evaluate it. Research enables interventions to be refined using data obtained during their application. Important research topics that must accompany cervical cancer elimination efforts include: 1) maximising access to effective vaccination; 2) adapting screening, including screen-and-treat, to low and middle-income countries (LMIC); 3) evaluating treatment methods for precancerous lesions in LMIC; 4) reaching disadvantaged or vulnerable groups with preventive interventions; 5) modelling vaccination and screening over time to inform cervical cancer control measures; 6) establishing cancer registry-based disease surveillance to be able to measure progress.
PIGMENTED WART AS A TYPICAL LESION CAUSED BY HPV4/65 (GAMMAPAPILLOMAVIRUS-1) CAN BE DIFFERENTIATED CLINICALLY AND HISTOPATHOLOGICALLY FROM OTHER HPV-RELATED LESIONS.

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Background and Aims

The predominant asymptomatic skin HPV types come primarily from the genera Betapapillomavirus and Gammapapillomavirus, members of these genera are very successful, infecting children at a young age to produce persistent subclinical infections. Among Gammapapillomaviruses, only HPV4/65 and 60 (Gammapapillomavirus-4) are generally thought to cause apparent symptomatic lesions in immunocompetent general population. Lesions caused by HPV4/65 are known to induce wart-like lesions, so called pigmented wart, mainly on the palmoplantar skin with homogeneous intracytoplasmic inclusion bodies as well as increased melanin granules/the melanin blockade melanocytes characterized histologically.

Methods

In this study we have carried out PCR-based typing using degenerated primers to 40 pigmented warts diagnosed by clinical appearances and dermoscopic observations. On several cases, additional histopathological studies were also carried out.

Results

From pigmented warts, only HPV4/65 and its subtypes are identified. However no other Gammapapillomavirus-1 (HPV95/127), which are originally came from patient with immunodeficiency or asymptomatic healthy skin, are identified, suggesting HPV4/65 and HPV95/127, which are classified to same species (Gammapapillomavirus-1), have distinctive biology and pathogenicity. HPV4/65 are not detected from non-pigmented warts we tested. Importantly pigmented warts caused by HPV60, which are relatively rare, can be differentiated by clinical appearances from those caused by HPV4/65.

Conclusions

Pigmented wart is the typical HPV4/65-caused lesion among general immunocompetent population, which can be differentiated clinically and histopathologically from other warts caused by other HPV types, and is a good model to investigate HPV-type specific biology and pathogenicity.
GENOME ANNOUNCEMENT: COMPLETE GENOME SEQUENCES OF FOUR NOVEL HUMAN GAMMAPAPILLOMAVIRUSES ISOLATED FROM PENILE SKIN SWABS FROM SOUTH AFRICAN MEN.

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Background and Aims

Four novel human papillomavirus genotypes were detected in penile swabs by L1 FAP PCR and sequencing.

Methods

The full genomes of HPV219 (7108bp), HPV220 (7381bp), HPV221 (7381 bp) and HPV222 (7275 bp) were amplified using back to back primers, cloned into the TOPO XL Vector System, sequenced using Illumina MiSeq 300bp paired end sequencing and characterised.

Results

HPV219 is most closely related to HPV213 (87% identity in L1 ORF) of the γ13 species, HPV220 to HPV212 (72%) of γ17, HPV221 to HPV142 (80%) of γ10, HPV222 to HPV162 (73%) of γ19 species. The novel HPV types demonstrated the classical genomic organisation of γ-PVs, with seven ORFs encoding five early (E1, E2, E4, E6 and E7) and two late (L1 and L2) proteins. Typical of γ-PVs the novel types all lacked the E5 ORF. The long control region of the four HPV types contained a single TATA box (TATAAA) and varying numbers of palindromic E2-binding sites (ACC-N₆-GGT). Two conserved zinc binding domains (CxxC(x)₂₉CxxC) were identified in the E6, and one in the E7 proteins of all four viruses. Only E6 of HPV219 contained a putative PDZ binding domain x(T/S)x(L/V) in the N-terminal, a variety of PDZ domain-containing proteins are targeted mostly for degradation through the HPV E6 PDZ binding domain. The LxCxE pRB (retinoblastoma binding protein) domain, was only present in HPV222.

Conclusions

We discovered four novel HPV genotypes of the γ-PVs genera, hence expanding our knowledge of the heterogeneity of γ-PVs. Their role in carcinogenesis, if any, warrants further study.
Changes in oral bacterial communities are associated with HPV status for oral and oropharyngeal cancers

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Background and Aims

Human papillomavirus (HPV) infection has been the major etiological factor in a subset of head and neck cancers, in particular oral cavity (OCC) and oropharyngeal cancers (OPC). In this study, we used oral rinse samples to characterise the bacterial communities of patients with OCC and OPC, and the effects of HPV status on the oral microbiota specifically.

Methods

The study cohort consists of 52 OCC and OPC patients (31 HPV-positive; 21 HPV-negative). The composition of the oral bacterial communities was analysed using 16S rRNA gene amplicon sequencing using the MiSeq platform and the genus-level differences between community profiles and HPV status analysed using the QIIME and Calypso bioinformatics work packages.

Results

Redundancy analysis of the oral bacterial communities are significantly different between the HPV-negative and HPV-positive cancer patients ($P = 0.05$), with representatives of Gemella ($P = 0.02$), Haemophilus ($P = 0.01$) and Neisseria ($P = 0.03$) shown by Kruskal-Wallis testing to be positively associated with HPV in OCC and OPC.

Conclusions

This indicates that the oral bacterial communities may play a role in chronic HPV infection and therefore should be further investigated as a risk factor.
MOLECULAR IDENTIFICATION AND CHARACTERIZATION OF A NOVEL HPV35 LINEAGE
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Background and Aims

Human papillomavirus (HPV) type 35 is associated with ~2% of cervical cancers worldwide. This HPV type belongs to the oncogenic α-9 clade, which contains the highly oncogenic HPV16. Since the α-9 HPVs are sexually transmitted, they represent a complementary approach to understand human evolution and population structure.

Methods

HPV35-positive cervical samples were collected worldwide for whole-genome sequencing using a customized Ion AmpliSeq panel on an Ion Torrent NGS platform. Phylogenetic relationships between HPV35 variants were explored by performing multisequence alignment on 440 whole genome HPV35 sequences sampled from 31 different countries using MAFFT followed by RAxML. 28 reference sequences were used to scaffold the phylogenetic tree. Data was visualized using R.

Results

Full genome sequence analysis of HPV35-positive samples showed an overall sequence similarity of 99.6±0.3%. Phylogenetic analysis was able to identify previously reported A-lineages (A1, A2 and A3) and a previously unknown B-lineage clade that differed from the A-lineage by 0.84±0.16%. Sub-lineages were identified to have a mean full genome variance of 0.33±0.25%. The majority of the novel B lineage sequences originated in India, where the B lineage was determined to have a prevalence of 57% (16/28) amongst the analyzed samples.

Conclusions

Full genome phylogenetic analysis of HPV35 revealed a novel B lineage clade of HPV35 that differed significantly from all previously identified HPV35 A lineages. The apparent isolation of this lineage to India suggests population separation over 100,000 years ago.
STUDYING THE MOUSE PAPILLOMAVIRUS LIFE CYCLE BY TRACKING VIRAL DNA AND RNA IN SELECTED LAVAGES AND TISSUES

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Background and Aims

Viral DNA and RNA have been used for mouse papillomavirus (MmuPV1) detection in previous studies. In the current study, we wished to determine whether these two methods are comparable for viral detection and whether, together, the methods can reveal novel mechanisms of the virus life cycle.

Methods

We tested over 100 lavage and tissue samples from ten different mouse strains infected with MmuPV1. For lavage samples, vaginal, anal or oral swabs were collected periodically and transferred into Trizol for RNA/DNA isolation. For tissue samples, tail, muzzle, vagina, anus, and tongue tissues were harvested at the termination of the studies. RNA was extracted with Trizol following a Polytron homogenization. DNA was extracted following either the Trizol DNA extraction protocol or the DNeasy blood and tissue protocol (Qiagen). Viral E1^E4 mRNA transcripts were quantitated with a QRT-PCR kit and viral DNA was quantitated with a QPCR kit both from Agilent Technologies.

Results

Overall there was agreement between viral DNA and viral RNA detection in tissue and lavage samples. Interestingly, some tissues including back and mammary tissues showed strong viral DNA but had undetectable viral RNA.

Conclusions

Both viral DNA and viral RNA are valid measures for tracking infections. The pattern of viral DNA and RNA detection in different tissues may reveal novel mechanisms of the virus life cycle and may help to shed light on the tissue selectivity normally seen in papillomavirus infections.
Background and Aims

Besides UV radiation, cutaneous human papillomaviruses (HPVs) are considered as cofactors in multi-step process of non-melanoma skin cancer (NMSC) development. The rodent *Mastomys coucha* is naturally and persistently infected with the cutaneous papillomavirus MnPV and reflects the situation of HPV infection on patients in many aspects.

Methods

Animals were chronically UVB irradiated. Emerging squamous cell carcinomas (SCCs) were characterized in detail.

Results

We could show that only the cooperation of chronic UVB radiation and MnPV infection leads formation of SCCs. These were both well-differentiated, supporting productive infections and therefore harboring high amounts of episomal and transcriptionally active MnPV-DNA or dedifferentiated with locally very low amounts or even absent MnPV-DNA, despite seropositivity of the animals against MnPV-L1. The presence of DNA damage markers in MnPV-infected cells indicated the interference with DNA repair, leading to an accumulation of mutations. Notably, like in humans, *Trp53* was mutated in most SCCs preferentially at two hot-spot mutations, which completely impaired its transactivation efficiency in functional assays. A correlation between mutated p53 and EMT markers indicated dedifferentiation of SCCs after loss of functional p53. Here, MnPV is no longer required to maintain the malignant phenotype resulting in a loss of viral DNA.

Conclusions

This is the first study showing a “hit-and-run” mechanism for a cutaneous papillomavirus in NMSC development. Currently, we are focusing on the mechanisms of the virus-host interplay. Furthermore, we investigate how chronic UVB irradiation is influencing the seroconversion of the animals and whether recently developed broad protective L2-based vaccines can prevent NMSC formation in this preclinical model.
Background and Aims

We wanted to determine if papillomavirus infections could be transmitted through the blood. Using the well-established rabbit papillomavirus (CRPV) model and a newly developed mouse papillomavirus (MmuPV1) model, we asked two major questions: 1) Can bloodborne papillomavirus and/or viral DNA yield infections/tumors at relevant local sites? 2) Can transfusion of blood from infected animals (donors) to naïve animals (recipients) induce infections in these recipients?

Methods

New Zealand White rabbits and HSD: Nu nude mice were intravenously infused with CRPV virions or viral DNA and MmuPV1 respectively. Tumor growth at the pre-scarified cutaneous sites was recorded photographically. The infections at mucosal sites (mice only) were monitored by periodically collecting lavages/swabs, isolating DNA and RNA, and analyzing the nucleic acids by Q-PCR and Q-RT PCR. The infections were further confirmed after the termination of the studies by RNAseq, immunohistochemistry, in situ hybridization and histology.

Results

The rabbits infused with both virions and viral DNA developed tumors at prewounded back skin sites. Naïve animals grew tumors at pre-wounded sites after being transfused with blood from a rabbit infected with virus. Nude mice infused with virions exhibited infections at both cutaneous and mucosal sites. Interestingly, we also detected virus in the stomach tissues in some mice. Blood from nude mice with active local infections also transmitted infections to naïve mice following blood transfusion.
Conclusions

Blood transfusions are capable of transmitting papillomavirus infections. Omission of HPV testing in the blood donor screening can put the recipients at risk for infections, especially in the case of immunosuppression.
PROGESTERONE-BASED CONTRACEPTIVES PROMOTE LOWER GENITAL TRACT PAPILLOMAVIRUS INFECTIONS BUT DO NOT CONTRIBUTE TO DISEASE PROGRESSION IN A MOUSE PAPILLOMAVIRUS INFECTION MODEL

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Background and Aims

Contraceptives such as the injectable contraceptive Depo-Provera (Depo medroxyprogesterone, DMPA) are used by an estimated 34 million women worldwide. DMPA has been associated with increased risk of several viral infections including HSV-2, HIV and HPV. Human papillomaviruses (HPVs) are ubiquitous in humans and cause 5% of all cancers. Using a newly established mouse papillomavirus (MmuPV1) model, we tested the hypotheses that contraceptives increase the susceptibility to viral infection and that long-term contraceptive administration induces more severe disease.

Methods

For the infection study, both immunocompromised and immunocompetent mice were treated with either DMPA or PMSG with hCG and subsequently infected with MmuPV1 at the lower genital and anal tracts without wounding. To study the impact of long-term contraceptive treatment on infected individuals, MmuPV1-infected at the lower genital and anal tracts were treated with contraceptives including DMPA, 17β-estradiol, and non-hormone based contraceptive Cilostazol (CLZ, Pletal) up to 9 months respectively. The infections were monitored by periodically collecting lavages/swabs, isolating DNA and RNA, and analyzing the nucleic acids by Q-PCR and Q-RT PCR. Infections were further confirmed after the termination of the studies by immunohistochemistry, in situ hybridization, and histology.

Results

DMPA treatment significantly increased viral titers at the lower genital and anal tracts vs. the PMSG and hCG treated group (P<0.01, student t test). Infected animals with long-term contraceptive treatment did not generate higher grades of histology than the control group.

Conclusions

Contraceptives promote viral infection but seem not to play a role in cancer development in the mouse papillomavirus model.
INTEGRATION OF ONCOGENES VIA SLEEPING BEAUTY AS A MOUSE MODEL OF HPV16+ ORAL TUMORS AND IMMUNOLOGIC CONTROL

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Background and Aims

Human papillomavirus type 16 (HPV16) is the etiologic factor for cervical cancer and a subset of oropharyngeal cancers. Tumor implantation models are traditionally used to study HPV-associated buccal tumors. However, these models fail to address precancerous phases of disease progression and display tumor microenvironments distinct from those observed in patients. Previously, K14-E6/E7 transgenic mouse models have been used to generate spontaneous tumors, but the rate of tumor formation is inconsistent, and the host often develops immune tolerance to the viral oncoproteins. We aim to develop a novel spontaneous HPV+ tumor model to study HPV+ tumor biology and therapeutic interventions.

Methods

We performed submucosal injection of oncogenic plasmids expressing HPV16-E6/E7, NRasG12V, luciferase, and sleeping beauty (SB) transposase, followed by electroporation in the buccal mucosa. We evaluated responses to immunization with a pNGVL4a-CRT/E7(detox) therapeutic HPV DNA vaccine and tumor cell migration to distant locations.

Results

Mice transfected with plasmids encoding HPV16-E6/E7, NRasG12V, luciferase, and SB transposase developed tumors within 3 weeks. We also found transient anti-CD3 administration is required to generate tumors in immunocompetent mice. Bioluminescence signals from luciferase correlated strongly with tumor growth, and tumors expressed HPV16-associated markers. We showed that pNGVL4a-CRT/E7(detox) administration resulted in antitumor immunity in tumor-bearing mice. Lastly, we demonstrated that the generated tumor could migrate to tumor-draining lymph nodes.

Conclusions

Our model provides an efficient method to induce spontaneous HPV+ tumor formation, which can be used to identify effective therapeutic interventions, analyze tumor migration, and conduct tumor biology research.
SEROPOSITIVITY TO MULTIPLE ANOGENITAL HPV TYPES IS ASSOCIATED WITH CURRENT ANOGENITAL HPV INFECTION, ABNORMAL CYTOLOGY AND SEROPOSITIVITY FOR NON-GENITAL HPVS

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Background and Aims

Antibodies against human papillomaviruses (HPV) are biomarkers for current or past infections. We assessed whether antibodies against multiple HPV types were determinants of current multiple anogenital HPV infections, abnormal cytology and seropositivity for cutaneous HPVs.

Methods

1,848 Slovenian women attended two rounds of cervical cancer screening three years apart and provided data on HPV antibodies and HPV DNA at both visits. Antibodies against 15 anogenital HPV types and 6 cutaneous HPVs were determined using pseudovirion-luminex serology and anogenital HPV DNA using Linear Array. Women were grouped as either HPV seronegative, having antibodies to 1-2 HPV types or to ≥ 3 HPV types.

Results

Presence of antibodies to multiple anogenital HPV types at baseline was associated strongly with (i) presence of HPV DNA at the cervix ($\chi^2=68.8; p<0.0001$), (ii) multiple types of HPV DNA at baseline ($\chi^2=58.6; p<0.0001$), (iii) HPV DNA at follow-up ($\chi^2=22.9; p<0.0001$) (iv) abnormal cytology ($\chi^2=9.8; p=0.0017$), (v) concomitant presence of antibodies to any of six non-genital HPV types ($\chi^2=40.1; p<0.0001$). Presence of antibodies to ≥3 anogenital HPV types tended to persist over time.

Conclusions

Seropositivity against at least 3 anogenital HPV types is associated with current multiple anogenital HPV infections, abnormal cytology and seropositivity to non-genital HPVs.
DEVELOPMENT AND CHARACTERIZATION OF A NOVEL HPV ANTI-L2 MONOCLONAL ANTIBODY PANEL

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Background and Aims

HPV L2 is a popular vaccine target because of the conserved nature of the protein. As a means to better define the topology of the viral capsid and analyze the exposure of L2 in the context of the assembled HPV capsid, we developed and characterized a panel of 32 mAbs which target the L2 N-terminus aa11–200.

Methods

Balb/c mice were immunized with L2 peptide aa11–200, spleen cells were harvested and used to produce hybridoma cells. Hybridoma supernatants were screened by immunofluorescence (IF) and ELISA for HPV16 L2 specificity. Positive supernatants were further characterized by fine epitope mapping with overlapping peptides, intact and denaturing ELISAs, and cross-reactive binding/neutralization assays. Select mAbs were digested into Fab fragments (Pierce).

Results

Several of the mAbs are completely novel and bind portions of the L2 protein that have not yet been targeted. Many mAbs neutralize pseudo-infection in a pre-attachment neutralization assay. Two mAbs, 7I and 9E, are extensively cross-reactive by IF and together recognize HPV5,6,11,16,18,31,33,35,39,45,52,58,59, and CRPV.7I and 9E are not nearly as cross-reactive in the ability to neutralize pseudo-infection. Fab fragments were generated from several of the L2 reactive mAbs and at this time we are unaware if anyone else has been successful at generating anti-L2 Fabs.

Conclusions

Used in combination, these unbiased mAb/Fab probes will be beneficial in future studies to unravel of the placement of L2 using cryo-electron microscopy and help better define the role of L2 in the HPV lifecycle.
Background and Aims

Cyclophilin B (CypB) has been shown to be highly-expressed in HPV-related cancers such as head and neck or cervical cancers. We develop naked CypB-specific DNA vaccine to treat these CypB-expressing cancers.

Methods

Mice were first immunized with CypB-specific naked NDA vaccine. Splneocytes of the mice were harvested and cultured with 6 potential CD4+ CypB-specific long peptides or 10 potential CD8+ CypB-specific short peptides to identify potent H-2 Db-and Kb-restricted CD4+ helper and CD8+ cytotoxic T cell epitopes of CypB. To evaluate if naked DNA vaccine could generate antigen-specific immunologic responses, flowcytometric analysis, ELISPOT and ELISA were performed. To evaluate if naked DNA vaccine could generate effective anti-tumor effects, in vivo tumor protection and treatment experiments were performed.

Results

We first identified one short and one long CypB peptide could be CypB epitope to induce higher numbers of CypB-specific, IFN-g-secreting CD8+ or CD4+ T lymphocytes. The naked DNA vaccine immunized mice could generate higher numbers of CypB-specific CD4+ helper and CD8+ cytotoxic T cells compared with the other ineffective vaccines. The in vivo experiments showed that CypB-specific naked NDA vaccine could effectively prevent tumorigenesis of antigen-specific over-expressing tumor cells in mice 60 days after tumor challenge. Although, antigen-specific naked DNA vaccine could not effectively to inhibit the tumor growth of CypB over-expressing tumor cells in the therapeutic experiments, vaccinia CypB-specific vaccine could suppress the tumor growth of CypB over-expressing tumor cells in the therapeutic experiments.

Conclusions

CypB-specific DNA vaccine could have the potential to prevent and treat CypB-specific HPV-related tumors.
DELAYED NEUTRALIZING ANTIBODY TREATMENT PROTECTS AGAINST CUTANEOUS AND MUCOSAL MOUSE PAPILLOMAVIRUS INFECTIONS
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Background and Aims

Mouse papillomavirus (MmuPV1) has shown broad tissue tropism in athymic nude mice. In the current study, we investigated whether passive immunization using a neutralizing monoclonal antibody could provide protection at different time points after viral delivery and whether all susceptible sites could be protected.

Methods

Two athymic nude mouse strains (Hsd: NU and NU/J) were used for the study. The mice were administered an in-house neutralizing antibody (MPV.A4) i.p or i.v at -24, 0, +6, and +24 hours following viral delivery at both cutaneous and mucosal sites. Lesions at the two cutaneous sites (the muzzle and the tail) were monitored biweekly and recorded photographically. Viral RNA and DNA were monitored periodically by Brilliant III QRT-PCR and Q-PCR kits (Agilent Technologies) using RNA and DNA extracted from lavages from the three mucosal sites (the lower genital tract, the anal tract and the tongue). Issues harvested at the termination of the study were also examined for viral presence via immunohistochemistry to detect capsid protein and in situ hybridization to detect viral DNA.

Results

Animals were protected against infections at the two cutaneous sites as well as the three mucosal sites up to 6 hours post viral delivery. No protection was found in the animals immunized 24 hours after the delivery of virus.

Conclusions

The mouse papillomavirus model may be valuable for the development of antibody-based therapeutics for HPV infections.
USING A TOPONOME IMAGING SYSTEM (TIS) TO STUDY VIRAL-HOST INTERACTION IN MOUSE PAPILLOMAVIRUS (MMUPV1) INFECTED TISSUES

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Background and Aims

We have recently established a mouse papillomavirus (MmuPV1) model to study HPV-associated diseases in both cutaneous and mucosal tissues. Here we applied the Toponome Imaging System (TIS™) to further characterize viral-host interaction in this model. TIS enables: 1) identifying in situ up to 100 proteins in a single tissue section; 2) visualizing how probed proteins interact within cells to form super molecular structures that differ in combinatorial molecular phenotypes (CMPs) (Nat Biotechnol 24:1270–8, 2006; Proc Natl Acad Sci 110:11982–7, 2013). This is the first exploratory study using TIS to characterize the toponome of different immune cells in the mouse lower genital tract infected with MmuPV1.

Methods

Sections from flash-frozen lower genital tracts of MmuPV1+ and MmuPV1- mice were immune-stained with FITC-tagged antibodies to anti-mouse cell surface proteins including CD4, CD8, Ly6C, Ly6G, MHCII, CD53, nuclear Histone H1, cytokeratin, and an anti-MmuPV1 capsid L1 (MPV.A4) antibody. 3D de-convoluted z-stack images offered a bird’s eye view of the molecular landscape of these proteins in situ. The final data were presented as an image exhibiting frequencies of CMPs in tissues and a list of these CMPs in a color-coded table.

Results

The frequencies of CMPs in the infected and non-infected areas were distinguished by viral presence in the MPV.A4+ cells. Interestingly, the MPV.A4+ cells co-existed with the Ly6G and MHCII positive cells.
Conclusions

This study demonstrates the ability of TIS in identifying changes in the cellular environment during viral infections and providing new insights leading to further mechanistic studies on virus-associated disease progression.
IPVC8-0014
POSTER SESSION

BASIC RESEARCH - IMMUNOLOGY

IMMUNE MECHANISMS FOR THE RELATIONSHIP BETWEEN ONCOGENIC HPV INFECTION AND THE RISK OF HIV ACQUISITION

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Background and Aims

HPV is one of the most common STIs globally and a necessary factor for cervical cancer development. While high risk HPV (HR-HPV) infection has been associated with increased HIV risk, the underlying mechanisms remain unclear. Since STIs are associated with inflammation, this study investigated whether the immune responses associated with HR-HPV infection contribute to the inflammatory genital environment known to increase the risk of HIV infection.

Methods

This study included baseline assessments of 167 HIV negative women participating in the CAPRISA 008 trial. The Roche Linear Array assay was used to detect the presence of 37 HPV genotypes in CVL pellets, and concentrations of cytokines were assessed in matching CVL supernatants using multiplex ELISA technology. The frequencies of activated (CD38+ and/or HLA-DR+) or proliferating (Ki67+) T cells (CD3+), NK cells (CD56+CD16+), and HIV target cells (CCR5+CD4+) were assessed on complementary cytobrush-derived specimens by flow cytometry.

Results

The study demonstrated a 50.8% HPV prevalence, with 52.9% of infections attributed to HR-HPV. In multivariate analyses controlling for STI and BV, women with HR-HPV had significantly higher concentrations of MCP-1 (β=0.127pg/ml) and IL-13 (β=0.117pg/ml), and greater frequencies of lymphocytes (β=1.987pg/ml) relative to women without HR-HPV. Women with HR-HPV also had trending increases in IL-1β, IL-12p70, eotaxin, IL-8, IP-10, MIG, VEGF and IL-2 concentrations.

Conclusions

This study demonstrated an association between HR-HPV and cellular and cytokine biomarkers of inflammation, suggesting an association with increased risk of HIV acquisition. Longitudinal investigations are needed to confirm a biological mechanism for the relationship between persistent HR-HPV infection and HIV acquisition.
IPVC8-0249
POSTER SESSION

BASIC RESEARCH - IMMUNOLOGY

INfiltration of plasma cells Into stroma Is possibly associated with higher grade of CIN

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Background and Aims

Cervical intraepithelial neoplasia (CIN) is a well-known precancer state caused by human papilloma virus (HPV). Although contribution of T cells in the clearance of HPV-infected cells in CIN patients has been intensively studied, that of humoral immunity has not been elucidated in detail. In this study we focused on plasma cells which infiltrate into stroma of CIN lesions.

Methods

We collected 415 biopsy samples from 328 CIN patients, and the proportion of lymphocytes, plasma cells, neutrophils, and eosinophils were estimated based on microscopic findings of Hematoxylin-eosin (HE) staining. CIN grade, HPV genotype, and clinical risk factors, including taking steroid or oral contraceptives, were also assessed.

Results

We classified profiles of immune cells into 3 groups according to the proportion of lymphocytes and plasma cells; plasma cell-dominant group (n=28, 6.7%), lymphocyte-dominant group (n=342, 82.4%), and the others (n=45, 10.8%). Although profiles of immune cells were not associated with HPV genotypes or any clinical risk factors, it was associated with CIN grades; CIN3 lesions were highly observed in the plasma cell-dominant group compared to other groups; 46.4% in the plasma cell-dominant group and 10.3% in other groups (Chi-square test, p<0.0001). To validate the assessment of HE staining, representative 20 samples were stained with anti-CD138 and anti-CD3 antibodies. Findings of immunohistochemistry were well correlated with the morphological findings by HE staining.

Conclusions

Here we demonstrated that infiltration of plasma cells into stromal region was associated with higher grade of CIN. It is possible that increased number of infiltrated plasma cells might contribute to CIN progression.
THE HPV STANDARDIZATION INITIATIVE: HPV SEROLOGY LABORATORY AT THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH

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Background and Aims

As protection against HPV infection is believed to be mediated by HPV-specific antibodies, HPV serology measurements are being proposed as endpoints in clinical trials of modified regimens of existing vaccines and follow-on products. However, there is a lack of standardized assays, procedures, and reagents accessible to the scientific community for assessment of immune responses to HPV prophylactic vaccines. Hence, the HPV Serology Laboratory at Frederick National Laboratory for Cancer Research, was established in January 2017 to work with National Cancer Institute (USA) and the Bill & Melinda Gates Foundation to address this challenge by standardizing and harmonizing serological assays and reagents for HPV antibody testing within HPV prophylactic vaccine trials.

Methods

The goal is to expedite standardization efforts by developing a critical set of qualified immunoassay reagents, and validated assays that will be made available to the HPV scientific community. Furthermore, we plan on providing accessible standard operating procedures for reagent production methods and immunoassay testing and qualification methods.

Results

The HPV Serology Laboratory is currently developing qualified HPV Virus-Like Particles for 9 HPV types included in currently licensed vaccines, HPV antibody secondary standards, serology-based proficiency panels, qualified serology assays, and testing guidelines. This work is being conducted in partnership with several other HPV serology laboratories in the world.

Conclusions

Achieving these goals will enable comparisons of data across different HPV vaccines and different studies and, thus, it will facilitate vaccine development and implementation of new vaccine indications and new vaccine candidates.
EVALUATION OF DIFFERENT TRANSFECTION METHODS FOR HPV L1L2 VLP PRODUCTION IN MAMMALIAN CELLS FOR USE IN SEROLOGY ASSAYS

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Background and Aims

Currently licensed HPV vaccines are based on Human Papillomavirus (HPV) L1 virus-like particles (VLPs). HPV VLPs are used extensively in HPV research and as critical reagents in the assessment of HPV-induced immune responses. There are a variety of available methods to create HPV VLPs for use in the research setting; however, transfection methods are expensive and time-consuming. Our team is currently producing HPV VLPs for the nine HPV types included in the currently administered vaccines to be used as assay reference reagents by the serology scientific community to aid in standardization and harmonization of HPV serology testing in vaccine trials. With the aim of reducing costs and saving time in VLP production while maintaining robust HPV particle assembly, we have investigated different transfection approaches in a mammalian-based HPV L1L2 VLP production system.

Methods

Aspects of consideration include transfection reagents and efficiency, cell viability, materials, and method optimization in the context of final VLP output via HEK293TT transfection with HPV-6 L1L2 plasmid. VLP structure is confirmed by electron microscopy as well as epitope confirmation assays.

Results

Results demonstrate that cost-efficient reagents such as PEI and Transporter™ 5 are as efficient as Lipofectamine in producing particles. Similarly, adaptation of various transfection methods and use of large-scale production techniques lead to faster production time with similar output.

Conclusions

By reducing costs and time to produce VLPs, it becomes more feasible to create large production sets of VLPs in less time and with less financial burden for immune monitoring teams.
EFFECTIVE MIGRATION OF SKIN DENDRITIC CELLS TO THE DRAINING LYMPH NODE IS DEPENDENT ON HPV16E7-RB INTERACTION

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Background and Aims

High-risk human papillomaviruses (HPV) infect keratinocytes of squamous epithelia. HPV E7 protein induces epithelial hyperplasia by binding Rb family proteins and disrupting cell cycle termination. Murine skin expressing HPV16E7 as a transgene from a keratin 14 promoter (K14.E7) demonstrates dysfunctional antigen presenting cells, ineffective antigen presentation by keratinocytes, and production of immunoregulatory cytokines. Grafted hyperplastic K14.E7 skin is not rejected from immunocompetent non-transgenic recipient animals.

Methods

To establish the contribution of E7, of E7-Rb interaction and of epithelial hyperplasia to altered local skin immunity, K14.E7 skin was compared with skin from K14.E7 mice with mutant Rb unable to bind E7 (K14.E7xRbΔL/ΔL mice) that have normoplastic epithelium.

Results

K14.E7xRbΔL/ΔL keratinocytes, unlike K14.E7 keratinocytes, were susceptible to E7 directed CTL-mediated lysis in vitro. However, K14.E7xRbΔL/ΔL skin, like K14.E7 skin, was not rejected from immunocompetent non-transgenic animals. Migration of Langerhans cell and CD11b⁺ dendritic cells from grafted skin to lymph node at day 11 after grafting was impaired in mice recipient of K14.E7xRbΔL/ΔL grafts when compared with K14.E7 grafts or K5mOVA grafts.

Conclusions

We conclude that Rb and HPV16E7-Rb interaction facilitate effective migration by skin-derived dendritic cells.
VAGINAL MICROBIOME (VM) INSTABILITY AND INFLAMMATORY PROFILES IN A PROSPECTIVE STUDY OF HPV 16 ACQUISITION, PERSISTENCE AND CLEARANCE.

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Background and Aims

To examine the role of the VM instability and inflammatory states in a prospective study of HPV 16 clearance.

Methods

Five to eight visits from 14 women, selected at time of HPV16 preacquisition, persistence and post clearance, had cervicovaginal lavage samples examined for cytokines using Luminex platform, the microbiome composition using 16S ribosomal RNA (rRNA) sequence analysis, and the metabolomic profile. Four visits from 8 control subjects no history of HPV detection ever were also examined. The microbiome community states types (CST) were identified.

Results

Using Markov chain modelling (figure 1), women with no HPV history had stable CSTs (e.g. they were likely to remain in their same CST through-out). In comparison, women with HPV infection were more likely to transit between the 3 states (CST I, III and IV). For cytokine comparisons, women with no HPV history had higher levels of several cytokines compared to pre-acquisition samples (figure 2). Post-clearance cytokines were similar to women with no HPV history. Metabolites associated with inflammation and tumor growth were more common during persistence than preacquisition.
Conclusions

Our data suggest that VM instability is associated with a vulnerability to HPV 16 acquisition. The higher levels of inflammatory markers post-clearance is evidence of a successful anti-viral activity. The higher levels of cytokines seen in women after clearance as well as in women with no history of HPV may suggest that a certain level of inflammatory surveillance is required to maintain an HPV negative state.
EVALUATION OF IMMUNE RESPONSES INDUCED BY A NOVEL HPV 16 E7 PEPTIDE-BASED THERAPEUTIC VACCINE WITH CANDIDA SKIN TEST REAGENT AS AN ADJUVANT IN C57BL/6 MICE

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Background and Aims

Cellular and humoral immune responses, to a novel HPV therapeutic vaccine, were evaluated in C57BL/6 mice.

Methods

This newly designed vaccine consisted of 3 HPV 16 E7 peptides covering the entire protein (E7 1-35, E7 36-70, and E7 71-98) and Candida skin test reagent as a vaccine adjuvant. Mice were injected intradermally with (1) adjuvant alone, (2) peptides alone, (3) peptides with adjuvant, or (4) phosphate-buffered saline 3 times 3 weeks apart. The animals were sacrificed 2 weeks later. Splenocyte proliferation, intracellular cytokine secretion in splenocytes, Th1, Th2, and regulatory T-cells in spleen, serum cytokine levels, and serum antibody against the E7 peptides were evaluated. Statistical significance was determined with one-way analysis of variance followed by the Dunnett’s test for group comparisons.

Results

Significantly increased proliferation was demonstrated in mice injected with the peptides alone and with the peptides and adjuvant. However, only the peptides and adjuvant group showed significantly increased percentage of IFN-γ secreting CD4 and IFN-γ secreting CD8 T-cells. Interestingly, the adjuvant alone group also resulted in increased IFN-γ secreting CD4 T-cells. In serum, IFN-γ increase was shown only in the adjuvant alone group. Antibody production was demonstrated for the adjuvant alone and the peptides and adjuvant group.

Conclusions

Overall, the peptides and adjuvant group and adjuvant alone group demonstrated robust immune responses suggesting that adjuvant alone may be sufficient to raise anti-HPV immune response.
INDUCTION OF MEMORY B CELL RESPONSES AFTER A THREE-DOSE BIVALENT HPV VACCINATION OF 16 YEAR OLD GIRLS

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Background and Aims

For long-term immunogenicity to HPV, the induction of memory B-cells responses are important. Therefore, B-cell memory immunity in girls vaccinated with bivalent HPV-vaccine at 16 years of age was followed-up yearly.

Methods

After vaccination at 16 years of age with three doses of bivalent HPV-vaccine, the numbers of HPV-type-specific memory B-cells were measured at 1 and 2 years post-vaccination (n=20) and in non-vaccinated women (n=10) by polyclonal stimulation of purified B cells (CD19+) followed by ELISPOT-assays specific for virus-like particles (VLPs) of types, 16,18,31, and 45. HPV type-specific antibodies were determined in B-cell-culture supernatants and in serum, by a VLP-based multiplex bead-based immunoassay.

Results

B-cell immune responses for all measured HPV types were shown 1 and 2-years post-vaccination. The numbers of memory B-cells were significantly higher for type 16 and 18, compared to type 31 and 45. HPV-specific memory B-cells were not detectable in the non-vaccinated group. After HPV vaccination significant correlations (P<0.01) were observed between the numbers of memory B-cells and the IgG levels in the supernatants for HPV-type 16 and 18. No significant correlations were found between the HPV type-specific numbers of memory B cells and serum antibody levels.
Figure 1: The total number of spots (IgG ASCs) specific for HPV A) type 16, B) type 18, C) type 31 and D) type 45, after 5 days of stimulation with CpG, IL2, IL10 and IL15 in the three different groups. The lines indicate the geometric mean spots per group.
Figure 2: Linear regression and correlation between type-specific IgG antibody levels in B-cell culture supernatants expressed in LU/ml (X-axis) and the number of type-specific ASCs (Y-axis) of girls participating in the second group (1-year post vaccination) for A) HPV type 16, B) type 18, C) type 31, and D) type 45. Significant correlation, * p<0.05, ** p<0.01.
Conclusions

Bivalent HPV vaccination induces HPV-specific memory B-cell immunity. Moreover, cross-reactivity against type 31 and 45 is observed which might indicate cross-protection against these types. Our results show that measuring the HPV type-specific IgG levels in the B-cell-culture supernatants are a good proxy for HPV type-specific memory B-cell responses, which enables simultaneous detection of B-cell immunity to multiple HPV types.
Combination of poly-γ-glutamic acid and aluminum salts improves vaccine efficacy by enhancing antigen-specific immunogenicity

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Background and Aims

Vaccination is the most effective strategy to protect against infectious diseases, and adjuvants are key vaccine components that improve antigen-specific immune responses. Here, we developed a novel adjuvant by combining poly-γ-glutamic acid (γ-PGA) with alum (PGA/Alum), and then examined the physiochemical properties of PGA/Alum, its ability to enhance the innate immunity of dendritic cells (DCs) and the mechanisms underlying this effect.

Methods

Here, we first analyze the physiochemical properties, efficacy and action mechanisms of PGA/Alum. We then used ovalbumin (OVA) as a model antigen, and examined the antigen-specific immune responses generated by OVA-loaded PGA/Alum in vitro and in vivo.

Results

PGA/Alum-OVA-administered mice showed robust increases in their antigen-specific humoral and cellular immune responses compared to mice exposed to γ-PGA-OVA or Alum-OVA. Importantly, the PGA/Alum-OVA-induced antibodies had higher antibody-dependent cellular cytotoxicity than those induced by γ-PGA-OVA or Alum-OVA. Enhanced activation/antigen processing of DCs and increased migration of antigen-loaded DCs from injection sites to draining lymph nodes were observed in PGA/Alum-OVA-administered mice.

Conclusions

Finally, the efficacy of PGA/Alum as a vaccine adjuvant was evaluated using HPV16 VLP vaccine antigen. Indeed, PGA/Alum drastically enhanced the protective efficacy of the HPV16 vaccine antigen. Taken together, our results show that PGA/Alum may be a promising vaccine adjuvant for influenza-related and other infectious diseases.
NANO-PULSE STIMULATION INDUCES IMMUNOGENIC APOPTOSIS IN HPV-INDUCED MURINE TUMORS AND INITIATES AN ADAPTIVE IMMUNE RESPONSE

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Background and Aims

It has been previously reported that Nano-Pulse Stimulation (NPS) treatment of several cancers eliminates primary tumors and slows progression of secondary or tumor re-challenge events. Here, we investigated NPS treatment in an HPV-induced tumor model.

Methods

NPS treatments were optimized to induce immunogenic apoptosis in the C3.43 tumor cell line as detected by caspase 3/7 activation. Subdermal tumors were generated by s.c. implantation in the flank followed by 10 days of growth. NPS was applied to tumors at 600 pulses at 30 kV/cm with 3 pps. HPV16-specific T cell responses were examined via ELISpot. Tumor infiltrating lymphocytes (TIL) were phenotyped via flow cytometry. Selective depletion of CD4 and CD8 cell populations was carried out prior to tumor re-challenge. Overall tumor growth and survival were assessed in each experiment.

Results

In vitro NPS treatment of C3.43 cells resulted in a 2-fold increase in activated caspase 3/7. Tumor clearance was seen in multiple mice receiving NPS. ELISpot results indicated treated mice had no detectable CD8+ T cell reaction to HPV16 peptides. TIL analysis of mice unable to clear tumors suggest an ongoing immune response. Mice clearing tumors showed some level of protection against re-challenge. Selective depletion of CD8+ T cells eliminated protection.

Conclusions

Application of NPS reduces tumor size and generates CD8+ T cells that recognize tumor neantigen(s) associated with the C3.43 tumor model. This method may be utilized in the future to induce an anti-tumor response driven by effector CD8+ T cells capable of eliminating secondary tumors and protecting individuals from disease recurrence.
IPVC8-0191
POSTER SESSION

BASIC RESEARCH - IMMUNOLOGY

UNDERSTANDING CD4+ T CELL RESPONSE TO HPV16 E7 ANTIGEN IN A MOUSE MODEL OF PRECANCEROUS SKIN
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Background and Aims

Persistent infection of high-risk HPV16/18 virus in keratinocytes (KCs) leads to consistent expression of E6/E7 oncoproteins. The expression of these oncoproteins induces hyperproliferation of the epithelium and chronic inflammation, which will collectively promote progression to cancer. Currently, prophylactic HPV vaccines are available, but these vaccines only target limited numbers of HPV types and do not benefit patients with established HPV-associated diseases. New effective immunotherapy for these afflicted patients is therefore needed. Our research is aimed to understand the underlying mechanisms of HPV-induced immunosupression in skin lesions. The insights can potentially guide the development of immune therapeutic strategies to restore the immune response in HPV-associated disease.

Methods

Using a mouse model expressing the HPV16 E7 oncoprotein under the control of the keratin 14 transcriptional promoter (K14E7), we are able to mimic immunosuppressive, hyperplastic skin lesions of HPV infection. Here, we examined CD4+ T cells and KCs in K14E7 skin using flow cytometry.

Results

We found a strong CD4+ T cell infiltration in K14E7 skin. These CD4+ T cells are characterized by their high expression of regulatory markers such as Foxp3, CTLA-4 and PD-1. Moreover, we show that KCs in K14E7 skin express high levels of MHC II antigen presenting molecules and co-stimulatory molecules.

Conclusions

We hypothesize that these CD4+ regulatory T cells contribute to immunosuppression in K14E7 skin by directly interacting with KCs. Future experiments will be needed to identify antigen-specific CD4+ T cells by using E7 peptide-MHC II tetramers, and demonstrate KC-CD4+ T cell interaction via live-cell imaging.
BASIC RESEARCH - REGULATION OF GENE EXPRESSION

CHANGES IN CELL PROLIFERATION AND APOPTOTIC GENE EXPRESSION PROFILES INDUCED BY HPV16 E6 ONCOPROTEIN VARIANTS IN CELLS TREATED WITH CISPLATIN

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Background and Aims

To analyze the effect of HPV16 E6 oncoprotein variants E\(^{-}\)G350, AA\(^{-}\)a, AA\(^{-}\)c, E\(^{-}\)C188/G350, E\(^{-}\)A176/G350 in cell proliferation and in pro-apoptotic and anti-apoptotic genes expression in C33-A cells treated with cisplatin.

Methods

From cultures of C33-A cells transfected with HPV16 E6 gene of E\(^{-}\)G350, AA\(^{-}\)a, AA\(^{-}\)c, E-C188/G350, E-A176/G350 variants and E-prototype, we determined the mean inhibitory concentration (IC\(_{50}\)) of cisplatin by cell proliferation assays with MTT. Then we treated with IC\(_{50}\) of cisplatin C33-A cells and analyzed their proliferation. The level expression of the pro-apoptotic genes (BAX, SLC25A6, CD70 and HIPK2) and anti-apoptotic genes (cIAP1, cIAP2, and IGF1R) was analyzed by RT-qPCR in basal conditions and under treatment with cisplatin.

Results

The C33-A-E-G350 and C33-A-AA-c variants require a higher concentration of cisplatin than C33-A-E-P to induce the death of 50% of population. Both C33-A-HPV16 E6 E-G350 and HaCaT-HPV16 E6 E-G350 cells were more resistant to treatment with cisplatin vs. E-prototype transfected cells. However the HaCaT cells was more sensitive to radiotherapy. When we analyzed the expression of genes in response to treatment with cisplatin, we found overexpression of the antiapoptotic genes cIAP1, cIAP2 and IGF1R and of the proapoptotic genes Bax and SLC24A6 in the cells expressing E6 of the E-G350 variant. While, the european variant E-A176/G350 overexpress cIAP1 and IGF1R genes. Interestingly, these genes decreased their expression with the AAs variants.

Conclusions

The polymorphic changes in the E6 oncogene of the HPV16 variants are sufficient to alter cell proliferation and the expression of genes involved in apoptosis in response to chemotherapy.
TRANSCRIPTIONAL COFACTOR VGLL1 IS REQUIRED FOR TEAD-MEDIATED TRANSCRIPTION OF HPV EARLY GENES

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Background and Aims

TEAD family transcription factors bind to their recognition sequences in gene promoters, but require transcriptional cofactors to regulate transcription. TEAD1 (originally called TEF-1) was shown to be involved in HPV16 early gene expression. However, the mechanisms by which TEAD1 regulates the HPV early promoter and its relevant cofactors remain unclear.

Methods

Binding of transcription factors to the HPV16 long control region (LCR) was examined by DNA pulldown and chromatin immunoprecipitation assays. Involvements of transcription factors in HPV early gene expression were assessed by siRNA knockdown experiments.

Results

VGLL1, one of cofactors for TEADs, bound to the HPV16 LCR depending on TEAD1, and both TEAD1 and VGLL1 associated with the HPV16 LCR in CaSki cells. VGLL1 knockdown in CaSki or HeLa cells reduced E7 levels and increased p53 levels through suppression of the HPV early promoter, resulting in an induction of apoptosis and a repression of cell proliferation. The inhibitory effect of VGLL1 knockdown on the viral early promoter was relieved by simultaneous knockdown of VGLL1 and TEADs, suggesting a functional link between VGLL1 and TEADs. These results indicate that VGLL1 keeps the HPV early promoter in an active state by associating with TEADs on the promoter.

Conclusions

VGLL1 is required for HPV gene expression through interaction with TEADs.
Background and Aims

4A3 and 4A4 are natural glycosylated substances isolated from *S. longipedunculata*, a plant used in African traditional medicine for treatment of cancer. Our previous studies revealed that 4A3 and 4A4 activate apoptosis and exhibiting IC50 of 0.02502 and 0.04833 (µg/L) respectively. The 4A4 in its original state maintained higher specificity, with selectivity index of 58.9 on caski cell line than normal lung fibroblast cell line (HFL1). Considering the critical role of HR-HPV E6 etiological molecule in promoting carcinogenesis, our aim was to investigate the pathway for signal transduction of apoptosis by these isolates.

Methods

Relevant assays were conducted on caski and BU25TK cell lines, positive with HPV and these include: MTT assay; scratch assay; fluorescence microscopy with Annexin V and propidium iodide (PI) and finally RT-qPCR for gene analysis

Results

Results show reduced cell proliferation due 4A3 and 4A4 treatment, with significant reduction in cell migration on both cells within 48h and 72h, respectively. Late apoptosis was activated by 4A3 in contrast to 4A4’s early apoptosis. RT-qPCR data revealed a fold-change inhibition of anti-apoptotic proteins MCL-1 and BCL2L1, with diminished level of AKT-3, VEGFA, MALAT1 and CDH1. More so, the expression of proapoptotic genes (p53, BAD and Caspase 8) were non-significantly altered.

Conclusions

The primary suspects for enhanced apoptosis may be linked to low signal expression of AKT-3 and antiapoptotic proteins (MCL-1 and BCL2L1). This activity is probably mediated via multiple channels of PI3K-AKT/mTOR/NF-kB dependent pathways, making the isolates very attractive as candidates for anticancer development. Chemical structural determination is on-going
EGFR/MEK/ERK SIGNALING: AN ACHILLES’ HEEL FOR HPV-INDUCED TUMORIGENESIS

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Background and Aims

We aimed to better understand how high-risk HPV E6 and E7 oncogene expression is regulated in premalignant cells and epithelial tissues and to investigate means by which these oncogenes become dysregulated during malignant progression. Many reports suggest that EGFR signaling can promote E6/E7 mRNA transcription, other studies show that EGFR and its downstream effector phospho-ERK1/2 become overactive during CIN progression and that E6 and E7 oncoproteins can stimulate these pathways. Thus, we investigated how EGFR signaling impacts HPV oncogene regulation.

Methods

Monolayer and 3D organotypic epithelial tissue cultures of HPV-infected keratinocytes and HPV-positive cancer cell lines. HPV-positive tumor xenografts.

Results

EGFR signaling is downregulated in contact-inhibited cells and during epithelial differentiation. These phenotypes correspond with loss of E6 and E7 expression. Whereas EGFR activation stimulates HPV oncogene transcription in these settings, pharmacological inhibition of EGFR, MEK, or ERK leads to HPV oncogene suppression. FDA-approved EGFR and MEK inhibitors suppress the growth of tumor xenografts concomitant with reduced HPV oncogene expression and restoration of tumor suppressor functions. Preliminary in vitro data suggest that these antiviral effects and restored tumor suppressor functions sensitize HPV-positive cells to cisplatin and radiation.

Conclusions

Our data suggest that EGFR/MEK inhibitors should be investigated further for their specific anti-HPV effects in clinical settings. We are initiating further studies to test whether MEK inhibitor can suppress HPV oncogene expression in patients with HPV-positive tumors and determine whether MEK inhibitor used as a neo-adjuvant can sensitize HPV-positive tumor xenografts to radiation in vivo.
Background and Aims

Several mechanisms have been proposed for reduction of tumor suppressive miR-145 associated with tumorigenesis and chemotherapeutic resistance, such as cigarette smoke exposure, promoter methylation and human papillomavirus (HPV) infection. However, the down-regulation of miR-145 in oral squamous cell carcinoma (OSCC) that is associated with tumor virus infection is still limited. We sought to investigate the relationship between HPV and Epstein-Barr virus (EBV) with the down-regulation of miR-145 in OSCC.

Methods

Eighty-six OSCC tissues were collected from OSCC patients. Tumor and normal adjacent tissues were isolated using laser capture microdissection (LCM), then subjected to extract DNA and RNA. DNA was used to detect HPV and EBV infection. miR-145 promoter methylation was examined by methylation-specific PCR. The expression of miR-145, DNMT1 and DNMT3B was quantified by quantitative real-time PCR.

Results

The miR-145 expression was significantly down-regulated in tumor tissues and associated with HPV or EBV infection and HPV-EBV co-infection. The study of roles of HPV and EBV on the miR-145 expression found that miR-145 promoter methylation significantly increased in tumor tissues particularly in EBV-positive tumor tissues. DNMT3B expression was significantly up-regulated in tumor tissues and increased in tumor tissues with HPV or EBV, especially in HPV-EBV co-infection whereas DNMT1 expression was not significantly different in each group. Moreover, up-regulated DNMT1 and DNMT3B and down-regulated miR-145 were significantly associated with histological grade of OSCC.

Conclusions

HPV and EBV infection are involved in down-regulation of miR-145 via DNMT3B induction and promote promoter methylation in development of OSCC.
ANALYSIS OF HPV-18 TRANSCRIPTIONAL ACTIVITY DURING CELL DIFFERENTIATION

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Background and Aims

The HPV infectious life cycle is closely linked to the differentiation program of the host epithelium. This synchronization occurs partly due to the composition of transcription factor (TF) binding sites within the viral long control region (LCR), and the differential expression of these factors throughout the different layers of the stratified epithelium. Until this moment, very little progress has been made regarding HPV-18 gene expression in the context of different stages of the viral life cycle.

Methods

For this purpose, we established a HaCat cell differentiation model ascertained by morphological characteristics, and cell proliferation and cytokeratins expression analyses.

Results

In these cells, a reduction in HPV-18 P105 transcriptional activity was observed along the five days of culture in differentiating conditions. We proceeded with a comprehensive investigation of the protein levels of 345 TFs in nuclear extracts of undifferentiated and differentiated HaCat cells utilizing a DNA/Protein Array. This analysis identified different protein levels of 33 TFs between undifferentiated and differentiated cells. In silico analysis was performed to search for putative TF binding sites within the HPV-18 LCR for the 33 TFs.

Conclusions

ChIP experiments are underway to access in vivo binding of selected TFs. Additionally, we are investigating the impact of these TFs upon HPV-18 early transcriptional activity. Expanding this knowledge will contribute to better understand the biology and pathogenesis of HPV-18 associated diseases.

Financial Support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Grants numbers 15/26345-0 to LS; 16/16528-2 to ALR).
IPVC8-0782
POSTER SESSION
BASIC RESEARCH - REGULATION OF GENE EXPRESSION

CHANGES IN ADHESION GENES EXPRESSION INDUCED BY HPV16 E6 ONCOPROTEIN VARIANTS IN C33-A CELLS AND CERVICAL BIOPSIES


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Background and Aims

To analyze the effect of HPV16 E6 oncoprotein variants E-G350, AA-a, AA-c, E-C188/G350, E-A176/G350 in adhesion genes expression in C33-A cells and cervical biopsies HPV16⁺.

Methods

From cultures of C33-A cells transfected with HPV16 E6 gene of E-G350, AA-a, AA-c, E-C188/G350, E-A176/G350 variants and E-prototype, we analyzed the level expression of adhesion genes (CDH2, SRPX, PCDH9, CDH18, CDH6, NID1, AMOTL1, E6 and E7) by RT-qPCR in C33-A cells and cervical biopsies.

Results

In C33-A cells we found that AA-c E6 oncoprotein variant induces overexpression of the PCDH9 and SRPX genes, while the E-G350 variant overexpressed the PCDH9 and CDH18 genes. On the other hand, in samples of cervical cancer positive to the HPV16 AA8 variants, we found overexpression of AMOTL1, CDH6, NID1 and SRPX genes. While positive samples to the HPV16 E-G350 variant overexpressed the SRPX gene compared to the E-prototype. We also determined the E6 and E7 oncogene expression and found that the AA-a and AA-c variants express highest levels of both E6 and E7 oncogenes. When we analyzed the protein expression of cadherins, we found that the highest expression of N-cadherin was observed in the cells expressing E6 of the E-G350 variant. Furthermore, cells expressing E6 of the variant AA-a express twice as much Cadherin-9 as compared to cells expressing E6 of the E-Prototype.

Conclusions

The results suggest that the HPV16 E6 oncoprotein variants differentially affects the expression of genes related to cell adhesion, possibly through different mechanisms not yet known that could confer different oncogenic potential.
ANALYSIS OF PREDICTED TRANSCRIPTION FACTOR BINDING SITES IN LCR SEQUENCES OF HPV-16 VARIANTS USING THE TRANSFAC DATABASE

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Background and Aims

Background
Long control region (LCR) contains DNA-protein binding motifs involveds in replication

Aims
To evaluate using the TRANSFAC database, if changes in LCR region modify the pattern of transcription factor binding sites prediction for HPV-16 variants.

Methods

Six LCR sequences representative of each variant (E(reference), As, AA, Af1, Af2 and NA), were obtained from Medline and HPV Sequence Database (Los Alamos National Laboratory). First, we searched for putative transcription factor binding sites associated with positions with divergent nucleotides among the different variants. Second, we analyzed which differences were exclusives for AA variant (it is considered one of the most aggressives variants). Finally we sought to find similarities with sites described in regulatory sequences of other viruses associated or not with cancer development.

Results

All nucleotide substitutions except a C/T transition at nt 7689, modified the pattern of transcription factor binding sites prediction respect to E reference sequence. In addition, A/C change at nt. 7729 (NA, AA) was related with transcription binding sites for retinoic acid receptor alpha and thyroid hormone receptor described for herpes simple virus type 1. T/G transition at nt. 7743(AA) were associated with NF-1 and C/EBP alpha sites described for hepatitis B virus S gene promoter and murine sarcoma virus, respectively.

Conclusions

These results suggest that variations in regulatory sequences may modify gene expression and these modifications may be the basis of mechanisms of carcinogenesis common to several viruses.
HNRNP K REGULATING HPV 16 E2/E6 GENES IN CERVICAL LESIONS

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Background and Aims

hnRNP K, which contains structural domains and combined sites with HPV16 genes, plays an important role in regulating the viral transcription and replication, but the role of hnRNP K and relationship with HPV16 in cervical lesions is unclear. The aim of the present study was to explore the roles and potential molecular mechanisms of hnRNP K by regulating HPV16 E2/E6 expression in the progression of cervical carcinogenesis.

Methods

HPV infection and the expression of hnRNP K and HPV16 E2/E6 genes were measured in 257 women with a diagnosis of normal cervix (n=67), cervical intraepithelial neoplasm (CIN ¹, n=69; CIN ²/³, n=68) and cervical squamous cell carcinoma (n=53) who come from the community and hospital cohorts in Shanxi province, China. Meanwhile, hnRNP K was down or up regulation by shRNA interference in Siha cells was performed in vivo.

Results

The hnRNP K protein levels were gradually increased ($\chi^2_{\text{trend}}=29.84$, P=0.001) and the ratio of HPV16 E2/E6 was decreased (H=31.95, P<0.001) with the severity of cervical lesions, showing negatively correlation ($r=-0.243$, P=0.030). Both the mRNA expression of HPV16 E2 or E6 (P<0.05) and HPV16 E6 protein expression levels (P<0.05) were decreased after down-regulated hnRNP K, while their expression was increased (P<0.05) with hnRNP K up-regulation in Siha cells.

Conclusions

hnRNP K over-expression might increase the risk of CIN ²/³ and SCC and there might be a synergistic action with low ratio of HPV16 E2/E6. hnRNP K could up-regulate the expression of HPV16 oncogene E6 through binding to gene regulatory elements of HPV16.
HUMAN PAPILLOMAVIRUS 16 ONCOPROTEINS REGULATED NEGATIVE CO-STIMULATORY MOLECULE TIM-3/GALECTIN-9 THROUGH DNA METHYLATION IN CERVICAL CANCER

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Background and Aims

Infection with high risk human papillomavirus is essential to cause cervical cancer. Tim-3 binding to Galectin-9 can cause immune tolerance and lead to immune escape of tumor cells. Our previous study showed that Tim-3 decreased and Galectin-9 increased with the lesions severity in the cervical exfoliated cells. We want to dig out the detailed role of co-stimulatory signals Tim-3/Galectin-9 and their epigenetic regulation mechanism in cervical cancer.

Methods

The methylation status of Tim-3/Galectin-9 was detected by methylation-specific PCR in cell lines SiHa, HeLa and C-33A. Tim-3/Galectin-9 and DNMT3A expression was assessed by real-time quantitative PCR and western blotting.

Results

The Tim-3/Galectin-9 promoter was partially methylated in SiHa and C-33A cells. The methylation level of the Tim-3/Galectin-9 promoter decreased in a dose-dependent manner after cell lines were treated with 5-Aza-2'-deoxycytidine (5-Aza-CdR). The gene expression of Tim-3/Galectin-9 increased accordingly afterwards. In the C-33A cell line which over-expressing HPV16 oncoproteins E6/E7, Tim-3 expression was higher and Galectin-9 expression was lower than in C-33A cell line, meanwhile, the expression level of DNMT3A was decreased when HPV 16 oncoproteins E6/E7 present. Besides, the methylation level of the Tim-3 promoter was decreased and the Galectin-9 was increased at that moment.

Conclusions

HPV 16 oncoproteins E6/E7 might participate the negative co-stimulatory signals epigenetic regulation through decreasing DNMT3A expression level.
**Role of Superoxide Dismutase 2 (SOD2) Protein in the Transformation Process Mediated by HPV**

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**Background and Aims**

Oxidative stress reflects an imbalance in the maintenance of the intracellular redox state resulting in the accumulation of oxidant species that may contribute to tumorigenesis. SOD2 protein contributes to cell homeostasis and can be induced by the activation of the NFκB pathway in several cell types following treatment with Interleukin-1β (IL-1β) and Tumor Necrosis Factor Alpha (TNF). The aim of this study is to elucidate the involvement of SOD2 in the pathogenesis associated with HPV and in the effect of proinflammatory cytokines.

**Methods**

SOD2 protein levels were determined by western blot (WB) in Primary human keratinocytes (PHK), cervical cancer cell lines. Afterwards, PHK transduced with HPV16 oncogenes and cervical cancer cell lines were treated with TNF and IL-1β and the expression of SOD2 protein was determined by WB. Also, the oxygen consumption rate in the mitochondria of SiHa and HeLa was determined.

**Results**

Was found higher levels of SOD2 expression in: SiHa and HeLa. The expression of E7 and/or E6/E7 appears to be associated with lower levels of SOD2 protein. Treatment with proinflammatory cytokines induced an increase in SOD2 in all treated lines after 16 and 24 hours of treatment. Differential protein levels of SOD2: observed in the cell types evaluated after 3 hours of treatment. The transduced E6 oncoprotein lines showed higher levels of SOD2 induced by cytokines IL-1β and TNF, after 3 hours of treatment.

**Conclusions**

SiHa and HeLa have higher levels of SOD2 protein; acute expression of HPV16/E7 in PHK is associated with lower levels of the protein SOD2; PHK, PHK transduced with E6 and/or E7 oncogenes of HPV16 and in SiHa and HeLa, the intracellular localization of SOD2 is predominantly mitochondrial; SiHa has a more oxidative profile, whereas HeLa shows a more glycolytic profile.
Background and Aims

Human papilloma virus (HPV) infection is a primary cause of cervical cancer. Although HPV-derived transcripts are involved in carcinogenesis, the expression patterns of HPV-derived transcripts and their dependence on HPV genotypes have not yet been fully elucidated.

Methods

In this study, we enrolled 427 patients with abnormal cervical cytology, and assessed the associations between HPV-derived transcripts and cervical intraepithelial neoplasia (CIN) grades and/or HPV genotypes. We focused on four HPV-derived transcripts, namely; the oncoproteins E6 and E6*; E1^E4, a gene related to keratinization; and L1, a gene involved in viral production, in four major HPV genotypes: HPV16, HPV18, HPV52, and HPV58.

Results

We found that the detection rate of E6/E6* increased along with CIN progression (p<0.01), especially with HPV16 (p=0.01), whereas there was no significant tendency in the detection rate of E1^E4 or L1 among CIN grades. In addition, we found that L1 gene expression was HPV type-dependent; almost all HPV52-positive specimens (46/59 [78.0%]), around half of HPV58-positive specimens (27/61 [44.3%]), around one-third of HPV16-positive specimens (20/65 [30.8%]), and only one HPV18-positive specimen expressed L1 (1/9 [11.1%]).

Conclusions

We thus demonstrated that HPV-derived transcripts are HPV genotype-dependent. In particular, the expression patterns of E1^E4 and L1 can be used to infer HPV genotype-dependent patterns of carcinogenesis.
FUNCTIONAL ANALYSIS OF A PEPTIDE SELECTED BY PHAGE DISPLAY IN HEAD AND NECK TUMOURS

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Background and Aims

Head and neck cancer is the sixth most common cancer type worldwide with an estimated incidence of 530,000 new cases and almost 300,00 deaths/year. Human papillomavirus as a risk factor in head and neck tumors is well established and the overall incidence of HPV related tumors is increasing. Stratifin play important roles in a wide range of physiological and pathological process and several studies have shown that 14-3-3σ expression is dysregulated in human cancers, including head and neck cancers.

Methods

By taking advantage of Phage Display technology, here we isolated a specific peptide able to distinguish between head and neck tumors derived-cell lines (both HPV positive and negative) from normal oral cells. This specificity is conferred by binding to stratifin (or 14-3-3σ), which is differentially expressed in these cell lines.

Results

By immunohistochemistry, we have shown the binding of our peptide and the expression of 14-3-3 in tissues from a series of head and neck cancer.

Conclusions

We aim to check the biological activity of this peptide in the modulation of 14-3-3σ by accessing cell growth in a panel of head and neck tumor cell lines. Furthermore, we aim to analyze the role of this protein through CRISPR activation and knockout.
Cervical cancer is the second most common cause of death in women worldwide. The causative agent is Human Papillomavirus. In this study we evaluated the effect of anti cancer drugs Doxorubicin, Cisplatin and Paclitaxel on HPV-positive CaSki and HeLa; HPV negative C33A cell lines. MiR-214 has been shown to be down regulated in cervical cancer cells and plays an important role in cell proliferation.

Methods

Here, we either knocked out miR-214 by Crispr/Cas9 or over expressed it by stable transfection. Measurement of apoptosis was done by Annxin V FITC/PI staining of cells.

Results

Interestingly, Crispr mediated knockdown of miR-214 resulted in decreased apoptosis upon Paclitaxel treatment compared to vector control in HeLa. Conversely, over expression of miR-214 caused increased apoptosis in response to Paclitaxel over control. However, Doxorubicin and Cisplatin had little effect on apoptosis in a miR-214 background. CaSki cells showed a similar profile for apoptosis levels. The HPV negative C33A cells showed very little change in apoptosis whether miR-214 knocked out or over expressed.

Conclusions

From the studies it can be concluded that HPV positive cell lines HeLa and CaSki showed more sensitivity towards Paclitaxel as compared to Doxorubicin and Cisplatin. Therefore, Paclitaxel is more effective against cervical cancer cells. HPV negative C33A cells did not showed any effect of miR-214 towards the drugs and was the most resistant of the three cell lines. Therefore, it might be possible that HPV can modulate apoptosis in CaSki and Hela cells through miR-214. Further studies are being undertaken in our lab.
Background and Aims

The E6 and E7 proteins of HR HPVs are both required for the efficient immortalization of human keratinocytes. We recently established a new technique to rapidly and conditionally immortalize human epithelial cells using a feeder co-culture system in the presence of a ROCK inhibitor, Y-27632. We attempt to understand the common mechanisms by which human epithelial cells become immortalized.

Methods

Retroviruses were used to establish cultures of human keratinocytes with HPV16 E6, E7 or E6E7. KGM and F medium were used for synthetic culture system and co-culture system, respectively. We evaluated hTERT expression with RT-PCR, and actin stress fibers with IF.

Results

In the co-culture system, we observed that fibroblasts or fibroblast-conditioned medium, like E6, were able to induce telomerase in the keratinocytes. We have also noted in this system that E7 and the ROCK inhibitor induced similar changes in actin stress fiber formation, an important component of the cytoskeletal control of cell proliferation. We found that wt E7, but not an immortalization-defective E7 mutant, was able to immortalize keratinocytes when co-cultured with feeder cells or conditioned medium. Conversely, we demonstrated that E6 cooperates with Y-27632 to immortalize human genital keratinocytes when cultured in synthetic medium, suggesting that ROCK inhibition substitutes for E7 functions during cell immortalization.

Conclusions

Our data suggest that both telomerase induction and cytoskeletal alterations are required for the efficient immortalization of epithelial cells, irrespective of culture conditions.
Background and Aims

HPV-18 nucleotide variability was studied resulting in findings regarding phylogeny and evolution. However, functional studies are limited. Epidemiological studies showed that while African (Af) variants are mainly detected in invasive squamous carcinoma, Amerindian (As+AI) and European (E) are more prevalent in adenocarcinoma and adenosquamous carcinoma. Our aim was to characterize the biological and biochemical properties of E6/E7 HPV-18 variants in primary human keratinocytes (PHK).

Methods

We transduced two different PHKs pools with E6/E7 from Af and As+AI variants. Cells were continually grown until immortalization (p30).

Results

We did not observe a "crisis" for all transduced PHKs, independently of the variant; nevertheless, As+AI PHKs reached the endpoint significantly sooner than Af PHKs. Early passage PHKs transducing E6/E7 from both HPV-18 variants showed a higher expression of E6*I RNA compared to complete E6 for both variants; but E6 protein levels were higher in Af PHKs, p53 protein levels were also lower in these cells. p16 levels were increased for both HPV-18 variants transduced PHKs; p21 was found decreased in both variants transduced cells. In late passage cells, p16 and PCNA levels were higher.

Conclusions

This is the first report comparing the biological and biochemical properties of HPV-18 variants in PHKs which is the natural host cells of these viruses.

Financial Support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Grants numbers 15/26345-0 to LS; 15/26346-6 to EMN).
The PTPN21 cytoplasmic protein tyrosine phosphatase is targeted by HPV E7
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Background and Aims

Activation of signalling pathways ensuring cell growth are essential for the proliferative competence of human papillomavirus (HPV) infected cells. Protein tyrosine kinases and phosphatases are the key regulators of cellular growth control pathways. Recently identified potential cellular targets of HPV E7 are the cytoplasmic protein tyrosine phosphatases PTPN14 and PTPN21. Our aim was to investigate the E7-PTPN21 interaction.

Methods

In order to study the effect of E7 on PTPN21 expression, we analysed PTPN21 protein levels in HPV positive and HPV negative cervical cancer cell lines, and also in cell lines transfected with E7 expression plasmids. Furthermore, we investigated the interaction between E7 and PTPN21 by using in vitro and in vivo protein interaction assays.

Results

We show that the E7 proteins of both high-risk and low-risk mucosal HPV types can interact with PTPN21, a non-receptor protein tyrosine phosphatase closely related to PTPN14 and involved in the control of growth factor signalling. This interaction is independent of pRb and requires the CR3 region of the E7 oncoprotein. We also show that high-risk E7 has opposing effect on the protein levels of these two cytoplasmic phosphatases, as in HPV positive cervical cancer cell lines and HPV-16 E7 transfected HEK293 and C33A cells, E7 promotes PTPN14 degradation and conversely elevates PTPN21 protein levels.

Conclusions

Our results suggest that diverse HPV E7 oncoproteins can perturb PTPN21 regulated pathways, and also suggest that this interaction could be important for the viral life cycle and potentially also in the development of malignancy.
CHARACTERIZATION OF E1C, A DIAGNOSTICALLY RELEVANT HUMAN PAPILLOMAVIRUS16 RNA

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Background and Aims

HPV16 E1C mRNA is frequently expressed in high-grade cervical cancer precursor lesions and therefore a candidate for triage tests in cervical cancer screening (Höfler D et al., 2015). This project aims to elucidate functions of E1C by identifying the postulated E1C protein in HPV16-transformed cells and analyzing the functional effects of E1C overexpression on oncogenes such as HPV16 E6 and E7.

Methods

To identify HPV16 E1C protein, a murine E1C-specific monoclonal antibody capable of detecting recombinant E1C fusion proteins has been established. In order to understand the functional effects of E1C overexpression on HPV16 transcription, lentiviral transduction has been carried out in two clones of the HPV16-positive CIN1 lesion-derived W12 cell line, W12-epi with episomal and W12-int with integrated HPV16 DNA.

Results

The E1C-specific antibody could not detect the postulated 9kDa E1C protein in HEK cells, transcribing nearly 1500 E1C mRNA copies/cell from a plasmid carrying an E1C gene. Upon E1C overexpression, W12-int cells showed a 2-fold increase in E6*I and 1.5-fold increase in E7 full length transcripts, however no increase of E6 full length transcript was observed. W12-epi cells in contrast showed no significant changes in these three transcripts.

Conclusions

The inability to detect the putative HPV16 E1C protein points to the possibility of an unstable protein. Cell proliferation and apoptotic assays will be performed to further assess a tumorigenic or anti-tumorigenic potential of E1C. In addition, microarray and mass spectrometry based approaches can deduce the involvement of host transcriptomics and proteomics and help in further dissecting the functions of HPV16 E1C.
HIGH RISK A-PAPILLOMAVIRUS ONCOGENES INDUCE ABERRANT TRANSLESION SYNTHESIS.

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Background and Aims

High risk α-papillomaviruses (HPV) cause cervical cancers (CaCx) that are dependent on HR α-HPV E6, E7 and associated with genomic instability. Replication stress is a significant endogenous source of DNA damage and induced by HPV 16E7. In response, the translesion synthesis pathway (TLS) switches replicative polymerases for a TLS-specific polymerase (Pol-η) to avoid replication fork stalling or collapse.

Methods

An extensive comparison of 362 cervical tissues from 8 datasets demonstrate, with the exception of Pol-η, the TLS pathway is upregulated in CaCx and premalignant lesions.

Results

Histological analysis of cervical tissues correlated with this bioinformatics analysis as TLS protein abundance increased with CaCx progression. Immunoblots of CaCx cell lines and primary keratinocytes expressing HPV oncogenes reveal elevated TLS protein levels are driven primarily by HPV 16E7, while HPV 16E6 prevents increases in Pol-η. HCT116 p53 knockout cells do not induce Pol-η, suggesting a p53-dependent mechanism. In response to stress, cells expressing HPV oncogenes do not form TLS repair complexes and have elevated markers of replication fork stall and collapse. Moreover, these cells are sensitive to stress induced by UV, Cisplatin, Mitomycin and Chlorambucil. While increased TLS gene expression was associated with reduced survival in several other cancers. CaCx was an exception. In CaCx tumors, upregulated TLS expression was a significant and positive prognostic factor for survival. Conversely, there was a greater than 11-year decrease in median months survival in the 20% of women that upregulated Pol-η or related TLS-polymerases.

Conclusions

Our data suggest that HPV oncogenes both induce and inhibit TLS.
A COMBINED TEST TO AVOID CERVICAL CANCER PROGRESSION

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Background and Aims

Cervical cancer is a major public health problem in Morocco. The cervical cancer has a long precancerous period that provides an opportunity for the screening and treatment. Improving screening tests is a priority goal for the early diagnosis of cervical cancer.

Methods

This study was conducted to evaluate the combination of p16INK4a protein expression, human papillomavirus (HPV) typing, and histopathology for the identification of cervical lesions with high risk to progress to cervical cancer among Moroccan women. A total of 96 cervical biopsies were included in this study. Signal amplification in situ hybridization with biotinylated probes was used to detect HPV. Immunohistochemistry was used to evaluate the expression of p16INK4a protein.

Results

HPV DNA was detected in 74.0% of the biopsies (71/96). Of the seventy-one positive HPV cases, we detected 67.6% (48/71) of high risk (HR)-HPV (HPV 16 and 18), 24% of low risk-HPV (HPV 6 and 11), 1.4% intermediate risk-HPV (HPV 31, 33, and 35), and 7% coinfections (HPV 6/11 and 16/18). Overexpression of p16INK4a protein was observed in 72.9% (70/96) of the biopsies. In addition, p16INK4a protein detection was closely correlated with recovery of HR HPV.

Conclusions

Our result showed that p16INK4a expression level is correlated with HR-HPV status, and then it can be used as a predictive biomarker for cervical cancer.
CRYO EM STRUCTURES REVEAL V5 AND U4 CONFORMATIONAL EPITOPES

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Background and Aims

Cancers attributable to human papillomavirus (HPV) place a huge burden on the health of both men and women. The current commercial vaccines are genotype specific and provide little therapeutic benefit to patients with existing HPV infections. Identifying the conformational epitopes on the virus capsid supports the development of improved recombinant vaccines to maximize long-term protection against multiple types of HPV.

Methods

Fragments of antibody (Fab) digested from the neutralizing monoclonal antibodies H16.V5 (V5) and H16.U4 (U4) were bound to HPV16 capsids and the structures of the two virus-Fab complexes were solved to near atomic resolution using cryo-electron microscopy.

Results

The structures reveal virus conformational changes, the Fab-binding mode to the capsid, the residues comprising the epitope and indicate a potential interaction of U4 with the minor structural protein, L2. Competition enzyme-linked immunosorbent assay (ELISA) showed V5 outcompetes U4 when added sequentially, demonstrating a steric interference even though the footprints do not overlap.

Conclusions

Combined with our previously reported immunological and structural results, we propose that the virus may initiate host entry through an interaction between the icosahedral five-fold vertex of the capsid and receptors on the host cell. The highly detailed epitopes identified for the two antibodies provide a framework for continuing biochemical, genetic and biophysical studies.
MOLECULAR AND STRUCTURAL MODELING OF HPV-16 E6 ONCOPROTEIN AND VARIANTS IN THE INTERACTION WITH P53 AS TARGET PROTEIN

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Background and Aims

Intratypical variants in the nucleotide sequence of LCR, L1 and E6 genes HPV-16 have been described. Amino acid changes of viral proteins such as E6 oncoprotein are involved in the differential cancer progression behavior, due to the modifications on the interaction networks generated by the E6 and their targets, mainly p53. Intratypical variants of E6: E-G350, E-A176/G350, E-C188/G350, AAa and AAC are the most frequent and related with differential oncogenic risk in Cervical Cancer in Southern Mexico.

Since the resolution of the 3D structure of the HPV-16 E6 oncoprotein is available, it has been analyzed the interaction effect with some of its protein and drug targets. However, the effect of the intratypical variants in the 3D structure or the interaction with targets has not been evaluated.

Methods

Through an in silico approach, including molecular modeling, docking and molecular dynamics, it was generated the 3D structure of these variants. Although there are amino acid changes in the intratypical variants, the general 3D structure remains without change, but physicochemical properties did, such as isoelectric point and stability index. Also, it was analyzed the effect of the amino acid change in the E6-E6AP-P53 interaction.

Results

The results shown differential interaction profiles between reference and variants in P53-E6-E6AP, but no with direct E6-E6AP interaction, those different profiles were related with an increase of number and type of non-bonded interactions, mainly in AA variants in comparison with European variants.

Conclusions

These results may explain the most aggressive behavior of Asiatic-American variants in cancer progression.
Background and Aims

Background: Cancer of uterine cervix, the top most cancer in Indian women caused due to persistent infection by high-risk Human papillomaviruses (HPVs) types particularly type 16/18. However, HPV infection alone is not sufficient, but in conjunction with host genetic factors which play a plausible role for the development of cervical carcinogenesis. HPV integration is the root cause for HPV mediated cervical carcinogenesis. After integration E6 and E7 oncoproteins release and targets MAPK and PI3K/Akt/mTOR pathways at different points which results in genetic makeup modulations of different members of these pathways and imbalance the equilibrium of the cell.

Aim: Present study was designed to evaluate the most prominent SNPs in MAPK and PI3K/Akt/mTOR pathways by using Sequenom MassARRAY iPLEX platform.

Methods

We screened a total of 780 subjects (142 pre-cancer+328 invasive carcinoma+310 healthy controls) for SNP genotyping of 33 SNPs falling in these two pathways along with HPV infection and other associated risk factors.

Results

Of the 33 SNPs, 7 SNPs lying in those genes which have been reported to have carcinogenic potential with their significant role in MAPK and PI3K/Akt/mTOR pathways, were found to be significantly associated with cervical cancer. Among them, 5 SNPs i.e. MMP7 (rs10502001, rs17098318), MMP9 (rs17576), p73 (rs1885859) and ETS1 (rs11221332) were noticed to be increased in cases while two SNPs in c-Jun (rs3748814) and c-MYC (rs4645852) were higher in controls.

Conclusions

This information on genetic modulations of MAPK and PI3K/Akt/mTOR pathway can be used in designing of various kinds of diagnostic tools or also in molecular targeted therapies.
Human papillomavirus (HPV) is an important infectious agent attributing to majority of cervical cancers, with HPV-16 and HPV-18 responsible for nearly 70% of the cases. Different HPV types may display a different global distribution pattern, with HPV52 has an unexpected high prevalence in Eastern Asian countries. Cancer-causing HPVs exert their oncogenicity through the combined activities of E6 and E7 oncoproteins. Previous studies revealed that different HPV-52 variants may display dissimilar oncogenities, and the oncogenic roles of HPV-52 E6 and E7 are yet to be well-elucidated. Therefore, in this study, we aimed to investigate the oncogenic properties of HPV-52 E6 prototype and its natural variants, designated as V1, V2 and V3.

Methods

We employed various phenotypic and molecular approaches.

Results

Our results showed that HPV52 E6 prototype and variants possess a similar ability in immortalizing primary cells extracted from baby rat kidney (BRK). At molecular levels, HPV52 E6 prototype and variants can target p53 and PSD95/ Dlg /ZO-1 (PDZ) proteins, including Dlg and MAGI, at a similar extent. It is intriguing to observe that in a p53-null background, HPV52 E6 prototype can degrade p53 better than HPV16 E6, and V3 possess a stronger binding affinity with E6AP. Nonetheless, HPV52 E6 variants may target other cellular pathways in a different manner, and this remains to be further elucidated.

Conclusions

Our findings will help to provide crucial information for advanced therapeutic designs and clinical management, especially for the Eastern Asian populations.
HIGH-RISK HPV PERSISTENCE AS LATENT AND SUB-CLINICAL INFECTIONS; PATTERNS OF VIRAL GENE EXPRESSION

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Background and Aims

Immune regression leads to the clearance of papillomavirus-associated disease, but does not necessarily clear infection, with viral genomes persisting in the epithelial basal layer at sites of previous disease. Under these conditions, host immune surveillance by skin-resident memory T-cells, is thought to restrict viral gene expression, allowing viral persistence, either as a subclinical active infection or as latent virus genomes in the basal layer.

Methods

Here we have characterised HPV latency at the cervix, using hysterectomy tissue from women between the ages of 31 and 81.

Results

By whole tissue section PCR, HPV DNA was apparent in 9 out of the 87 cases examined, with 7 of these showing no evidence of HPV associated pathology, despite being HPV–positive. In these cases, regional HPV positivity was found when basal cells were isolated by laser capture microdissection and PCR. 5 of these cases harboured HPV16, allowing viral gene expression to be examined using an RNAscope approach. As suggested from animal models, E2 gene expression was apparent in the basal layer. E7 levels were barely detectable, with transcription patterns fitting well with an immune-mediated suppression of productive infection.

Conclusions

In two of our subclinical/latent infections, viral DNA was also detected in the cervical smear taken before the hysterectomy. A productive HPV52 micro-lesion was identified in one of the HPV-negative sections, which was missed during initial HPV testing. Our data suggest that immune regression controls cervical HPV infections, allowing their persistence either as latent or subclinical (active) infections, depending on the potency of the immune response.
Background and Aims

Objective

Methods
miRNA profiling in cervical cancer samples as well as in controls

Identification of deregulated novel miRNAs

Prediction of putative targets of identified novel miRNAs (miRanda, TargetScan, miRtarbase and Mirwalk)

Functional enrichment analysis (GO, BioCarta and KEGG)

Validation of identified proteins by Western Blotting

Results

On analysis NFKB1, IKB, MDM2, TP53, AKT1 and BAD, members of PI3K/Akt pathway, were emerged as some of the most putative targets of 3 miRNAs. Till date, we could check the expression of NFKB1, TP53 and MDM2 by western blotting. NFKB1, P53 and MDM2 were found to be up-regulated in presence of HPV infection and also found to be positively associated with the advancement of cervical carcinoma. On the other hand, the expression of IKB was found to be decreased with the progression of cervical carcinoma.

Conclusions

Developing this information on altered regulatory mechanism of miRNAs and its target, together with the HPV proteins, becomes imperative for rational design of newer diagnostic/therapeutic interventions in the Indian context.
HPV16 infects the anogenital and oropharyngeal mucosal epithelia. During early stages of infection, establishment of persistence is a pivotal step in the pathogenesis of the virus. Epidemiological data repeatedly indicates that the cervix has a unique vulnerability and susceptibility to HPV mediated carcinogenesis. There is no clear understanding how tissue specific responses to virus infection, can shape the outcome of disease. Elucidating these differences will illuminate key cellular mechanisms the virus employs to establish persistence and initiate disease progression.

Methods

Gene expression microarray analysis was performed to identify differential changes in gene expression in organotypic raft tissues, persistently infected with HPV16 derived from cervix, tonsil and foreskin keratinocytes, mimicking early stages of infection.

Results

The upregulated genes in all the three tissues belonged to categories of cell cycle, mitotic processes, cell division, and DNA replication. In the foreskin, genes related to immune responses and cellular responses to viruses and cytokine signaling were distinctly downregulated. In the cervix, particularly genes involved in epidermis development and keratinocyte differentiation were downregulated. Significant downregulation was observed in genes involved in extracellular matrix organization and cell adhesion especially in the tonsil tissue. Pathway analysis and experimental validations identified important cellular pathways like TGFβ, STAT1 and cell cycle progression to be differentially modulated among the three tissue types.

Conclusions

Studies have emphasized the role of chronic inflammation in the development of HPV induced cervical cancer. The different modulation of important immune signaling pathways such as TGFβ and STAT1 may explain the sensitivity of the tissues for progressive HPV infections.
Activation of NFκB leads to phosphorylation-dependent degradation of HPV E1

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Background and Aims

We previously reported that HPV16 E1 induces activation of NFκB, which in turn limits E1-dependent replication of the viral genome by facilitating proteasomal degradation of the E1. These results suggest that E1 and NFκB constitute a negative feedback loop to regulate HPV genome replication (Nakahara T, et al. J. Virol. 2015;5040-5059). In this study, we aimed to identify an E3 ubiquitin ligase that mediates the NFκB-dependent degradation of the E1.

Methods

Protein motif analysis indicated that HPV16 E1 encodes a phosphodegron recognized by F-box protein, βTrCP. This motif in E1 was conserved among most of papillomaviruses. The protein stability of HPV16 E1 wild type or mutants that lack putative phosphorylation sites within the degron was examined with or without co-expression of βTrCP.

Results

1. The protein stability of HPV16 E1 mutant defective for phosphorylation within the βTrCP recognition motif was increased compared to the wild type E1.
2. Co-expression of βTrCP reduced steady state levels of HPV E1 in a manner dependent on putative phosphorylation sites.
3. HPV16 E1 mutant with defect in putative phosphorylation sites was resistant to NFκB dependent degradation.

Conclusions

These results suggest that activation of NFκB induces phosphorylation-dependent degradation of E1 mediated by E3 ubiquitin ligase complex, SCFβTrCP. Our preliminary results imply that HPV16 genome encoding E1 with defect in βTrCP recognition motif replicates with higher copy numbers than that of the wild type in human cervical keratinocytes. Significance of NFκB-dependent degradation of E1 in the viral life cycle will be discussed.
TRICURIN, A BOTANICAL COMBINATION OF CURCUMIN, RESVERATROL, AND EPIGALLOCATECHIN GALLATE, INDUCES CELL CYTOTOXICITY IN HPV-POSITIVE CERVICAL CELL LINES WHILE SPARING PRIMARY UNINFECTED CERVICAL KERATINOCYTES

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Background and Aims

Despite advances, HPV-induced cervical carcinomas remain a major cause of mortality worldwide. We previously reported that a unique botanical combination consisting of curcumin from the spice turmeric, resveratrol from grapes, and epigallocatechin gallate from green tea, kills HeLa cells. This synergistic combination, which we call TriCurin, stimulates p53 and caspase-3 expression while down-regulating HPV18 E6. We now asked whether this was specific for HeLa cells.

Methods

HeLa (HPV18+) and SiHa (HPV16+) carcinoma cell lines, primary cervical keratinocytes from a hysterectomy specimen obtained from a patient with a negative HPV test and normal cytology, and human foreskin keratinocytes were treated with increasing concentrations of TriCurin or solvent. Trypan blue exclusion, caspase-3 activity, LDH release, and DNA fragmentation were measured at 8 and 24 hrs.

Results

Both HeLa and SiHa cells show a three-fold increase in caspase-3 activity and beginning of DNA degradation as early as 8 hours following treatment with TriCurin. There is also a drastic increase in LDH release corresponding with cell-death, suggesting that TriCurin can induce both apoptosis and marked cell necrosis, not previously described. The LD50 of TriCurin at 24 hours was 12.6 and 22.8 µM in HeLa and SiHa cells, respectively, compared to 79.1 µM for primary cervical keratinocytes. Foreskin keratinocytes showed no detectable cytotoxicity at concentrations of up to 40 µM TriCurin.

Conclusions

TriCurin is a promising therapeutic candidate that targets HPV-infected tumorigenic cells, while sparing uninfected normal epithelial cells, with a large therapeutic index. The induction of necrosis could induce immune-mediated clearing of HPV-infected tissue in vivo.
Background and Aims

Both the human papillomavirus (HPV) and the herpes simplex virus (HSV) account for a high percentage of all sexually transmitted infections within the human population. We have previously demonstrated that HSV infection enhances uptake and infection of HPV in non-HSV-infected cells, however the paracrine signaling caused by HSV-infected cells that lead to global changes in epithelial cell populations remained elusive. HSV utilizes moieties called extracellular vesicles (EVs) to transmit HSV-viral proteins and transcripts to neighboring, non-HSV infected cells, manipulating the cell-microenvironment to one that is pro-infectious.

Methods

HaCaT and HeLa cells were infected with HSV-1. 24h post infection cell supernatants were collected and subjected to differential centrifugation steps to eliminate non-EV sized particles and cell debris. EVs were collected using Total Exosome Isolation Reagent (Thermo Fisher) and analyzed for cellular and viral contents via western blot. Target cells were then treated with EVs and analyzed for surface expression of attachment factors and ability to be infected with HPV pseudovirions.

Results

Treatment of human keratinocytes with HSV-EVs result in the presence of HSV-1 proteins without actual HSV viral replication occurring. Delivery of these viral proteins also results in a pro-HPV infectious microenvironment through the upregulation of attachment factors such as syndecan-1 (2.5-fold at 16hrs), contributing to the increase in infection of HPV pseudovirions (2- and 2.5-fold, respectively) due to enhanced attachment of virions.
Conclusions

HSV-EVs can directly manipulate target epithelial cells and render them more susceptible to subsequent HPV infection, potentially explaining why there is a syndemic relationship between the two viruses.
NON-MAMMALIAN VIRUSES PROVIDE INSIGHTS INTO THE EVOLUTION OF VIRAL ONCOGENES

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Background and Aims

The Papillomaviridae is a large family of small double-stranded DNA viruses. Members of this viral family have been isolated from a wide array of hosts and infections are typically host species-specific. It has been proposed that these viruses have co-speciated alongside their hosts for millions of years. Surprisingly, infection with a handful of viruses is pathogenic to their natural hosts. During the normal viral lifecycle, the papillomavirus E6 and E7 proteins manipulate the cellular environment to allow for efficient viral replication. Despite being important to the viral lifecycle, these proteins are highly variable, and not considered part of the core papillomavirus genome. Understanding the evolution of these proteins will provide important insights into viral oncogenesis.

Methods

To further understand the evolution of these viral oncogenes, we used a metagenomics approach to identify novel papillomaviruses not associated with mammalian hosts. Viral proteins were analyzed within a phylogenetic framework.

Results

These non-mammalian viruses have some unique features, not shared with their amniote infecting relatives. Our analysis suggests that papillomaviruses arose between 400 and 600 million years ago. These viruses provide evidence that the evolution of the key viral oncoproteins involved repeated gains and losses of distinct domains.

Conclusions

Our data suggests that these ‘accessory’ proteins are evolutionarily malleable, and the gain/loss of functional domains is likely associated with the colonization of new niches on the host.
SYNTHESIS-DEPENDENT MICROHOMOLOGY-MEDIATED END JOINING (SD-MMEJ) IS A DOMINANT MECHANISM FOR HPV MICROHOMOLOGY-MEDIATED INTEGRATION

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Background and Aims

HPV attributes up to 5% human cancers, especially cervical cancer. HPV integration into human genome is a key carcinogenetic event. However, the exact mechanism of virus integration remains unclear. This study aims to explore the HPV integration pattern and further provides basic theory for practical application of blocking virus integration.

Methods

First, we collected 902 HPV-cellular breakpoints from DIPS-PCR, NGS and published data. All the breakpoints were sequences with specific base resolution. Then, we designed a SD-MMEJ for HPV-integration (SMHI) computational model to analyze the sequence characteristic nearby HPV integration breakpoints and the elements among flanking region, including transposable element (TE), tandem repeat (TR) and microhomology units. Generally, our algorithm intended to calculate and reveal the exact mechanism involved in HPV integration.

Results

Our findings showed that HPV tends to integrate into clustered genomic hotspots with the enrichment of microhomologies, transposable elements and tandem repeats, indicating that microhomology and genomic instability are key factors for mediating HPV integration. Furthermore, more than 60% breakpoints possess direct or inverted repeat motif within 20bp flanking region, which is consistent with the characteristic of synthesis-dependent microhomology-mediated end joining (SD-MMEJ), implying that SD-MMEJ plays a dominant role in HPV integration compared with the other two mechanisms, FoSTeS/MMBIR and NHEJ.

Conclusions

Our findings systematically summarize the integration mechanism of HPV, and have practical application of blocking HPV integration in patients with persistent infection.
Papillomaviruses (PVs) have coevolved with their host by using cellular factors like Bromodomain containing protein 4 (Brd4) to support genome maintenance, gene transcription and replication initiation. The C-terminal domain (CTD) of the Brd4 protein represents a highly conserved primary binding site for the N-terminal domain (TAD) of E2, which is important for E2’s function as a transcription activator. Previously, a second interaction site via the PDID (phosphorylation-dependent interaction domain) of Brd4 with the C-terminus of E2 was described. In this study we analyzed the second putative interaction site of Brd4 with HPV31 E2.

Methods

We used FACS/FRET analysis to measure in vivo protein-protein interactions, luciferase-based reporter assays to determine functional activity and EMSA assays to analyze DNA binding capacity.

Results

In our study we could confirm an interaction between BRD4-PDID and 31 E2. However, mutations in the C-terminus of E2 that were described to interfere with the binding to PDID showed no loss of binding of E2 in FACS/FRET assays. However these 31E2 mutants displayed a loss of function in transactivation and replication assays, which is consistent with data obtained by EMSA, suggesting impaired DNA binding as a major phenotype. Currently we perform FACS/FRET with isolated domains of BRD4 and/or E2 to identify the respective binding domain within E2 to be able to functionally analyze the role of the second interaction domain of Brd4 with E2 in the context of the viral life cycle.

Conclusions

We conclude that there might be another interaction site in E2 that interacts with the PDID-domain of Brd4.
HIGH-RISK HPV TYPES ARE ASSOCIATED WITH NEOPLASIA AND CANCER AT PARTICULAR EPITHELIAL SITES. THE MOST IMPORTANT OF THESE IN TERMS OF NUMBERS, IS THE UTERINE CERVIX, WHICH HAS A COMPLEX EPITHELIAL STRUCTURE. THROUGHOUT A WOMEN'S LIFE, STRATIFIED EPITHELIUM CAN FORM FROM SUB-COLUMNAR K17-POSITIVE RESERVE CELLS THAT ARE LOCATED WITHIN THE CERVICAL TRANSFORMATION ZONE. THIS PROCESS, KNOWN AS METAPLASIA, IS A NATURAL DEFENSIVE RESPONSE TO LOCAL IRRITATION, AND HAS FOR MANY YEARS BEEN IMPLICATED IN THE UNIQUE VULNERABILITY OF THE CERVIX TO HPV-DRIVEN CANCER.

METHODS

HERE, WE HAVE LOOKED AT THE REGULATION OF VIRAL GENE EXPRESSION IN THE DIFFERENT EPITHELIAL CELL TYPES OF THE CERVIX, IN ORDER TO BUILD UP A TIME COURSE FROM INITIAL HIGH-RISK HPV INFECTION, TO THE DEVELOPMENT OF HIGH-GRADE NEOPLASIA.

RESULTS

PRODUCTIVE INFECTION, AS OCCURS IN MATURE SQUAMOUS ECTOCERVICAL EPITHELIUM, IS ASSOCIATED WITH CONTROLLED EXPRESSION OF E7, AND A LOWER EXPRESSION OF E6, WITH A DECLINE IN GENE EXPRESSION AS INFECTED BASAL CELLS COMMIT TO DIFFERENTIATION. IN INFECTED COLUMNAR CELLS OF THE ENDOCERVIX, E6/E7 GENE EXPRESSION APPEARS UNIVERSALLY UPREGULATED, LEADING TO 'FOLDING' OF THE ENDOCERVICAL LINING OF THE CERVICAL CRYPTS AND HSIL. IN AREAS OF ACTIVE RESERVE CELL METAPLASIA, THIS HIGH LEVEL VIRAL GENE EXPRESSION INHIBITS DIFFERENTIATION AND INCREASES CELL DENSITY AND EPITHELIAL THICKNESS.

CONCLUSIONS

OUR RESULTS SUPPORT THE LONG-STANDING MODEL, THAT THE INTRINSIC CELL-TYPE SPECIFIC REGULATION OF VIRAL GENE EXPRESSION IN RESERVE AND COLUMNAR CELLS WITHIN THE CERVIX UNDERLIES NEOPLASIA, AND THAT A SIMILAR PARADIGM MAY EXPLAIN CELL VULNERABILITY IN THE TONSILLAR CRYPTS AND THE ABSENCE OF PRECURSORS LESIONS.
E1 IS DISPENSABLE FOR MAINTENANCE REPLICATION IN DIVIDING KERATINOCYTES, BUT IS NECESSARY FOR VIRAL GENOME AMPLIFICATION IN CONFLUENT KERATINOCYTES MEDIANED BY E6 DEGRADATION OF P53

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Background and Aims

The E1 and E2 proteins of HPV11 and 16 play a direct role in viral replication. Here we have examined the requirement of these two proteins for the synchronous replication HPV16 and 11 with the host cell genome, such as occurs in the epithelial basal layer during disease-persistence and latency.

Methods

To model this, we have used a keratinocyte growth protocol that allows maintenance and first commitment to differentiation to be studied.

Results

HPV11 and HPV16 were both maintained in exponentially growing keratinocytes, despite differences in viral transcription and rate of cell proliferation. HPV16 genome levels rose dramatically post-confluence however, while HPV11 genome copy number declined. E1-deficient mutants of both HPV types were however maintained at wild-type levels prior to confluence, reinforcing the emerging view that maintenance-replication is E1 independent. Loss of functional E1 prevented HPV16 confluence-dependent genome amplification, indicative of switch in replication mode upon commitment to differentiation. Exogenous E6 expression rescued wild type HPV11 replication post-confluence via the degradation of p53, but was not sufficient to elevate E1-deficient HPV11 episomal copy number. Our results show that both low and high-risk HPV types can switch between E1-independent and E1-dependent replication modes, and that this requires the expression of E6 as cell density increases and keratinocytes commit to differentiation.

Conclusions

Our results suggest both HPV types can replicate in the absence of the E1 viral helicase during genome maintenance and latent persistence in the basal layer. These observations have implications for drug and immune-based therapeutic strategies designed to clear viral episomes.
OPPORTUNISTIC ORAL HPV INFECTIONS IN HIV/AIDS: PRIMARY HUMAN THREE-DIMENSIONAL TISSUE TREATED WITH HIV PROTEASE INHIBITORS IS PERMISSIVE TO HPV16 INFECTION AND PROGENY VIRION BIOSYNTHESIS

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Background and Aims

Since the introduction of Highly Active Anti-Retroviral Therapy (HAART), rates of the AIDS-defining cervical cancer has decreased, but non-AIDS-defining oropharyngeal cancer has increased, in HIV/AIDS patients. Opportunistic HPV infections manifest as oral warts. HAART cytotoxicity manifests as adverse off-target damage of the mucosal epithelium, potentially exposing underlying tissue to infection by HPVs, and incidence of oral disease.

Methods

Three-dimensional organotypic primary epithelial tissues were treated with a HAART drug and infected with infectious native HPV16 virus. Infectivity was measured according standard methods. Biosynthesis of progeny virion was distinguished from input using BrdU labeling of newly synthesized genomes. Progeny virion were visualized by co-localizing BrdU labeled genomes with HPV16 L1 using confocal imaging.

Results

Amprenavir treated primary human gingiva and cervical tissues were more sensitive to HPV16 infection compared to controls, as detected using the HPV16 E1^E4 transcript. In gingiva tissue, stages within the HPV life-cycle showed increased viral titers. Infectivity of progeny virion was associated with capsid maturation that correlated with extended time in culture.

Conclusions

Our data that showed infection of three-dimensional epithelial tissue with HPV16 virus, as well as labeling of capsid-genome complexes of newly synthesized virions. Amprenavir treatment differentially regulates expression of multiple gene networks and signaling pathways that support virus biosynthesis. Increased viral load determines viral persistence and potential progression to head-and-neck cancers in patients undergoing HAART treatment. Critical to this process is the identification of mechanisms of HPV infection/trafficking in relation to tissue damage, that synergize with signaling pathways activated upon drug metabolism in oral epithelium.
NUCLEAR LAMINS NEGATIVELY REGULATE INFECTION KINETICS OF THE HUMAN PAPILLOMA VIRUS

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Background and Aims

Human papillomavirus (HPV) infection is the prime cause of cervical cancers and a growing number of oropharyngeal cancers in humans. In the past decade, many molecular details of the infectious life cycle of HPV have been exposed. As a consequence, the cellular entry and trafficking mechanisms are now well-established. But, the mechanisms of nuclear entry and egress of HPV are still unknown.

Methods

To shed light on the mechanisms of nuclear entry, we have investigated infection kinetics using recombinant HPV pseudovirions (PsV) particles that harbour an EGFP reporter and high content fluorescence microscopy.

Results

Infection of HeLa cell cultures with PsV revealed a time- and concentration-dependent increase of intracellular fluorescent EGFP signal starting from 24h onwards. Although previous studies have shown that HPV predominantly enters the nucleus during mitosis, many DNA viruses are known to interact with the lamina to facilitate their entry. To determine if the nuclear lamina plays a role in the nuclear entry of HPV, we infected A-type lamin-depleted (LMNA knockout (KO)) cells with PsV and examined their infection kinetics. The depletion of A-type lamins resulted in an increased nuclear dysmophy and plasticity. We found that LMNA KO cells displayed a significantly increased infection rate as compared to their respective controls, pointing to an enhanced susceptibility for infection.

Conclusions

We are currently exploring whether this feature is a generic trait of different lamin perturbations and we are performing targeted experiments to pinpoint the exact causative mechanism.
NUCLEOSOME POSITIONING ON EPISOMATIC HUMAN PAPILLOMAVIRUS DNA IN CULTURED CELLS

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**Background and Aims**

Nucleosome positioning affects gene expression and DNA replication. The position of nucleosomes on human papillomavirus (HPV) DNA during genome maintenance and amplification was investigated in order to provide insight into the control of HPV life cycle.

**Methods**

Nucleosome positioning on episomal HPV DNA was examined in cultured normal Immortal Keratinocytes (NIKS) under different growth conditions (pre or post confluence) following transfection with wild-type HPV16 or 18 genomes. Cells were permeabilized by NP-40 and treated with micrococcal nuclease (MNase). Mononucleosomal DNA was gel-purified and the obtained MNase-resistant fraction was quantified by real-time PCR. PCR amplicons were set every 30bp of HPV genome spanning the long control region and E6 gene. Each amplicon was 140bp long including 30mer primers and the neighboring amplicons overlapped by 110bp.

**Results**

In proliferating (pre-confluent) HPV16-transfected NIKS, nt.11-240 and nt.3 11-570 of the HPV16 genome were relatively MNase-resistant. In differentiating NIKS (post-confluent), nt.11-150 and nt.191-330 of HPV16 DNA became more MNase-resistant and nt.41-240 became less MNase-resistant. In proliferating NIKS transfected with HPV18, nt.11-270 and nt.431-570 of HPV18 DNA were relatively MNase-resistant. In differentiating NIKS transfected HPV18, nt.41-300 of HPV18 DNA became less MNase-resistant.

**Conclusions**

The MNase-resistant regions of the episomal HPV DNA, which are expected to be in a less accessible conformation, changed according to host cell culture conditions and the initiation of epithelial differentiation. Some features were common to HPV16 and HPV18 and could be general among other HPV types.
Background and Aims

Recent studies have suggested that HPVs are not susceptible to certain high-level disinfection protocols and that medical instruments may provide transmission of nosocomial HPVs infections. We aimed to determine the infectious load of HPVs from clinical lesions and to investigate HPV virions derived from model systems and clinical lesions in their abilities to be neutralized in classical disinfection protocols.

Methods

Infectious HPV virions were isolated from the 293T transfection system, organotypic epithelial tissue cultures, mouse xenografts. Clinical samples from respiratory papillomas and anogenital warts were obtained under IRB approval using emery paper to swab the apical tumors and were typed using the Seegene Anyplex™ HPV28 detection platform. A TCID$_{50}$ assay was validated using RT-qPCR approaches to measure the end-point detection of viral E1$^*$E4 mRNAs in infected HaCaT keratinocytes. Suspension-based disinfection protocols employed ortho-phthalaldehyde (OPA), hypochlorite and alcohols.

Results

Preliminary assessment of HPV infectious titers suggest that compared to common warts, clinical RRP and anogenital samples have low levels of virions present at apical surfaces. In contrast to other reports, we found HPVs from a variety of sources were susceptible to a 2.5 to 4 log$_{10}$ reduction in infectious titer when exposed as directed to the disinfectants.

Conclusions

We conclude that HPVs are susceptible to a variety of disinfection protocols. We plan to carefully assess the infectious titers of virions present HPV-induced lesions to better determine the risk of transmission from HPV-induced warts.
COTTONTAIL RABBIT PAPILLOMAVIRUS E1 AND E2 PROTEINS MUTUALLY INFLUENCE THEIR SUBCELLULAR LOCALIZATIONS

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Background and Aims

Lysine at position 111 is highly conserved in all papillomavirus E2 proteins and is important for transcriptional activation and intracellular localization. In this study, we examined the role of the K111 residue of the cottontail rabbit papillomavirus (CRPV) E2 protein for the interaction with the E1 protein and the consequences with regard to subcellular localization and activity.

Methods

Residue K111 of E2 was either exchanged to arginine, alanine or glutamine. Both the NLS (nuclear localization signal) and NES (nuclear export signal) sequence of E1 was mutated. Luciferase-based reporter assays were used to measure transactivation and viral DNA replication. Immunofluorescence microscopy was performed to analyze the intracellular localization of E1 and E2. In vivo FACS/FRET analysis were conducted to study in vivo protein-protein interaction of E2 and Brd4.

Results

We could confirm for the CRPV E2 protein, that residue K111 is important for nuclear localization and transcriptional activity. However, the addition of the SV40NLS to the N-terminus of the K111 mutants causes a relocalization to the nucleus without gain in function. FACS/FRET analysis indicated reduced affinity of E2 K111Q to Brd4. Furthermore, in the presence of E1 protein E2 K111Q was nuclear, but without viral DNA replication activity. We found, that E1 can direct the K111Q mutant to the nucleus without direct binding and functional E1 NLS.

Conclusions

Direct binding of E2 to E1 can direct E1 to the nucleus independently from the E1 NLS and on the other hand, E1 can direct E2 to the nucleus without direct binding and an intact NLS.
HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION; A POSSIBLE RISK FACTOR OF SINONASAL TUMOR DEVELOPMENT

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Background and Aims

Sinonasal squamous cell carcinomas (SNSCCAs) are tumors with unknown etiology and pathogenesis. This study aimed to investigate the association of human papillomavirus (HPV) infection in malignant transformation of SNSCCAs.

Methods

Formalin-fixed paraffin-embedded (FFPE) tissues were collected from 80 nasal polyps (NPs), 83 sinonasal inverted papillomas (SIPs) and 71 SNSCCAs. HPV DNA detection and genotyping were performed by real-time PCR and reverse line blot hybridization, respectively. HPV E6/E7 expression level was determined using real-time PCR. HPV genome physical statuses and genome copy/cell were investigated using TaqMan real-time PCR. The physical statuses were calculated using the ratio of HPV E2 gene copy number to E6 gene copy number.

Results

HPV infection was 16.3% (13/80), 10.8% (9/83) and 15.5% (11/71) in NPs, SIPs and SNSCCAs, respectively. The two most common high-risk HPV (HR-HPV) types were HPV 18, and 58 which were distributed in all sample groups. HR-HPV 18, 58 and 16 positive cases were determined for physical status, oncogene expression and genome copy in total 14 samples consisting of 6 NPs, 4 SIPs and 4 SNSCCAs. The integration of HR-HPV was found 50% (2/4) in SNSCCAs, while in NPs and SIPs were 33.3% (2/6) and 25.0% (1/4), respectively. Interestingly, E6 and E7 expression level was significantly higher in SNSCCAs than in NPs and SIPs. The mean HPV genome copy/cell was 10.0, 3.9 and 110.6 copies/cells in NPs, SIPs and SNSCCAs, respectively.

Conclusions

Our study suggested a link between HR-HPV infections which have overexpressed of oncogenes together with high viral copy numbers and the development of SNSCCA.
Background and Aims

To characterize the competitive viral gene expression of HPV multiple-type infection in cervical cancer tissues.

Methods

The total viral RNA extracted from twenty-seven cervical cancer tumor tissues were deep sequenced on an Illumina HiSeq. Advanced bioinformatic pipeline was applied to identify viral gene transcriptome and expression. The presence of HPV DNA in tissue samples was detected using a L1-target sequencing assay.

Results

All surveyed tissue samples were positive for oncogenic HPV DNA. HPV16 was the most predominant type, presenting its DNA in 6/17 (35%) of HPV single-type infections and 9/10 (90%) of multiple-type infections. The RNA-seq revealed high-quality sequences matching HPV genome in 26/27 (96%) of samples, with reads abundance ranging between 6 and 6,578 parts per million (p.p.m) of total library size (a median of 215). Sixteen of seventeen HPV single-type infections had consistent genotype results between DNA and RNA data. However, only one expressed viral type was detected in tissues with HPV multiple-type infection, indicative of competitive expression of HPV genome inside tumors. Interestingly, six of nine HPV16-positive multiple-type infections lacked expressed HPV16 genes, suggesting a random HPV superinfection exclusion in tumor tissues. Additionally, the splicing sites of viral transcriptome were characterized and compared between different HPV types.

Conclusions

The findings indicate a competitive expression of oncogenic HPV multiple-type infection in cervical cancer tissues. The development of tumors may be contributed by the expression of one single oncogenic HPV type. It may provide knowledge for better understanding of HPV expression and pathogenesis in cervical cancer.
Vaginal Microbial Profile and Distribution of Human Papillomavirus (HPV) Genotypes of Young African American (AA) Women with Asymptomatic Bacterial Vaginosis (BV) in the United States

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Background and Aims

Bacterial vaginosis (BV) is associated with high levels of anaerobic organisms which can damage the vaginal epithelium and increase the risk of HPV infection. The co-occurrence of BV and HPV increases the risk of developing cervical cancer. The purpose of this research is to classify the vaginal microbial profile and distribution of HPV genotypes of young African American (AA) women with asymptomatic BV.

Methods

Dry stored vaginal swabs of ten AA women were analyzed. These swabs were obtained from a previously conducted prospective, randomized, open label trial. Descriptive analyses and whole genome sequencing were conducted on the vaginal swabs to determine the vaginal microbial profile and distribution of HPV.

Results

The mean age of the sample was 21 years, 80% had never been treated for BV in their lifetime and 60% had prior pregnancies. The microbial taxa of the sample included species from the genera Anaerococcus and Actinomyces, orders Lactobacillales, Prevotella amnii and Atopobium vaginae. HPV was identified in 40% of the sample. HPV was more abundant among women who had at least one new sex partner, women who had two or more sex partners as well as women who had vaginal sex without a condom with two or more partners. Atopobium vaginae and Mobiluncus mulieris were more abundant among participants with HPV compared to those without. These associations were not statistically significant.

Conclusions

This preliminary data identifies possible hypotheses to be investigated on a larger scale to detect statistically significant differences between the vaginal microbiota of women with and without HPV.
Background and Aims

While most human Gammapapillomavirus have been predominantly isolated from skin, some authors have detected Gammapapillomavirus from cervical and penile swabs suggesting a certain degree of mucosal tropism. In this study, we used untargeted next generation sequencing to estimate the prevalence of all human papillomavirus (HPV) including Gammapapillomavirus isolated from cervical swabs of young women in Luxembourg collected for a vaccine effectiveness study.

Methods

DNA extracts of 740 cervical swabs from women with a mean age of 23 years were enriched by untargeted rolling-circle amplification and sequenced on Illumina Miniseq platform. Reads were mapped to the PaVE collection of 286 known genotypes. Genomes were assembled using SPAdes and their similarity to known genotypes determined using BLAST.

Results

Two putatively novel Gammapapillomavirus genotypes were detected showing 87% nucleotide similarity in the L1 gene between themselves and 77% and 87% similarity, respectively, with the closest known genotype HPV101. Gammapapillomavirus all belonging to the gamma-6 species were detected in 26 (3.5%) samples: HPV101 (2, 0.3%), HPV103 (4, 0.5%), HPV108 (10, 1.4%), MF588696 (3, 0.4%), putatively novel type 1603168A (5, 0.7%), and putatively novel type 16002169 (3, 0.4%). Of the 26 Gammapapillomavirus positive samples, 21 (81%) also harboured Alphapapillomavirus among whom 5 (19%) had ASC-US or LSIL cytology.

Conclusions

Our study confirms previous work that Gammapapillomavirus may be occasionally detected in cervical swab samples. Our finding that Gammapapillomavirus infection of the cervix is limited to genotypes belonging to the gamma-6 species as well as their role in pathogenesis needs to be confirmed in other populations.
Background and Aims

The human genome has increasingly been shown to exhibit a vast degree of invasion by viral genomes. During the process of evolution several RNA and DNA viruses have become integrated into the vertebrate genome, that may account for as much as 10% of the human genome. The aim of this study was to identify viral sequence integration that may be associated with the aetiology of oesophageal squamous cell carcinoma (OSCC) in the South African population.

Methods

We compared the viral DNA sequences present in normal and tumour OSCC samples. DNA from normal and tumour biopsies were subjected to whole genome sequencing and subtracted from the reference human HG20 sequence to identify all non-human DNA sequences. All sequences were aligned to the reference human genome HG20 using the ELAND and CASAVA software packages. The unmapped reads were then aligned against a complete set of the NCBI RefSeq Viral Genomes (build 64) using the Burrows Wheeler Aligner.

Results

A large number of viral DNA and RNA sequences were identified; these included Human Papilloma viruses, Herpes simplex viruses, adenoviruses, Hepatitis C viruses and Human Endogenous Retrovirus K113.

Conclusions

Although it is unlikely that the role played by viruses alone may be sufficient for the process of malignant transformation, these results highlight the role played by Human Papilloma viruses in enabling genomic instability of the host cell and support a model wherein the frequent assault of the human genome by widespread viral integration significantly widens oncogenic opportunities in patients with OSCC.
Background and Aims

While nearly all cervical tumors are infected with HPV, infection alone is not sufficient for tumor development. Although most cervical HPV infections are cleared by cell-mediated immunity, progression to malignancy is linked to an immunosuppressive tumor microenvironment, and recent evidence has linked dysbiosis of the vaginal microbiome with the extensive reprogramming and remodeling of the cervical stroma. In this study, we sought to identify host and microbial prognostic biomarkers in the cervical tumor microenvironment.

Methods

Using expression-based cell-deconvolution methods on RNAseq from 372 cervical carcinomas, we performed hierarchical clustering on principle components to identify three patient clusters, which were identified as either immune-rich, stromal-rich, or an intermediate immune/stromal type. Furthermore, we used microbial transcriptomics to identify microbes significantly associated for both patients with or without tumor recurrence.

Results

Patients with immune cell-enriched tumors exhibited a favorable prognosis. However, both the intermediate and stromal enriched tumors had significantly worse overall and disease-free survival ($p = 0.038$ and $0.0021$), with the stromal type having the worst prognosis. Gene set enrichment analysis (GSEA) revealed that genes associated with epithelial-mesenchymal transition were more strongly associated with the stromal subtype, while the immune type was strongly associated with genes involved in p53 pathways and networks. Furthermore, tumor recurrence was associated with higher abundance of proinflammatory microbes.

Conclusions

We have identified, for the first time to our knowledge, microbes associated with cervical cancer prognosis while confirming that tumors with higher stromal invasion and marked immunosuppression exhibit the worst prognosis.
VIRAL GENOME VARIATION IN NON-CERVICAL HPV16-ASSOCIATED HIGH GRADE PRE-CANCER LESIONS AND INVASIVE CANCERS

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Background and Aims

HPV16 genome variation has been associated with risk of cervical cancer progression. However, the role of viral variation in non-cervical cancers is unknown. We have evaluated the HPV16 genome in non-cervical cancers to analyze the (sub)lineage and single-nucleotide variant (SNV) distribution among different geographical and anatomical locations.

Methods

HPV16 whole-genome sequences were determined by next generation sequencing (NGS) in 609 non-cervical high-grade pre-cancer and invasive cancers included in the Institut Català d’ Oncologia (ICO) international collection. 455 FFPE samples passed the DNA quality controls and (sub)lineages were classified based on the maximum-likelihood tree topology. We evaluated associations of each SNV and the combined effects by viral gene region comparing pre-cancers and cancers, and among cancer sites.

Results

262 pre-cancer lesions (anal, vagina, vulva and penis) and 347 cancers (anal, vagina, vulva, penis and head and neck) from 5 geographical areas (275 Europe, 52 Oceania, 243 Latin America, 26 Asia and 13 Africa) were evaluated. The most common lineage was A (73.6 % A1, 12.8% A2, 0.4% A3 and 1.8% A4), followed by D (0.2% D1, 1.8 D2 and 6.5 % D3), C (0.9% C and 1.1 % C1) and B (0.7% B and 0.2% B1). A1-A3 variants were more frequent in Latin America than in Europe or Oceania. A deep analysis to uncover differences in lineages and SNVs between pre-cancers and cancers will be presented in the IPV2018 conference.
Conclusions

NGS analysis will determine if HPV16 genome variability is an important factor associated with the risk of progression in non-cervical HPV associated cancers.
Background and Aims

HPV16 is the most carcinogenic type, responsible for ~60% of all invasive cervical cancers (ICC), while the genetically closely related Alpha 9 types, HPV31 and HPV35, account for ~4% and 2% of ICC, respectively. We hypothesize that the huge variability in risk is linked to viral genetic variation. HPV16/31/35 differ by only ~35% (~2500bp) of their complete amino-acid sequence (~20% in L1, ~300bp). HPV16/31/35 represent a natural comparison and a unique opportunity to discover the role of genomics in HPV carcinogenesis.

Methods

To investigate differences and similarities among HPV16/31/35, we HPV whole-genome sequenced 6,096 cervical cell specimens from the NCI-KPNC PaP cohort, using custom Ion AmpliSeq panels. We aligned the amino-acid sequences of 3,442 HPV16, 2,071 HPV31 and 583 HPV35 samples, including 2,654 controls with benign infections (≤CIN1), 1,762 CIN2 and 1,680 CIN3/cancer. We compared HPV16/31/35 genomes using phenotype-genotype case-control approaches to determine which SNPs, haplotypes, gene regions, or amino-acids make an HPV more or less carcinogenic.

Results

We identified distinct genetic variation profiles between cases and controls and among types. In particular, HPV16 was the most variable type, nonsynonymous rare variation was higher in controls, and E7 conservation was linked to carcinogenicity. Contrastingly, E6 and E7 variation pattern did not differ between cases-controls for HPV31/35. Currently, we are assessing the association of non-conserved amino-acids with CIN3+. Our preliminary data revealed specific amino-acids associated with variable risk among types.

Conclusions

Using this large nested case-control study, we are identifying HPV genetic profiles linked to ICC and the unique carcinogenic potential of HPV16.
BASIC RESEARCH - GENOMICS OF HPV-ASSOCIATED DISEASE

DEVELOPMENT OF A PAPILLOMAVIRUS SPECIFIC GENOME ANNOTATION TOOL

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Background and Aims

High-throughput sequencing technologies combined with ‘viral metagenomic’ have dramatically expanded the universe of known (papilloma-) viruses. Importantly, this implies that many novel papillomaviruses are not discovered and described by experts in papillomavirus genomics. There is a need to develop analytical approaches to reconstruct, annotate, and classify viral genomes. We report on the development of a papillomavirus-specific annotation tool: “PuMA”.

Methods

PuMA utilizes open source software. The underlying code was written in python. PuMA will be deployed as part of a growing online Cyberinfrastructure for Viral Ecology known as iVirus.

Results

At present, PuMA annotates the main viral open reading frames, several viral transcripts, and cis binding sites for the E2 and E1 viral proteins. The PuMA algorithm was optimized using a subset of papillomavirus genomes present in the Papillomavirus episteme (PaVE). Following optimization, PuMA annotations were compared to the entire PaVE database. PuMA correctly annotates the majority of papillomavirus genomes currently in the PaVE. Finally, PuMA produces files that can be used for streamlined submission to NCBI’s GenBank.

Conclusions

High-throughput sequencing, comparative genomics, and epidemiological analyses depend on uniformly curated reference genomes. We developed PuMA; an easy to use papillomavirus-specific annotation tool that automates the consistent and uniform annotation of viral genomes. These genomes form the foundation for further bioinformatic studies.
HUMANS PAPILLOMAVIRUS (HPV) INFECTIONS AMONG FEMALE SEX WORKERS IN COTE D'IVOIRE

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Background and Aims

Background: Human Papillomaviruses (HPV) are small virus non-enveloped double-stranded circular DNA. Many studies have indicated that having multiple sexual partners may lead to higher HPV transmission. Female sex workers (FSWs) may be at greater risk of infection compared to the general population. The risk of HPV infection and cervical cancer is especially high. The aim is to determine the prevalence and the genotypes of Humans Papillomavirus (HPV) that circulate in female sex workers populations in Cote d'Ivoire.

Methods

Methods: From December 2015 to May 2016, cervical samples from 350 female sex workers were tested for some HR-HPV. HPV DNA was amplified using PGMY09 /11 primers. HPV DNA were genotyped using the multiplex PCR with HPV 16, 18, 31, 33, 35, 45 and 51 primers.

Results

Results: The mean age was 32.5 years. HPV DNA was obtained in 51.5% of women. 168 (94.38%) specimens harboring HPV DNA were genotyped by multiplex PCR versus 5.61 %, which were not genotyped by multiplex PCR. 168 strains permit to identify 204 strains with 88.69 % with single infection while 11.30 % a multiple infection. Among multiple infection 36.84 % had respectively double and triple HPV infection and 26.31 % had four HPV infections. HPV genotypes prevalence were: HPV 16 (22.47%), HPV 18 (26.97%), HPV 35 (11.23%), HPV 31 and HPV 33 (7.86%) respectively and HPV 45 (7.30%). Any case of HPV genotype 51 was founded.

Conclusions

Conclusion: HPV infection in female sex workers is high. The most genotypes in female sex workers are type 16 and 18.
CHARACTERISATION AND OPTIMISATION OF PRODUCTION OF HUMAN PAPILLOMAVIRUS PSEUDO-VIRIONS IN TOBACCO PLANTS

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Background and Aims

HPV pseudovirions (PsVs) are L1/L2 capsids containing up to 8Kb of plasmid-like DNA. PsVs are used to test neutralising antibodies elicited by vaccines, for studying the virus life cycle, and potentially for delivery of therapeutic DNA vaccines. PsVs are typically produced in mammalian cells; however, it has recently been shown that HPV PsVs can be produced in plants, a potentially safer, cheaper and more easily scalable means of production. Research has also shown that using pseudogenome DNAs between 5-7Kb increases yields of bovine papillomavirus PsVs in mammalian cells.

The objective of this research was to determine the optimal DNA size for encapsidation by plant-produced PsVs, allowing for higher yields of stable particles.

Methods

Target DNA constructs encoding EGFP ranging in size from 5 – 8kb were infiltrated into Nicotiana benthamiana plants with plant expression vectors encoding the L1 and L2 capsid proteins. PsVs were purified by iodixanol gradient ultracentrifugation and L1 expression was quantified by gold stain densitometry and western blots. Quantitative PCR was used to quantify encapsidated DNA. Transmission electron microscopy (TEM) was used to determine quality of particle formation.

Results

The qPCR and L1 comparison together with TEM showed that 5Kb and 5.8Kb sized target DNA yielded the most well-formed particles. Fluorescent microscopy and GFP fluorimetry indicated comparable mammalian cell- and plant-made PsV infectivity.

Conclusions

This research could contribute towards cheaper testing of new HPV VLP vaccines and virus life cycle research. It could also lead to the production of effective and cheap plant-made therapeutic DNA vaccines.
THE EXPRESSION PROFILES OF IMMUNE INHIBITORY MOLECULES ON TUMOUR INFILTRATING T CELLS AND ANTI-PD-1 AND INTERLEUKIN 10 COOPERATE TO ENHANCE T CELL FUNCTION IN VITRO

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**Background and Aims**

Immune checkpoint inhibitors show great promise as therapy for cervical cancer, heightening the need to dynamically determine the expression profiles of immune inhibitory molecules and its effect on T cell immune function.

**Methods**

We studied the expression of inhibitory molecules on tumour infiltrating T cells, tumour cells and IL-10 receptor on the T cells in a TC-1 tumour mouse model, and in samples collected from cervical intraepithelial neoplasia (CIN) or cervical cancer patients by flow cytometry.

**Results**

The numbers of T cells expressing inhibitory molecules such as PD-1 and CTLA-4 are significantly increased if the T cells isolated 3 weeks after tumour inoculation compared with those isolated 2 weeks. The numbers of INFγ secreting T cells isolated from tumours three weeks after tumour inoculation were significantly lower than those isolated 2 weeks after tumour inoculation. The numbers of PD-1+CD4+ T cells or PD-L1+ CD45-CD326+ cells in from cervical cancer tissue samples significantly higher than those from CIN. The numbers of IL-10R+ CD8 + T cells from cervical cancer were significantly lower than those from CIN. Anti-PD-1 combined with IL-10 significantly increase the proportion of CD3+CD4+IFN-γ+ T cell, CD3+CD8+IFN-γ+ T cell, whether PD-1 positive or negative than those treated with IL-10 or anti-PD-1 antibody respectively control.

**Conclusions**

Our results suggested that Anti-PD-1 and interleukin 10 cooperate to enhance the function of tumour infiltrating T cells, at least in vitro.
IPVC8-0481
POSTER SESSION

BASIC RESEARCH - PAPILLOMAVIRUS VACCINES (I.E. NEW DEVELOPMENTS)

CAERIN PEPTIDES INCREASE THE EFFICACY OF A THERAPEUTIC VACCINE CONTAINING INTERLEUKIN 10 SIGNALLING INHIBITOR THROUGH RECRUITING MORE T AND NK CELLS TO THE TUMOUR SITE

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Background and Aims

Therapeutic vaccines against cervical cancer remain to be effective. Previously, we demonstrated that blocking the signalling of a cytokine, interleukin 10 at the time of immunisation elicits significant higher numbers of antigen specific T cells.

Methods

HPV16 E6 / E7 transformed TC 1 tumour mouse model to verify efficacy of a therapeutic vaccine combined with Caerin peptides. Flow cytometry and ELISA were used to detect and analyze the function of tumour infiltrating T cells and pro-inflammatory chemokine MCP-1 secreted by the TC-1 cells.

Results

In the current paper, we demonstrate in a HPV16 E6/E7 transformed TC-1 tumour mouse model that blocking IL-10 signalling at the time of immunisation although temporally better prevents TC-1 tumour growth but does not increase the survival time of the TC-1 tumour bearing mice compared with vaccination without IL-10 signalling blockade. The function of tumour infiltrating T cells isolated 3 weeks after TC-1 transplantation are more suppressed than those isolated two weeks after tumour transplantation. We further demonstrate that Caerin peptides derived from amphibian skin secretion were able to inhibit TC-1 tumour growth both in vitro and in vivo, are environmentally stable and promote the TC-1 cells secreting pro-inflammatory chemokine MCP-1.

Conclusions

Caerin peptides increase the survival time of TC-1 tumour bearing mice after therapeutic vaccination with a HPV16E7 peptide based vaccine containing IL-10 inhibitor, through recruiting more T and NK cells to the tumour site.
BASIC RESEARCH - PAPILLOMAVIRUS VACCINES (I.E. NEW DEVELOPMENTS)

COMPARATIVE PROTEOMIC STUDY OF THE ANTI-PROLIFERATIVE ACTIVITY OF FROG HOST-DEFENCE PEPTIDE CAERIN 1.9 AND CAERIN 1.1 ON TC-1 CELLS TRANSFORMED WITH HPV16 E6 AND E7

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Background and Aims

Caerin are a family of peptides isolated from the glandular secretion of Australian tree frogs, the genus *Litoria*, and have been previously shown to have anti-cancer activity against several cancer cells. In this work, we used two host-defence peptides caerin 1.1 and 1.9, to investigate their ability to inhibit a murine derived TC-1 cell transformed with human papillomavirus 16 E6 and E7 growth *in vitro*.

Methods

We used a proteomics strategy to quantitatively examine: (i) the changes in the protein profiles of TC-1 cells; and (ii) the excretory-secretory products of TC-1 cells following caerin peptides treatment.

Results

Caerin 1.9 inhibits TC-1 cell proliferation, although inhibition is more pronounced when applied in conjunction with caerin 1.1. To gain further insights into the anti-proliferative mechanisms of caerin 1.9 and its additive effect with caerin 1.1, Caerin 1.9 treatment significantly altered the abundance of several immune-related proteins and related pathways, such as the Tec kinase and ILK signalling pathways, as well as the levels of pro-inflammatory cytokines and chemokines.

Conclusions

In conclusion, caerin peptides inhibit TC-1 cell proliferation, associated with modification in signalling pathways that would change the tumour microenvironment which is normally immune suppressive.
Background and Aims

Human Papillomavirus (HPV) is the main cause of cervical cancer, which is the second most severe cancer of women worldwide, particularly in developing countries. Although vaccines against HPV infection are commercially available, they are neither affordable nor accessible to women in low income countries.

Methods

To develop an alternative vaccine production platform against HPV infection, we have investigated the expression of a modified HPV-16 L1 gene fused with glutathione-S-transferase (GST). Previous reports have shown that this modified L1 gene (L1_2xCysM) leads to the assembly of L1 protein to pentameric capsomeres. This pentameric shape of L1 protein is very crucial to activate proper immune response against Papillomavirus.

Results

In total 7 transplastomic lines with healthy phenotypes were generated. Site specific integration of the GST-L1_2xCysM was confirmed by molecular analysis. Southern blot analysis verified homogenous transformation of all transplastomic lines. Antigen capture ELISA with the conformation-specific antibody Ritti01, showed protein expression as well as the retention of immunogenic epitopes of L1 protein. In their morphology, GST-L1 expressing tobacco plants were identical to wild type plants and yielded fertile flowers. They developed green leaves and formed normal flowers producing viable seeds that germinated uniformly on selection medium.

Conclusions

Taken together, the current study on plant-based expression of capsomeres supports the development of cost-effective thermostable HPV vaccines. This data helps in enriching our knowledge for future development of cost-effective plant-made vaccines against HPV, which is highly desirable for resource poor countries.
Background and Aims

Therapeutic HPV vaccine is an agent to induce E7-specific Th1 immune responses to treat CIN2-3. Our previous clinical trial has demonstrated that oral administration of HPV16 E7-expressing Lactobacillus casei (L. casei), GLBL101c, to CIN3 patients elicited mucosal Th1-immune response to E7 at the lesions and resulted in the regression of HPV16-related CIN3. Here we examined optimization of the E7-expressing L. casei for induction of the mucosal immune responses to E7.

Methods

Various doses of HPV16 E7 molecule were displayed on the L. casei cell by anchoring. By flow cytometry and immunization of mice, the optimal dose of displayed E7 was decided. The optimal dose of E7 was expressed and transferred onto the cell surface by our expression system. The induction of mucosal immune response to E7 was evaluated using gut intraepithelial lymphocyte (IEL) obtained from the immunized mice.

Results

Flow cytometry revealed that surface-bound E7 molecule was saturated beyond 1.0 μg/10^8 cells. Immunization with E7-bound L. casei showed the induction of E7-specific mucosal IFNγ-producing cells was dependent on displayed E7-doses. A new agent, L. casei with endogenous expression of E7 (IGMKK16E7), showed the optimal amount of displayed E7. Immunization with IGMKK16E7 demonstrated 4-fold higher induction of E7-specific mucosal IFNγ-producing cells when compared with the former one (GLBL101c).

Conclusions

Mucosal Th1 immune response to E7 paralleled the amount of displayed E7. Our new system provided the optimal E7-expressing L. casei for displayed E7 amount and induction of mucosal Th1 immune response. IGMKK16E7 may be a more promising therapeutic for treatment of CIN2-3 when compared with GLBL101c.
THERMOSTABILIZATION OF RG1-VLPS, A BROAD-SPECTRUM HPV VACCINE CANDIDATE

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Background and Aims

Licensed HPV L1 VLP vaccines provide protection against a limited subset of high-risk (hr) HPV types and thus do not eliminate the need for costly cervical screenings in vaccinated women. Additionally, the greatest burden of cervical cancers are found in resource-poor countries in which vaccine distribution is hindered in part due to cold-chain requirements. Chimeric RG1-VLPS present the HPV16 L2 cross-neutralization epitope RG1 (aa17-36) on a surface loop of HPV16 L1-VLPs. In animal immunizations, RG1-VLPs induced robust HPV16-specific protection and cross-protection against all 12 other hr HPV, several other mucosal low-risk and cutaneous HPV types. Consequently, RG1-VLPs are being produced currently for first-in-human clinical studies.

Methods

As an approach to facilitate vaccine distribution, aluminum hydroxide-adjuvanted RG1-VLPs were stabilized by lyophilization, incubated at different temperatures (4°/20°/37°/50°C) for 1 day/week/month, and mice immunized 3x i.m. to determine the extent of antigen thermostability.

Results

Robust anti-HPV16 L1-VLP and anti-RG1 peptide ELISA titers were detected in immune sera from all lyophilized RG1-VLP-immunized groups. In addition, HPV16 type-specific neutralization and cross-neutralization against hr HPV18/31/39 and Beta HPV5 were detected by pseudovirion neutralization assays for all groups. A trend for reduced (cross-)neutralization was seen in the highest (50°C) temperature groups only. By ELISPOT IFN-gamma T cell responses were detected in mice immunized with lyophilized RG1-VLPs incubated at 4°/20°/37°/50°C for 1 month.

Conclusions

Lyophilized RG1-VLPs are a promising thermostable broad-spectrum HPV vaccine candidate with sustained immunogenicity after prolonged incubation at increased temperatures. Providing a stabilized form of RG1-VLP may circumvent cold-chain requirements thus facilitating vaccine distribution in low resource settings.
The role of cervical microbiome in response to HPV therapeutic vaccination was investigated.

Methods

In a single-arm, dose-escalation, Phase I clinical trial of PepCan (NCT01653249), 34 women with biopsy-proven HSIL received 4 injections at a 3 week-interval. Cervical ThinPrep (Hologic, Marlborough, MA) specimens were collected prior to vaccination and 3 months after the last vaccination. DNA was PCR-amplified using bacterial 16S rRNA gene primers, and the amplicons were hybridized to the PhyloChip Array™, version G4 (Second Genome, South San Francisco, CA). Alpha diversity metrics, beta diversity metrics, principal coordinate analyses, and permutational analysis of variance (PERMANOVA) were performed.

Results

Richness per sample ranged from 72 to 365 empirical Operational Taxonomic Units (eOTUs), and no correlations were found in alpha diversity and beta diversity in relation to vaccination. However, phyla *Caldithrix* (*Padj*<0.0001) and *Nitrospirae* (*Padj*<0.0001) and the family *Micromonosporaceae* (*Padj*<0.0001) were enriched in the microbiomes, prior to vaccination, of histological vaccine non-responders compared to responders. A PERMANOVA using Bray-Curtis dissimilarities performed for various demographic and immune parameters showed significant contributions to the beta diversity for race, HPV 16, percent peripheral Th1 cells, and HLA-B40 (*P*<0.001, 0.014, 0.037, and 0.024 respectively). Significant differences at the eOTU level were described for race and HPV 16.

Conclusions

Further studies are warranted (1) to explore the role of certain cervical microbial composition in predicting non-responsiveness to therapeutic vaccination, and (2) to understand the contributions of race and HPV 16 positivity to beta diversity.
ANTIBODY PERSISTENCE AFTER A SINGLE DOSE OF QUADRIVALENT HPV VACCINE AND THE EFFECT OF A DOSE OF NONAVALENT VACCINE GIVEN 3-8 YEARS LATER

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Background and Aims

This study assessed the persistence of antibodies after a single dose of quadrivalent vaccine (4vHPV) and the effect of a dose of nonavalent vaccine (9vHPV) given 3-8 years later on antibody titers. Such data might be of interest in the decision-making process concerning the completion of the 2-dose course in non-compliant vaccinees in jurisdictions which switched from 4vHPV to 9vHPV.

Methods

Girls who received a single dose of 4vHPV were eligible to participate. Blood specimens were collected just before and one month post-9vHPV administration. The specimens were tested by ELISA for antibodies to 9 HPV types included in the 9vHPV.

Results

31 girls aged 13-18 years (mean 15.5 years) participated in the study. Pre-9vHPV administration all participants were seropositive to the 4 HPV types included in the 4vHPV and 58%-87% were seropositive to the additional five HPV types included in the 9vHPV. GMTs were 8.1AU/ml, 9.7 AU/ml, 22.4IU/ml and 8.0IU/ml for HPV6, HPV11, HPV16 and HPV18, respectively. The GMTs were lower for the other five HPV types (2.4-4.2AU/ml). One month post-9vHPV administration all 31 participants were seropositive to 9 HPV types with a 25.3-73.3-fold increase in GMTs.

Conclusions

High seropositivity observed several years after a single dose of 4vHPV and 100% seropositivity to all 9 types after a dose of 9vHPV suggest that this schedule might be used in non-compliant vaccinees or when switching the immunization program from 4vHPV to 9vHPV vaccine.
Background and Aims

The real-world impact and effectiveness (VE) of quadrivalent HPV (4vHPV) vaccination on HPV infection and disease was previously assessed in 2016, ten years after 4vHPV licensure. Our aim was to update the evidence related to impact and VE of 4vHPV on cervical abnormalities, including cytological abnormalities and histologically-confirmed cervical intraepithelial neoplasia.

Methods

Medline and Embase were searched for observational studies evaluating real-life benefits of 4vHPV (01/03/2016-12/04/2018). Reviews, conference, disease-burden, modeling, awareness, clinical trial studies and studies with mixed 4vHPV and 2vHPV were excluded. Impact was defined as population prevented fraction of abnormalities by comparing population before and after vaccination program or trends over time and VE as proportion of prevented abnormalities comparing vaccinated and unvaccinated individuals.

Results

Of 1533 publications identified in the last 2 years, 8 studies (5 impact, 3 VE) from Australia, Canada and US provided data related to 4vHPV and cervical abnormalities, compared to 16 studies in previous review. Significant impact on high-grade (HG) cervical abnormalities in vaccine era were observed especially among females 15 to 24 years of age with estimated 6%-20% annual percentage declines. The impact of vaccination on reductions of histologically confirmed cervical lesions among women 25-29 years, who were aged 18-26 years at vaccination, was newly reported in one study. VE of 50%-62% for HG and of 28%-73% for low-grade cytological cervical abnormalities were reported.

Conclusions

The impact and effectiveness of 4vHPV on reductions of cervical abnormalities is becoming increasingly evident, including first signs of a decline among 25-29 years old women who received catch-up vaccination.
IPVC8-0653
POSTER SESSION

BASIC RESEARCH - PAPILLOMAVIRUS VACCINES (I.E. NEW DEVELOPMENTS)

EFFECTIVENESS AND IMPACT OF THE QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINE ON ANOGENITAL WARTS: A SYSTEMATIC LITERATURE REVIEW UPDATE

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Background and Aims

The real-world impact and effectiveness (VE) of quadrivalent HPV (4vHPV) vaccination on HPV infection and disease was previously assessed in 2016, ten years after 4vHPV licensure. Our aim was to update the evidence related to anogenital warts (AGWs).

Methods

Medline and Embase were searched for observational studies evaluating real-life benefits of 4vHPV (01/03/2016-12/04/2018). Reviews, conference, disease-burden, modeling, awareness, clinical trial studies and studies with mixed 4vHPV and 2vHPV were excluded. VE was defined as proportion of prevented AGWs comparing vaccinated and unvaccinated individuals and impact as the population prevented fraction of AGWs comparing incidence/prevalence of AGWs before and after vaccine introduction or assessing trends over time.

Results

Of 1533 publications identified in the last 2 years, 12 studies (4 VE, 8 impact) from Australia, Canada, Germany, Italy, Sweden, US, and New Zealand provided data related to 4vHPV and AGWs, compared to 15 studies in previous review. VE of 56%-80% was observed 7-years after implementation of vaccination program for females, greatest in females below 22-years and with completion of 3-doses, although 2-doses spaced at least 5 months apart provided similar protection. Impact of 14%-62% in females (vaccine coverage 25%-81%) and of 17%-68% in males (vaccine coverage 0%-8%) was observed 3-7 years after vaccination program in females.

Conclusions

Real-world evidence supports effectiveness and impact of 4vHPV in males and females. The decline in AGWs in young vaccinated females most likely reflects direct effects of 4vHPV. Countries report substantial impact on males, which may represent indirect protection, given recommendation for male vaccination are only recently implemented.
IPVC8-0776
POSTER SESSION

BASIC RESEARCH - PAPILLOMAVIRUS VACCINES (I.E. NEW DEVELOPMENTS)

DEVELOPMENT OF A THERAPEUTIC CANCER VACCINE BASED ON P16INK4A
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Background and Aims

The cyclin-dependent kinase inhibitor p16⁰INK⁴a is strongly overexpressed in human papilloma virus (HPV)-induced tumors, whereas it is barely detectable in normal tissue. Therefore, it is an established surrogate marker for high risk HPV infections and considered to be an interesting target for therapeutic vaccination in cancers associated with HPV.

In a phase I/IIa trial to monitor toxicity and immunogenicity of a p16⁰INK⁴a peptide vaccine in patients with advanced HPV-associated, p16⁰INK⁴a-overexpressing cancers, we could show the induction of a humoral and cellular immune response against p16⁰INK⁴a without any severe vaccine-related side effects.

Presently we are establishing a p16⁰INK⁴a-positive tumor mouse model in order to explore the effect of a p16⁰INK⁴a-based vaccine on tumor growth and its potential to be combined with current immunotherapies.

Methods

Before and respectively after the immunizations with p16⁰INK⁴a-derived peptides, C57BL/6 mice were challenged with p16⁰INK⁴a-expressing TC-1 cells to analyse the tumor response of a therapeutic and respectively prophylactic vaccine approach.

Results

The vaccination with p16⁰INK⁴a-derived peptides induced an antibody response against p16⁰INK⁴a detected by ELISA as well as IFNγ-producing CD4+ and CD8+ T cells measured by ELISpot. We are currently performing the tumor regression and protection experiments with p16⁰INK⁴a-positive TC-1 cells in C57BL/6 mice.

Conclusions

The established murine system allows us to address the question whether a p16⁰INK⁴a-based vaccine is able to induce the regression and/or prevent the further outgrowth of a p16⁰INK⁴a-expressing tumor.

The generation an effective tumor response against p16⁰INK⁴a could lead to a new therapeutic approach for HPV-induced cancers.
Women with bacterial vaginosis (BV) have increased risk for human papillomavirus (HPV) cervical infection and HPV persistence. *Gardnerella vaginalis* is the main BV-associated bacteria and also the major source of bacterial sialidases in the cervicovaginal environment. Sialidase-producing *G. vaginalis* are responsible for vaginal biofilm formation, which hinders BV treatment. Sialidases are encoded by the GVSI gene in *G. vaginalis* and its detection was recently proposed as a potential marker for HPV persistence.

**Methods**

We enrolled 1799 women attending the primary health care unities of Botucatu city for routine Pap-test. We genotyped cervicovaginal samples for HPV using Roche's Linear Array test. A total of 304 (10.9%) participants were positive for HPV16 and/or HPV18 at enrollment and, until now, 122 of them returned for follow up after 12 months, when HPV status was re-accessed. Participants were divided in clearance (n=57) and persistence (n=65) groups if they tested, respectively, negative or positive for the same genotype detected at enrollment. We used real time PCR for determining GVSI cervicovaginal load. Loads of GVSI were compared between the groups using Mann-Whitney test.

**Results**

Frequency of GVSI gene was 86.0% (n=49) and 84.6% (n=65) in clearance and persistence groups, respectively. Cervicovaginal GVSI loads were not increased in persistence (7.05e+009; 0.0-1.6e+015 copies/μL) in relation to clearance group (1.3e+011; 0.0-1.8e+015 copies/μL), (p=0.31).

**Conclusions**

Our preliminary data do not support the use of GVSI/load alone as marker for persistent HPV16 and/or HPV18 cervical infection. Future studies should investigate other bacterial genes that could be combined to GVSI to predict HPV persistence.
Aims. Management of HPV lesions requires better therapeutic options than presently available. We developed a three-dimensional epithelial tissue culture system from primary human keratinocytes harboring HPV-18 replicons, fully recapitulating a robust infectious program. Investigations of virus-host cell interactions identified critical regulatory pathways on which HPV DNA amplification depends, revealing potential host targets for anti-viral therapies. Our strategy is to repurpose existing pharmacologic agents to inhibit viral DNA amplification, interrupt HPV transmission, or preferentially eradicate HPV-infected cells. Methods. Inhibitors are delivered to raft cultures topically or through the medium for up to two weeks. Durability of responses is evaluated by post-treatment chase. We then probe for HPV DNA amplification, cellular DNA replication, viral protein and targeted host proteins, tissue morphology and differentiation, as well as indicators of DNA damage or apoptosis. To model various stages of neoplasias, 3D raft cultures are established from HPV-immortalized or -transformed epithelial cells. Moreover, 3D cultures can be grown directly from patient lesions, and tissues can be transferred reciprocally between patient-derived xenografts in SCID mice and the raft culture system. Results. Squamous epithelia tolerate pharmaceutical agents previously abandoned because of toxicity upon systemic delivery, supporting the potential for new drug indications against epitheliotrophic viruses. Conclusions. The authenticity of this experimental model of HPV infections and diseases should greatly reduce preclinical research time and expense. As proof of principle, several molecularly distinct inhibitor candidates we have found to be safe and effective have advanced to clinical trials to treat benign HPV lesions.
POTENTIAL BIOMARKER OF HUMAN PAPILLOMAVIRUS 16 GENOME METHYLATION FOR PREDICTION OF ANAL INTRAEPITHELIAL NEOPLASIA

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²Chulalongkorn University, The Thai Red Cross AIDS Research Centre, Bangkok, Thailand

Background and Aims

Quantitative measurement of human papillomavirus (HPV) 16 early promoter and L1 genes methylation were analyzed in anal cells to determine the potential biomarker for screening of HPV related anal cancer.

Methods

The methylation patterns of the HPV16 genes including early promoter (CpG 31, 37, 43, 52 and 58) and L1 gene (CpG 5600, 5606, 5609, 5615, 7136 and 7145) were analyzed in 178 anal samples with histology diagnosed as normal, anal intraepithelial neoplasia 1 (AIN1), AIN2 and AIN3 using pyrosequencing assay.

Results

Low methylation levels of early promoter (<10%) and L1 genes (<20%) were found in all detected normal anal cells, while medium to high methylation (>20-60%) was found in some of AIN1-3 samples. Interestingly, there was slightly increased in L1 gene methylation from normal to AIN3, especially at CpGs 5600 and 5609.

Conclusions

Medium to high methylation level (>20-60%) of HPV16 5’L1 regions especially at CpGs 5600 and 5609 were demonstrated in some of AIN1-3 lesions when compared to those of the normal lesion indicating potential of using HPV16 L1 gene methylation as a biomarker for HPV related cancer screening.
LUMINEX AND MULTIPLEX QPCR FOR DETECTING HPV GENOTYPES IN URINE SAMPLES.
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¹Norwegian Institute of Public Health, Department of Molecular biology, Oslo, Norway
²Norwegian Institute of Public Health, Department of Infectious Disease Epidemiology and Modelling, Oslo, Norway
³Norwegian Institute of Public Health, Biobanks, Oslo, Norway

Background and Aims

Norwegian girls have been invited to the HPV-vaccination program since 2009. As part of the national HPV-surveillance programme, urine samples from 17 and 21 years old girls have been collected before and at several timepoints after vaccination and used as a measure of HPV prevalence in the population. These data also provide a measure of the effect of the vaccine on the prevalence of HPV genotypes in the population.

We question the performance of Luminex method when vaccination results in a change in prevalence of HPV16 and/or HPV18, which may lead to variations in our ability to detect certain other genotypes.

Methods

The original method for HPV genotyping in DNA from these urine samples was Luminex, where a mix of primers should amplify a region of L1 that can hybridize to specific oligos from 37 distinct HPV genotypes. The oligonucleotides are coupled to specific detectable beads, enabling multiplex detection of the HPV genotypes.

We have also established an alternative multiplex qPCR assay, where a total of 15 HPV genotypes can be detected with specific Taqman probes against E6 or E7. We have combined detection of 4 targets in each reaction by choosing specific, compatible fluorescent probes.

Results

We validate the performance of Luminex and qPCR to detect specific genotypes in the presents or absents of HPV 16/18.

Conclusions

We have compared the strengths and weaknesses of Luminex and multiplex qPCR for HPV detection from urine samples, and will share data illustrating the strengths and weaknesses of both Methods.
DETECTION OF FELIS CATUS PAPILLOMAVIRUS TYPE 3 AND 4 DNA FROM SQUAMOUS CELL CARCINOMA CASES OF CATS IN JAPAN

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²The University of Tokyo, Veterinary Pathology, Tokyo, Japan

Background and Aims

In domestic cats, five types of papillomaviruses, designated as FcaPV (Felis catus papillomavirus), have been identified. Association of FcaPV with feline squamous cell carcinoma (SCC) has been reported in some regions, including Europe, Oceania and America. In Asian countries, including Japan, however, there is limited information about FcaPVs. To further understand the association of FcaPVs with SCC, detection and characterization of FcaPVs were performed with twenty-one feline SCC biopsy samples from cats in Japan.

Methods

All of the 21 feline SCC biopsy samples used in this study were collected in Japan, and histopathologically diagnosed at the Department of Veterinary Pathology, the University of Tokyo, between 2013 and 2015. DNAs from 21 samples were extracted with a Qiagen DNA FFPE Tissue kit. PCR assays were performed with two consensus primers that are commonly used to detect the DNA of papillomaviral ORF L1 and E1. Additionally, L1 gene based type specific primers for FcaPV type 2 (FcaPV-2), FcaPV-3 and FcaPV-4 were designed and used in this study.

Results

Three out of 21 tested samples were FcaPV positive using type specific primers designed in this study: One sample was positive for FcaPV-3, and two were positive for FcaPV-4. One FcaPV-4 positive sample could not be detected by the consensus primer sets. Sequence analysis revealed that in both of the two FcaPV-4 positive samples, 334th tryptophan in L1 ORF was deleted compared with the reference sequence.

Conclusions

This study suggests that FcaPV-3 and FcaPV-4 are associated with feline SCCs in Japan.
INHIBITORS OF BRD4 SUPPRESS HPV16 E6 EXPRESSION AND ENHANCE CHEMORESPONSE AGAINST CISPLATIN: A POTENTIAL NEW TARGET IN CERVICAL CANCER THERAPY?

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1University Hospital Tuebingen, Institute of Medical Virology, Tübingen, Germany

Background and Aims

Although a vast amount of research underlines the roles of the HR HPV E6 and E7 oncogenes in HPV-induced carcinogenesis of cervical cancer, it remains unclear whether these oncogenes are also involved in the resistance of the cancer against chemotherapy.

Methods

We examined the role of the HPV16 E6 oncogene in cisplatin resistance by analysing its expression in newly established cisplatin-sensitive versus -resistant cervical cancer cell lines (CC7, CC10). Resistant variants were obtained by interval exposure treatment with 1-2 µM cisplatin for 8-9 months.

Results

Our results demonstrate that the expression level of HPV16 E6 directly correlates with the extent of cisplatin resistance in novel as well as established (SiHa) drug resistant cervical cancer cell lines. Overexpression of HPV16 E6 in cisplatin-naïve cells rendered these cells more resistant to cisplatin. Reducing E6 expression by JQ1 treatment reversed the drug resistant phenotype and strongly enhanced chemoresponse only in HPV-positive cisplatin-resistant variants and not in HPV-negative C33A cervical cancer cells.

Conclusions

The level of E6 directly correlated with the extent of cisplatin sensitivity and was shown to be increased in newly established drug-resistant cell line variants, while reducing E6 expression using Brd4-inhibitors enhanced chemoresponse when co-delivered with cisplatin. Inhibition of Brd4 could represent a new therapeutic option by increasing treatment response in cervical cancer cells and might allow lower cisplatin dosages, thus reducing negative side effects.
Background and Aims

Human-derived specimens emerged as critical resources for basic and transitional research in gynecologic cancer which is critical in accelerating development of molecular-based diagnostics and therapeutics for precision medicine. Biobanking requires effective and efficient management of not only tissue sampling and storage, but also systematic management of bioinformatics and distribution of utilize high-quality research materials. We would like to introduce a biobank experience for biospecimen of common gynecologic cancer as well as HPV related disease.

Methods

Human-derived specimens and data stored in the bank target primary gynecologic cancer tissue, serum, plasma, urine, saliva, ascites and liquid-based cervical cytology sample for HPV related disease. Specimen extraction was administered starting from 2012, and it was administered before or during the treatment using the low-invasive method with the patients agreement.

Results

Currently, specimen and data in the bank numbers total of 53,462. Starting from May 2012 to Dec 2017, 18,766 serum, 14,243 plasma, 3,617 lymphocyte, whole 99 blood, 3,986 frozen tissue, 5,649 ascite, 36 HOSE, 3,545 urine, 350 saliva, 1,198 thin-prep, 440 cervicovaginal fluid, 8 TMA and 1,637 paraffin block units were stored.

Conclusions

Resources of gynecologic cancer bank is continuing to grow steadily since 2012, and quality resource is being developed through proper management. As such, these resources are utilized to publish a number of outstanding research papers. It is necessary to continue to acquire and manage resources continually to establish the mechanism and the treatment method of the gynecologic cancer that are not confirmed to this point.
Background and Aims

Human papillomavirus (HPV) vaccines are designed to prevent HPV infection and HPV-related diseases. Recent economic analyses have assessed the cost-effectiveness of HPV vaccination from a health care payer perspective excluding indirect costs. Indirect costs may include: loss of productivity at the workplace (i.e. presenteeism), absence due to employee’s disease (i.e. absenteeism), permanent disability and death. The aim of this study is to identify and summarize all available evidence on indirect costs related to HPV-associated diseases in males and females.

Methods

MEDLINE, EMBASE, Cochrane CENTRAL, EconLit and NHS EED were systematically searched for cost-analyses published in the last 10 years in English to identify lost work productivity costs due to HPV-associated diseases.

Results

Seventeen publications were identified that included indirect costs in patients with an HPV-associated disease. The indirect costs were calculated based on the number of workdays lost using a human capital or societal approach. The annual burden of these indirect costs has been evaluated in Germany, Sweden, Finland, Spain, Brazil, Malaysia and Korea for genital warts, cervical intraepithelial neoplasia, female cancers and male cancers (Table 1). Annual indirect costs per patient have been evaluated in US, Germany, Spain, Italy, Mozambique and Ethiopia (Table 2).
<table>
<thead>
<tr>
<th>HPV-associated disease</th>
<th>Country</th>
<th>Total indirect cost – lost workdays*</th>
<th>Year of currency</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital Warts</td>
<td>Korea</td>
<td>$2,608,318</td>
<td>2015</td>
<td>Park 2018</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>€13,114,200</td>
<td>2005</td>
<td>Castellsagre 2009</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>€547,701</td>
<td>2006</td>
<td>Herse 2011</td>
</tr>
<tr>
<td>CIN-1</td>
<td>Malaysia</td>
<td>MR128,310</td>
<td>2008</td>
<td>Aljunied 2010</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>€361,010</td>
<td>2006</td>
<td>Herse 2011</td>
</tr>
<tr>
<td>CIN-2</td>
<td>Finland</td>
<td>€462,208</td>
<td>2006</td>
<td>Herse 2011</td>
</tr>
<tr>
<td>CIN-3</td>
<td>Finland</td>
<td>€444,209</td>
<td>2006</td>
<td>Herse 2011</td>
</tr>
<tr>
<td>CIN-2/3</td>
<td>Malaysia</td>
<td>MR230,880</td>
<td>2006</td>
<td>Aljunied 2010</td>
</tr>
<tr>
<td>Precancerous lesions</td>
<td>Brazil</td>
<td>$39,988,278</td>
<td>2006</td>
<td>Novara 2015</td>
</tr>
<tr>
<td>CC</td>
<td>Sweden</td>
<td>€40,578,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td></td>
<td>Brazil</td>
<td>€7,051,158</td>
<td>2006</td>
<td>Novara 2015</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>€6,440,673</td>
<td>2006</td>
<td>Herse 2011</td>
</tr>
<tr>
<td></td>
<td>Malaysia</td>
<td>MR11,843,312</td>
<td>2008</td>
<td>Aljunied 2010</td>
</tr>
<tr>
<td>Precancerous lesions + CC</td>
<td>Sweden</td>
<td>€23,730,984</td>
<td>2009</td>
<td>Östernsson 2015</td>
</tr>
<tr>
<td></td>
<td>Malaysia</td>
<td>MR12,378,392</td>
<td>2008</td>
<td>Aljunied 2010</td>
</tr>
<tr>
<td>Vulva cancer</td>
<td>Sweden</td>
<td>€2,201,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td>Vagina cancer</td>
<td>Sweden</td>
<td>€2,222,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td>Anal cancer (Female)</td>
<td>Sweden</td>
<td>€4,596,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>€2,127,995</td>
<td>2008</td>
<td>Heitland 2013</td>
</tr>
<tr>
<td>Anal cancer (Male)</td>
<td>Sweden</td>
<td>€2,202,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>€2,152,109</td>
<td>2008</td>
<td>Heitland 2013</td>
</tr>
<tr>
<td>Tonsil Cancer (Female)</td>
<td>Sweden</td>
<td>€1,578,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td>Tonsil Cancer (Male)</td>
<td>Sweden</td>
<td>€5,321,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td>Base of tongue Cancer (Female)</td>
<td>Sweden</td>
<td>€838,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td>Base of tongue Cancer (Male)</td>
<td>Sweden</td>
<td>€1,570,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td>Penis Cancer</td>
<td>Sweden</td>
<td>€1,528,000</td>
<td>2006</td>
<td>Östernsson 2017</td>
</tr>
<tr>
<td>Head and Neck Cancer (Female)</td>
<td>Germany</td>
<td>€50,690,382</td>
<td>2008</td>
<td>Klussmann 2013</td>
</tr>
<tr>
<td>Head and Neck Cancer (Male)</td>
<td>Germany</td>
<td>€6,318,999</td>
<td>2008</td>
<td>Klussmann 2013</td>
</tr>
</tbody>
</table>

CC: cervical cancer, CIN: cervical intraepithelial neoplasia; HPV: human papillomavirus; MR: Malaysian ringgit

*Indirect costs of lost workdays can be caused by: sick leave, sickness allowances, mortality, disability pensions granted, medical procedures, visits, early retirement, travel time to and from care site, wait time. This differs per study.
Table 2: Annual work productivity loss costs per HPV-associated disease and country - per patient

<table>
<thead>
<tr>
<th>HPV-associated disease</th>
<th>Country</th>
<th>Total indirect cost – lost workdays*</th>
<th>Year of currency</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital Warts</td>
<td>Spain</td>
<td>€ 232</td>
<td>2005</td>
<td>Castellsague 2009</td>
</tr>
<tr>
<td>Genital Warts (female)</td>
<td>Spain</td>
<td>€ 269</td>
<td>2005</td>
<td>Castellsague 2009</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>€ 132</td>
<td>2005</td>
<td>Merito 2008</td>
</tr>
<tr>
<td>Recurrent case</td>
<td>Germany</td>
<td>€ 142</td>
<td>2005</td>
<td>Hillemans 2008</td>
</tr>
<tr>
<td>Resistant case</td>
<td>Germany</td>
<td>€ 232</td>
<td>2005</td>
<td>Hillemans 2008</td>
</tr>
<tr>
<td>Genital Warts (male)</td>
<td>Spain</td>
<td>€ 204</td>
<td>2005</td>
<td>Castellsague 2009</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>€ 82</td>
<td>2005</td>
<td>Merito 2008</td>
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<tr>
<td>Recurrent case</td>
<td>Germany</td>
<td>€ 116</td>
<td>2005</td>
<td>Hillemans 2008</td>
</tr>
<tr>
<td>Resistant case</td>
<td>Germany</td>
<td>€ 204</td>
<td>2005</td>
<td>Hillemans 2008</td>
</tr>
<tr>
<td>LSIL</td>
<td>Germany</td>
<td>€ 442</td>
<td>2005</td>
<td>Petry 2008</td>
</tr>
<tr>
<td>HSIL</td>
<td>Germany</td>
<td>€ 430</td>
<td>2005</td>
<td>Petry 2008</td>
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<tr>
<td>Carcinoma in situ</td>
<td>Germany</td>
<td>€ 1,293</td>
<td>2005</td>
<td>Petry 2008</td>
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<td>VaIN 2/3</td>
<td>Germany</td>
<td>€ 928</td>
<td>2007</td>
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<td>Cervical lesions</td>
<td>US</td>
<td>$2,990</td>
<td>2008</td>
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<td>Cervical Cancer</td>
<td>Mozambique</td>
<td>$2,296</td>
<td>2015</td>
<td>Haidari 2017</td>
</tr>
<tr>
<td></td>
<td>Ethiopia</td>
<td>Birr 3,000</td>
<td>2011</td>
<td>Hailu 2013</td>
</tr>
</tbody>
</table>

HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion (Pap IVb); LSIL: low-grade squamous intraepithelial lesion (Pap III); US: United States; VaIN: vaginal intraepithelial neoplasia

*Indirect costs of lost workdays can be caused by: sick leave, visits for diagnostic purposes in association with surgical interventions, productivity loss, mortality, travel time to outpatient visits/inpatients hospital stay, time foregone in seeking care. This differs per study.

Conclusions

This study shows the published indirect costs due to lost workdays related to HPV-associated diseases. These indirect costs are substantial and must be accounted for in HPV economic models to show a complete and valid cost-effectiveness assessment.
Background and Aims

Human papillomavirus (HPV) infection is cause of various diseases including cancer. In several studies, HPV DNA was detected also in non-small cell lung cancer (NSCLC) patients. Nevertheless, the significance of HPV infection in NSCLC remains unclear. The aim of this study was to determine the HPV prevalence in Czech NSCLC patients and its potential clinical significance.

Methods

A cohort of 80 primary NSCLC patients was selected. DNA was isolated from both formalin-fixed paraffin-embedded tissue (FFPE) as well as fresh frozen (FF) tissue samples of each patient. All samples were tested for KRAS, EGFR and BRAF mutations. The presence of HPV16, 18, 31 and 56 E2 and E6 DNA was tested by quantitative multiplex real-time polymerase chain reaction (qPCR).

Results

The qPCR limit of detection (LOD) was determined to four HPV copies/reaction using dilution series of HPV plasmids DNA. Sensitivity and specificity was evaluated using 402 DNA samples isolated from cervical/cervicovaginal swabs. qPCR, cobas® 4800 HPV Test (Roche Diagnostics GmbH) and PapilloCheck® HPV-Screening (Greiner Bio-One) were tested in parallel. Sensitivity and specificity of the method were 0.756-0.993 and 0.639-1.000, respectively. Finally, despite very low LOD, no HPV positivity was found in FFPE as well as FF NSCLC samples in our study cohort.

Conclusions

In conclusion, our finding did not confirm any etiologic correlation between HPV16, 18, 31 and 56 and primary NSCLC in the Czech population.

This work was financially supported by NPU LO1304, TE02000058 and EATRIS-CZ.
CYTOKERATIN7 EXPRESSION IN HISTOLOGIC AND CYTOLOGIC SPECIMENS OF CYSTIC NECK METASTASIS FROM HPV POSITIVE SQUAMOUS CELL CARCINOMA OF THE TONSIL: A CASE REPORT
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2Gachon University Gil Medical Center, Internal Medicine, Incheon, Republic of Korea
Background and Aims

The majority of cystic squamous cell carcinomas (SCCs) of the neck have been shown to be metastatic tumors from tonsillar SCCs associated with high-risk human papillomavirus (HR HPV). Recent studies have demonstrated cytokeratin (CK)7 involvement in the development of HPV positive SCC, but no report has been issued on its simultaneous expression in primary tonsillar and metastatic tumor with cystic change.

Methods

We present a case of HPV positive tonsillar SCC of a 42-year-old male that initially manifested as a cystic neck mass expressing CK7, CK19, and p16 in primary and metastatic tumors.

Results

Immunohistochemical examination revealed diffuse CK19 and p16 expression, and patchy CK7 expression in the solid components of primary and metastatic tumors. However, in cystic components of metastatic tumors the expression of CK7 and CK19 was preserved but p16 expression was absent, which was consistent with immunocytochemical findings of fine-needle aspirates from cystic neck mass. In immunocytochemistry performed on aspirates of a branchial cleft cyst for the comparison of cystic SCC and benign cyst, CK19 staining was positive but CK7 and p16 staining was negative.

Conclusions

These results suggest that CK7 immunocytochemistry on aspirated material from cystic neck mass may be a useful adjunct for distinguishing cystic metastasis of tonsillar SCC from branchial cleft cyst, although a larger scale study would be required.
HPV16 VIRAL CHARACTERISTICS IN PRIMARY AND RECURRENT VULVAR CARCINOMA
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¹Faculty of Medicine and Health- Örebro University, Dep. of Laboratory Medicine, Örebro, Sweden
²Faculty of Medicine and Health- Örebro University, Dep. Of Oncology, Örebro, Sweden

Background and Aims

In vulvar carcinoma, two separate carcinogenic pathways are suggested; one associated with human papillomavirus (HPV) and HPV16 the most common genotype. Prognostic factors include tumor size, recurrences and lymph node spread. The prognostic role of HPV in primary vulvar cancer is to some extent investigated but less in known about viral spread and impact in recurrent disease.

The aim of this study was to evaluate HPV markers in sets of primary tumors and recurrent disease and to follow viral occurrence and levels of the viral characteristics. In addition, to evaluate if any of the viral characteristics provide advantages for spread or recurrences.

Methods

A cohort of ten HPV16-positive vulvar squamous cell carcinomas with regional, distant spread and/or recurrences were investigated for HPV genotype, HPV16 variant, HPV16 viral load, HPV16 integration(E1/E6, E2/E6) and HPV16 E2BS3 and 4 methylation. Digital droplet PCR assay for E1/E6 and E2/E6 was developed.

Results

In all 10 case series, HPV genotype and variant of HPV16 variant was identical in primary tumor and corresponding regional, distant and recurrent lesions. Viral load in regional lymph nodes were significantly lower compared to primary vulvar samples (Related-samples Wilcoxon signed rank test; p=0.043) while other investigated viral characteristics varied inconsistently between lesion and point in time. Fewer recurrences were found in cases where primary tumors showed a high E2/E6 integration ratio (Mann-Whitney U-test; p= 0.056).

Conclusions

This study shows that for HPV positive vulvar carcinoma, the virus is consistently found in recurrent lesions but levels of viral characteristics is subject of change.
Molecular detection and genetic evolutionary by nucleotide similarities of animal papillomavirus types to their closest related HPV sequences deposited in Gen Bank.

Background and Aims

Papillomaviruses (PV) are classified in the *Papillomaviridae* family presenting 39 genera, 62 species and 69 known animal papillomaviruses with high genetic variability described specially in *Alphapapillomavirus* genus. The present molecular study described nucleotide sequence similarity of human and animal papillomavirus types.

Methods

DNA extractions from blood and tissues of wild and domestic animals were performed. Genomic DNA was performed by β-globin gene using the primers GH20/PC04 that amplify 268bp. Partial amplification of L1 open reading frame was performed by PCR with MY09/MY11 oligonucleotides and degenerated primers FAP59/FAP64, designed by Swedish human tumor samples amplifying a 478bp fragment able to detect cutaneous tumors of HPV types and normal skin samples. Furthermore, this study describes morphological alterations inside warts-like samples and the SiHa (HPV-16) and HeLa (HPV-18) cell lines (3x10⁶ cells) as positives controls and as possible markers of cervical cancer by electron microscopy. The amplified products were purified by GFX PCR DNA purification kit and sequenced by the BigDye® protocol. The quality of the sequences obtained was evaluated by Chromas program and Biological Sequence Alignment Editor. The sequences were compared with available sequences of the Gen Bank database using Basic Local Alignment Search Tool program.

Results

PV DNA bands from biological samples were detected. Virus-like particles were detected morphologically. Putative new types of papillomavirus were isolated by phylogenetic analysis.

Conclusions

Nucleotide sequence similarities of animal papillomavirus types to their closest related PV types and HPV sequences deposited in Gen Bank were reported suggesting that the sequences share the same ancestry of the genetic evolutionary.
TYPESEQER2: A NOVEL LOW COST, HIGH THROUGHPUT NEXT GENERATION SEQUENCING HPV GENOTYPING ASSAY

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Background and Aims

Recently we developed a low cost, high throughput HPV genotyping assay to facilitate studies of HPV natural history, screening and vaccination. We are now developing an improved version with faster processing times and additional features, capable of concomitant detection of 42 HPV types.

Methods

HPV Genotyping detection was based on a novel single-step PCR followed by NGS. Type-specific primers with linker sequences were designed for amplification of 42 HPV types and a human control gene. Amplification of HPV targets followed by addition of sequencing adapters and barcodes occurred within a single PCR. Amplicons were sequenced on the ThermoFisher Ion S5. Analysis of lineage-specific genomic sites allowed for classification of 13 High Risk (HR) types by variant lineage. After successful evaluation of the assay in 77 pilot samples, we will evaluate it in 1200 clinical specimens previously genotyped with our version 1 genotyping assay.

Results

To date we have developed the workflow for 26 of the 42 targets and tested performance on 77 previously genotyped clinical samples, 13 of which were HR-HPV negative by both assays. Positive agreement was 96.9% for HR-HPV, and 86% for HPV16. Of the HPV positive samples, 65% showed perfect concordance, and 23% had one type difference. Estimated throughput is 768 samples per 1.5 days, with a 75% reduction in processing time compared with version 1. Reagent costs are approximately US$5 per sample.

Conclusions

We have developed a novel low cost and streamlined genotyping assay capable of detection of 42 HPV types.
THE AGE OF CERVICAL CANCER SCREENING IN BANGLADESH: ISSUES IN CONCERN.
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Background and Aims

Bangladesh adopted VIA as a method of cervical cancer screening since 2005. Cervical cancer screening begins at the age of 30. 40% of Bangladeshi women are under 30, 94% of them are married. Invasive cancer are <1% in this age group, but total 2,87,847.74 female may have invasive cancer as they are not within screening group. Issues in concern are starting age of cervical cancer screening, methods of screening, compliance with the method, detection of the disease in pre invasive state. The aim of this study is to include women under 30 years of age within screening program, also to detect the disease in pre invasive state.

Methods

This prospective cohort study included 30 cases new cervical cancer patients under 30 years from 1200 new cervical cancer patients attended at National Institute of Cancer Research and Hospital, Bangladesh from June 2014-2016. Age of marriage, parity, oral contraceptive use, stage of the disease, treatment and overall survival were studied. These patients were on follow up for 30 months.

Results

The percentage of cervical cancer was 2.5% under 30 years. Among the cases 70% were inoperable stage and 17% died 12 months after diagnosis. 37% were unavailable for follow up. Mean survival was 11 month. Only 17% of patients got standard of care.

Conclusions

Cervical cancer screening under 30 years of age would pick up significant number of patient in pre invasive curable state and decrease morbidity. Screening young women provides opportunity for health education and could reduce psychological burden of screen positivity.
Background and Aims

Large loop electrosurgical excision of the transformation zone (LLETZ) can effectively prevent progression of cervical high-grade squamous intraepithelial lesions (HSIL) to invasive cancer. The aim was to evaluate the appropriateness of treating women with HSIL+ on conventional cytology and high-grade colposcopy without histology confirmation in opportunistic cervical cancer screening settings of Latin America.

Methods

This is a nested analysis within the ESTAMPA study (NCT01881659). Briefly, 30-64 years old women from well-defined catchment areas in nine Latin American countries are referred to colposcopy if HPV positive or abnormal cytology. To minimize the number of untreated women we offered immediate treatment at colposcopy to women with HSIL+ cytology and high-grade colposcopy impression, without histologic confirmation. We were interested in confirming that most of these women actually had HSIL that required treatment. The main outcome was cervical intraepithelial neoplasia grade 2 or worse (CIN2+) locally reported on LLETZ specimens.

Results

Between May, 2013 and March, 2018, n=19,119 of the n=26,544 recruited women (72%) were screened with cytology, and 8% had abnormal results (1.9% unsatisfactory, 4.6% low-grade squamous intraepithelial lesion – LSIL – or less, and 1.5% HSIL+). Among the n=290 women with HSIL+, n=77 (27%) had a high-grade colposcopic impression and 26 were treated with LLETZ without histological confirmation. Of these, 73% (95%CI 54-86) had CIN2+.

Conclusions

HSIL+ cytology and LLETZ specimens' histology were highly correlated (79%) among women where the colposcopic impression was also high-grade. It appears that in this group of women, the majority of women had disease that needed to be treated.
Background and Aims

The optimal cervical cancer screening algorithm may differ in populations with limited resources and a high burden of HIV co-infection when compared to other health care systems. HIV co-infection leads to higher rates of HPV infection and cytological abnormalities. The study aims to test performance of various screening and triage tests in a South African setting to aid in the development of a relevant screening strategy informed by local data.

Methods

This a preliminary report on the first 300 women, unscreened in the last five years, comparing rates of abnormalities between HIV negative and positive women using cytology, immunocytochemistry, HRHPV testing with partial genotyping and VIA/VILI.

Results

124/300 (41%) women were HIV positive and the majority (92%) were on anti-retroviral therapy. Using ASCUS as threshold, HIV positive women had higher abnormal cytology results (19% vs 11%). The rate of HSIL was 4.8% and 0.6% in HIV positive and negative women respectively. More HIV infected women had positive screen with VIA (19% vs 7%) and VILI (27% vs 13%). Overall the rate of hrHPV detection in cytology positive women was 71% and 24% had types 16 and/or 18. Overall the rate of abnormal cytology in women who tested hrHPV positive was 32%. Immunocytochemistry with p16/Ki-67 double stain was positive in 69% of samples with positive cytology.

Conclusions

Population specific data is essential when designing optimal screen and triage algorithms. In high HIV prevalence areas, optimal combinations of screen and triage tests must be adequately specific to identify those at highest risk for disease.
DNA methylation as a biomarker for predicting response to chemotherapy in colorectal cancer

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Background and Aims

Colorectal cancer is the third most common cancer worldwide, with an estimated 1.7 million new cases diagnosed annually. The 5-year survival rate for colorectal cancer is approximately 65%, with younger patients having a poorer prognosis. Methylation of DNA cytosine-phosphate-guanine (CpG) islands is a common epigenetic alteration that can lead to gene silencing. This study aimed to investigate the relationship between DNA methylation and response to chemotherapy in colorectal cancer.

Methods

DNA methylation analysis was performed using bisulfite sequencing on tumor samples from 100 patients with colorectal cancer. The patients were classified as responders or non-responders based on their clinical outcomes. The DNA methylation status of 20 genes was analyzed, and the association between DNA methylation and clinical outcome was assessed using logistic regression.

Results

The results showed that DNA methylation of the MGMT gene was significantly associated with chemotherapy response. Patients with higher DNA methylation of the MGMT gene had a higher likelihood of response to chemotherapy. Additionally, DNA methylation of the RASSF1A gene was associated with non-response to chemotherapy.

Conclusions

DNA methylation analysis can be used as a biomarker to predict response to chemotherapy in colorectal cancer. Patients with higher DNA methylation of the MGMT gene are more likely to respond to chemotherapy, while those with higher DNA methylation of the RASSF1A gene are more likely to be non-responders. These findings could potentially be used to tailor chemotherapy regimens to individual patients, improving treatment outcomes.
HPV primary screening is the goal of cervical screening programmes in developed countries. In Malawi visual inspection with acetic acid (VIA) is recommended, but interest in HPV testing is increasing. Choice of HPV test is a difficult issue for LMIC, with specific practical implications rarely considered adequately.

**Aim:** To assess validity of a quality-assured HPV test to complement a same day ‘screen and treat’ [SAT] programme.

**Methods**

Liquid-based specimens from women attending routine screening in Central Malawi were tested using Cepheid Xpert® HPV, with varying collection media, regular IQC and reproducibility studies. Results were linked to clinic findings.

**Results**

More than 2000 Xpert® HPV have now been performed with HR-HPV prevalence remaining ~20% and HPV31+ more prevalent than HPV16/18/45 [Cubie et al. IPV 2017]. Self-collected specimens showed slightly higher prevalence but comparable HR-HPV types. Inter-laboratory reproducibility of 473 specimens gave 93% agreement when specimens with initial invalid results were re-tested and included. HPV results from 905 women with matched clinical outcomes showed 20.2% to be VIA+ and eligible for same day treatment and a further 17.3% to have lesions suspicious of cancer. VIA screening also designated significant numbers of HPV- specimens as VIA+/suspicious cancers. These findings require further investigation.

**Conclusions**

Xpert® HPV is straightforward to use with rapid turnaround and good reproducibility, suitable as a near-patient test in SAT programmes. More work is required in LMIC to demonstrate cost and clinical effectiveness, while VIA may be valuable beyond cervical screening in LMIC by providing a unique opportunity for gynaecology examination.
LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCREENING FOR HPV RELATED DISEASE SCREENING: IMPLEMENTATION, EVALUATION AND IMPACT

ONE-YEAR FOLLOW-UP RESULTS FROM A RAPID HPV TESTING STUDY IN AN EXISTING SEE-AND-TREAT CERVICAL SCREENING PROGRAMME IN TANZANIA (AISHA)


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8Ocean Road Cancer Institute, Director, Dar es Salaam, Tanzania

Background and Aims

To report 1 year follow-up results in women who were screened with visual inspection with acetic acid (VIA) and HPV testing in an operational cervical screening study in Tanzania.

Methods

A total of 1,246 women age 30-50 had valid VIA (6.2% pos) and rapid HPV (24.1% pos, careHPV®) screening results across 6 screening clinics from Dar es Salaam (D) and Kilimanjaro (K) region. VIA-positive women received cryotherapy immediately or were referred if cryotherapy was not available on-site. VIA-negative/HPV-positive women were recalled and treated if positive for a second VIA2 examination. Women positive for any screening test were recalled by telephone for a 1-year follow-up visit and all received colposcopy and biopsy if indicated.

Results

Among the 413 women needing a 1-year visit, only 247 attended (38% in D and 49% in K). The main reasons for non-attendance in D and K, respectively, were: phone not reachable (28% and 47%); did not attend the given appointment (19% and 1%); and moved since screening visit (12% and 0%). Follow-up biopsy results were 9 normal; 8 CIN1 and 2 invasive cervical cancer (ICC), both VIA- and HPV-positive at follow-up although none showed signs of invasive disease during the screening round; 1 had received cryotherapy and 1 LEEP (CIN1 histology) at the screening round.

Conclusions

Only one third to half of screened women could be followed-up after 1 year in our setting mainly due to unreachable telephone numbers. Except for 2 ICC, we did not detect any other high grade cervical disease among the women followed-up.
Background and Aims

The World Health Organization (WHO) recommends screen-and-treat algorithms with HPV-testing as the preferred primary cervical cancer screening test for low- and middle-income countries (LMIC), with or without visual inspection with acetic acid (VIA) or other molecular triage tests before ablative treatment. However, evidence on VIA as triage is scanty and it is not yet clear whether the benefit of combining HPV testing with VIA triage (increasing specificity and decreasing overtreatment) will outweigh the drawback of this algorithm (decreasing sensitivity).

Methods

The CESTA study will recruit 6,000 women to evaluate the benefits, side-effects and cost-effectiveness of 2 main screen and treat algorithms: (i) Screening by HPV test and VIA triage of HPV-positive women followed by ablative treatment; and (ii) screening by HPV test alone (modelling). Treatment will be randomized into cryotherapy and thermal ablation in order to compare side-effects, safety and acceptability. In addition, E6/E7 oncoproteine test will be assessed as an objective molecular triage method and cervical samples will be stored for future analysis of other molecular methods.

In a phase 2, implementation studies will be carried out on the impact on feasibility and cost-effectiveness of different programme approaches: (i) self-collection versus clinician-collection HPV sample; (ii) Point of care HPV testing versus non POC HPV testing; (iii) HPV+VIA+treat versus HPV+treat strategies.

Results

A pilot study in 350 women has been conducted in Durban, South Africa and 1 is planned in Dakar, Senegal.

Conclusions

We need better insight in how to implement cost-effective screen-and-treat algorithms using HPV-testing and cervical ablation in LMIC.
IMPLEMENTING HPV SELF-COLLECTION AT COMMUNITY LEVEL IN RURAL BOTSWANA
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Background and Aims
Botswana faces challenges of access to health care with the third highest HIV prevalence globally at 21.9% among 15 – 49 year olds (UNAIDS, 2016), and cervical cancer as the leading cause of cancer and related deaths. Cytology and visual inspection with acetic acid for cervical cancer screening are offered for free but coverage remains low. HPV self-collection is expected to improve coverage.

Methods
A mixed methods prospective cohort study of women aged 30–49 with no recent or previous cervical cancer screening participated in HPV self-collection, from 4 Kweneng District clinics; 2 had a community component; Thamaga and Lephepe. Samples were routed through the subnational lab or directly to a hospital where the Cepheid GeneXpert® platform was used to test for high-risk HPV and treatment offered to all HPV positives. CommCare® mobile data collection platform was used for client follow-up and tracking results.

Results
412 women were enrolled from the 2 sites; 206 (60%) were recruited from market and work places, school events or health posts. 128 (51.6%) recruited at community were HIV positive. 77 (31%) tested HPV positive. 211 (85%) were notified of their results within 1-week and 242 (97.6%) within 3 weeks. 71 (92%) HPV positives were assessed for treatment; 41 (58%) within 3-weeks of result notification. 67 (87%) have completed treatment; 63 (94%) cryotherapy and 4 (6%) LEEP.

Conclusions
Community based HPV self-collection is feasible if integrated into existing district structures. Electronic data system and phone calls optimized client follow-up. Decentralizing testing sites support faster results' notification and access treatment.
DETECTION OF HIGH RISK HPV AMONG HIV-INFECTED AND HIV-UNINFECTED WOMEN UNDERGOING CRYOTHERAPY OR LOOP ELECTROSURGICAL EXCISION PROCEDURE (LEEP)

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Background and Aims

Cervical cancer is a common malignancy among Kenyan women, and is more in HIV-infected women. This 36 month long longitudinal study was done to assess risk factors associated with treatment failure among HIV-infected/uninfected women undergoing cryotherapy or LEEP.

Methods

157 women with an abnormal VIA were enrolled in Eldoret, Kenya. The decision to treat with cryotherapy or LEEP was made based on the extent of the lesion. Women ineligible for cryotherapy underwent colposcopy and biopsy. Those with CIN2 or worse lesions underwent LEEP. HPV typing was performed on cervical swabs using the Roche Linear Array.

Results

Of 157 participants, 73 (46.5%) were HIV-infected, 84 (53.5%) were HIV-uninfected. HIV-infected women were older than HIV-uninfected women (38.7 years vs. 33.5 years, p<.001). Forty nine (67.1%) of the HIV-infected women were receiving ART; median duration between HIV diagnosis and enrollment was 6.2 years (IQR 4.5, 10.1); median CD4 count (available for 48) was 561.5 cells per mL (IQR 344.5, 735.5). HIV-infected women were less likely to be eligible for cryotherapy than HIV-uninfected women (32.9% vs. 51.2%, p=.024). Cryotherapy was performed on 37 HIV-infected and 60 HIV-uninfected women. LEEP was performed on 60 HIV-infected and 60 HIV-uninfected women.
HPV analysis of cervical swabs has been completed for 115 women (Table 1).

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>HIV-infected (n=49)</th>
<th>HIV-uninfected (n=66)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any HPV (%)</td>
<td>75.5</td>
<td>53.0</td>
<td>.019</td>
</tr>
<tr>
<td>Any HR-HPV(^1) (%)</td>
<td>67.3</td>
<td>47.0</td>
<td>.037</td>
</tr>
<tr>
<td>IARC HR-HPV(^2) (%)</td>
<td>61.2</td>
<td>39.4</td>
<td>.024</td>
</tr>
<tr>
<td>Nine-valent HR-HPV vaccine types(^3) (%)</td>
<td>40.8</td>
<td>30.3</td>
<td>.322</td>
</tr>
<tr>
<td>HPV 16 (%)</td>
<td>20.4</td>
<td>12.1</td>
<td>.300</td>
</tr>
<tr>
<td>Number of HR-HPV types (mean)</td>
<td>1.4</td>
<td>0.8</td>
<td>.017</td>
</tr>
</tbody>
</table>

\(^1\) Oncogenic ("High-Risk"): HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

\(^2\) HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66

\(^3\) HPV 16, 18, 31, 33, 45, 52, 58

Conclusions

In this study of Kenyan women with abnormal VIA at enrollment, HIV-infected participants were less likely to be eligible for cryotherapy than HIV-uninfected women. HIV-infected women were more likely than HIV-uninfected women to have detection of oncogenic HPV types and multiple oncogenic HPV types.
Background and Aims

Since the release of the 2013 guidelines for cervical cancer screening by the World Health Organization (WHO), a screen-and-treat strategy with HPV testing is being considered for primary screening in limited-resource settings.

Methods

In 2016, nurses from the Women’s Health Program (WHP) of the Cameroon Baptist Convention Health Services (CBCHS) educated approximately 3,000 women in villages on cervical cancer prevention. At a follow-up visit, they explained to non-pregnant women aged 30-65 how to self-collect vaginal specimens for careHPV testing in their local dialect. The cytobrush specimens were transported in coolers to a CBCHS laboratory. The nurses returned to villages to inform women of their results, examined HPV positive women in the primary health center using visual inspection with acetic acid and Lugol’s iodine (VIA/VILI) to guide treatment. Thermal coagulation was offered to all HPV positive patients, except those with LEEP-eligible lesions or with lesions suspicious for cancer, who were referred for appropriate treatment.

Results

Of the 1,351 women screened by careHPV, 208 (15.4%) were HPV-positive. Up to 165 HPV-positive women (79.3%) were examined, and 17 (10.3%) were VIA/VILI positive. Treatment consisted of thermo-coagulation in 163, LEEP in one woman, and hysterectomy in one woman for ICC (79.3% treatment rate). The cytobrushes broke off in the vagina of two women (removed in the village) and in the bladder of another (surgically removed).

Conclusions

Screening for cervical cancer with self-collected HPV tests is feasible in rural areas of Cameroon. Education on the proper sampling procedure and follow-up of women who are HPV positive are essential.
IPVC8-0396
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCREENING FOR HPV RELATED DISEASE SCREENING: IMPLEMENTATION, EVALUATION AND IMPACT

A SYSTEMS PRACTICE APPROACH TO SUSTAINABLE IMPLEMENTATION OF HPV-BASED SCREENING IN THE PERUVIAN AMAZON

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Background and Aims

Improving screening program effectiveness in LMICs has great potential for reducing the global cervical cancer burden over the next 20-30 years. While implementation of new technologies such as HPV molecular testing is likely to increase the efficacy of screening, sustainable program effectiveness will require simultaneous strengthening of health systems and adaptation of screening delivery to the local context.

Methods

We have applied a Systems Practice Framework (SPF) to the development of HPV and/or VIA-based screening programs, adapted to the Micro Red Sur health network in the Peruvian Amazon. The SPF is a participatory, iterative process involving system understanding, finding/acting on leverage opportunities, and learning/adapting through post-implementation monitoring and evaluation of the intervention. Triangulation of qualitative and quantitative data facilitates development of a visual screening landscape map which traces patients/data/specimens through the actual continuum-of-care.

Results

By applying the SPF, we engaged more than 90 multi-level stakeholders, revealing fragmentation, redundancy, and inefficiency in the system. Dialectic discussions with a broad spectrum of stakeholders (including review of the landscape map and evidence-based knowledge transfer) identified the following leverage points: increase screening coverage, reduce loss-to-follow-up, and implement an electronic registry. System-wide comparison of alternative strategies led to consensus recommendation to adopt HPV testing/self-sampling to increase coverage and to offer ablative treatment of all HPV-positive women in lieu of colposcopic referral to increase completion of continuum-of-care.

Conclusions

Application of a participatory Systems Practice Framework to design context-adapted screening implementation plans may lead to better acceptability, adoption, and sustainability of screening interventions in LMIC compared with ‘top-down’ approaches.
Background and Aims

Simple, accessible evidence-based tools that consider the trade-offs associated with operational feasibility and screening test performance are needed to guide development of cervical cancer screening delivery strategies that are sustainable in local contexts.

Methods

An Excel-based tool was developed with the following operational and performance input metrics: total population size, screening interval, and estimated CIN3+ prevalence; screening coverage, diagnostic triage coverage, treatment coverage; and screening/diagnostic test sensitivity/specificity. The program output reflects these system impacts: number of women screened/referred/treated, leverage points to further improve system effectiveness (i.e. point in the system where the most precancers being missed), and overall impact (percent precancers identified/treated/overtreated). Outputs facilitated screening system operational design discussions with key stakeholders in two different LMIC contexts in El Salvador and Peru.

Results

In both contexts, current screening was based on Pap cytology with colposcopic referral, with poor participation observed across the entire continuum-of-care. In facilitated group exercises, stakeholder teams used the GSSA to compare various VIA- or HPV-based adaptations to current screening across several Implementation Outcome domains including feasibility, cost, acceptability, fidelity, and sustainability, in addition to test performance. HPV-based scenarios were considered to have the highest potential to increase coverage (reach) and test sensitivity. Because of the higher referral burden in this scenario, direct ablative treatment at the primary level was preferred over tertiary colposcopic referral to improve completion of continuum-of-care.

Conclusions

The GSSA tool can provide a useful visual tool for planners to weigh implementation trade-offs against test performance to select the most appropriate screening strategy for their context.
Since 2014, PATH has provided technical assistance to three Central American governments to introduce and scale up HPV DNA testing for cervical cancer screening within their public health systems. We encouraged governments to use self-sampling as a routine strategy for both community-based and clinic-based screening. Nicaragua and Guatemala chose self-sampling as a primary strategy upon test introduction in 2015; Honduras initially used a clinician collection strategy but incorporated self-sampling at selected sites in 2017. We hypothesized that self-sampling would be highly acceptable and overcome infrastructure barriers, encouraging uptake. Our aim was to use program indicators to describe uptake of self-sampling and use of HPV testing by under-screened and never-screened women.

Methods

Ministries of Health collected indicators from HPV-screened women on sampling modality and time elapsed since previous screening. Countries reported consolidated indicators to PATH for analysis.

Results

From 2015 to 2017, 199,506 women were screened with HPV tests in these three countries. Preliminary findings indicate that in Nicaragua and Guatemala, 95.2% and 91.5% of women, respectively, elected self-sampling; 46.7% and 27.6% of women, respectively, had never been screened before; and an additional 13.1% and 30.1%, respectively, had a previous screening test three years ago or more. In communities in Honduras where self-sampling was offered in 2017, 74.2% elected this modality.

Conclusions

As low- and middle-income countries adopt HPV testing for cervical cancer screening, self-sampling can be an effective strategy for encouraging uptake and reaching under-screened women. Other countries can learn from the Central American experience.
LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCREENING FOR HPV RELATED DISEASE SCREENING: IMPLEMENTATION, EVALUATION AND IMPACT

KENYA SELF HPV SAMPLING COMPARED TO PROVIDER OBTAINED SAMPLES FOR CERVIX CANCER SCREENING IN BOTH HIV AFFECTED AND UNAFFECTED WOMEN IN WESTERN KENYA

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Background and Aims

This study was done in western Kenya to demonstrate that rural women can collect samples that can help in the detection of high risk HPV

AIM: Determine the ability of women in western Kenya to collect vaginal-cervical samples useful in screening for high risk HPV using Xpert HPV assay testing.

Methods

A cross sectional study was conducted in cervical cancer screening clinics where clients were counselled and consented. Then they were instructed on self-collection and the clinician collected a cervical swab thereafter before VIA was done. The self collected sample and clinician collected sample were subjected to Xpert HPV assay testing for high risk HPV DNA.

Results

A total of 361 women participated in the study with an average age of 36 years. Half were HIV affected.

164 (47.0%) of self collected samples were HPV positive and 124 (36.2%) provider collected samples were positive. 178 women had a high risk HPV test from one of the methods of collection. When self collected samples were positive, 54/160 (33.7%) provider collected samples were negative for Hr HPV. When provider samples were positive 18/124 (14.5%) self collected samples were negative. There was no difference in rates of missed HPV in HIV affected and unaffected women. When VIA was compared to HPV testing as many as 90% of these women had a negative VIA when their HPV testing was positive

Conclusions

More high risk HPV was detected through self sampling than provider sampling

False negative test in higher in the provider collected group

Negative VIA does not predict for HPV status
Background and Aims

Introduction: Cervical cancer, ranked as the most frequent cancer in women in India, still remains a leading cause of cancer deaths because of high HPV infection rates and lack of comprehensive cervical Pap smear testing of susceptible women.

Objectives: To assess prevalence of Reproductive tract symptoms and infections (RTI) among the women attending the camp

To assess Pap smear findings among these women and sensitivity and specificity of Visual Inspection with Acetic acid (VIA) using PAP as gold standard

Methods

Methods: A camp based cross sectional study was done in Chirakkal village of Kerala, India to assess reproductive tract symptoms, diseases, Pap smear and VIA findings. Quantitative data was collected using a pre tested questionnaire, per vaginal examination, Pap smear and VIA test done. Analysis was done with descriptive statistics using epi info.

Results

Results: Ninety nine women attended the camp. Age of the women ranged from 21 to 70 years and 98 women were ever married. Twenty four women had RTI symptoms like discharge PV, post-menopausal bleed, dyspareunia and mass PV. Salient PV findings were bulky vagina which bled on touch, thick white discharge, cystocele. Pap results showed high grade intra epithelial lesion in one woman and inflammation with atypical cells in 7 women. There were 34 positive VIA findings and the sensitivity and specificity of VIA when compared to Pap smear was 63% and 68% respectively.

Conclusions

Low cost and easy techniques need to be used to screen women for cervical cancer to ensure more attendance in screening camps
Background and Aims

There is considerable heterogeneity in rates of cervical cancer within China, particularly between urban and rural regions. Whereas a new screening initiative has recruited upwards of 20 million rural women, there is no organised screening for urban settings. We aimed to evaluate effectiveness and cost-effectiveness of screening in urban China, using Shenzhen City as an example.

Methods

We use an extensively validated platform (‘Policy1-Cervix’) to evaluate a range of strategies that have been implemented as pilot studies, recommended as guidelines within China, and articulated in resource-stratified guidelines from the American Society of Clinical Oncology. We simulated primary HPV, cytology and co-testing strategies, considering alternate triaging, age-ranges and screening intervals.

Results

Of the 19 strategies considered, the most effective involved 3- to 10-yearly primary HPV testing (reducing age-standardised cancer mortality by 37-70%). The most cost-effective strategy involved 5-yearly primary HPV testing with partial genotyping triage for ages 25-65, discharged to 10-yearly screening for low-risk women, i.e. after 2 consecutive negative routine tests (ICER = $5464/LYS or $5372/QALY; willingness-to-pay threshold<1xGDP [$8123]). It gave a mortality reduction of 62% and a number-needed-to-treat per cervical cancer death prevented (NNT) of 12. Starting from this strategy, mortality reduction was still 62% if partial genotyping was replaced with cytology triage, 64% if the 5-yearly interval continued for low-risk women, and 60% if the start-age increased to 30. Each of these changes gave similar NNTs (10-12).

Conclusions

The most cost-effective strategy for urban China is 5-yearly primary HPV testing with partial genotyping triage for ages 25-65 (10-yearly for low-risk women).
Profile of HPV Infection Among Women within a High HIV Setting: A Snap Shot from Botswana

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Background and Aims

Cervical cancer is as a leading cause of avoidable cancer deaths in Botswana, a country with a HIV prevalence (22.9%), despite investment by the MOH to expand cervical cancer services. This review looks at the status of HPV infection, a precursor to Cervical Cancer.

Methods

A prospective cohort study was done in 5 health facilities over six months. After client education, self-collected samples using a brush were taken for testing. Specimens were analyzed, including HPV genotyping using the Cepheid GeneXpert®. All clients with HPV infection were to undergo visual inspection and treatment (VAT), while the HPV negative client were managed as per national guidelines.

Results

Of the 1022 samples, 1,019 were valid (99%) and analyzed. Out of these, 343 (33%) tested positive for HPV infection. All 1,019 clients (100%) had an HIV test done, with 570 (56%) testing HIV positive. HIV Positive client had twice as high HPV infection at 67% (n=343) than HIV negative clients at 33%. The study analyzed HPV subtypes, with 29 (8.4%) HPV 16 only, 39 (11%) both 18 and 45 only, 64 (19%) contained some mixed subtypes including either 16, 18 or 45. However 211 (63%) had Other HPV subtypes excluding 16, 18, 45. Of the 676 HPV negative clients, 340 (50.3%) were HIV positive and 336 (49.7%) HIV negative.

Conclusions

HPV testing showed high HPV positivity, but more persistent HPV infection within HIV positive clients. There is a considerable proportion of oncogenic HPV infections and Botswana needs to consider continuing HPV screening given the profile of persistent HPV infection.
Low and Middle Income (LMIC) Settings - Screening for HPV Related Disease
Screening: Implementation, Evaluation and Impact

HPV self-sampling acceptability and preferences among women living with HIV in Botswana
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Background and Aims
To describe the acceptability, experiences, and preferences of HPV self-sampling among women living with HIV in Botswana.

Methods
We recruited women ≥25 years attending an HIV clinic in Gaborone. Women self-sampled with a flocked swab and had a speculum exam for a provider-collected sample; samples were tested using Cepheid GeneXpert HPV. Descriptive statistics were conducted on survey responses. Open-ended questions were thematically categorized.

Results
We recruited 104 women for the pilot study. Most (94%) women had a history of cervical screening, and 39 reported a previous negative experience with speculum exam. Over 90% agreed that self-sampling was easy, comfortable, and expressed confidence in doing it correctly. Although 12 women reported a problem handling the swab or transport medium, only three samples were inadequate. Nearly all women (95%) were willing to self-swab again; however, only 20 (19%) stated their preference for future screening was self-sampling over speculum exam. We found no differences in willingness or preferences by screening history, but urban-residing women and those with higher education were more likely to prefer self-sampling. Self-sampling was preferred because it was easier, less embarrassing, and less painful. Speculum exams were preferred because of trust in providers’ skills, being able to see where to swab, and low self-efficacy.

Conclusions
Self-sampling is acceptable among women living with HIV in Botswana. However, traditional exams were preferred largely due to strong trust in providers’ skills and low self-efficacy to self-sample correctly. Self-sampling may be an important alternative to provider screening, though education and support will be critical to program success.
Background and Aims

Differences between cytology and human papillomavirus (HPV) screening methods have been well documented. With increasing interest in low cost visualization methods for screening, a better understanding of how these two screening methods relate to colposcopic impression is necessary. Such an analysis was done on a high-risk, colposcopy patient population in California.

Methods

Colposcopy exam results recorded on the EVA System app from N=248 patients were analyzed retrospectively. The specific parameters of interest included colposcopic impression, latest cytology and HPV test results, and other patient data including age and HIV status.

Results

Of the 239 HPV+ patients, 196 had a low grade lesion colposcopic impression (CIN1), 37 had high grade lesion impression (CIN2-3), four had cervicitis, one had cancer, and one was normal. Of the 9 HPV- patients, eight had a low grade lesion colposcopic impression, and one had high grade lesion impression. Cytology results were distributed as 22 normal, 6 ACH-H, 151 ASCUS, 52 LSIL, and 17 HSIL for the entire patient population. For low grade colposcopic impression, the cytology breakdown was 17 normal, 2 ACH-H, 30 ASCUS, 40 LSIL, and 7 HSIL; For high grade colposcopic impression, the cytology breakdown was 3 normal, 4 ACH-H, 13 ASCUS, 7 LSIL, and 10 HSIL (Fig.)
Conclusions

For HPV+ patients, there was general agreement between cytology and colposcopic impression. However, there were several cases in which cytology negative patients had a positive colposcopic impression. Further analysis of these cases is needed.
Background and Aims

Cervical cytology screening has been a standard procedure for many decades in detection of pre-malignant and malignant lesion of uterine cervix. However, the incidence of cervical cancer is still high especially in developing countries. In Makassar Indonesia, cervical screening sample collection was performed by medical doctors or nurses, using conventional Pap test sampling. However, it was still ineffective and has low coverage. This was due to socio-cultural obstacles and lack of knowledge of the importance of cervical examination. This study aims to analysis the acceptability of self-sampling collection to detect HPV in cervical cytology screening.

Methods

This case control analytic study applied to 101 women in some public health centres in Makassar. Specimen samples were collected by the women themselves using self-collection kit, and delivered to HPV testing.

Results

This case control analytic study applied to 100 women in some public health center in Makassar. Specimen samples were collected by the women themselves using self-collection kit, and delivered to HPV testing. The median age of samples was 40-49 years (41%). Most of samples were a house wife (74%), multiparous (89%), not using family planning method (58%). Most of them did not know about the importance of routine cervical screening (80%), and self-sampling collection was knew for them (100%). Sixty three samples found that self-sampling method was easy to perform with no obstacles, and 80% of samples were willing to repeat the method.

Conclusions

This study found that self-sampling collection could be used in Makassar as a new alternative method for cervical cancer screening.
HUMAN PAPILLOMAVIRUS INFECTION IN GENITAL WOMEN IN FOUR REGIONS OF SENEGAL

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3Laboratory of Bacteriology and Virology- Aristide Le Dantec Hospital, Dakar, Dakar, Senegal

Background and Aims

Introduction: Cervical cancer is the most frequent cancer among women in Senegal. However, there are few data concerning the HPV types inducing neoplasia and cervical cancers and their prevalence, in the general population of Senegal.

Aims: The aim of this study is to determine the prevalence of HPV infection in Senegalese women aged from 18 years and older

Methods

Materials and Methods: A study was performed on 498 cervix samples collected from healthy women aged 18 and older in Dakar. 438 other samples were collected from three other regions, Thiès, Saint Louis and Louga. The samples were screened for 21 HPV genotypes using an HPV type-specific E7 PCR bead-based multiplex genotyping assay (TS-MPG) which is a laboratory-developed method for the detection of HPV.

Results

Results: The prevalence for pHR/HR-HPV in the region of Dakar was 20.68%. HPV 52 (3.21%) was the most prevalent HPV type, followed by HPV 16 (3.01%) and HPV 31 (3.01%). In the regions of Thiès, Louga and Saint Louis, the prevalence for pHR/HR-HPV was 29.19%, 23.15% and 20%, respectively.

Conclusions

Conclusion: The study revealed the specificity of the HR-HPV prevalence in Dakar and other regions of Senegal. The patterns differs from the one observed in the other regions of the world and rise the issue of the development of vaccination program in the country. Such a program should take into account the real HPV prevalence for an effective protection of HPV-associated diseases.
Background and Aims

Human papillomavirus (HPV) infection is responsible for nearly all cervical cancer cases. The lengthy progression from infection to cancer makes screening highly effective in reducing cervical cancer cases and related deaths. Cytology-based screening programs have reduced the burden of cervical cancer in developed regions. However, cytology-based screening must be performed frequently and is poorly suited to low resource settings, where the majority of cervical cancer cases and deaths occur. Molecular diagnostics are gaining usage but they are expensive and use is generally limited to centralized laboratories. For screening programs to achieve the same level of success in low resource settings, an assay with high sensitivity and predictive value over a long period is imperative. Global Good and QuantuMDx are developing a point of care molecular diagnostic for the detection and genotyping of thirteen individual high-risk HPV types.

Methods

The cassette-based assay is fully integrated, enabling sample to results in under thirty minutes. The cassette runs on a portable, low-cost, battery-operated device. The sample is loaded onto the cassette for sample preparation, PCR amplification, and DNA microarray hybridization.
Results

The assay detects an internal control and genotypes thirteen HR-HPV types if present, allowing for risk stratification. To date, we have evaluated this assay with 86 physician-collected specimens (vaginal and cervical swabs from two cohorts). The assay demonstrated agreement for overall HPV positivity and individual genotypes compared to reference HPV assays.

Conclusions

We expect the simplicity, affordability, and risk stratification provided by this assay to enable same day diagnosis and management at point of care.
IPVC8-0401
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCREENING FOR HPV RELATED DISEASE SCREENING: IMPLEMENTATION, EVALUATION AND IMPACT

HPV DNA IN CERVICAL NEOPLASIA IN TWO TIME PERIODS
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¹Christian Medical College, Gynaecologic Oncology, Vellore, India
²Christian Medical College, Clinical Virology, Vellore, India

Background and Aims

HPV DNA has been detected in around 80 % of cervical intraepithelial neoplasia (CIN) and over 99 % of cervical cancers. We aimed to study the HPV prevalence and genotype variation, with time, in women with cervical neoplasia.

Methods

In 2003-04, HPV DNA was detected in 119 women with cervical cancer and 11 women with CIN using PCR and Line blot assay (Roche). In 2013-14, HPV DNA was detected in 93 women with cervical carcinoma and 17 women with CIN using Hybrid Capture II (Qiagen) and Linear Array (Roche). The proportion of women with HPV DNA (within categories) as well as the genotypes were compared across the two time periods.

Results

In the first time period (2003-4), HPV DNA was positive in 91% (10/11) of women with CIN and in 95% (113/119) of patients with cervical cancer. Single infection was seen in 77% (100/130) women and multiple infection in 18% (23/130). HPV 16 was seen in 78 women (60%) of women.

In the second time period (2013-14), HPV DNA was positive in 94 % (16/17) of women with CIN and in 96 % (89/93) of women with invasive cancer. Single infection was seen in 56% (62/110) women and multiple infection in 32% (35/110) women. HPV 16 was the commonest genotype and was seen in 77 women (70%).

Conclusions

The HPV epidemiology has remained more or less unchanged over a 10 year period. This is reassuring for a HPV vaccination programme. Minor variations may be due to differences in tests employed.
Background and Aims

Although the risk of cervical cancer (CC) is higher in women living with human immunodeficiency virus (HIV) infection, screening for cervix cancer is extremely low among HIV positive women in India. Given the limited usefulness of cytology-based screening programs, the current study evaluated the diagnostic performance of Visual Inspection with 5% Acetic Acid (VIA) and Human Papilloma Virus (HPV) testing as cost-effective alternatives for resource-limited settings.

Methods

Retrospective analysis of 291 HIV Positive women attending cervical cancer screening services in a tertiary centre in Mumbai was undertaken. All underwent simultaneous screening with Visual inspection with acetic acid (VIA), conventional cytology and HPV DNA testing followed by colposcopy and histopathology. Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) to detect cervical intraepithelial neoplasia (CIN) 2/3 on histology were estimated.

Results

Screen positivity rate for cervical cancer screening by VIA, high-risk HPV DNA and conventional cytology was 36.1%, 32.3%, 5.8% respectively. At the CIN2+ disease threshold, the sensitivity, specificity, PPV, NPV estimates were 80.00% (59.30-93.17), 68.42% (62.46-73.96), 19.23% (15.46-23.67), 97.33% (94.30-98.77) for VIA, 80.00% (68.78-97.45), 70.68% (64.81-76.08), 22.00% (18.22-26.32), 98.43% (95.58-99.45) for HPV DNA and 64.00% (42.52-82.03), 98.12% (95.67-99.39), 76.19% (56.13-88.89), 96.67% (94.50-98.00) for cytology (HSIL cutoff).

Conclusions

The diagnostic performance of VIA and HPV DNA were comparable and performed better than cytology, suggesting VIA as a cost effective alternative screening test that can be incorporated within the existing health services of the Integrated STD/HIV testing and counselling centers established under National AIDS Control program in India.
The efficiency of screening and treatment algorithms can greatly impact women’s ability to access and complete the care continuum. This study aims to describe the women-level perspective navigating different screening-and-treatment program structures in Iquitos, Peru.

**Methods**

The distance, time, and cost burdens women face to access cervical cancer screening-and-treatment were quantified across 9 communities. GIS location of all facilities providing services were analyzed in ArcGIS. Time was subdivided into active time (e.g. travel and services), and passive time (e.g. waiting to obtain results). Costs were obtained from local health providers and hospital treasury reports. The current and a newly developed program were analyzed and compared.

**Results**

The current program (comprised of VIA at a health center, colposcopy/biopsy receipt at a hospital, and cryotherapy at a hospital) required screen-positive women to travel an average of 83 kilometers, spend 14 active-hours and 46 passive-days to complete services, and cost 69USD. A new program (comprised of HPV DNA testing at a health center, return visit for results and VIA if positive, and cryotherapy at a health center) required women to travel an average of 18 kilometers, spend 6 active-hours and 36 passive-days to complete services, and cost 22USD. These burdens varied considerably across urban, peri-urban and rural women.

**Conclusions**

Comparison of these real-life scenarios highlights the impact of program structure and geography on the burden women face to complete obtain screening-and-treatment. Next, these results will be compared to women’s self-reported willingness to pay and travel.
IPVC8-0207
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCREENING FOR HPV RELATED DISEASE SCREENING: IMPLEMENTATION, EVALUATION AND IMPACT

HPV-INDUCED MALIGNANCIES EARLY SCREENING AS A PREDICTOR FOR PRE-EXPOSURE PROPHYLAXIS RETENTION IN MEN WHO HAVE SEX WITH MEN AND TRANS POPULATIONS IN THE DOMINICAN REPUBLIC
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¹Universidad Iberoamericana, research deanat/ Institute of Tropical Medicine and Global Health, Santo Domingo, Dominican Republic

Background and Aims

Elimination of HIV transmission has been cumbersome for many countries, however, many innovative interventions has been demonstrating the significant reduction of new HIV infections. One of these is Pre-Exposure prophylaxis (PrEP) that is part of an integrated and patient-centred approach has been implemented in countries like the Dominican Republic. The objective of this study was to evaluate the role of early HPV-Induced malignancies screening in MSM/ Transgendered women (TG) populations.

Methods

Patients were selected by convenience while attending for HIV/STI screening based on their self-identification as MSM or TG at an HIV primary care unit in Santo Domingo. The questionnaire was applied to all with negative HIV results and exploring their knowledge, attitudes, benefits of early HPV-related screening procedures and PrEP use.

Results

Of 151 interviews, 82% were MSM, and 18% were TG. They were asked if they ever heard about PrEP as an HIV prevention tool. 61% of MSM and 39% of TG confirmed having heard of PrEP. The 89% referred being aware of the importance of anal pap smear as early detection for HPV infection. 94% in the MSM perceived that having done an anal pap smear would be a reason to visit a PrEP clinic.
Table 1. Knowledge and Perceived Benefits in HIV and HPV Prevention

<table>
<thead>
<tr>
<th>Knowledge of Preventive Actions in HIV and HPV</th>
<th>MSM % (n=123)</th>
<th>Trans % (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of condoms during sex</td>
<td>96.7% [119]</td>
<td>96.4% (27)</td>
</tr>
<tr>
<td>Use of PrEP to prevent HIV</td>
<td>61% (75)</td>
<td>39.3% (11)</td>
</tr>
<tr>
<td>Use of new needles for drugs or hormones</td>
<td>100% [123]</td>
<td>82.1% (23)</td>
</tr>
<tr>
<td>Performing Circumcision to reduce HIV and HPV</td>
<td>75.6% (93)</td>
<td>32.1% (9)</td>
</tr>
<tr>
<td>Anal Pap Smear for early detection of anal cancer</td>
<td>85.3% (105)</td>
<td>89.3% (25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perceived benefits in HIV and HPV</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>You know how to prevent HIV infection</td>
<td>100% [123]</td>
<td>96.4% (27)</td>
</tr>
<tr>
<td>You are currently taking steps to prevent HIV and HPV</td>
<td>82.9% [102]</td>
<td>82.1% (23)</td>
</tr>
<tr>
<td>You feel confident that if you receive PrEP and always use condoms you are fully preventing HIV and HPV</td>
<td>96.7% [119]</td>
<td>71.4% (20)</td>
</tr>
<tr>
<td>You have the ability of demanding an anal pap smear</td>
<td>81.3% [100]</td>
<td>85.7% (24)</td>
</tr>
<tr>
<td>You have symptoms of HPV infection, you know what to do</td>
<td>0% (0)</td>
<td>17.8% (5)</td>
</tr>
<tr>
<td>You think that performing an anal pap smear is a reason for your visits to the PrEP clinic</td>
<td>94.3% [116]</td>
<td>67.9% (19)</td>
</tr>
</tbody>
</table>

Conclusions

From a perspective of a differentiated care in patients attending STI/HIV clinics is necessary not only be limited to HIV preventive techniques, also it is required an integrated approach. This study reveals the need of more marketing of the importance of the use of PrEP to scale-up within the populations, we propose a package of services should be provided to engage these populations.
Background and Aims

The frequency of malignant lesions in the anal region is significantly higher among people living with HIV/AIDS. These lesions are intrinsically related to HPV infection and its progressions are associated with a deficient immune chemotaxis. Despite molecular techniques for viral identification, cytology is still a cost-effective tool for the screening intraepithelial lesions of the anal canal. The objective of this study was obtain a baseline and monitoring the evolution of premalignant lesions related to HPV at risk populations from the Dominican Republic.

Methods

Patients attending primary care units for HIV management were invited to participate. Anal cytology was offered as part of their follow-up in those clinics, for a period of two years. Samples were collected on a liquid base (ThinPrep®), stained with PAP and evaluated by light microscopy.

Results

A total of 118 self-identified HIV (+) MSM agreed to participate. The age range was 19-75 years. The distribution of patients and their evolution were followed as shown in Figure 1. On table 1 it is shown the main clinical characteristics of the cases and their evaluation. On image 1 is presented the findings on LSIL.
<table>
<thead>
<tr>
<th>Case in follow-up</th>
<th>Initial diagnostic</th>
<th>Follow-up diagnosis</th>
<th>Follow-up period (in month)</th>
<th>Relevant data</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 yo MSM</td>
<td>LSIL</td>
<td>LSIL</td>
<td>16</td>
<td>Keeps viral load high and CD4 count less than 100 cell/mm³</td>
</tr>
<tr>
<td>19 yo MSM</td>
<td>HSIL</td>
<td>LSIL</td>
<td>20</td>
<td>Increase in CD4+ count from 45 to 400.</td>
</tr>
<tr>
<td>21 yo MSM</td>
<td>LSIL</td>
<td>NILM</td>
<td>12</td>
<td>Increase in CD4+ count</td>
</tr>
<tr>
<td>69 yo MSM</td>
<td>LSIL</td>
<td>NILM</td>
<td>12</td>
<td>Increase in CD4+ count</td>
</tr>
<tr>
<td>33 yo MSM</td>
<td>LSIL</td>
<td>NILM</td>
<td>17</td>
<td>data not available</td>
</tr>
</tbody>
</table>
Figure 1. Patient distribution

Total participants 118 MSM

- Abnormal 30
  - ASC-US 4
  - LSIL 25
  - HSIL 1
  - Unsatisfactory 3

- NILM 85

- Follow-up
  - Follow-up LSIL

- NSIL 3
  - LSIL 1
Conclusions

The follow-up for at least one year presents the association between the decrease in viral load, the increase in the CD4+ count and the regression of squamous lesions, and the non-regression in cases in which this therapeutic objective is not optimized. The rating of a second follow-up sampling was low (15%) suggesting a need of strengthening HIV programs throughout the continuum of care in patient-centered approaches.

Image 1. LSIL. Squamous cells with increased relations nuclei and cytoplasm, and atypia coloectic. (magnification of 40x)
LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCREENING FOR HPV RELATED DISEASE SCREENING: IMPLEMENTATION, EVALUATION AND IMPACT

CERVICAL CANCER SCREENING THROUGH A CLOUD-BASED ALGORITHMIC ANALYSIS OF CERVICAL IMAGES ON A MOBILE PLATFORM

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²MobileODT Ltd., Tel Aviv, Israel
³Gynaecology, Thomson Medical Center, Singapore
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⁵School of Computing, National University of Singapore, Singapore

Background: For decades, the search for an accurate, low cost, and portable cervical cancer screening test was elusive. The best screening test today - self sampled HPV tests - has higher negative predictive value than positive predictive value, and also suffers from high loss to follow up. Recently, a cervical image pathology classifier based on deep learning was developed to run on a local workstation. However, automated visual evaluation (AVE) algorithms need to run on a mobile platform to make an impact in low resource settings.

Methods An AVE classifier was developed using cervical images captured on a mobile colposcope. This classifier is based on an inception v3 algorithm. It was trained on 2000 images with manual annotations, and validated on 100 images with histopathology annotations. The AVE classifier was deployed on the cloud, called by an application running on a mobile phone. Here, a cervical image captured at the point of care is sent to the cloud, and a binary response is returned.

Results The AVE round trip runtime was

Conclusion A proof of concept AVE classifier was demonstrated on a mobile platform. Deploying an accurate AVE classifier on a mobile phone has potential change cervical cancer care.

Conflicts of Interest: YB and DL are employees of MobileODT, and both own stock in MobileODT. DL also sits on MobileODT’s Board of Directors.
HIGH RISK HUMAN PAPILLOMAVIRUS SCREENING RESULTS WITH THE HYBRID CAPTURE 2 SYSTEM IN THE CITY OF COCHABAMBA, BOLIVIA

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¹Universidad Mayor de San Simón, Laboratory of Virology - Faculty of Medicine, Cochabamba, Bolivia
²CIES, Salud Sexual y Reproductiva, Cochabamba, Bolivia

Background and Aims

Bolivia has one of the highest rates for cervical cancer prevalence, incidence and mortality in America. Since the infection by a high-risk genotype of human papillomavirus (HR-HPV) is a necessary cause for cervical cancer development, the introduction of HPV tests is crucial to decrease the incidence rate of this pathology. The Hybrid Capture 2 technique (HC2) has been considered the gold standard for HR-HPV detection around the world. Since early 2016 the HC2 system has been introduced in Bolivia to screen women for cervical cancer. In this study, we summarize our findings concerning HR-HPV and HPV16/18 prevalence in the city of Cochabamba.

Methods

From March 2016 to April 2018, 3532 women were screened for cervical cancer in the outpatient clinic of “CIES Salud Sexual y Reproductiva” in the city of Cochabamba, Bolivia with the HC2 system. In a group of 898 women, the prevalence of HPV16/18 was determined with type-specific PCR. The HPV prevalence was correlated to cytological findings.

Results

The general HR-HPV prevalence in our study population is 20.5%. Among women who are infected by HR-HPV, the prevalence of HPV16 and HPV18 is 17.4% and 5.0% respectively. Concerning cytological findings, the prevalence of HR-HPV in women with normal, ASC-US, L-SIL and H-SIL results are 28.2%, 28.9%, 50.0% and 66.7% respectively.

Conclusions

Early detection of pre-cancerous lesions of the cervix by detecting HR-HPV infections with the HC2 can successfully aid to decrease cervical cancer incidence in Bolivia.
DETECTION OF HYPERMETHYLATED GENES AS MARKERS FOR CERVICAL SCREENING IN WOMEN LIVING WITH HIV

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²Cancer Center Amsterdam VU University Medical Center, Department of Pathology and Department of Epidemiology and Biostatistics, Amsterdam, The Netherlands
³University of Pretoria and National Health Laboratory Services, Department of Medical Virology, Pretoria, South Africa
⁴University of Pretoria, Department of Obstetrics and Gynaecology, Pretoria, South Africa

Background and Aims

The aim of this study was to evaluate the performance of hypermethylation analysis of ASCL1, LHX8 and ST6GALNAC5 in physician-taken cervical scrapes for detection of cervical cancer and cervical intraepithelial neoplasia (CIN) grade 3 in women living with HIV (WLHIV) in South Africa.

Methods

Samples from a prospective observational cohort study were used for these analyses. Two cohorts were included: a cohort of WLHIV who were invited for cervical screening (n=321) and a gynaecologic outpatient cohort of women referred for evaluation of abnormal cytology or biopsy proven cervical cancer (n=108, 60% HIV seropositive). Cervical scrapes collected from all subjects were analysed for hypermethylation of ASCL1, LHX8 and ST6GALNAC5 by multiplex quantitative methylation specific PCR (qMSP). Histology endpoints were available for all study subjects.

Results

Hypermethylation levels of ASCL1, LHX8 and ST6GALNAC5 increased with severity of cervical disease. The performance for detection of CIN3 or worse (CIN3+) as assessed by the area under the receiver operating characteristic (ROC) curves (AUC) was good for ASCL1 and LHX8 (AUC 0.79 and 0.81, respectively), and moderate for ST6GALNAC5 (AUC 0.71). At a threshold corresponding to 75% specificity, CIN3+ sensitivity was 72.1% for ASCL1 and 73.8% for LHX8 and all samples from women with cervical cancer scored positive for these two markers.

Conclusions

Hypermethylation analysis of ASCL1 or LHX8 in cervical scrape material of WLHIV detects all cervical carcinomas with an acceptable sensitivity and good specificity for CIN3+, warranting further exploration of these methylation markers as a stand-alone test for cervical screening in low-resource settings.
Background and Aims

High-risk human papillomavirus (HR-HPV) infections is a major cause of oral and oropharyngeal cancer (OOPC). Scarcity of such evidence from Sri Lanka, prompted us to undertake a comparative study on HPV associated OOPC using different biological specimens from OOPC patients.

Methods

Blood, saliva and oral rinse samples of OOPC patients (N=90) and age/gender matched non-cancer healthy controls were collected. Additionally, formalin fixed paraffin embedded (FFPE) tumour tissue of OOPC patients and of cancer suspected, negative individuals were used as controls. Serum was assayed for anti-HPV IgG antibodies to HPV16 and HPV18 on in-house established indirect ELISAs. DNA extracted from saliva, exfoliated oral cells and FFPE tumour tissue were amplified by PCR using Gp5+/6+ primers. The amplicon sequences were analysed by NCBI BLAST service.

Results

HPV positivity in 11% of OOPC FFPE tissue included HPV16 (90%) and HPV18 (10%) HR types. All controls scored negative on PCR. Of the 10 HPV PCR positive samples, only 8 (80%) screened positive in all FFPE, oral rinse and saliva specimens. HPV seropositivity was detected in 9% of the OOPC group and 1% of the controls; Anti-HPV16 IgG were detected in 87.5% of OOPC patients and in 2% of non-cancer controls while these values for anti-HPV18 IgG were 12.5% and 2%, respectively. Compared to controls the test group showed a congruent 4-fold increased risk of developing OOPC as detected by both ELISA and PCR (ELISA; OR=4.1; 95%CI=1.21-14.23 and PCR; OR=4.3; 95%CI=1.165-16.521).

Conclusions

This study provides the first synonymous serologic and molecular evidence of HPV association with OOPC in Sri Lanka.
Background and Aims

BACKGROUND: Appropriate collection and use of health information is critical for planning, scaling, and improving cervical cancer programs. Limited coordination, training, and standardization of data practices result in low quality data that are largely unusable. Failure to recognize the data’s usefulness contributes to limited investment in the collection of quality data. Lack of globally endorsed indicators, data collection, collation, and use tools has hampered scale-up of programs. Standard tools have been developed and adapted for country’s use.

Methods

METHODS: Since 2009, Jhpiego has developed indicators, data collection and collation tools, and guiding information to improve the quality, coverage, and scale of programs. Materials have been adapted to meet each country’s needs and data has been integrated into HMIS. Three country case studies will be discussed.

Results

RESULTS: In intervention facilities, more than 370,000 women have been screened using VIA across Mozambique, Tanzania and Botswana with 8% (28,650) VIA positive, 15% (4,202) with large lesions, and 71% (17,343) of eligible women receiving cryotherapy on the same day (SVA). Ministries of Health can monitor their results against standard benchmarks (5 – 10% VIA positive; at least 80% SVA) resulting in better planning, targeting for quality assurance, tailoring of intervention, and monitoring of scale-up. Additional tools used measured service availability, readiness, and quality. These tools have been incorporated into a toolkit that is in the process of being CDC/WHO globally endorsed.

Conclusions

Generating high quality data is feasible with upfront investment for tool adaptation and roll-out. Use of data can improve service quality and program effectiveness.
Background and Aims

HPV detection has been recommended for cervical cancer screening. At present, the availability of HPV tests in developing countries is limited due to costs or laboratory conditions. This study was aimed to evaluate the performance of DALTONbio DH3, a Chinese HPV detection technique based on hybrid capture with HPV16/18 genotyping, in cervical cancer screening.

Methods

From July to August 2017, women in HPV demonstration study in Shanxi Province were screened by co-testing strategy (cytology and cobas4800). The residual cytology samples were tested by DH3. Women with any abnormal result would be referred to colposcopy and biopsied, if necessary.

Results

Totally, 740 women were included. The positive rates of 14 types of hrHPV detected by DH3 and cobas4800 were 16.09% and 19.42% (p<0.01), while for HPV 16/18 were 3.88% and 4.58% (p=0.46). The agreement rates of overall HPV, HPV 16/18 and other 12 hrHPV types between DH3 and cobas4800 were 87.43%, 52.94% and 59.09%, respectively. For detecting CIN2+, the sensitivity, specificity, positive and negative predictive value of DH3 were 100%, 84.85%, 4.42% and 100%, respectively. In comparison, the corresponding results of cobas4800 were 100%, 81.49%, 3.65% and 100%.

Conclusions

These findings showed that DH3 had similar performances with cobas4800 in cervical cancer screening.
THE STUDY OF HPV SELF-SAMPLING IN CERVICAL CANCER SCREENING.
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Background and Aims

To study the compliance of HPV self-sampling with doctors’ sampling, and explore the feasibility and significance of the cervical cancer screening model based on HPV self-sampling.

Methods

Study on HPV self-sampling in the cervical cancer screening site from March to April, 2018. For the women, they agree to participate in the project. The staff showed how to self-sample. After self-sampling, the gynecologists took cervical sample directly. Two HPV sampling were tested by real-time fluorescence quantitative PCR (qPCR). Results: A certain number of people were randomly selected to conduct the questionnaire survey, and the significance of the screening model based on the special self-sampler was analyzed.

Results

Compared with doctor’s-sampling, the negative coincidence rate of self-sampling was 97.55%. The overall coincidence rate reached 97.1%. 1375 women participate the survey of Self-sampling. Among them, 88.60% cases feel convenient in operation, and 81.45% with no discomfort, 92.10% of women can be completed in 5 min from sampling, occasional bleeding was 5.24%, again to HPV sampling model involved in screening the willingness of the degree of 86.69%.

Conclusions

This study found that the special sampler based on HPV screening model could effectively improve women’s screening exercise. And Self-sampling has the similar ability to test high risk patients as gynecologist’s sampling.
IPVC8-0104
POSTER SESSION
LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCALE UP OF HPV VACCINATION IN GAVI-ELIGIBLE COUNTRIES

HUMAN PAPILLOMAVIRUS (HPV) VACCINE INTRODUCTION IN CAMBODIA: EVALUATING THE HPV DEMONSTRATION PROJECT
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Background and Aims

In 2017, the Cambodia Ministry of Health introduced HPV vaccine in six operational districts as a Gavi-supported demonstration project. Two doses were administered six months apart to a target of 11,646 9-year-old girls through schools and health facilities. A post-introduction evaluation (PIE), coverage survey and costing evaluation were conducted to better understand vaccine delivery to this age group.

Methods

Purposively selected stakeholders from the central to community level were interviewed in the PIE, concurrent with the second HPV dose. A community-based stratified cluster survey of caregivers and girls assessed documented vaccination coverage, acceptability and knowledge/attitudes two months after introduction. Delivery cost, cost per dose and cost per fully immunized girl (FIG) were estimated using the World Health Organization’s (WHO) Cervical Cancer Prevention and Control Costing (C4P) Tool.

Results

Stakeholders viewed the HPV campaign as feasible, smoothly implemented and well-received and supported inclusion of HPV vaccine into the national immunization program. Among coverage survey respondents, 84% (95% confidence interval [CI]: 78%-88%) had documentation of receiving two HPV doses. Of those, 90% reported being vaccinated in school. Though vaccine acceptance was high, community knowledge of HPV was limited. Financial cost (monetary expenditures) was US $15.49 per FIG and economic cost (expenditure plus opportunity costs) was US $38.68 per FIG.

Conclusions

A school-based delivery strategy was effective for reaching 9-year-old girls; costs were within a range seen from other demonstration projects. Accurately enumerating and reaching out-of-school girls, migrants and other hard-to-reach populations remains a global challenge. Lessons from the demonstration project will inform national introduction.
THE ADDED BENEFIT OF SCALING UP HPV VACCINATION IN GAVI ELIGIBLE COUNTRIES: FLOW-ON EFFECTS OF LOSS OF A MOTHER ON THE FAMILY

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Background and Aims

Losing a mother in early childhood results in an increased risk of childhood death due to loss of maternal care, especially in less developed settings. Cervical cancer is thus potentially implicated in childhood, as well as adult female deaths. In this study we aimed to quantify the additional deaths in children each year in Gavi-eligible countries (2017 eligibility).

Methods

A microsimulation model, adapted to the demographic and reproductive profiles of each country, was developed to simulate woman and their children. After a woman’s death, children under 5 years were assumed to be subject to increased risk of death for a 12 month period, with the elevated risk based on published rates.

Results

For each woman dying between the ages of 15-54 in Gavi-eligible countries, there is an additional 8-30\% probability of an additional child death (varies by setting). For the year 2015, an estimated 286,528 child deaths occurred due to the death of a mother (6\% of all under-5 deaths). Of these, 21,920 are due to any cancer death in the mother, 7,198 (range:3,161-11,255) are due to cancers attributable to modifiable risk factors, and 3,331 (range:2,533-4,019) are preventable deaths according to the World Bank’s DCP-3 recommended prevention interventions (including cervical screening and HPV vaccination), and 3,125 are specifically due to cervical cancer death in the mother.

Conclusions

A substantial number of childhood deaths are attributed to the death of a mother, many of which could be prevented. These findings illustrate the wider societal benefits of cervical cancer prevention in low resource settings.
Background and Aims

Although guidelines recommend HPV vaccination for girls aged 9-14 years, several international advisory groups have proposed vaccinating women up to age 50 years. We aim to provide insights on the value of expanding multi-cohort HPV vaccination in Gavi-eligible countries.

Methods

We used a hybrid modeling approach that captured HPV transmission, cervical carcinogenesis, and population demographics to project long-term health and economic outcomes associated with HPV vaccination. Scenarios reflecting 70% coverage (100% lifelong protection) of women up to ages 18, 26, 30, 40 or 50 years were compared to current guidelines. We assumed 2-dose and 3-dose vaccine schedules for girls aged 9-14 and 15-50 years, respectively, and an aggregate vaccine and delivery cost of $6.90 per dose. Programs with incremental cost-effectiveness ratios less than the gross domestic product per capita were considered cost-effective.

Results

The marginal benefit of the vaccine decreased as the catch-up age increased. For example, fifty years after initiating the vaccination program, vaccinating women up to age 18 years yielded an absolute reduction in cancer incidence of 14%, compared to current recommendations, while vaccinating women up to ages 26, 30, 40 or 50 years yielded additional reductions of 16%, 4%, 5%, and 1%, respectively. Even so, it was considered cost-effective to vaccinate women up to age 40 years for 40% of the countries and up to age 50 years for 36% of the countries.

Conclusions

Expanded use of HPV vaccines in low-income countries may be considered cost-effective, but would require significant upfront economic investments.
Background and Aims

In 2016, Liberia implemented a human papillomavirus (HPV) vaccine demonstration program, targeting 14,218 ten-year-old girls in two counties to receive two HPV doses, primarily through school-based vaccination. First-dose administrative coverage was 98% and 89% in Bong and Nimba counties, respectively. We conducted a community-based household-level coverage survey to evaluate vaccination delivery and acceptability.

Methods

A cluster survey, among eligible girls (10 years old and residing in the counties during first-dose delivery) was conducted; coverage estimates were calculated by record review (vaccination card or health facility register). We assessed social mobilization and reasons for vaccine acceptance.

Results

Of 5466 households visited, we surveyed 306 eligible girls in Bong (40 clusters) and 278 eligible girls in Nimba (30 clusters). Complete two-dose coverage was 24% in Bong and 26% in Nimba. Among girls receiving at least one dose (36% in Bong and 70% in Nimba), most (60% in Bong and 90% in Nimba) were vaccinated at school. Reasons for missed or incomplete vaccination were school absence, not being enrolled in school, vaccine stock-out, not being aware of the campaign, and misunderstanding of age eligibility among healthcare workers, teachers and community. There was low community knowledge of HPV and minimal vaccine refusal.

Conclusions

Low coverage was achieved among target-age girls, which was inconsistent with reported high administrative coverage, and likely due to narrow age targets and geographic parameters in a demonstration program. Because vaccine acceptance was high, nationwide introduction can be successful with improved micro-planning, social mobilization to increase awareness of campaigns and training on vaccine eligibility.
INTRODUCTION OF HUMAN PAPILLOMAVIRUS (HPV) VACCINE INTO NATIONAL IMMUNIZATION PROGRAMS: OPPORTUNITIES TO EVALUATE IMPLEMENTATION IN EARLY-INTRODUCING GAVI-ELIGIBLE COUNTRIES

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Background and Aims

The World Health Organization recommends two doses of human papillomavirus (HPV) vaccine for girls aged 9-14 years. Countries should determine delivery strategies to obtain optimal coverage in this novel target population. WHO recommends countries consider vaccinating multiple age cohorts in the first year to accelerate vaccine impact. Some programmatic experience has been gained from Gavi-supported demonstration projects. However, because few Gavi-eligible countries have introduced nationally, gaps remain in understanding scale-up, equity and sustainability.

We propose in-depth evaluations in several Gavi-eligible countries introducing HPV vaccine into national immunization programs. Project objectives include: 1) document the experience through country case studies; 2) evaluate training of healthcare workers, teachers, and other stakeholders; 3) evaluate completeness of microplanning and quality of reporting; 4) understand initial and ongoing costs of national introduction; 5) characterize hard-to-reach populations and explore interventions to improve equity.

Methods

This evaluation will utilize a mixed-methods approach including desk reviews, interviews, focus groups, surveys and cost analyses to collect input from various stakeholders, to comprehensively describe and evaluate national introduction in a small group of countries.

Results

Not available

Conclusions

Lessons learned will provide data to inform programmatic decision-making and forecast resource needs in participating countries, as well as subsequent countries introducing HPV vaccine. Understanding cost to deliver HPV vaccine can inform the Gavi program, as well as countries transitioning from donor support or middle-income countries considering
introduction. Successful introduction of HPV vaccine offers opportunities to explore new platforms for delivering health services (e.g., schools) and strengthen ties with stakeholders not routinely involved in immunization programs.
IMMUNOGENICITY AND SAFETY OF THE HUMAN PAPILLOMAVIRUS- VACCINE IN HIV-INFECTED YOUNG WOMEN IN UGANDA.

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Background and Aims

The objective of this study was to determine whether the 3- dose quaudrivalent HPV vaccine series is immunogenicity and safe in HIV–infected young women in Uganda

Methods

We enrolled 99 16- to 23-year-old women in a phase II, open-label, multi-center trial, conducted from 2009-2011 by the Uganda HIV/AIDS surveillance report, STD/AIDS control programme

Interventions.

Outcome measures were immunogenicity 4 weeks after dose 3, measured by 1) geometric mean titters (GMTs) and 2) seroconversion rates for HPV-6, -11, among those seronegative and HPV DNA negative for each type. Immune responses were compared to those of a historical comparison group of HIV-negative women (N=267) using univariate methods. Clinical and laboratory adverse events were assessed after each dose.

Results

The mean age of subjects was 21.4 years, 80% were Non-Hispanic Black, 69 were not taking antiretroviral therapy (ART) and 30 were taking ART. No differences in GMTs were noted among participants taking ART vs. the comparison group, but GMTs were lower in participants not taking ART vs. the comparison group for HPV-16 (2393 vs. 3892 mMU/mL, p=.012) and HPV-18 (463 mMU/mL vs. 801, p=.003). Seroconversion rates were 100% for HPV-6, -11, -16, and -18 among participants taking ART. Rates ranged from 92.3% (for HPV-18) to 100.0% (for HPV-6) among participants not taking ART. One severe adverse event (fatigue) was noted.

Conclusions

In a sample of HIV-infected women, who were HPV DNA and HPV seronegative, immune responses to HPV vaccination were generally robust and the vaccine was well-tolerated.
IPVC8-0650
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - SCALE UP OF HPV VACCINATION IN GAVI-ELIGIBLE COUNTRIES

COSTING THE HUMAN PAPILLOMAVIRUS VACCINE INTRODUCTION IN NEPAL

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Background and Aims

In 2016 and 2017, Nepal conducted an HPV vaccine demonstration program with support from Gavi, the Vaccine Alliance. Two cohorts of adolescent girls were targeted in Kaski and Chitwan districts. A costing analysis was conducted with the objective to estimate the cost of adding HPV vaccine to the national immunization program in Nepal, based on the costs witnessed during the demonstration program.

Methods

Data on costs of the first year of demonstration program were collected retrospectively. Financial as well as economic costs were collected using an ingredients micro-costing approach and the WHO Cervical Cancer Prevention and Control Costing (C4P) tool. Costs were categorized into introduction and recurrent costs. The cost of scaling up HPV vaccine provision to the whole country was projected over a five year period.

Results

The financial cost of the first year of HPV vaccine demonstration was US$ 80,626 (59% introduction costs, 41% recurrent costs). The economic cost was US$ 290,313. The projected financial cost for national scale up is US$ 3,566,884 with 59% in the first year of nationwide introduction. The total economic cost for 5 years is US$ 29,005,710. Projected financial cost per fully immunized girl is US$ 1.70.

Conclusions

The costing analysis show relatively lower costs for national introduction of HPV vaccine due to economies of scale and integration within the existing routine immunization activities. The costing analysis could inform the government in identifying resources requirement and decision making for national introduction of HPV vaccine.
The time-varying cost-effectiveness of HPV vaccination in low- and middle-income countries

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Background and Aims

Model-based analyses, showing routine HPV vaccination to be highly cost-effective in many low- and middle-income countries (LMIC), often base their evaluation on the lifetime health gains and costs of a fixed number of vaccinated cohorts. However, decision-makers may be interested in how cost-effectiveness changes over time. We simulated a routine HPV-16/18 vaccination program in 48 GAVI-eligible LMIC to examine how long it takes for the program to become cost-effective.

Methods

We used a hybrid modeling approach capturing HPV transmission, cervical carcinogenesis, and population demographics to simulate 100 years of a routine vaccination program (70% coverage of 9-year-old girls with two-dose HPV-16/18 vaccination) starting in 2017. At every year, we accumulated costs and disability-adjusted life years (DALYs), and calculated incremental cost-effectiveness ratios (ICERs) comparing vaccination to no vaccine.

Results

In its first year (2017), the vaccination program is not cost-effective in all 48 countries due to the cost of vaccination without immediate health gain. After 25 years (2041), vaccination becomes cost-effective in a few countries, with more countries added every subsequent year. After 50 years (2066), the program is very cost-effective in most countries and even cost-saving in a few. At 100 years (2116), vaccination is either cost-saving or very cost-effective worldwide. (Figures.) The median number of years for the program to become cost-effective among all 48 countries was 35 years.
Cumulative Cost-Effectiveness (ICER) of Routine 2-Dose HPV Vaccination
Analytic population: All females aged 9+ in each year

2041: 70Cov, Routine

Cumulative Cost-Effectiveness (ICER) of Routine 2-Dose HPV Vaccination
Analytic population: All females aged 9+ in each year

2066: 70Cov, Routine
Conclusions

While initially not cost-effective, within 20 to 50 years, routine vaccination becomes cost-effective in GAVI-eligible countries when considering the accumulated costs and DALYs averted in the entire population up to each year.
Background and Aims

Background

Cervical cancer accounts for over 10,000 new cases per annum in Nigeria with a high morbidity and mortality among those affected. While this disease can be prevented through HPV vaccination and screening, it remains the second most common cancer type in Nigeria. Despite cervical cancer vaccines availability in Nigeria, the uptake is low due to lack of awareness, affordability etc.

Aims

This study's aim was to determine the knowledge and acceptability of HPV screening and vaccination.

Methods

This cross-sectional study was conducted using a self-administered questionnaire, among female users of a community based cervical cancer screening services in Lagos, Nigeria with the level of significance set at <0.05.

Results

A total of 174 women were screened in 2017, with a mean age ± SD of 38.3 ± 12.7 years. The study showed that 18 women (10.3%) were aware of HPV, while 12 women (6.9%) had heard of HPV DNA testing. Among the women who were aware of HPV, 8 (44.4%) specified that it infects only women, 8 (44.4%) specified that it infects both sexes, 17 (94.4%) indicated that HPV was transmitted through sexual intercourse and 9 (50%) indicated that HPV infection can be prevented through vaccination. Acceptance to vaccinate was recorded in 16 (88.9%) of the HPV aware respondents.

Conclusions

Knowledge of HPV infection, vaccination and willingness to receive the vaccine is low. There is an urgent need to intensify community health education and screening campaigns.
Background and Aims

Cervical is the most common cancer in some parts of Nigeria and a leading cause of cancer mortality in women in the country. Visual inspection with acetic (VIA), a low-cost method of cervical cancer screening, is used in many resource-poor settings. The aim of this study was to determine the colposcopic findings in women referred to the Lagos University Teaching Hospital, Lagos, Nigeria, following a positive VIA test.

Methods

The records of 211 women who were referred to LUTH from various cancer screening centres in Lagos, between January 2008 and June 2014, for colposcopy following a positive VIA test were retrieved from the Colposcopy Clinic. A structured form was used to extract data on demographic characteristics, colposcopic findings and histology results.

Results

One hundred and eighty-three out of 211 (86.3%) records were complete for analysis. Fifty (23%) of the women were postmenopausal, 129(60.38%) of the women had normal colposcopic findings out of which 22 (17.05%) had cervical ectropion and 5 (3.88%) had atrophic changes. 25 (13.66%) had cervical intraepithelial neoplasia (CIN) (CINI 19(10.38); CIN II and III 6(3.28%) and invasive cancer 2(1.09%). Cervicitis, cervical polyps and warty changes on the cervix were found in 11(6.11%), 4(2.19%) and 4(2.19%) respectively. Colposcopy was unsatisfactory in 3(1.64%).

Conclusions

The study has shown a high incidence of over diagnosis of premalignant lesion of the cervix using VIA. An objective, low cost and possibly point of care test for cervical cancer screening may be what would be appropriate in resource poor settings.
Low and Middle Income (LMIC) Settings - Cervical Screening and Combined Screening Vaccination Strategies in LMIC

Knowledge and Uptake of Cervical Cancer Screening Among Female Students from Selected Universities in Lusaka, Zambia

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Background and Aims

Approximately 85% and 87% of the world’s incident cervical cancer (CC) cases and deaths respectively are from developing countries. Young women, especially those of university age, are at higher risk of contracting STIs such as HPV. We sought to identify factors associated with knowledge and uptake of CC screening among female students.

Methods

This was a cross-sectional study design. Multivariable logistic regression was used to identify factors independently associated with odds of knowledge and uptake of CC screening.

Results

About 141 (29%) of the 483 students surveyed had high knowledge of CC, 62 (13%) reported ever screened for CC. Students who resided within school campus were about 2 times more likely to have adequate knowledge of CC compared to those who resided outside school campus (aOR=1.86; 95% CI =1.13 to 3.04; p=0.014). Students who were aged >30 were 3.4 times more likely to have adequate knowledge compared to those aged <19 (aOR=3.42; 95%CI=0.62 to 18.81; p= 0.014). Students who were sexually active at the time of the study were 3.4 times more likely to screen for CC compared to those who were not (aOR=3.42; 95% CI=1.72 to 6.72; p<0.0001). Students with high knowledge of CC were 2.4 times more likely to screen for CC compared to those with inadequate knowledge (aOR=2.41;95% CI= 1.24 to 4.71; p= 0.010).

Conclusions

Knowledge and uptake of cervical cancer screening among students were very low. The need to intensify Information, Education and Communication on CC could provide an important first step to improving knowledge and uptake of screening.
CURRENT SITUATION OF HUMAN PAPILLOMAVIRUS INFECTIONS IN TUNISIAN WOMEN
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Background and Aims

Human papillomavirus (HPV) infections are a significant public health problem with global estimations over 520,000 new cases and 274,000 deaths due to cervical cancer. In Tunisia, cervical cancer is the third cause of cancer in women but only a few prevalence studies conducted in specific populations are available. The present study aims to estimate the national prevalence of HPV infection and cervical cancer testing among Tunisian women.

Methods

We conducted a population-based cross-sectional study in 2014. We included all sexually active women aged ≥18 years, attending primary health care centers the day of the study. Data collection was based on a standardized questionnaire including socio-demographic data, behavioral factors and previous cervical screening. Betaglobin positive PCR-tests were followed by HPV detection and typing. Ethical considerations were respected.

Results

The total number of surveyed women was 1494, of which 1229 were betaglobin positive. Age was in average 40.4±0.9 years. Overall prevalence of HPV infection was 7.8% (95% CI [3.4 - 14.4%]). The most common genotypes were HPV6 (25.4%) and HPV16 (14.1%). The prevalence of previous cervical screening was 36.6% [34.3%-39.2%]. It was significantly associated with age; from 13.9% for those <30 years to 49.3% for those ≥ 50 years.

Conclusions

Our survey provides an important overview of the current situation of HPV infection among Tunisian women. National prevalence of HPV infection was 7.8% but only 36.6% of women had a previous cervical cancer screening. This coverage remains poor, thus the need of targeted education and encouraging strategies to reduce cervical cancer burden in Tunisia.
Background and Aims

Primary prevention of cervical cancer with the introduction of the Human Papilloma Virus vaccine is the next generation means to reduction of the disease burden in developing countries. Kenya has had only two pilot projects for HPV vaccination with little information on the knowledge of cervical cancer amongst adolescents and their amenability to accepting cervical cancer prevention strategies.

Objective: To compare the knowledge of cervical cancer and acceptability of prevention strategies among vaccinated and non-vaccinated adolescents after an HPV vaccination initiative in Eldoret, Kenya.

Methods

A Cross Sectional Comparative Study carried out in public schools in Eldoret with 180 students proportionately allocated from each school. Data collection was carried out using interviewer-administered questionnaires following IREC approval and written parental consent.

Results

A significantly higher proportion of the vaccinated adolescents had heard of cervical cancer, 58 (96.7%) vs. 61 (50.8%), p < 0.0001 and the HPV vaccine (56 (93.3%) vs. 6 (5.0%), p <0.0001). The school remained the common source of information for both groups. The two groups also showed similarity in their selection of cervical cancer prevention strategies acceptable to them like delaying sexual debut. Similar proportions of participants from each cohort would accept to be screened for cervical cancer (85.0% vs. 86.7%, p = 0.940).

Conclusions

Vaccination promotes cervical cancer knowledge among adolescents. There is need for incorporating health education in schools and providing adolescent-centered cervical cancer prevention strategies.
Background and Aims

To review cost implications for cervical cancer prevention in Sri Lanka for rational introduction of HPV vaccine to National Immunization Programme

Methods

Review country specific data (research and national programmes) with cost implications for primary and secondary cervical cancer prevention. Country specific research data, data from National Cancer Control and Cervical cancer screening programmes were collected and reviewed with costing by scenario building technique in forecasting for best preventive practices.

Results

Cervical cancer screening (2000 women, 20-59 years), identified 12 Carcinoma-in-situ (CIN) I cases, and 2 CIN II cases and one cervical cancer case by Pap smears with projected progression proportion of 1.15 cervical cancers for screen detected cases.

Annually screen only 161,830 women (on single call, 2016) through the National programme but need to screen (Pap) 1739 to prevent one cervical cancer and 1.5 million women annually to prevent 850 cervical cancer cases incurring minimum of US$ 7.4 million (excluding screen detected case management cost).

Attributable risk estimated for high risk HPV (16,18) was 69% at its prevalence of 1.2%. Preventing one case, need to vaccinate (with 16,18) 2521 women annually, forecasting minimum US$ 28.9 million in preventing total 850 cases (based on access to GAVI vaccine price, 3 dose schedule). But National Immunization Programme practically targets one age cohort incurring minimum US$ 1.6 million with results expected in 10-12 years.

Conclusions

Different programme cost implications suggested introducing HPV vaccination to the National programme in Sri Lanka for comprehensive cervical cancer prevention as the best practice.
Background and Aims

Although routine programed cervical cancer screening using the Pap test is not yet established in most developing countries, limited screening is carried out. The technique can also report cervico-vaginal cellular changes including infections and inflammations. Hence, cytological findings from limited cervical cancer screening would inform screening policy in developing countries. The aim of the study is to report cytology findings of cervical smears of non-pregnant women referred for opportunistic cervical cancer screening.

Methods

Pap smear samples were obtained from April 2017 to December, 2017, prepared according to conventional cytology and reported according to Bethesda 3(2015). A structured questionnaire was used to collect information on age, history and knowledge of Pap smear test and clinical data.

Results

A total number of 195 cases were studied with mean age 40.43 years (SD±10.44). The clinical summary reported included-postcoital bleeding 13(6.67%), abnormal vagina discharge 46(23.59%), and non-specific abdominal pain 133(68.21%). Few respondents 56(28.72%) were aware of the Pap test, of which 47/56 knew the reason for the test and 18/47 had taken the test before. Non-neoplastic atypical cytology was reported in 42(21.54%) out of the 195 including; 17/42-candida infections, 14-bacterial vaginosis and 10-inflammatory cellular changes. One case each was suspicious for HPV infection and adenocarcinoma. NILM but absent EC/TZ component was reported in 79/195(40.51%); 60/79 were 30 years and above. Unsatisfactory cytology was reported in 7/195(3.58%).

Conclusions

The study reported low incidence of cervical lesions and HPV co-testing would detect hrHPV infections that have not yet induced cytopathic effect on the cervico-vaginal epithelium.
IPVC8-0649
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - CERVICAL SCREENING AND COMBINED SCREENING VACCINATION STRATEGIES IN LMIC

PROJECTED LONG TERM IMPACT OF HPV VACCINATION AND CERVICAL SCREENING IN INDIA
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Background and Aims

India has the largest burden of cervical cancer globally. Here we use Osmanabad district in Western India as an example rural region to investigate the effectiveness of cervical screening and HPV vaccination.

Methods

We used an extensively validated platform (‘Policy1-Cervix’) to evaluate the impact of a range of screening and vaccination strategies, calibrated to data representative of Osmanabad. We investigated the impact of bivalent, quadrivalent and nonavalent vaccination, assuming vaccination of female pre-adolescents using a 2-dose schedule and considering cross-protection for each vaccine type. We also simulated American Society of Clinical Oncology resource-stratified recommendations for ‘basic’ and ‘limited’ settings, using primary HPV with visual assessment for triage once (at age 30) or twice (at ages 30 and 40) per lifetime in both unvaccinated and vaccinated cohorts.

Results

If 50-80% vaccination coverage is achieved, reductions in cervical cancer mortality of 34-56% (quadrivalent), 38-62% (bivalent) and 42-68% (nonavalent) are predicted for unscreened cohorts; the number needed to vaccinate (NNV) to avert a cancer death is 64-136. If 60-80% screening coverage is achieved in unvaccinated cohorts, mortality reductions would be 20-27% (once lifetime) and 34-45% (twice lifetime); the number needed to screen (NNS) to avert a cancer death is 354-368. Screening in cohorts offered vaccination results in an overall reduction in cancer mortality of 47-74% (quadrivalent), 50-78% (bivalent) and 53-82% (nonavalent), but NNS increases above 500.

Conclusions

For older unvaccinated cohorts, twice-lifetime HPV screening could reduce cervical cancer mortality rates by up to 45%. For younger cohorts, vaccination alone could reduce mortality by up to 68%.
Background and Aims

Human papillomaviruses (HPV) are ubiquitous and the most common cause of sexually-transmitted infections worldwide. Within the Eastern Caribbean, public awareness about HPV is limited. HPV-related carcinomas disproportionately affect low- and middle-income countries (LMIC). Cervical cancer (CC) is the second most prevalent cancer with highest incidence and mortality in the Caribbean among women aged 15-44 years. Several socio-economic/genetic factors predispose Caribbean women to persistent infections, studies show women of African descent retain viral DNA for longer with reduced clearance of high-risk types. HPV-vaccination programs have increasingly been explored in recent years as one strategy to reduce high-disease burden.

Methods

Eastern Caribbean public-health agencies lack sufficient data to establish effective HPV-vaccination programs and regional genotype-prevalence for invasive carcinomas is largely unknown. There’s homogeneity of high-risk HPV-genotypes within the Caribbean, which are different from those seen in the US. A comprehensive literature review conducted through EBSCOhost search.

Results

Combined cytology screening and HPV-testing initiatives to develop regionally-appropriate vaccination policies, can aid with efforts to mitigate the preventable disease burden of CC. Although HPV heterogeneity exists globally, early research indicates HPV-genotypes 16/18 as the most prevalent genotypes for carcinoma in-situ and invasive CC. Introduction of Gardasil-9-vaccine (nanovalent), may be beneficial as it has a projected 89.5% protection against CC in LMICs within the Caribbean.

Conclusions

Regional investigations for the identification of other oncogenic high-risk HPV strains in LMICs, are vital to ensure region-specific prevention and control which may provide data for the future development of third-generation HPV vaccines. Until then, regional prevention programs will continue to need strengthening.
IPVC8-0111
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - CERVICAL SCREENING AND COMBINED SCREENING VACCINATION STRATEGIES IN LMIC

EVALUATION OF A SINGLE DOSE OF HUMAN PAPILLOMA VIRUS (HPV) VACCINE IN PREVENTING CERVICAL NEOPLASIA: EARLY FINDINGS FROM AN INDIAN STUDY
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Background and Aims

Human papillomavirus (HPV) vaccination is a major strategy for prevention of HPV related diseases. A single dose of HPV vaccination if found effective will substantially improve vaccine introduction and coverage. They were followed up for immunogenicity and HPV infection outcomes.

Methods

In a multi-centre cluster randomized trial of two vs three doses of quadrivalent HPV vaccination (GARDASIL®) in India, suspension of the vaccination due to events unrelated to the study led to 4348 (25%) girls aged 10-18 years received three doses on days 1, 60, 180 or later, 4979 (28%) received two doses on days 1 and 180 or later, 3452 (19%) received two doses on days 1 and 60, and 4950 (28%) received one dose.

Results

One dose recipients demonstrated a robust and stable immune response over a 4-year period against HPV 16 and 18. The cumulative frequency of and HPV 16 and 18 infections up to 7 years of follow-up were similar and uniformly low in all the study groups; the frequency of HPV 16 and 18 infection was significantly higher in unvaccinated matched control women than among vaccine recipients.

Conclusions

Our results indicate that a single dose of quadrivalent HPV vaccine is immunogenic and provides lasting protection against HPV 16 and 18 infections similar to the three- and two-dose vaccine schedules. Significant and long-lasting protective effect of a single dose can be a strong argument to introduce one dose of the HPV vaccine in many low income countries where the current standard of care for cervical cancer prevention is ‘no intervention’.
IPVC8-0370
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - CERVICAL SCREENING AND COMBINED SCREENING VACCINATION STRATEGIES IN LMIC

INCREASING OUR UNDERSTANDING OF FACTORS ASSOCIATED WITH CERVICAL CANCER SCREENING UPTAKE IN PERUVIAN WOMEN BY INCORPORATING GEOSPATIAL INFORMATION

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2George Washington University, Health Policy and Management, Washington-DC, USA
3Tulane University, Global Community Health and Behavioral Sciences, New Orleans, USA

Background and Aims

Access to services has been shown to be strongly associated with cervical cancer screening uptake. Therefore, this study investigated geospatial features contributing to utilization of cervical cancer screening, using self-reported screening and geolocating data from a Knowledge, Attitudes, and Practice survey implemented in Iquitos, Peru in Fall, 2017.

Methods

Traditional factors, such as sociodemographic and health characteristics, were incorporated into spatial generalized mixed-effects regression models to understand how accounting for factor spatial variation influences their association with screening uptake. Spatial statistics were used to determine if screened households tended to cluster together or cluster around facilities offering screening in greater numbers than expected, given the underlying population density.

Results

Health insurance status and partner support of screening participation were significantly associated with cervical cancer screening in univariate spatial models but were no longer significant when taking into account all factors spatially-related to screening. Based on K-function plots, screened households displayed overall greater clustering among each other and around their assigned community health post than unscreened households.

Conclusions

This study highlights the importance of considering geospatial features when determining factors associated with cervical cancer screening uptake. The spatial dependency and clustering of screened households around a screening facility suggests that mobile campaigns could improve screening access for distant households. Additional research should directly explore the effect of neighborhood communication and dynamics around health services given the observed clustering of screened households.
HEALTH IMPACT OF DELAYED IMPLEMENTATION OF CERVICAL CANCER SCREENING IN INDIA: A MODELLING ANALYSIS

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⁴London School of Hygiene and Tropical Medicine, Department of Health Services Research and Policy, London, United Kingdom

Background and Aims

To estimate the health impact of delaying implementation of organized cervical cancer screening in India, the country with the highest burden of cervical cancer.

Methods

We used an individual-based microsimulation model of human papillomavirus (HPV) infection and cervical cancer (calibrated to epidemiologic data from India) and a population model to project the lifetime cervical cancer cases and deaths averted under different implementation scenarios of screening. We assumed 10% to 20% coverage of women aged 30 to 34 years. The following scenarios with one-visit VIA and one- and two-visit HPV DNA testing once-in-a-lifetime were considered from 2017 to 2026: 1) immediate implementation of screening with currently available screening tests; 2) immediate implementation of screening with currently available screening tests, with a switch to point-of-care one-visit HPV testing in five years; and 3) five-year delayed implementation of screening with current screening tests or one-visit HPV testing.

Results

Immediate implementation of two-visit HPV testing with a switch to one-visit HPV testing was the most effective strategy, and averted 574,100 cases and 382,500 deaths over the lifetimes of 81.4 million women screened between 2017 and 2026. Among immediate implementation strategies involving only currently available screening tests, two-visit HPV testing averted 111,100 more cases than VIA. Delayed implementation with a one-visit HPV test averted 209,300 cases and 139,100 deaths.

Conclusions

Delaying implementation of screening programs in high-burden settings will result in substantial morbidity and mortality among women beyond the age for adolescent HPV vaccination.
THE VALUE OF HIV TESTING FOR CERVICAL CANCER SCREENING

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\textsuperscript{2}Harvard University, Center for Health Decision Sciences, Boston, USA
\textsuperscript{3}Harvard University, Global Health and Population, Boston, USA

Background and Aims

HIV increases cervical cancer risk. In South Africa, 24% of 15-49 year old women are HIV-positive and up to 48% are undiagnosed. We evaluated the impact of increasing HIV testing on cervical cancer screening in South Africa.

Methods

We developed a microsimulation model describing the natural history of HIV, HPV, and cervical carcinogenesis, and patterns in testing and treatment. We calibrated the model to South African epidemiologic data. We compared three screening tests – cytology, HPV-DNA, and visual inspection with acetic acid (VIA) – for HIV-positive diagnosed, HIV-positive undiagnosed, and HIV-negative women. For each scenario, we varied screening frequency from annual to every five years, age to start testing from 25 to 30, and frequency of HIV testing. Costs include screening and treatment for HIV and cancer. Health outcomes include cancer cases averted and quality-adjusted life years.

Results

We found that with current HIV testing, HPV-DNA was optimal every three years for HIV-positive diagnosed women from diagnosis and cytology every five years for HIV-negative and undiagnosed women from age 25. With more frequent HIV testing, the optimal strategy changes to VIA screen-and-treat every five years for HIV-positive diagnosed women and HPV-DNA every five years for HIV-negative and undiagnosed women from age 30.

Conclusions

Our results indicate it is optimal to screen HIV-negative and undiagnosed women more frequently than current guidelines. With more frequent HIV testing the preferred strategy changes to more sensitive but less frequent tests for HIV-positive women and allows HIV-negative women to start screening at an older age.
Background and Aims

To describe the surgical oncology experience at a major regional hospital in Malawi and to identify barriers to improved outcomes.

Methods

Patients were identified with a suspected diagnosis of cancer from January 1, 2017, through March 7, 2017. Cancer cases were classified according to patient demographic characteristics, disease location, and therapeutic intent. The Malawi data were compared with US data from the Surveillance Epidemiology and End Results database.

Results

A malignant diagnosis was suspected in 255 of the 1440 patients undergoing a major resection (17.8%) (mean patient age, 53 years). The most common cancers in males were prostate, esophageal, and gastric. In females, the most common cancers were breast, colon, and esophageal. Many of the procedures were performed with palliative intent.

Conclusions

Cancer surgery comprises a significant proportion of the surgical caseload in low-income countries. Patients often present with late-stage, inoperable cancer. The participation of the surgical community is critical for addressing barriers to effective cancer care.
Background and Aims

Accurate estimation of healthcare costs plays an essential role in cost-effectiveness analyses; however, detailed information on the component costs of healthcare is limited in China. Here, we aimed firstly, to develop a novel framework to extrapolate microcosting data from rural Xiangyuan to derive detailed province-specific cost estimates, and secondly, to characterise the relationship between this detailed extrapolation method and more commonly-used extrapolation methods based on economic macro-indicators.

Methods

A detailed multistep scaling process was used to extrapolate costs for each province, starting with costs related to cervical screening from a microcosting study performed in rural Xiangyuan, in which we considered the delivery of services at different levels in each province (township, county, provincial), the differential in costs between inpatient/outpatient services, and costs by urban/rural regions. To explore the validity of a simplified approach, we used regression modelling to characterise the relationship between these detailed costs, and those obtained using two different macro-indices: GDP per-capita (which is commonly used for cost scaling), and HDI.

Results

Costs varied substantially by urban/rural regions and between provinces; for example the ratio of highest to lowest province costs for Visual Inspection with Acetic Acid was 4.1, and for cervical cancer treatment was 4.7. Costs using simplified GDP-based scaling estimates were ~14-23% higher, whereas HDI-based scaling estimates were ~4-8% higher than the reference costs.

Conclusions

The costs of health care in China vary substantially not only between urban and rural populations but also between provinces. Macro-economic scaling with an HDI-based method performed better than a GDP-based scaling method.
IPVC8-0334
POSTER SESSION

LOW AND MIDDLE INCOME (LMIC) SETTINGS - ECONOMICS AND MATHEMATICAL MODELLING FOR LMIC

COST-EFFECTIVENESS AND PUBLIC-HEALTH IMPACT OF A NONAVALENT HPV VACCINE COMPARED WITH A BIVALENT OR QUADRIVALENT HPV VACCINE IN PHILIPPINES USING A TRANSMISSION DYNAMIC MODEL

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²Merck Sharp & Dohme, Market Access, Makati, Philippines
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⁴Merck & Co.- Inc., Center for Observational and Real World Evidence, North Wales, USA
⁵Merck & Co.- Inc, Center for Observational and Real World Evidence, North Wales, USA

Background and Aims

6,670 women are diagnosed with cervical cancer (CC) and 2832 die from the disease annually in the Philippines. The national immunization program (NIP) includes vaccination of 9-13 year-old public school girls in 56 cities/provinces, with a 2-dose quadrivalent human papillomavirus vaccine (4vHPV). The nonavalent vaccine (9vHPV) prevents about 90% of genital warts (like 4vHPV), and prevents an additional 20% of CC burden (compared with 2vHPV/4vHPV). We assessed the public health impact and cost-effectiveness of 9vHPV vaccination vs bivalent vaccine (2vHPV) or 4vHPV vaccination.

Methods

A transmission dynamic model was used to assess the public health impact and cost-effectiveness of vaccinating 9-13 year-old public-school girls with 9vHPV in preventing HPV-related cervical cancer (CC) and genital warts in Philippines. We assumed a 2-dose schedule, and 85% coverage.

Results

The 9vHPV had 339,806 fewer cases of CIN 2/3, 90,357 fewer cases of CC, and 37,693 fewer CC deaths compared to both 2vHPV and 4vHPV, and 16,157,310 fewer cases of genital warts compared to 2vHPV. This resulted in disease cost avoided of $466,163,869 and $79,241,435 compared with 2vHPV/4vHPV, respectively, and an incremental cost-effectiveness ratio of $2,046/QALY and $2,496/QALY compared with 2vHPV and 4vHPV, respectively.

Conclusions

Adding 9vHPV vaccine to the Philippines NIP resulted in additional public health benefit, reduced disease costs, and was highly cost-effective (threshold willingness-to-pay of $2,951 GDP-per-capita) compared with either 2vHPV or 4vHPV vaccination. Introducing 9vHPV into NIP should be considered for reducing HPV-related diseases. Results are conservative as they do not include the impact on other cancers.
Table 1: Public-health Impact of vaccination with 9vHPV

<table>
<thead>
<tr>
<th>HPV-related Disease</th>
<th>Cumulative Reduction in HPV-related Disease Incidence with nonavalent vaccine (9vHPV) compared with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bivalent Vaccine (2vHPV)</td>
</tr>
<tr>
<td># of CIN1 compared to 9vHPV</td>
<td>318,243</td>
</tr>
<tr>
<td># of CIN 2/3 compared to 9vHPV</td>
<td>339,806</td>
</tr>
<tr>
<td># of Genital warts compared to 9vHPV</td>
<td>16,157,310</td>
</tr>
<tr>
<td># of Cervical cancer cases compared to 9vHPV</td>
<td>90,357</td>
</tr>
<tr>
<td># of Cervical cancer deaths</td>
<td>37,693</td>
</tr>
</tbody>
</table>

Table 2: Number of cases of conization among mid-adult women

<table>
<thead>
<tr>
<th>Year</th>
<th>CKC</th>
<th>LEEP</th>
<th>Both</th>
<th>Total</th>
<th>CKC</th>
<th>LEEP</th>
<th>Both</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>2,753 (20%)</td>
<td>10,557 (77%)</td>
<td>406 (3%)</td>
<td>13,716 (100%)</td>
<td>2,553 (20%)</td>
<td>9,967 (77%)</td>
<td>387 (3%)</td>
<td>12,907 (100%)</td>
</tr>
<tr>
<td>2013</td>
<td>2,194 (19%)</td>
<td>8,781 (78%)</td>
<td>330 (3%)</td>
<td>11,305 (100%)</td>
<td>2,037 (19%)</td>
<td>8,323 (78%)</td>
<td>311 (3%)</td>
<td>10,671 (100%)</td>
</tr>
<tr>
<td>2014</td>
<td>2,287 (19%)</td>
<td>9,429 (78%)</td>
<td>330 (3%)</td>
<td>12,046 (100%)</td>
<td>2,132 (19%)</td>
<td>8,801 (78%)</td>
<td>313 (3%)</td>
<td>11,246 (100%)</td>
</tr>
<tr>
<td>2015</td>
<td>1,433 (19%)</td>
<td>5,941 (78%)</td>
<td>231 (3%)</td>
<td>7,605 (100%)</td>
<td>1,324 (19%)</td>
<td>5,563 (78%)</td>
<td>217 (3%)</td>
<td>7,104 (100%)</td>
</tr>
<tr>
<td>2016</td>
<td>1,440 (18%)</td>
<td>6,194 (79%)</td>
<td>221 (3%)</td>
<td>7,855 (100%)</td>
<td>1,316 (18%)</td>
<td>5,757 (79%)</td>
<td>206 (3%)</td>
<td>7,279 (100%)</td>
</tr>
</tbody>
</table>
IPVC8-0208
POSTER SESSION
LOW AND MIDDLE INCOME (LMIC) SETTINGS - ECONOMICS AND MATHEMATICAL MODELLING FOR LMIC

IS A CERVICAL CANCER SCREENING PROGRAMME COST-EFFECTIVE FOR SAMOA?
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³University of Auckland, Obstetrics and Gynaecology, Auckland, New Zealand

Background and Aims

Cervical cancer is a leading cause of cancer-related deaths of women, of which 85% of deaths are in countries without vaccination and screening programmes. Samoa is such a country, with an estimated cervical cancer incidence of 17.1 per 100,000 women (1).

Methods

Based on how cervical cancer progresses in the Samoan context and recent technology advances for detecting the Human Papillomavirus, we developed a Markov Model (using TreeAge Pro software) to evaluate the cost-effectiveness of cervical cancer screening programmes. Several scenarios were explored with respect to different screening tools and frequencies, ranging from screening once at age 35 to screening every 5 years between the ages of 30 and 59.

Results

Assuming 50% coverage of the eligible population, all screening scenarios were found to be highly cost-effective in terms of quality-adjusted life years (QALYs) gained; in particular, 5-yearly screening from age 30 was the best, including reducing cervical cancer incidence by 41%. Greater population coverage would decrease cancer incidence further.

Conclusions

This model could be used to support other decision-making with respect to investments in cervical cancer prevention in pursuit of the most cost-effective use of available resources.

IPVC8-0339
POSTER SESSION
LOW AND MIDDLE INCOME (LMIC) SETTINGS - VACCINE AND SCREENING IMPLEMENTATION IN NON GAVI-ELIGIBLE/MIDDLE INCOME COUNTRIES

HPV VACCINE ACCEPTABILITY WITHIN AN HPV-BASED CERVICAL CANCER SCREENING PROGRAM IN MEXICO CITY

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³National Institute of Public Health, Center for Population Health Research, Cuernavaca- Morelos, Mexico
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⁵Wolfson Institute of Preventive Medicine- Queen Mary University of London, Centre for Cancer Prevention, London, United Kingdom
⁶Departments of Pathology and Obstetrics and Gynecology, University of New Mexico, Albuquerque- New Mexico, USA
⁷Albert Einstein College of Medicine, Department of Epidemiology and Population Health, Bronx- New York, USA

Background and Aims

A combined human papilloma virus (HPV) screening and vaccination strategy among adult women has been proposed as an appealing tool for cervical cancer prevention in low and middle-income countries. However, acceptability of this combined intervention warrants further evaluation before implementation.

To evaluate acceptability of vaccination within a combined HPV-screening and vaccination strategy in women 25-45 years within Mexico City Public Health Services.Methods

Within a questionnaire, open-ended questions on acceptability were collected, transcribed and coded. Systematic qualitative analysis was done to order answers using emergent codes on factors that could facilitate or impede vaccination.

Results

A total of 2,450 women 25-45 years were interviewed over 10 months. Most women (98%) accepted vaccination; the main reasons for acceptance were: 1) Prevention of infection and self-care; 2) Perceiving the vaccine as necessary given sexual behavior (number of partners, sexual practices); 3) Fear (of sexually transmitted infections, cancer, HPV or of dying especially in relation to leaving children motherless); 4) Perceived vaccine benefits (no cost, immunity, perceived curative properties). Barriers to vaccination included: 1) Lack of information; 2) Fear of adverse reactions or of combining the vaccine with medications; 3.) Fear of vaccines in general or lack of trust in this specific vaccine; 4.) Not perceiving oneself as at risk.
Conclusions

HPV vaccination is highly acceptable among adult women attending cervical cancer screening in Mexico. Mass media, social network, eHealth campaigns and individualized face-to-face counseling could encourage HPV vaccination dealing with negative factors affecting vaccine uptake.
Background and Aims

Certain populations are at much greater risk of HPV infection and of developing related diseases, including cancers, and may have less access to preventive services. The CONDESA Study is being implemented in Mexico City to offer a comprehensive preventive intervention against HPV, associated cancers and other sexually transmitted infections (STIs), to vulnerable groups.

The CONDESA Study will evaluate the effectiveness of a vaccination-screening-treatment strategy in four groups in Mexico City: men who have sex with men, transgender women, people living on the street and people being treated for sexual assault. Facilitators and barriers to HPV prevention care will be explored. Prevalence and incidence of other STIs will be assessed.

Methods

This mixed-methods study combines HPV vaccination with early detection and treatment of HPV infection and HPV-related diseases. Men and women (including transwomen) will perform self-collection of anal, vaginal, oral and urine samples (only in women) for HPV testing; other STIs will also be tested for and treated. Diagnostic confirmation of neoplastic lesions and genital warts will be performed, and treatment provided. Qualitative interviews in a subsample of the study population will explore experiences and perceptions of the vaccination-screening-treatment strategy and related barriers.

Results

The impact of these interventions on decreased levels of high-risk HPV infection and intraepithelial lesions in anal canal and cervix will be evaluated during 12-months follow-up.

Conclusions
This study will provide scientific evidence on the effectiveness of a vaccination-screening-treatment strategy to decrease the burden of HPV-related neoplasms in highly vulnerable populations.
LOW AND MIDDLE INCOME (LMIC) SETTINGS - VACCINE AND SCREENING IMPLEMENTATION IN NON GAVI-ELIGIBLE/MIDDLE INCOME COUNTRIES

PARENTAL ATTITUDES TOWARDS FEMALE AND MALE ADOLESCENT HUMAN PAPILLOMAVIRUS VACCINATION IN BRAZIL

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2University of California Berkeley, School of Public Health, Berkeley, USA
3Emory University, Rollins School of Public Health, Atlanta, USA

Background and Aims

HPV vaccines are recommended for the prevention of HPV-related disease, but vaccination coverage remains low worldwide. We aimed to assess parental acceptance of the HPV vaccine in Brazil and examined intentions for female and male HPV vaccination.

Methods

We conducted a random-digit-dial survey of parents with children 18 year old or less in seven major Brazilian cities from July/2015 to October/2016. A knowledge, attitude and practices questionnaire was developed and validated, using the Health Belief Model.

Results

826 out of 2,324 (35.5%) eligible parents completed the interview. Parental acceptance of the HPV vaccine for daughters and sons was high (92% and 86%, respectively), but despite that only 58.4% of the girls eligible for HPV vaccination through the NIP had received a two-dose scheme. “No vaccination/missed vaccination at school” was the most common reason not to have had HPV vaccination. Parents refusing vaccination were less likely to know that: HPV is sexually transmitted and causes genital warts, HPV vaccination is more beneficial before sexual debut, and HPV vaccine reactions are minor, and were more likely to believe it can cause severe adverse events. Attitudes associated with HPV vaccine acceptance included: general belief in vaccines, trust in the NIP and in the HPV vaccine efficacy.

Conclusions

One year after its introduction in the NIP, most parents surveyed in Brazil accept HPV vaccination for their daughters and sons. Low coverage in the NIP are likely to be due to challenges in adolescent vaccine delivery and HPV vaccination barriers at health-care centers, rather than to vaccine hesitancy.
The aim was to evaluate the impact of HPV vaccination and resource-stratified cervical screening options in Vietnam, a low-and-middle-income country (LMIC) not eligible for Gavi support.

Methods

We used a dynamic model of screening and vaccination (‘Policy1-Cervix’) to evaluate the impact and cost-effectiveness of 50-80% coverage with quadrivalent(‘HPV4’), bivalent(‘HPV2’) and nonavalent(‘HPV9’) vaccines assuming a 2-dose schedule (cost-per-dose US$8.5-$10.8 respectively). We also evaluated the impact and cost-effectiveness of screening using resource-stratified guidelines recommended by the American Society of Clinical Oncology (ASCO), considering a range of primary test and triage options and age-ranges, which differed for rural and urban regions. Strategies were considered “very cost-effective” or “cost-effective” if the ICER (incremental cost-effectiveness ratio, when compared to the next least costly strategy) was ≤1XGDP(US$2215) or ≤3XGDP(US$6645), respectively.

Results

HPV vaccination is predicted to reduce cancer rates by 37-60% (HPV4), 40-65% (HPV2) and 43-71% (HPV9), and with vaccine cost per dose of US$8.5-10.8 all vaccines were very cost-effective compared to no intervention (CER<US$518/ life year saved [LYS]). In older unvaccinated women, primary HPV testing 2-3 times-per-lifetime was very cost-effective (CER<US$1957/LYS) and could reduce cancer rates by 27-36% (depending on triage test and age-range). For urban regions where it might be feasible, primary HPV triaging with partial genotyping yielded similar efficacy for fewer treatments compared to triaging with Visual Assessment for Treatment (VAT) (number-needed-to-treat to prevent a cancer 17-29 vs. 24-60).

Conclusions

HPV vaccination and primary HPV DNA-based screening could reduce cervical cancer rates in Vietnam by 37-71% and 27-36%, respectively, and both are very cost-effective.
LOW AND MIDDLE INCOME (LMIC) SETTINGS - VACCINE AND SCREENING IMPLEMENTATION IN NON GAVI-ELIGIBLE/MIDDLE INCOME COUNTRIES

WILLINGNESS TO PARTICIPATE IN ROUTINE HPV VACCINATION PROGRAMS AMONG FEMALE HAIRDRESSERS IN LAGOS NIGERIA

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Background and Aims

The uptake of HPV vaccination currently remains low in Nigeria. There have been calls among stakeholders for its inclusion in the national routine immunization schedule. This study was conducted to assess the willingness of female hairdressers in Lagos to participate in routine HPV vaccination programs in the near future.

Methods

Self administered questionnaires were administered to 223 female hairdressers and hairdressing apprentices aged between ten and twenty six years. The data was analyzed with SPSS version 18 data editor. Univariate Odds Ratios (OR) and 95% Confidence Intervals (CI) were used to determine the correlates of Willingness to Receive (WTR) Hepatitis B vaccination by the girls.

Results

A total of 88 girls (39.5%) reported that they would be willing to receive the vaccination. Greater willingness was associated more advanced years of training (OR = 1.23, 95% CI: 1.15–1.53), fewer doses of vaccine (OR = 1.25, 95% CI: 1.05–1.52), lower cost of vaccines (OR = 1.36, 95% CI: 1.13–1.45) and incentives (OR = 1.38, 95% CI: 1.12–1.42). Decreased WTR was associated with concerns about harm to the receiver (OR = 0.44, 95% CI: 0.22–0.64), stigma (OR = 0.71, 95% CI: 0.52–0.78) and previous sexual exposure (OR = 0.88, 95% CI: 0.53–0.96).

Conclusions

The low level of WTP among the respondents indicates that much work needs to be done in health education if HPV would be included in the routine immunization schedule.
LOW AND MIDDLE INCOME (LMIC) SETTINGS - VACCINE AND SCREENING IMPLEMENTATION IN NON GAVI-ELIGIBLE/MIDDLE INCOME COUNTRIES

METHODS OF THE FASTER-TLALPAN STUDY IN MEXICO

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Background and Aims

Strategies combining HPV vaccination with HPV-based screening are needed to transform the highly inefficient screening paradigms that have been the norm in lower and middle-income countries.

To describe the methods of the FASTER-Tlalpan Study designed to evaluate the impact of a combined high-risk (hr) HPV-based screening and HPV vaccination strategy which seeks to extend screening intervals.

Methods

Users of the Cervical Cancer Screening Program in Tlalpan borough in Mexico City (10,000 women, aged 25-45 years) will be invited to participate in the study. Participants will be assigned to one of three groups: 1) HPV16/18 vaccine and HPV-based screening; 2) HPV6/11/16/18 vaccine and HPV-based screening; 3) Control group-only HPV-based screening. Safety profiles at different screening intervals will be defined based on surveillance of persistent HPV infection and development of precancerous lesions. Participants will receive diagnostic confirmation and treatment as necessary. The study has two main endpoints: 6-month persistent infection as a surrogate of pre-cancer or cancer occurrence at 2.5, 5 and 10 years of follow-up and CIN2+ incidence.

Results

So far the trial has recruited 2,450 women; with a participation of 98%, a mean age of 36 years, 70% have been pregnant at least once, mean age at first intercourse of 18 years, hrHPV positivity of 17.6% and HPV16 of 4.1%. 
Conclusions

The FASTER-Tlalpan study in Mexico will provide data on the potential benefits of combining HPV vaccination and hrHPV-based screening in order to reduce the cost of preventive strategies by extending screening intervals with acceptable patient safety.
The HPV vaccination rate in Japan has fallen to nearly zero percent after the spread of news of possible adverse events became a wide-reaching social issue. This unfavorable situation needs changing. This study aimed to clarify the effects of an intervention using scientific information showing World Health Organization comments on vaccines’ effects, along with statistics on cervical cancer in Japan.

Methods

We collected data in March 2018 via a website. Recruited participants were ≥20 years old and completed a 10-item questionnaire. The first five questions covered HPV knowledge, while the second five addressed awareness of HPV vaccines and screening tests. We randomly assigned each participant to respond to the questionnaire with or without intervention using scientific information on an easy-to-read slide.

Results

There were 1,660 (830 male, 830 female) participants, of whom 61.0% were married. Only 29.2% of respondents were aware of positive effects of HPV vaccination, while 32.7% were aware of negative effects. Although only 21.2% of respondents had a positive attitude toward HPV vaccination for their daughters, there were 40 (4.8%) more respondents in the intervention group with a positive attitude (p=0.01). However, despite the intervention, the proportion of those who expressed their desire to receive a screening test or to inform others of HPV-related problems did not increase (p=0.38, 0.11, respectively).

Conclusions

We found that simple scientific information could increase positive awareness of HPV vaccination. Even short interventions of this sort may have the potential to immediately modify people’s thinking about the topic.
Background and Aims

As in any developing countries state of West Bengal in India has a huge burden of cervical cancer patients in advanced stage coming from rural area where awareness regarding the usefulness of palliative care is rather poor. Our goal is to give a pain free good quality of life in these advanced stage cervix cancer patients. Objective of this study is to identify the main difficulties in achieving the above goal in a rural village setting in India.

Methods

Advanced cervix cancer patients in need of palliative care in various villages in of rural India were selected for this study. Their symptoms and managements in that rural surroundings were evaluated by an NGO (under the guidance of a senior palliative care specialist) working in that area. An attempt was made to identify the main obstacles in getting proper palliative care in a rural setting.

Results

Pain, fatigue are the main symptoms effecting these patients. In most patients pain and other symptoms control were grossly inadequate due to lack of properly trained manpower in the rural India. However regular homecare visits by a group of social workers were of immense help in the last few months of life. NGO team was well guided by a palliative care specialist.

Conclusions

There is a wide gap of trained manpower in this filled in rural areas of India. Dedicated groups from rural area itself need encouragement and proper training, so that difficult symptoms can be managed locally along with necessary social and psychological support to these patients.
CERVICAL CANCER SCREENING AND HPV VACCINE ACCEPTABILITY AMONG RURAL AND URBAN WOMEN IN CONGO BRAZZAVILLE DEPARTMENTS.

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Background and Aims

To determine cervical cancer screening coverage, knowledge, attitudes, barriers toward screening tests among rural, urban women areas Congo, as well as explore how they view acceptability of HPV vaccine and potential barriers to vaccination.
Methods

Questionnaires conducted using multistage random sampling within urban, rural areas in Congo. Women aged 18–55 participate in survey. Overall response rate 97.5%, a final sample 303 rural 272 urban dwelling women. Primary and secondary outcome measures Descriptive and simple test statistics were used to compare across rural and urban strata. Multivariate logistic regression models were used to estimate ORs and 95% CIs.

Results

Women (82%) reported had heard of cervical cancer, while self-reported cervical cancer screening among women was very low (6%). In urban areas, factors associated with screening were: older age (OR=4.14, 95% CI 1.86 to 9.24 for ages 40–49, and OR=8.38, 95% CI 2.10 to 33.4 for >50 years), having health insurance (OR=4.15, 95% CI 1.52 to 11.4), and having knowledge about cervical cancer (OR=5.81, 95% CI 1.58 to 21.4). In contrast, among women residing in rural areas, only condom use (OR=6.44, 95% CI 1.12 to 37.1) was associated with screening. Women from both rural and urban areas had low vaccine-related knowledge; most indicated they would be highly accepting if it were readily available (93%).

Conclusions

Current proportion women screened cervical cancer low in Congo. Study identified several modifiable factors that could be addressed to increase screening rates. Although best implemented concurrently, the availability of prophylactic vaccination for girls may provide an effective means of prevention if they are unable to access screening in future.
LOW AND MIDDLE INCOME (LMIC) SETTINGS - PSYCHOSOCIAL IMPACT OF NEW HPV AND CERVICAL CANCER PREVENTION STRATEGIES

FEMALE PERSPECTIVES ON MALE INVOLVEMENT IN A HUMAN-PAPILLOMAVIRUS-BASED CERVICAL CANCER SCREENING PROGRAM IN WESTERN KENYA

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Background and Aims

To be effective, population-based cervical cancer prevention programs must be tailored to meet the needs of the target population. One important factor in cervical cancer screening may include male involvement. To iteratively improve a screening program employing self-collected human-papillomavirus (HPV) testing in western Kenya, we sought to understand the role of male partners and leaders in decision-making and accessing screening.

Methods

We carried out semi-structured, in-depth interviews (IDIs) with women and community health volunteers who took part in a multiphase trial of implementation strategies for HPV-based cervical cancer screening. IDIs were coded and themes related to decision-making, screening and treatment barriers, and influence of male partners, family, and community leaders were identified and analyzed.

Results

595 in-depth interviews (IDIs) were included in the analysis. Women reported a general acceptance of community leader involvement in education and screening campaigns, acknowledging that most community leaders were male. Women experienced both support and opposition from their male partners. Partner support took the form of financial support for transportation and emotional support and encouragement, while opposition ranged from perceived negative reactions to lack of permission, isolation, and abandonment. Though most women described their own partner as supportive, many felt that other male partners would not be supportive. Most participants believed that increased HPV and cervical cancer knowledge would increase partner support.

Conclusions

There was a clear interest in involving male partners in the cervical cancer prevention process, specifically in increasing knowledge and awareness. Future research should explore engaging male partners in education campaigns.
Sexual risk-taking among adolescents in Nigeria is a major public health concern, which leads to unwanted pregnancies, unsafe abortions and increased transmission of HIV/AIDS and other sexually transmitted infections. The aim of this study was to assess sexual risk behaviour among in-school adolescent females in Ogun State, Southwest, Nigeria.

Methods

A cross-sectional study was completed with a sample of female students at three secondary schools in Ijebu-Ode, Nigeria. Using the multi stage sampling technique, data were collected using validated semi-structured interviewer-administered questionnaires.

Results

A total of 131 female respondents participated, who ranged between 13 and 19 years of age, with a mean of 16±1.27 years. Nineteen (14.5%) of the respondents had been exposed to sexual relations with the mean age of sexual debut at 13.4±2.78 years. Participants with sexual exposure reported vaginal sex (89.5%), digital sex (36.8%) and oral sex (5.3%). None of the participants practices anal sex. Among the participants, 42.1% had more than 1 sexual partner, 47.4% used condoms during sex, and 36.8% claimed that their partner had refused using a condom at one sexual encounter. Participants reported financial worries (44.3%), low self-esteem (29%), watching pornography (26%), victim of physical violence (22.1%) or victim of rape (3.8%).

Conclusions

Sexually active adolescents are involved in risky sexual behaviour. The factors that may impair judgement and hinder safe sexual practices are highlighted. Behaviour change communication and youth friendly services should be provided to this group of people.
AGE-SPECIFIC HPV PREVALENCE AMONG ADOLESCENT GIRLS IN JOS, NORTH-CENTRAL NIGERIA

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Background and Aims

Knowledge of the age-specific prevalence of HPV types among adolescent girls in SSA is essential to determine the best age for introduction of HPV vaccination, monitoring of vaccine efficacy and provision of insight into persistent infection.

Methods

We randomly selected 205 girls, age 9–20 years living in Jos, Nigeria. Informed consent and assent were obtained prior to training on self-collection of vulvo-vaginal samples using sterile swab stick and first void urine. HPV detection was carried out using HPV SPF10-DEIA/LiPA25. Data analysis was done using STATA14®.

Results

The mean(SD) age of the girls was 14.9(2.3) years. AnyHPV was detected in 29.3% of participants. The earliest age at which anyHPV and high-risk HPV (hrHPV) infections were detected in either urine or vulvo-vaginal samples were 10 and 11 years of age respectively. The prevalence of anyHPV, hrHPV, lrHPV and multiple hrHPV peaked at 16 years of age. The prevalence of hrHPV infection was 3.4% among the 9–12 years age group, 7.8% among 13–16 years and 5.4% among 17–20 years old. The commonest hrHPV types detected were 52 (10.2%), 18 (6.3%) and 51 (4.4%).
Figure 1: Age-specific Prevalence of HPV among adolescent girls in Jos, North-Central Nigeria

Figure 2: Age-group HPV Prevalence among adolescent girls in Jos, North-Central Nigeria

Conclusions
While a larger study is warranted, our findings suggest that in this population, HPV vaccination starting at 9 years of age would cover the at-risk population.
COMPARISON OF TYPE-SPECIFIC HPV DETECTION IN URINE AND VULVO-VAGINAL SAMPLES FROM ADOLESCENT GIRLS IN JOS, NIGERIA

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Background and Aims

To compare self-collected vulvo-vaginal swab and first void urine for the detection of HPV among adolescent girls in Jos.

Methods

We randomly recruited 205 girls, age 9–20 years from ten public and private high schools in Jos, Nigeria. After informed consent and assent, each participant self-collected vulvo-vaginal samples and first-void urine which were tested using SPF10-DEIA/LiPA25. Data were analyzed using STATA14®.

Results

The mean (SD) age of participants was 14.9 (2.3) years. We detected anyHPV in 13.2% of vulvo-vaginal and 21.0% of urine samples. 7.8% and 11.2% of vulvo-vaginal swab and urine had hrHPV respectively. The commonest hrHPV types in vulvo-vaginal swab were 52 (3.9%), 51 (2.4%) and 18 (1.5%), and in urine were 52 (6.8%), HPV 18 (5.4%) and HPV 51 (2.9%). Approximately 10% and 14% of vulvo-vaginal samples and urine samples had single infections; and 3.4% and 7.3% had multiple infections respectively. Multiple hrHPV infection was detected in 2.9% of vulvo-vaginal swab and 5.9% of urine samples. Of the 27 vulvo-vaginal swabs and 43 urine samples positive for anyHPV, in only 10 (37.0%) instances were both vulvo-vaginal and urine samples positive for anyHPV. There was poor concordance between the urine and vulvo-vaginal samples for anyHPV (κ = 0.15, p=0.03).
Conclusions
The poor concordance suggests that first-void urinary HPV is not a suitable proxy for vulvo-vaginal HPV infection in this population.
Cervical cancer is a common malignancy among Kenyan women, and is more common in women with HIV infection. Women were evaluated in a prospective longitudinal study to define modifiable factors predicting incidence and persistence of HPV and cervical dysplasia in HIV-infected/uninfected women with normal visual inspection with acetic acid (VIA) at enrollment.

Methods

From September 2015 to October 2016, 223 women ages 18 to 45 years old were enrolled in a cervical cancer screening clinic in Eldoret, Kenya. Cervical swabs, behavioral data, and HIV-related data were collected at enrollment. HPV typing was performed using the Roche Linear Array.

Results

This analysis consists of 219 evaluable participants including 115 HIV-infected (median age 36 years) and 104 HIV-uninfected women (median age 33 years) (p=0.0009). There was a significant difference in number of lifetime sex partners between HIV-infected (median 4, IQR 3-8) and HIV-uninfected women (median 3, IQR 1.5-4), p=0.0001. 86.8% of HIV-infected women were receiving anti-retroviral therapy (ART); median duration between HIV diagnosis and enrollment was 7.2 years (IQR 4.1-10.3); median CD4 count was 471 (IQR 310-612). HPV detection is shown in Figure 1 and Table 1.
Figure 1. Percent of Women with Type-Specific High Risk HPV Detection in HIV-Infected and HIV-Uninfected Cohorts.
Conclusions

Oncogenic HPV types were highly prevalent in Kenyan women. HIV-infected women were more likely to have detection of HPV 16, other oncogenic HPV types, and multiple types in spite of ART. In this longitudinal study, other factors will be included in future analyses, such as behaviors, presence of concomitant sexually transmitted infections, the effect of HIV viral load, CD4 count, and ART.

Table 1. HPV detection in 115 HIV-infected and 104 HIV-uninfected women

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>HIV Infected</th>
<th>HIV Uninfected</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any HPV (%)</td>
<td>59.1</td>
<td>35.6</td>
<td>.0005</td>
</tr>
<tr>
<td>HR-HPV(^1) (%)</td>
<td>47.0</td>
<td>27.9</td>
<td>.0037</td>
</tr>
<tr>
<td>LR-HPV(^2) (%)</td>
<td>32.2</td>
<td>17.3</td>
<td>.0113</td>
</tr>
<tr>
<td>HPV 16 (%)</td>
<td>10.4</td>
<td>2.9</td>
<td>.0272</td>
</tr>
<tr>
<td>Nine-valent HR-HPV vaccine types(^3) (%)</td>
<td>26.1</td>
<td>17.3</td>
<td>.1168</td>
</tr>
<tr>
<td>HR-HPV not covered by nine-valent vaccine(^4) (%)</td>
<td>32.2</td>
<td>15.4</td>
<td>.0038</td>
</tr>
<tr>
<td>Two or more HR-HPV types (%)</td>
<td>20.0</td>
<td>6.7</td>
<td>.0041</td>
</tr>
<tr>
<td>Number of HR-HPV types (mean)</td>
<td>1.3</td>
<td>0.6</td>
<td>.0001</td>
</tr>
</tbody>
</table>

\(^1\) Oncogenic (“High-Risk”) HPV  
\(^2\) Non-oncogenic (“Low-Risk”) HPV  
\(^3\) HPV 16, 18, 31, 33, 45, 52, 58  
\(^4\) HPV 26, 35, 39, 51, 53, 56, 59, 66, 67, 68, 69, 70, 73, 82, 83, 89
THE KNOWLEDGE LEVEL OF HUMAN PAPILLOMAVIRUS INFECTIONS, RELATED DISEASES AND VACCINE UPTAKE AMONG TERTIARY STUDENTS

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Background and Aims

Human papillomavirus (HPV) is a common sexually transmitted virus and apart from cervical cancers, other conditions are related to the infection. The aim of the study is to report on the knowledge of human papillomavirus infection among undergraduate university students.

Methods

A survey was conducted from 1st January and 31st May, 2017 by convenient sampling 399 university students using a semi-structured questionnaire to collect data on the knowledge level of human papillomavirus infections and related diseases.

Results

Majority of the study participants 372/399 (93.2%) were within 18-24 years of age. Most of respondents (87.7%) were aware of HPV infections and 56.6%, 49.4% and 19% knew the HPV infection to be associated with cervical cancers, genital warts and vaginal cancer respectively. Less than 10% knew that HPV infections can also be associated with conditions such as cancers of the anus, penile, oral cavity, oropharynx and throat. Although 52.6% indicated unprotected sex as a mode of infection transmission, merely 14% recognized oral sex as a mode of spreading the infection, and 26.1% stated condom usage will prevent HPV infections. None of the study participants had been vaccinated against HPV infection, 237(59.4%) were unaware of HPV vaccination.

Conclusions

The study generally reported low knowledge level of HPV infections and related diseases, hence the need to increase educational campaign across the country. There is also the need to describe HPV antibodies in such an unvaccinated population since this would provide a cumulative measure of viral exposure.
IPVC8-0620
POSTER SESSION
LOW AND MIDDLE INCOME (LMIC) SETTINGS - OTHER PUBLIC HEALTH / EPIDEMIOLOGY RESEARCH

BETWEEN THEORY AND REALITY: ACCEPTABILITY OF HPV VACCINE AMONG WOMEN IN NORTHERN NIGERIA
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Background and Aims

The bivalent HPV vaccine (cervarix®) has been available in Federal Teaching Hospital Gombe (FTHG) since 2013 (5 years ago). Uptake of the vaccine in reality has remained very low despite relative high acceptability among different population groups in the study area theoretically. There was history anti-vaccine activities in northern Nigeria. This study aims at highlighting the acceptability of HPV vaccine among two population groups and its overall uptake in the last five years in Gombe, Nigeria.

Methods

Data about vaccine uptake in relation to changes in time/cost, was obtained from public health unit of Federal Teaching Hospital Gombe (FTHG). A survey of vaccine acceptability among female healthcare workers and women from general population was conducted using interview based questionnaire.

Results

Acceptability in terms of willingness to allow daughters/wards to take up HPV vaccine was 86.0% (117/136) among female healthcare workers and 97.5% (197/202) among women from general population. From July 2013 to April 2018, only 50 clients received cervarix® whose cost within the period ranged between 5,250.00 naira (=15USD) and 8,000.00 naira (=22USD). Less than half (46%) of those who received that vaccine completed three doses while up to 24% had only a single dose. The number of vaccine recipients was observed to be decreasing with increasing price over the five-year period.

Conclusions

Although theoretically having high acceptability, cost of HPV vaccine is one of the major determinants of real uptake in Nigeria which have very low health insurance coverage and yet to incorporate the vaccine in to its national immunization schedule.
HUMAN PAPILLOMAVIRUS SEROIMMUNITY AMONG AN UNVACCINATED FEMALE COHORT IN NORTHERN NIGERIA- IS AGE AN IMPORTANT CO-FACTOR?

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Background and Aims

The prevalence rates of both Human Papillomavirus (HPV) infection and cervical cancer is on the increase in Nigeria, especially in the northern part, mainly due to the predominance of relevant risk factors in this area. Only a negligible population of women in Nigeria have been vaccinated against HPV, probably because the HPV vaccines are currently not on the National immunization schedule. To the best of our knowledge, the current study is the first in north-eastern Nigeria, to report the sero-immunity of the prevalent HPV genotypes (6, 11, 16 & 18) among unvaccinated sexually active women.

Methods

Sera from one hundred and eighty-two (182) consenting sexually active women from Gombe, Nigeria was used to detect the presence of IgG antibodies against the four most prevalent HPV genotypes (6, 11, 16 & 18) using ELISA.

Results

Age of participants ranged from 15 to 50 years, with majority (77.8%) being within 20-35 year bracket. Only a few (19.2%) were primiparous while about half (51.7%) were multiparous. HPV IgG seroprevalence was 19.2% (35/182). Although not statistically significant, prevalence was higher among younger women with 26.3% (<20 years), 19.0% (20-35 years) and 14.3% (>35 years) for the different age groups.

Conclusions

The HPV sero-immunity against the prevalent HPV genotypes observed among the unvaccinated women in our study suggests prior exposure to HPV. There is an urgent need to encourage HPV vaccination with the quadrivalent vaccine particularly among the at risk female age groups, who should be followed up using cervical cancer screening tests.
ASSESSING THE SIGNIFICANCE OF MALE CIRCUMCISION AND THE USE OF CONDOMS ON HPV TRANSMISSION AMONG COLLEGE FEMALES IN UGANDA

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Background and Aims

About 3,915 new cervical cancer cases are diagnosed annually in Uganda and about 2,275 cervical cancer deaths occur annually in Uganda. According to 2011 Uganda Demographic and Health Surveys, 26.8% of males are circumcised and 2.8% male-female sexual encounters involved correct use of condoms.

This 4 year longitudinal study explicitly evaluated the temporal relationship between male circumcision with condom use on transmission of HPV related diseases among college females (18-35yrs) in Uganda.

Methods

We followed 67 female college students who reported their first intercourse with a male partner either during the study period or within two weeks before college. Visual Inspection with Acetic Acid (VIA) was performed at every 4-6 months for 4 years. Every 4-6 months, a questionnaire about their recent daily sexual behavior especially with circumcised or uncircumcised men.

Results

The incidence of genital HPV infection was 37.8 per 100 patient-years at risk among women whose partners used condoms for all instances of intercourse as compared with 89.3 per 100 patient-years at risk in women whose partners didn't used condoms. In women reporting 100 percent condom use by their circumcised male partners, no cervical lesions were detected in 26 patient-years at risk, whereas 13 incident lesions were detected during 67 patient-years at risk among women whose uncircumcised partners didn't use condoms or used them less consistently.

Conclusions

In sexually active college females, consistent condom use by their male circumcised partners significantly reduced the risk of cervical and vulvovaginal HPV related disease. A more specific and sensitive HPV DNA testing is highly recommended.
Background and Aims

Currently, there is no national cervical screening or HPV immunization program in Vietnam. This study aims to synthesize available data on the current burden of disease and to project the burden of cervical cancer to 2050 if no major interventions are implemented.

Methods

We reviewed published data sources on risk factors for HPV prevalence, high-grade lesions, cervical cancer incidence and mortality in Vietnam from 1990-2017. We then used the available data to project the number of new cervical cancer cases for the period 2012-2049.

Results

Data on cervical cancer incidence and mortality are limited; two cancer registries have been certified by the International Agency for Research on Cancer, which cover only urban populations representing ~20% of the national population. The reported age-standardized incidence rate of cervical cancer in Hanoi was 6.7, compared to 28.8 and 14.1 per 100,000 women in Ho Chi Minh City for 1995-1998 and 2009-2012, respectively. Cancer mortality data are not uniformly available from cancer registries or mortality surveys because cause of death has not been routinely ascertained. Based on available urban population registry data, estimated rates in the rural population, and forward projection of existing trends, we estimate that without any further intervention, the number of new cases will increase from 6,930(range 5,671-8,493) in 2012 to 8,562(range 5,775-12,762) in 2049, giving a total of 379,617(range 276,879-542,941) new cases over the period 2012-2049.

Conclusions

These findings support the need for delivery of HPV vaccination and cervical screening in Vietnam.
Background and Aims
The human papillomaviruses are the most common sexually transmitted infections worldwide and a major cause of morbidity and mortality amongst young women. It is important to determine their prevalence as distribution of genotypes differs according to geographic location, race and genetic make-up. A cross sectional study was conducted at the College of Health Sciences, University of Zimbabwe and Central Hospital School of Nursing in 2014.

Aim: to detect and type genital human papillomavirus (HPV) in young female medical and nursing students.

Methods
Self-collected cervico-vaginal swab specimens from female college students were processed and genomic DNA extracted. HPV-DNA was detected by consensus polymerase chain reaction (PCR) using two primer sets, MY09/MY11 and GP5+/GP6+. Positive PCR samples were typed by DNA sequencing.

Results
Cervico-vaginal swabs were self-collected by 125 students. The age range of the participants was 20-25 years with a mean age of first sexual activity of 19.22 years. One hundred and fourteen (114) out of the 125 swabs from the students had genomic DNA successfully extracted. Of these swabs, 36 tested positive for HPV-DNA, giving an HPV prevalence of 31.58%. Both high-risk (HPV 16, 18, 35, 45, 58, 53 and 56) and low-risk (HPV 6, 11, 40, 53, 54, 72, 81 and 86) genotypes were detected among the sexually-active students.

Conclusions
A high prevalence of HPV infection in medical and nursing students was observed. Further studies are necessary to establish the true prevalence of HPV types in young and healthy women and the data generated will be useful in informing reproductive public health policies.
Background and Aims

Cervical cancer, usually diagnosed in late-stage, is the most common cancer among women in Uganda. We aimed to report the prevalence and predictors of treatment initiation at government-funded tertiary care referral centers.

Methods

We recruited women newly diagnosed with cervical cancer at Mulago Hospital and/or the Uganda Cancer Institute to participate in an observational study to evaluate barriers and facilitators to cervical cancer care. A baseline survey was followed up phone interview to ascertain treatment status 4-6 weeks later. We used univariate and multivariate analysis to investigate associations between explanatory variables and treatment initiation.

Results

Between April-November, 2017, 138 participants enrolled and 76% (105) were reached for follow-up. Of these, 68% (71) reported starting treatment. The majority (86%, n=61) started neoadjuvant chemotherapy; others reported hospice (4%, n=3), surgery (9%, n=6), and radiation (1%, n=1). Of those who had not started (32%, n=34), most (79%, n=27) planned treatment. Those declining recommended therapies cited preference for alternative/traditional remedies (71%) and insufficient funds (43%). In multivariate analysis, urban residence was associated with higher odds of treatment initiation (OR 3.38, 95% CI 1.02-11.18). The median duration from first presentation at any health center to treatment was 121 days. Among participants planning or actually undergoing therapy, the most common reasons cited for delay were insufficient funds (72%) and pursuit of alternative/traditional remedies (19%); reasons were not significantly different among those who started versus not-yet-started treatment.
Table 1: Characteristics of women with cervical cancer by treatment initiation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total N</th>
<th>Have not started treatment %</th>
<th>Started treatment %</th>
<th>Unadjusted Odds Ratio for Treatment Initiation (95% CI)</th>
<th>Adjusted* Odds Ratio for Treatment Initiation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (N, %)</td>
<td>N=105</td>
<td>N=34 (32%)</td>
<td>N=71 (68%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age yrs (median)</td>
<td>48 (median)</td>
<td>48 (median)</td>
<td>52 (median)</td>
<td>1.00 (0.97-1.04)</td>
<td>0.99 (0.94-1.04)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; primary</td>
<td>46</td>
<td>26</td>
<td>74</td>
<td>1.00 (0.97-1.04)</td>
<td>1.00 (0.94-1.04)</td>
</tr>
<tr>
<td>≥ primary</td>
<td>53</td>
<td>36</td>
<td>64</td>
<td>0.63 (0.27-1.50)</td>
<td>0.83 (0.28-2.41)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Industry/business</td>
<td>42</td>
<td>36</td>
<td>64</td>
<td>1.00 (0.97-1.04)</td>
<td>1.00 (0.94-1.04)</td>
</tr>
<tr>
<td>Farming/domestic</td>
<td>62</td>
<td>30</td>
<td>70</td>
<td>1.29 (0.56-2.95)</td>
<td>2.11 (0.57-7.74)</td>
</tr>
<tr>
<td>Urban versus rural</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>47</td>
<td>36</td>
<td>64</td>
<td>1.00 (0.97-1.04)</td>
<td>1.00 (0.94-1.04)</td>
</tr>
<tr>
<td>Urban</td>
<td>58</td>
<td>29</td>
<td>71</td>
<td>1.37 (0.60-3.11)</td>
<td>3.38 (1.02-11.18)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single/divorced</td>
<td>61</td>
<td>36</td>
<td>64</td>
<td>1.00 (0.97-1.04)</td>
<td>1.00 (0.94-1.04)</td>
</tr>
<tr>
<td>Married</td>
<td>44</td>
<td>27</td>
<td>73</td>
<td>1.50 (0.65-3.50)</td>
<td>1.40 (0.50-3.91)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>61</td>
<td>33</td>
<td>67</td>
<td>1.00 (0.97-1.04)</td>
<td>1.00 (0.94-1.04)</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>44</td>
<td>32</td>
<td>68</td>
<td>1.05 (0.46-2.40)</td>
<td>1.13 (0.32-4.04)</td>
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<tr>
<td>HIV serostatus</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV -</td>
<td>67</td>
<td>30</td>
<td>70</td>
<td>1.00 (0.97-1.04)</td>
<td>1.00 (0.94-1.04)</td>
</tr>
<tr>
<td>HIV +</td>
<td>36</td>
<td>36</td>
<td>64</td>
<td>0.75 (0.32-1.78)</td>
<td>0.57 (0.19-1.78)</td>
</tr>
<tr>
<td>Surgical candidacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somato/NS invasive</td>
<td>92</td>
<td>30</td>
<td>70</td>
<td>1.00 (0.97-1.04)</td>
<td>1.00 (0.94-1.04)</td>
</tr>
<tr>
<td>Surgery recommended</td>
<td>13</td>
<td>46</td>
<td>54</td>
<td>0.51 (0.16-1.66)</td>
<td>0.32 (0.08-1.28)</td>
</tr>
</tbody>
</table>

* Adjusted for age, education, occupation, urban/rural, marital status, parity, HIV serostatus and surgical candidacy
Conclusions

Women residing in urban areas had higher odds of initiating treatment. Regardless of treatment initiation, participants reported similar barriers.
PREVALENCE AND RISK FACTORS ASSOCIATED WITH ANOGENITAL WARTS AMONG ANTI-RETROVIRAL THERAPY-EXPERIENCED HIV-INFECTED PATIENTS IN A RURAL KENYAN POPULATION

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²Fountain Healthcare Hospital, Medicine, Eldoret, Kenya

Background and Aims

Human Papilloma Virus (HPV) infection-related pathology among people living with HIV (PLHIV) is common, most of which manifest within the anogenital region as warts and other neoplastic conditions. However, the prevalence and risk factors associated with anogenital warts among PLHIV in rural Kenya are scarce. Thus the objective was to determine the prevalence and risk factors associated with presence of anogenital warts among antiretroviral therapy (ART) experienced PLHIV in a rural Kenyan population.

Methods

This was a cross sectional study carried out among HIV-positive patients seeking care at the HIV clinic of Baringo County Referral Hospital in Kabarnet, Baringo County, Kenya between January 2018 and March 2018. 5% acetic acid was used to soak the anal region for visualization of any warts. Risk ratios were used to assess for possible risk factors predisposing to the formation of anogenital warts.

Results

224 HIV-positive patients were studied, with a median age of 42 years (IQR of 12). 21% (n=47) were noted to have evidence of anogenital warts, with a higher preponderance among females than males (55.3%, n=26). CD4 ≤ 250 cells/mm³ (RR: 1.41, 95% CI: 1.21-1.64, p<0.001) and detectable HIV RNA levels (RR: 3.61, 95% CI: 2.44-5.35, p<0.001) were significantly associated with presence of anogenital warts.

Conclusions

The prevalence of anogenital warts among PLHIV in Baringo was noted to be high and thus active screening of the anogenital region and high-resolution anoscopy (HRA) for deep-seated anal lesions is recommended for those with evidence of anogenital warts.
Background and Aims

**Background:** Cervical cancer is a public health problem for adult women in developing countries. Many industrialized countries have achieved significant successes in reducing invasive cervical cancer burden over the past six decades mainly due to introduction of screening programmes.

**Aim:** To determine the prevalence of abnormal cervical smears, HPV DNA status of the abnormal smears and p16/Ki67 pattern in LSIL and borderline cases.

Methods

**Methods:** Five hundred (500) consenting women attending the Gynaecology clinic of the Ahmadu Bello University Teaching Hospital Zaria, Nigeria were recruited consecutively. Smears were reported using the Bethesda Classification. All abnormal smears had HPV DNA testing and genotyping done. Dual staining using p16/Ki67 were done on LSIL and borderline cases.

Results

**Results:** Five hundred (500) women were screened and the mean age was 40.5 ± 9.7 years. The prevalence of abnormal smears was 5% and the cytological diagnoses comprise of Negative (95.6%), Low Grade Squamous Intraepithelial Lesion (LSIL, 2.6%), High Grade Squamous Intraepithelial Lesion (HSIL, 1.2%) and Atypical Squamous Cells of Undetermined Significance (ASC-US, 0.6%). Hr-HPV DNA was positive in 52% of cases with abnormal smears and the most prevalent genotypes encountered were types 16, 18 and 33. The evaluation of p16INK4a and Ki67 biomarkers in LSIL and borderline smears revealed that 6 out of 18 cases were positive and subsequently reclassified to HSIL.

Conclusions
**Conclusion:** Hr-HPV was prevalent among subjects with abnormal smears and types 16, 18 and 33 were the most prevalent, therefore introduction of molecular testing in routine screening and HPV vaccination are encouraged.
COMPARISON OF P16INK4A/KI-67 DUAL-STAIN CYTOLOGY TO VIA ENHANCED BY DIGITAL CERVICOGRAPHY (VIA-DC) FOR CERVICAL CANCER SCREENING IN HIGH-RISK-HPV POSITIVE WOMEN IN RURAL ETHIOPIA

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5Charité Universitätsmedizin Berlin, Department of Gynecology, Berlin, Germany
6Dabat Research Center, Dabat Research Center, Dabat, Ethiopia
7Health Bureau of the Amharic Region, Health Bureau of the Amharic Region, Bahir Dar, Ethiopia

Background and Aims

P16INK4A/KI-67 dual-stain cytology has shown to combine high sensitivity with high specificity for detection of high-grade cervical lesions likely to progress into invasive cervical cancer. We investigated diagnostic performance of the p16INK4A/KI-67 dual-stain biomarker in a population of high-risk (hr)HPV positive rural Ethiopian women in comparison to VIA enhanced by digital cervicography (VIA-DC).

Methods

HPV self-sampling using the Evalyn® Brush (Rovers®) was offered to eligible women above 25 years of age (mean age: 38.5 years; range: 25-66 years) in the community of Chila, Northwest Ethiopia. HPV genotyping was performed using the AID HPV Array® Screening Platform (AID/GenID GmbH, Strassberg, Germany) at the HPV reference lab, Addis Ababa University. hrHPV-positive women were invited to the clinic for nurse-led VIA-DC using MobileODT®, collection of a LBC sample for p16INK4A/KI-67 dual-stain cytology (CINtecPLUS®) and confirmatory colposcopy/biopsy by a gynecologist to detect high-grade cervical intraepithelial lesions (CIN2+).

Results

Of 693 women approached, 637 women (91.9%) were eligible. 526 of the eligible women (82.6%) enrolled in the study and performed self-sampling in their home. 17% of women tested hrHPV positive with HPV type 16 being the most prevalent genotype. 36.4% of the hrHPV-positive women showed infection with multiple HPV genotypes. All hrHPV positive women are currently invited for follow-up management including VIA-DC, dual-stain cytology and colposcopy/biopsy.

Conclusions
Self-sampling was highly acceptable by rural Ethiopian women. hrHPV prevalence is high. The study is currently ongoing and sensitivity and specificity of p16$^{INK4a}$/Ki-67 dual-stain cytology in comparison to nurse-led VIA-DC to detect CIN2+ and early cancer among HPV-infected women will be presented.
HPV primary screening requires a triage system for HPV positive women (currently, cytology). FDA approved a protocol with partial genotyping as triage. Some clinical validated HPV tests perform simultaneously complete or partial genotyping.

Main objective is to compare performances (for CIN2+ lesions) of partial genotyping as triage compared to current protocol.

Methods

In Tuscany, a screening validated HR-HPV test, that perform a partial genotyping of positive samples, distinguishing HPV16 and HPV18 from other HR-HPV types (other HPV), is used. We considered women aged 34-64 years, participating to HPV primary screening in Florentine area. Cytology triage and colposcopy have been performed not knowing partial genotyping results.

Results

Among 20638 HPV tests executed with partial genotyping, 1529 (7.4%) resulted positive, 452/1529 (29.6%) to HPV16 and/or HPV18, of which 172/452 (38.1%) in coinfection with other types.

Cytology triage resulted abnormal for 418/1529 (27.3%) and inadequate for 21/1529 (1.4%), with a colposcopy referral rate (RR) of 28.7% (439/1529). Adhesion to colposcopy was 92.3% (405/439; 138/405 (34.1%) CIN2+ were found.

For 183/452 (40.5%) HPV16 and/or HPV18 positive women, cytology triage was abnormal or inadequate and 80/170 (47.1%) resulted CIN2+. For 256/1077 (23.8%) other HPV positive women, cytology triage was abnormal or inadequate and 58/235 (24.7%) resulted CIN2+.

Conclusions

Partial genotyping as triage does not result in a change in colposcopy RR compared to cytology (29.6% vs 28.7%, ns). Women with HPV16/18 infection have actually a greater risk of CIN2+ (47.1% vs 24.7%, p<0.002), but 42% (58/138) of CIN2+ were diagnosed in other HPV positive
women. Therefore, it cannot be used as a substitute triage method. The use of partial genotyping should be further evaluated.
PERFORMANCE OF IMMUNOCYTOCHEMISTRY WITH P16INK4A/KI-67 AS A STRATEGY TO TRIAGE HIGH RISK HPV POSITIVE WOMEN

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3Laboratorio CITOMED, Laboratorio CITOMED, Cuernavaca-Morelos, Mexico
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5University of California UCLA, David Geffen School of Medicine, Los Angeles, USA
6McGill University, Division of Cancer Epidemiology, Montreal- QC, Canada
7George Washington University, Department of Global Health, Washington DC, USA
8University of California- Los Angeles- Fielding School of Public Health, Department of Health Policy and Management, Los Angeles- California, USA

Background and Aims

The expression of progression markers such as p16INK4a and Ki-67 is associated with the loss of cell cycle control, a critical step in carcinogenesis, and has been shown to be a promising triage test.

To evaluate the performance of liquid based cytology (LBC) and p16INK4a/Ki-67 dual-stained cytology as a triage strategy for the detection of cervical intraepithelial neoplasia (CIN2+/CIN3+) in high-risk HPV (hrHPV) positive women.

Methods

A nested case-control study in hrHPV positive women (n=412) was conducted within the FRIDA screening study in Mexico. For this analysis, our study population included those hrHPV positive women referred to colposcopy because of positivity either by HPV16/18 and/or ASCUS+ cytology (28%), and a subsample of HPV16/18 negative and normal cytology women (12%). We included 103 (CIN2+) cases and a random selection of 309 controls matched by age (103 CIN1 and 206 Normal). Among all cases and controls, LBC and p16INK4a/Ki-67 dual-stained cytology were performed from the remaining Preservcyt specimen. We evaluated the crude performance of these tests as triage for CIN2+ and CIN3+ detection.

Results

p16INK4a/Ki-67 dual-stained cytology had a sensitivity of 70% (95%CI: 60.1-78.5) and a specificity of 84% (95%CI: 79.0-87.6) for the detection of CIN2+. To identify CIN3+ lesions, the sensitivity was 75%
(95%CI: 63.4-84.5) and the specificity was 83% (95%CI: 77.7-88.0). Meanwhile, LBC alone showed a sensitivity of 45.1% (95%CI:38.5-55.3) and specificity of 77.5% (95%CI: 72.3-82.1) to detect CIN2+.

Conclusions

p16\textsuperscript{INK4a}/Ki-67 dual-stained cytology shows acceptable performance as a triage test to detect CIN2+ in hrHPV positive women.
PERFORMANCE OF E6 PROTEIN AS A TRIAGE TEST IN HPV16/18 POSITIVE WOMEN

R. Hernández-López1, S. Naveen2, J. Salmerón2, L. Torres-Ibarra1, J. Cuzick3, B. Moscicki4, A. Lorincz3, E. Franco5, P. Gravitt6, E. Lazcano-Ponce1

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Background and Aims

Detection of elevated levels of E6 oncoprotein in cervical epithelial tissue constitutes a potentially valuable marker in identifying women at highest risk for pre-cancer or cancer among women testing positive for HPV DNA.

To evaluate the clinical performance of the HPV16/18-E6 oncoprotein as a triage method for the detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) in women positive for HPV16/18 DNA.

Methods

This study was conducted in the cohort of HPV16/18 positive women participating in the Mexican FRIDA Study. Women positive for HPV16/HPV18 by Cobas4800® HPV testing were tested with the OncoE6™ Cervical Test. The cervical sample collected in Preservcyt® and used for the HPV16/18 genotyping was also used to perform the E6 Oncoprotein test. All women with a positive HPV16/18 result were referred to colposcopy for histological verification. The clinical performance of HPV16/18-E6 oncoprotein was computed only among HPV16/18 positive samples.

Results

Among HPV positive women, 739 (18.2%) were positive for HPV16/18, of which 123 (16.6%) were E6 positive. The performance estimates were conducted among 524 women with complete histological information. The detection of HPV16/18-E6 oncoprotein among women infected with HPV 16/18 presented a sensitivity of 30.3%, and a specificity of 83.6% for the identification of CIN2+ (n=18) and a sensitivity of 35.4% and a specificity of 83.6% to detect CIN3+ (n=44), respectively. Sensitivity and specificity for cancer (n=4) were 100% and 82.5%, respectively.

Conclusions

The E6 Oncoprotein could be useful to identify HPV16/18 positive women with CIN2+ who require an immediate referral to colposcopy.
Background and Aims

Antibody responses to human papillomavirus (HPV) have been regarded as critical indicators representing diagnostic and prognostic features of cervical cancer. The aim of the present study is to investigate the seroprevalences of anti-HPV antibodies during development of cervical cancer.

Methods

Seroprevalences of nine types of anti-HPV antibodies (antibodies against E6, E7 and L1 antigens of HPV types 16, 18 and 58) were investigated in Korea women with cervical intraepithelial neoplasia (CIN) I, II and III and cervical cancer using enzyme-linked immunosorbent assay.

Results

The seroprevalences of nine types of anti-HPV antibodies were increased in CINs or cervical cancer when compared to normal cytology. The seroprevalences of anti-HPV16 E6 and E7, anti-HPV18 E6 and E7 and anti-HPV58 E7 antibodies in cancer group were higher than those in CIN stages. It appeared that the seroprevalences of antibodies against HPV16, 18 and 58 E7 have tendencies to increase with increasing severity of cervical lesion. Whereas there were little differences in the seroprevalence rates of antibodies against L1 antigens of HPV16, 18 and 58 between cervical cancer and CIN stages. The correlations between HPV DNA-positivity and seropositivity of anti-HPV E6, E7 or L1 antibodies were found only in the HPV16 DNA-positive cervical cancer cases for the antibodies against HPV16 E6 and L1.

Conclusions

The seroprevalences of antibodies against E7 antigens (HPV16, HPV18 and HPV58) were found to be the best indicators for reflecting the severity of cervical lesions. Our study results provide new insights of the HPV sero-epidemiology features during cervical cancer development.
KERATIN-BASED SAMPLE VALIDITY TESTING IMPROVES TRIAGE OF HPV 16/18/45 POSITIVE WOMEN USING HRHPV E7-ONCOPROTEIN TESTING

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3Leopold-Franzens-Universität Innsbruck, Institute for Biomedical Aging Research Innsbruck Austria AND Tyrolean Cancer Research Institute, Innsbruck, Austria
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Background and Aims

HPV-tests based on the detection of viral oncoproteins are suitable for implementation as a triage method to colposcopy for hrHPV-positive women. The diagnostic capabilities, however, may be limited without assessment of specimen validity to reduce false negative results of these tests.

Therefore, two novel ELISA assays were combined for detection of hrHPV E7-oncoproteins 16/18/45 plus detection of Keratins-5/8/18 from potential basal squamo-columnar junction target cells. Methods

Two sandwich ELISAs – recomWell HPV 16/18/45 and recomWell Keratin 5/8/18 - were developed for detection of hrHPV E7-oncoproteins and basal keratinocytes.

Cervical samples were obtained in PreserveCyte medium from 2637 women who participated in the PIPAVIR studies. All samples were characterized by cytology and HPV-genotyping, and E7-ELISA and Keratin-ELISA measurements were performed.

Results

Keratin detection was analyzed and the proportion of invalid samples with results below cutoff was determined. An increase of invalid samples was found in CIN1+ samples (12.4%) in comparison to HPV-negative samples with normal cytology (4.1%).

Sensitivity, specificity, PPV and NPV for recomWell HPV 16/18/45 were calculated with HPV 16/18/45 positive samples. An increase in sensitivity of 8.9% was achieved for the CxCa-group when calculated with regard to the results of the recomWell Keratin 5/8/18 validity testing. On the contrary, specificity (97.9%/98.0%), PPV (19.5%) and NPV (99.9%) remained constant when compared to the results without validity testing.
## Conclusions

Validity testing of cervical samples with recomWell Keratin 5/8/18 in combination with hrHPV E7-oncoprotein testing is mandatory to increase sensitivity for disease with a maximum of specificity, PPV, and NPV.

<table>
<thead>
<tr>
<th>E7 result</th>
<th>Keratin result</th>
<th>Sens. Normal Cytology</th>
<th>Sens. CIN1</th>
<th>Sens. CIN2</th>
<th>Sens. CIN3</th>
<th>Sens. CIS/ CxCa</th>
<th>Spec. CIS/ CxCa</th>
<th>PPV CIS/ CxCa</th>
<th>NPV CIS/ CxCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>All samples</td>
<td>All samples</td>
<td>10/120</td>
<td>7/45</td>
<td>1/28</td>
<td>15/31</td>
<td>8/10</td>
<td>1642/1675</td>
<td>8/41</td>
<td>1642/1644</td>
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<tr>
<td>Positive</td>
<td>Positive</td>
<td>8.3%</td>
<td>15.6%</td>
<td>3.6%</td>
<td>48.4%</td>
<td>80.0%</td>
<td>99.0%</td>
<td>19.5%</td>
<td>99.9%</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>10/118</td>
<td>7/37</td>
<td>1/25</td>
<td>15/29</td>
<td>8/9</td>
<td>157/1604</td>
<td>8/41</td>
<td>157/1572</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>8.6%</td>
<td>18.9%</td>
<td>4.0%</td>
<td>51.7%</td>
<td>88.9%</td>
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PREDICTIVE VALUE OF P16/KI-67 DUAL-STAINED CYTOLOGY FOR THE PROGRESSION OF CERVICAL DYSPLASIA

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Background and Aims

The objective of this study was to investigate the predictive value of p16/Ki-67 dual-stained cytology for the progression of disease.

Methods

Cytology p16/Ki-67 dual-staining test was performed on 691 liquid-based residual samples from a cohort of women with ASC-US/LSIL and co-testing human papillomavirus (HPV) positive. Among them, 250 women were followed up for at least a year. Study end points were HSIL detection in 1 and 2 year's follow-up.

Results

Positivity of p16/Ki-67 dual stained cytology was well correlated to progression of disease compared with positivity of HPV 16/18. During 1 year follow-up, 23 of 250 women experienced progression of disease into HSIL. For positivity of p16/Ki-67 dual stained cytology, Sensitivity (60.9%) for the detection of HSIL or specificity (81.5%) for normal or low grade cytology was higher than those of HPV 16/18 tests (13.0% and 89.0%, respectively) (p<0.001). During 2 years follow-up, 11 of 190 women experienced progression of disease into HSIL. For positivity of p16/Ki-67 dual stained cytology, Sensitivity (45.5%) for the detection of HSIL or specificity (82.1%) for normal or low grade cytology was higher than those of HPV 16/18 tests (18.2% and 89.9%, respectively) (p=0.025).

Conclusions

p16/Ki-67 dual stained cytology could provide both high sensitivity and specificity for the prediction of HSIL in Pap cytology. Positive p16/Ki-67 dual-stained cytology in low grade cytology was highly associated with the progression of disease in 1 or 2 years follow-up. Therefore, in cases of positive dual-stained cells morphologically showing benign atypical features, further follow-up would be necessary.
HPV GENOTYPE DISTRIBUTION IN CERVICAL NEOPLASIA IN MEXICAN WOMEN

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Background and Aims

Data on type-specific HPV prevalence in cervical neoplasia among Mexican women may help to evaluate the relevance of using an extended genotyping for triaging high-risk HPV (hrHPV) positive women.

To estimate the prevalence and type distribution of HPV in high-grade cervical lesions among Mexican women.

Methods

This study is nested in the Mexican FRIDA study and included 323 negatives for NILM, 460 CIN1, 31 CIN2, 71 CIN3 and 4 cancers histologically ascertained in women aged 30-64 years. The women were those referred to colposcopy either by HPV16/18 genotyping (by cobas4800 HPV test) or ASCUS+. HPV-type determination was performed with Oncclarity™ HPV Assay (Becton Dickinson) on PreservCyt samples collected at the first screening visit. Type-specific HPV prevalence were estimated in according to histological grade. We also estimate the positive predictive value (PPV) of each genotype or pool of them for CIN2+.

Results

HPV16 was the most frequent among our population (33.1%), and increased according to lesion severity from CIN1 to cancer: 31.1%, 51.6%, 50.7% and 100%, respectively. Among CIN2+ lesions, the most frequent HPV types other than HPV16 were HPV33/58 (17.9%) and the pool of HPV56/59/66 (15.2%). The highest PPV’s for CIN2+ were yield with HPV52 (20.4%) followed by HPV16 (19.1%), HPV33/58 (19%), HPV31 (12.4), respectively.

Conclusions

The presence of other non-16/18 hrHPV suggests the relevance of extended genotyping to identify women at increased risk for cervical cancer within HPV-based screening programs. Other non-16/18 hrHPV could provide an acceptable PPV to be included as additional triage alternatives.
Background and Aims

The studies conducted in Xuzhou, China were aimed to evaluate the efficacy of PAX1, HPV16/18, and TCT for women who had hr-HPV infection with cervical lesions and cancer.

Methods

The inclusion criteria: women who has HPV resistant infection for more than 3 years without continuous follow-up women. The exclusion criteria included: women had history of reproductive tract cancers, had therapy for cervical lesions, had received HPV vaccination or at pregnancy. The residue cervix cells from the cervical area were collected for TCT, HPV-typing and PAX1 testing following the operation instruction of kits. The pathologic results were as gold standard in the study. The sensitivity, specificity, and accuracy for type 16/18 HPV, TCT, and PAX1 were analyzed.

Results

Total 105 subjects were recruited with histological reports including less than LSIL group (n=37), HSIL group (n=37), and cervical cancer group (n=31) in colposcopy room of Xuzhou Maternity and Child Health Care Hospital. The results showed that the PAX1 was significantly better results than TCT and HPV 16/18 in patients with HSIL and worse lesions than those with less than LSIL (P<0.05). The area of under ROC curve of PAX1 is 0.878 (95%CI : 0.806-0.950P=0.000). The sensitivity and specificity of PAX1 were 79% and 97%.

Conclusions

The current results indicated that the PAX has potential testing for the triage of the persistent hr-HPV infection women with cervical lesions.
EFFECT OF P16/MCM2 AND P16/KI-67 ON THE DETECTION OF CERVICAL INTRAEPITHELIAL NEOPLASIA: A PROSPECTIVE STUDY FROM CHINA

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Background and Aims

To investigate the clinical performance of p16/mcm2 and p16/Ki-67 immunocytochemical dual staining in predicting high grade cervical lesions.

Methods

2,067 women who underwent cervical cancer screening were selected. p16/Ki-67 and p16/mcm2 were performed on the remaining liquid-based cytology (LBC) samples of 125 HPV-positive women and 114 randomly selected HPV-negative women. Women with HR-HPV infection or cytological abnormalities were referred for colposcopy and biopsy. The accuracy of p16/Ki-67 and p16/mcm2 for detection of cervical intraepithelial neoplasia grade 2 or worse were calculated and compared with cytology and HPV tests. A third-year follow up were performed on all women, with cumulative rates and relative risks (RR) calculated.

Results

The expression of p16/Ki-67 and p16/mcm2 in HPV16/18 group and other 12 HR-HPV group was significantly higher than that in HPV negative group (p<0.05), with odds ratios (ORs) of 16.27 and 4.52 for p16/Ki-67, and 31.28 and 9.10 for p16/mcm2. The sensitivities to detect CIN2+ and CIN3 + were 94.1% and 92.9% for p16/Ki-67, and 88.2% and 85.7% for p16/mcm2. The two biomarkers were significantly higher than that of LBC and HPV16/18 genotyping (p <0.05). The three-year cumulative rates of CIN2+ were 69.0%, 48.4%, 34.8% and 50.0% for p16/Ki-67, p16/mcm, LBC and HPV16/18. Women tested positive on both p16/Ki-67 and p16/mcm2 at baseline had the highest RR value of 39.64 compared to those both negatives.

Conclusions

p16/Ki-67 and p16/mcm2 dual staining can enhance the sensitivity of cytology in a single round of screening, and they can be predictors of high grade cervical lesions in the following years.
Background and Aims

Due to the low specificity of HPV DNA testing, triage testing for positively screened women is required to reduce overtreatment harms. Triage options in low income settings are limited. Specific biomarkers that could be readily detected during the patient encounter through in vivo imaging present a novel promising triage strategy. We used a gene-expression based biomarker discovery approach for development of in vivo imaging markers.

Methods

The Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) recruited women referred for colposcopy with abnormal screening results. Gene expression levels were determined in mRNA microarrays of SUCCEED tissue from 128 patients at all stages of progression to cervical cancer, and differential expression of genes compared between cervical intraepithelial neoplasia grade 3 (CIN3) and combined CIN1/normal tissues. Candidate biomarkers with nominally significant p-values (<0.01) and higher expression in CIN3 (fold-change >2) were examined for membrane localization and enzymatic activity (Figure 1).
Results

We found 48 potentially plasma membrane-bound proteins that could be amenable to in vivo staining and visualization. Validation of 11 top candidate genes through immunohistochemical staining of SUCCEED tissues using both conventional histology evaluation and automated image analysis is under way, which will be followed by the investigation of the in vivo imaging potential of validated candidates using both antibody-based and enzyme-activated optical imaging methods.

Conclusions

The discovery of membrane biomarkers of cervical cancer and precancerous lesions may enable the development of specific, sensitive, low cost in vivo detection tests for prevalent precancers.
HUBUNGAN TIPE HUMAN PAPILLOMAVIRUS (HPV) DAN KADAR TGF-B1 DENGAN INFEKSI HUMAN PAPILLOMA VIRUS (HPV) PERSISTEN

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Background and Aims

The aim is to analyze the affect of persistence HPV infection to HPV genotypes and and to compare the TGF-b1 level in persistence and clearance of HPV infection.

Methods

Prognostic study with hystorical cohort design from gynecology oncology outpatient clinic and women health center. Samples were tested for positive HPV DNA genotyping and normal cytology from cervical samples by using HPV XpresMatrix Test Kit with PCR amplification and hybridization technology. The patients were evaluated for HPV DNA genotyping and the level of serum TGF-b1 by using Quantikine kit with human TGF-b1 immunoassay.

Results

From 544 data of HPV DNA genotyping and cervical cytology of 486 patients, most population were HPV negative and normal cytology, 16.04% cases of HPV infection were found, whereas 39.74% of patients with HPV infection were normal cytology. The most HPV DNA genotype in population with cervical cytology abnormality were type 52 (22.59%), 16 (19.35%), and 18 (16.13%) in single HPV infection, and type 51 (31.2%) in multiple HPV infection. Among subjects with naïve HPV infection, we found 6/10 (60%) of persistence HPV infection, 3/10 (30%) of HPV clearance, and 1/10 (10%) of HPV reinfection. The most HPV type causing persistence infection were type 16 (20%) and 52 (20%). TGF-b1 value 44.595.17 pg/mL did not find any significant difference with HPV persistence status (95% CI (-14.778,68 – 22.543,35); p=0,492). There was no significant difference of category of TGF-b1 value with HPV persistence.

Conclusions

The most HPV type causing persistence infection were type 16 and 52.
Background and Aims

Background. The effectiveness of triage algorithms for HPV-based cervical cancer screening programs warrants further research, especially in low- and middle-income countries with high cervical cancer burden.

Objective. To assess the performance of three strategies for the triage of hrHPV+ women: (1) liquid-based cytology (LBC), (2) HPV16/18 genotyping and (3) HPV16/18 genotyping and reflex LBC.

Methods

The nested study was part of the FRIDA Study, a demonstration project conducted within the public health care system of the Ministry of Health in Tlaxcala, Mexico, which enrolled 36,212 women aged 30 to 64 years attending routine cervical cancer screening. LBC and HPV16/18 genotyping were conducted concurrently in all hrHPV+ women. Women positive on either LBC (ASCUS+) or HPV16/18 test were referred to colposcopy, along with a random sample of women negative to both tests (12%). The colposcopy evaluation included a minimum of four biopsies and an endocervical sample.

Results

A total of 4,091 women (11%) were hrHPV+. Crude sensitivity and specificity estimates for the three strategies were: LBC, 44.7% and 73.1%; HPV16/18 genotyping, 57.4% and 53.6%; HPV16/18+ and reflex LBC, 87.8% and 32.6%, respectively. After correcting for verification bias, the sensitivities and specificities were 29% and 89% for LBC, and 36% and 82% for HPV16/18 genotyping, respectively.
HPV16/18+ plus reflex LBC in HPV 16/18- yielded the highest adjusted sensitivity (55%) but the lowest adjusted specificity (73.6%).

Conclusions

Although a combination of screening tests applied sequentially might provide the greatest health benefit and lowest resource utilization, research is needed to further improve the specificity.
FIRST-VOID URINE: A POTENTIAL BIOMARKER SOURCE FOR TRIAGE OF HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTED WOMEN

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3University of Antwerp, Proteinscience Proteomics & Epigenetic Signalling - Proteomics, Wilrijk, Belgium
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Background and Aims

Thus far, investigations have been primarily confined to the identification of biomarkers to distinguish between productive and transforming high-risk (HR)-HPV-infections in cervicovaginal specimens and tissue biopsies. Here, we review urinary biomarkers for triage of HR-HPV-positive women and for detection of cervical cancer (CxCa), and elaborate on the opportunities and challenges that have emerged regarding the use of first-void urine (FVU) for the analysis of both morphological- and molecular-based biomarkers.

Methods

A literature search was performed in PubMed and Web of Science (27/04/2018) for studies investigating the use of urine as biomarker source for triage of HR-HPV-infections and CxCa-detection.

Results

Eight studies were identified reporting on morphological- (micronucleus frequency) and molecular-based biomarkers (protein class, enzyme activity, oxidative stress, host and viral gene methylation) that are in preclinical exploratory or clinical assay development phases. Although large-scale validation studies are still needed, we can conclude that methylation of host and viral genes in urine has been proven feasible for use as molecular CxCa biomarker. This is promising and underscores our hypothesis that HPV and biomarkers are washed away with FVU. Similar to the limitations of self-collected cervicovaginal specimens, FVU will likely not fulfil the high-quality cellularity standards required for morphological biomarkers. Molecular biomarkers might overcome this issue, yielding high-throughput, objective, and reproducible results.

Conclusions

When using proper sampling, transport, storage, preanalytical biomarker concentration techniques, and sensitive assays, FVU is expected to be a valuable source of CxCa-associated molecular biomarkers, offering to test both primary HR-HPV DNA and biomarkers in the same sample (one-step triage).
To evaluate the screening methods for diagnosis of cervical diseases.

**Methods**

7,406 Women who underwent opportunistic screening for cervical diseases and colposcopy was studied. Diagnostic results from cytology, HR-HPV testing, and co-testing were compared and analyzed by $\chi^2$ test, using SPSS 17.0

**Results**

A total of 7406 women recruited during this four years. The HSIL lesion diagnosed by co-testing (99.27 %) was higher than that of hr HPV test (97.39 %) and cytology (84.60 %). Cervical cancer diagnosed by co-testing (98.10 %) was higher than that of hr HPV test (90.51 %) and cytology (86.71 %). 5,351 women showed abnormalities with liquid-based cytology (≥ ASC-US); colposcopy confirmed advanced cervical diseases (≥ CIN2) in 1914 women, and the sensitivity and specificity of liquid-based cytology for advanced cervical diseases (≥ CIN2) were 84.01 % and 31.85 %, respectively; the positive and negative predictive value (PPV and NPV) were 30.05 % and 85.11 %, respectively. In total, 6,184 and 1222 women showed positive and negative results for high-risk HPV testing. The sensitivity and specificity for diagnosis of advanced cervical diseases (≥ CIN2) were 92.06 % and 19.67 %. The PPV and NPV were 29.82 % and 86.99 %, respectively. 4,793 women were positive for co-testing with liquid-based cytology and high-risk HPV testing. The sensitivity and specificity of co-testing for diagnosis of advanced cervical diseases (≥ CIN2) were 98.86 % and 16.64 %; the PPV and NPV were 32.46 % and 97.29 %, respectively.

**Conclusions**

Co-testing with liquid-based cytology and high-risk HPV screening showed increased sensitivity, PPV and NPV, indicating the usefulness of this method in clinical opportunistic screening for cervical diseases.
Background and Aims

The aim of the present study is to determine the hrHPV viral concentration cut-off of the RIATOL qPCR genotyping assay to assure satisfactory accuracy to detect high grade intraepithelial neoplasia in a screening population.

Methods

1600 samples of the VALGENT3 panel were analysed with the RIATOL qPCR test. Analytical results were reported for each hrHPV type as viral concentration. The VALGENT3 samples are a standardised set of LBC samples with well documented follow-up data. All samples were also tested with the HC2 assay as comparator test. A zone of viral concentration cut-offs was defined by relative ROC analysis where the sensitivity and specificity were not inferior to HC2.

Results

The RIATOL qPCR had a sensitivity and specificity for CIN2+ of 97.6% (93.2-99.5%) and 85.1% (82.9-87.1%) respectively when the analytical cut-off was used. At a cut-off of 6.5 log copies/ml, the RIATOL qPCR had a sensitivity of 96.0% (91.0-98.7%) and a specificity of 89.5% (87.6-91.2%). At this cut-off, accuracy of the qPCR was non-inferior to the HC2 with a relative sensitivity of 1.00 [0.95-1.05 (p=0.006)] and relative specificity of 1.00 [CI: 0.98-1.01 (p=0.0069)].

Conclusions

This study demonstrates that HPV tests that provide viral concentrations allow flexibility to optimize the clinical accuracy required for primary cervical cancer screening. For test-of-cure, screening exit and epidemiological surveillance, preferable the analytical detection limit is used. Therefore, we strongly support the use of an adjustable cut-off for HPV testing with clear distinct values for different goals.
VALIDATION OF EUROARRAY HPV TEST USING THE VALGENT FRAMEWORK

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Background and Aims

Validation of HPV Genotyping Tests (VALGENT) projects offer a framework for analytical and clinical validation of HPV technologies; in the third iteration of VALGENT (3), EUROArray HPV test (EUROIMMUN, Lübeck, Germany) was assessed.

Methods

VALGENT-3 comprised 1,300 consecutively-collected, plus 300 cytologically-abnormal, Slovenian cervical screening samples. DNA was tested for high-risk-HPV on EUROArray at the Scottish HPV Reference Laboratory & HPV Research Group (Edinburgh) and compared against Hybrid Capture II (HC2) for sensitivity and specificity for histologically-confirmed cervical intraepithelial neoplasia grade 2 or worse (CIN2+). High-risk-HPV was defined as ≥1 of 13 genotypes targeted by HC2. EUROArray was considered non-inferior when Pni<0.05. Intra- and inter-laboratory reproducibility were performed on 150 HC2-positive and 350 HC2-negative DNA samples in Edinburgh, and Royal Women’s Hospital (Melbourne, Australia), respectively.

Results

Relative sensitivity of EUROArray for CIN2+ was statistically inferior to HC2 at 0.93 (95% CI, 0.87-1.00, Pni=0.1413). Relative specificity was non-inferior at 1.00 (0.98-1.03, Pni=0.0008). Using a lower signal cut-off for HPV16 resulted in sensitivity of 0.94 (95% CI, 0.88-0.97) and specificity 0.90 (95% CI, 0.89-0.92), both statistically non-inferior (Pni<0.001). Intra- and inter-laboratory agreement for high-risk-HPV were 98.4% (95% CI, 96.9-99.3) and 94.5% (95 % CI, 92.1-96.4), respectively. Kappas for intra- and inter-laboratory agreement were 0.96 (95% CI, 0.91-1.00) and 0.85 (95 % CI, 0.80-0.89), respectively.

Conclusions

Using manufacturer-defined detection cut-offs, EUROArray has non-inferior clinical specificity but lower sensitivity than HC2. By lowering the HPV16 cut-off, clinical sensitivity became non-inferior. This
modification will need to be validated further. EUROArray HPV reported excellent intra- and inter-laboratory reproducibility.
COMPARISON OF HPV DNA DETECTION IN ANAL SAMPLES FROM HIV-POSITIVE MEN WHO HAVE SEX WITH MEN USING TWO PCR-BASED TESTS

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Background and Aims

To evaluate analytical performance of HPV detection using Anyplex™ II HPV28 Detection against Linear Array HPV Genotyping Test in anal samples of men.

Methods

231 DNA samples of men who have sex with men (MSM) HIV-infected recruited in an anal cancer prevention program. HPV infection detection was carried out employing Linear Array Genotyping HPV Test (LA, Roche Diagnostics) which identifies 37 HPV types and Anyplex™ II HPV28 Detection (Anyplex, SeeGene) which detects 28 HPV types. The analysis of concordance is referred to positivity for HPV types common to both genotyping methods.

Results

LA and Anyplex rendered a valid result in 231 (100 %) and 228 (98.7%) samples, respectively. According to LA, 196 samples (84.8%) tested positive for HPV infection and among them 162 (82.65%) presented an infection with multiple HPV types. HPV16 (31.1%) and 53 (25%) were the types most detected. By Anyplex, 202 samples (88.6%) were positive, 165 samples (81.6%) showed more than one HPV type and HPV53 (28.2%) and 16 (27.2%) were the types most identified. For the global detection of HPV infection the agreement between both assays was 92.5% with a kappa value of 0.68 (95% CI: 0.54-0.82), (McNemar’s P value= 0.049). The analysis of the comparison of the number of types detected by both tests was moderate (agreement=64.5%; κ=0.53 [95% CI: 0.45-0.61]).

Conclusions
Anyplex shows a good agreement with LA in the detection of anal HPV infection, although decreases to moderate for the identification of the number of HPV types present in a sample.
To assess clinical performance of the Abbott RealTime High Risk HPV test (RealTime) and Roche Cobas 4800 HPV test (Cobas) for detection of high grade cervical lesions within the VALGENT-3 cohort (JCV 2016;76:S14–S21). In addition, we compared analytical and genotype-specific performance of the RealTime and Cobas.

Methods

VALGENT-3 panel constitutes 1,300 continuous samples obtained from Slovenian women aged 25-64 years who attended routine national cervical screening program, in addition to 300 samples obtained from women with cytopathological abnormalities. The main outcome measures were clinical sensitivity and specificity for CIN3+ of the RealTime and Cobas. Non-inferiority of the RealTime and Cobas compared to the standard comparator test Hybrid Capture 2 (hc2) was assessed using relative sensitivity and specificity.

Results

Clinical sensitivity and specificity of RealTime for detecting CIN3+in women aged ≥30 were 98.5% (95%CI, 91.8-100) and 94.5% (95%CI, 92.9-95.9), and of Cobas 97.0% (95%CI, 89.5-99.6) and 94.0% (95%CI, 92.3-95.4), respectively. The sensitivity of the RealTime for the detection of CIN3+ in women aged ≥30 was the same as that of HC2 (relative sensitivity, 1.02; 95%CI, 0.96-1.07; \( P_{\text{McNemar}}=0.56 \)), but its specificity was significantly higher (relative specificity, 1.02; 95%CI, 1.01-1.03; \( P_{\text{McNemar}}=0.0006 \)). Similar results were observed for Cobas with relative sensitivity 1.00 (95%CI, 0.95-1.05; \( P_{\text{McNemar}}=1.00 \)) and significantly higher relative specificity (1.01; 95%CI, 1.00-1.03; \( P_{\text{McNemar}}=0.03 \)).

Conclusions

RealTime and Cobas demonstrated non-inferior clinical performance compared to hc2 in women aged ≥30 with similar clinical sensitivity and significantly higher clinical specificity. In addition, high analytical and genotyping concordance was observed between the RealTime and Cobas.
To assess human papillomavirus (HPV) type-specific concordance between Linear Array HPV Genotyping Test (Linear Array), Anyplex II HPV28 Detection (Anyplex) and 21 HPV GenoArray Diagnostic Kit (GenoArray) within the VALGENT-3 cohort.

Methods

Type-specific agreement for 12 high-risk (hr) HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) and 6 low-risk HPV types (HPV6, 11, 42, 53, 66, and 68) common to all three tests were assessed by Cohen’s kappa statistic (κ) and McNemar statistics in VALGENT-3 population, which comprised 1,600 samples obtained from Slovenian women (1,300 consecutive cases from routine cervical cancer screening enriched with 300 cytological abnormal samples).

Results

Excellent to good agreement between Linear Array, Anyplex and GenoArray was observed for 12 hrHPV types overall and for all individual HPV types, except for HPV42 and HPV68. Whilst Anyplex and GenoArray were in good agreement with each other (κ=0.792 for HPV42 and κ=0.765 for HPV68), they were in fair agreement with Linear Array (κ=0.291 and 0.336 for HPV42 and κ=0.313 and 0.281 for HPV68, respectively) (Fig. 1). Additionally, positivity rate of hrHPV overall and some individual HPV types determined by Anyplex and GenoArray was statistically significantly higher than that determined by Linear Array.

Conclusions

Anyplex, GenoArray and Linear Array showed excellent agreement for the large majority of HPV genotypes assessed within VALGENT-3.
The detection of high-risk human papilloma virus (hrHPV) in vaginal self-collected sample offers greater acceptability and could be an alternative to improve the coverage of the Cervical Cancer Screening Program in Mexico (CCSPM). However, the detection rate of hrHPV may vary among different HPV tests.

To estimate the hrHPV positivity rate in self-collected vaginal samples compared to cervical samples, by Cobas4800® (Roche) and Onclarity™ (Becton Dickinson).

Methods

We collected 4,291 paired samples (vaginal self-collected and cervical) among women aged 25 to 64 years who were users of the CCSPM in Mexico City. The HPV detection for both samples were performed using Cobas4800® and Onclarity™ HPV assays. hrHPV detection rate was evaluated with each test.

Results

In cervical samples hrHPV positivity was 15.1% (95% CI: 14.0-16.2) by Cobas4800® and 13.2% (95% CI: 12.2-14.2) by Onclarity™ (McNemar test p<0.001). In vaginal samples, the hrHPV positivity was 18.5% (95% CI: 17.3-19.6) by Cobas4800® and 15.1% (95% CI 13.9-16.2) by Onclarity™ (p<0.001). The HPV16/18 proportion in Cobas4800® hrHPV positives was 20.5% and 20.8% in cervical and vaginal samples, respectively (p<0.02); by Onclarity™ it was 19.5% and 18.7% in cervical and vaginal samples, respectively (p<0.001).

Conclusions

Positivity rates were lower with Onclarity, assuming similar sensitivities for both tests, these differences may suggest better specificity of Onclarity HPV™ assay. Further research is warranted to evaluate the performance of these tests as primary screening tools, in particular for self-collected samples.
IPVC8-0426
POSTER SESSION

CLINICAL RESEARCH - HPV DIAGNOSTICS AND BIOMARKERS III: QUALITY AND PERFORMANCE VERIFICATION FOR CLINICAL HPV TESTS

HPV GENOTYPES THAT CROSS-REACT IN THE LINEAR ARRAY TEST
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Background and Aims

Linear Array Genotyping Test (LA) is one of the gold standards used for HPV genotyping, however, Next-Generation Sequencing (NGS) allows genotyping of a broader spectrum of HPVs with a high specificity.

Derived from a previous study of the IMSS Research Network on HPV, which suggested that there might be cross-reaction of some HPV genotypes in the LA test, the aim of this study was to elucidate this point.

Methods

Double stranded L1 fragments (gBlocks) from different HPVs were used to perform LA test, additionally, 14 HPV83+ and 26 HPV84+ cervical samples determined with LA, were individually genotyped by NGS.

Results

From the LA HPV83+ samples, 64.3% were truly HPV83+, while 42.9% were found to be HPV102+. On the other hand, 69.2% of the LA HPV84+ samples were HPV84+, while 3.8%, 11.5% and 30.8% of the samples were indeed HPV 86, 87 and 114 positive, respectively.

Conclusions

We demonstrated that there is cross-hybridization between alpha3-HPV genotypes 86, 87 and 114 with HPV84 probe in LA strips and between HPV102 with HPV83 probe; this may be causing over or under estimation in the prevalence of these genotypes. In the upcoming years, a switch to more specific and sensitive genotyping methods that detect a broader spectrum of HPV genotypes needs to be implemented.
APPLICATION OF THE SELF-SAMPLING DIAGNOSTIC TEST FOR EVALUATION OF HUMAN PAPILLOMA VIRUS IN WOMEN

L. Bashirova

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Background and Aims

Aim of the study was to estimate the prevalence of human papilloma virus (HPV) of high carcinogenic risk (HCR) in women in the Lipetsk region using a diagnostic test of self-sampling of vaginal discharge for HPV test.

Methods

It examined 455 female residents aged between 21 and 65. The selection of the material for the HPV-HCR study was performed both by the woman herself from the vagina with Qvintip device and by a gynecologist from the cervical canal. The material obtained by the specialist was placed in a test tube of the Eppendorf type with a transport medium; the material selected by the patient alone was placed in a dry test tube according to Qvintip instructions. Samples were studied by PCR in scraping of epithelial cells for the detection of HPV-PCK (16,18,31,33,35,39,45,52,58,59,67). The independent and medical selection of the vaginal discharge for HPV-test was evaluated according to the women's interview on convenience of using this system.

Results

According to the Qvintip-test, 35 women were identified with the results of the test (7.7%), 38 patients (8.4%) were identified with the HPV-HCR detected by the doctor.

Results of the interview: 320 out of 455 (70.3%) patients preferred the method of self-sampling of the material. The proportion of women who reported preferring to take samples by a doctor was significantly lower - 135 patients - 29.7% (p <0.001).

Conclusions

Thus, for Qvintip device for self-selection of material for testing on HPV-HCR, high diagnostic efficiency, simplicity and convenience in use are characteristic.
We report the performance of an assay that measures both expression of E6, E7 mRNA and cellular proliferation on a cell by cell basis with residual cervical cytology samples.

Methods

Residual de-identified cervical cytology samples in ThinPrep media were used to determine intra-run, inter-operator, inter-system, inter-day, and inter-site reproducibility. Negative percent agreement (NPA), positive percent agreement (PPA), and overall agreement (OA) were determined by pairwise comparisons. The inter-run and inter-operator portions of this study, samples were pooled based on HPV DNA status. Samples were split and tested at two sites for the inter-site study: TriCore Reference Laboratories (TRL) and IncellDx. Samples were analyzed on three Beckman Coulter CytoFLEX cytometers, one at TRL and two at IncellDx. Results were compared based on a dual cut-off of ≥ 4.6% E6, E7 expression and ≥ 4% Post G1.

<table>
<thead>
<tr>
<th>Metric</th>
<th>Samples</th>
<th>Sites</th>
<th>Operators</th>
<th>Instruments</th>
<th>Days</th>
<th>Non-Redundant Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-Run</td>
<td>HPV DNA +/- Pools</td>
<td>IncellDx</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>24</td>
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<tr>
<td>Inter-Operator</td>
<td>HPV DNA +/- Pools</td>
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<td>2</td>
<td>1</td>
<td>8</td>
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<td>Inter-System</td>
<td>Individual Samples</td>
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<tr>
<td>Inter-Day</td>
<td>Individual Samples</td>
<td>TRL</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>240</td>
</tr>
<tr>
<td>Inter-Site</td>
<td>Individual Samples</td>
<td>IncellDx and TRL</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>56</td>
</tr>
</tbody>
</table>

Results
Conclusions

The reproducibility of the HPV OncoTect 3Dx assay is acceptable in most of the reproducibility measurements at the two laboratory sites. Inter-system PPA of 50% is a result of insufficient positive samples in the dataset. There were only 4 samples with concordant positive calls and another 4 samples with discordant calls resulting in Inter-system PPA of 50%. With additional positive samples, it is expected that this value would improve.

<table>
<thead>
<tr>
<th>Reproducibility Metric</th>
<th>Results (HPV DNA- Pool)</th>
<th>Results (HPV DNA+ Pool)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-Run</td>
<td>NPA = 100%</td>
<td>NPA = 100%</td>
</tr>
<tr>
<td></td>
<td>PPA = 100%</td>
<td>* PPA = NA</td>
</tr>
<tr>
<td></td>
<td>OA = 100%</td>
<td>OA = 100%</td>
</tr>
<tr>
<td>Inter-Operator</td>
<td>NPA = 85%</td>
<td>NPA = 100%</td>
</tr>
<tr>
<td></td>
<td>* PPA = NA</td>
<td>* PPA = NA</td>
</tr>
<tr>
<td></td>
<td>OA = 71%</td>
<td>OA = 78%</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Reproducibility Metric</th>
<th>Non-pooled Sample Results</th>
</tr>
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<tbody>
<tr>
<td>Inter-System</td>
<td>NPA = 95%</td>
</tr>
<tr>
<td></td>
<td>PPA = 50%</td>
</tr>
<tr>
<td></td>
<td>OA = 52%</td>
</tr>
<tr>
<td>Inter-Day</td>
<td>NPA = 92%</td>
</tr>
<tr>
<td></td>
<td>PPA = 100%</td>
</tr>
<tr>
<td></td>
<td>OA = 93%</td>
</tr>
<tr>
<td>Inter-Site</td>
<td>NPA = 92%</td>
</tr>
<tr>
<td></td>
<td>* PPA = NA</td>
</tr>
<tr>
<td></td>
<td>OA = 86%</td>
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*No positive concordant results present*
Background and Aims

We report the performance of an assay that measures both expression of E6, E7 mRNA and cellular proliferation on a cell by cell basis with residual cervical cytology samples.

Methods

Residual de-identified cervical cytology samples in ThinPrep media were used to determine intra-run, inter-operator, inter-system, inter-day, and inter-site reproducibility. Negative percent agreement (NPA), positive percent agreement (PPA), and overall agreement (OA) were determined by pairwise comparisons. The intra-run and inter-operator portions of this study, samples were pooled based on HPV DNA status. Samples were split and tested at two sites for the inter-site study: TriCore Reference Laboratories (TRL) and IncellDx. Samples were analyzed on three Beckman Coulter CytoFLEX cytometers, one at TRL and two at IncellDx. Results were compared based on a dual cut-off of ≥ 4.6% E6, E7 expression and ≥ 4% Post G1.

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Results
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The reproducibility of the HPV OncoTect 3Dx assay is acceptable in most of the reproducibility measurements at the two laboratory sites. Inter-system PPA of 50% is a result of insufficient positive samples in the dataset. There were only 4 samples with concordant positive calls and another 4 samples with discordant calls resulting in Inter-system PPA of 50%. With additional positive samples, it is expected that this value would improve.
IN HOUSE HPV DNA DETECTION: ANALITICAL AND CLINICAL EVALUATION IN OROPHARYNX SAMPLES

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Background and Aims

Given the HPV-related carcinoma as a clinical variant of HNSCC, the inclusion of HPV status as a parameter is very important, hence the molecular staging system to answer the needs of a new approach to oropharyngeal carcinomas. Aim: Evaluate the analytical and clinical performance of an in house HPV DNA detection assay in an oropharynx carcinoma cohort.

Methods

We analyse data from 557 patients (2008-2017) with an oropharynx lesion. The clinical evaluation is based on the analysis of symptoms, histological characterization of the tumor and other IHQ(p16). The collected samples were processed for HPV, with a in house real-time SYBRGreen detection (n=514), with specific primers-SPF10 and melt curve analysis. For the analytical evaluation we estimate the sensitivity, specificity, reproducibility, robustness and interference of the assay on oropharynx samples.

Results

In this cohort, 90% (462/514) were biopsies, collected from oral cavity and oropharynx. Overall, HPV was detected in 32%. The analytical sensibility results proved to be reliable for the detection of different genotypes with a detection limit of 5IU/PCR for HPV16 and HPV18. HPV genotyping was performed in all HPV(+) samples, where 60% (59/98) were HPV16. Histologic result were confirmed in all evaluated samples - 90% were SCC.

Conclusions

Detection of HPV is a strong biomarker since the less aggressive behavior associated with HPV positivity can justify therapeutic de-intensification. The methodology evaluated for this cohort provides strength, reliability and accuracy on the result produced. It all provides new data for HPV detection assays in oropharynx samples, enabling to be applied in clinic required situations.
COMPARISON OF CLINICAL AND ANALYTICAL PERFORMANCES OF TWO CLINICALLY VALIDATED TESTS FOR THE HPV PRIMARY SCREENING OF CERVICAL CANCER

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²ISPRO Oncological Network- Prevention and Research Institute, Clinical Epidemiology and Registries, Firenze, Italy

Background and Aims

In Italy, HPV screening program is started in 2013. In Tuscany Region, the program was implemented in women aged 34-64 years and two different HPV tests, both validated for screening according to European guidelines, were used: HC2® (Qiagen®) (from 2013 to 2016) and Cobas® 4800 (Roche®) (from 2016).

The objective of the study is to analyse the impact of the transition from HC2® to Cobas® on HPV primary screening, comparing clinical and analytical performances.

Methods

The study was conducted on two levels:

1) on the same population (of Florentine area), comparing screening indicators before and after passing from one test to another;
2) on the same set of samples (HC2® positive re-analysed on Cobas®); discordant samples were typed by a RLB method (AB Analitica®).

Results

1) On the same population, HPV positivity resulted, respectively, 9.8% on HC2® and 7.4% on Cobas® (p<0.0001). The rates of abnormal/inadequate cytology triage were comparable. At immediate colposcopy, we found that CIN2+ PPV (23.8% vs 34.1%, p<0.0009) and the rate of normal colposcopies/histologies (43.9% vs 34.3%, p<0.004) were different among women of HC2® group and Cobas® group, respectively.
2) About re-analysed samples, 32.4% resulted HR-HPV negative on Cobas®. Discordant samples resulted on typing 7% HR-HPV positive, 43.8% HPV negative and 49.2% non HR-HPV positive.

Conclusions

The use of HC2® as primary screening test, compared to Cobas®, has registered: greater HPV positivity, lower CIN2+ PPV, higher frequency of normal colposcopies/histologies at immediate colposcopy. Furthermore, Cobas® is resulted more specific than HC2®: 93% of discordant samples (HC2® positive/Cobas® negative) resulted HR-HPV negative to typing. It is ongoing the E6-E7 genotyping of discordant samples, since Cobas® and AB Analitica® have the same target (L1), while HC2® detects whole genome.
Background and Aims

Despite proved oncogenic potential, HPV68 genotype may be excluded from HPV screening tests and from newly developed vaccines due to its rarity in cervical cancer. HPV68 may exist in two subtypes (a and b), differing in 6% E6, 5% E7 and 7% L1 ORF sequence, and the HPV68a subtype is usually not detectable by primers targeting L1 gene. The aim of the study was to evaluate the efficacy of routinely used cobas® 4800 HPV Test (targeting L1 gene) in HPV68a detection.

Methods

Cervical swabs (n=2198) obtained by physicians and self-sampled cervicovaginal swabs (n=217) were analysed for the presence of HPV by cobas® 4800 HPV Test (cobas, Roche) and PapilloCheck® HPV-Screening test (PapilloCheck, Greiner Bio-One). Real-time PCR followed by high resolution melting (HRM) curve analysis was used for HPV68a/b subtyping.

Results

HPV68 was detected in 39 of 2198 (1.77%) cervical swabs and 4 of 217 (1.84%) cervicovaginal swabs using PapilloCheck, with 33 single-type positive cases altogether. Cobas gave false negative result in 20 of 33 (60.6%) HPV68+ cases. HPV68a subtype was detected in all (20/20) false negative cases by HRM analysis. HPV68a subtype was detected in 5 of 13 (38.5%) and HPV68b in 8 of 13 (61.5%) of true positive cases, respectively.

Conclusions

Though cobas is routinely used HPV screening test, the false negative result was detected in 60.6% of HPV68 single-type infection cases due to its lower sensitivity for HPV68a. Prevalence of HPV68 genotype reported from cobas screening could be therefore underestimated.
THE SIGNIFICANCE AND UTILITY OF HPV-DNA TESTING IN WOMEN WITH ATYPICAL GLANDULAR CELLS IN PAP TEST

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1Asan Medical Center, Obstetrics and Gynecology, Seoul, Republic of Korea

Background and Aims

To analyze the correlation between clinically significant histologic results and HPV infection in women with atypical glandular cells (AGC) in Pap smear.

Methods

Among women with AGC in the Pap tests from Jan. 2001 to Dec. 2015, those who underwent subsequent HPV-DNA testing and histologic examination within one year were analyzed. Histologic results were: CIN2/3, endometrial hyperplasia with atypia, squamous cell ca, AIS and adenoca.

Results

Among 1013 women with AGC in Pap test, 311 (30.7%) had both histologic examination and HPV-DNA testing within 1 year. A total of 111 women (35.7%) was identified as HPV positive. Cervical squamous lesions were the most common in 45 (40.5%) cases of HPV positive women. In the AGC subtype analysis, cervical squamous or glandular lesions were significantly more common in HPV positive group compared with HPV negative group (61.2% vs. 10.5%, p < 0.001). In contrast, regardless of age and AGC subtype, endometrial lesions were not associated with HPV infection (8.1% vs. 4.5%, p = 0.12). In all age groups, cervical squamous or glandular lesions were statistically significant in HPV positive group compared with HPV negative group. The most common HPV genotypes in women with AGC were HPV 16 (32.2%), followed by HPV 18 (25.5%).

Conclusions

HPV-DNA testing in women with AGC may be a useful tool for predicting clinically significant cervical lesions but not for endometrial lesions. It is important to evaluate women with AGC by individualizing by age, AGC subtype and HPV status.
Background and Aims

Current HPV testing methods identify only a fraction of all known HPV types. This study focused on further evaluation on a target enriched whole genome sequencing-based (eWGS) genotyping assay covering all known HPV types.

Methods

Libraries were prepared using RNA baits targeting whole genomes of 191 HPV types, Agilent SureSelectXT2 protocol and sequenced with Illumina HiSeq2500. Data were analyzed with CLC genomics workbench. Thresholds for HPV typing included mapped reads ≥1000, depth ≥20, and genome coverage ≥50%. Reproducibility and limit of detection (LOD) were evaluated with data from two libraries prepared from pooled plasmids representing 9 vaccine HPV types at varying input levels (1-625 copies/reaction). Each library was sequenced twice giving four replicates.

Results

eWGS showed high correlation in the number of reads mapped to HPV reference genomes between the two flow-cell lanes within (R²=1) and between experiments (R²=0.99). The number of mapped reads was positively correlated to copy number (β=13.9, p<0.0001). eWGS's reproducibility at 625 and 125 copies was high for the number of mapped reads (CV: 10.1%) and for genome coverage (CV: 0.5%). HPV genotyping was reproducible for all 9 types at 625 copies. LOD was determined as 25 copies. eWGS showed no bias for HPV genotyping under single or multiple infection (p=0.22-0.99).

Conclusions

The universal eWGS method for HPV genotyping reduces type-competition and has sensitivity competitive with widely used consensus PCR methods. This approach, using defined samples varying in complexity and copy number, analyzed in replicate and duplicate assays, is applicable to most WGS methods.
COMPARISON OF ROCHE COBAS TEST AND HC2 TEST FOR THE DETECTION OF HIGH-RISK HPV IN A POPULATION-BASED STUDY

Methods

A total of 5459 women were recruited from well-woman clinics. Cervical ThinPrep specimens were collected for cytology assessment and HPV detection by both cobas and HC2 tests. Linear Array (LA) genotyping assay was used as confirmatory test to resolve the discordant results between two tests. Analytical performance and clinical relevance of both tests were determined and compared.

Results

The positivity of cobas and HC2 test were found in 395 (7.2%) and 415 (7.6%) samples, respectively. Overall, the absolute agreement of two tests was 93.2% and the Kappa value showed a moderate inter-assay agreement of 0.504. Discordant cases were analyzed by LA test. More hr-HPV genotypes were detected in cobas+/HC2- cases (33.9% vs 7.5%), whereas less hr-HPV genotypes, but more lr-HPV genotypes were found in cobas-/HC2+ (7.9% vs 25.4%) cases. Four hundred and sixteen cases with indications were referred to colposcopy clinic for further evaluation. High-grade CIN and SCC were found in 17 and one case, respectively. The cobas test showed a higher test specificity than HC2 test (68.6% vs 46.2%), though the sensitivity of cobas test was lower than HC2 test (83.3% vs 94.4%).

Conclusions

The cobas test demonstrated comparable analytical performance to the HC2 test with less cross-reactivity with lr-HPV genotypes. With increase of specificity, cobas test showed better clinical performance.
Utility of Onclarity HPV Genotyping for Screening and Triage in 30 to 69 Years Old Women in Germany

K.U. Petry¹, A. Denecke¹, A. Iftner², T. Iftner²

¹Klinikum Wolfsburg, Obstetrics and Gynecology, Wolfsburg, Germany
²University of Tübingen, Experimental Virology, Tübingen, Germany

Background and Aims

HPV testing shows a better sensitivity for CIN3+ than cytology based screening programs but the optimal triage strategy of HPV+ cases remains a challenge.

Methods

We compared the performance of HC2 and Onclarity as primary screening tests among 7,396 women (30-69 years) attending for their first or second round in a primary co-testing program and evaluated possible triage algorithms for different HPV genotype combinations.

Results

99.0% of HC2 negative cases tested negative with Onclarity too (6,698/6,764) but only 446 out of 597 HC2+ cases tested positive with Onclarity. In most discordant cases Linear Array detected HPV, including non HR-types. We diagnosed 32 CIN3+ and 36 CIN2 cases, all of whom were HC2+, while Onclarity missed 1 CIN2 and 2 CIN3 cases, including one adenocarcinoma in situ associated with HPV67. A triage concept with transferal of HPV16+ cases only showed the best PPV (16.8%) but a low sensitivity (59.4%) for CIN3+, while transferal of HPV 16/18/31/33/45/58+ cases showed a higher sensitivity (79.3%) and lower PPV (10.9%) that still exceeded the German threshold of 10% for transferal to colposcopy. HPV16 dominant in CIN3+ in younger women and in new lesions in round 2 but not in older women in round 1.

Conclusions

In comparison with HC2 as a screening test, Onclarity genotyping showed non-inferior NPV and sensitivity for CIN2+ (100% vs 95.4%) while its PPV and specificity (91.8% vs 93.5%) were better. Genotyping for more types than 16/18 seems to be a useful triage especially in 45+ years old women at first HPV screening.
ROLE OF HPV-MRNA DETECTION IN HPV INFECTIONS
M. Rongioletti¹, C. Vaccarella¹, S. Valente¹, S. Mariani¹, P. Catalano¹, G. Toscano¹, A. Luciano¹, L. Di Veroli¹, F. Papa¹, R. Squitti¹
¹Fatebenefratelli Hospital 'San Giovanni Calibita'- Isola Tiberina- Rome- Italy, Department of Biology Medicine- Research and Development Division, Rome, Italy

Background and Aims

HPV DNA has been identified in almost all cervical cancers and women with active HPV infection (HPVI) express E6/E7 oncogenes. As only a small proportion of infections progress towards cancer, it is important to distinguish transient HPVIS from persistent or progressive ones.

Methods

From May 2015 to January 2018 we analyzed a consecutive pool of 2786 patients (10% male) with clinical suspicion of HPV infection. We analyzed our database comprehensive of conventional pap smear and / or cytological analyses of other districts than the uterine cervix, HPV-DNA test genotyping, E6 / E7-mRNA expression from HPV types 16, 18, 31, 33, 45 along with histological samples.

Results

All subjects performed HPV genotyping and 519 of them were followed by E6 / E7-mRNA qualitative expression analysis. 121 were positive (5% of them were men). Among these subjects, 20% had a positive pathological result based on Bethesda classification for histological and cytological reports. Among positive mRNA analysis, 24% exhibited an aggressive histology, that resulted only in 7% of mRNA negative. Anal and oral district show no positive mRNA analysis at difference from HPV genotyping that resulted positive among 100% of the studied sample.

Conclusions

Since mRNA analysis had a poor predictive value on the aggressiveness of the histological phenotype, genotyping analysis remains the main screening tool for the evaluation of HPV infection. The mRNA analysis is effective for assessing the aggressiveness of the infection in the uterine districts, but it appears less informative for other districts commonly involved.
Background and Aims

In Norway, HPV DNA primary screening is to be implemented for women 34-69 years, but women 25-33 years are still screened by cytology. A 3-type HPV mRNA test is more specific than a 14-type HPV DNA test, and may be used in young women. We wanted to estimate the positive predictive value (PPV) for CIN2+ using cytology and HPV mRNA 16, 18, and 45 in women 25-33 years.

Methods

From April 2016, the Department of Clinical Pathology, University Hospital of North Norway, introduced cytology and 3-type HPV E6/E7 mRNA test (PreTect SEE; direct genotyping 16, 18 and 45); in women 25-33 years. In total, 4,428 women aged 25-33 had valid cytology and HPV mRNA result and were included in 2016 and followed-up until February 2018. Histologically confirmed CIN2+ was used as study endpoint.

Results

Of the 4,428 women, 273 (6.2%) had a positive HPV mRNA test, 1,002 (22.6%) had ASC-US+, 212 (4.8%) had ASC-H+ and 236 (5.3%) had CIN2+. The PPV for CIN2+ for HPV mRNA, ASC-US+ and ASC-H+ were 48.7% (133/273), 22.2% (222/1002) and 55.2% (117/212), respectively. Cytology alone missed 5.9% (14/236) of CIN2+. For women with a negative co-test (Cyt-/HPV-) the risk of CIN2+ were 0.09% (4/4,428).

Conclusions

The 3-type HPV mRNA test has low positivity rate and high PPV for CIN2+ in women 25-33 years. Women with a negative co-test have low risk of CIN2+. Cytology and HPV mRNA co-testing will reduce the risk of cervical cancer in young women.
VARYING SIGNAL-TO-CONTROL HIGH-THRESHOLD HPV-DNA ASSAY POSITIVITY CUT-POINTS PREDICT ANAL HISTOLOGICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HHSIL) FOR HIV-INFECTED AND -UNINFECTED MSM

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Background and Aims

Improving specificity and accuracy for anal hHSIL screening tests decreases healthcare costs.

Methods

295 MSM were evaluated using nylon-flocked (NF) and Dacron swab-collection protocols and HPV-DNA assay, Hybrid-Capture 2 (HC-2), to predict hHSIL confirmed by High-Resolution Anoscopy and biopsy. Sensitivity, specificity, and area under Receiver-Operating Characteristic curves (AUCs) were evaluated for five subject/control relative-light unit (RLU) ratio positivity cut-points: >0.3, >1, >2, >4, and >10. Multivariable logistic regression analyses assessed odds of hHSIL for each swab and cut-point to predict hHSIL, adjusting for number of anoreceptive-intercourse (ARI) partners (prior 24 months).

Results

Subjects were White (73%), 55 (σ=11.5) years-old, ever-smokers (77%); 40% were HIV+ with >500 CD4 cells/mm³, 19% with <500. ARI partnerships were associated with HC2-positivity and hHSIL; 54% of affected men reported >1 ARI partners versus 32% of unaffected (p=0.0031). Nearly 2-9% tested HC2+ using one swab over the other, across five HC2-positivity cut-points: >0.3, >1, >2, >4, >10. Adjusted and unadjusted models suggested good accuracy for predicting hHSIL on all cut-points (Table 1). Specificity for NF-swab was statistically significantly (SS) greater for cut-points >4 and >10, versus >1, the cervical-screening standard (76%, 69% vs. 56%; Table 2), which was also observed for Dacron-swab (67%, 67% vs. 54%). Sensitivity did not vary for Dacron-swab cut-points except >0.3. For NF-swab sensitivity, cut-points >2 and >4 showed no SS difference than >1; however, sensitivity for >10 was SS lower (65% vs. 81%, Table 2).
Table 1: Comparison of Unadjusted and Adjusted Area Under Receiver Operating Characteristic Curves (AUC) for Two Anal Swab Collection Protocols using High-Risk Human Papillomavirus Hybrid-Capture 2 Assay to Predict Histological High-grade Squamous Intraepithelial Lesion (HSIL). Where Assay Positivity is Set to Five Subject-to-Control Cutpoints.

<table>
<thead>
<tr>
<th>Swab Protocol</th>
<th>MF-swab</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Positive</td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>p</td>
<td># Positive</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>P0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>218</td>
<td>0.65</td>
<td>0.72</td>
<td>0.38</td>
<td>238</td>
<td>0.60</td>
<td>0.64</td>
</tr>
<tr>
<td>P1</td>
<td>177</td>
<td>0.69</td>
<td>0.74</td>
<td>0.07</td>
<td>179</td>
<td>0.67</td>
<td>0.71</td>
</tr>
<tr>
<td>P2</td>
<td>161</td>
<td>0.71</td>
<td>0.76</td>
<td>0.008</td>
<td>166</td>
<td>0.69</td>
<td>0.73</td>
</tr>
<tr>
<td>P4</td>
<td>148</td>
<td>0.71</td>
<td>0.76</td>
<td>0.009</td>
<td>146</td>
<td>0.69</td>
<td>0.74</td>
</tr>
<tr>
<td>P40</td>
<td>130</td>
<td>0.70</td>
<td>0.75</td>
<td>0.006</td>
<td>130</td>
<td>0.71</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Adjusted for the effect of number of anoreceptive intercourse partners*
| Decoy HC2 cutoff | Sensitivity (95% CI) | \(>3\) & 3 & \(>2\) | \(>1\) & 2 | Specificity (95% CI) | \(>3\) & 3 & \(>2\) | \(>1\) & 2 | \(>0\) & 1 | \(>0\) & 0 |
|------------------|----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| \(\geq 3\)       | 50% (41%, 59%)       | ref              | -               | -               | 76% (69%, 82%)  | ref              | -               | -               | -               | -               |
| \(\geq 1\)       | 79% (72%, 86%)       | 0.001            | ref             | -               | 54% (46%, 62%)  | 0.0001           | ref             | -               | -               | -               |
| \(\geq 2\)       | 77% (70%, 84%)       | 0.001            | 0.76            | ref             | 64% (59%, 67%)  | 0.003            | 0.32            | ref             | -               | -               |
| \(\geq 4\)       | 72% (65%, 79%)       | 0.009            | 0.15            | 0.32            | ref             | 67% (60%, 74%)  | 0.11            | 0.02            | 0.21            | ref             |
| \(\geq 20\)      | 76% (69%, 83%)       | 0.001            | 0.66            | 0.99            | 0.4            | 67% (59%, 74%)  | 0.09            | 0.02            | 0.25            | 0.09            |

| HF-sweab-HC2 cutoff | Sensitivity (95% CI) | \(>3\) & 3 & \(>2\) | \(>1\) & 2 | Specificity (95% CI) | \(>3\) & 3 & \(>2\) | \(>1\) & 2 | \(>0\) & 1 | \(>0\) & 0 |
|---------------------|----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| \(\geq 3\)         | 91% (86%, 96%)       | ref             | -               | -               | 38% (32%, 47%)  | ref             | -               | -               | -               |
| \(\geq 1\)         | 81% (74%, 88%)       | 0.33            | ref             | -               | 56% (49%, 64%)  | 0.003           | ref             | -               | -               |
| \(\geq 2\)         | 79% (72%, 86%)       | 0.11            | 0.88            | ref             | 65% (59%, 72%)  | 0.0001          | 0.14            | ref             | -               |
| \(\geq 4\)         | 75% (67%, 82%)       | 0.009           | 0.3             | 0.46            | ref             | 68% (62%, 76%)  | 0.001           | 0.02            | 0.48            | ref             |
| \(\geq 20\)        | 65% (56%, 73%)       | 0.001           | 0.005           | 0.01            | 0.11            | 76% (69%, 82%)  | 0.0001          | 0.003           | 0.04            | 0.22            |

*p* value for the specific comparisons of sensitivity or specificity to a referent (ref) cutoff: \(>0\) & 1, \(>2\) & 4
Conclusions

Higher specificity of higher assay-positivity cut-points decreases false-positive findings, improves positive-predictive power with sensitivity comparable to cervical cytology.
Human papilloma virus (HPV) detection in formalin-fixed paraffin-embedded tissue (FFPE) is widely used for diagnostic and prognostic purposes. RNA-based in situ hybridization (RNA ISH) assay offers high sensitivity and robust chromogenic signal detection. However, in some cases, equivocal staining patterns are encountered.

Methods

262 cases tested for the presence of high risk (HR) HPV using RNAscope assay (ACD) were reviewed. The cocktail probe containing 7 HR HPV types (16, 18, 31, 33, 35, 52, 58) was used. The assay includes a control probe to ensure presence of detectable RNA in the tissue. Signals in the nucleus and cytoplasm of the lesional cells were considered positive. RNA control failed in 10 cases. The most common equivocal pattern consisted of focal nuclear-only signals. Immunohistochemistry (IHC) for p16 was performed concurrently in 207 cases. P16 was considered positive in cases with over 70% of lesional cells with strong expression. Cases with the extent of expression approaching 70%, variable intensity were considered p16 equivocal.

Results

HPV ISH and p16 IHC showed concordant results in 161 cases. The data is summarized in Table 1.

<table>
<thead>
<tr>
<th>HR HPV ISH</th>
<th>Number of cases</th>
<th>P16 expression (N= 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>129</td>
<td>114/117 (97%)</td>
</tr>
<tr>
<td>Negative</td>
<td>85</td>
<td>10/62 (16%)</td>
</tr>
<tr>
<td>Equivocal</td>
<td>38</td>
<td>9/28 (32%)</td>
</tr>
<tr>
<td>Total</td>
<td>252</td>
<td>133</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Equivocal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>117 (1%)</td>
<td>2 /117 (2%)</td>
</tr>
<tr>
<td>Negative</td>
<td>47/62 (76%)</td>
<td>5/62 (8%)</td>
</tr>
<tr>
<td>Equivocal</td>
<td>13/28 (46%)</td>
<td>6/28 (21%)</td>
</tr>
</tbody>
</table>

* One HPV positive case had complete absence of p16 expression in the tumor with preserved focal staining in adjacent non-neoplastic tissue.

Conclusions
RNA ISH for HR HPV provides robust detection in most of cases. Equivocal results are encountered in up to 15% of cases. P16 IHC provides greater confidence in ISH calls. Discordant HPV ISH and p16 results could be related to presence of HPV type not covered by the assay or alterations in p16 expression unrelated to HR HPV. Evaluation of the equivocal and discordant cases by alternative HPV testing methods is in progress.
CLINICAL RESEARCH - HPV SELF-COLLECTION

COMPARISON OF CERVICAL, VAGINAL AND URINE SAMPLES FOR DETECTING HUMAN PAPILLOMAVIRUS (HPV) WITH DIFFERENT COMMERCIAL METHODS FOR HPV DETECTION

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5Sejong biomed cooperation, Diagnosis R&D center, Seoul, Republic of Korea

Background and Aims

Less or non-invasive HPV testing using self-collected vaginal and urine samples may provide an opportunity to improve screening coverage. To compare HPV DNA detection with the realtime HR-S HPV, Anyplex II HPV 28 and Cobas 4800 HPV test on clinician-collected cervical, self-collected vaginal and urine samples.

Methods

Cervical, vaginal, and urine samples were collected from 101 patients, including 84 patients diagnosed with high grade squamous intraepithelial lesion and 17 patients diagnosed with ovarian disease. HPV prevalence, clinical performance and concordance was compared across the different methods of sampling and HPV test.

Results

In HPV 16/18, the concordance of HPV test using self-collected vaginal and urine samples compared with cervical samples was almost perfect (k=0.81-0.86) and substantial (k=0.59-0.63), respectively. In other high risk HPV (hrHPV), the concordance of HR-S HPV (k=0.69-0.72) on self-collected vaginal and urine samples compared to cervical samples was higher than Anyplex (k=0.52-0.53), and cobas HPV test (k=0.36-0.51). Compared to the different HPV test using each sampling methods, HR-S HPV showed a higher concordance compared with Anyplex HPV, whereas it showed a lower concordance compared to cobas HPV.

Conclusions

Self-collected vaginal and urine samples showed a nearly perfect and considerable agreement with cervical samples in HPV 16/18 detection, respectively. The HR-S HPV showed a good agreement with Anyplex HPV, but not with cobas HPV. The HPV test using self-collected vaginal samples may be a promising alternative for women who are reluctant to participate in screening for cervical cancer, but the HPV test using urine will be needed to further studies.
A RANDOMIZED, CONTROLLED TRIAL OF TWO STRATEGIES OF OFFERING THE HOME-BASED HPV SELF-SAMPLING TEST TO NON-PARTICIPANTS IN THE FLEMISH CERVICAL CANCER SCREENING PROGRAM.

I. Benoy1,2,3, E. Kellen4,5, D. Vanden Broeck1,3,6, P. Martens4, A. Haelens7, J. Bogers1,2,3,6, E. Van Limbergen4,5

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2University of Antwerp, AMBIOR- Laboratory for Cell Biology & Histology, Antwerp, Belgium
3NRC, National Reference Centre HPV, Brussels, Belgium
4CVKO, Centre for Cancer Detection, Flanders, Belgium
5University Hospital Leuven, Campus St. Rafael, Leuven, Belgium
6Ghent University, Centre for Reproductive Health, Ghent, Belgium
7Belgian Cancer Registry, Belgian Cancer Registry, Brussels, Belgium

Background and Aims

We conducted a randomized, controlled trial to evaluate different strategies of offering an HPV-self sampling program, and compared this with two control groups.

Methods

All total of 35,354 women who did not participate in the Flemish cancer screening program were included in the study: 9,118 received a HPV self-collection brush; 9,098 were offered the opportunity to order an HPV-selfsampling brush, 8,830 received the recall letter; 8,849 received no intervention at all.

Results

Within 12 months after the mailing, 18.7% of the women who had received the brush, participated by returning a self-sample sample, while 10.6% women allocated to the opt-in group did so. 10.5% women who received the standard recall letter, had a PAP smear taken within a period of 12 months; while 8% women did so without receiving an intervention at all. Participation in postmenopausal women was higher than in women younger than 50 in both self-sampling arms. Screening by means of the self-sample kit increased by age, contradictory when screening is performed by a PAP smear. Of those testing hrHPV positive (9.5%), 88.9% attended for follow up cytology. The mean DNA concentration, found in the self-sampler, decreased by age, causing a higher number of inconclusive results.

Conclusions

Our results support the efficacy of a self-sampling strategy to increase participation in the Flemish screening program. Self-sampling seems particularly acceptable to postmenopausal non-responders. Future research should focus on the performance of different self-sampling devices in postmenopausal women as low DNA concentrations exponentially increased over age.
EXPERIENCE WITH HPV SELF-SAMPLING AND CLINICIAN-BASED SAMPLING IN WOMEN ATTENDING REGULAR CERVICAL SCREENING IN THE NETHERLANDS

N. Polman¹, Y. de Haan², N. Veldhuijzen³, D. Heideman², H. de Vet³, L. Massuger⁴, F. van Kemenade⁵, C. Meijer², J. Berkhof⁶

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²VU University Medical Center, Cancer Center Amsterdam- Department of Pathology, Amsterdam, The Netherlands
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⁵Erasmus University Medical Center, Department of Pathology, Rotterdam, The Netherlands

Background and Aims

Several countries have implemented HPV self-sampling for screening non-attendees. It is generally assumed that screening responders also prefer self-sampling over clinician-based sampling, however, little research has been conducted with respect to experiences and preferences of women from a regular screening population.

Methods

Women participating in the IMPROVE-study were randomised (1:1) to self-collected or clinician-collected HPV testing, and HPV-positive women were retested using the other collection method. Among a subset of participating women, three different questionnaires were sent out: Q1) HPV-negative women from the self-sampling group were asked about their experiences with self-sampling (n=2,366); Q2) HPV-negative women in the clinician-collection group were asked about their experiences with clinician-based sampling (n=2,092); and Q3) HPV-positive women from both study groups were asked about their experiences with both self-sampling and clinician-based sampling (n=497).

Results

Response rates (Q1-Q3) ranged from 71.6 to 79.4%. HPV-negative women in the self-sampling group Q1 reported significantly lower levels of shame, nervousness, discomfort and pain during sampling than HPV-negative women in the clinician-based sampling group Q2 (p-values <.001). However, trust in a HPV-negative test result was slightly higher among HPV-negative women from Q2 as compared to Q1 (p-value .005). Similar results were obtained among women who performed both self- and clinician-based sampling Q3. Besides, the large majority (76.5%) of women in Q3 preferred self-sampling over clinician-based sampling in future screening.

Conclusions

Women from a regular screening population have a positive attitude towards self-sampling but express some concerns with respect to test accuracy. The majority prefers self-sampling over clinician-based sampling in future screening.
IPVC8-0804
POSTER SESSION

CLINICAL RESEARCH - HPV SELF-COLLECTION

DESIGNING A TUBE AND A CAP FOR TRANSPORTATION OF BIOLOGICAL LIQUIDS USING FINITE ELEMENT ANALYSIS (FEA)
K. Beyers¹, T. Van Mulder², N. Meers¹, A. Ríos Cortés¹, M. Gernaey³, K. Sorgeloos⁴, V. Vankerckhoven⁴
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²University of Antwerp, Vaccines & Infectious Diseases, Antwerp, Belgium
³Voxdale BVBA, R&D Department, Wijnegem, Belgium
⁴Novosanis NV, Management, Wijnegem, Belgium

Background and Aims

Collection tubes are often very fragile with regard to leakage, during long storage, in low pressure air freight, or with liquids with low surface tension. Additionally, plastic creep can weaken the tube-cap tension over time and cause delayed failure.

The aim of this study was to define a tube geometry that operates without seal, whilst exposed to under pressure of up to 56kPa (while in plane cargo @39,000 feet).

Methods

To design a cap-tube closure, 3 types of materials were used:

(i)3D CAD models were built to run FEA simulations in order to evaluate the concepts.

(ii)3D prints were made to assess initial fit and usability aspects (closing torque, comfort),

(iii)Injection moulding tools were produced to mould parts in HDPE for the caps, and in Polypropylene for the tubes.

These materials were tested using these methods:

(i)In the FEA model, different sizes of caps and tubes were assembled, with different overlaps, to simulate tolerance deviations.

(ii)The tubes were closed at 1Atm, before they were submerged in a water filled clock, with vacuum applied at -85kPa.

Results

The FEA showed that the smallest tolerated cap with the biggest tube still produces a closing pressure of 30N/mm². Taking reductions due to plastics creep into account, this connection would survive negative pressure of 100kPa.

This was confirmed in the conclusive immersion test at -85kPa.
Conclusions

The design featured an internal thread concept with inlying closure ring. It is to be expected that filled tubes (e.g. with preservative) with this design could ensure proper storage/shipment without leakage for 12 months or more.
SAMPLE CELLULARITY AND HIGH-RISK HPV TYPE-SPECIFIC VIRAL LOAD ASSESSMENT OF VAGINAL AND FIRST-VOID URINE SAMPLES COMPARED TO CLINICIAN-COLLECTED CERVICAL SAMPLES IN WOMEN REFERRED TO COLPOSCOPY

C.E. Cocuzza\textsuperscript{1}, M. Martinelli\textsuperscript{1}, R. Musumeci\textsuperscript{1}, A. Rizzo\textsuperscript{1}, G. Brenna\textsuperscript{1}, C. Crotti\textsuperscript{1}, G. Di Martino\textsuperscript{2}, F. Sina\textsuperscript{2}, C. Stefania\textsuperscript{2}, R. Frusco\textsuperscript{1}, F. Landoni\textsuperscript{1}, A. Piana\textsuperscript{3}

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\textsuperscript{2}San Gerardo Hospital ASST, Gynaecology, Monza, Italy
\textsuperscript{3}University of Sassari, Department of Biomedical Sciences, Sassari, Italy

Background and Aims

The aim of this study was to evaluate sample cellularity and high-risk HPV viral load detection in first-void urine (FVU) and vaginal self-collected samples (VSC) as compared to physician-collected cervical samples (gold standard) in women with a recent diagnosis of cervical dysplasia.

Methods

Self-collected vaginal samples using FLOQSwabs\textsuperscript{™} (Copan), FVU using Colli-Pee (Novosanis) and physician-administered cervical samples were collected from women referred to San Gerardo Hospital for colposcopy. Samples were analysed at the Clinical Microbiology Laboratory of the University of Milano-Bicocca. Nucleic acids were extracted by NucliSENS easyMAG (bioMérieux); sample cellularity and normalized viral load were evaluated using “in house” HR-HPV type-specific and human CCR5 gene quantitative real-time PCR assays. HPV detection was further confirmed using Anyplex II HPV28 (Seegene).

Results

Preliminary data obtained from 50 enrolled patients has shown adequate sample cellularity for all analyzed sample types (mean values for urine, vaginal and cervical samples: 8.05E+06, 2.27E+06 and 4.85E+06 cells/sample, respectively). Concordant HPV detection for at least one type was demonstrated in 100% VSC and in almost 90% of FVU samples as compared to cervical samples. HPV-16 resulted the most frequently HR-type detected, with a mean viral load of 2.76E+06, 1.49E+05 and 8.60E+03 GU/10\textsuperscript{4} cells in cervical, vaginal and urine samples, respectively.

Conclusions

Preliminary results show an adequate cellularity for all sample types. HPV detection using Anyplex II HPV28 in self and clinician-collected samples showed a high degree of concordance. First-void urine and vaginal self-collected samples may offer a promising alternative in cervical cancer screening programs.
Background and Aims

Home-based urine sampling could offer a solution to increase participation rates in cervical cancer screening populations. The aim of the study was to design and develop a next-generation Colli-Pee® allowing for standardized and guaranteed collection of first-void urine that is optimally suited for postal delivery and home-based collection.

Methods

As part of an EU Grant, two co-creation sessions were organized in collaboration with living labs Happy Aging (BE) and EIZT (NL). A total of 20 healthy volunteers evaluated and scored new designs (prototypes) of the urine collection device. Additionally, insights were gathered on home-based collection and internet offerings.

Results

A distinct choice was made for the prototype that scored best for time of sampling (8.3), user-friendliness (8.3), and choice of material (8.6). Hygiene, no chance for leakage/spilling, ergonomics and user-friendliness were the characteristics that were rated most important to preserve in the definitive product variant of the Colli-Pee®. We did not see differences in preference between the Netherlands and Belgium with regard to the design.

Next, a larger usability study was conducted to provide insights into the entire process of home-based sampling: from the online request and receiving the Colli-Pee® with a flexible, comfortable funnel to the actual collection of urine and returning of the sample to the lab. During this study, no analyses were performed on the urine sample. The returned samples were checked for leaking and the collected volume; and the condition of the returned box was evaluated.

Conclusions

The next-generation Colli-Pee® was well-accepted and offers a solution for home-based collection.
SELF-COLLECTED AND CLINICIAN-COLLECTED ANAL SWABS SHOW MODEST AGREEMENT FOR HPV DNA TESTING

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⁶UCSF School of Medicine, Department of Medicine, San Francisco, USA
⁷University of Zimbabwe, Obstetrics and Gynaecology, Harare, Zimbabwe

Background and Aims

Self collection of anal swabs facilitates HPV DNA testing in anal cancer screening, and yet it is understudied. We evaluated level of agreement of self-collected (SC) and clinician-collected (CC) anal swabs when used for HPV DNA testing among women presenting for cervical cancer screening.

Methods

A cross sectional study performed at a tertiary hospital visual-inspection- with-acetic-acid clinic (VIA), in Harare, Zimbabwe. Women aged ≥18 years, reporting for routine cervical cancer screening, were recruited. In a clinic setting and on the same day, the women provided anal swabs in duplicate and simultaneously; firstly CC and then SC. HPV detection and genotyping were performed using next generation amplicon sequencing of a 450bp region of the L1 gene. Level of agreement was calculated using the kappa and McNemar tests.

Results

A total of 300 women provided 600 samples for HPV DNA testing. HPV DNA was detected in 75/300 (25%) of SC and in 67/300 (22%) of CC. Detection rates with CC were HPV52 (13%), HPV62 (12%) and HPV70 (10%), with SC were HPV62 (15%) and 11% for HPV44 , HPV52, HPV53 and HPV68. The agreement between the two methods was 0.55 in kappa value (k), with a McNemar Chi-square value of 0.75 (p=0.39).

Conclusions

Self-collection and clinician collection of anal swabs gave moderate agreement, with non-statistically significant difference. We therefore cautiously recommend self-collected anal swabs for HPV DNA testing in this study setting.
CLINICAL RESEARCH - HPV SELF-COLLECTION

ACCEPTABILITY OF SELF-COLLECTION HPV TESTING FOR CERVICAL CANCER SCREENING: URINE AND SELF-SAMPLING WITH BRUSH

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Background and Aims

To evaluate the acceptability of two non-invasive HPV testing methods, urine self-collection and self-sampling with a brush, for cervical cancer screening.

Methods

Enrolled were 361 women aged 25-65 years undergoing loop electrical excision procedure for treatment of high grade squamous intraepithelial neoplasia or colposcopy either following an abnormal cytology result or a positive high-risk HPV result with normal cytology. Each participant provided a urine sample followed by a self-swab cervico-vaginal brush sample. After these self-collections, participants completed a questionnaire on demographic and acceptability measures. Data were analyzed both quantitatively and qualitatively through thematic analysis.

Results

Most individuals felt positively about both urine (80%) and brush self-collection (69%), with more preferring urine (79%) over brush (21%) self-sampling (p<10^(-15)). If tested for HPV again, participants reported a preference for urine self-collection (66%) as compared to self-sampling with a brush (22%) and provider-collected pap smear (12%) (p<10^(-15)). Noted attributes of both urine sampling and self-swab with a brush were ease of use and non-invasiveness. Participants described no concerns with providing a urine sample; the most common concern with brush self-collection was whether it had been performed it correctly (14%).

Conclusions

Self-collection for HPV testing with urine and self-sampling brush are both highly accepted among high-risk individuals, with urine preferred over self-sampling with a brush. If these self-collection modalities are proven to be effective for the detection of high-grade pre-cancers, they have the potential to increase uptake of cervical cancer screening.
CONVENTIONAL SAMPLING VERSUS VAGINAL SELF-COLLECTION, “DRY” AND “WET”, IN CERVICAL CANCER SCREENING: EVALUATION OF CLINICAL SENSITIVITY AND DEFINITION OF AN ANALYSIS PROTOCOL FOR HPV TEST

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Background and Aims

A ISPRO (Florence) research project on self-collection involved 5200 women “non-responder” to cervical cancer screening call: some performed collection at the clinic ("Control-arm"), others received at home “Dry” self-sampler device FLOQSwab® (Copan) or “Wet”, with 1ml of MSwab® (Copan). We investigated sensitivity and reproducibility of high-risk (hr-)HPV test on self-collection with two protocols:

- "Dry-samples" were resuspended in 4ml of ThinPrep® (Hologic) and “Wet-samples” in 4ml of MSwab®+TP® (1:4);

- 1:5 dilution of resuspended samples, that opens up the possibility of validating the analysis of self-sampling samples in 20ml of TP®.

Methods

From HC2® (Qiagen) hr calibrator (HPV16 plasmid, 100 copies/µl), absorbed on FLOQSwab®, we evaluated clinical sensitivity (5000 HPV16 copies/reaction), LOD (600 and 1200 HPV16 copies/ml) and FLOQSwab® absorption capacity. The 455 returned self-sampling samples (Dry and Wet) were resuspended in 4ml, analysed for hr-HPV test on Cobas4800® (Roche), then diluted 1:5. Results were compared using Cohen's «Kappa» index.

Results

All 5000 HPV16 copies/reaction replicates are positive. All samples in MSwab®+TP® and 95% in TP® resulted positive with 1200 HPV16 copies/ml. Only 60% of tests in TP® and 65% in MSwab®+TP® were positive with 600 HPV16 copies/ml. FLOQSwab® adsorption resulted 230µl. The HPV positivity in 4ml protocol is “Dry” 10.7% and “Wet” 12.5% (MeanBG-CT=27.92), compared to “Control-arm” 9.2%. Cohen's «Kappa» index is 0.94 (MeanBG-CT=30.81).

Conclusions
FLOQSwab® LOD for HPV16 is 1200 HPV16 copies/ml and 4ml protocol is valid at HPV test clinical sensitivity (5000 HPV16 copies/reaction). The excellent Cohen’s «Kappa» index obtained among samples with 4ml protocol and 1:5 dilution opens up the possibility to validate self-collected samples analysis in 20ml of ThinPrep.
VAGINAL SELF-COLLECTION VERSUS CERVICAL CLINICIAN-COLLECTED SAMPLES FOR CERVICAL CANCER SCREENING: WHAT WOULD YOU CHOOSE? RESULTS FROM SELF SAMPLING SATISFACTION QUESTIONNAIRES


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Background and Aims

An ongoing ISPRO (Florence) research project on self-collection involved 5200 “non-responder” women: some performed sample collection at the clinic; others received at home “Dry” self-sampler device FLOQSwab® (Copan) or “Wet” device, containing 1 ml of MSwab® (Copan) both together with a satisfaction questionnaire, designed with the purpose to investigate the acceptability of self-collection rather than of clinician-collection of the sample.

Methods

The questionnaire consists of three areas: easy of use of the self-collection system, possible physical problems (pain or bleeding) related to the use of the self-collection device and expression of preference between self-collected and physician-taken cervical sample. The results were evaluated with an average score, based on the scores given to each question. “Chi-square test” was used to compare the difference between scores.

Results

The questionnaire was compiled by 99% of women who attended self-sampling: 90.6% found the self-collection system very easy/easy and 97.8% found easy the collection procedure and understood the instructions for the withdrawal. Related to the self-collection, discomfort or bleeding, 92.2% had no pain; finally, 81.4% of women preferred self-collection method rather than cervical clinician collection. There was no significant differences (p>0.05) between the two arms for type of self-sampling device methods or by level of education.

Conclusions

From questionnaire, it emerges that most of women found self-collection procedure easy or very easy; they did not report any particular pain, discomfort or bleeding and preferred self-collection, “Dry” or “Wet”, for reasons of time and comfort. Therefore, there is a good acceptability of the self-sampling system.
Background and Aims

An ongoing ISPRO (Florence) research project on self-collection involved 5200 "non-responder" women living in Florence, Massa-Carrara and Viareggio areas. Some women performed sample collection at the clinic, others received at home “Dry” self-sampler device FLOQSwab® (Copan) or “Wet” device, with 1 ml of MSwab® (Copan). Self-collected samples are not suitable for Pap test, so we evaluated, as an alternative triage to direct sending to colposcopy, HPV genotyping and methylation of CpG-islands of human CADM1, MAL, hsa-miR-124-2 and FAM19A4 genes.

Methods

The hr-HPV test was carried out on Cobas4800® (Roche). Genotyping was performed using Anyplex™ II PCR System (Seegene). After DNA extraction with QIAamp® DNA mini kit (Qiagen), DNA was modified with EpiTect®-Bisulfite kit (Qiagen). The methylation status of CADM1 and MAL was evaluated using Pyrosequencing (Qiagen) and of hsa-miR-124-2 and FAM19A4 gene promoters with QIAsure (Qiagen).

Results

52/455 (11.4%) returned self-samples resulted hr-HPV positive and 41/52 (79%) women attended colposcopy. Complete results are available for 17 samples, only CADM1 and MAL results are available for additional 4 samples (6 CIN2+, 6 CIN1 and 9 negative). Hypermetilation of hsa-miR-124-2 was observed for 1 CIN2, 2 CIN1 and 2 negative samples; hypermethylation of FAM19A4 was observed for no CIN2, 1 CIN1 and 4 negative samples. No sample was hypermethylated neither for CADM1 nor for MAL. No difference was evidenced in HPV types distribution between CIN2+ and negative samples.

Conclusions

The study is still in progress; these are preliminary results and molecular analysis, including evaluation of methylation status of L1-I, L1-II and L2 viral genes, have yet to be concluded on samples of Florence, Massa-Carrara and Viareggio.
VAGINAL AND URINE SELF-SAMPLING COMPARED TO CLINICIAN-COLLECTED CERVICAL SAMPLING FOR HPV AND STIS TESTING IN WOMEN REFERRED TO COLPOSCOPY

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Background and Aims

The aim of this study was to evaluate HPV detection in first-void urine (FVU) and vaginal self-collected samples as compared to physician-collected cervical samples (gold standard) in women with a recent diagnosis of cervical dysplasia.

Methods

Self-collected vaginal samples using FLOQSwabs\textsuperscript{™} (Copan), FVU using Colli-Pee (Novosanis) and cervical samples were collected from women attending the San Gerardo Hospital and analysed at the University of Milano-Bicocca (Monza, Italy). All samples were extracted by NucliSENS easyMAG (bioMérieux), assessed for sample cellularity using quantitative real-time PCR detecting CCR5 gene. HPV and STIs detection was carried out using Seegene Anyplex\textsuperscript{™}II HPV28 and STI-7 (Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum, Ureaplasma parvum), respectively.

Results

Data obtained showed an adequate sample cellularity for all analyzed samples (mean value for urine, vaginal and cervical samples: 8.05E+06, 2.27E+06 and 4.85E+06 cells/sample, respectively). Concordant HPV detection for at least one type was demonstrated in 100% vaginal self-collected and in almost 90% of urine samples. HPV-16 resulted the most frequently HR-type detected. Preliminary results have shown a higher STIs positivity in self-sampling samples compared to physician-collected samples (57% vs 53%, respectively). HPV and other STIs co-infections were shown in 51% of women.

Conclusions

Preliminary results showed an adequate cellularity for all analysed sample types. HPV and STIs detection in self and clinician-collected samples showed a high degree of concordance. These data demonstrate promising results for the use of urine and vaginal self-collected samples in cervical cancer screening programs.
SELF-COLLECTION PREFERENCES FOR HRHPV TESTING IN A COHORT OF COLLEGE AGED WOMEN

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Background and Aims

There are currently 80 million people in the U.S. infected with high risk HPV (hrHPV). Persistent hrHPV infections types 16 and 18 account for approximately 70% of cervical cancers worldwide, while HPV types 6 and 11 are responsible for approximately 90% of genital warts. Furthermore, approximately half of all newly diagnosed cases of sexually transmitted infections occur in patients 15-24 years of age. Self-sampling for hrHPV testing has been proposed as an alternative to in-clinic testing, because self-collection may facilitate more widespread screening. However, further investigation is needed to identify factors which may be associated with adoption of self-collection. This study assessed the relationship of self-collection preferences for hrHPV testing and socio-demographic and behavioral risk factors.

Methods

This was a prospective cohort study (2013-2014) of 639 sexually active college aged females that received healthcare at our institution. Associations between the categorical variables of interest were conducted with a Pearson’s Chi-square.

Results

We found that Whites (75%), when compared to Blacks (24%), were more likely to prefer self-collection methods, $\chi^2 = 7.815, p = .005$. However, no additional statistically racial significant differences were found. Women in monogamous relationships (47%) were more likely to choose self-collection, when compared to those that were single and dating (18%), $\chi^2 = 4.91, p = .026$ and single and not dating, $\chi^2 = 6.3432, p = .011$. There were no significant association of self-collection and education, insurance, STI history and contraceptive use.

Conclusions

These factors may provide guidance for strategies to promote more wide-spread adoption of self-sampling for hrHPV screening.
SELF-COLLECTION FOR UNDERSCREENED WOMEN: IMPLICATIONS OF ONGOING RESTRICTIONS


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Background and Aims

HPV-based screening on a self-collected sample (‘self-collection’) provides a new opportunity to screen hard-to-reach women. As self-collection is slightly less accurate than HPV testing on a clinician-collected sample, self-collection is restricted in Australia to women aged 30+ years who are never screened or ≥2 years overdue. We quantified the loss of effectiveness in the self-collection pathway, compared to the recommended pathway (5-yearly HPV screening on a clinician-collected sample, from age 25).

Methods

To separate the impact of different aspects of the self-collection pathway, we modelled the following hypothetical programs involving self-collection, restricted to: i) women 30+ and ≥2 years overdue (current restrictions); ii) women 25+ and ≥2 years overdue; iii) initially unscreened women (not screened before 30); and iv) same restrictions as clinician-collected samples (women aged 25+; ≥5 years since last routine screening test).

Results

Compared to the recommended screening pathway, the self-collection pathway would increase cancer cases and deaths by ~33-36% in unvaccinated cohorts (~20% in cohorts offered vaccination); this increase would only be ~4-5% if self-collection was available 5-yearly from age 25. The loss of effectiveness caused by the requirement to be ≥2 years overdue is ~17-29% in unvaccinated cohorts (~17-20% in cohorts offered vaccination); while that due to the restriction that women be aged 30+ is ~10%.

Conclusions

The loss of effectiveness in the self-collection screening pathway in Australia is primarily driven by imposing a longer interval of at least seven years and to a lesser extent the delayed start age; lower test accuracy plays a comparatively smaller role.
Cervical self-sampling in combination with high-risk HPV testing has been demonstrated to be sensitive and feasible for cervical cancer screening. The quality of samples collected with a self-sampling device in remote areas of Ethiopia remains unknown. The aim was, therefore, to compare the quality of samples collected from two rural districts of Ethiopia.

**Methods**

Two rural districts, Dabat from Northern and Butajira from Southern parts of Ethiopia were selected. Instructions how to use Evalyn brush (Rovers Medical Devices, The Netherlands) was given to eligible and willing women. In the first district, self-collection was done at home. In the second district, self-collection was done in a private room under supervision at the local health post. The quality of sample was measured with detection of Gap-DH, an internal control for verification of adequate DNA. DNA extraction and HPV testing was performed using AID HPV DNA Array (AID GmbH, Strassberg, Germany) at the HPV Reference Laboratory, Addis Ababa University, Ethiopia.

**Results**

Results from the first 130 women recruited in either study (home-based self-collection and Health Post self-collection) were compared (260 in total). Out of the 130 self-sampled at home, 46 (35.4%) showed poor collection (human DNA signal below quality cut-off). Of the 130 health post collected self-samples, only five (3.8%) showed insufficient quality.

**Conclusions**

Specimens collected at the health post demonstrated to be superior to home self-collection. Collection under supervision and follow-up is thus critical for women in the rural areas to optimize use of the self-sampling devices for HPV DNA testing.
For high-risk HPV testing the sensitivity and specificity of a urine sample is similar to a self-collected vaginal sample and a physician-taken LBC sample

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Background and Aims

To compare the clinical performance of high-risk HPV testing in self-collected vaginal (SVS) samples, urine samples and physician-taken liquid-based cytology (LBC) samples in women referred for colposcopy.

Methods

272 Women referred to colposcopy at the gynecological departments at Lillebaelt Hospital and Odense University Hospital, Denmark has been in-rolled in the study.

Before the medical examination the women made a urine sample and a SVS sample. At colposcopy a LBC sample and cervical biopsies were taken. The urine, SVS and LBC samples were analyzed for the presence of high-risk HPV using the Cobas HPV test, Roche. The biopsies were evaluated and used as gold standard.

Results

The concordance between both SVS and urine and SVS and LBC was 91% and for urine and LBC 83%. The clinical performance for detecting CIN2+ and CIN3+ are presented in the Table.

<table>
<thead>
<tr>
<th></th>
<th>SCV sample</th>
<th>CI</th>
<th>Urine</th>
<th>CI</th>
<th>LBC</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>CIN2+</td>
<td>97%</td>
<td>89.5 - 99.5</td>
<td>95%</td>
<td>87.3 - 98.7</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>CIN2+</td>
<td>43%</td>
<td>36.2 - 49.6</td>
<td>45%</td>
<td>38.0 - 54.5</td>
<td>44%</td>
</tr>
<tr>
<td>PPV</td>
<td>CIN2+</td>
<td>35%</td>
<td>28.3 - 42.0</td>
<td>35%</td>
<td>28.6 - 42.5</td>
<td>35%</td>
</tr>
<tr>
<td>NPV</td>
<td>CIN2+</td>
<td>98%</td>
<td>92.3 - 99.6</td>
<td>97%</td>
<td>91.1 - 99.1</td>
<td>97%</td>
</tr>
</tbody>
</table>

|            | CIN3+      | 100%     | 90.4 - 100 | 100%     | 90.4 - 100 | 97%      | 85.8 - 99.9 |
| **Sensitivity** | CIN3+      | 38%      | 32.3 - 44.7 | 40%      | 34.4 - 46.8 | 39%      | 33.1 - 45.5 |
| PPV        | CIN3+      | 20%      | 14.7 - 26.3 | 20%      | 15.2 - 27.0 | 20%      | 14.5 - 26.1 |
| NPV        | CIN3+      | 100%     | 95.9 - 100 | 100%     | 96.1 - 100 | 99%      | 94.2 - 99.9 |
The sensitivity for detecting CIN2+ was high; 96%, 95% and 94% for SVS, urine and LBC, respectively. For CIN3+ the values were 100%, 100% and 97%, respectively. The specificity for detecting CIN2+ was 42%, 45% and 44% and, for SVS, urine and LBC and at CIN3+ 38%, 42% and 40%, respectively. One woman was diagnosed with a carcinoma all three samples were HPV positive.

Conclusions

These data indicate that the sensitivity, specificity as well as the negative and positive predictive values of a urine sample is high and identical to the performance of both a SCVS sample and a physician-taken LBC sample to identify CIN2+ and CIN3+.
Mixed-Methods Evaluation of a Multi-Component mHealth Intervention for Triage After HPV Self-Collection: The ATICA Study Protocol

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Background and Aims

High adherence to triage by HPV+ women with self-collected tests is challenging. The ATICA study (Application of Communication and Information Technologies to Self-Collection, for its initials in Spanish) will evaluate the effectiveness of a multi-component mHealth intervention aimed at increasing triage adherence among HPV+ women with self-collected tests, compared to usual care. The project is funded through an R01 grant awarded by NCI/NIH.

Methods

ATICA study is an effectiveness-implementation hybrid type I trial that uses a mixed methods approach. A cluster-randomized trial design including 200 community health workers (CHWs) will evaluate whether the mHealth intervention increases adherence to cytology triage within 120 days after testing positive. The intervention will consist of mobile phone text messages (SMS) sent to HPV+ women informing them that the test result is ready for collection and advising them to go to the health center. An email/SMS message will be sent to CHWs to promote contacting women who did not adhere to triage within 60 days after testing positive. We will use the Consolidated Framework for Implementation Research (CFIR) and the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) frameworks to evaluate implementation of the intervention.

Results

Planning of field work and randomization of CHWs was carried out through collaborative work with Jujuy health authorities. Formative research was carried out to design content of SMS text messages and the automatic messaging system. Field work will begin in July 2018.

Conclusions

Findings from the ATICA project will be highly applicable to programs that use or are planning to incorporate HPV self-collection.
Background and Aims

HPV infection can ‘clear’ or persist and CIN can regress or progress. Ultimately, persistent infection, with the same oncogenic HPV genotype, is necessary for progression to CIN3 and cancer. Persistence is defined as type-specific HPV infection identified during index screening that is present during follow-up, at an interval of 6 to 12-months.

Methods

For this systematic review, PubMed was searched from 2001 through 2018 for relevant studies, and supplemented by hand-searching. Eligible studies included prospective studies of women and retrospective studies of residual specimens from women who had been screened or underwent colposcopy and were retested using HPV genotyping tests and had cytology and histopathology results. The reference standard was ≥CIN3. The timeframe for follow-up was ≥6-months.

Results

A PRISMA flow diagram is presented. Nine original research articles, with 25,337 women, met inclusion and exclusion criteria. Persistence of the same HPV genotype confers a vastly higher risk of ≥CIN3 than a new infection. Within persistence, there is a greater than tenfold risk stratification from highest with HPV 16 to lowest with HPV 56/59/66.

Conclusions

Reporting HPV genotype results provides discrimination and stratification of both current and future ≥CIN3 risks. HPV genotyping could be utilized as follow-up to distinguish type-specific persistence versus clearance, to support risk-based clinical decisions, and reduce unnecessary colposcopy. Guideline panels must decide whether to separate reporting by individual genotypes or to group genotypes with similar risks into risk tiers.
Background and Aims

Current guidelines focus on the point of care and a single screening encounter. Management guidelines include 1-2 rounds follow-up of abnormal results. In the real world, care of women involves continuity of care and serial testing. An index negative test result confers different risk, depending on prior test results.

Methods

The current best evidence was utilized for the natural history of HPV infection, clearance, reactivation, persistence, progression, and regression. The concepts of sexual debut, opt-in vaccination, and new exposure were utilized. A continuity of care extending for 3 testing occasions was selected. A heuristic algorithm was built to describe all possible testing results and underlying infection and disease over the continuity of care period.

Results

A heuristic algorithm graphic is presented with footnotes explaining the elements. Two tables are presented for all the modeled continuity of care results over 3 serial tests, applied to the 2012 ACS, ASCCP, ASCP screening guidelines for the prevention and early detection of cervical cancer and the 2012/2013 ASCCP consensus guidelines for the management of women with abnormal cervical cancer screening tests. The first table reports limited genotyping (16/18), yielding 8 possible results over 3 serial tests; the second presents results using extended genotyping, yielding 14 possible results over 3 serial tests.

Conclusions

Future guideline panels may choose to consider continuity of care and serial testing as an aspect of clinical decision making tools. A model for the natural history of HPV infection and the possible permutations supports the guideline panelist and stakeholder considerations.
Background and Aims

Cervical cancer screening and management guideline originators have not yet included an analysis of the body of science published during the last decade about the clinical value of extended HPV genotyping in cervical cancer screening, triage, and in follow-up of women with abnormal results and in test-of-cure. This secondary research study provides an analysis of the current state of the evidence regarding applications of HPV extended genotyping for cervical cancer screening and management.

Methods

For systematic review, PubMed was searched from 2001 through 2018 for relevant studies, and supplemented by hand-searching. Eligible studies included prospective studies of women and retrospective studies of residual specimens from women that were screened or tested using human papillomavirus DNA assays that reported extended genotype results, cytology, and histopathology results. The reference standard was ≥CIN3.

Results

A PRISMA flow diagram is presented for this systematic review. Twelve original research articles, reporting for 222,674 women, met inclusion and exclusion criteria. Applying the principle of similar management for similar risk, the risk prediction results from the systematic used are used to for extended genotype algorithms for ASC-US triage, cotesting, and primary HPV screening. Extended genotype results provide stratification and risk discrimination of both current and future ≥CIN3.

Conclusions

Extended genotyping appears very promising as triage in all screening paradigms to discriminate risk and support risk-based clinical action steps by the principle of equal management for equal risk. Guideline panels must decide whether to separate reporting and management by individual genotypes or to group genotypes with similar risks into risk tiers.
Background and Aims

NANOG, a homeodomain-containing transcription factor, is pivotal for tumorigenesis and progression of various human cancers as well as the self-renewal of embryonic stem cells at the earliest stages of pluripotency. However, the role of NANOG in cervical cancer has not been elucidated yet. Here, we investigated the expression and clinical significance of NANOG in cervical cancer.

Methods

Immunohistochemical analyses of NANOG and CD59 were performed using tissue microarray analysis of 178 cervical cancers and 126 cervical intraepithelial neoplasia (CIN) patients and compared the data with clinicopathologic variables, including the survival of cervix cancer patients.

Results

NANOG expression increased during tumor progression from normal to cancer (p < 0.001). High expression of NANOG and CD59 strongly associated with chemoradiation resistance (p = 0.001), and tended have large-sized tumor compare with that of low expression of NANOG and CD59 group (p = 0.067). Furthermore, CD59 expression was correlated with that of NANOG (Spearman’s rho = 0.221, p < 0.001). Kaplan-Meier plots demonstrated that patients with high (+) expression of CD59 showed shorter disease-free survival than patients with low (-) CD59 expression (77.4% vs. 88.9%, p = 0.034). Notably, patients with combined NANOG+/CD59+ expression displayed significantly worse disease free survival and overall survival than patients with NANOG-/CD59- (64.7% vs. 94.1%, p < 0.001; 82.4% vs. 97.1%, p = 0.035, respectively).

Conclusions

High expression of NANOG or combined NANOG/CD59 is an indicator of poor prognosis in cervical cancer, suggesting their potential utility as prognostic tests in clinical assessment.
Confirmation of Human Papilloma Virus (HPV) Status in Cervical Cancer with Prior Negative Pre-Treatment HPV DNA Test

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Background and Aims

Previous our study showed that 18.5% of cervical cancer was high-risk human papilloma virus (hrHPV) negative on pre-treatment HPV DNA test, and hrHPV negativity was associated with worse disease-free survival (DFS). So, we raise the questions as to whether these negative hrHPV results represent truly hrHPV-negative cervical cancer or false-negative HPV DNA test. The aim of this study was to detect HPV in cervical cancer with prior negative HPV DNA test and to evaluate survival outcomes according to true HPV status.

Methods

We investigated the hrHPV status on the surgical specimens of 30 cases of cervical cancer using polymerase chain reaction (PCR). PCR primers were set for detecting the presence of common L1 region and E7 regions of HPV 16,18,31,33,45,52,58.

Results

Ten (33.3%) of the 30 cases were positive for HPV L1 region and 6 (20.0%) were positive E7 region of 7 types of hrHPV. HPV was detected in 12 (40.0%) and 60.0% of cervical cancer was HPV negative. Kaplan-Meier survival plots showed truly HPV-negative was associated with worse DFS (P = 0.0392).

Conclusions

Our findings demonstrate that truly HPV-negative cervical cancer was 60% in cervical cancer with prior negative HPV DNA test. Moreover, these truly HPV negative group was associated with worse DFS. Thus, before HPV DNA tests can be used as the primary screening method for cervical cancer, the existing tests may need to be improved.
Background and Aims

Approximately 85% of cervical cancer cases and deaths occur in resource-constrained countries where best practices for prevention, particularly for HIV-infected women, still need to be developed. The objective of this study was to assess cervical cancer prevention capacity in select HIV clinics located in resource-constrained countries.

Methods

A cross-sectional survey of sub-Saharan African sites of four NIH-funded HIV/AIDS networks was conducted. Sites were surveyed on the availability of cervical cancer screening and treatment among HIV-infected and HIV-uninfected women. Descriptive statistics, and chi-square or Fisher’s exact test were used as appropriate.

Results

Fifty-one out of 78 (65%) sites responded. Access to cervical cancer screening was reported by 49 (96%) sites. Of these sites, 39 (80%) performed screening on-site. Central African sites were less likely to have screening on-site (P= 0.02) versus other areas. Visual inspection with acetic acid (VIA) and Pap testing were the most commonly available on-site screening methods at 31 (79%) and 26 (67%) sites, respectively. High-risk HPV testing was available at 29% of sites with VIA and 50% of sites with Pap testing. Cryotherapy and radical hysterectomy were the most commonly available on-site treatment methods for premalignant and malignant lesions at 29 (74%) and 18 (46%) sites, respectively.

Conclusions

Despite limited resources, the majority of sites surveyed had the capacity to perform cervical cancer screening and treatment. The existing infrastructure of HIV clinical and research sites may provide the ideal framework for scale up of cervical cancer prevention in resource-constrained countries with a high burden of cervical dysplasia.
Background and Aims

Human papillomaviruses (HPV) L1 and E2 proteins are expressed in cervical cells during lytic stage of HPV infection whereas p16INK4A overexpression is a biomarker of high-risk HPV-associated cervical neoplasia. This study aimed to identify serologic biomarkers for monitoring HPV-associated cervical neoplasia.

Methods

Sera and cervical tissues from women with histological classification with no-squamous intraepithelial lesion (No-SIL), low-grade SIL, high-grade SIL and cervical squamous cell carcinoma were studied. Serum antibodies against HPV16L1 and HPV16E2 as well as p16INK4A were determined by western blot. DNA was extracted from cervical tissue samples and HPV DNA was detected by polymerase chain reaction. The cases presenting with HPV16L1 or HPV16E2 antibody or HPV DNA were diagnosed with HPV infection status.

Results

Seropositivity to HPV16L1 and HPV16E2 were found in 22.4% and 39.6%, respectively and 60% of samples were positive for HPV DNA. Seventy-five % (87/116) of cases showed HPV infection status and were associated with severity of cervical lesion. Seropositivity of p16INK4A were 23.3%. Serum antibody to p16INK4A was associated with HPV-infected women (odds = 5.444, 95%CI = 1.203-24.629, P = 0.028) and precancerous cervical lesion (odds = 5.132, 95%CI = 1.604-16.415, P = 0.006). Interestingly, the concurrent detection of anti-HPV16E2 and anti-p16INK4A antibodies was significantly associated with HPV-infected women (odds = 1.382, 95%CI = 1.228-1.555).

Conclusions

This result suggests that serum antibody to p16INK4A might be used as a good candidate biomarker for monitoring HPV-associated cervical lesion progressed to cancer.
EFFICACY OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HIGH RISK HPV+ WOMEN. PRELIMINARY RESULTS

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Background and Aims

To evaluate the efficacy of a Coriolus versicolor-based vaginal gel (Papilocare®) to clear HPV and to normalize pap smear in high risk HPV+ women.

Methods

An exploratory, prospective, observational non-controlled study. High risk HPV+ vaccinated and unvaccinated women older than 24 years were included during routine follow-up visits and treated with Papilocare® 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months (except menstrual days).

Primary endpoint: composite efficacy variable consists of percentage of patients with normal pap smear and/or HPV clearance at month 6 vs baseline. Secondary variable: percentage of patients clearing HPV 16-18 vs baseline.

Results

A total of 86 patients, mean age 42.1 years (24 to 81) were included. At 6 months, 53% of women negativized pap smear and/or cleared HPV and were classified as responders to treatment. A total of 25 patients were positive to HPV 16-18 at baseline (12 and 13 with positive and negative pap smear, respectively). Overall, at 6 months, 48% of these patients cleared HPV 16-18 (50% and 46% of patients with positive and negative pap smear, respectively; p<0.0001 vs baseline, chi-square test).

Conclusions

In these preliminary analyses, Papilocare® shows positive trend to improve pap smear alterations and HPV clearance in women infected by high risk HPV, after 6 months; these findings need to be confirmed upon analyses completion.
MULTI-MARKER ASSAY OF CERVICAL SQUAMOUS CELL CARCINOMAS: EVIDENCE FOR PRECISION MEDICINE DIAGNOSTICS

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Background and Aims

Previously, we examined EGFR pathway mutations and expression markers in 105 HPV16-positive formalin-fixed cervical squamous cell carcinomas. Pathway expression and mutation statuses were not simple predictors of downstream events and vice versa suggestive that actionable pathway identification by partial diagnostic tests is liable to error. A subset of specimens (4 EGFR-positive vs. 4 EGFR-negative) have now been investigated using multi-marker technologies to better appraise the scope of cancer impacted cell processes.

Methods

mRNA expression profiling was performed for 2,560 genes impacting 24 different cellular pathways (HTG EdgeSeq Oncology Biomarker Panel) and for 2,083 miRNAs (HTG EdgeSeq miRNA Whole Transcriptome Assay); additionally, samples were screened for genomic aberrations (Affymetrix OncoScan Assay).

Results

HTG data were obtained for 7 samples (Table 1). OncoScan data obtained for 5 samples showed multiple heterogeneous copy number variation (CNV) and loss of heterozygosity (LOH) events.

Table 1. Gene and miRNA expression among EGFR+ vs. EGFR- cervical carcinomas

<table>
<thead>
<tr>
<th></th>
<th>mRNAs &gt;2-fold</th>
<th>mRNAs &gt;5-fold (5.2-16.7)</th>
<th>miRNAs &gt;2-fold (&gt;2-10.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-Regulated</td>
<td>164 (6.4%)</td>
<td>7 (0.3%)</td>
<td>17 (0.8%)</td>
</tr>
<tr>
<td>Down-Regulated</td>
<td>263 (10.3%)</td>
<td>17 (0.7%)</td>
<td>50 (2.4%)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td>0.0656</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Conclusions

A variety of cancer pathways are implicated by the up/down-regulation and CNV/LOH data; none of the 7 >5-fold up-regulated genes are directly EGFR pathway-related. The findings support the hypothesis that diagnosing tumors on the basis of a single pathway and/or by selective markers is a
suboptimal approach thereby supporting the case for precision medicine panomic testing. Creative exploration of cell pathway interactomes may allow the discovery of novel diagnostic strategies.
A Coriolus versicolor-based vaginal gel (Papilocare®) is recently available in Spain to prevent and treat the HPV-dependent low grade cervical lesions. Recommended dose: 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months (except menstrual days).

To analyze how Papilocare® is being used in our hospital and to evaluate treatment results in our patients.

Methods

A retrospective, observational study. Medical records of patients who completed 3 or 6 months treatment period during 2017 were analyzed. Baseline characteristics of Papilocare® users were described.

Pre and post treatment number of patients with ASCUS/LSIL, positive-HPV and high risk positive HPV were assessed.

Results

A total of 86 medical records were analyzed. Most of them (84%) were treated for 6 months. Mean age was 38.4 years (from 18 to 72 years), 43.5% were vaccinated before treatment with Papilocare®, 32.5% were smokers and 42% used condoms regularly in all their sexual relationships. Baseline pap smear: Normal 11 (13%), ASCUS 3 (3.5%), LSIL 65 (75.5%) and HSIL 7 (8%). HPV test was performed in 68 patients of which 57 (89%) were high risk HPV.

After treatment, reductions of 54% (from 68 to 31; p≤0.0001 Chi-Square test), 57% (from 68 to 29; p≤0.0001) and 58% (from 57 to 24; p≤0.0001) were observed in number of patients with ASCUS/LSIL, positive-HPV and high risk positive HPV, respectively vs baseline.

Conclusions

In our hospital, most of patients using Papilocare® have LSIL. In this preliminary analysis, significant reductions of patients with pap smear alterations and high risk HPV were observed after 3-6 months application of Papilocare®.
P16/Ki67 DUAL STAINING IMPROVES THE DETECTION SPECIFICITY OF HIGH GRADE CERVICAL LESIONS

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Background and Aims

To investigate the specificity of p16/Ki67 dual staining in the detection of high grade cervical lesions.

Methods

A total of 223 patients were enrolled with an average age of 39 years old. All samples were detected by p16/Ki67 immunocytochemical dual staining, Liquid-based cytology and High-risk HPV test. And each patient had histopathological diagnosis.

Results

The specificity of p16/Ki67 dual staining was 68.33%, which was significantly higher than that of cytology 38.33% and 21.67% of high-risk HPV (P <0.05), and p16/Ki67 dual staining had similar sensitivity with HR-HPV test for CIN2+ detection (90.18% vs 93.87%, P=0.286). In triage cases of ASC-US and LSIL liquid-based cytology, the specificity of p16/Ki67 double staining was significantly higher than that of HPV test(66.67% vs 3.70%, P <0.05) and its sensitivity was similar to that of HPV test. The sensitivity and specificity of dual staining for CIN2+ detection in triage of HR-HPV positive women were 90.85% and 70.21% which were higher than those of cytology (83.01% and 42.55%) and HPV16/18 test(70.59% and 44.68%).

Conclusions

p16/Ki67 dual staining could improve the specificity of high grade cervical lesions detection and have similar sensitivity to HPV test. When triaging women with ASC-US or LSIL liquid-based cytology, or positive HR-HPV, by p16/Ki67 dual staining, the specificity of lesion detection was increased. p16/Ki67 dual staining could reduce colposcopy referalls and avoid excessive diagnosis and treatment.
HIGH RISK HPV TEST IN DETECTION OF CERVICAL CANCER AND PRECANCEROUS LESION

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Background and Aims

To investigate the role of high risk HPV (HR-HPV) test in the detection of CIN2+ lesions.

Methods

A total of 2626 women who were screened at Peking University Third Hospital from September 2016 to May 2017 were recruited. The liquid based cytology (Hologic Thinprep), high-risk HPV test (Roche Cobass4800), colposcopy and cervical biopsy were applied in all women.

Results

The age of all women ranged from 18 to 85 years old, the average age was 38.02 years old. The results of pathological diagnosis showed that 60.2% (1580/2626) was ≤CIN1, 26.6% (699/2626) was CIN2, 10.3% (270/2626) was CIN3, and 2.9% (77/2626) was cervical cancer. The detection rate of CIN2+ was 90.2% by cytology and 96.8% by HR-HPV test. The CIN2+ detection rate of HR-HPV test was significantly higher than cytology (p=0.000). The detection rate of CIN2+ was 99.5% by cotesting, which was significantly higher than the two former methods (p=0.000, p=0.000). Logistic regression analysis showed that compared with patients with HPV negative women, the risk of CIN2+ in HPV positive women was 5.337 (p=0.000, 95%CI:3.673-7.753). When HPV positive women were further classified, logistic regression analysis showed that women who has HPV16 type single infection or multiple infections were checked out the highest risk of CIN2+ [OR value was 11.093 (95% CI: 7.332 16.784), 10.356 (95% CI: 6.780 15.817)]

Conclusions

HR-HPV test is superior to cytology in detection of CIN2+. And cotesting can improve the detection of CIN2+ and reduce missed diagnosis. HR-HPV infection, especially HPV 16 positive, is related with CIN2+ lesions.
IPVC8-0147
POSTER SESSION

CLINICAL RESEARCH - DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS PRECURSORS

DOES THE SIZE AND TOPOGRAPHY OF HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESIONS VARY WITH AGE IN WOMEN REFERRED FOLLOWING HIGH GRADE CERVICAL CYTOLOGY: RETROSPECTIVE CASE SERIES.

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Background and Aims

High grade squamous intraepithelial lesions are heterogenous with variable potential for malignancy. They are the precursor lesion for squamous cell carcinoma of the uterine cervix, with treatment of these lesions reducing the risk of invasive cancer by 95%. Despite being effective excisional treatments are not without morbidity, in particular in relation to obstetric outcomes, and as such clinicians are challenged to adequately excise HGSIL whilst minimising morbidity.

In tailoring excisional treatments, clinicians are influenced by the woman’s age, prior treatments, cervical cytology, colposcopic findings and future fertility plans. Despite older age (≥50) being a risk factor for recurrent disease there is little published on the histopathological extent of CIN3 across different ages. This study aimed to quantify this in order to help guide the clinician on choosing the appropriate treatment modality

Methods

We reviewed demographic and clinical data of 80 women (19 aged 20-29, 22 aged 30-39, 22 aged 40-49 and 17 aged ≥50) referred with high grade squamous cervical cytology. Lesions were measured and the extent of disease quantified.

Results

The PPV of a HGSIL Pap smear for predicting CIN3 in women ≥50 was 0.72. Older women were more likely to have discrepant colposcopic findings, invasive malignancy (18%), endocervical gland involvement (65%), deeper involved crypts, paradoxical maturation, necrosis and positive margins however their volume of disease was second to that in the 30-39 age group.

Conclusions

This study objectively demonstrated that as women age areas of HGSIL are larger and more likely to harbour micro invasive disease than their younger counterparts.
INCREASED CKAP2 EXPRESSION CAN SERVE AS AN INDEPENDENT PROGNOSTIC FACTOR FOR POOR SURVIVAL IN PATIENTS WITH CERVICAL CARCINOMA

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Background and Aims

To study the expression level of Cytoskeleton-associated protein 2 (CKAP2) in cervical cancer tissues, and to analyze the relationship between abnormal expression of CKAP2 and clinicopathological factors of cervical cancer.

Methods

We first screened CKAP2 as a new candidate oncogene in two independent data sets (TCGA and gse27678). Immunohistochemistry, RTPCR and Western blot were used to verify the expression of CKAP2 in cervical cancer tissues, which association with clinical features was further analyzed by statistical method.

Results

The expression of CKAP2 was significantly upregulated in cervical carcinoma tissues when compared with adjacent normal counterparts. Then we detected the clinical relevance of CKAP2 expression in cervical carcinoma. All the human cervical carcinoma tissues were further classified into the high-CKAP2 group (n=125) and low-CKAP2 group (n=122) using the median expression value of CKAP2 as the cutoff point. The results showed that increased CKAP2 expression was significantly correlated with age, FIGO stage, lymph node metastasis, recurrence and tumor size, but not other clinical characteristics. The survival time of cervical carcinoma patients showed that patients with under-expressed CKAP2 expression notably lived longer than patients with over-expressed CKAP2 expression. We next performed univariate and multivariate analysis of prognostic factors for overall survival with the Cox regression model. We identified three prognostic factors, including FIGO stage, Lymph node metastasis and CKAP2 expression, can served as independent prognostic factors for poor overall survival.

Conclusions

These findings suggest that CKAP2 may associate with cervical carcinoma development and progression.
Synaptonemal complex protein 3 (SCP3), a member of the Cor1 family, has been pronounced in malignancies. However, the role of SCP3 in cervical cancer has not been elucidated yet. Here, we investigated the expression and clinical significance of SCP3 in cervical cancer.

Methods

Immunohistochemical analyses of SCP3, NANOG, pAKT, and CYCLIN D1 were performed using tissue microarray analysis of 608 patients with primary invasive cervical cancer of cervical intraepithelial neoplasia (CIN) and compared the data with clinicopathologic variables, including the survival of cervix cancer patients.

Results

CYCLIN D1 expression increased during tumor progression from normal to cancer (p < 0.001). Furthermore, the correlation between the expressions of SCP3 and pAKT, CYCLIN D1, or NANOG was assessed in cervical neoplasias specimens. SCP3 expression was positively correlated with that of pAKT, CYCLIN D1, or NANOG (Chi-square test; p = 0.018, p = 0.023, and p = 0.003, respectively).

Kaplan-Meier plots demonstrated that patients with combined SCP3+/CYCLIN D1+/NANOG+ and SCP3+/pAKT+/CYCLIN D1+/NANOG+ expression showed significantly worse overall survival (mean survival time; 108 months vs. 166 months, p = 0.005 and 93 months vs. 165 months, p = 0.001, respectively) than the other patients. The Cox proportional hazards model revealed that a combination of high SCP3, pAKT, CYCLIN D1, and NANOG expression was independent positive prognostic factors with respect to overall survival (Hazard ratio = 7.58 [2.36-24.36], p = 0.005)

Conclusions

High expression of SCP3 or combined SCP3/pAKT/CYCLIN D1/NANOG is an indicator of poor prognosis in cervical cancer, suggesting their potential utility as prognostic tests in clinical assessment.
DETECTION OF HUMAN PAPILLOMA VIRUS (HPV) MRNAS IN SENTINEL LYMPH NODES FROM CERVICAL CANCER

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Background and Aims

Sentinel node dissection (SLN) in combination with ultrastaging (serial H&E sections, cytokeratin staining) is becoming a routine approach in early cervical cancer surgery. However, sensitive identification of SLN metastases is crucial and HPV-mRNA-positive SLN seem to be of prognostic value. Up to 15% of patients with cervical cancer and pN0-status develop recurrent disease.

Methods

In order to implement HPV testing of SLN in clinical routine, a prospective study (approved by our Ethics Committee) was performed for detection of hrHPV-mRNAs (Aptima, Hologic) and of hrHPV DNA (ART HPV, Abbott). To determine concordance between both tests, two parallel specimen of cervical tissue, SLN and further lymph node tissues were obtained. Preparation of total mRNA was performed using the RNeasy Mini Kit (Qiagen) according to the manufacturer’s protocol.

Results

From the 6 patients tested so far, a comparison of tumor tissue and up to 9 different sentinel, para-aortal, iliac, and pelvic lymph nodes per patient (total 54 tests) demonstrated 100% concordance between the ART HPV and Aptima assay whereby the Aptima assay detected additional HPV-positive lymph nodes in 3 patients. Limiting dilutions using a HPV-positive patient RNA extraction sample revealed an Aptima assay detection limit between 1ng and 2ng total mRNA.

Conclusions

These data suggest an elevated sensitivity for detection of HPV mRNAs when compared to corresponding DNA counterparts although further patient measurements are ongoing to substantiate our findings.
CARRIAGE OF ALPHA-, BETA- AND GAMMA-PAPILLOMAVIRUSES IN UTERINE CERVIX, ORAL CAVITY AND INNER THING AMONG FEMALE SEX WORKERS IN HONG KONG

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Background and Aims

At present, very little is known about the concurrence of HPV infection in different body sites in women. We conduct this study to investigate the simultaneous prevalence of HPV infection in oral cavity, inner thigh and uterine cervix among women in Hong Kong, which may provide important insights into the HPV tissue tropism and provide evidence for auto-inoculation of HPV infection.

Methods

100 commercial sex workers, attending a public sexually transmitted disease clinic were recruited. Five sets of specimens were collected: i) an upper oral brush sample, ii) a lower oral brush sample, iii) two tonsillar swabs, iv) two inner thigh swabs, v) a cervical scrape sample. The HPV infection spectrum was detected using Next-Generation Sequencing.

Results

The overall prevalence of HPV in the oral cavity samples, inner thigh samples and uterine cervix samples was 10.3%, 40% and 47% respectively. α-HPV was the most prevalence HPV type detected. While more β-HPV was found in inner thigh (15%), compare to 2 % and 4 % in oral cavity and uterine cervix respectively. γ-HPV was rarely found in oral cavity (0.7%), but more common in inner thigh and uterine cervix (9%). Five concordant type-specific oral-thigh HPV infection, 1 concordant oral-cervical and 10 concordant thigh-cervical infection was detected.

Conclusions

The HPV carriage on different body sites was relatively low in Hong Kong female sex workers. Only 5% participants had HPV infection in all of the three body sites. The percentage concurrence in inner thigh-uterine cervix is high (77.3%), which suggested that HPV may transmitted via auto-inoculation.
Background and Aims

HPV oncogenicity depends on viral, cellular and environmental factors, host genetics and immunity. There is evidence that some biomarkers have potential usefulness to distinguish between transient and carcinogenic HPV infections, but currently there are no routinely used markers to achieve this distinction.

Methods

From cervical samples of women from southern Mexico, a set of cellular biomarkers was analyzed in LSIL, HSIL and cervical cancer (CC) to identify lesions that are likely to progress to CC. The expression of p16^{INK4a}, Ki-67, cyclin-E, TOP2A/MCM2, telomerase was determined by immunocytochemistry.

Results

The expression of the cellular markers were significantly higher in CC than in HSIL, LSIL, and non-SIL. Thus, the expression level of all tested cellular markers is increased according to cervical lesion severity.

Statistical analyses showed that, of the five biomarkers, TOP2A/MCM2 provided the largest explanation (93.8%), followed by p16^{INK4a} (91%), cyclin E1 (91%), Ki-67 (89.3%), and telomerase (88.9%).

Conclusions

TOP2A/MCM2 was the best biomarker for discriminating between LSIL and HSIL, followed by p16^{INK4a}and cyclinE1.
THE CLINICAL SIGNIFICANCE OF HPV-DNA TESTING IN KOREAN WOMEN WITH ATYPICAL GLANDULAR CELLS IN PAP TESTS: AN ANALYSIS OF 311 CASES AT A SINGLE INSTITUTION

Background and Aims

To analyze the correlation between clinically significant histologic results and human papillomavirus (HPV) in women with atypical glandular cells (AGC) in Papanicolaou (Pap) test

Methods

Data were obtained from the database at Asan Medical Center, for women with AGC in the Pap tests from January 2001 to December 2015. Among these women, those who underwent subsequent HPV-DNA testing and histologic examination, including colposcopy-directed biopsy, loop electrosurgical excision procedure, endocervical curettage, endometrial biopsy, and hysterectomy within one year, were identified.

Results

Of the 1013 women with AGC in Pap test, 311 (30.7%) had both histologic examination and HPV-DNA testing within 1 year. A total of 111 women (35.7%) was identified as positive for HPV. In the AGC subtype analysis, statistically cervical squamous or glandular lesions were significantly more common in HPV positive group compared to HPV negative group (61.2% vs. 10.5%, p < 0.001). In contrast, regardless of age and AGC subtype, endometrial lesions were not associated with HPV infection (8.1% vs. 4.5%, p = 0.12). In all age groups, cervical squamous or glandular lesions were statistically significant in HPV positive group compared to HPV negative group.

Conclusions

The data from our study indicate that, HPV-DNA testing in women with AGC may be a useful tool for predicting clinically significant cervical lesions (squamous or glandular). On the other hand, it had no significant contribution in predicting endometrial lesions. In conclusion, it is important to evaluate women with AGC in Pap test by individualization, considering age, AGC subtype, and HPV status.
Background and Aims

This retrospective study aimed to investigate the outcome of observational management of cervical intraepithelial neoplasmia (CIN) 2 in women younger than 30 years-old.

Methods

We identified 304 women under 30 years with biopsy-confirmed CIN2 between 2004 and 2015. We compared women who had observational management (repeat cervical cytology, human papillomavirus (HPV) test, and colposcopy every 6 months within 24 months) with women who received immediate treatments (loop electrosurgical excision procedure (LEEP) or laser vaporization of transformation zone).

Results

Among 304 women, 172 (56.6%) met the definition for observational management, and 93 (30.6%) received immediate treatments. The remaining 39 women (12.8%) were lost to follow-up during observation or after treatment. Of 172 women with observational management, within 24 months, 122 women (70.9%) showed spontaneous regression, while 50 women (29.1%) showed persistent or progressive disease (29 women of persistence and 21 women of progression). No woman with observational management progressed to invasive cancer. Fifty women with persistence or progression were treated with LEEP and no showed recurrence. HPV 16/18 infection at initial visit (hazard ratio 5.27; 95% CI 1.15-24.93; \( P < 0.05 \)) and persistent HPV 16/18 infection (15.52; 2.41-83.55; \( P < 0.01 \)) were significantly associated with disease persistence and progression.

Conclusions

Based on 70.9% regression rate of observational management and 100% success rate of deferred treatment in this study, immediate treatment of CIN2 may not be necessary for all women younger than 30 years-old. However, women with HPV 16/18 infection may require immediate treatment.
CERVICAL CANCER SCREENING RESEARCH IN THE PROSPR I CONSORTIUM: RATIONALE, METHODS, AND BASELINE FINDINGS FROM A U.S. COHORT

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Background and Aims

Little is known about the effect of evolving risk-based cervical cancer screening and management guidelines on United States (US) clinical practice and patient outcomes. We describe the National Cancer Institute’s Population-based Research Optimizing Screening through Personalized Regimens (PROSPR I) consortium, methods, and baseline findings from its cervical sites: Kaiser Permanente Washington, Kaiser Permanente Northern California, Kaiser Permanente Southern California, Parkland Health & Hospital System/University of Texas Southwestern (Parkland-UTSW), and New Mexico HPV Pap Registry housed by University of New Mexico (UNM-NMHPVPR).

Methods

Across these diverse healthcare settings, we collected data on human papillomavirus (HPV) vaccinations, screening tests/results, diagnostic and treatment procedures/results, and cancer diagnoses on nearly 4.7 million women aged 18-89 years from 2010-2014. We calculated baseline (2012 for UNM-NMHPVPR; 2010 for other sites) frequencies for sociodemographics, cervical cancer risk factors, and key screening process measures for each site’s cohort.

Results

Healthcare delivery settings, cervical cancer screening strategy, race/ethnicity, and insurance status varied among sites. The proportion of women receiving a Pap test during the baseline year was similar across sites (26.1-36.1%). Most high-risk HPV tests were performed either reflexively or as co-tests, and utilization pattern varied by site. Prevalence of colposcopy or biopsy was higher at Parkland-UTSW (3.6%) than other sites (1.3-1.4%). Incident cervical cancer was rare. HPV vaccination among age-eligible women not already immunized was modest across sites (0.1-7.2%).

Conclusions
Cervical PROSPR I makes available high-quality, multilevel, longitudinal screening process data from a large and diverse cohort of women to evaluate and improve the effectiveness of US cervical cancer screening delivery.
DOES HUMAN PAPILLOMAVIRUS TESTING PREDICTS RESIDUAL/RECURRENT DISEASE IN PATIENTS WITH POSITIVE MARGINS AFTER LEEP?

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Background and Aims

The purpose of this study was to evaluate the human papillomavirus (HPV) testing during follow-up as predictive factors for residual/recurrent disease in patients with positive margins after loop electrosurgical excision procedure (LEEP) for high grade intraepithelial lesion (HSIL).

Methods

We retrospectively analyzed medical data of patients who were treated using LEEP between January 1, 2000 and December 30, 2015. Post-LEEP follow-up was performed by liquid base Pap smear and HPV genotyping real-time PCR. Residual/recurrent disease was defined as cytology of atypical squamous cells of unknown origin (ASC-US) or worse without a histology, or low grade squamous intraepithelial lesion (LSIL) histology or worse, at 4months or 12months after the LEEP was performed.

Results

A total of 1,509 LEEPs were performed during the study period, and 1,263 patients with LSIL histology or negative surgical margin were excluded. Among 246 patients, 191 (77.6%) were observed and 55 (22.4%) were received re-operation. During follow-up, 59 patients (31%) had residual/recurrent disease in observation group. Positive HPV genotyping real-time PCR at 4months after the LEEP was a significantly associated with residual/recurrent disease (relative risk 2.25; 95% confidence interval 1.55–3.80; P<0.05).

Conclusions

HPV genotyping real-time PCR at 4months after the LEEP might be useful in finding patients requiring closer surveillance and furthermore, in reducing the number of reoperation in patients with positive margins after LEEP.
HPV type attribution at different stages of cervical lesions proven by conization

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Background and Aims

The aim of this study was to assess the type-specific prevalence of high risk HPV at different stages of cervical lesions and the proportional attribution of HPV stratified by age.

Methods

We collected 1203 patients who underwent conization biopsy at Konyang University Hospital from October 2012 to November 2017. All the patients had the corresponding HPV DNA testing results within 3 months before conization biopsy. Type attribution was estimated using weight to account for lesions with multiple types detected.

Results

HPV was detected in 86%. Single infection was 74.7% and multiple ones were 11.2%, ranging from 13.7% in CIN2 lesion, 12.4% in microinvasive squamous cell carcinoma(MiSCC) and 12.2% in CIN3/CIS lesions. HPV 16/18 account for 29.9% of all lesions and their proportion increased at higher grade cervical lesions (16.5% in CIN1, 18.1% in CIN2, 34.4% in CIN3/CIS, 53.6% in MiSCC and 67.6% in invasive squamous cell carcinoma (InvSCC). The attribution of HPV 31/33/35/52/58 was 27.4% and the proportion was increased at CIN lesions but not consistent at invasive cancer lesions (20.1% in CIN1, 31.1% in CIN2, 32.0% in CIN3/CIS, 20.2% in MiSCC ad 16.2% in InvSCC). In subgroups stratified by age, the fraction of HPV 16/18 in higher cervical lesions declined in older women, while the proportion of HPV 31/33/35/52/58 increased.

Conclusions

Overall, 57.3% of lesions were attributable to 7 oncogenic HPV types: 29.8% of HPV 16/18 and 27.4% to HPV 31/33/35/52/58. The importance of the high risk HPV type except 16/18 increased in older woman to the progression of the cervical lesions.
Many international epidemiological surveys of adenocarcinoma presenting as cervical adenocarcinoma (CADC) find HPV-negativity in up to 30% of cases. HPV-positive usual cervical adenocarcinoma (ADC-CX) is the commonest, but awareness of variation in pathological diagnosis and the existence of non-HPV pathways are important for assessing the role of HPV in CADC.

Methods

We studied pathological diagnosis with immunohistochemistry (IHC) in a structured global sample of 113 paraffin-embedded CADC blocks and 45 were analysed for microsatellite instability and next generation sequencing tumorigenic mutation analysis of 48 somatic genes. H/E, p16, progesterone receptor (PR) and TP53 sections were examined. We confirmed DNA adequacy by qPCR and HPV presence with SPF10-PCR-DEIA-LiPA25v1 and multiplex PCR for hr-HPV E6/E7.

Results

Only 55/77 initially diagnosed ADC-CX were confirmed by IHC. HPV-positive usual ADC-CX was most frequent (49/113 cases) but eight ADC-CX confirmed on the cervical sample had no HPV. Endometrial adenocarcinoma (ADC-ENDO) was an important misclassification: all were hr-HPV-negative and 13/14 PR positive. Serous, clear-cell and gastric CADC were identified and 17/113 remained uncertain. In genetic analysis 10/17 HPV-positive ADC-CX showed no tumour gene mutations. 3 HPV-negative ADC-CX showed TP53, PIK3CA, CDKN2A mutations. One Asian HPV-negative ADC-CX and one gastric type showed probable germline STK11 mutations. ADC-ENDO showed frequent PIK3CA, PTEN and CTNNB1 mutations. Most serous, clear-cell, gastric and unclassifiable CADC showed TP53 mutations.

Conclusions

CADC is globally variable, mostly HPV-associated, with some well-differentiated adenocarcinoma associated with STK11 germline and TP53 mutations, some endometrial and other misdiagnoses. Detailed investigation of breakthrough CADC is important in HPV-screened or vaccinated populations.
PERFORMANCE OF METHYLATED PAX1 GENES FOR MONITORING OF THE RESPONSE OF NEOADJUVANT CHEMOTHERAPY IN CERVICAL CANCER

M. Li

1Peking Univ. People’s Hospital, obstetrics and gynecology, Beijing, China

Background and Aims

To explore the value of methylated PAX1 genes in predicting or monitoring the effect of neoadjuvant chemotherapy (NACT).

Methods

Sixteen I b- II b primary cervical cancer patients were treated with NACT. Tissues from cervical biopsy (before NACT) and radical hysterectomy (after NACT) were collected from February 2009 to October 2015 at the Peking University People’s Hospital (Beijing, China). The methylation levels of the PAX1 gene were determined using qPCR. The different M-index values of the PAX1 gene before and after NACT were evaluated.

Results

The methylation level of PAX1 was higher in squamous carcinoma (SCC) tissues than in non-cancerous matched tissue (NCMT) parts (p<0.001). The patients with stage II tumors had significantly higher PAX1m levels than those with stage I tumors. The methylation level of PAX1 decreased significantly after NACT treatment (p<0.05). Patients with complete regression (CR) or partial regression (PR) showed significantly lower methylation for PAX1 after NACT than the patients with stable or no change response to NACT (p=0.026), the change of methylation level was positively correlated with the change of tumor size.

Conclusions

The detection of methylated PAX1 genes may have a potential to predict and monitor the response of NACT, especially for those chemotherapy resistant and intractable cervical cancer.
CLINICAL ANALYSIS OF 52 CASES OF CERVICAL CANCER DURING PREGNANCY IN CHIAN

M. Li

1Peking Univ. People's Hospital, obstetrics and gynecology, Beijing, China

Background and Aims

To summarize and analyze the clinical characteristics and the treatment of cervical cancer during pregnancy in China.

Methods

52 cases of cervical cancer during pregnancy from 13 hospitals including Beijing, Shanghai, Zhejiang, Henan, Jiangxi, Guizhou, Shanxi, Jiangsu, Chongqing, Hunan, Liaoning and Hainan were analyzed retrospectively.

Results

Fifty two patients out of 330,138 pregnant women (0.016%) were diagnosed. The mean age is 33 years old. 28.8% of cervical cancer was found on the first trimester, 71.2% on the second and third trimester of the pregnancy. FIGO stage IA1 accounted for 3.9%, and IB1 above was 92.3%. 90.7% of cases presented with irregular bleeding in the vagina. 73.1% of the patients had no cytological examination performed during or before the pregnancy. 63.5% of the patients had never been screened for more than five years. All of the cervical cancer with first trimester terminate the pregnancy. Six cases of cervical cancer with second trimester keep the fetus, with two cases of radical trachelectomy plus cesarean section, two cases of NACT+cesarean section+radical hysterectomy, one case of NACT+cesarean section+concurrent chemoradiotherapy, One case of cesarean section+radical hysterectomy in 28 week pregnancy.

Conclusions

Cervical cancer during pregnancy are more often found in the middle and late trimester of pregnancy, mostly presented in the middle and advanced stage of cervical cancer, and most of which haven't been screened for cervical cancer within five years. Most cases of cervical cancer during pregnancy treated after termination of pregnancy. In the middle of trimester, NACT is proposed until fetal maturity followed by surgical staging after delivery.
THE PREPARATION OF AN INNOVATIVE HUMAN PAPILLOMAVIRUS TYPE 16 VACCINE AND EXPLORING ITS BIOLOGICAL ACTIVITY AND IMMUNOGENICITY IN VITRO AND IN VIVO

S. Liao\(^1\), D. Deng\(^1\), S. Wang\(^1\), J. Lei\(^1\), D. Ma\(^1\)

\(^1\)Tongji Hospital- Tongji Medicine College- Huazhong University of Science and Tec, gynaecology and obstetrics, Wuhan, China

Background and Aims

A new vaccine is urgently needed that can prevent and treat pre-cancerous lesions or cervical cancer. Thus, we generate a new chimeric virus-like particle (cVLPs) containing both whole length L1 and the three key carcinogenic epitopes (E5–E6–E7) on HPV16.

Methods

We applied prediction algorithms for MHC class I ligands and for binding affinity to TAP to identify epitopes on HPV16 E5, E6, and E7 that were most likely to be targeted by CTLs. And we created the HPV16 cVLPs fusion proteins by the Bac to Bac baculovirus expression system and explored the bio-function and immunogenicity of purified cVLPs both in vitro and in vivo.

Results

The fusion protein formed cVLPs by self-assembly and located in the nucleus displaying a strong immunogenicity and bioactivity ability. In vivo, we tested this vaccine in murine TC-1 cells infected with a recombinant AAV fused with HPV16E5 DNA (rTC-1 cells), which served as a cell model; we also tested it in immune-competent mice loaded with rTC-1 cells, which served as an ectopic tumor model. To prolong immunogenic capability, we used a new immune strategy of continuous re-injections, where three injections were performed at one-week intervals (days 0, 7, 14), then last injection on day 120.

Conclusions

Our studies revealed that the insertion of the E5–E6–E7 peptides behind L1 did not disrupt the assembly of cVLPs and provided potent immunogenicity and bioactivity, which created a powerful basis for further preparations of HPV16 vaccines with prophylactic and therapeutic effects for HPV16-related diseases.
Automated analysis of p16 staining of cervical biopsies

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¹National Cancer Institute, Division of Cancer Epidemiology and Genetics, Rockville MD, USA
²STCMSB, Steinbeis Center for Medical Systems Biology, Heidelberg, Germany
³University of Calgary, Department of Pathology and Laboratory Medicine, Calgary, Canada
⁴University of Heidelberg, Hamamatsu Tissue Imaging and Analysis Center and Steinbeis Center for Medical Systems Biology, Heidelberg, Germany

Background and Aims

p16 is a marker of transforming HPV infections. The Lower Anogenital Squamous Terminology (LAST) recommends p16 staining in specific situations to clarify histologic interpretations and enhance diagnostic accuracy. Here we present an automated method for quantification of p16 on histological slides, which has the potential to improve the accuracy and reproducibility of p16 evaluation of cervical histology.

Methods

Slides from biopsies of all grades of cervical disease were obtained from the Study to Understand Cervical Cancer Early Endpoints and Determinants, which recruited women referred for colposcopy due to abnormal screening results. p16 staining was performed using the CINTEC kit according to manufacturer’s instructions and whole slides were scanned on an Hamamatsu NanoZoomer. Automated image analysis was used to quantify the area of positive p16 staining (Figure 1), and manual analysis classified each slide as negative, focal positive, or diffuse positive for p16. Automated and manual analyses were compared to evaluate the automated algorithm.
Results

Average percent staining increased with severity of stage of diagnosed clinical disease and with manual annotation of diffuse positivity (Tables 1-2). This proof of principle shows that automated p16 analysis is feasible as an aid in the diagnosis of high-grade squamous intraepithelial lesions (HSIL).
Conclusions

Automated analysis of p16 has potential to facilitate the use of cervical pathology. Future work will investigate automated measurements of p16 staining restricted to the epithelium and determine the utility of automated p16 staining to differentiate HSIL from LSIL lesions according to the LAST specifications.

Table 1: Automated and manual analysis of p16 staining

<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Negative</th>
<th>Focal positive</th>
<th>Diffuse positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>56</td>
<td>0.007578</td>
<td>0.0096</td>
<td>0.38%</td>
<td>20</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>CIN1</td>
<td>36</td>
<td>0.040172</td>
<td>0.061815</td>
<td>0.84%</td>
<td>7</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>CIN2</td>
<td>39</td>
<td>0.075309</td>
<td>0.102434</td>
<td>3.71%</td>
<td>4</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>CIN3</td>
<td>41</td>
<td>0.077707</td>
<td>0.098847</td>
<td>3.67%</td>
<td>2</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>Cancer</td>
<td>37</td>
<td>0.29745</td>
<td>0.207393</td>
<td>29.70%</td>
<td>1</td>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>Total</td>
<td>209</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Automated and manual analysis of p16 staining. Results of automated analysis and manual classification of p16 staining in 209 slides from the SUCCEED study. Abbreviations: CIN = cervical intraepithelial neoplasia, SD = standard deviation

Table 2: Median p16 staining by manual annotation and histology

<table>
<thead>
<tr>
<th>Histology</th>
<th>Negative (%)</th>
<th>Focal positive (%)</th>
<th>Diffuse positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.27</td>
<td>0.40</td>
<td>1.00</td>
</tr>
<tr>
<td>CIN1</td>
<td>0.73</td>
<td>0.17</td>
<td>3.77</td>
</tr>
<tr>
<td>CIN2</td>
<td>0.56</td>
<td>0.85</td>
<td>3.50</td>
</tr>
<tr>
<td>CIN3</td>
<td>1.82</td>
<td>0.57</td>
<td>4.62</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.57</td>
<td>20.13</td>
<td>31.99</td>
</tr>
</tbody>
</table>

Table 2: Median whole-slide p16 staining percentage in slides manually annotated for p16 staining, stratified by cervical histology.

Conclusions

Automated analysis of p16 has potential to facilitate the use of cervical pathology. Future work will investigate automated measurements of p16 staining restricted to the epithelium and determine the utility of automated p16 staining to differentiate HSIL from LSIL lesions according to the LAST specifications.
OBSERVATION OF A ROBUST IMMUNE INFLAMMATORY RESPONSE FOLLOWING FRICATIONAL-FABRIC BIOPSY DURING COLPOSCOPY

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²Integrated Pathology Laboratory, Pathology, Phoenix, USA

Background and Aims

Conventional punch biopsy and endocervical curettage have not been shown to be immunogenic in residual excisional specimens. As an alternative to conventional tools, hooked fabric (Kylon®)-based brush biopsy replacements have emerged. Ectocervical and endocervical tissue sampling traps abundant diagnostic histologic samples with simple pressure and rotation using friction and trapping of de-bonded epithelium and stroma. This is a retrospective review to investigate evidence of an immune response after frictional colposcopic biopsy.

Methods

After IRB approval, 14 cases from 11 different colposcopists referred for colposcopy after abnormal screening were reviewed, where biopsy evidence led to loop excision treatment. Fabric-based ectocervical and endocervical biopsies were performed using the single use disposable FDA guided pressurized rotational method. Loop excision specimens were evaluated and prior biopsy sites inspected. The presence of an immune inflammatory cell reaction was evaluated.

Results

Twelve of 14 high-grade cases had complete records. Six cases showed a robust inflammatory response that persisted under the biopsy excavation sites in stroma from the excision specimen with a colposcopy to excision interval of 15-27 days (Median 16.5 days, Mean 18.2 days). (Fig 1). In patients
without such evidence, the interval ranged from 7-122 days (Median 32 days, Mean 47.6 days).

**Figure 1:** Three of six cases with varying degrees of re-epithelialization/metaplasia post fabric biopsy or curettage showing a robust cell mediated immune response.

**Conclusions**

Firmly applying and rotating hooked fabric frictional brushes to perform colposcopic biopsy/curettate may induce an inflammatory immune response, evident in 6 of 8 cases treated within 30 days of colposcopic biopsy. Cases that did not show an immune response, which may be due to uncontrolled patient or operator factors, is worthy of future study.
CLINICAL RESEARCH - DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS PRECURSORS

DO WE HAVE TO DISTINGUISH BETWEEN ASCUS AND LSIL OR ASC-H AND HSIL IN THE HPV-VACCINATED WORLD?
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¹Korea University Ansan Hospital, Department of Obstetrics and Gynecology, Ansan, Republic of Korea

Background and Aims

To prove that making distinction between the cytology of ASCUS and LSIL or ASC-H and HSIL in the real world may not be necessary.

Methods

We investigated women visited for cervical cancer screening at Korea University Medical Center from February 2004 to December 2014. Through chart review, we collected data of cervical biopsies of four groups: ASCUS, LSIL, ASC-H, and HSIL. Using Cochran-Mantel-Haenszel statistics method, we compared the results of cervical biopsy of ASCUS group and LSIL group, or ASC-H group and HSIL group.

Results

Of 216,723 women enrolled for Papanicolaou smears, after excluding the results of cervical biopsy other than WNL, CIN1, CIN2, CIN3, and cervical cancer, total 855 women were included in this study. There were 161 women with cytology result of ASCUS, 425 women with LSIL, 22 women with ASC-H, and 247 women with HSIL. By performing statistical analysis, the p-value for the comparison between ASCUS group and LSIL group was < 0.0001, which does not accept the hypothesis of this study. Conversely, the p-value for the comparison between ASC-H and HSIL was 0.26834 which is above the significant value accepting the hypothesis of the study.
Table 1. The distribution of histology of ASCUS vs. LSIL

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Histology</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WNL</td>
<td>CIN1</td>
</tr>
<tr>
<td>ASCUS</td>
<td>31 (19.3)</td>
<td>78 (48.4)</td>
</tr>
<tr>
<td>LSIL</td>
<td>37 (8.7)</td>
<td>195 (45.9)</td>
</tr>
</tbody>
</table>

All values are number (%).
ASCUS: Atypical Squamous Cells of Undetermined Significance, LSIL: Low-grade squamous intraepithelial lesion, WNL: Within normal limits, CIN: Cervical Intraepithelial neoplasm

Table 2. The distribution of histology of ASC-H vs. HSIL

<table>
<thead>
<tr>
<th>Cytology</th>
<th>Histology</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WNL</td>
<td>CIN1</td>
</tr>
<tr>
<td>ASC-H</td>
<td>4 (18.2)</td>
<td>11 (50.0)</td>
</tr>
<tr>
<td>HSIL</td>
<td>39 (15.8)</td>
<td>99 (40.1)</td>
</tr>
</tbody>
</table>

All values are number (%).
ASC-H: Atypical Squamous Cells cannot exclude HSIL, HSIL: High-grade Squamous Intraepithelial Lesion, WNL: Within normal limits, CIN: Cervical Intraepithelial neoplasm

Conclusions

Although the cytology results of ASCUS and LSIL are necessary to be distinguished, making distinction between the cytology of ASC-H and HSIL in the real world may not be necessary. Further study of comparing cytology of these groups may be helpful to simplify the colposcopy results in the HPV-vaccinated world.
Background and Aims

Background: Cervical cancer (CC) is one of the leading causes of cancer death in women after breast cancer, a female genital malignancy that results mainly from infection with the human papilloma virus (Sally N.A et al., 2014). This results in transformation of the cervical epithelial cells (Musa et al., 2014). CC is really alarming and poses serious Public health challenge to Nigerian women and Africa at large. This research study aimed at screening for the early detection of CC leading to its prevention and eradication, its Prevalence among the young female students, Staff of Unijos and its environs. Also to determine the level of awareness of HPV infection as a risk factor for CC and its Knowledge among these women.

Methods

Methodology: Stratified random sampling method was utilized among consenting women. The total of 250 Pap smear samples collected from the study subjects were screened using Papanicoulaou stains, and examined microscopically.

Results

Result: Out of the 250 samples screened, 8(3.2%) had Low Squamous Intra epithelia Lesion, positive indication of CC and the highest prevalence in the age group of 16-25. A total of 350 women were made aware.

Conclusions

Conclusion: The screening and adequate data information gathered on the prevalence of CC revealed high prevalence and risk of its infection, while the descriptive statistical analysis proved high percentage of unawareness.
HUMAN PAPILLOMAVIRUS GENOTYPE AND PROGNOSIS OF CERVICAL CANCER: FAVORABLE SURVIVAL OF PATIENTS WITH HPV 16-POSITIVE TUMORS

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¹Showa university school of medicine, Department of Obstetrics and gynecology, Shinagawa-ku, Japan
²Faculty of Medicine- University of Tsukuba, Obstetrics and Gynecology, Tsukuba, Japan
³Ibaraki Prefectural Central Hospital, Obstetrics and Gynecology, Kasama, Japan

Background and Aims

The impact of human papillomavirus (HPV) genotype on survival in patients with invasive cervical cancer (ICC) is controversial.

Methods

We investigated the prognostic impact of HPV type on ICC by analyzing the clinical data for 137 women treated for ICC at a single institution between 1999 and 2007. The study subjects were divided into three groups according to HPV genotype: HPV16-positive (n=59), HPV18-positive (n=33), and HPV16/18-negative ICC (non-HPV16/18, n=45).

Results

The median follow-up time was 102.5 months (range, 12–179). There was no correlation between HPV genotype and FIGO stage. The 10-year overall survival (10y-OS) rates in women with FIGO stage I/II disease were similar among HPV genotypes: 94.7% for HPV16 (n=39), 95.2% for HPV18 (n=26), and 96.4% for non-HPV16/18 (n=29). However, the 10y-OS rates in women with FIGO stage III/IV tumors were 73.7% for HPV16 (n=20), 45.7% for HPV18 (n=7), and 35.7% for other types (n=16), with significantly higher survival in HPV16-positive compared with HPV16-negative ICC (10y-OS; 73.7% vs. 39.5%, P=0.04). This difference in FIGO stage III/IV tumors remained significant after adjusting for age and histology (hazard ratio 0.30, 95% confidence interval 0.09–0.86, P=0.02).

Conclusions

These results suggest that detection of HPV16 DNA may be associated with a favorable prognosis in patients with FIGO stage III/IV ICC. Given that most women with FIGO stage III/IV tumors received radiotherapy, this finding may imply that HPV16-positive tumors are more radiosensitive. Elucidating the mechanism underlying the association between HPV16 and better survival may lead to new treatment approaches for patients with advanced cervical cancer.
Background and Aims

Radical trachelectomy is an alternative treatment for preserving fertility in patients with cervical cancer. Because women with operable cervical cancer opting for fertility preservation are scarce, not many cases have been reported, especially with robotic procedure. Here we report our cases series.

Methods

We retrospectively evaluated 10 clinically stage IA2~IB1 cervical cancer patients who underwent robotic radical trachelectomy in a Samsung Medical Center from 2009 to 2016.

Results

Of ten patients, 7 patients were squamous cell carcinoma and 3 were adenocarcinoma. The median age of patients was 29 years (range, 26~34). Median estimated blood loss, operation time, and hospital stay were 225 mL (range, 80~800), 310 minutes (range, 160~508), and 9 days (range, 7~25) respectively. The oncological outcome was highly satisfactory. All patients survived and are currently disease free. Other complications included urinary tract infection for 2 patients, right leg lymphedema for 1 patient. All complications were manageable with little long-term effects. Three patients attempted to conceive, and one pregnancy was observed with preterm delivery in 32 weeks.

Conclusions

Robotic radical trachelectomy is considered a complicated but useful surgical procedure for fertility-preserving surgery in early stage cervical cancer patients.
A CORRELATION OF SERUM LEVEL OF CRP, SCC AND PROGNOSIS IN CERVICAL CANCER

B.R. Park¹, C.A. Lee¹, J.S. Kim¹
¹Soonchunhyang university hospital, Department of Obstetrics & Gynecology, Seoul, Republic of Korea

Background and Aims

C-reactive protein (CRP) is the prototypical biomarker of inflammation. The causal relationship between inflammation and cancer is widely accepted. Also squamous cell carcinoma antigen (SCC-Ag) level have been shown to be associated with prognosis with cervical squamous cell carcinoma (CSCC). The purpose of this study was to analyze the relationship between preoperative levels of both SCC-Ag and CRP, with clinicopathologic factors and prognosis in CSCC patients.

Methods

We investigated 191 patients with cervical cancer treated from 2000 to 2017 at Soonchunhyang medical center in Seoul. Medical records were all reviewed retrospectively. Serum level of SCC-Ag, CRP were measured when first diagnosed same as before treatment start. Also followed up when treatment ended. Pathologic classification, FIGO stage were reviewed and especially recurrence rate was highlighted.

Results

Among the 191 patients, 50 are dead and 141 are alive at this study started. The median age was 51 years old when they had first diagnosed. Alives' median age is 64, and Dead's is 52 years old. 81% were diagnosed pathologically squamous cell carcinoma and 10.5% were diagnosed adenocarcinoma. Time of follow-up length was 22.1 months. 108 cases were stable disease, 33 cases were progressive disease, 49 cases were dead related to the cancer, 1 death was not related and 15 cases were recurred.

Conclusions

Serum CRP and SCC-Ag were elevated in higher FIGO stage group. It therefore has significant potential as a biomarker for risk stratification in CSCC.
LOW CIN3+ BURDEN BUT INCREASED RISK OF COLPOSCOPY FAILURE IN THE SECOND AND THIRD ROUNDS OF A SCREENING PROGRAM BASED ON HPV TESTING

K.U. Petry¹, A. Denecke¹, R. Mikolajczyk², J. Horn²
¹Klinikum Wolfsburg, Obstetrics and Gynecology, Wolfsburg, Germany
²University of Halle, Department of Epidemiology, Halle, Germany

Background and Aims

We already showed a significantly increased risk of missing CIN3+ at first colposcopy in women with normal cytology but HPV persistence compared with abnormal cytology cases in the first screening round of a co-testing project (WOLPHSCREEN). Little is known about colposcopy performance in subsequent screening rounds.

Methods

WOLPHSCREEN started 2006 with Pap and HC2 co-testing every five years. 11,947 participants 35 to 69 years old entered the second screening round between February 2011 and December 2016. HPV+ cases with abnormal cytology, p16/Ki-67 positive triage or HC2 persistence for 12+ months were transferred to colposcopy. Histological assessment of minor and major changes was obligatory. Colposcopy failure (CF) was defined as any CIN3+ occurring after a colposcopy diagnosis of ≤ CIN1 unless colposcopy images showed convincingly development of new lesions in type 1 or 2 transformation zones (TZ).

Results

The cumulative CIN3+ prevalence was significantly lower (0.19%) than in the first screening round (0.96%). While first colposcopy did not miss any out of 124 CIN3+ lesions with abnormal screening Pap smears, CF was high (8.1% first and 15.4% in subsequent rounds) in HC2+ women with normal cytology. Major reasons for the observed high CF were failure of curettage in type 3 TZ and hiding of glandular lesions. Histological assessment of major changes only would have increased CF to 31%.

Conclusions

Colposcopy has a relevant impact on the performance of HPV screening and may benefit from revised SOPs. Well indicated diagnostic excisions in postmenopausal women with HPV persistence and type 3 TZ could reduce colposcopy failures.
CLINICAL RESEARCH - DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS PRECURSORS

LOW CIN3+ BURDEN BUT INCREASED RISK OF COLPOSCOPY FAILURE IN THE SECOND AND THIRD ROUNDS OF SCREENING PROGRAMS BASED ON HPV TESTING

K.U. Petry¹, A. Denecke¹, J. Horn², R. Mikolajczyk²
¹Klinikum Wolfsburg, Obstetrics and Gynecology, Wolfsburg, Germany
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Conclusions

Colposcopy has a relevant impact on the performance of HPV screening. Histology assessment even of minor changes and well defined indications for excision of type3 TZ in HPV+ postmenopausal women may prevent that CIN3+ lesions are missed.
EFFICACY OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL TO REPAIR CERVICAL MUCOSA WITH HPV LESIONS. INTERIM ANALYSIS RESULTS

J. Cortés¹, S. Palacios², D. Dexeus³, S. González⁴, L. Serrano⁴, A.C. López⁵, C. Centeno⁶, P. Coronado⁷, J.A. López Fernández⁸, J. de la Fuente⁹, C. Vanrell¹⁰, Y. Gaslain¹¹, J. Combalia¹¹, C. Emsellem¹²

¹Senior Consultant in Gynecological Oncology, Private practice, Palma de Mallorca, Spain
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Background and Aims

To evaluate the efficacy of a Coriolus versicolor-based vaginal gel (Papilocare®) to repair cervical mucosa in women with HPV-related pap alterations and consistent colposcopy image.

Methods

A randomized, open-label, parallel-group, controlled clinical trial. Currently recruiting 96 positive-HPV women age 30 to 65 with pap result of ASC-US or LSIL or AG-US and concordant colposcopy image, randomized into 3 groups:
A) Papilocare® 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months;
B) Papilocare® 1 cannula/day for 3 months + 1 cannula/alternate days for 3 months;
C) no treatment.

Preliminary analysis of percentage of patients with normal pap and concordant colposcopy image at 3 months in both total and high-risk genotype virus population are presented. Pap smear evaluation is being centrally-conducted in IECM laboratory (Lugo, Spain). Papilocare® arms (A+B) were combined for this analysis.

Results

Data from 50 patients at 3 months are available. 70% of patients using Papilocare® (n=30) had negative pap and colposcopy vs. 40% in control group (n=20) (p<0.05; Fisher test).

High risk genotypes virus was detected in 37 patients. At 3 months, normal pap and concordant colposcopy image was observed in 68% of patients using Papilocare® (n=22) vs 33.3% of patients in control group (n=15) (p<0.05; Fisher test).
Conclusions

In these preliminary results, Papilocare® shows a significant difference in repairing HPV-cervical lesions at 3 months versus control in both total and high-risk genotype virus populations; these findings need to be confirmed upon study completion.
BACKGROUND AND AIMS
To evaluate the effect of a Coriolus versicolor-based vaginal gel (Papilocare®) on cervical epithelialization and vaginal microbiota in positive-HPV women with no colposcopy lesions.

METHODS
An exploratory, prospective, observational study. Sexually active positive-HPV women aged >25y with negative pap and no colposcopy cervical lesions were included and treated with Papilocare® once daily for 21 consecutive days.
Primary endpoint: change in epithelialization degree of the cervix mucosa evaluated by standard colposcopy and rated by investigator from 5 = No ectopy o 1= severe ectopy and bleeding.
Secondary endpoints: 1) changes in vaginal microbiota were evaluated by pyrosequencing; 2) patient satisfaction.

RESULTS
21 patients were included. Papilocare® improved the cervix epithelialization mean score (3.79 vs 4.47 baseline vs final; 20% of improving; T test p<0.006) with a maximum score of 5 observed in 63% of women. Both a reduction in vaginal diversity (4 vs 2.5 in Shannon index baseline vs final; T test p<0.006) and an increase of proportion of Firmicutes (phylum to which the lactobacilli belong) were shown. Specifically, significant increase of Lactobacillus crispatus and iners was observed (T test p<0.005). A "moderate/complete satisfaction" was reported by 84% of evaluated patients.

CONCLUSIONS
In this pilot study, Papilocare has demonstrated to improve significantly the cervix epithelization among HPV-positive women without cervical lesions. Reduction of microbiome diversity and increase of concentration of specific species of lactobacillus (iners and crispatus) suggests a restoration of the microbiota composition. These results might explain the mechanism of action of Papilocare. These findings need to be confirmed in a larger study.
CLINICAL RESEARCH - DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS PRECURSORS

EFFICACY OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL TO CLEAR HPV. INTERIM ANALYSIS RESULTS

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Background and Aims

To evaluate the efficacy of a Coriolus versicolor-based vaginal gel (Papilocare®) to clear HPV at 6 months.

Methods

A randomized, open-label, parallel-group, controlled clinical trial. Currently recruiting 96 positive-HPV women age 30 to 65 with pap result of ASC-US or LSIL or AG-US and concordant colposcopy image, randomized into 3 groups:
A) Papilocare® 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months;
B) Papilocare® 1 cannula/day for 3 months + 1 cannula/alternate days for 3 months;
C) no treatment.

Preliminary analysis of percentage of patients with HPV clearance at 6 months in both total and high-risk genotype virus population are presented.

HPV genomic evaluation has been centrally-conducted in IECM laboratory (Lugo, Spain). Papilocare® arms (A+B) were combined for this analysis.

Results

Data about HPV clearance from 26 patients are available. HPV clearance was observed in 56% of patients using Papilocare® (n=16) vs 30% in control group (n=10) (p=ns; Fisher test).

High risk genotypes viruses were detected in 18 patients. At 6 months, 50% of patients in Papilocare® group (n=12) showed HPV clearance vs 17% (n=6) in control group (p=ns; Fisher test).

Conclusions
In these preliminary results, Papilocare® shows a positive trend in HPV clearance at 6 months, especially in high risk genotype virus population; these findings need to be confirmed upon study completion.
USE OF A CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN PATIENTS WITH PRECANCEROUS HPV LESIONS. INTERIM ANALYSIS RESULTS


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Background and Aims

To evaluate the efficacy of a Coriolus versicolor-based vaginal gel (Papilocare®) to repair cervical mucosa in women with HPV-related cytology alterations and consistent colposcopy image.

Methods

A randomized, open-label, parallel-group, controlled clinical trial. Currently recruiting 96 positive-HPV women age 30 to 65 with pap result of ASC-US, LSIL or AG-US and concordant colposcopy image, randomized into 3 groups:

A) Papilocare® 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months;
B) Papilocare® 1 cannula/day for 3 months + 1 cannula/alternate days for 3 months;
C) no treatment as usual practice.

Interim analysis of secondary endpoints - changes in epithelialization of the cervix evaluated by standard colposcopy and in perceived stress evaluated by PSS14 - are presented. Papilocare® arms (A+B) were combined for this evaluation.

Results

Data from 47 patients at 3 months and 29 patients at 6 months are available.

20.7% and 47.5% of patients in Papilocare® group improved the cervix epithelialization at month 3 and 6 respectively vs 22.2% and 16.7% in control group (p=ns).

A trend to stress reduction vs basal was observed in the treatment group at month 3 (-0.9 points) and was significant at month 6 (-2.9; p=0.045, Student’s t-test). Patients in control group showed a trend to stress increase at month 3 and 6 (+0.5 and +4.7; p=ns). There were not significant differences between treatment groups.

Conclusions
In these interim analysis results, Papilocare® shows a positive trend in cervix epithelialization and a significant stress reduction; these findings need to be confirmed upon study completion.
BACKGROUND AND AIMS

Request for self-care is increasing, and health care tries to meet this request. Condom use is expected to increase regression of cervical intraepithelial neoplasia (CIN). We undertook a randomized controlled trial to test acceptability and effect of this self-care. Here we report on participation as a measure of acceptability.

METHODS

A randomized controlled trial recruiting woman with CIN grade 2 (CIN2) and scheduled for passive follow-up for 3-6 months. The intervention group is advised to convince partners to use condoms at every intercourse in the period between diagnosis and follow-up visit. The control group receives standard care.

RESULTS

In total, 854 women were diagnosed with CIN2, and 250 matched a consent form obtained by the gynaecologist (29%). Women without a match could fall outside the age group (18-44 years); be scheduled for immediate conisation; did not provide consent; or were forgotten to be asked. Of the 250 women, 61 did not meet inclusion criteria, leaving 189 women for randomization (76%).

Of the 98 patients randomised to the intervention group, 63 agreed to participate (64%); 15 agreed on phone, but did not return written consent; 8 did not want to participate; 5 withdrew later; 11 could not be reached; and one patient was excluded.

CONCLUSIONS

This study introduces a self-care tool for women with CIN2. Participation in the intervention group was lower than expected. It was surprisingly difficult to reach women even after several calls and text messages. This suggests that self-care is less popular than expected.
Background and Aims

Thermoablation has emerged as a viable alternative to cryotherapy in the treatment of cervical pre-cancer. However, protocols differ by probe tip size, shape and temperature. We modified the most widely-used device in collaboration with the manufacturer to meet the needs of low-resource settings.

Methods

Twenty-one patients aged 25-65 scheduled for hysterectomy for indications other than cervical pathology underwent thermoablation with a 16mm flat tip at 120°C for 40 seconds. In a second study, the probe tip was reshaped and 25 patients underwent thermoablation with a 20mm conical tip at 100°C for 40 seconds. Participants verbally rated pain during treatment on a scale of 0 (no pain) to 10 (worst pain). Subsequently, cervical samples were obtained by cone biopsy and prepared for routine histological processing. Depth of tissue necrosis was measured at its deepest point by expert pathologists.

Results

Initially, mean depth was 2.7mm (SE = .26) in the anterior lip and 2.5mm (SE = .15) in the posterior lip. After the tip was modified, mean depth increased to 4.0 mm (SE = .22) in the anterior lip (p<.001) and to 3.8mm (SE = .19) in the posterior lip (p<.001). Pain intensity was similar in both studies at 3.1 (SE = .43) vs. 3.4 (SE = .35) (p=.53).

Conclusions
Treatment with the 20mm conical tip at 100°C resulted in greater depth of necrosis than the 16mm flat tip at 120°C. Further research is needed to determine the optimal treatment approach. Standardized guidelines for thermal ablation will eliminate variation in technique.
APPLICATION OF A MULTISTATE MARKOV MODEL FOR PREDICTING PROGNOSIS OF HPV16-, HPV18-, HPV52-, AND HPV58-POSITIVE CERVICAL LESIONS
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Background and Aims
Cervical intraepithelial neoplasia (CIN) has a natural history of undergoing bidirectional change, and patients move intricately among a series of states. A model capable of estimating the risks of simultaneous transitions between multiple states is more suitable for assessing the fate of CIN patients than the traditional Cox hazard model.

Methods
In this study, we applied a continuous multistate Markov model using cross sectional dataset to predict the CIN fate for each high-risk human papilloma virus (HPV) genotype. For data collection, we reviewed 1,485 patients who were diagnosed with cervical epithelial lesions in our center during 2008-2014 (normal: 159, CIN1: 319, CIN2: 322, CIN3: 494, and cervical cancer: 191 cases). Associations between HPV genotypes and clinico-pathological characteristics were analyzed.

Results
Among CIN2-3, HPV16, 52, and 58 were most prevalent, whereas HPV16 and 18 were prevalent among cervical cancers. The multistate Markov model revealed that HPV18-positive patients were most likely to progress to cancer with predicted ten-year risks of 13, 21, and 35% for CIN1, CIN2, and CIN3 patients; HPV16-positive patients were likely to upgrade to CIN before progressing to cancer with predicted ten-year risks of around 10%; HPV52- and 58-positive patients were unlikely to progress to cancer with predicted ten-year risks of less than 5% and were likely to have persistent CIN states.

Conclusions
The estimation of the multistate Markov model suggests that HPV18-related cancers develop more rapidly than those of other genotypes. Prognostic prediction and management might be more difficult for HPV18-related cervical lesions than for lesions associated with other high-risk HPVs.
BACKGROUND AND AIMS

Persistence of Human Papilloma Virus (HPV) after treatment of cervical neoplasia may be indicative of local recurrence. The aim of this study was to determine the prevalence of HPV in cervix or vagina after treatment of cervical neoplasia and to ascertain association with local recurrence.

METHODS

Data was collected retrospectively from online hospital medical records. The cohort consisted of women who had undergone treatment for CIN 2, CIN 3 or cervical cancer between January 1st, 2014 and 31st December, 2016 at a teaching hospital in India for whom post treatment HPV results were available. Local recurrence was defined as a positive vaginal or cervical biopsy or positive radiological (PET CT) findings.

RESULTS

Out of a total of 101 patients, 26 had CIN 2 or 3 and 75 had cervical cancer. Positive HPV detection occurred in 46.2% of precancers and 18.7% of cancers at a mean duration of 14.9 and 8.2 months post treatment respectively. Of the 12 precancers with positive post-treatment HPV, 7 (58.3%) had recurrence whereas among 14 cancers, 3 (21.4%) had recurrence. The Relative Risk (RR) was 4.1 (95% CI 1.1, 16.1), Odds Ratio (OR) 8.4(95% CI 1.3, 55.4) and p-value 0.03 for recurrence with a positive HPV test after treatment as compared to a negative HPV result. For cancers RR was 2.6(0.7, 9.7), OR was 3.1(0.6, 14.7) with p=0.16.

CONCLUSIONS

Positive HPV detection post treatment is a risk factor for local recurrence in cervical neoplasia especially in premalignant lesions. Hence HPV detection may be useful for post treatment surveillance.
Background and Aims

To clarify the severity of epithelial lesions and determine cervix uteri (CU) and individual prognosis, it is necessary to develop and implement into clinical practice the immunohistochemical markers, which allow determining the outcome of the cervix intraepithelial neoplasm (CIN).

The aim. With this purpose in mind, in this paper we study a molecular biological marker associated with proliferation and apoptosis.

Methods

Methods and materials. Within the framework of the state grant, the expression of Ki-67 in tissues of the pathologically altered CU (CIN and early stages of cervical cancer) was studied by the staff of our centre. Immunohistochemical study was performed by immunoperoxidase method.

Results

Results. Analysis of the results of Ki-67 expression in the cervical epithelium study showed a low grade of expression when CIN 1. As the intensity of the lesion increased, the expression grade was more apparent. Significant differences regarding biomarker of proliferation were found between unaltered cervical epithelium and severe dysplasia. It should be noted that with severe SIL (CIN 2, CIN 2-3, CIN 3 and Tis) the variability of Ki-67 expression was observed. This is most likely due to subjective CIN 2 and CIN 3 in the morphological study of the biopsy material. The level of Ki-67 expression increases with the expansion of changes in the cervix, when cell proliferation and reactive squamous cell metaplasia intensifies. The collection of material continues.

Conclusions

Conclusion. Thus, the determination of the Ki-67 expression promotes examining the biological nature of the pathological process in the cervical epithelium.
Background and Aims

Cervical cancer screening is undergoing a transition from cytology- to HPV-based screening.

Methods

Current screening guidelines provide for colposcopy referral based on HPV 16 and 18 infection. However, we now know that this paradigm is incomplete: select non-HPV 16/18 infections can pose a significant risk for CIN2+ disease that is similar or greater than that posed by HPV 18. The corollary to this is also clear: approximately half of all high-risk HPV types pose very little risk for cervical cancer and could be managed less aggressively. Moreover, in vaccinated cohorts HPV 16/18 infections are switching from major to minor contributors of CIN2+ disease, shifting our attention to non-HPV 16/18 high-risk types. We illustrate these points using data from the BD Onclarity US-PMA trial and peer-reviewed publications.

Results

Patients with infections that have negligible 3-year risks for disease could be re-tested in one year and only if the infection is persisting, then sent to colposcopy, whereas patients with a high risk of disease could be referred for immediate follow up. Grouping of patients with similar risk further reduces complexity, aligning with the basic tenet of current screening guidelines - “equal management of equal risk”. The application of these basic principles can also logically be extended to other screening paradigms such as test of cure, self-sampling and risk-based colposcopy, leveraging the risk-stratifying power of type-specific persistence.

Conclusions

We conclude that extended genotyping enables simplified management strategies based on currently established action thresholds which can be adapted to different geographic prevalence rates and risk of disease.
COMPARISON OF HIGH-RISK HPV INFECTION CHARACTERISTICS IN ADOLESCENT AND YOUNG WOMEN FROM TWO CROATIAN COUNTIES

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Background and Aims

Sexually active adolescents are at high risk for acquiring HPV. Persistent infection with high-risk HPV (hrHPV) types is necessary for the development of cervical cancer. The aim of this study was to compare the prevalence hrHPV infection between adolescent and young women from two biggest Croatian counties: the City of Zagreb (CZ) and the Split-Dalmatia County (SDC), considering severity of cervical lesions and and distribution of the most important types.

Methods

The study included women younger than 30 years of age with abnormal Pap test who were tested on hrHPV infection with molecular Cobas HPV Test. All positive samples were subsequently tested with Linear Array test which enables type-specific detection of 37 high- and low-risk HPV genotypes.

Results

No significant difference was determined in the overall prevalence of hrHPV infection between the two counties. Among 3542 cervical swabs analyzed in the CZ, 39.7% was hrHPV positive, while in the SDC the positivity rate among 1594 tested samples was 36.2%. Analyzing the population of hrHPV positive adolescent and young women, the highest prevalence of HPV16 was observed. In the CZ, further analysis showed that hrHPV genotype 51 was the second most prevalent HPV type (HPV16 32% and HPV51 27%), associated with low grade cervical abnormalities, while in the SDC HPV51 was significantly less frequently detected (p<0.01). The presence of HPV16 and HPV18 in cervical samples significantly increased with the severity of cervical lesions (p<0.01).

Conclusions

Significant epidemiological differences of hrHPV infection in population of adolescent and young women in two studied regions was detected.
Background and Aims

To compare the risk of CIN3+ among women who had a normal cytology (non-exposed cohort) at study start with women who had a negative 5-type HPV mRNA test in triage of ASC-US/LSIL (exposed cohort). A three year CIN3+ risk below 2.0% is considered acceptable to recommend return to routine screening.

Methods

After exclusion of women who had a previous history of CIN1+ and HSIL, we identified 1063 women who had an HPV mRNA negative triage of ASC-US/LSIL over the years 2006 through 2011, and a control cohort of 25 948 women who had a normal cytology during 2006/2007. All women, aged 25-69 at study start, were followed through December 31, 2014. The HPV test targeted E6/E7 mRNA from the types HPV16, 18, 31, 33 and 45 (PreTect HPV-Proofer).

Results

The crude cumulative proportion of CIN3+ were 0.24% (95% CI: 0.17-0.31) and 0.73% (0.60-0.86) at 42 and 78 months of follow-up for the non-exposed cohort, and 1.45% (0.55-2.4) and 2.6% (0.94-4.3) for ASC-US/LSIL. The exposed cohort had significant more extensive follow-up than the control cohort. Over the entire study period 20 cervical cancers were diagnosed in the non-exposed cohort (incidence 8.4 per 100 000 woman-years) compared to none in the exposed cohort.

Conclusions

Women who have a negative mRNA-test for HPV16, 18, 31, 33 and 45 at triage for ASC-US/LSIL have low risk for CIN3 within the first two screening intervals after triage, and may return to screening at 3-year interval.
Background and Aims

to analyze the clinical performance of PD-L1 and HPV-L1 proteins dual-stained cytology and pathology triaging the high-risk human papillomavirus (hr-HPV) positive participants in Chinese women.

Methods

2332 women (age ranging 20-70) attending HPV and liquid-based cytology (LBC) based primary screening were enrolled into a regional prospective study in 2017. Women infected with HPV 16 or 18 or other kinds of hr-HPV types with abnormal cytology (atypical squamous cells of unknown significance or worse) were referred to colposcopy and biopsy. HPV-L1 and PD-L1 were immunochemical stained in cervical intraepithelial neoplasia grade 2 or worse (CIN2+). All tests were performed on the same sample. All statistical tests were two-sided.

Results

401 HPV positive women were received colposcopy. The positivity of HPV-L1 decreased with histology severity, from 74.1% in normal, 52.7% in CIN1, 34.9% in CIN2, 11.2% in CIN3 to 7.7% in cervical cancer. And PD-L1 increased from 15.1% in normal, 33.8% in CIN1, 45.7% in CIN2, 65% in CIN3 to 96.6% in cervical cancer. The two markers’ expressions were significantly difference in HPV16/18 group (OR: 9.11 (95% CI: 7.22-16.19)) comparing with hr-HPV negative group. The sensitivity and specificity of HPV-L1 and PD-L1 to detect CIN2+ in HPV-positive women were 91.33% and 82.56% respectively.

Conclusions

HPV-L1 and PD-L1 dual staining provided a significantly higher sensitivity and non-inferior specificity, which might be considered as efficient triaging tools to perfect HPV primary screening.
Background and Aims

To evaluate the clinical value of conization in the diagnosis and treatment of cervical cancer patients.

Methods

125 patients diagnosed with cervical cancer after cold knife conization in our hospital between 2008.1 and 2016.9 were reviewed. The pathological profiles of conization specimens and treatment options were analyzed.

Results

Among them, there were 116 squamous cell carcinomas, 7 adenocacinomas, 1 neuroendocrine carcinoma and 1 adenoid basal carcinoma. In 116 squamous cell carcinomas, there were stage Ia1(n=77), stage Ia2 (n=5)and stage Ib1(n=34). In 7 adenocacinomas, there were stage Ia1(n=3), stage Ia2 (n=2)and stage Ib1(n=2). Among 41 patients with stage Ia1 squamous cell carcinomas undergoing further surgery, 14 (34.1%) had residual diseases, including CIN II(n=9), CIN3(n=4) and squamous cell carcinoma(n=1). No recurrence was found in 36 cases without further surgical intervention. All cases of stages Ia2 and Ib1 underwent repeat surgery.

Conclusions

Cold knife conization plays a very important role in the diagnosis and treatment of cervical cancer patients. Further treatment options should be selected individually and comprehensively based on such factors as patient’s age, degrees of dysplasia, surgical margin status, fertility requirements and so on.
LONG-TERM PERFORMANCE OF HPV GENOTYPING, HPV E6/E7 mRNA EXPRESSION, AND P16/KI-67 CYTOLOGY FOR DETECTION OF ANAL PRECANCER IN HIV+ MSM

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Background and Aims

Biomarkers currently being evaluated for triage of human papillomavirus (HPV)-positive women in cervical cancer screening may have applications for anal cancer screening in high-risk populations such as HIV-positive (HIV+) men who have sex with men (MSM). Here, we evaluated the longitudinal performance of several biomarkers including HPV16/18 genotyping, HPV E6/E7 mRNA, and p16/Ki-67 dual stain (DS) in a population of HIV+ MSM.

Methods

This study includes 363 HIV+ MSM enrolled at an HIV/AIDS clinic between August 2009 and June 2010 with passive follow-up through October 2015. All men had anal cytology and high-resolution anoscopy-directed anal biopsies at baseline. We evaluated the longitudinal performance of biomarkers to detect high-grade anal intraepithelial neoplasias (AINs) based on composite endpoints of biopsy and cytology results.

Results

At baseline, we observed 148 <AIN1, 106 AIN1, and 109 AIN2+. Among the 162 HIV+ MSM with follow-up cytology and/or histology (median = 2.8 years), 7 incident AIN2+ were diagnosed in those with baseline <AIN1 (10.8%) and 13 incident AIN2+ in those with baseline AIN1 (20.6%). Risks of AIN2+ according to baseline biomarker status were: 24.7% for DS+; 11.3% and 32.4% for HR-HPV+ (non-16/18) and HPV16/18+, respectively; and 33.3% for E6/E7 mRNA+. Risk of AIN2+ was lowest for HIV+ MSM testing DS- (2.3% vs. 5.6% for HR-HPV- and 6.3% for E6/E7 mRNA-). Corresponding Kaplan Meier curves are shown in Figures 1-3.
Figure 1. Kaplan Meier curves for AIN2+ detection by p16/Ki-67 dual stain at baseline.
Figure 2. Kaplan Meier curves for AIN2+ detection by HR-HPV status at baseline.
Conclusions

Biomarkers evaluated for cervical cancer screening show long-term risk stratification for AIN2+. Baseline biomarker negativity indicates low risk of AIN2+ in this population.

Figure 3. Kaplan Meier curves for AIN2+ detection by HPV E6/E7 mRNA status at baseline.
Anal cytological abnormalities and HPV detection with different primer sets in HIV-positive men in eastern India

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Background and Aims

Oncogenic Human papillomavirus (HPV) infections are closely associated with anal cancer which is high among human immunodeficiency virus (HIV) infected men. The aim of this cross-sectional study was to assess the HPV prevalence alongside with the effectiveness of different consensus primers in detection, genotyping and associated risk factors in HIV positive men.

Methods

We screened 102 HIV positive treatment naïve men attending the ART (antiretroviral treatment) center with anal papanicolaou smear cytology and HPV testing by using four different consensus primer sets (MY09/11, MY/GP, E6 and E6/E7). HPV type (16, 18, 31, 35, 52, 58, 66, and 68) was determined by SYBR Green based real-time PCR. Risk factors were analyzed by using univariate and multivariate logistic regression models.

Results

Prevalence of anal cytological abnormalities was (48/88, 54.54%). HSIL, LSIL, ASCUS, ASC-H, NILM and reactive inflammatory changes were present in (1, 1.13%), (23, 26.13%), (13, 14.77%), (11, 12.5%), (25, 28.4%) and (15, 17.04%) subjects. HPV prevalence was (82/102, 80.39%) with MY09/11 (35.29%), MY/GP (49.01%), E6 (52.94%), and E6/E7 (65.68%). The most prevalent HPV were HPV-18, 16, 31, 35, and 66 (33.33%, 16.66%, 9.8%, 5.8% and 6.80%) and multiple HPV types were identified in 36.58% (30/82). In the univariate analysis four risk factors were history of anal intercourse, age at first intercourse, smoking and HPV detection by PCR. In multivariate analysis two risk factors were history of anal intercourse and age <19 yr at first intercourse.

Conclusions

HPV detection rate is affected by choice of consensus primer selection as HPV viral genome is highly conserved.
Background and Aims

Squamous cell carcinoma of the anus (SCCA) is increasing in incidence. High-grade squamous intraepithelial lesion (HSIL), its immediate precursor, arises in the mucosa or perianal skin. SCCA without mucosal involvement is rare and diagnostically challenging. This phenomenon has been described in the cervix after HSIL treatment. We describe six cases of submucosal SCCA.

Methods

All patients with SCCA seen in our practice from February 2014 through February 2018 were included in this study. We described all six who presented without mucosal involvement.

Results

Six patients developed submucosal SCCA. The first case occurred in 2009 and all subsequent cases occurred within the past three years. The median age at diagnosis was 58 (range 41-83) years, 4 were male, 5 were HIV+, and none had inflammatory bowel disease. Five patients had a prior or concurrent HSIL discrete from the SCCA.

Two HIV+ patients (TJ and JG) developed SCCA within fistula tracts three years after initial abscess drainage. Two (JE and YW) developed submucosal SCCA after multiple HSIL ablations. Two HIV+ patients (LR and JP) developed submucosal SCCA remote from prior HSIL. LR was diagnosed with SCCA in a submucosal rectal nodule after hemorrhoid rubber band ligation and JP developed SCCA deep to the mucosa within an anal canal sinus tract diagnosed by PET/CT.

Conclusions

We described 6 cases of SCCA without apparent mucosal involvement. One must maintain a high index of suspicion in high risk individuals with submucosal nodules or recurrent abscesses/fistulae. Previous anal procedures may increase risk for submucosal variant SCCA.
RELIABILITY AND ACCEPTABILITY OF SELF- VERSUS CLINICIAN-COLLECTED ANAL SWABS FOR CYTOLOGY IN HIV-POSITIVE MEN: RESULTS FROM THE NOMAD-2 STUDY

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Background and Aims

HIV-positive men who have sex with men (MSM) have anal cancer rates 50-100 times higher than the general population. This, coupled with little evidence on how best to approach anal cancer screening, highlight the importance of developing novel and feasible screening methods for this malignancy. The objective of this study was to compare the reliability and acceptability of self- versus clinician-collected swabs for anal cytology.

Methods

Participants were recruited from a Canadian specialty HIV clinic from 02/2016 to 02/2018. Participants were randomized to one of two specimen collection orders: clinician-collected then self-collected, or self-collected then clinician-collected. Participants were provided a self-collection instruction card. Swabs were sent for anal cytology, as per the Bethesda system. The primary outcome was sample adequacy, defined as minimum 1-2 nucleated cells per high-powered field.

Results

Results from 91 HIV-positive MSM with median age 51 (IQR: 39, 57) were analyzed. Median CD4 count was 670 cells/mm³ (IQR: 523,736) and 91% had suppressed HIV viral load. Of the self-collected samples, 90% were adequate for cytology, and 86% of the clinician-collected samples were adequate. Inter-rater reliability for sample adequacy between self- and clinician-collected samples (n=91) showed a percent agreement of 80%, percent positive agreement of 89%, and a Gwet’s AC1 estimate of 0.75 (95%CI: 0.62-0.87). Most found self-collection comfortable (76%), easy (90%), and would be comfortable doing self-collection again (93%).

Conclusions

These data demonstrate that both self-and clinician-collected samples for anal cytology are reliable methods in MSM living with HIV. Participants also overwhelmingly found this to be an acceptable intervention.
Background and Aims

Human papillomavirus (HPV)-associated anal cancer is emerging as a leading cause of non-HIV-related death in HIV-positive MSM. Anal cancer rates in HIV-positive MSM are up to 100-times higher than the general population. There are no universally-accepted guidelines for anal cancer screening, even in high risk populations, due to a paucity of evidence to support its effectiveness. We assessed the acceptance rate to invitations for anal cancer screening, and describe preliminary pathology results.

Methods

The HPV-SAVE Study is an ongoing Canadian study on screening and treatment of anal cancers and pre-cancers in HIV-positive MSM. HIV-positive MSM were invited to have anal cytology testing in their physician’s office. Those with abnormalities were referred for high resolution anoscopy (HRA) and anal biopsies. Cytology was graded as per the Bethesda classification, and histology was described per the Lower Anogenital Squamous Terminology (LAST) nomenclature.

Results

Out of 1992 invitations as of 03/2018, 512 men (25.7%) agreed to be screened. Median age is 47 years (interquartile range, 37-58), and 85% had undetectable HIV viral load. Cytology results from 442 satisfactory Pap tests were: 210 negative (47.5%), 51 LSIL (11.5%), 12 HSIL (2.7%), 148 ASCUS (33.5%), 21 ASC-H (4.8%). In 81 participants referred for HRA, 211 biopsies were done (mean 2.6 biopsies/person; range 1-4), yielding HSIL in 42 (51.9%) of the men, and one invasive carcinoma.

Conclusions

MSM living with HIV had moderate acceptance of invitations to have anal cancer screening, with over half of screened men having abnormal cytology. A majority of those undergoing HRA had high-grade histology diagnosed.
Primary anal adenocarcinoma is a rare disease accounting for approximately 10% of all malignancies of the anal canal. This cancer is currently sub-optimally treated with non-targeted modalities varying with clinician's perception/experience (no consensus treatment recommendation). Moreover, the pathogenesis, mutational landscape and immune microenvironment of anal glandular neoplasms are still completely unknown.

Methods

In the present study, we first assessed HPV infection in each collected tumor sample (n=74) and examined their histological features. The immune microenvironment (CD4, CD8, Foxp3, PD-1, PD-L1), the microsatellite instability as well as the mutational status of multiple clinically relevant genes (KRAS, NRAS, BRAF, PIK3CA, EGFR,...) were then determined. Finally, the prognostic value of several risk factors was analyzed.

Results

Two region-specific subtypes of anal canal adenocarcinoma were identified. In contrast to "colorectal-type" anal adenocarcinoma, a significant proportion of glandular neoplasms arising from the anal glands/transitional zone was etiologically linked to HPV16 or 18 infection. In addition, anal gland/transitional-type cancers harbored less mutations in downstream effectors of the EGFR signaling pathway and were characterized by a prominent T-cell infiltration.

Conclusions

Altogether, the in-depth characterization of anal glandular neoplasms supports a novel dualistic model of anal carcinogenesis (anal glands/transitional zone versus colorectal mucosa).
To evaluate the histological progression and response to electroablative treatment of high grade squamous anal intraepithelial neoplasia [HSIL (AIN-2/3)] in HIV-positive men who have sex with men (HIV-MSM).

**Methods**

A cohort of 209 HIV-MSM with HR-HPV infection or altered anal cytology were selected for high resolution anoscopy (HRA) between June 2013 and June 2016. Patients with basal LSIL (AIN-1) and negative histology or HRA were classified as Low-risk patients (LRP); patients with basal HSIL (AIN-2/3) were classified as High risk patients (HRP).

**Results**

Virological, cytological and histological findings in LRP and HRP are summarized on tables 1, 2 and 3.

**LRP** (n=174): Histological progression to HSIL (AIN-2/3) occurred in 14 (8%) patients 71.4% were HSIL (AIN-2) and 28.6% HSIL (AIN-3). HSIL cyto-histological concordance at incidence was 100%. HSIL (AIN-2/3) complete response after treatment was 92.9%.

**HRP** (n=35): 24 of them were HSIL (AIN-2) and 11 HSIL (AIN-3) including 1 prevalent anal carcinoma. HSIL (AIN-2/3) complete response after treatment was 82.9%, slightly lower in HSIL (AIN-3) patients (63.6%) with 19 persistences, 3 recurrences and 12 metachronies. The presence of >2 affected quadrants was related to higher prevalence of HSIL (AIN-2/3), p=0.014 and clinical HIV stage
C with no HSIL (AIN-2/3) treatment response, p=0.02. Basal HSIL and ASCUS cytology in HRP (22.9% and 34.29% respectively) was significantly reduced at the final cytology control (11.4% and 20% respectively).

Conclusions

High percentage of cure in treated HSIL (AIN-2/3), slightly lower in HRP and with higher evolutive persistences, recurrences and metachronies.
CLINICAL RESEARCH - DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS PRECURSORS

INCREASED CADM1 DNA METHYLATION IS ASSOCIATED WITH PREVALENT ANAL INTRAEPITHELIAL NEOPLASIA GRADE 3+ IN GAY AND BISEXUAL MEN

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Background and Aims

High methylation on CADM1, MAL and miR-124-2 genes is an accurate method for detection of high-grade cervical lesions and cancer. There are few data on DNA methylation of these genes to anal intraepithelial neoplasia (AIN). Objective: To determine whether high DNA methylation would be of value in the detection of AIN.

Methods

Anal cytology samples were collected from participants of the Study of the Prevention of Anal Cancer (SPANC) at baseline. DNA was extracted and subjected to bisulfite conversion and methylation-specific-qPCR. Samples negative for an internal control were excluded from further analysis. Participants with cytological and/or histological AIN grade 3 (AIN3) or worse were stratified as composite AIN3+; remaining participants were stratified as <AIN3. The mean percentage DNA methylation ± standard deviation (SD) of each marker was compared between disease grades.

Results

Results were available for 487 participants (aged 35-75). Of these 142 (29%) had composite AIN3+ and 171 (35%) were HIV-positive. CADM1 mean [± SD] methylation was significantly higher in participants with AIN3+ (4.74% [±10.15]) than <AIN3 (2.69% [±9.76]); p=0.038. In HIV-positive participants, CADM1 mean methylation was significantly higher in AIN3+ (5.77% [±13.55]) than <AIN3 (1.99% [±5.58]); p=0.011, but was not different in HIV-negative participants. When restricted to hrHPV+ (n=306), CADM1 mean methylation was significantly higher in AIN3+ compared with <AIN3 in both HIV-negative and HIV-positive (Table 1). MAL and miR-124-2 methylation levels were not
significantly different between disease grades.

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>Methylation Markers</th>
<th>&lt;AIN3 % [±SD]</th>
<th>AIN3+ % [±SD]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk HPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=183</td>
<td>MAL</td>
<td>5.67% ± 9.18</td>
<td>6.62% ± 8.41</td>
<td>p=0.483</td>
</tr>
<tr>
<td></td>
<td>miR-124-2</td>
<td>4.23% ± 6.42</td>
<td>6.12% ± 10.17</td>
<td>p=0.125</td>
</tr>
<tr>
<td></td>
<td>CADM1</td>
<td>2.17% ± 3.98</td>
<td>4.31% ± 6.85</td>
<td>p=0.008</td>
</tr>
<tr>
<td>Positive (hrHPV+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=306</td>
<td>MAL</td>
<td>9.99% ± 13.79</td>
<td>10.45% ± 6.85</td>
<td>p=0.860</td>
</tr>
<tr>
<td></td>
<td>miR-124-2</td>
<td>5.77% ± 6.55</td>
<td>6.04% ± 6.41</td>
<td>p=0.811</td>
</tr>
<tr>
<td></td>
<td>CADM1</td>
<td>2.01% ± 6.42</td>
<td>6.02% ± 14.22</td>
<td>p=0.039</td>
</tr>
</tbody>
</table>

Table 1. Mean percentage DNA methylation of CADM1, MAL and miR-124-2 genes in high-risk-HPV positive participants comparing those with < AIN 3 and AIN3+, stratified by HIV status

Conclusions

Increased CADM1 methylation in anal cytological samples of hrHPV+ men could be of value identifying patients with prevalent AIN3 lesions.
Utility of Anal Symptoms and Self-Reported Anal Warts as Predictors of Anal HSIL Among Gay/Bisexual Men in the Study of the Prevention of Anal Cancer

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Background and Aims

The association of intra-anal HSIL with symptoms has not been previously investigated.

Methods

The Study of the Prevention of Anal Cancer (SPANC) is a community-recruited cohort of gay and bisexual men (GBM) aged ≥35 years. Self-reported anal symptoms (discharge, itch, sores, lump, pain with defecation, bleeding, tear, tenesmus) and history of anal warts within the last year were collected at baseline. Anal cytology and high-resolution anoscopy ± biopsy were undertaken. Men with intra-anal composite-HSIL (i.e. detected on cytology and/or histology) were compared to those with no evidence of squamous intra-epithelial lesion (SIL).

Results

Among 616 participants, 414 were diagnosed with either composite-HSIL (n=231, 37.5%) or were SIL-negative (n=183, 29.7%). Over half reported any anal symptom in the last month (n=231, 55.6%). There was no significant association between composite-HSIL and any anal symptom within the last month or last 6 months. Only 1 (0.6%, 95% CI 0.1-3.0%) person in the SIL-negative group reported a history of anal warts within the last 12 months, compared with 28 (12.4%, 95% CI 8.2-17.0%) men diagnosed with composite-HSIL (p<0.001). For the detection of composite-HSIL, self-reported history of anal warts within the last year had a sensitivity of 12.4%, specificity of 99.4%, positive predictive value of 96.6% and negative predictive value of 47.8%.

Conclusions
Anal symptoms were not associated with intra-anal composite-HSIL. A self-reported history of anal warts in the last year may be a useful marker for the presence of anal HSIL in GBM. However, the majority of men with anal HSIL did not report recent anal warts.
Background and Aims

Oncogenic human papillomaviruses (HPV) play an etiological role in the majority of anal squamous cell carcinomas (ASCC), as indicated by the detection of HPV DNA and the cell cycle regulator protein p16\textsuperscript{INK4A}. While it has been assumed that these two markers are also of prognostic relevance in ASCC patients, heterogeneous survival data have been reported.

Our meta-analysis aims to accurately determine the prognostic relevance of oncogenic HPV DNA and p16\textsuperscript{INK4A} in ASCC among the published literature.

Methods

All published studies analyzing overall survival (OS) stratified by HPV DNA and p16\textsuperscript{INK4A} in ASCC were identified by a systematic search. Individual patient data (IPD) was requested from all investigators. OS was analyzed by Cox-Regression using p16\textsuperscript{INK4A} and HPV DNA, and adjusted for relevant covariates.

Results

Sixteen eligible studies were identified. We obtained IPD of 666 patients (from eight studies). Overall, 81.8% of 658 ASCC overexpressed p16\textsuperscript{INK4A} and in 84.3% of 555 ASCC oncogenic HPV DNA was detected. The case fatality rate of p16\textsuperscript{INK4A}-negative ASCC was significantly higher compared with p16\textsuperscript{INK4A}-positive ASCC (35% and 18%, respectively, p<0.001). p16\textsuperscript{INK4A}-overexpressing and HPV DNA-positive ASCC patients showed statistically significant better OS (HR=0.42 (95% CI, 0.30-0.61) and HR=0.39 (95% CI, 0.27-0.57), respectively). In a multi-variable analysis incorporating both markers, p16\textsuperscript{INK4A}-negative, but HPV DNA-positive ASCC represented the patient group with the worst OS (HR=3.25 (95% CI, 1.88-5.62)).

Conclusions
This meta-analysis demonstrates that oncogenic HPV DNA and p16\textsuperscript{INK4A}-overexpression are detected in the majority of ASCC and predict significantly better patient survival.
PERSPECTIVES  -  GENERAL PRACTICE

E6 PROTEIN AS A BIOMARKER FOR ANAL CANCER SCREENING IN HIV-POSITIVE MEN
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Background and Aims

Molecular biomarkers have potential to enhance accuracy of anal cancer screening in HIV-positive individuals. Our objective was to evaluate HPV-16/HPV-18 E6 proteins as anal cancer screening biomarkers in HIV-positive men.

Methods

In 2015/2016, we enrolled HIV-positive men presenting for anal cancer screening, diagnosis, or treatment at an anal dysplasia clinic in Seattle, Washington. Anal specimens were collected with Anex(R) Brush (Rovers Medical Devices) by an anoscopist during visits; men returning for follow-up during the study period could contribute multiple specimens. Specimens were HPV-genotyped by PCR, and tested for HPV-16/HPV-18 E6 protein by the OncoE6™ Anal Test (prototype test by Arbor Vita Corporation). Demographics and cytology and histology results were extracted from medical records. High-grade dysplasia was defined as ≥HSIL on cytology or ≥AIN2 on histology.

Results

Eighty-four HIV-positive men (median age 50 years, range 27-77) contributed 132 specimens. Forty-nine specimens (37.1%) were HPV-16 or HPV-18 positive. Thirty-eight HPV-16/HPV-18-positive specimens had corresponding cytology or histology results; 25 (65.8%) had high-grade dysplasia. E6 protein was detected in 3/25 specimens from men with high-grade anal dysplasia (12% sensitivity) and 0/13 specimens from men without high-grade dysplasia (100% specificity).

Conclusions

In HIV-positive men, HPV-16/HPV-18 E6 protein detection was highly specific, but not sensitive for detecting high-grade anal dysplasia. E6 protein may be informative for risk stratification to identify high-grade anal lesions that are more likely to progress to cancer or to recur after treatment. A larger study including follow-up of E6 positive high-grade anal dysplasia may be warranted.
HIGH EFFICACY OF COLPOSCOPIC-GUIDED LASER-SKINNING COLPECTOMY (COLASCO) FOR THE TREATMENT OF HIGH-GRADE VAIN AND MICROINVASIVE CANCER OF THE VAGINA

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Background and Aims

Treatment of extended VaIN 3 is a challenge because conservative/destructive management may miss invasive cancer while surgery may cause unnecessary mutilation. CoLaSCo is a CO2-laser procedure to excise the vaginal epithelium with a depth of 2-3 mm. This treatment is an alternative to radical methods like irradiation or vaginectomy.

Methods

We undertook a retrospective analysis of the incidence of complications and effectiveness of laser–skinning colpectomy among 47 patients with VIN 3 lesions covering 20-100% of the vaginal surface, treated between Jan 2014 and Jun 2017.

Results

The overall rate of perioperative complications was low. The mean blood loss was less than 50 ml. One patient was exposed to vaginal vault perforation without any harm to neighboring structures (2.12%). The final histologic specimen showed micro- or early vaginal cancer in 8 cases (17%). During 6-48 months follow-up stenosis and shortening of the vagina occurred in 4 (8.51%) of patients and 11 (23.4%) developed recurrent VaIN 2-3, mainly small lesions. 2 patients developed invasive cancer of the vagina (8.33%).

Conclusions

Colposcopic-guided laser-skinning colpectomy had no serious adverse effects and is likely to minimize the morbidity rate. This method appears to be an alternative conservative approach to radical surgery in the detection of microinvasive cancers and management of extended VaIN3 with a high risk of progression.
Background and Aims

Usual VIN is a vulvar lesion associated with human papillomavirus infection. The classic treatment is surgery, but it has a high rate of recurrences and morbidity. Less aggressive therapies are currently being sought to improve these outcomes. Imiquimod is a topical administration drug which has demonstrated a high effectiveness and low morbidity.

The objective of the study is to analyze the efficacy of imiquimod in the treatment of VIN (complete/partial response), to describe the adverse effects and need to discontinue treatment.

Methods

A retrospective study was conducted with women visited at the Gynecology Department, Hospital Universitari de Bellvitge (Hospitalet de Llobregat, Barcelona, Spain) from March 2011 to August 2018. Patients had histological diagnosis of usual VIN and were treated with imiquimod. Ten cases were included.

Results

Mean age was 48.4 ± 12.9 years, (median 46.5 years, range 28 - 81 years). Mean follow-up was 34.9 ± 23.52 months (median 29 months, range 13-72 months).

Complete response was observed in 60% of the cases, partial response in 30%, and no response in 10%. Two cases (20%) required surgery.

Seven patients showed side effects (70%): three (30%) had burning and three (30%) had pain. Erythema was observed in four cases (40%), erosion in two (20%) and edema in another patient (10%). Three patients (30%) had no adverse effects. The treatment was discontinued in 5 cases (50%).

Conclusions

Imiquimod is a good treatment option for usual VIN, despite the high frequency of side effects.
Background and Aims

The incidence of HPV-induced vulvar intraepithelial neoplasia (VIN) is increasing especially in younger patients. The aim of the study was to evaluate various treatment modalities for VIN for recurrence and possible risk factors influencing the outcome.

Methods

In a retrospective single center setting, data were collected from 80 women with the initial diagnosis of high-grade VIN at Hannover Medical School, Hannover, Germany, between 2005 - 2010. Demographic and clinical characteristics of the patients were collected. Different treatment modalities such as CO2 laser vaporization, excision with cold knife or the combination of both were evaluated.

Results

Mean age at first diagnosis was 47.3 years old, with the majority being 30 - 54 years old. The most affected region was the posterior fourchette with 35%. Nearly 50% of the patients presented with multifocal VIN. 82.4% were positive for high-risk HPV, especially type 16 and 18. Risk factors present were immunosuppression in 27.5% and smoking in 48.8%. 62.5% were treated with laser vaporization, 32.5% with excision and 5% with both modalities. Overall, 56.3% experienced a relapse/persistence, and 36.2% thereof were re-treated within 6 months after initial therapy. Patients treated with cold knife suffered a relapse in 69.2%, in comparison to laser vaporization with 48%. Factors influencing the outcome were positive margins after surgical excision and multifocality of the VIN lesions.

Conclusions

Despite modern therapy, the rate of relapse in VIN remains high. Therefore, careful follow-up is necessary. Additionally, a high coverage rate of immunization against HPV might reduce the appearance of VIN in the next decades.
Within the past two decades, a significant increase in the incidence rate of HPV related invasive vulvar carcinomas (IVC) in younger women was observed. The aim of this study was to identify the differences in prognosis of HPV related IVC in comparison to the HPV negative tumors.

Methods

In the present analysis 135 patients, diagnosed with IVC at the Medical University of Vienna between 1995 – 2012, were included in this trial. HPV-DNA detection was done by PCR using SPF-10 broad-spectrum primers and genotyping by reverse hybridization line probe assay (LiPA25). Clinico-pathological features and disease free (DFS) - and overall survival (OS) were calculated with respect to HPV status.

Results

30/135 (22.2%) patients were diagnosed with HPV- positive IVC. HPV 16 was the dominant HPV–type (75%), followed by HPV 31 (6%) and HPV 33 (3%). Patients with HPV– positive IVC were significantly younger (p<0.001). The mean DFS of HPV positive patients was 30 (6-65) months compared to 9 (4-30) months, the OS 72 (17-119) vs. 16 (7-67) months, respectively (p<0.002).

Conclusions

HPV–positive vulvar cancers occur at an earlier age and the prognosis is favorable when compared to HPV–negative tumors.
Background and Aims

To investigate the efficacy and side effects for fractional CO2 laser in the treatment of vulvar lichen sclerosus (VLS)

Methods

42 patients with VLS symptoms were enrolled prospectively from August 2015 to February 2017 in Peking University People's Hospital. VLS lesions was treated with fractional CO2 laser (SmartXide2; DEKA Laser, Florence, Italy), a total of 3 ~ 5 times, each time per-month. Visual analogue scale (VAS) was assessed the degree of vulvar pruritus, skin chapping, dyspareunia before and after treatment. After the treatment, satisfaction survey was done.

Results

The rate improvement of VLS symptoms was 90.47% (38/42) with fractional CO2 laser (P < 0.001). The pruritus score of vulva (6.75±1.79 vs. 1.78±1.36) were significantly lower than that before treatment (P < 0.05). The dyspareunia score (4.88±2.79 vs.2.15±1.29, P < 0.05) were improved significantly at the third after treatment one month. After treatment 24 h, there were 4 cases with mild pain, 6 cases with local mild hyperemia, 4 cases with mild swelling. No adverse events due to fractional CO2 laser treatment occurred. During 3 ~ 12 months follow-up, 6 cases (14.28%) with the skin color from white to gray, 6 cases recovered sex from 13 cases. The overall satisfaction rate was 95.23% (40/42).

Conclusions

The fractional CO2 laser is effective, minimal injury and acceptable side effects for vulvar lichen sclerosus, and may be a new treatment for it.
INCIDENT HERPES SIMPLEX VIRUS TYPE 2 INFECTION INCREASES THE RISK OF SUBSEQUENT EPISODES OF BACTERIAL VAGINOSIS.

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Background and Aims

Herpes simplex virus type 2 (HSV-2) infected women have a higher prevalence of bacterial vaginosis (BV) compared to HSV-2-seronegative women.

Methods

To explore the temporal association between these conditions, we evaluated the frequency of BV episodes before and after HSV-2 acquisition in a prospective study of 406 HSV-2/HIV-1-seronegative Kenyan women, of whom 164 acquired HSV-2.

Results

Incident HSV-2 was associated with increased likelihood of BV (adjusted OR, 1.28; 95% CI, 1.05-1.56; P = .01).

Conclusions

Our findings strengthen the evidence for a causal link between genital HSV-2 infection and disruption of the vaginal microbiota.
EVALUATION OF A RAPID MULTIPLEX ISOTHERMAL AMPLIFICATION REAL TIME PCR AMPFIRE HPV ASSAY ON FINE NEEDLE ASPIRATES AND OROPHARYNGEAL SWABS FROM PATIENTS WITH ORAL TUMORS
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6Atila Biosystems Inc., Research & Development, Mountain View- CA, USA

Background and Aims

To evaluate a novel rapid isothermal DNA amplification real time PCR Ampfire HPV assay on fine needle aspirates (FNA) of neck cervical lymph nodes and oropharyngeal swabs (OPS) from the base of the tongue and tonsils of patients with oral tumors.

Methods

FNA and OPS stored at -20°C were thawed and processed in an Ampfire HPV assay, an isothermal real time PCR with fluorescent detection (Atila Biosystems, Mountain View, California) and compared to the cobas HPV DNA assay (Roche Molecular Systems, Pleasanton, California). 73 patients were studied. FNA from 56 patients and OPS from 40 patients were compared. Tumor tissues were processed for p16 antigens by immunohistochemistry. Positive (PA), negative (NA) and overall agreements (OA) and kappa values were calculated.

Results

Comparing HPV results of Ampfire to cobas on FNA samples, %PA was 97.3, %NA 89.5 and %OA 94.6, (k 0.88). Comparing HPV results for OPS, %PA was 87.5, %NA 87.5, %OA 87.5, (k 0.66). Comparisons of agreements of the 2 HPV assays on FNA to p16 staining of tumors were similar: %PA 73.2-75.6, %NA 75.0 and %OA 73.1-75.5 (k 0.33-0.36). FNA samples were more predictive of p16 positive tumors than OPS with both HPV assays.

Conclusions

The Ampfire HPV assay performed on stored FNA and OPS from patients with oral tumors showed strong agreements with the cobas HPV DNA results yielding identical genotypes. Both DNA assays on FNA were equally predictive of p16 positive tumors. Ampfire did not require DNA extraction and yielded results within 1 hour.
Background and Aims

Detection of precancerous lesions forms the base of cervical screening, which has seen dramatic reductions in the incidence and mortality from HPV-induced cervical cancer. However, precancerous lesions for HPV-positive oropharyngeal cancer are not well described and there is limited research on a minimally invasive pap-test equivalent for oropharyngeal cancer. The aim of this study was to use brushings from conscious oropharyngeal cancer patients to investigate the detection of HPV 16, and cytological abnormalities.

Methods

Brushings were taken from the tumour site and/or an adjacent site (eg. Contralateral tonsil). p16 results were provided in pathology reports. A liquid based cytology preparation was made and a qPCR for the detection of HPV 16 performed on all specimens. On HPV 16 DNA positive specimens, the viral load per copy of human beta-globin was calculated and RNA extracted in order to detect transcriptionally active virus.

Results

Seventy seven brushings were collected from 54 patients, of these 81% were p16 positive. The relative risk of HPV 16 DNA detection and abnormal cytology in brushings taken from an abnormal appearing site were 3.0 (95% CI: 1.4-6.3) and 4.0 (95% CI: 1.5-10.3) times greater than the risk from a normal brushing site. Cellular changes comparable to cervical precancerous lesions were present in 27 samples. All of the eight samples showing a continuum of dysplastic change were from p16 positive patients.

Conclusions

These results show the detection of viral DNA and cytological abnormalities is possible in brushings from conscious patients. The cellular changes comparable to cervical precancerous lesions warrant further investigation.
DETECTION AND PREVALENCE OF HUMAN PAPILLOMAVIRUS IN LARYNGEAL SQUAMOUS CELL CARCINOMA IN AZERBAIJAN POPULATION
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Background and Aims

There is enough evidence for the carcinogenicity of HPV₁₆ type in the head and neck cancers. This study aimed to address key information gaps of the prevalence of HPV infection in laryngeal squamous cell carcinoma (LSCC) in Azerbaijan population.

Methods

50 LSCC pretreatment FFPE biopsy tumor materials, 10 cervical cancer FFPE samples and 38 fresh pretreatment LSCC tumor materials were analyzed using RT-PCR tecnology and Anyplex II HPV28 genotyping assay. The FFPE tumor material with HPV-positive history from cervical cancer was as control in this study.

Results

DNA extraction from FFPE and fresh samples was successful for all 98 tumor materials. The results of HPV genotyping of cervical cancer patients (n=10) with Anyplex II HPV28 assay detected 8 HPV₁₆-positive cancers, 1 samples with HPV18-positive and 1 cancer material with HPV₁₆+HPV₁₈+HPV₅₈. It was expected results, because Pap smear method already validated HPV-positive history in these patients. Basing this we expect to get true information about HPV-related LSCC. Anyplex II HPV28 genotyping assay was detected only one HPV-positive sample of 88 LSCC: it was low-risk cancer-related HPV₅₄ subtype in 47 age’s patient with 20 years tobacco and alcohol consumption history. High-risk cancer-related HPV₁₆ and HPV₁₈ subtypes have no detected in analysis patients.

Conclusions

Thus, we suggested that PCR techniques and Anyplex II HPV28 genotyping assay available for detection HPVs in LSCC. Our results support us to believe that Azerbaijan belong to HPV low-incidence geographic region of laryngeal squamous cell carcinoma patients, but large scale population based studies are needed to confirm our findings.
P16 ALONE IS INSUFFICIENT TO USE FOR RISK STRATIFICATION IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA IN JAPAN
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Background and Aims

Oropharyngeal squamous cell carcinoma (OPSCC) was traditionally associated with smoking and alcohol consumption. Recently, however, human papillomavirus (HPV) has been recognised as another primary cause of OPSCC. The incidence of OPSCC has been increasing in the United States and Western Europe, as also in Japan. The 8th edition of the AJCC/UICC TNM staging came into effect for use with HPV-mediated OPSCC in 2017. Immunohistochemical analysis (IHC) for p16 overexpression is used to classify HPV-mediated OPSCC in the 8th edition. However, due to other genetic perturbations, several patients overexpress p16 without any relation to HPV. Moreover, the prognosis for p16 positive, HPV negative OPSCC remains unclear.

Methods

We retrospectively analyzed 195 patients with OPSCC treated at Hokkaido University Hospital, Sapporo, Japan between 1998 and 2015. p16 IHC and HPV-PCR were performed on tumor tissues.

Results

Of the 195 OPSCC patients, 111 (57%) were p16 positive, and 84 (43%) were p16 negative. Of the 111 p16 positive cases, 20 (18%) were HPV-DNA negative. Smoking status was significantly frequent among p16 positive, HPV-DNA negative patients as compared with p16 positive, HPV-DNA positive. The 3-year overall survival rate was significantly lower in the p16-positive, HPV-DNA negative patients as compared with p16 positive, HPV-DNA positive (60.0% vs 90.1%, p<0.01).

Conclusions

Outcomes for p16 positive, HPV-DNA negative OPSCC are significantly different from p16 positive, HPV-DNA positive. p16 IHC alone is insufficient to use for risk stratification in OPSCC.
Background and Aims

Oral cancer is an important health problem in South East Asia, several parts of Europe and Africa. Though tobacco and alcohol are the important causative agent, Human Papilloma Virus (HPV) infection is also attributed in the carcinogenesis of oral and oropharyngeal cancer. However information on the prevalence of HPV virus in oral cancers from India is sparse. The objective of the study is to identify the frequency of HPV infection in oral cancer and its correlation to p16\textsuperscript{INK4A} expression and to assess its impact on treatment response and survival.

Methods

A total of 201 paraffin embedded tissue blocks of oral squamous cell carcinoma (SCC) patients treated at Regional Cancer Centre, Thiruvananthapuram, India during the period of 2009-2011 were retrieved. HPV DNA was isolated from these tissue blocks by Polymerase chain reaction and expression of p16\textsuperscript{INK4A} was analyzed by immunohistochemical method. Survival curves were obtained by using the Kaplan-Meier method and were compared with log rank test.

Results

The frequency of HPV 16 in oral SCC patients in the present study was 6.6% and all the HPV positive cancers were carcinoma tongue. All HPV positive cases showed intense p16\textsuperscript{INK4A} expression and the survival was better.

Conclusions

In future the expression of p16\textsuperscript{INK4A} and HPV status will be a good marker in decision making for oral cancer management.
FREQUENCY OF HUMAN PAPILLOMA VIRUS INFECTION IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA AND ITS CLINICAL SIGNIFICANCE
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Background and Aims

The incidence of Oropharyngeal Squamous Cell Carcinoma [OPSCC] in less developed countries are low compared to developed countries. Recently there is an increase in OPSCC among younger age group of patients without tobacco and/or alcohol use, which could be due to Human Papilloma Virus [HPV] infection. Several studies have reported a favourable outcome in HPV positive tumour compared to HPV negative tumour. However this information from less developed country like India is sparse. The objective of this study is to identify the frequency of HPV infection in Oropharyngeal Squamous Cell Carcinoma and its correlation to P16INK4A expression and to study the impact on treatment outcome

Methods

One hundred paraffin embedded tissue blocks of histologically proven OPSCC patients who had treatment at Regional Cancer Centre [RCC], Trivandrum, India during the period January 2010 to December 2012 were included in this study. The demographic, clinical, treatment and follow up information were collected in a structured preforma. HPV DNA was isolated from the paraffin embedded tissue blocks by Polymerase Chain Reaction [PCR]. Expression of p16INK4A was analyzed by immunohistochemical [IHC] method. All statistical analysis were performed using STATA statistical software, version 14 (StataCorp, College Station, TX)

Results

The prevalence of HPV infection in the present study was 31%, with highest prevalence in tonsillar subsite (40%). The five year survival for combined HPV DNA and P16 positive was 96%. HPV positive patients had 61% decreased risk of death compared to HPV negative patients.

Conclusions

HPV status will be a good marker in taking decision on treatment planning in oropharyngeal squamous cell carcinoma patients.
Background and Aims

In Pakistan oral cancer is the second leading malignancy after breast cancer, attributed to extensive use of several precarious chewable tobacco formulations. The human papillomavirus (HPV), as proven, plays a crucial role in OSCC, so this study was designed to determine the association between OSCC and oncogenic strains of HPV (16/18) in this population.

Methods

DNA from oral rinse of 300 subjects was taken. The subjects included 100 cases with OSCC and 200 controls. Samples were analyzed by both conventional and real time PCR using "HPV consensus Gp5+/Gp6+ and HPV 16, 18 specific primers".

Results

Out of 300 persons, 74/300 (25%) were found to be infected with HPV: “46/100(46%) from cases and 28/200(14%) from controls”. The distribution was: HPV16, 6/300 (8%): 4/100 (9%) from OSCC group and 2/200 (8%) from controls while HPV 18 was 9/300(12%): 5/100(11%) from cases and 4/200(16%) from controls. Out of 300 subjects, 26(35%) were infected by “both HPV 16/18 (23(50%) from cases and 3(12%) from controls”. Persons who were infected with HPV 16&18 had higher chances to develop OSCC as compared to those who didn't have HPV 16/18 (AOR: 21.4, 95% CI: 5.73 – 80.8).
Conclusions

The exposure to high risk strains of Human papilloma virus (16/18) in combination can be fabricotor of trouble ($p < 0.001$, Adjusted odds ratio; 21.42) in OSCC.
A STUDY OF P16 IMMUNOHISTOCHEMISTRY AND HPV 16/18 DNA DETECTION BY CHROMOGENIC IN SITU HYBRIDIZATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA

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Background and Aims

About 15-20% of Head and Neck Squamous Cell Carcinomas (HNSCC) are positive for HPV. Among these, 90-95% are positive for HR-HPV 16/18. Most of HPV associated HNSCC are located in Oropharynx. The HPV related tumours have a better prognosis than HPV negative HNSCC and are characterised by p16 oncoprotein overexpression in tumour cells. The aim of the study was to evaluate p16 overexpression and its correlation with HPV 16/18 DNA detection and with various clinicopathological features in HNSCC in a bid to determine whether p16 can be used as a surrogate marker for HPV.

Methods

100 consecutive patients with HNSCC were included. Immunohistochemistry (IHC) for p16 was performed. HPV 16/18 DNA was evaluated using chromogenic in situ hybridization (CISH).

Results

Out of 100 HNSCC cases, 55% were located in oral cavity, 28% in oropharynx and 16% in larynx. 41% cases showed p16 overexpression while HPV 16/18 DNA was detected in 20% cases. The association between p16 expression and HPV 16/18 was significant (p< 0.001). Oropharyngeal tumours most frequently expressed p16 and showed a significant association with both p16 overexpression (p=0.046) and presence of HPV 16/18 DNA (p=0.014). The sensitivity of p16 overexpression was 95% and overall specificity was 72.5%. The strength of agreement between HPV 16/18 DNA detection and p16 overexpression was moderate (k=0.484). No correlation was found between p16 overexpression and various clinicopathological features like tumour size, lymph node involvement etc.

Conclusions

The present study supports the use of p16 IHC as a surrogate biomarker for HPV detection.
HIGH-RISK HUMAN PAPILLOMAVIRUS DETECTION IN OROPHARYNGEAL CANCERS: COMPARISON OF SALIVA SAMPLING METHODS
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Background and Aims

Human papillomavirus (HPV), a virus central to the etiology of cervical cancer, is also detected in up to 70% of oropharyngeal cancers (OPC). Accumulating evidence has suggested the utility of salivary oral rinse as a diagnostic fluid to detect HPV DNA, but there are many methods for collecting saliva.

Methods

Salivary oral rinse and unstimulated whole mouth saliva (UWMS) samples were collected from 45 patients who have been diagnosed with OPC tumours. We compared the sensitivity of detecting HPV-16 in these two saliva types.

Results

For saliva samples collected by UWMS and salivary oral rinse samples from 45 patients with OPC, a positive correlation was observed between the relative amounts in samples collected by the two methods for HPV-16 E2 DNA ($r = 0.95, p < 0.0001$), and also for HPV16 E6/7 DNA ($r = 0.93, p < 0.0001$). Genotypes of detected HPV were concordant between the two sample methods. There was a significant correlation between the two sample methods in the ratio of HPV16 E2 DNA to HPV16 E6/7 DNA ($r = 0.46, p < 0.01$). In line with previous studies, for the majority of samples, the E2 to E6/7 ratio was consistent with the presence of HPV DNA derived from tissues with both episomal and integrated HPV16 DNA, suggesting that salivary HPV-16 could be used as a potential non-invasive biomarker to determine HPV status in OPC.

Conclusions

Detection of HPV in saliva samples collected by either method yielded comparable results, and showed good sensitivity for detection of HPV derived from OPC.
THE PREVALENCE OF HPV-16 IN AUSTRALIAN PATIENTS WITH ORAL POTENTIALLY MALIGNANT DISORDERS AND ORAL CANCER

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Background and Aims

The role of human papillomavirus type 16 (HPV-16) infection in oropharyngeal cancer (OPC) has widely been studied. However, the role of HPV16 in oral potentially malignant disorders (OPMD) and oral cancers (OC) have not been extensively investigated.

Methods

We compared the prevalence of HPV-16 in unstimulated whole mouth saliva (UWMS), salivary oral rinses, oral swab and tissue specimens from OPMD (n=83) and OC (n=105) patients. HPV-16 DNA was detected using nested PCR method. HPV-16 positivity in OC patients was carried out using p16INK4A immunohistochemistry (IHC) analysis.

Results

The inter-rater agreement between tumour p16INK4A expression and oral HPV-16 infection was considered as fair (κ = 0.361) in OC. In fact, p16INK4A-positive OC patients (n = 19), only 6 had detectable oral HPV-16 DNA, yielding a low sensitivity (31.6%, 95% CI: 15.36, 53.99). Both of the saliva sampling methods (UWMS and salivary oral rinses) gave similar HPV-16 results. The HPV-16 prevalence was higher in OC when compared with OPMD [6.7% (7/105) versus 3.6% (3/83), odd ratio (OR): 1.89, 95% confidence interval (CI): 0.47, 7.53]. Interestingly, current smokers were 5.90 (95% CI 0.51, 68.61) and 1.55 (95% CI 0.33, 7.33) times more likely to develop HPV-16 associated OPMD and OC respectively when compared to non-smokers.

Conclusions

These results suggest a possible association between smoking and oral HPV-16 infection in both OPMD and OC patients. Further studies with a larger cohort are warranted to confirm these findings.
Background and Aims

Limited information is available regarding the involvement of HPV in head and neck squamous cell carcinomas (HNSCC) in Romanian patients. We aimed to determine the overall proportion of HPV-positive HNSCC at different anatomical sites in patients of Northeastern Romania and the HPV type distribution.

Methods

One hundred ninety formalin-fixed paraffin-embedded tissue samples (99 oral cavity tumors, 28 oropharynx, 49 pharynx and 14 larynx/hypopharynx) were analyzed for HPV DNA and RNA using Luminex-based assays, and for overexpression of p16\(^{INK4a}\) (p16) by immunohistochemistry.

Results

Twenty-three out of the 190 (12.1%) cases were HPV DNA-positive, that comprise half of the oropharyngeal cases (14/28, 50.0%), and 9/162 (5.6%) of the non-oropharyngeal cases. HPV16 was the most frequent HPV type (20/23, 86.9%), followed by HPV18 (5/23, 21.7%) and HPV39 (1/23, 4.3%).
4.3%). Only two (2/190, 1.1%) HNSCC cases (one oropharyngeal and one hypopharyngeal) were HPV-driven, i.e. positive for both HPV DNA and RNA, both being negative for p16. Only one HPV DNA-positive oropharyngeal case tested positive for p16, but negative for HPV RNA.

**Conclusions**

In conclusion, only a small subset of Romanian HNSCC is HPV-driven.

Acknowledgments: "RGU is supported by the University of Medicine and Pharmacy Grigore T. Popa, Iasi, Romania (grant no. 30336 /28.12.2017)."
Background and Aims

Laryngeal cancer is the sixth most common cancer worldwide. In Hong Kong, larynx was the fourth most common site of head and neck cancers following nasopharynx, thyroid and oral cavity; and with an age-standardized incidence of 2.5 and 0.2 per 100,000 men and women, respectively.

The causal relationship between human papillomavirus (HPV) and Laryngeal squamous cell carcinoma (LSCC) remains controversial. Therefore, a retrospective cross-sectional study was conducted in a major otorhinolaryngology referral center in Hong Kong, to delineate the role of HPV in LSCC among Southern Chinese patients in Hong Kong.

Methods

Eighty-five Chinese patients with histology-confirmed LSCC diagnosed between 2005 and 2010 were examined for the status of HPV by PCR, and the expression of p16 and p53 by immunohistochemistry. The HPV, p16 and p53 findings were correlated with clinicopathological features, recurrence and 5-year survival.

Results

HPV DNA was detected in one patient (1.2%, 95% CI: 0.2-6.4%) who had glottic cancer and harbored HPV-6. Overexpression of p16 and p53 were detected in 11 (12.9%) and 47 (55.3%) cases, respectively. Recurrence occurred in 22.4% of patients at a median of 13 months. The 5-year overall survival and disease-specific survival were 55.7% and 72.4%, respectively. Overexpression of p16 or p53 was not associated with clinicopathological features, recurrence or overall survival.

Conclusions

HPV plays a limited role in laryngeal cancer in Hong Kong Southern Chinese. In contrast to oropharyngeal cancer, p16 cannot be used as a surrogate marker for oncogenic involvement of HPV and cannot predict survival in laryngeal cancer.
THE PREVALENCE AND DISTRIBUTION OF HPV TYPES IN NASAL INVERTED PAPILLOMA IN CHINESE HAN POPULATION
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Background and Aims

Human papillomavirus (HPV) was reported as a possible etiological agent for Nasal inverted papilloma (NIP). However, the prevalence of HPV types in NIP was not well known.

Methods

102 formalin-fixed paraffin-embedded NIP biopsy samples were obtained from patients and 20 samples were got from healthy controls. HPV DNA genotyping was achieved by a flow-through hybridization and gene-chip method and genotyping of 21 different HPV types. The incidences of HBV subtype infection in patients with NIP and its distribution across age, gender and stage were described.

Results

Patients with NIP had higher incidence of HPV infection (64.7%) compared with healthy control. The positive rate was higher in patients with advanced Krouse Stage and in patients more than 59 years old. HPV 11 was the mostly-seen type in patients at Krouse Stage T1 and T2, and HPV 58 was found in 45.0% of patients with T3 NIP. There tends to be a difference in HPV infection rate between patients with NIP only and patients with NIP and dysplasia with no statistical significance. The most common HPV types in patients with NIP and dysplasia were HPV11 (40.8%) and HPV58 (27.6%) respectively.

Conclusions

The prevalence of HPV in NIP was high (64.7%) and HPV infection was more seen in older patients and patients with advanced Krouse Stage. Different HPV type distribution was found across Krouse Stage and the degree of dysplasia.
HIGH-FREQUENCY ULTRASOUND IN THE DIAGNOSIS OF GENITAL WARTS

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Background and Aims

To optimize the approaches to the noninvasive diagnosis and differential diagnosis of genital warts, to reduce the number of relapses of genital warts

Methods

To assess the informativeness of this method were examined 69 women without visible genital warts
29 – with genital warts. In 7 patients from group of patients without visible signs of GW found the echo-signs of genital warts, 5 of them the diagnosis was confirmed by vulvoscopy after the test with acetic acid. In 3 women from a group of patients with the GW of the echo-signs of genital warts is not identified.

Results

Diagnostic sensitivity was 94%. False-positive result was noted in 6% of cases. The specificity of the method was 100%. There has not been a single case of a false-negative result. Of the 31 patients with detected echoes-signs of GW, 15 the diagnosis was verified histologically.

Conclusions

In the diagnosis of GW HF ultrasound is used to visualize the complex changes of the internal structure of the skin and mucous membranes, characteristic only for this disease, to detect subclinical lesions that are invisible to the naked eye, to evaluate the depth of lesions, which allows further to hold a rational destruction and to reduce the number of relapses.
Background and Aims

We aimed to compare the efficacy of imiquimod (IMIQ) or podophyllotoxin (PDX) cream to treat anogenital warts and to establish whether quadrivalent HPV vaccine (Gardasil®, Merck) increases wart clearance or prevents recurrence.

Methods

A randomised, controlled, multi-centre, partially-blinded factorial trial in patients with new or recurrent anogenital warts: not treated within 3 months; no prior qHPV-vaccine; attending any of 22 sexual health clinics. Open, equal randomisation, stratified by gender, previous warts, HIV, to IMIQ 5% (16W), or PDX 0.15% cream (4W, up to 16W if warts persist). Simultaneous blinded randomisation to Gardasil® or saline control (0-2-6 months). Cryotherapy permitted after W4 at investigator-discretion. Composite primary outcome of wart clearance at 16W and remaining clear to 48W; analysis by logistic regression with multiple imputation for missing follow-up values. Planned sample size reduced from n=1000 to n=500 because of recruitment delays.

Results

503 participants enrolled; mean age 31 years; 66% male (20% of males MSM); 50% previous warts; 2% known HIV+. Adjusted OR(95%CI) for IMIQ relative to PDX 0.81(0.54,1.23); vaccine relative to placebo 1.46(0.97,2.20). aOR for primary outcome components (same comparators) of wart-free at W16 0.77(0.52,1.14) and 1.30(0.89,1.91) and remaining wart-free at 48W (in those wart-free at W16) 0.98(0.54,1.78) and 1.39(0.73,2.63) respectively.

Conclusions

Though the effect of vaccine was not statistically significant, the odds of clearance at 16W+48W (primary outcome) were 46% higher with vaccine, consistent with the effects seen in the component outcomes, wart-free at 16W, and 48W. IMIQ and PDX had similar efficacy; no evidence of a lower recurrence with IMIQ.
A PROSPECTIVE STUDY OF HUMAN PAPILLOMAVIRUS INFECTION IN MALE PATIENTS WITH ANOGENITAL WARTS AND MATCHED HEALTHY CONTROLS

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Background and Aims

To determine the distribution of HPVs in anogenital warts (AGW) and corresponding hair follicles and to study the dynamics/persistence of HPV infection during/after treatment, in order to improve understanding of mechanisms involved in recurrence of AGW.

Methods

Initially, AGW tissues and at least 5 hairs were obtained from 3 anogenital sites (scrotal, pubic and perianal) and eyebrows of each of the 32 male patients, treated according to international standards. Additionally, 5 hairs per case-matched sampling sites were obtained from each of the 32 age-matched healthy sexually active male volunteers, with no history of AGW. Both groups were sampled every 3 months for up to 24 months. Following DNA extraction, samples' integrity was verified by beta-globin real-time PCR (RT-PCR) and tested for the presence of HPV using HPV6/11 RT-PCR and GP5+/6+/68 PCR.

Results

All initial AGW harbored single HPV infections, with HPV6 (88.5%), HPV11 (8.6%) and HPV40 (2.9%). In 78.1% of patients, at least 1 initial pool of hairs was HPV-positive, always for the same HPV as the corresponding AGW, and no mixed infections were detected. Nevertheless that after removal of initial AGWs, follow-up hairs were HPV-negative in 53.1% of patients, HPV-positive hairs persisted for up to 24 months in other patients. In 31.3% of patients, AGW reoccurred even after no AGW and HPV-positive hairs were detected for at least two months. No HPV-DNA was detected in samples of the control group.

Conclusions

Hair follicles are most probably not involved in AGW persistence/recurrence, warranting further research of other contributing factors.
Background and Aims

Giant condyloma acuminatum (GCA), also known as Bushke-Lowenstein tumor, is a locally aggressive and destructive tumor of the anogenital and perianal regions, thought to be induced by human papillomavirus (HPV) infections. While anogenital warts in patients with human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) is common, cases of GCA in HIV/AIDS patients are rarely reported, hence decision-making regarding its management can be complex.

Methods

We report a case of a 43-year-old woman with AIDS, who presented to us with an extensive GCA of the vulva for several years. It was painful and bled on prolonged sitting. Physical examination revealed multiple verrucous lesions coalescing on bilateral labia majora and minora, extending to the clitoris, inguinal folds and the perianal region.

Results

She was successfully treated with staged carbon dioxide laser debulking, antiretroviral therapy and HPV vaccine. After 2 years of treatment, all her warts were cleared. On her 7-month follow-up, she remained disease-free, and her CD4 count was 228.

Conclusions

Many different therapeutic options, alone or in combination, have been reported for the treatment of GCA, with varying success. A wide local excision is the treatment of choice, but has significant morbidity, especially in AIDS patients. Other treatment modalities include radiation therapy, topical and intraläsional chemotherapy, systemic interferon α-2b or interleukin-2, carbon dioxide laser, and topical therapies including imiquimod and podophyllin. We present a novel treatment regime and propose this therapeutic combination of staged carbon dioxide laser debulking, antiretroviral therapy, oral acitretin and HPV vaccine for treatment of GCA in patients with HIV/AIDS.
9-VALENT HPV VACCINE EFFICACY, IMMUNOGENICITY, AND SAFETY IN ASIAN CLINICAL TRIAL PARTICIPANTS


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Background and Aims

The 9-valent HPV (9vHPV) vaccine extends protection to 5 oncogenic types (31/33/45/52/58) versus quadrivalent HPV (qHPV; 6/11/16/18) vaccine. Burden of HPV52/58-related cervical disease by country was estimated based on data from the HPV Information Centre. The epidemiological data indicated HPV52/58 occur in higher proportions of cervical cancer and precursor lesions in some Asian countries versus the US or Australia. Contribution of HPV52/58 to cervical cancer in China, Korea, Malaysia, Singapore, and Thailand was higher than in the US. Use of 9vHPV over qHPV vaccine could increase protection against cervical cancer by 14.4%–38.6% in these countries versus 16.3% in the US.

Methods

Efficacy, immunogenicity, and safety for 9vHPV vaccine was assessed in Asian participants (from Hong Kong, India, Japan, South Korea, Taiwan, and Thailand) from (1) a randomized, double-blinded, qHPV vaccine-controlled efficacy trial in women (aged 16–26 years; NCT00543543); and (2) an immunogenicity trial that included girls/boys (aged 9–15 years; NCT00943722).

Results

Among Asian trial participants, 9vHPV vaccine efficacy against HPV31/33/45/52/58-related persistent infection was 90.4%–100% across individual countries. Among all Asian participants, efficacy was 91.3% (95% CI: 74.5–97.7) and 100% (95% CI: 86.3–100) against HPV52- and HPV58-related persistent infection, respectively. Robust antibody responses to all vaccine types were observed (>97% seroconversion at Month 7).

Conclusions

The 9vHPV vaccine is efficacious, immunogenic and well-tolerated in Asian participants. Together with epidemiological data, results indicate the 9vHPV vaccine will substantially extend protection over existing vaccines in Asian countries. Findings support implementing 9vHPV vaccination in Asia.
OUTCOME AFTER LOOP ELECTROSURGICAL EXCISION PROCEDURE OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) 3 DEVELOPED IN HPV-VACCINATED WOMEN

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Background and Aims

This retrospective study was conducted to compare outcome after loop electrosurgical excision procedure (LEEP) of cervical intraepithelial neoplasia (CIN) 3 developed in human papillomavirus (HPV)-vaccinated women with outcome after LEEP of CIN3 detected in non-vaccinated women.

Methods

Between January 2010 and December 2015, 808 women younger than 45 years-old underwent LEEP for CIN3 and followed. 93 women (11.5%) were diagnosed with CIN3 subsequent to vaccination with the quadrivalent or bivalent HPV-vaccine (pre-vaccination group), and 249 (30.8%) were followed without vaccination before and after LEEP (non-vaccination group). The remaining 466 women (57.7%) were vaccinated after LEEP. Follow-up after LEEP was performed every 6-months within the first 2 years, and yearly thereafter.

Results

Irrespective of vaccination, 78 patients (9.7%) developed recurrence. 8/93 patients (8.6%) in pre-vaccination group developed recurrence, whereas 33/249 (13.3%) in non-vaccination group did (P = 0.01). After LEEP, 5/93 patients (5.4%) in pre-vaccination group showed persistent HPV infection of the same types as before, while 21/249 (8.4%) in non-vaccination group did (P = 0.03). 4/93 patients (4.3%) in pre-vaccination group were newly infected with HPV of different types after LEEP, while 17/249 (6.8%) in non-vaccination group were done (P = 0.03). Multivariate analysis showed that the risk of recurrence was higher for women who did not receive HPV-vaccination (HR = 3.102; 95% CI, 1.363-7.062; P < 0.01).

Conclusions

HPV-vaccination before diagnosis of CIN3 may prevent the recurrence after receiving LEEP for CIN3.
Background and Aims

HPV vaccination in the United States lags behind other developed countries. Educational interventions are primarily directed at patients and parents rather than healthcare providers despite evidence that provider recommendation is a key determinant of vaccine uptake. To summarize the available evidence, a systematic review of provider educational interventions was undertaken along with a review of available resources from American organizations.

Methods

A systematic search was performed using PubMed, Web of Science and ERIC with MeSH terms “education”, “HPV”, “vaccine”, and “attitude”. Full text articles were obtained for studies that described the knowledge and attitudes of providers and/or impact of educational interventions. Data extraction was performed by two independent reviewers. Websites of American organizations with an interest in HPV vaccination were manually searched for provider resources.

Results

931 publications were identified, and 56 articles were fully reviewed with 19 ultimately included. Providers’ knowledge on HPV was generally low with a correspondingly low vaccine recommendation rate. Provider knowledge and high-quality recommendation were associated with increased odds of vaccine series initiation (9-fold) and completion (3-fold). Two randomized trials assessing provider-specific education with complimentary interventions (e.g., individualized feedback) demonstrated increased vaccine series initiation and completion. Most American organizations have provider-specific resources; however, the effectiveness of these materials has not been established.

Conclusions

HPV knowledge among providers remains low and resources from national organizations have not been validated. Coordinated efforts to create and evaluate shared provider-specific educational resources has the potential to improve vaccine uptake in countries which, similar to the United States, also rely on provider recommendations.
EFFICACY, IMMUNOGENICITY AND SAFETY OF THE QUADRIVALENT HPV L1 VIRUS-LIKE PARTICLE (VLP) VACCINE IN 16- TO 26-YEAR-OLD JAPANESE MEN

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Background and Aims

The quadrivalent HPV L1 VLP (qHPV) vaccine protects against infection and disease related to HPV6/11/16/18. A Phase 3 efficacy, immunogenicity, and safety study of qHPV vaccine was conducted in Japanese men.

Methods

In this randomized, double-blind study (NCT01862874), 16–26-year-old Japanese men received 3 doses of qHPV vaccine or placebo (Day 1, Month 2, Month 6). Serum was collected 4 weeks post-Dose 3 for analysis of vaccine HPV type antibody responses. Swab samples were collected for analyses of persistent infection. Primary efficacy and immunogenicity analyses were based on per-protocol populations that included participants who received all 3 vaccinations and were HPV-naïve prior to Day 1 through 4 weeks post-Dose 3 for the relevant type. Vaccine-related serious adverse events (SAEs) were collected throughout the study.

Results

A total of 1124 Japanese men were randomized and 1062 completed the 3-dose vaccination series. Anti-HPV6/11/16/18 responses in the qHPV vaccine group were markedly induced at Month 7; >97% of participants who received qHPV vaccine seroconverted to each vaccine HPV type at Month 7. Efficacy of qHPV vaccine against HPV6/11/16/18-related 6-month persistent infection was 83.3% (95% CI: 24.9, 98.2). There were no vaccine-related SAEs or discontinuations due to an adverse event in the qHPV vaccine group.

Conclusions

The qHPV vaccine was highly immunogenic and efficacious in preventing HPV6/11/16/18-/related persistent infection in Japanese men. The qHPV vaccine was generally well tolerated in this population.
9-VALENT HPV VACCINE EFFICACY, IMMUNOGENICITY, AND SAFETY IN LATIN AMERICAN CLINICAL TRIAL PARTICIPANTS

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Background and Aims

The 9-valent HPV (9vHPV; HPV6/11/16/18/31/33/45/52/58) vaccine expands potential cervical cancer protection to ~90%, versus ~70% with quadrivalent HPV (qHPV; HPV6/11/16/18) vaccine. We assessed 9vHPV vaccine efficacy, including against cervical cytological abnormalities and procedures, immunogenicity and safety in Latin American participants from international trials.

Methods

Participants were from (1) a randomized, double-blinded, qHPV vaccine-controlled efficacy trial in young women (aged 16–26 years; NCT00543543); and (2) an immunogenicity trial that included girls and boys (aged 9–15 years; NCT00943722). Participants (N=5312) received 3 vaccine doses (Day 1, Month 2, Month 6). In the efficacy trial, gynecological swabs were collected for cytological and HPV DNA testing. HPV antibodies were assessed in serum samples in both trials.

Results

Among Latin American young women, the 9vHPV vaccine demonstrated 92.3% (95% CI: 54.4, 99.6) efficacy against HPV31/33/45/52/58-related high-grade cervical, vulvar, and vaginal dysplasia. Efficacy against HPV31/33/45/52/58-related cervical cytological abnormalities (ASC-US positive for high-risk HPV types or worse) and procedures (biopsy or definitive therapy) was 93.0% (95% CI: 88.2, 96.1) and 94.3% (95% CI: 87.2, 97.6), respectively. Most (>99%) 9vHPV vaccine recipients seroconverted for all 9 HPV types at Month 7, with higher antibody titers in girls/boys compared with young women. Persistent immune responses were observed over 5 years. The most common adverse events were injection-site–related and of mild to moderate intensity.

Conclusions

The 9vHPV vaccine is efficacious, immunogenic, and well tolerated in Latin American participants. These data support 9vHPV vaccination programs in Latin America, a region with substantial cervical cancer burden.
DURABILITY OF CROSS-PROTECTION AFFORDED BY THE PROPHYLACTIC BIVALENT HPV VACCINE: DATA ANALYSIS FROM THE COSTA RICA HPV VACCINE TRIAL (CVT)

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7International Agency for Research on Cancer, Early Detection and Prevention Section, Lyon, France

Background and Aims

CVT previously demonstrated that the bivalent HPV16/18 vaccine protects against non-vaccine HPV types (HPV31/33/45) for at least seven years after vaccination. Here, we aimed to determine the extent of cross-protection provided by the vaccine 11 years post-vaccination.

Methods

Current analyses were restricted to women who had cervical samples tested at both 9 and 11 years. Samples from 956 women vaccinated as part of CVT and a set of 1107 age-matched, non-randomized, unvaccinated women were tested for the presence of HPV DNA using TypeSeqer next-generation sequencing technology. We defined the outcome as prevalent HPV infections at year 9 and/or 11. Vaccine efficacy (VE) was calculated by comparing HPV prevalence between women who received three doses of the HPV vaccine and unvaccinated women.

Results

With median time since vaccination being 11.2 years, significant cross-protection was observed against prevalent HPV31/33/45 infections (VE=60.5%, 95%CI: 45 to 72%). Cross-protection was more robust for HPV31 (VE=69.6%, 95%CI: 48 to 83%) and HPV45 (VE=67.2%, 95%CI: 43 to 82%) than HPV33 (VE=31.6%, 95%CI: -35 to 67%). We found the VE reported here to be similar to the HPV31/33/45 VE observed at year 4 (VE=59.3%, 95%CI: 47 to 69%), and at year 7 (VE=62.0%, 95%CI: 46 to 74%). Acquisition of non-protected HPV types was similar between vaccinated and unvaccinated women (~25%), i.e. difference in HPV prevalence by vaccination status was not attributable to differential genital HPV exposure.

VE against prevalent HPV infections 9/11 years post-vaccination.
Conclusions

Cross-protection afforded by the bivalent vaccine against HPV31/33/45 remained stable and was sustained after 11 years post-vaccination.

<table>
<thead>
<tr>
<th>HPV types</th>
<th>Vaccinated (3 doses)</th>
<th>Unvaccinated</th>
<th>Vaccine efficacy (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># with outcome/ # of women (%)</td>
<td># with outcome/ # of women (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>14/956 (1.5%)</td>
<td>70/1107 (6.3%)</td>
<td>76.8% (59.8% to 87.4%)</td>
<td>&lt;0.001</td>
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<tr>
<td>18</td>
<td>5/956 (0.5%)</td>
<td>46/1107 (4.2%)</td>
<td>87.4% (70.3% to 95.6%)</td>
<td>&lt;0.001</td>
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<tr>
<td>16/18</td>
<td>18/956 (1.9%)</td>
<td>112/1107 (10.1%)</td>
<td>81.4% (69.9% to 89.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>31</td>
<td>16/956 (1.7%)</td>
<td>61/1107 (5.5%)</td>
<td>69.6% (48.2% to 83.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>33</td>
<td>13/956 (1.4%)</td>
<td>22/1107 (2.0%)</td>
<td>31.6% (-35.3% to 66.5%)</td>
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</tr>
<tr>
<td>45</td>
<td>15/956 (1.6%)</td>
<td>53/1107 (4.8%)</td>
<td>67.2% (42.8% to 82.1%)</td>
<td>&lt;0.001</td>
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<tr>
<td>31/33/45</td>
<td>43/956 (4.5%)</td>
<td>126/1107 (11.4%)</td>
<td>60.5% (44.5% to 72.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>35</td>
<td>21/956 (2.2%)</td>
<td>28/1107 (2.5%)</td>
<td>13.2% (-53.1% to 51.3%)</td>
<td>0.67</td>
</tr>
<tr>
<td>39</td>
<td>38/956 (4.0%)</td>
<td>54/1107 (4.9%)</td>
<td>18.5% (-23.3% to 46.5%)</td>
<td>0.34</td>
</tr>
<tr>
<td>51</td>
<td>56/956 (5.9%)</td>
<td>62/1107 (5.6%)</td>
<td>-4.6% (-50.2% to 27.3%)</td>
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<tr>
<td>52</td>
<td>68/956 (7.1%)</td>
<td>68/1107 (6.1%)</td>
<td>-15.8% (-62.3% to 17.4%)</td>
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<tr>
<td>56</td>
<td>55/956 (5.8%)</td>
<td>43/1107 (3.9%)</td>
<td>-48.1% (-121.8% to 0.6%)</td>
<td>0.05</td>
</tr>
<tr>
<td>58</td>
<td>37/956 (3.9%)</td>
<td>61/1107 (5.5%)</td>
<td>29.8% (-5.4% to 53.7%)</td>
<td>0.10</td>
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<tr>
<td>59</td>
<td>49/956 (5.1%)</td>
<td>61/1107 (5.5%)</td>
<td>7.0% (-35.5% to 36.4%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Other oncogenic HPV</td>
<td>243/956 (25.4%)</td>
<td>273/1107 (24.7%)</td>
<td>-3.1% (-22.5% to 13.3%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Non-oncogenic HPV</td>
<td>505/956 (52.8%)</td>
<td>600/1107 (54.2%)</td>
<td>2.5% (-9.7% to 13.4%)</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Background and Aims

Human Papillomavirus (HPV) infection causes significant disease burden in China. Here we report a randomized, double-blind, placebo-controlled multicenter trial conducted in Chinese healthy women to assess the safety and efficacy of a quadrivalent HPV (types 6, 11, 16, 18) L1 virus-like–particle vaccine (Gardasil®) against persistent infection and genital diseases.

Methods

3006 participants aged 20 to 45 years were enrolled and randomized (1:1) to receive HPV vaccine or placebo at Day 1, Month 2 and 6. The efficacy was followed up till Month 78.

Results

0 and 7 cases of HPV 16/18-related CIN2/3, AIS or cervical cancer were observed among 1,265 and 1,237 participants in the vaccine and placebo groups, respectively, translating into an efficacy of 100%. The efficacy against HPV 6/11/16/18-related genital diseases or infection were: 1) 100% for CIN plus; 2) 91.0% (95%CI: 77.7, 97.2) for 12-month PI; 3) 91.8% for 12-month PI, CIN plus or EGLs. No EGLs case was observed. 926 (61.8%) and 856 (57.1%) participants reported AEs in the vaccine and placebo groups, respectively. Injection-site AEs were more frequent in the vaccine group (37.6% vs. 27.8%, p<0.001). Systemic AEs incidences were similar (51.4% vs. 50.1%). 38 (2.5%) and 43 (2.9%) participants reported SAEs in the vaccine and placebo groups, respectively. Incidences of congenital anomaly in infants and aborted fetuses were 2.3% (11/488) in vaccine group and 1.4% (6/444) in placebo group ( p=0.3371).

Conclusions

The quadrivalent HPV vaccine demonstrated good safety profile and high efficacy against persistent infection, any-grade and high-grade cervical precancerous lesions in Chinese healthy adult women.
A DOSE REDUCTION IMMUNOBRIDGING AND SAFETY STUDY OF TWO HUMAN PAPILLOMAVIRUS (HPV) VACCINES IN TANZANIAN GIRLS (DORIS): ENROLLMENT AND PROGRESS TO DATE

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Background and Aims

The DoRIS trial is evaluating whether a one-dose HPV vaccination regimen can induce comparable immune responses to two and three doses among Tanzanian girls. The enrollment process and progress to date are described.

Methods

This is a randomised open-label dose-reduction immunogenicity and safety trial in 930 HIV-negative Tanzanian girls aged 9-14y. Participants were enrolled into 6 study arms at a ratio of 1:1:1:1:1:1; with girls receiving 3, 2 or 1 doses of 2-valent (Cervarix®) or 9-valent HPV vaccine (Gardasil-9®; 155 per arm). Vaginal swabs were taken for HPV-DNA at enrollment. Participants will be followed up for 36m, with blood taken for immunogenicity at 6 timepoints.

Results

Parents of 5949 girls attending 54 schools in Mwanza were invited to school meetings to discuss the study. Of these, 1524 (26%) attended and most were interested in their daughters participating. 995 girls were screened and 930 enrolled. Preliminary HPV-DNA results on vaginal swabs suggest that HPV prevalence at enrollment was <2%. Reasons for screen-failure included withdrawal of consent before randomisation (n=10), significant medical findings (n=23), HIV-infection (n=8), refusal to consent/assent (n=5) and other reasons (n=19). Month 12 visits have commenced. To date, retention is high at 99%. 11 girls have left the study: 6 have withdrawn, 4 are lost to follow-up and 1 has died.

Conclusions
Parent attendance at school meetings to discuss this dose reduction trial was low but participation interest was high once they attended. The screening to enrollment ratio was encouragingly low. Results are likely to inform policy on HPV vaccination regimens.
IMMUNOGENICITY AND SAFETY OF A PICHIA-EXPRESSED BIVALENT HUMAN PAPILLOMAVIRUS VACCINE IN DIFFERENT AGE GROUPS OF CHINESE FEMALES WITH DIFFERENT DOSING REGIMENS

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Background and Aims

To compare the immunogenicity and safety of a bivalent HPV vaccine among Chinese girls received 2 or 3 doses and young women received 3 doses.

Methods

A total of 900 healthy Chinese females were enrolled in a randomized, age-stratified and non-inferiority Phase IIB immunogenicity study. Girls (9-14 years) were randomized 1:1 to receive the HPV vaccine at Month 0, 2, 6 (n=300, 3-dose regimen) or 0, 6 (n=300, 2-dose regimen). Women (18-26 years) received the vaccine at Month 0, 2, 6 (n=300, 3-dose regimen). Serum samples for neutralizing antibody analysis were collected at Month 0, 6, 7, 12. Adverse events within 7 months and serious adverse events (SAEs) throughout the trial were assessed.

Results

Of the 900 subjects enrolled, 861 of them (95.67 %) completed the study. The GMT ratios were noninferior for girls (3 doses) to women (3 doses), girls (2 doses) to women (3 doses): 1.23 (95 % CI, 1.07-1.45) for HPV-16 and 2.82 (95 % CI, 2.29-3.39) for HPV-18, 1.62 (95 % CI, 1.41-1.91) for HPV-16 and 2.69 (95 % CI, 2.19-3.24) for HPV-18, respectively. Girls (2 doses) had GMT levels of 8511.38 for HPV-16 and 7079.46 HPV-18 at Month 7. The vaccine was well tolerated and no vaccine-related SAEs were reported.

Conclusions

Among Chinese girls who received 2 or 3 doses, neutralizing antibody responses to HPV-16 and HPV-18 at Month 7 are noninferior to those of Chinese women who received 3 doses. Immune persistency trial is ongoing and will be evaluated.
INTERIM REPORT ON SUBJECT RECRUITMENT FOR PHASE II RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL WITH TWO TREATMENT ARMS: PEPCAN, A THERAPEUTIC HPV VACCINE, AND ADJUVANT-ONLY

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Background and Aims

The aims of this study were to (1) inquire reasons why women agreed or declined to participate and (2) to identify effective recruitment strategies.

Methods

Women with an abnormal Papanicolaou smear were eligible to enroll; only those with biopsy-confirmed CIN II or III were vaccinated. To probe reasons for participation or non-participation in the study, women who agreed to participate answered a questionnaire at enrollment. Potential subjects who were qualified but declined participation were mailed a different questionnaire. Recruitment efforts included visits to clinics, informational letters to statewide gynecologic service providers and potentially eligible patients in-house, and advertisements (pamphlets, brochures, Facebook, Instagram, and Google).

Results

Motivations for joining the study were personal health needs (30 of 43, 70%), contribution to medical science (16%), possible free treatment (9%), and others (5%). For potential subjects who declined to participate, 57% (4 of 7) had individualized reasons. Not knowing whether they would receive PepCan (vaccine) or Candida (adjuvant-only) accounted for 29% while lack of transportation was mentioned in 14%. Participants were recruited through a telecolposcopy network (17 of 43, 40%), outside referral (38%), in-house referral (12%), and advertisement (10%). Of 16 outside referral patients, 94% (15 of 16) were recruited from clinics visited by study staff.

Conclusions

Patients were primarily motivated by their health needs to participate in the study. Not knowing which treatment one would receive did not seem to be a significant deterrent. Staff visits to clinics appear to be an effective recruitment strategy.
VIVA TRIAL: HPV VACCINE TO INTERRUPT RECURRENTS OF VULVAR AND ANAL LESIONS
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4Fred Hutchinson Cancer Research Center, Human Biology and Public Health Science Division, Seattle, USA
5University of Washington, Pathology, Seattle- WA, USA
6University of Washington, Obstetrics and Gynecology, Seattle- WA, USA
7University of Washington, Medicine and Surgery, Seattle- WA, USA
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9University of Washington- Fred Hutchinson Cancer Research Center, Medicine- Epidemiology- Laboratory Medicine- Vaccine and Infectious Diseases Division, Seattle- WA, USA

Background and Aims

Approximately 30% of vulvar and anal high-grade squamous intraepithelial (HSIL) lesions recur within 5 years of treatment with rates as high as 60% among HIV-positive men within one year following ablative therapy. Recurrent lesions require multiple treatments leading to substantial morbidity, psychosocial trauma, and high medical expenses. Observational studies suggest that the prophylactic HPV vaccine may reduce recurrences of HSIL in treated patients.

Methods

We are conducting a randomized, double-blind, placebo-controlled trial to test whether receipt of the 9-valent humanpapillomavirus (HPV) vaccine (Gardasil-9) leads to a 50% reduction of HSIL recurrence among vaccine-naïve persons who were previously treated for vulvar or anal HSIL. Eligible participants are ages 27-69 and HSIL-free at enrollment. HIV infection is permitted, if the participant is on antiretroviral therapy.

Results

Potential participants with diagnosis of HSIL are ascertained from the local Cancer Registry in Seattle; 634 letters were mailed to those that met the initial eligibility criteria. Screening interviews by phone were conducted with 129 individuals, and 53 participants enrolled upon successful completion of screening visit. We found that 30% of screened participants were ineligible due to persistent HSIL at entry visit (5 vulvar HSIL and 22 anal HSIL); 60% of them are HIV-infected persons.

Conclusions
We will discuss rationale, study design, progress, and main challenges of the VIVA trial and provide descriptive characteristics of those eligible and ineligible for the trial. Management of persons with persistent, or rapidly recurring HSIL remains challenging.
HEALTHCARE PRACTITIONERS’ ANAL CANCER SCREENING PRACTICES AMONG HIV-POSITIVE PATIENTS: A QUALITATIVE STUDY

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¹University of Arizona, College of Public Health, Tucson, USA
²Arizona State University, College of Health Solutions, Phoenix, USA

Background and Aims

HIV-positive individuals suffer disproportionate burden from anal cancer, a cancer caused by persistent infection with oncogenic HPV strains. It is believed that anal cancer can be controlled through timely screening for anal intraepithelial neoplasia (AIN). Little is known about healthcare practitioners’ AIN screening practices among their HIV-positive patients.

Methods

To explore practitioners’ AIN screening practices, we conducted in-depth interviews with a variety of healthcare professionals (e.g. nurses, primary care physicians, surgeons) who provide care to HIV-positive patients. To date, we have completed 17 interviews and anticipate completing eight additional interviews.

Results

The majority of providers screened their patients for AIN via the anal Pap smear, four of whom used the opportunity of the anal Pap smear as a time to recommend the HPV vaccine. Most providers referred patients with high grade AIN (AIN 2 and 3) to either a general or colorectal surgeon to undergo further screening via high resolution anoscopy. Seven providers expressed frustration with the lack of screening and treatment guidelines aimed at preventing and controlling anal cancer. These practitioners reported following cervical cancer screening guidelines to guide how often they screened and proposed treatment. Two colorectal surgeons discussed how patients may be over-treated for AIN 2 and 3, and they described the role of biomarkers to determine whether or not they should treat these presumptive cancerous lesions.

Conclusions

In the absence of defined screening and treatment guidelines, practitioners who provide care for HIV-positive patients are proactive in screening to help prevent and control anal cancer.
IPVC8-0039
POSTER SESSION

CLINICAL RESEARCH - MANAGEMENT OF HPV DISEASE IN HIV-INFECTED PEOPLE

DETECTION, GENOTYPING OF HUMAN PAPILLOMAVIRUS (HPV) IN CERVICOVAGINAL SECRETIONS OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) POSITIVE INDIAN WOMEN AND CORRELATION WITH CLINICOPATHOLOGICAL FINDINGS

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Background and Aims

Genital human papillomavirus (HPV) infection especially types 16 and 18 account for about 90% of all cases of cervical cancer.

Our objective was to provide baseline data on HPV genotypes prevalent in Indian HIV-1 infected women.

Methods

One hundred HIV seropositive women, between 18-60 years were enrolled at Department of Gynaecology OPD, All India Institute of Medical Sciences, Delhi. Pap smear and cervical samples were collected in Digene® STM (Qiagen Gaithersburg Inc., USA). HPV DNA was amplified by the short PCR fragment primer set (SPF10) and HPV genotyping was done by the INNOLiPA HPV Genotyping Extra kit, (Fujirebio).

Results

The prevalence of any HPV type was 66.7% (62/93). HPV 16 and 18 comprised 48.4% (30/62) of total positive samples and 53.5% of these had abnormal Pap smears. Multiple genotypes (2 to 8) were seen in 72.5% of the HPV DNA positive samples. The median CD4 count in the HPV negative group was 502 cells/mm^3; in those with any HPV type, 313 cells/mm^3; and in the group with HPV 16 and, or 18, 239 cells/mm^3. The samples harbouring HPV-16 and /or HPV-18 with without other high risk types had a higher frequency of low grade squamous intraepithelial lesions (LSIL) and high grade squamous intraepithelial lesions (HSIL) on cytology, than those with other HPV types (low risk or high risk types other than HPV 16/18.

Conclusions

HPV prevalence is high in HIV infected women, screening and preventive measures should be initiated early in this population.
Background and Aims

The effectiveness of the HPV vaccine may be suboptimal in perinatally HIV-infected (PHIV) youth who have lower reported rates of protection with other vaccines. Our aim was to compare antibody titers to HPV4 vaccine types and rate of abnormal cervical cytology (ACC) between PHIV and perinatally HIV-exposed, uninfected (PHEU) youth receiving 1-3 doses of HPV4.

Methods

Study population was followed in the Pediatric HIV/AIDS Cohort: a multi-centered study. Seroconversion and geometric mean titer (GMT) against HPV 6,11,16,18 were examined using the most recent available biorepository serum sample. Clinical outcome of effectiveness was ACC obtained from ongoing chart abstraction.

Results

For 310 PHIV and 148 PHEU, respectively, mean (SD) age at first vaccination was 13.7 (2.5) and 12.4 (2.1) years; p<0.001, and mean years from last HPV4 dose to specimen was 3.0 (1.6) and 2.8 (1.4); p=0.14. 62-90% of PHIV and 87-99% of PHEU seroconverted (p<0.05 for all comparisons). GMTs were lower in the PHIV vs PHEU within each category of HPV4 doses received (figure). Higher GMTs were associated with lower HIV-1 RNA viral load (VL), and higher CD4% at first HPV4. Among 56 PHIV and 7 PHEU sexually-active vaccinated females, 33 PHIV and 1 PHEU had AC, yielding an incidence rate ratio of 5.2 (95% CI 0.7 to 41.7). There was a trend association for low CD4% and high
Conclusions

Antibody titers to HPV4 was lower for all serotypes in PHIV compared to PHEU. Protection against AC was also diminished in PHIV females.
CLINICAL RESEARCH - MANAGEMENT OF HPV DISEASE IN HIV-INFECTED PEOPLE

NO CORRELATION BETWEEN CERVICAL HPV-16 DNA VIRAL LOAD AND CLEARANCE IN PERINATALLY HIV-INFECTED AND UNINFECTED ASIAN YOUNG ADULTS

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Background and Aims

We aimed to assess whether cervical human papillomavirus (HPV) type 16 DNA viral load (HPV-VL) correlated with cervical clearance in Asian youth.

Methods

Perinatally HIV-infected (PHIV) and HIV-uninfected (HU) sexually active youth were monitored for HPV infections in Thailand and Vietnam from 2013-2017. HU controls were matched by sex, age, and lifetime number of sexual partners. Cervical HPV genotypes and other data were assessed every 48 weeks for 3 years. Participants with HPV-16 DNA at baseline had HPV-VL assessed by real-time PCR. The Kaplan-Meier method and Wilcoxon rank sum tests were used to assess associations between HPV-16 clearance, HPV-VL, and other characteristics by exposure groups.

Results

Twenty-one (14 PHIV, 7 HU) youth with median (IQR) age 19 (17-20) years tested positive for HPV-16 DNA in baseline cervical samples. Median HPV-VL was 2.93 (2.69-4.10) log₁₀ copies/10,000 human cells in PHIV and 3.25 (2.60-4.67) in HU. We found no difference in time to cervical HPV-16 clearance between PHIV and HU (log-rank P=0.44, Figure 1) and no linear association with increasing log₁₀ HPV-VL and HPV-16 clearance using Kaplan-Meier. Baseline HPV-VL was not significantly different amongst those who did and did not clear the virus (PHIV, P=0.79; HU, P=0.48) (Figure 2). No relationship was observed between ages, lifetime sexual partners, time-updated number of sexual partners in the last 6 months, positive Chlamydia trachomatis tests, and whether participants had ever been pregnant, and HPV-16 clearance.

Conclusions

Cervical HPV-16 DNA viral load was not associated with clearance of cervical HPV-16 in this cohort.
Abstract for 32nd IPV Conference in Sydney. Histone acetyl transferases (HAT) and deacetylases (HDAC) mediate chromatin remodeling and the activity of many non-histone proteins to regulate transcription. In addition, S-phase progression depends on HDACs to deacetylate histones in newly replicated chromatin. High-risk HPV-18 DNA amplification depends on HPV E7-induced S-phase reentry in differentiated cells in raft cultures developed from primary human keratinocytes (PHKs). We propose that suprabasal cellular DNA replication and viral DNA amplification would be adversely affected by HDAC inhibitors. Methods. We examined effects of pan-HDAC inhibitors, Vorinostat, Belinostat and Panobinostat, in raft cultures of HPV18-infected PHKs and of HPV16-positive cervical cancer CaSki cells. These inhibitors are FDA-approved against lymphomas and multiple myelomas. Results. HPV-18 infection elevated several HDACs. Vorinostat (suberoyl-anilide-hydroximic-acid, SAHA) prevented host DNA replication and viral DNA amplification at 5 µM and abrogated progeny virus production. When compared to vehicle-treated, infected raft cultures, Vorinostat reduced E6 protein, inhibited activities of E6 and E7 proteins, induced DNA damage, elevated the pro-apoptotic protein Bim and induced apoptosis. Vorinostat induced very few apoptotic nuclei in uninfected raft cultures. Pan-HDAC inhibitors Belinostat and Panobinostat also reduced viral DNA amplification and induced cytotoxicity in HPV18 raft cultures. Importantly, Vorinostat was highly toxic to raft cultures of CaSki cells. Conclusions. HDAC inhibitors are potential therapeutic agents to treat benign HPV infections, abrogating progeny virus production and interrupting transmission. Vorinostat also has possible application to treating HGSIL. Clinical trials are warranted by the observed safety, efficacy and relative specificity in this experimental tissue culture model. Support. Pilot research grant from the UAB Comprehensive Cancer Center to NSB and an Anderson Family Endowed Chair to LTC.
Background and Aims

It has been widely known that HPV-DNAs were detected in digital Bowen’s disease (BD) and genital Bowenoid papulosis (BP). High-risk HPV DNA is predominantly associated with anogenital cancer and cervical cancer.

Imiquimod 5% cream is well known to be clinically effective and safe in the management of a wide variety of benign and malignant skin conditions (e.g., basal cell carcinoma, actinic keratosis, and condyloma). The toll like receptor-7 agonist Imiquimod acts as an immune response modifier, stimulating the innate and adaptive immune responses, inducing the production of interferon-alpha and other cytokines.

The aim of this study is to evaluate the efficacy of topical imiquimod 5% cream for digital BD and genital BP.

Methods

Skin biopsy of the 5 legions was performed before and after treatment. Part of each sample underwent routine histopathology, the rest was stored for PCR analysis. After diagnosis, the topical 5% imiquimod cream was applied to the 5 lesions 5 days per week for 2 or 3 months. Subsequently, we performed PCR analysis using GP 5+/6+ primers and directly sequenced the PCR products.

Results

Clinicopathologically, 5 cases showed complete remission, at least within 3 months treatment. PCR analysis showed that two digital BD contained HPV 16 DNA, whereas 2 out of 3 genital BP contained HPV 16 and HPV 34 DNA, respectively.

Conclusions

Our results indicates that the topical imiquimod 5% cream therapy is useful in the treatment of HPV associated digital BD and genital BP, in which the enhanced immune response may have contributed in the elimination of HPV-DNAs.
A STRATEGY OF CO-TESTING AND SIMULTANEOUS IMIQUIMOD IN PATIENTS WITH PERSISTENT HPV INFECTION

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Background and Aims

Persistent HPV infection implies a high risk of progression to precursor of cervical cancer. It is necessary not only to detect disease sensitively but also to eradicate HPV infection. Pap and HPV co-testing is known to be effective to watch persistent HPV infection. Imiquimod is active agent against HPV-related disease such as genital warts and CIN. This study aimed to evaluate the utility of regular co-testing and applying imiquimod simultaneously in patients with persistent HPV infection.

Methods

Women with normal cervical cytology and positive HPV test for more than 1 year was defined as persistent HPV infection. ThinPrep ® liquid-based cervical cytology and Hybrid Capture II ® HPV test were performed every 3 to 6 months and followed for 1 year. HPV viral load was measured in relative light unit (RLU). At the same time imiquimod 5% cream was applied at exocervix and in endocervix after acquisition of cervical cytology and HPV test.

Results

Thirty-five women were enrolled for this study. Thirteen women (37.1%) resulted in normal cytology and negative HPV. Fifteen women (42.9%) resulted in normal cytology and 50% or more decrease in HPV viral load. Four women (11.4%) resulted in ASC-US/normal cytology and increase or less than 50% decrease in HPV viral load. Three women (8.6%) resulted in LSIL or HSIL. Fever was the most common adverse events in nine cases (25.7%).

Conclusions

Regular co-testing and applying imiquimod simultaneously are supposed to be a safe and effective strategy for watching and treating persistent HPV infection.
DEmethylation treatment represents a promising therapeutic strategy for HPV-induced (pre-)cancerous lesions

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Background and Aims

We previously demonstrated efficacy of the demethylating agent decitabine to reverse the transformed phenotype in a panel of HPV-induced cancer cell lines. Since treatment efficacy may generally vary between cells cultured in monolayer culture or in a three-dimensional (3D) tissue context we intended to generate 3D cultures of HPV-transformed cells to confirm that demethylating therapy holds the potential to act as a targeted treatment strategy against HPV-induced (pre-)cancer.

Methods

Distinct 3D tumor models from different HPV-transformed cervical cell lines (HeLa, SiHa, CaSki, and SW756) were generated as spheroids and co-cultures of tumor cells and normal keratinocytes and assessed for proliferation, induction of cell death and cellular senescence by different markers upon treatment with the demethylating agent decitabine.

Results

Multicellular tumor spheroids were generated from several HPV-transformed cell lines (HeLa, SiHa, CaSki, and SW756). Co-cultures of different HPV-transformed cell lines (HeLa and SiHa) and normal keratinocytes could be successfully established and proved to be stable during month-long cultivation. HPV-transformed cells formed nest-like structures among stratified normal epithelium, modeling pre-cancerous lesions. Treatment of both 3D culture models revealed reduced cell proliferation, induction of apoptosis and cellular senescence that occurred in a time- and dose-dependent manner.

Conclusions

Biological effects of demethylating treatment can be analyzed in realistic 3D HPV (pre-)cancer models indicating remarkable potential of this therapeutic approach against HPV-induced lesions.
Background and Aims

In our laboratory, we have recently identified inhibiting Aurora A kinase as a selective approach to treat HPV-driven malignancies like cervical cancer, using Alisertib (MLN8237). However, Phase 1/2/3 clinical trials for oral Alisertib showed serious side effects related to the systemic delivery used. As cervical cancer is localised in the early stages, localised delivery is feasible. This research focuses on designing a novel approach for topically targeting cervical cancer using Alisertib-loaded intra-vaginal rings and tests them in-vitro and in-vivo.

Methods

Matrix-type silicone intra-vaginal rings were designed, manufactured and optimised. Pharmacokinetics were tested in-vitro by incubating the rings under sink conditions in simulated vaginal fluid and safety was evaluated in-vivo in mice by implanting the rings for one week and then sectioning the vaginal tract to investigate for any indications of inflammation.

Results

The silicone rings maintained continuous release of Alisertib over three weeks in the in vitro studies and exhibited root time kinetics. Mice vaginal tract sectioning showed no signs of inflammation related to the topical application of the drug over one week.

Conclusions

Localising this novel approach will aid in reducing the required drug dose, avoiding the first pass metabolism, and reducing/avoiding the systemic side effects of the drug. Moreover, due to the direct contact between the delivery system and the surface of the malignancy, we presume that it will result in a significant improvement in therapy outcomes. This study provides an exciting opportunity to advance our knowledge of localising the treatment of cervical cancer.
IMPACT OF HPV VACCINATION IN A HIGH-COVERAGE COUNTRY: PREDICTED TREATMENTS RATES FOR PRECANCEROUS CERVICAL ABNORMALITIES IN AUSTRALIA 2017-2070

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Background and Aims

Treatment of precancerous cervical abnormalities may be associated with an increased risk of adverse obstetric outcomes including preterm delivery. Australia introduced routine quadrivalent HPV vaccination (HPV4) in 2007, nonavalent vaccination (HPV9) in 2018, and 5-yearly HPV screening in 2017. We investigated the impact of vaccination on precancer treatments.

Methods

Using POLICY1-Cervix, a dynamic model, we estimated rates of women ever undergoing precancer treatment in Australia over 2017-2070. Two sets of screening assumptions were explored for young cohorts offered routine HPV9: i) continued 5-yearly HPV screening; and ii) twice-lifetime HPV screening (which prior work suggests will remain cost-effective in these cohorts).

Results

First-precancer treatment rates are predicted to reduce from 1.13 in 2017 to 0.59 in 2070 per 1,000 women (47% reduction) with ongoing HPV4 vaccination; to 0.25 with HPV9 vaccination and ongoing 5-yearly screening (78% reduction); or to 0.17 (85% reduction) with twice-lifetime screening for cohorts offered HPV9. The number of treated women will reduce from ~13,000 in 2017 to ~11,000 by 2070 assuming ongoing HPV4 vaccination, ~4700 with HPV9 vaccination and ~3200 assuming twice-lifetime screening for HPV9 cohorts (despite an expected 74% increase in the female population aged up to 85 years). Changing from HPV4 to HPV9 is expected to avert precancer treatments in ~181,000 women over 2017-2070; twice-lifetime screening in HPV9 cohorts will prevent an additional 44,000 women undergoing treatment.

Conclusions

HPV vaccination and less frequent HPV-screening will substantially reduce the number of women treated for precancer, potentially reducing the incidence of future treatment-related obstetric complications.
POTENT EFFICACY OF REBACIN ON REGRESSION OF CERVICAL INTRAEPITHELIAL NEOPLASIA

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Background and Aims

It is well noted that expression of HPV viral oncogenes E6/E7 plays an important role in high grade cervical intraepithelial neoplasia (CIN) formation and tumorigenesis. We previously reported that REBACIN can potently repress E6/E7 gene expression in TC-1 and Hela cells, as well significantly suppress E6/E7-induced tumor growth in animal models. Our studies further demonstrated marked efficacy of REBACIN on virus clearance in patients with persistent HPV infections. The current study evaluated the effect of REBACIN on cervical lesion regression in CIN2 patients.

Methods

15 CIN2 patients received RABCIN treatment for one or two courses. One regimen included a 3-month vaginal administered every other day except menstrual cycles. The efficacy of REBACIN were assessed at baseline and in 2 to 30-month follow ups which determined the cervical lesion changes and HPV status by colposcopy, cytology and histology.

Results

After first course treatment, 12 of 15 patients showed complete regression of CIN2 to cytology normal and HPV negative. Of the additional 3 patients who remained HPV positive, 2 was found regressed to CIN1, and 1 became cytology normal. The 2 CIN1 patients then received the second course of REBACIN. These two had their lesions and viruses cleared post treatment.

Conclusions

REBACIN demonstrated notable 86.7% efficacy in regression of high grade cervical lesion, and 93.3% efficacy in HPV infection clearance. These evidences further support REBACIN as an effective intervention therapy in the control of persistent HPV infection and cervical premalignancy and malignancy development.
HYALURONAN IN VOCAL FOLDS AND FALSE VOCAL FOLDS IN PATIENTS WITH RECURRENT RESPIRATORY PAPILLOMATOSIS

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Background and Aims

Describing mass and localization of hyaluronan (HA) and localization of HA receptor CD44 in vocal folds and false vocal folds in patients with recurrent respiratory papillomatosis (RRP).

Methods

Biopsies from vocal folds and false vocal folds were collected from 24 RRP patients. Twelve patients were studied with histochemistry staining for HA and CD44 in the epithelium, stroma and RRP lesions. The remaining 12 patients were analyzed for HA molecular mass distribution with gas-phase electrophoretic molecular mobility analyzer (GEMMA). Eight vocal fold samples and four false vocal fold samples were successfully analyzed.

Results

Faint HA staining was seen in 3 of 23 stains of the epithelium of vocal folds and false vocal folds combined, whereas more extensive HA staining was seen in the stroma. CD44 was present throughout the epithelium, stroma, and RRP lesions in false vocal folds and vocal folds, it did however not concur with the expression of HA.

Analysis with GEMMA revealed very high mass HA in vocal folds and false vocal folds, though more varying amounts of HA were seen in the vocal folds compared to false vocal folds.
Figure 1. Mass distribution analysis of HA using GEMMA.
LMHA: Low mass Hyaluronan. HMHA: high mass hyaluronan. Two major peaks of HA were detected ranging from about 50 kDa to larger than HA standards (>10 MDa). There was a trend of relatively more of the very high mass HA (vHMHA) in the vocal folds compared to false vocal folds. HA from skin biopsy analyses at our laboratory did not show vHMHA.

Conclusions
HA was mainly distributed in the stroma. CD44 not binding to HA might explain the non-inflammatory response previously described in RRP. Very high mass, possibly crosslinked, HA was seen in both vocal folds and false vocal folds, but with a trend towards more variable amounts in vocal folds. A possibility to counteract inflammatory crosslinking of HA may be found for medical treatment options in RRP.
Background and Aims

Laryngeal papillomas (LP) are tumors formed by infection of the larynx with human papillomavirus type 6 or 11 (HPV-6 or HPV-11) and are multiple, recurrent and refractory diseases. HPV has nine genes, but the detailed functions exerted by these genes in the formation of recurrent and refractory LP have not been mostly elucidated. Therefore, we aimed to clarify the expression level of each gene in recurrent LP. Then, we attempted to elucidate localization of the most highly expressed gene, which may play a key role in formation of LP.

Methods

Genomic DNA and RNA were extracted from 13 frozen tissues of recurrent LP from 11 patients infected with HPV-6. The HPV-6 DNA copy numbers were determined by quantitative real-time PCR (qPCR), while the infection sites were determined by HPV-6 DNA in situ hybridization (DNA-ISH). Subsequently, RNAs were reverse-transcribed and quantified using qPCR to elucidate the expression levels of eight genes except E5a. Finally, we established E4 RNA-ISH.

Results

The average copies of the HPV-6 genomic DNA were 587000.3 ± 268240.5 copies/ng DNA. HPV-6 DNAs were widely distributed from basal layers to granule layers with the highest amount in the upper spinous layers. E4 and E5b mRNAs were the most highly expressed among the eight mRNAs. E4 gene was restrictedly expressed in granule cells from upper spinous cells, where the cells have a large amount of HPV-6 DNA.

Conclusions

These results suggest that E4 plays a key role in formation of multiple, recurrent and refractory LP such as viral genome amplification and/or virus release.
Background and Aims

Recurrent Respiratory Papillomatosis is a benign illness, mostly associated with low risk papillomavirus types 6 and/or 11. This papillomatosis is a public health issue representing an economic burden both to the public health system and the patients.

The objective of this work was to identify any other HPV types in larynx biopsies, besides the formerly reported types 6 and 11.

Methods

We collected 30 larynx biopsy samples from adult patients in the Otorhinolaryngology Service at the Hospital de Especialidades del CMN SXXI, Mexico City. Virus genotyping was done on DNA from each sample, by two techniques: 1) Sanger’s sequencing of PCR amplimers from MY09/MY11 and/or GP5+/GP6+ primers; and 2) Roche Linear Array HPV genotyping kit®. Also, in 20 out of the 30 samples we used the next generation sequencing analysis in a DNA sequencing platform (NSG).

Results

By Sanger’s sequencing we identified HPV-6 in 18 samples and HPV-11 in 12 samples. By Linear Array we got the same results, except that four of the samples were co-infected: one with HPV types 6 and 11; two with HPV 6 and 16, and one with HPV 11 and 16. In the 20 samples sequenced by NSG, we found that nine samples were infected with high risk HPV types: six samples with HPV-16, five samples with HPV-58 and four samples with HPV-31; all 20 of them were co-infected with other high and low risk HPV types.
Conclusions

The NSG of RRP samples allowed us to detect some high-risk genotypes in addition to HPV6/11 prototypes.
IPVC8-0352
POSTER SESSION

CLINICAL RESEARCH - RECURRENT RESPIRATORY PAPILLOMATOSIS

COMPARISON OF SPECIMEN COLLECTION METHODS FOR SURVEILLANCE OF JUVENILE ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS (JORRP)
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Background and Aims
JORRP is a rare disease caused by HPV and characterized by respiratory tract papillomas. It is frequently associated with HPV 6 or 11, targets of quadrivalent and 9-valent HPV vaccines. Because sampling methods might affect results, we compared HPV DNA detection in brush and tissue biopsies.

Methods
Specimens were collected during endoscopy of patients with JORRP aged <18 years. Brush biopsies were collected with Epicentre® Buccal Swabs in Digene® Specimen Transport Medium and stored at -20°C. Tissue from debulking was snap-frozen on dry ice and stored at -80°C. All were digested with proteinase-K, extracted with QIAamp® DNA Mini Kit, and tested for 37 HPV types using PCR. HPV DNA was measured by spectrophotometry.

Results
Brush-tissue pairs from 77 patients were tested. Concordance for any HPV was 81% between specimens, with 61 pairs positive in both methods, 1 pair negative in both methods and 15 pairs negative in brush but positive in tissue. No samples had inadequate DNA as indicated by beta-globin. Type-specific positive concordance was 79%. Most specimens were positive for just 1 HPV type (59 brush; 75 tissue). HPV 6 was the most prevalent type (53 brush; 65 tissue). DNA concentration from brush was less than from tissue (10.2±8.76 ng/µl versus 135.15±128.78 ng/µl, p=0.00002, measured in subset of 28 pairs).

Conclusions
Tissue had greater reliability than brush biopsies for detection of any HPV and type-specific HPV DNA. This may be due to greater DNA concentration in tissue. HPV typing of JORRP lesions can help monitor vaccination impact.
Background and Aims

Recurrent respiratory papillomatosis (RRP) is a disease characterized by benign neoplasms that can occur within the upper respiratory tract, specially the larynx. This disease has a bimodal age distribution and is categorized as juvenile or adult. HPVs 6 and 11 are the etiological agent of over 90% of RRPs. In this study, we analyzed the prevalence of viral variants in laryngeal papillomas, and further evaluated their association to clinicopathological characteristics of the individuals affected.

Methods

In total, 67 RRP samples were obtained at the Universidade Federal de São Paulo, Faculdade de Medicina de Ribeirão Preto/USP São Paulo, and Centro Clínico de Cabeza y Cuello in Guatemala. HPVs 6 and 11 variants characterization were performed by PCR-sequencing and samples were classified within lineages and sub-lineages.

Results

Overall, the most prevalent HPV-6 variants were B1 (50.0%) and B3 (36.0%), whereas for HPV-11 positive samples, A1 (37.5%) and A2 (63.5%) predominated. A higher prevalence of HPV-6 B1 variants was observed in juvenile RRP cases (10/15, 66.6% B3 and 2/15, 13.4% B1), compared to adult RRP cases (14/28, 50.0% B3 and 10/28, 35.72% B1). Similarly, HPV-11 A1 variants were more prevalent in juvenile RRP cases (3/10, 42.87% A1 and 7/10, 57.14% A2), than in adult RRP cases (6/14, 30.0% B3 versus 8/14, 70.0% B1). Nevertheless, these differences were not statistically significant.

Conclusions

There was a lack of association between any particular HPVs 6 or 11 variant and clinicopathological features associated to higher aggressiveness pointing towards more complex viral-host interactions underlying why some RRP lesions recur more.
Background and Aims

Vaccination against Human Papillomaviruses (HPV) with virus-like-particles (VLPs) consisting vaccines is recommended for girls from nine to fourteen years. The aim of this work was to evaluate mechanisms of the T- and B-cell mediated immunity against L1-VLPs of the HPV-Types 6, 11, 16 and 18 by fluorescent Enzyme-Linked-ImmunoSpot-Assay (EliSpot).

Methods

To evaluate T-cell mediated immunity, IFNy, IL-2 and IL-5 were simultaneously detected in one well. Our underlying hypothesis says that fully vaccinated donors should express the most IFNy, whereas partly vaccinated donors should express less IFNy when stimulated with VLPs, in contrast to almost no IFNy expression in non-vaccinated donors.

Results

This was proved with the EliSpot and the groups were clearly distinguishable. Also, fully vaccinated donors showed the highest IL-2 expression (Fig. 1). Furthermore, IL-5 expression was only detectable in vaccinated donors, which indicates functional T-cells against VLPs from HPV 11, 16 and 18. For evaluating functional B-cells and cross-protection potential of the different available vaccinations, VLPs from HPV 6&11 (low-risk-mix) and 16&18 (high-risk-mix) were labeled with different fluorescent dyes to evaluate B-cell numbers for both mixes in one well in parallel. We were able to detect dose-
dependent spot numbers for all HPV types in vaccinated donors which were for all types higher than for non-vaccinated donors.

Conclusions

The range for an effective vaccination should be confirmed by further investigations with more characterized donors. Furthermore, these trials could facilitate the detection of significant differences between vaccinated and non-vaccinated donors and open the possibility to define effectiveness of vaccination for cellular immune responses.
AN EXAMPLE OF AN ACTIVE PALLIATIVE CARE SERVICE IN A DEVELOPING COUNTRY: OUR EXPERIENCE IN THE GHARBIA CANCER SOCIETY, EGYPT.

M. Hablas

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Background and Aims

The need for palliative-care in middle and low resources countries, including Egypt, is emerging. The Gharbia Cancer Society (GCS) is a nonprofit, nongovernmental hospital, located in Tanta, the Capital of the Gharbia Governorate in the mid-Nile Delta. The Society provides acute care to patients with cancer including surgery, chemo-and radiotherapy. Review of 9 year-data of Gharbia-population-based-cancer-registry from 1999 to 2007 revealed 3480 cancer cases/year, with Age Standardized Rate (ASR) of 161.7/100,000 for males & 120.8/100.000 for females. About 70% of cases present in advanced stages (III&IV) with liver cancer the most frequent cancer in male and breast cancer as the most frequent cancer in females. The GCS started a comprehensive palliative-care services in April 2011 with 10-bed inpatient-unit and 6 days/week outpatient clinic. All palliative-care equipment were provided by public donations.

Methods

Through collaboration with National Cancer Institute, Bethesda-Maryland and the San Diego Hospice and The Institute for Palliative Medicine and Middle East Cancer Consortium, a fellowship training program was developed for a medical-oncologist in Palliative Medicine and End of Life Care training course for nurses.

Results

The program succeeded in convincing local health authorities to increase the recommended opioids dose and to allow more physicians to prescribe opioids for cancer pain. In a period of 24 months, symptom management and palliative-care were provided to 195 patients with advanced malignancies. The opioids consumption was increased by 30 folds.

Conclusions

The Major challenges for the program were inadequate public and health-professionals awareness of palliative-care services and lack of vehicles and finances to cover home visits. The initial results of the program warrant allocating more resources for coverage of a large number of trainees and instituting a home visits program.
THE ETIOLOGICAL ROLE OF HUMAN PAPILLOMAVIRUSES IN THE DEVELOPMENT OF A SUBSET OF ORAL SQUAMOUS CELL PAPILLOMAS
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Background and Aims

To investigate the prevalence, viral load and in-situ hybridization (ISH) patterns of HPVs in archival tissue samples of oral squamous cell papillomas (OSCPs) with different histopathological features, in order to determine whether the development of oral neoplasms was associated with HPV infection.

Methods

Samples of 104 OSCPs, obtained from the same number of patients, were tested for the presence of Alpha-, Gamma- and Mu-PVs, using GP5+/6+/68 PCR, low-risk Alpha-PV PCR, Gamma-PV PCR, HPV1/63 real-time PCR (RT-PCR) and HPV204 RT-PCR, together enabling detection of more than 100 different HPVs. Additionally, HPV6/11 RT-PCR was used in a combination with beta-globin RT-PCR to estimate the viral loads of detected HPVs. Moreover, HPV6 DNA ISH was used to determine whether nuclei of host cells harbored episomal/integrated viral replication patterns.

Results

A total of 12/104 (11.5%) OSCPs were Alpha-PV-positive, with HPV6 detected in nine samples (viral load range: 0.22-4.10 viral copies/cell), which all harbored episomal viral replication patterns, and HPV2, 27 and 44 each identified in one sample. All samples were Gamma/Mu-PV-negative. In comparison to HPV-negative tumors, superficial keratinization was associated with the presence of HPV (p<0.0001). In contrast, patients’ age, gender and degree of inflammation were not associated with HPV infection. While koilocytes were observed in a single, dysplasia was absent in all HPV-positive samples.

Conclusions

Nevertheless that based on our results only a subset of OSCPs was most probably associated with Alpha-PVs, further studies, preferentially using deep sequencing techniques, are needed to ascertain whether novel putative HPVs are also associated with OSCPs.
DROPLET DIGITAL PCR (DDPCR) FOR ABSOLUTE QUANTIFICATION OF VIRAL LOAD IN SINGLE AND MULTIPLE HPV POSITIVE CERVICAL CARCINOMAS.

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Background and Aims

Droplet digital PCR (ddPCR) is a method for measuring absolute quantities of amplified DNA fragments, in defined water-in-oil droplets. A two-color detection system is used, providing duplex detection of an HPV genotype together with a human control gene.

Methods

ddPCR assays for HPV 16, 18, 31, 33, 35, 45, 56 (targeting genes E6/E7) duplexed with human gene HBB were used for estimation of viral load and viral load per cell (HPV/ (HBB/2)) in a Swedish cohort of women with cervical carcinoma. Previous results have shown that women with a tumor holding multiple HPV have a worse prognosis compared to women with tumors with single infections.

Results

For tumors with multiple infections (n=11), total viral load spanned between 609 and 193 767 copies with a mean of 42 270 copies and median 7024 (all genotypes combined). Combinations present were HPV16+ HPV18 (n=2), HPV16+HPV31 (4), HPV16+HPV33 (n=1), HPV16+HPV35 (n=1), HPV16+HPV56 (n=1), HPV18+HPV31 (n=1), HPV31+HPV45 (n=1). Where present, HPV 18 had highest viral load (at least 10 fold) compared to the concurrent infection, followed by HPV16.

For tumors with single infections (n=130, HPV16, 18, 31, 33, 35, 45, 56), total viral load spanned between 0.98 and 222 140 viral copies. Mean copy number was 23 649 and median 3560.

Conclusions

Total viral load was higher in tumors with multiple infections compared to tumors with single infections.
Preterm Delivery: A Register Based Study from the Western Region of Sweden

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Background and Aims

Increasing evidence suggests that cervical intraepithelial neoplasia (CIN), with or without subsequent treatment, causes preterm delivery. Our aim was to explore association between abnormal cervical cytology and subsequent obstetric adverse outcomes.

Methods

Retrospective population- and register-based cohort study comprising 19 822 women in Western Region of Sweden, who had at least one abnormal cervical cytology (1978-2012) before age of 45 and subsequent singleton birth. The control group comprised 39 644 women with normal cervical cytology and subsequent singleton birth, matched by age and parity. Data was retrieved from the Swedish National Cervical Screening Registry, linked to Swedish Medical Birth Register. Study outcomes: preterm delivery before 37 and 34 weeks, low birth weight (≤ 2500 g), small for gestational age (SGA), preterm premature rupture of membranes (pPROM), neonatal mortality. Information on education level, country of birth, income was obtained. Multivariable log binominal regression analyses were applied.

Results

Preterm delivery before 37 weeks was more common among women with abnormal cervical cytology compared with controls, 6% versus 4.5%. Low versus high grade abnormal cervical cytology implied a higher risk; 5.8% versus 7% (p<0.001). Preterm delivery before 34 weeks, pPROM, low birth weight, but not SGA and neonatal mortality, were more common in women with abnormal cervical cytology. Being single parent was more common and education level was lower compared with women with normal cytology.

Conclusions

Abnormal cervical cytology may imply increased risk of preterm delivery. Further studies are needed to investigate if the risk is related to treatment.
HUMAN PAPILLOMAVIRUS, MYCOPLASMA AND UREAPLASMA PREVALENCE IN THE ANUS AMONG JAPANESE MEN WHO HAVE SEX WITH MEN.
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Background and Aims

The present study investigated human papillomavirus (HPV), Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma urealyticum prevalence in anal samples among human immunodeficiency virus (HIV)-infected Japanese men who have sex with men (MSM).

Methods

A total of 106 patients were enrolled. Anal samples were collected from each participant, and a HPV-DNA test and genotyping were performed using flow-through hybridization. Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma urealyticum genomes were determined by PCR-based methods.

Results

The β-globin gene was positive in 90 (85.0%) anal samples. Among the β-globin-positive samples, the HPV prevalence was 85.6% and High-risk HPV (HR-HPV) was detected in 61.1% of samples. Multiple HPV types were detected 56.7% of samples. Focusing on HPV type distributions, HPV6 was most common in anal samples, followed by HPV58, HPV16, and HPV52. Mycoplasma genitalium, Mycoplasma hominis, and Ureaplasma urealyticum were detected in 11.1%, 12.2%, 4.4%, respectively. There was no significant relation between the prevalence of anal HPV and the prevalence of anal Mycoplasma genitalium, Mycoplasma hominis and Ureaplasma urealyticum.

Conclusions

The present study demonstrated very high HPV prevalence compared with Mycoplasma spp. and Ureaplasma spp. in the anus among HIV-infected Japanese MSM patients. There was no significant relation between the prevalence of anal HPV infection and the prevalence of anal Mycoplasma spp. and Ureaplasma spp. infection.
Background and Aims

We investigated the prevalence of human papillomavirus (HPV) infection in urine in Japanese men. And we also tried to identify risk factors for HPV detection in urine samples.

Methods

845 men were enrolled in this study. Urine samples were collected from each patient, and their sediment cells were preserved in the liquid-based cytology solution. After DNA extraction from each sample, HPV-DNA amplification and genotyping were performed using Luminex multiplex polymerase chain reaction. In addition, a questionnaire survey regarding the sexual activity, and we analyzed the risk factors for urine HPV infection.

Results

803 patients were included in the analysis. HPV-DNA was detected in 6.2% of the urine. HPV and high risk HPV prevalences were the highest in men with urethritis, and were significantly higher than those without urethritis. Urethritis was an independent risk factor for urine HPV infection. On the other hand, a sub-analysis excluding men with urethritis demonstrated that prostate cancer was a significant risk factor for HPV detection.

Conclusions

Urethritis was the independent risk factor for the urine HPV infection. And, Prostate cancer was the risk factor for HPV detection in the urine of men without urethritis.
A DANISH CLINICAL CERVICAL CYTOLOGY BIOBANK. PILOT STUDIES OF SAMPLE PROCESSING AND QUALITY

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²University of Southern Denmark, Institute of Regional Health Research, Odense, Denmark
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⁴University of Copenhagen, Department of Gynecology- Rigshospitalet, Copenhagen, Denmark

Background and Aims

To identify an efficient workflow for establishing a clinical cervical cytology biobank with high cell yield and high quality of the stored material.

Methods

The biobank will consist of residual material from liquid-based cytology samples (ThinPrep, Hologic) collected from women participating in the national screening program for cervical cancer in the uptake area of Sygehus Lillebaelt, Denmark (approx. 50,000 women/year).

The amount of DNA in the original ThinPrep vial was measured and compared to the yield of DNA in the biobanked sample. DNA was purified using the Maxwell Blood kit, and the concentration measured by the Qubit instrument. As an estimate of quality the biobanked samples were examined by PCR with up to 600 bp amplicons. Different procedures for handling the samples were evaluated (e.g. choice of tubes, sedimentation time, pipetting procedures etc.).

Results

In figure 1 below the workflow is presented.

![Workflow Diagram]

Based on 10 samples, the DNA yield in storage tube 1+2 was 61% of the content in the primary tube.

PCR results showed that 600 bp amplicons could be amplified for all samples, revealing high quality DNA, which can be used for purposes like e.g. Next Generation Sequencing.

Conclusions
Using the presented workflow a cytology biobank is to be established. The handling of the samples will be automated using the Freedom Evo 200 robot (Tecan). Updated and further data on quality measurements of DNA and RNA will be presented. The biobank holds great potential for future clinical purposes as well as for research and quality assurance.
THE CLINICAL SIGNIFICANCE OF HUMAN PAPILLOMA VIRUS INFECTION IN PROSTATE CANCER

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Background and Aims

Epidemiological investigations confirm that prostate tissue is prone to sexually transmitted infection and Human Papilloma Virus (HPV) is the most common sexually transmitted infection. It is crucial to investigate the prognostic impact of HPV infection in prostate cancer from a clinical point of view. The overall aim of my research is to address the possibility of using therapeutic interventions against HPV infection in young boys to prevent the development of prostate cancer in their older age. Establishment of clinical importance of HPV infection in prostate cancer and its prognostic impact for overall survival.

Methods

The prostate cancer tissue specimens were obtained from Sahlgrenska University hospital, Gothenburg, Sweden. Only histopathologically confirmed cases were processed. The study is approved by the Ethics Committee of the Institute. High molecular-weight genomic DNA was isolated from tumor/control tissue samples and subjected to PCR genotyping for detection of the viral infection. Cases and controls was compared using univariate methods. An independent t-test was performed for the comparison of clinicopathological parameters.

Results

The pilot study identified HPV infection in advanced grade of prostate cancer cases in Sweden. HPV infection was identified in 57% of the prostate cancer cases with advanced pathological grade in Swedish men compared to 11% in the normal controls. The investigation comprised of detailed analysis of the correlation between the clinical parameters and HPV genotyping.

Conclusions

The research investigation substantiates the clinical significance of HPV infection in prostate carcinogenesis that has been underestimated till date.

The research investigation was funded by Swedish Research Council (Vetenskaprådet) Grant no. 2015-06705
DETECTION OF HUMAN PAPILLOMA VIRUS, ZIKA VIRUS AND CYTOMEGALOVIRUS IN CERVICAL CYTOLOGY SAMPLES OF PREGNANT WOMEN FROM GUAYAQUIL, ECUADOR, USING THREE MOLECULAR ASSAYS

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Background and Aims

Human papillomavirus (HPV), Cytomegalovirus (CMV) and Zika virus (ZIKV) are associated with genital and reproductive diseases. While the link between ZIKV and CMV with birth defects and the link between HPV and genital-anal cancers have been well established, their association with pre-term delivery risk (PDR) has not been fully addressed. In early 2016, the first cases of ZIKV transmission were documented in Ecuador. The aim of this work was to assess the relationship of these viruses with PDR in a distinct group of pregnant women from Guayaquil, Ecuador.

Methods

A case control study was performed using cervical cytology samples from low-income, pregnant women in Ecuador diagnosed with PDR, compared to matched controls. Three different rt-PCR techniques were used to analyze the presence of HPV, ZIKV and CMV.

Results

The general incidence of HPV was 16.9% (10/59) overall: 4/31 (12.9%) in cases and 2/28 (7.14%) in controls. The incidence of ZIKV was 45.7% (27/59) overall: 15/31 (48.3%) in cases and 12/28 (42.8%) in controls. The general incidence of CMV was 37.2% (22/59): 12/31 (38.7) in cases and 10/28 (35.7) in controls. There were no significant differences in the outcomes of neonates among the infected and uninfected populations. Two neonates were born with microcephaly to ZIKA positive case mothers.

Conclusions

While no statistically significant differences were found between the controls and cases, taken together, the incidence of all three infections was extremely high in this set of pregnant women.
KNOWLEDGE OF HPV AND THE VACCINE AMONG YOUNG AUSTRALIAN MEN IN THE HYM STUDY

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Background and Aims

To explore HPV and vaccine knowledge among 18-35 y/o Australian males recruited via social-media into a HPV-vaccine effectiveness study, The HPV in Young Males (HYM) Study. HYM participants are part of a population where all women of the same age were vaccine-eligible.

Methods

The HYM Study, which is a part of the National HPV Monitoring Program, utilises Facebook’s targeted advertising for recruitment. The study involves online consent and questionnaire (including specific validated HPV knowledge questions) and a self-collected penile sample for HPV genotyping (Roche Linear Array). The HYM Study data were analysed to measure the impact of the Australian HPV Vaccination program, which has recently been extended to include males.

Results

From March-2015 to December-2017, 810 men completed questionnaires (median age 27; range 23-31); 19% live outside major cities, 2% identify as Aboriginal or Torres Strait Islander and 58% identify as heterosexual. Overall, 91% and 80% were aware of HPV and the HPV vaccine respectively, however only 53% knew the current vaccine program included both males and females. High HPV knowledge was defined by a composite survey score of over 70% with 38% of participants demonstrating high HPV knowledge. High HPV knowledge was significantly associated with being university educated (p=0.005), identifying as gay or bisexual (p>0.001) and being Australian born (p=0.003).

Conclusions

In a community based cohort of most unvaccinated men, the factor most strongly associated with high-HPV knowledge was a man’s self-reported sexuality, with men who identified as gay or bisexual having higher HPV knowledge.
QUALITATIVE EVALUATION OF A MULTI-COMPONENT INTERVENTION TO IMPROVE SCHOOL-BASED HPV VACCINATION

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\textsuperscript{6}Telethon Kids Institute, Vaccine Trails Group- Wesfarmers Centre of Vaccines and Infectious Diseases-., Perth, Australia
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\textsuperscript{11}National HPV Vaccination Program Register, Medical Director, Melbourne, Australia
\textsuperscript{12}Princess Margaret Hospital for Children and University of Western Australia and Telethon Kids Institute, School of Paediatrics and Child health and Wesfarmers Centre of Vaccines and Infectious Diseases, Perth, Australia
\textsuperscript{13}The Royal Women’s Hospital and The University Melbourne and Murdoch Children’s Research Institute, Women’s Centre for Infectious Diseases, Melbourne, Australia
\textsuperscript{14}The University of Adelaide, School of Public Health, Adelaide, Australia
\textsuperscript{15}Faculty of Health- & Department of General Practice, University of Technology Sydney and The University of Sydney, Sydney, Australia

Background and Aims

We evaluated a multi-component intervention to improve student knowledge, vaccine-related psychosocial outcomes and HPV vaccine uptake in 40 schools across two Australian states. Elsewhere we reported significant improvements in student knowledge, decisional involvement, vaccine related confidence and anxiety and reduced time to vaccinate. Here we present data from a qualitative sub-study regarding vaccination day processes to help elucidate mechanisms for the observed effects.

Methods

We purposefully recruited 6 intervention and control 6 control ‘case study’ schools (from study sample of 40 schools). In each school we conducted: focus groups with students, interviews with teachers, school nurses, immunisation nurses and parents, and observations of vaccination day processes. Qualitative data were analysed using thematic and discourse analysis.
Results

We undertook 17 focus groups with 111 students, and interviews with 22 parents, 11 school personnel, 10 immunisation staff, and 20 school observations over 12 vaccination days (minimum 1 per school). In schools where there was less compliance with best practice guidelines for school vaccination day set-up, data indicated increased student fear and anxiety. Lack of privacy made students feel uncomfortable, embarrassed, nervous or scared. Lack of separation of pre- and post-vaccinated students caused increased anxiety by rumour generation or direct observation of negative student experiences. Waiting times, supervision and distractions were secondary factors.

Conclusions

Careful implementation of best practice guidelines for school immunisation day set up can improve student experience with vaccination, by assisting in the reduction of needle related fear and anxiety, and increasing efficiency on vaccination day.
Background and Aims

Opportunistic cervical cancer screening with yearly Pap-smears was implemented in Germany in 1971. Following the National Cancer Plan and the Cancer Screening and Registration Law (KFRG) the S3 guideline process was started.

Methods

With financial support from German Cancer Aid, 21 scientific societies worked on evidence-based statements and recommendations (GRADE systeme). Two independent scientific institutes (M.Arbyn, WIV-ISP, Belgium; J.Kleijnen, KSR, UK) developed systematic reviews for this guideline.

Results

Meta-analysis by KSR could prove a better protection from cervical cancer through HPV-based screening in comparison to cytology. Therefore, the guideline group recommends HPV-based screening with three to five year intervals for women 30 and older within an organized screening program. Co-testing is an option. Women above 25 should be screened with cytology every two years. Non-participants should be re-invited, then offered self-sampling. End point for the triage algorithm is to detect and treat CIN 3. Any combination of positive HPV test and Pap result of ASC-US or worse should be referred to colposcopy. A single positive Pap smear should be triaged with HPV or p16/Ki67 dual-stain. CIN 1 and 2 should be reevaluated after six months. Co-testing should be used as test of cure. The Federal Joint Committee (G-BA) as highest decision-making Body issues directives for the new organized screening program replacing 1y-cytology by 3-yearly co-testing for women 35 and older which will start in 2019. Yearly Pap screening between 20-34 years will be continued, at least for the next 6-8 years when the program will be re-evaluated.

Conclusions

Guideline is available at http://www.leitlinienprogramm-onkologie.de/leitlinien/zervixkarzinom-praevention/
TRENDS IN CERVICAL CANCER SCREENING AND HPV VACCINATION AMONG WOMEN IN A LARGE HEALTHCARE SYSTEM, UNITED STATES

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Background and Aims

There is concern that HPV vaccine availability may influence cervical cancer screening behaviors. We analyzed ecologic trends in screening and vaccination among women enrolled in a large integrated healthcare system in California, and examined differences in screening and vaccination by race/ethnicity to identify potential disparities.

Methods

During 2008-2015, we calculated the proportion of 21-24 year old women who were up-to-date for 1) cervical cancer screening (Pap documented in that year or the 2 prior years); and 2) HPV vaccination (3 doses). We analyzed temporal trends in screening and vaccination rates using Cochran-Armitage tests. We also estimated odds ratios comparing screening and vaccination by race/ethnicity for 2015.

Results

Among 21-24 year olds, screening declined from 67% (38,770/57,890) in 2008 to 61% (49,380/81,576) in 2015 (p<0.001); the greatest declines occurred among 21 year olds (55% to 38%, p<0.001). HPV vaccine completion increased from 5% to 39% (p<0.001). Compared to Whites, Asians were significantly less likely to be screened [OR 0.69 (0.66-0.71), p<0.001], Blacks were significantly more likely to be screened [OR 1.11 (1.05-1.17), p<0.001]; Hispanics were similar to Whites. Compared to Whites, Blacks and Hispanics were significantly less likely to complete vaccination [OR 0.72 (0.69-0.76), OR 0.84 (0.81-0.87), both p<0.001]; Asians were similar to Whites.
Figure 1: Cervical cancer screening and HPV vaccination completion among 21-24 year old women, Kaiser Permanente Northern California, 2008-2015.
Conclusions

Declines in cervical cancer screening among 21-24 year olds are concerning; individual-level studies are also needed to determine whether vaccinated girls/women are less likely to receive recommended screening. Quality improvement efforts should focus on reducing racial/ethnic disparities in screening and vaccination, in addition to increasing completion of catch-up vaccination.

Table 1: Cervical cancer screening and HPV vaccination among 21-24 year women by race/ethnicity, Kaiser Permanente Northern California, 2015*. (n=73,359)

<table>
<thead>
<tr>
<th></th>
<th>Proportion Screened</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>Proportion Vaccinated</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>n=13,894</td>
<td>55%</td>
<td>0.69 (0.66, 0.71)</td>
<td>&lt;0.0001</td>
<td>41%</td>
<td>1.01 (0.97, 1.06)</td>
</tr>
<tr>
<td>Black</td>
<td>n=7,110</td>
<td>66%</td>
<td>1.11 (1.05, 1.17)</td>
<td>0.0001</td>
<td>33%</td>
<td>0.72 (0.69, 0.76)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>n=20,834</td>
<td>65%</td>
<td>1.03 (0.99, 1.07)</td>
<td>0.107</td>
<td>36%</td>
<td>0.84 (0.81, 0.87)</td>
</tr>
<tr>
<td>White</td>
<td>n=31,521</td>
<td>64%</td>
<td>REF</td>
<td></td>
<td>41%</td>
<td>REF</td>
</tr>
</tbody>
</table>

*Excluding women with “other” or “unknown” race
CERVIXCHECK: AN ONLINE SERVICE FOR AT-HOME CERVICAL CANCER SCREENING TO SERVE UNDER-SCREENED POPULATIONS IN BRITISH COLUMBIA, CANADA

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Background and Aims

Women who do not attend screening are at significantly higher risk of cervical cancer. Screening rates in British Columbia (BC), Canada have plateaued in the last decade. We propose an innovative intervention, CervixCheck, to improve access, particularly among populations who face barriers to clinic-based health services.

Methods

CervixCheck is an online service for cervical cancer screening where women who have not screened in >3 years order a self-sampling kit mailed to their home for high-risk HPV testing. Negative results are provided online while positive results are given by phone. Leveraging an established online platform for STI testing, embedded in an organized provincial screening program, pilot sites include urban immigrant communities (Fraser), and rural Indigenous communities (Northern BC). Presented are the project design, planning and community readiness activities that have taken place prior to implementation of CervixCheck.

Results

In Fraser, a digital health literacy survey, and user testing have informed initial acceptability. In the North, community consultation, focus groups with Indigenous women, and participation in community wellness events have led to the co-creation of project protocols. Communication and training toolkits have been developed for clinicians for the management and follow-up of participants. CervixCheck prospective feasibility pilots will launch in November 2018.

Conclusions

CervixCheck is the first online service using HPV self-collection based testing and mailed samples aimed to improve screening reach in under-screened populations. The service is embedded within a publicly funded health care system allowing continuity of care and follow-up for participants. Results will inform for potential implementation in HPV-based screening programs.
In December 2017, Australia’s National Cervical Screening Program (NCSP) transitioned from two-yearly cytology to five-yearly HPV testing. The transition was delayed from May 2017 because the National Cancer Screening Register to support the renewed NCSP was not complete. The cytology workforce had already started to reduce, so the cytology reimbursement amount was temporarily increased to help compensate for the delay. The register delay led to a gap in sending routine screening reminders in the months following transition. These changes may have affected screening behaviour or laboratory capacity to process cytology.

Methods

We used national Medicare claims data to examine: i) whether cytology utilisation rates changed in the lead-up to the NCSP transition; ii) test utilisation rates (for primary screening and follow-up) in the transition period.

Results

Cytology test utilisation did not appear to decline substantially in the lead-up to either May or December 2017. Cytology volumes were 2.2% higher in May-November 2017 than in May-November 2016, but reimbursement costs were 66% higher. Screening test utilisation (per 100,000 population) appears lower than usual in the early post-transition months, and a higher proportion of tests than usual was performed for follow-up compared to primary screening. Cytology volumes remained high in the transition month then dropped markedly.

Conclusions

Data suggest there were no unusual changes in utilisation or delays in screening in the period leading up to transition, but that there may have been a backlog of cytology processed in December 2017. Apparently reduced rates of screening post-transition reinforce the importance of reminders.
In the US, low rates of HPV vaccine coverage persist among adolescent and young adult women. The postpartum hospital stay is an opportunity for catch-up immunization. Addition of routine administration of HPV vaccine during inpatient postpartum care could significantly increase vaccine coverage in women. In April 2017, a pilot inpatient postpartum HPV immunization program (IPP-HPV) was initiated at Yale New Haven Hospital, Connecticut, USA. Our aim was to explore the attitudes and experiences of postpartum women regarding IPP-HPV to assess facilitators of and barriers to implementation of the program.

Methods

Qualitative, semi-structured interviews were conducted with inpatient postpartum women eligible for IPP-HPV using purposive sampling for representation by race/ethnicity, language, and vaccine dose acceptance vs rejection. Interviews were audio-recorded and transcribed for thematic analysis.

Results

Of 19 women interviewed (median age 23 years, range 15-26 years), 17 had received and 2 declined the inpatient dose. Most identified their ethnicity as Hispanic (53%), and 42% self-reported their race as Black, 16% as White, and 37% as “other”. Two-thirds were English-speaking and 32% were Spanish-speaking. The majority (74%) had not received prior doses of HPV vaccine. Thematic
analyses identified facilitators of and barriers to IPP-HPV (Table 1).

<table>
<thead>
<tr>
<th>Facilitators</th>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived health benefits of HPV vaccine</td>
<td>Self-perception of low or no risk from HPV</td>
</tr>
<tr>
<td>Perceived health benefits of vaccines in general</td>
<td>Lack of knowledge/familiarity with HPV vaccine</td>
</tr>
<tr>
<td>Positive inpatient provider communication/explanation</td>
<td>Poor outpatient provider communication</td>
</tr>
<tr>
<td>Positive outpatient provider communication</td>
<td>Poor inpatient provider communication/explanation</td>
</tr>
<tr>
<td>Convenience of IPP-HPV program for patient</td>
<td></td>
</tr>
<tr>
<td>Accessibility of outpatient follow-up care for subsequent doses</td>
<td></td>
</tr>
<tr>
<td>Unremarkable postpartum vaccine administration experience</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

Postpartum women appreciated the program’s convenience and viewed the HPV vaccine as valuable to their health. Future studies are needed to assess whether interventions to improve communication skills of both outpatient and inpatient providers of obstetrical care about HPV infection and HPV vaccine are effective strategies for implementation of IPP-HPV.
ASSESSMENT OF LONG TERM AVIDITY IN ALASKAN NATIVE BOYS AND GIRLS FOLLOWING QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINATION

**Background and Aims**

Prophylactic HPV vaccination elicits effective protection via serum antibodies; however, there is no known serologic correlate of protection. Antibody avidity is a measure of binding strength and a surrogate of immunological memory. To date, no studies have assessed HPV antibody avidity in vaccinated boys, and few have looked at long-term HPV vaccine-derived antibody avidity in girls.

**Methods**

We assessed antibody titer and avidity to HPV6, 11, 16, and 18 following 3 doses of quadrivalent HPV vaccination (4vHPV; 0/2/6 months) using serum from a longitudinal cohort of Alaska Native boys (n=31) and girls (n=46) aged 9–14 years. Proper consent was obtained. Time points tested were following each dose and once each year following vaccine series completion (out to two years for boys, and three years for girls).

**Results**

Antibody titer and avidity increased for all types following each dose in boys and girls. Avidity remained stable for all types in boys and girls while antibody titers decreased in the years following vaccine series completion. Antibody titer and avidity did not correlate for any HPV type. Avidity for HPV6 at each time point after dose 2 was significantly lower in boys compared with girls (see table below) despite no difference in titers.

**Conclusions**

<table>
<thead>
<tr>
<th>Time of blood draw</th>
<th>HPV6</th>
<th>HPV11</th>
<th>HPV16</th>
<th>HPV18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Dose 1</td>
<td>0.43 (0.39, 0.47)</td>
<td>0.39 (0.33, 0.45)</td>
<td>0.37 (0.34, 0.40)</td>
<td>0.37 (0.34, 0.41)</td>
</tr>
<tr>
<td>Post Dose 2</td>
<td>0.63 (0.60, 0.66)</td>
<td>0.55 (0.50, 0.59)</td>
<td>0.57 (0.54, 0.60)</td>
<td>0.58 (0.52, 0.63)</td>
</tr>
<tr>
<td>Post Dose 3</td>
<td>0.63 (0.61, 0.65)</td>
<td>0.59 (0.56, 0.63)</td>
<td>0.68 (0.65, 0.71)</td>
<td>0.67 (0.63, 0.71)</td>
</tr>
<tr>
<td>Post Series Year 1</td>
<td>0.64 (0.62, 0.66)</td>
<td>0.55 (0.51, 0.60)</td>
<td>0.67 (0.64, 0.70)</td>
<td>0.67 (0.62, 0.71)</td>
</tr>
<tr>
<td>Post Series Year 2</td>
<td>0.64 (0.62, 0.67)</td>
<td>0.55 (0.49, 0.61)</td>
<td>0.66 (0.62, 0.69)</td>
<td>0.69 (0.64, 0.73)</td>
</tr>
<tr>
<td>Post Series Year 3</td>
<td>0.65 (0.62, 0.68)</td>
<td>NA</td>
<td>0.68 (0.64, 0.71)</td>
<td>NA</td>
</tr>
</tbody>
</table>
Although clinical significance is unclear, persistence of quality type-specific antibodies (indicated by avidity) reflects effective affinity maturation of B cells, indicating long-term protection after vaccination. Further study of these participants is underway to continue to assess long-term response.
HIGH RESOURCE SETTINGS - VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

HIV-POSITIVE MEN’S KNOWLEDGE, EXPERIENCE, AND ATTITUDES REGARDING HPV VACCINATION


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Background and Aims

We assessed self-reported receipt of and willingness to receive HPV vaccine among men living with HIV.

Methods

In 2016-17, 1,688 men attending 9 specialty HIV clinics in Ontario, Canada, answered questions regarding HPV. Unvaccinated men were asked their (1) likelihood of receiving HPV vaccine; and (2) attitudes towards vaccination based on the Theory of Planned Behaviour. We used logistic regression to identify independent correlates being “likely” or “very likely” to accept an offer of free vaccination; results are reported as adjusted odds ratios (AOR) with 95% confidence intervals.

Results

Men (median 53 years, IQR 45-59) self-identified as gay (72%), heterosexual (19%), bisexual (8%) or other (1%). 63% had heard of the HPV vaccine and 45% knew that it was recommended for males. Only 14% said a health professional had discussed it with them and 7% were vaccinated. Men’s willingness to get vaccinated depended on its cost: 17% if $500CDN; 56% if $90CDN; and 74% if free. It was also correlated with: younger age (AOR per 10+ years: 0.64, 0.56-0.74); beliefs that vaccine is safe (AOR: 1.76, 1.26-2.46), one’s doctor considers it important (AOR:3.70, 2.29, 5.97), and people important to them encourage it (AOR: 1.38, 1.04-1.83). Negative correlates were beliefs that one’s behavior does not place them at risk (AOR: 0.29, 0.22-0.38) or the vaccine would not help because of preexisting HPV (AOR: 0.29, 0.19-0.43).

Conclusions

Men were generally willing to accept HPV vaccination, but its cost was a major barrier. Facilitators included provider recommendations and self-perceived risk.
HIGH RESOURCE SETTINGS - VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

THE MORE YOU KNOW: HPV VACCINE UPTAKE VARIES BY DEPTH OF HPV KNOWLEDGE – FINDINGS FROM THE HITCH COHORT STUDY

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Background and Aims

To determine whether HPV awareness and depth of HPV knowledge are associated with HPV vaccine uptake.

Methods

This sample comprised of 502 females who participated in the HPV Infection and Transmission among Couples through Heterosexual activity (HITCH) cohort study during 2005-2011. Data collected at baseline included: HPV vaccination status; HPV awareness; HPV knowledge (16 items); perceived risk of HPV infection and cervical cancer; Pap testing history; sexual history/behaviors; and sociodemographics. HPV vaccine uptake data was collected during study follow-up visits. HPV knowledge items were summed to create three ordinal measures assessing: 1) global knowledge (16 items); 2) simple knowledge (11-item sub-score); and 3) in-depth knowledge (5-item sub-score). Multivariate logistic regression models separately examined associations of awareness and knowledge measures with vaccine uptake, adjusting for age at enrollment and the baseline empirical confounders; results were summarised using adjusted odds ratios (OR) and 95% confidence intervals (CI).

Results

Females who were aware of HPV at enrolment were more likely to get vaccinated by study completion (OR=2.56, CI: 1.20-5.46). The likelihood of HPV vaccine uptake rose with every unit increase in the overall HPV knowledge score (OR=1.21, CI: 1.04-1.40), and this association was mostly driven by in-depth HPV knowledge (OR=1.37; CI: 1.04-1.80).

Conclusions

The relationship between HPV knowledge and vaccine uptake among young women, is likely driven by familiarity with more complex aspects of HPV (e.g. transmission), as opposed to more common knowledge (e.g. a cause of cervical cancer).
HIGH RESOURCE SETTINGS - VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

ADOLESCENT AND PARENT KNOWLEDGE ABOUT MALES AND HPV VACCINATION: MIXED METHODS FINDINGS FROM A RANDOMIZED CONTROLLED TRIAL AND PROCESS EVALUATION


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Background and Aims

We evaluated a multi-component intervention to improve student knowledge, vaccine-related psychosocial outcomes and HPV vaccine uptake in schools. Here we present data regarding knowledge about HPV and vaccination specifically pertaining to males.

Methods

We randomly sampled 40 schools (6,967 students) from two Australian states, and randomly allocated schools to intervention (21) or control (19). Intervention schools implemented HPV education. Student knowledge about HPV was evaluated by questionnaire pre-HPV doses 1 and 3. We conducted focus groups with students and interviews with parents regarding males and HPV vaccination in 6
intervention and 6 control schools. Qualitative data were analysed using thematic and discourse analysis.

Results

The mean percent increase in knowledge questions answered correctly was higher in intervention schools than control for girls (34 (95%CI:28,39)) and boys (30 (25,34)) at pre-dose 1. There was no differential effect between the sexes at pre-dose 1 (P=0.14 for interaction). Similar results were observed pre-dose 3. Qualitative data demonstrated students in intervention schools understood both sexes could acquire and transmit HPV, and have HPV-related cancers and genital warts. Students in control schools were largely unclear as to why males receive the HPV vaccine. Parents in both intervention and control schools had limited understanding about males and HPV vaccination.

Conclusions

All students in intervention schools had better understanding about HPV and HPV vaccination in general, as well as in relation to males, than control schools. Parents may benefit from targeted education about males and HPV vaccination to support vaccination decision-making.
ALL FOR THEM: DEVELOPMENT OF A PARENT-FOCUSED SOCIAL MARKETING CAMPAIGN TO INCREASE HPV VACCINATION

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Background and Aims

Despite recommendation of a 2-dose vaccination schedule for early adolescents, Human Papillomavirus (HPV) vaccination rates still trail those of other adolescent vaccines in the US. Social marketing (SM) campaigns have effectively reached audiences using health messaging, including promotion of HPV vaccination. This study aims to develop a parent-focused SM campaign to positively impact psychosocial factors related to HPV vaccination, and increase vaccine uptake and series completion.

Methods

Our discovery process included audience segmentation, detailed team member surveys, and in-depth interviews with experts in HPV vaccination, related cancers, immunology, and health communication. The resulting campaign, developed in partnership with a cause-based marketing firm, was implemented along with comprehensive school-based vaccination clinics in medically under-served areas.

Results

All for Them builds on the effective bundling approach used in healthcare settings by encouraging parents to ensure full protection for their child by getting all of the recommended adolescent vaccines. Creative collateral illustrate concepts such as “You wouldn’t give your kid half a backpack” (tagline: “It’s All for Them. Because All is Better than Some.”) Bilingual (English/Spanish) materials are disseminated via multiple small media channels (school-based, community-based, and targeted online advertising). The campaign was disseminated to parents of students (n=23,483) in 28 public middle schools, as well as adults in targeted zip codes on social media (n=77,517). Of clinic participants due for HPV vaccination (n=595), 96% of parents consented for their child to receive the vaccine.
Conclusions

*All for Them* represents an innovative SM campaign that may positively impact parental decisions to vaccinate their child against HPV.
HIV-POSITIVE GAY MEN'S KNOWLEDGE AND PERCEPTIONS OF HUMAN PAPILLOMAVIRUS (HPV) AND HPV VACCINATION: A QUALITATIVE STUDY

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Background and Aims

Gay, bisexual, and other men who have sex with men (gbMSM) living with HIV are disproportionately impacted by HPV-associated anal cancer. Fortunately, HPV vaccination has proven efficacy in preventing both anogenital warts (condyloma) in males and anal cancer precursors in gbMSM.

Methods

We conducted in-depth, semi-structured interviews with 25 HIV-positive gay men in Toronto to gain an understanding of their knowledge and experiences related to HPV and HPV vaccination. Participants were part of the HPV-SAVE Study, a Canadian study on anal cancer screening, and they received invitations for screening from their primary care doctors. Interviews were analyzed using NVivo qualitative software following a Grounded Theoretical Approach.

Results

Men described a lack of prior knowledge of the health consequences of HPV for people living with HIV, coupled with financial barriers to vaccine access. Participants did not articulate concerns with vaccine safety in general. Men frequently reported initial beliefs that HPV was predominantly—or exclusively—a risk for females or only young girls, and thus had not considered the vaccine necessary. Some participants remained uncertain if the current availability of the vaccine, and their newly acquired knowledge of its importance, was “…too little, too late” because of their age and/or HPV exposure.

Conclusions

Improving access and uptake of HPV vaccination requires addressing both financial barriers to vaccination as well as increasing HPV health literacy, particularly by reframing the long-standing gendered associations of HPV. Clear, tailored messages regarding vaccination from healthcare providers would be beneficial for gbMSM, including gbMSM living with HIV.
EXAMINING THE FACTORS ASSOCIATED WITH CANADIAN HEALTHCARE PROVIDERS’ DECISION TO RECOMMEND HPV VACCINATION TO MALES

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Background and Aims

Human papillomavirus (HPV) is responsible for 90% of anal cancers—a malignancy disproportionately impacting men who have sex with men (MSM), particularly those living with HIV. Recognizing the importance of health-care provider (HCP) recommendation in vaccine uptake, we sought to characterize the attitudes of Canadian physicians, nurses, and pharmacists in recommending HPV vaccine to males, focusing on MSM and those living with HIV.

Methods

A 32-item online survey assessing the knowledge and attitudes of Canadian HCP (physicians, nurses and pharmacists) on HPV vaccination in males was administered via email link to HCP from 10/2017 to 04/2018.

Results

273 HCPs responded: 194 (71%) nurses, 39 (14%) physicians, and 38 pharmacists (14%), of which 120 (44%) considered themselves experts in STI care. 169 (62%) indicated that they universally recommend HPV vaccination to males, regardless of age, sexual orientation, and HIV serostatus. The most common group for whom vaccination was recommended were MSM under 26, regardless of HIV status (158/273; 58%). The most commonly-cited reason for this specific recommendation was the Canadian guideline recommending HPV vaccine to all MSM over the age of 9. Some HCP-identified barriers to vaccine recommendation were: lack of universal cost coverage (79%), the lack of availability of MSM-specific resources/education (57%), and inadequate time for discussion during clinic visits (28%).

Conclusions

Though reassuring in demonstrating support for vaccination of MSM by a majority of Canadian HCPs surveyed, this study highlights some HCP-based barriers to HPV vaccine recommendation to a group being increasingly recognized as a priority population for HPV vaccine receipt.
Background and Aims

HPV vaccination rates have lagged behind other adolescent vaccines in the USA. Endorsement from both providers and staff is needed for successful quality improvement (QI) interventions focused on HPV vaccination. We assessed differences in HPV vaccine attitudes and perceived support/assistance needs between providers and staff at pediatric practices participating in an HPV vaccine QI intervention study.

Methods

Providers (physician/nurse practitioner/physician assistant) and staff (clinical/non-clinical) in 24 pediatric practices in Tennessee, USA, were invited to complete a survey at study initiation. Surveys were completed by 137 providers and 218 staff. Analyses compared HPV vaccine attitudes and perceived support needs between providers and staff.

Results

Compared to staff, providers had more positive attitudes about HPV vaccination: confidence in effectiveness (64% vs 22% Very High, p<0.001), confidence in safety (60% vs 23% Very High, p<0.001), and likelihood to recommend to family member/friend (93% vs 55% Very Likely, p<0.001). Providers perceived higher strength of evidence for HPV vaccine guidelines (41% vs 10% Very Strong, p<0.001). Staff perceived that their own practice’s HPV completion rate would be higher relative to other practices in the region (58 vs 54 ranking, p=0.029). Compared to staff, providers perceived a greater need for support/assistance to increase HPV vaccine rates (51.0 vs 47.6, p=0.043) and support/assistance to implement QI (57.3 vs 47.9, p<0.001), on a 1-100 scale.

Conclusions

Pediatric practices may need to receive external support/resources to implement QI focused on HPV vaccination. Staff training about the safety, effectiveness, and importance of HPV vaccination may enhance the effectiveness of future QI interventions.
Background and Aims

For initial recommendation of HPV vaccine, the presumptive approach with equal emphasis on all vaccines (i.e., announcement of all adolescent vaccines due today) has been demonstrated as more effective than shared decision-making and/or singling out HPV vaccine. We examined the association of provider-level factors with use of the presumptive approach.

Methods

Providers (N=137) in 24 pediatric practices in Tennessee, USA, completed an online survey. Providers chose one of six statements closest to how they typically introduced adolescent vaccinations to 11-12 year-olds. The outcome variable was dichotomized (Yes/No) for selection of the presumptive approach: “Your child is due for three vaccines: Tdap, HPV, and meningococcal vaccines.” Generalized estimating equations (GEE), adjusting for clustering in practices, were fit on the outcome variable with provider type (physician/non-physician) and four scales: provider barriers to HPV vaccination (10 items; e.g., personal discomfort, lack of time), parental barriers to HPV vaccination (7 items; e.g., safety concerns, association with sexual activity), self-efficacy (6 items; confidence in ability to recommend HPV vaccine), and outcome expectations (4 items; belief that will influence patients’ decision), each ranging 0-100.

Results

Thirty-four percent of physicians and 36% of non-physicians used the presumptive approach (p=.80). Greater provider barriers (OR=0.58; CI=0.38-0.87) and parental barriers (OR=0.76; CI 0.59-1.00) were associated with lower odds of using of presumptive approach. Greater provider self-efficacy (OR=1.38; CI=1.01-1.76) and outcome expectations (OR=1.70; CI=1.30-2.22) were associated with higher odds of using presumptive approach.

Conclusions

Future interventions for increasing HPV vaccine uptake could target use of the presumptive approach by addressing these provider-level factors.
BARRIERS TO HUMAN PAPILLOMAVIRUS VACCINE SERIES COMPLETION IN AN INSURED POPULATION: RESULTS FROM A PILOT STUDY
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Background and Aims
Although human papillomavirus (HPV) vaccines are safe and efficacious, their role in cancer prevention is limited by the requirement for multiple doses. We conducted a pilot study to understand barriers to HPV vaccine series completion among Kaiser Permanente Washington members with clinical documentation of only one dose of vaccine.

Methods
We interviewed parents/legal guardians of eligible 11-17 year-old females (n=10) and males (n=18), and eligible 18-31 year-old females (n=20) and males (n=9), about their reasons for not completing the HPV vaccine series. We also collected sociodemographic, clinical, and health plan administrative data.

Results
Most participants were non-Hispanic white (70.4%). Reasons for not completing the HPV vaccine series varied by age and sex. Parents/legal guardians of boys were more likely to report not being aware additional doses were needed (41%) compared with parents/guardians of girls (14%), and were more likely to cite the inconvenience of returning for multiple doses (24% for boys vs. 14% for girls). However, parents/guardians of girls were more likely than those of boys to express concern about the HPV vaccine or vaccines in general (43% vs. 18%). Among adults, the most common reason for not completing the series was the inconvenience of returning for multiple doses (31% of females and 43% of males). Adult females were more likely to report not being aware additional doses were needed (31% compared to 0% of males).

Conclusions
Interventions to increase awareness of the multiple-dose requirement and address concerns about vaccines, particularly among families with girls, may facilitate completion of the HPV vaccine series.
Background and Aims

To evaluate factors related to dental and dental hygiene students' willingness to train (WT) and to willingness to administer (WA) the human papillomavirus (HPV) vaccine in the dental setting.

Methods

A 153-item online survey was administered to United States students in 15 oral health programs. Secondary data analyses were conducted in SAS Version 9.4. Unadjusted and multivariable logistic regression were conducted and odds ratios (OR), 95% confidence intervals (CI), and p-values (p<0.05) were reported.

Results

Data from N=306 students were analyzed. Receiving HPV vaccination information from professional journals or publications was positively associated with WT and WA (p<0.05). Agreeing that HPV vaccination recommendation (OR=1.95, 95%CI=1.14-3.35, p=0.015) and administration (OR=3.79, 95% CI=1.63-8.81, p=0.002) is in the dental professional’s scope was positively associated with WT and WA even when adjusting for other factors (not my role to recommend, not enough time to discuss, not comfortable discussing, previous patient communication about HPV). Those who saw 21 or more patients a week (OR=4.47, 95% CI=1.14-17.58, p=0.032) and who agreed that HPV vaccine administration was in the dental professional’s scope (5.9, 95% CI=2.27-15.3, p<0.001) had higher odds of WA even when adjusting for other factors (not enough information, not my role, not comfortable discussing, previous communication about HPV).

Conclusions

Engaging dental providers in HPV vaccine education and vaccine administration can reduce HPV oropharyngeal cancers, which have now surpassed cervical cancer rates in the United States. Professional guidelines and endorsement of HPV vaccination from professional organizations are needed to engage dental providers in HPV vaccination efforts.
HIGH RESOURCE SETTINGS - VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

COMPARISON OF SPF10-DEIA-LIPA SYSTEM VERSION 1 WITH TYPE-SPECIFIC QPCR FOR DETECTION OF HPV59 INFECTIONS, EVIDENCE FOR MISSING HPV59 INFECTIONS AND IMPACT ON VACCINE EFFECTIVENESS MEASUREMENTS

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Background and Aims

The broad spectrum L1-based SPF10-DEIA LIPA system is widely used for HPV detection and typing in many epidemiological studies. This assay is known to be highly sensitive for most high risk HPVs but is less sensitive at detecting HPV59 infections. Here we investigated the sensitivity of this system on the detection of HPV59 infections and show the impact on vaccine effectiveness (VE) estimates.

Methods

Anogenital swabs collected in a biennial cross-sectional study among 16- to 24-year-old visitors to sexually transmitted infection clinics before and after introduction of HPV vaccination were tested using the SPF10-DEIA LIPA system. HPV59 viral loads were determined using a highly sensitive HPV59 qPCR viral load assay. HPV59 subtypes were determined by L1 sequencing.

Results

In total 6080 anogenital swabs collected in 2009, 2015 or 2017 were included in this study. All samples were tested with the SPF10-DEIA-LIPA system before and after introduction of HPV vaccination were tested using the SPF10-DEIA-LIPA system. HPV59 viral loads were determined using a highly sensitive HPV59 qPCR viral load assay. HPV59 subtypes were determined by L1 sequencing.

In total 6080 anogenital swabs collected in 2009, 2015 or 2017 were included in this study. All samples were tested with the SPF10-DEIA-LIPA system before and after introduction of HPV vaccination were tested using the SPF10-DEIA-LIPA system. HPV59 viral loads were determined using a highly sensitive HPV59 qPCR viral load assay. HPV59 subtypes were determined by L1 sequencing.

HPV59 infections are missed by the SPF10-DEIA-LIPA system.

Associations of specific HPV59 subtypes and vaccination status of the participants in SPF10-DEIA-LIPA missed HPV59 infections were determined. Preliminary data suggest more missed infections in non-vaccinated participants and no differences in HPV59 subtypes in missed infections. VE measurements of the bivalent HPV vaccine against HPV59 infections based on both detection methods show a clear impact on the VE in preliminary results suggesting unmasking.

Conclusions

HPV59 infections are missed by the SPF10-DEIA-LIPA system.
HIGH RESOURCE SETTINGS - VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

EFFECTIVENESS OF HUMAN PAPILLOMAVIRUS VACCINATION IN LUXEMBOURG
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Background and Aims

In Luxembourg the HPV vaccination program was introduced in 2008, offering bivalent (BV) or quadrivalent (QV) vaccines to 12-17 year old girls free of charge. In this study we estimate its impact on HPV prevalence in vaccinated and unvaccinated women 7 years after program implementation.

Methods

A population based cross-sectional study among women aged 18-29 years was conducted in 2015-2017 in Luxembourg. Participants were recruited at Family Planning or at private gynaecology practices. Cervical swabs were tested using Anyplex II HPV28. Vaccination status was verified using vaccination records of the social security database. Data analysis was performed using logistic regression adjusting for age and number of sexual partners.

Results

Among 716 participants, vaccination with at least 2 doses of BV and QV was confirmed for 18.3% and 30.2% of participants, respectively, whereas 33.2% of participants had no vaccine records and reported not being vaccinated. Prevalence of HPV16/18 was 0.6% in vaccinated versus 8.0% in unvaccinated women (p<0.001). Prevalence of HPV39/59 was 9.4% in vaccinated versus 5.0% in unvaccinated women (p=0.048). Adjusted 2-dose vaccine effectiveness against HPV16/18, HPV6/11 and HPV31/33 was 87.0% (95%CI 38.5-97.3, p=0.01), 84.2% (95%CI 52.4-94.8, p=0.001), and 70.8% (95%CI 28.1-89.1, p=0.007) respectively. In women vaccinated before sexual debut, 2-dose vaccine effectiveness against HPV16/18 was 100%.

Conclusions

Our study confirms studies in other countries suggesting high effectiveness of HPV vaccination against vaccine types HPV6/11/16/18 and cross protection against HPV31/33. Further investigation is required to assess whether genotype replacement could be occurring.
IDENTIFYING EVIDENCE GAPS IN UNDERSTANDING FACILITATORS AND BARRIERS ASSOCIATED WITH EXPANDING HPV VACCINATION PROGRAMS TO MALES

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Background and Aims

Increased awareness of the Human Papillomavirus (HPV)-related disease burden in males is driving the expansions of female vaccination programs to males in some countries across the world.

This study aimed to assess current understandings of the key facilitators and barriers associated with policies for male HPV vaccination programs and identify evidence gaps.

Methods

We performed a literature review using three databases (PubMed, Google Scholar, Cochrane Reviews) to identify publications from 2007-2017 describing male HPV vaccination programs. Eligible literature included peer-reviewed research studies, commentaries, systematic reviews, and grey literature.

Results

We screened 160 publications and extracted data from 50. The existing literature is predominantly focused on estimating the HPV-related disease burden in males and females, or assessing vaccination coverage rates and effectiveness/impacts of female HPV vaccination programs. Only a few examined issues related to male HPV vaccination program strategies. Those that did, emanated from early adopters of male program (e.g. Australia, Austria, Canada, and the USA). Most studies described existing recommendations for male HPV vaccination or developed models to assess the potential impacts of vaccinating males on the country-wide HPV-related disease burden, and few showed the recognition of the HPV-burden as a gender-neutral public health problem.

Conclusions

Acknowledgement of the impact of HPV on males has led to a greater expansion of gender-neutral HPV vaccination programs, but little information exists on key drivers influencing policy and program expansion. Future studies evaluating these issues would be valuable to other countries that have not yet expanded their HPV vaccination programs to males.
EFFECTIVENESS OF ONE-DOSE OF QUADRIVALENT HPV VACCINE AGAINST HSIL AND CIN; A DATA-LINKAGE STUDY

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Background and Aims

Although originally approved for three-doses, HPV vaccines were later approved for a two-dose schedule for 9-14 year olds. Post-hoc analyses have shown similar efficacy compared to three-doses even after one-dose. We aimed to estimate effectiveness of one-dose of quadrivalent vaccine against high-grade squamous intraepithelial lesion (HSIL) and cervical intraepithelial neoplasia grade 2 or higher (CIN2+) in screened young women (YW).

Methods

Data-linkage was performed between the population Cervical Cancer Screening Program (CCSP) and immunization registries in British Columbia, Canada. Occurrence of HSIL and CIN2+ were compared in a screening cohort of YW born between 1994-2005 who were unvaccinated or vaccinated between 9-14 years of age with one-dose or were completely vaccinated (2-doses 150 days apart or 3-doses). Relative incidence rates (RR, (95%CI)) were calculated using adjusted Poisson regression.

Results

We found significant protection among YW completely vaccinated (n=12,910, mean age in years at vaccination 13.8±1.6), adjusted RR for HSIL 0.62 (0.49-0.80), CIN2+ 0.50 (0.34-0.74) compared to unvaccinated (n=12,762). No significant protection after one dose (n=348, mean age in years at vaccination 13.5±1.0) against HSIL and CIN2+ was observed, respective adjusted RR 0.98 (0.35-2.14) and 1.42 (0.35-3.85).

Conclusions

In this observational study, while no evidence of protection of one-dose against HSIL and CIN2+ was observed, YW who have received one-dose may have been previously exposed or had other underlying exposure risks, the sample size was small and the analysis could have been impacted by other biases from the administrative data. Further analyses with larger numbers are required to assess the impact of single dose vaccination.
HIGH RESOURCE SETTINGS - VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

AFTER A TWO-DOSE SCHEDULE IN GIRLS NO PREVALENT HPV16/18 INFECTIONS WERE FOUND; AN INTERIM ANALYSIS FROM THE QUADRIVALENT HPV VACCINE EVALUATION STUDY.

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Background and Aims

HPV vaccines were originally licensed in a three-dose schedule. However, for adolescents <15 years, two doses of vaccine are now recommended based on immuno-bridging studies. Limited data are available on effectiveness of <3 dose schedules. We report an interim analysis of HPV prevalence after two-doses of quadrivalent vaccine.

Methods

QUadrivalent HPV vaccine Evaluation STudy (QUEST) is a Canadian cohort of girls 9-14 years at enrollment. Based on their provincial program, girls received either two or three doses of vaccine. Comprehensive follow-up includes self-collected vaginal specimens, blood samples and online health surveys. First available swab of two-dose participants (available up to 2017-08-20) was used to obtain an interim HPV prevalence estimate. Samples were screened for high-risk (hr) HPV using the Roche Cobas HPV Test, and if positive, genotyped by Roche Linear Array HPV Genotyping Test.

Results

For this analysis, swabs from 1133 girls were available. Median time since first dose: 4.4 years (range 3.3-9.3), median interval between the two doses was 198 days (range 62-364), median age of participants at time of swab collection was 15.7 years (range 14.3-22.5) and 14.2% of participants reported to have ever had sexual intercourse. Among sexually actives a hrHPV prevalence of 9.32% (95%CI 5.31-14.90%) was observed. No infections with HPV16/18 were identified (0.00% 95%CI 0.00-2.43%).

Conclusions
In this analysis to estimate HPV prevalence among sexually active recipients of a two-dose quadrivalent HPV vaccination schedule, no HPV16/18 infections were identified, suggesting protection for at least 4 years. Long-term follow-up in the full cohort is awaited.
RATES OF CERVICAL INTRAEPITHELIAL NEOPLASIA IN WOMEN IN BRITISH COLUMBIA: A DATA LINKAGE EVALUATION OF THE SCHOOL-BASED HPV IMMUNIZATION PROGRAM

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Background and Aims

HPV vaccines are highly efficacious in the prevention of cervical cancer precursors in large-scale trials. However, monitoring of population-based data is critical to understand real-world vaccine impact. Our analysis evaluates the impact of the school-based quadrivalent HPV immunization program on cervical dysplasia in British Columbia, Canada.

Methods

Data linkage was performed using records from the provincial Cervical Cancer Screening Program and immunization registries. In screened women born in 1994 through 2005, the relative incidence rates (RR) of precancerous outcomes based on cytology and histopathology (CIN2, CIN3 and CIN2+) using adjusted Poisson regression were compared between HPV vaccine recipients and unvaccinated women.

Results

Women who received any HPV vaccine dose between the ages of 9-14 (n=14,199) had a RR=0.51 (95%CI 0.35-0.75) for CIN2+ compared to unvaccinated women (n=12,762). There was no significant difference in the RR of CIN2+ in women with incomplete series (not in accordance with recommended schedule at time of vaccination) compared to unvaccinated women. There was a significant increase in CIN2+, RR 2.50 (95%CI 1.25-4.68) in women who received complete HPV series (all recommended doses based on schedule) starting at 15 years or older (n=1,312), compared to women with complete series beginning at 9-14 years of age (n=12,910).

Conclusions

Women who received HPV vaccine at 9-14 years of age had half the rate of high grade cervical lesions compared to unvaccinated women. Pre-adolescent immunization should be encouraged, as per the provincial schedule. Continued program monitoring will be important for measuring long-term population impact.
IMPACT OF THE HUMAN PAPILLOMAVIRUS IMMUNIZATION PROGRAM ON RATES OF ANOGENITAL WARTS IN BRITISH COLUMBIA, CANADA 2000-2017


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Background and Aims

In September 2008 a publicly funded HPV-4 vaccine program was implemented for girls born in 1994 or later in British Columbia (BC), Canada. To determine the impact of the vaccine on anogenital warts (AGW), diagnosis rates were measured among women who have sex with men (WSM), men who have sex with women (MSW), and men who have sex with men (MSM).

Methods

AGW diagnoses were ascertained from an electronic medical record system used at 16 geographically dispersed high volume sexually transmitted infection clinics across BC. Clients born between 1970-1999 who accessed services from 2000-2017 were included. Rates were calculated as new AGW diagnoses over person-years (PY) at risk, and stratified by age group, period of clinic visit, and birth cohort. Age-period-cohort Poisson modeling produced adjusted relative rates (aRR).

Results

There were 204,832 clinic visits by 85,158 unique individuals: 28,366 (33%) WSM, 35,688 (42%) MSW and 14,534 (17%) MSM. Adjusted for age and period, overall AGW rates were lower among birth cohorts 1994-1999 compared to 1988-1993 (2.74 vs. 3.45 cases/100PY, aRR: 0.79, 95%CI: 0.64, 0.98). AGW rates were significantly lower among WSM (1.24 vs. 2.98 cases/100PY, aRR: 0.42, 95%CI: 0.27, 0.66), lower among MSW (2.95 vs. 3.91 cases/100PY, aRR: 0.75, 95%CI: 0.52, 1.11), but similar among MSM (3.30 vs. 3.08 cases/100PY, aRR: 1.21, 95%CI: 0.73, 1.57).

Conclusions

AGW rates were lower among WSM who had access to publicly funded vaccine, and MSW born after 1994, likely from herd immunity. No difference in AGW rates among MSM may reflect delayed access to HPV vaccine.
FACTORS ASSOCIATED WITH HPV VACCINATION COMPLETION IN A REPRESENTATIVE SAMPLE OF ADOLESCENTS IN PUERTO RICO

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Background:

Human papillomavirus (HPV) vaccination continues to lag behind other adolescent vaccines, especially in areas with pervasive disparities in HPV-related cancers. The purpose of this study was to examine HPV vaccine completion among adolescents in Puerto Rico.

Methods:

Consulta Juvenil IX was a survey in a representative sample (n=3,982) of 7th-12th grade students selected using a multi-stage stratified cluster sampling design. Students completed a self-administered questionnaire. HPV infection knowledge was assessed using a 6-item scale. Proportions were compared using chi-square tests. A multiple logistic regression model was fitted to evaluate characteristics related to vaccination completion by comparing teens only partially vaccinated with those who had completed the 3-dose series.

Results:

Although 44.5% of students had good HPV knowledge, only 33.7% reported any vaccination (10.5% completed the series and 23.2% only had 1-2 doses). Significantly more females knew about HPV or had been completely vaccinated than males. Full vaccination was also higher in private school students and among those who had good knowledge. Among sexually active students, 41.3% had good knowledge, but only 9.4% had been fully vaccinated. Characteristics associated with vaccination completion included: being female (OR: 1.5, 95%CI: 1.1-2.2), older age (OR: 1.9, 95%CI: 1.3-2.7), and attending private school (OR: 1.7, 95%CI: 1.2-2.4). Living with both parents, good HPV knowledge, and sexual activity were not associated with vaccination after adjusting for all covariates.

Conclusions:

Understanding what characteristics are associated with HPV vaccination completion is critical to reducing disparities in cervical and other HPV-related cancers, especially among Hispanic adolescents.
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MULTIPLEX IMMUNOASSAY TO MEASURE ANTIBODY RESPONSE TO NINE HPV VACCINE TYPES

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Background and Aims

Well-characterized multiplexed assays are important to measure the immune response to current HPV vaccines, evaluate new vaccine formulations and vaccine implementation strategies. We compared the nine-valent HPV virus-like particle (VLP) direct IgG ELISA developed on the Meso Scale Discovery (MSD) electrochemiluminescence (M9ELISA) platform to the Competitive Luminex Immunoassay (cLIA).

Methods

Sera (n=4426) from unvaccinated individuals previously tested with cLIA by Pharmaceutical Product Development (PPD) were re-assayed with M9ELISA. The M9ELISA plates were prepared with purified L1+L2 VLPs of HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 coated on 10-spot/well MSD microplates. Results of ELISA on three serial dilutions of serum were read on an MSD imager, and titers calculated using the parallel line method. Seropositivity was determined based on cut-off values generated from children’s sera. Evaluations included dynamic range, assay reproducibility and comparison to cLIA results.

Results

The dynamic range was about 1000-fold for each HPV type and reproducibility was within ≤25% coefficient of variation for all types. Seropositivity was higher with MSD ELISA than cLIA for all types. Overall agreement between assays ranged from 42-77% with positive percent agreement from 80 - 98%. Antibody titers showed weak to moderate correlation (r between 0.3-0.7) between assays.

Conclusions

As has been shown with other direct HPV ELISAs, the M9ELISA detects more positive samples than cLIA. The M9ELISA can serve as a useful platform for high-throughput, sensitive and simultaneous quantitation of the antibody responses to nine HPV vaccine types.
Background and Aims

Human papillomavirus (HPV) infection carries high disease burden in both genders, accounting for 5% of total cancers for males and females, the most common being oropharyngeal and cervical cancers. More countries are expanding HPV vaccination to males in National Immunization Programs.

We aim to describe the evolution and status of HPV gender-neutral vaccination (HPV-GNV) worldwide.

Methods

A comprehensive search using official government websites was conducted, complemented by a literature review (2008-2018) including publications in English, Spanish, and Portuguese describing male HPV vaccination programs.

Results

Twenty-six countries with HPV-GNV were identified; 10 in North and South America, 13 in Europe, and 3 in Middle-Africa/Asia-Pacific. HPV vaccination for males was first recommended as routine immunization in the US and Puerto Rico in 2011. Czech Republic was the most recent to include males for the nonavalent vaccine in early 2018. Antigua directly adopted an HPV-GNV program in 2017. The target age for male vaccination varies from 9 to 26 years according to each country’s recommendation and predominantly focuses on adolescents. Delivery locations vary by country, including schools and/or medical centers. In 2018, Germany and UK are evaluating expanding HPV vaccination to males; Sweden is awaiting final decision. In addition to HPV-GNV programs, several countries have elected to include GNV only among men who have sex with men.

Conclusions

Increasingly, countries are expanding HPV vaccination to include males to improve population-level HPV infection control and directly prevent HPV-related disease in males. HPV-GNV has accelerated, with more than 50% of countries adopting such recommendations in the last 2 years.
Background and Aims

Multilevel frameworks of HPV vaccination are needed to inform intervention development. However, no multilevel frameworks exist depicting factors associated with HPV vaccination among females and males and with both initiation and completion outcomes. We conducted a systematic review of reviews to identify individual-, provider-, and clinic-level factors associated with HPV vaccination outcomes among U.S. adolescents to develop a multilevel framework of HPV vaccination.

Methods

We searched Medline, PsychInfo, Pubmed, CINAHL and ERIC databases for reviews published 2006 to February 2017 that included parental-, provider-, or clinic-level factors associated with HPV vaccination in adolescents. Coders independently screened reviews and extracted data, including ratings of review quality. We integrated correlates and predictors of vaccination into a multilevel framework.

Results

Eleven reviews and one meta-analysis met inclusion criteria. Individual factors associated with vaccination outcomes included: adolescent and parent socio-demographic characteristics and interactions with the healthcare system; parental intentions; parental knowledge; parental beliefs about vaccine benefits, effectiveness, safety, and need; and parental perceived risk of child developing an HPV-related disease (Figure 1). Recommending the vaccine was the only provider-level factor associated with vaccination. Clinic-level factors included provider assessment and feedback and patient reminders.
Conclusions

This review consolidates findings of well-studied factors associated with HPV vaccination among U.S. adolescents. Further research is needed examining the association between parental intentions and vaccination outcomes at the individual-level, assessing provider psychosocial factors associated with vaccine recommendation behaviors and outcomes at the provider-level, and identifying factors associated with successful adoption and implementation of effective clinic-systems to increase vaccination outcomes.
IMPACT OF HPV VACCINATION ON HPV 16/18-RELATED PREVALENCE IN KOREAN WOMEN AGED 20 TO 60 WITH ABNORMAL CERVICAL CYTOLOGY


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Background and Aims

HPV vaccination have been provided for prevention of cervical cancer since 2007 in Korea. This study was to identify the impact of HPV vaccination on HPV 16/18-related prevalence in HPV-infected women older than twenty years in Korea.

Methods

During 2010-2016, 1,300 HPV-positive women with atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL) were enrolled in the HPV cohort study from five hospitals in Korea. Their HPV DNA testing were undergone at enrolment. Socio-demographic, epidemiologic and clinical data including HPV vaccination history were obtained through standardized case report form. These data were analyzed using chi-square test and logistic regression model to compare HPV 16/18-related prevalence between vaccinated and unvaccinated patients.

Results

335(25.8%) had vaccinated history among 1300 HPV-infected patients. For women who initiated vaccination >24 months, there was a significantly lower HPV 16/18 prevalence compared to women who were not vaccinated (adjusted prevalence ratio (aPR)=0.426, 95% confidence interval (CI)=0.205-0.886). Also, HPV 16/18/31/33/52 Prevalence were a significant lower in women initiated vaccination >24 months than unvaccinated women (aPR=0.574, 95% CI: 0.338-0.976). For impact of
>24 months after vaccination, HPV 16/18/31/33/52 prevalence were a significant lower especially in vaccinated women with LSIL than unvaccinated women (aPR=0.350, 95% CI: 0.129-0.945).

Conclusions

This study shows the impact of HPV vaccination on HPV 16/18-related prevalence in women with abnormal cervical cytology who initiated vaccination at least 24 months in Korea. We provide the preliminary information for evaluation of the impact of HPV vaccination among adult women.
Background and Aims

Schools are the primary setting for the delivery of adolescent HPV vaccination in Australia. Although this strategy has achieved high coverage, gaps persist and the reasons are mostly unknown. This study identifies school-level correlates of low vaccination initiation in NSW, Tasmania, and Western Australia with the aim to inform interventions to increase uptake.

Methods

We calculated 2016 school-level initiation percentages (first doses/total enrolments), with low initiation defined as levels ≤25th percentile. Using multivariable logistic regression, we investigated associations between socio-demographic and other school factors and low initiation at the school-level.

Results

The median school-level initiation percentage among the 1,286 schools included in the analysis was 85.5%; 327 schools were classified as having low initiation (≤75%). In the multivariable model, low initiation was more likely in schools catering for special educational needs (aOR=3.6, 95%CI=1.6-7.9) compared to mainstream schools; small (aOR=4.0, 95%CI=2.3-6.8) and medium-sized schools (aOR=2.9, 95%CI=1.8-4.6) compared to large schools; and schools with the lowest school attendance rates (aOR=2.5, 95%CI=1.5-4.3) compared to those with the highest rates. Schools with low initiation percentages were also more likely to be located in one of the three states (aOR=5.9, 95%CI=3.3-10.6) and significant heterogeneity (p= 0.0320) between remoteness areas was
observed, with a trend towards lower coverage in schools in remote areas (aOR=1.9, 95%CI=1.0-3.6) compared to schools in major cities.

Conclusions

These findings provide new information to further improve HPV vaccination initiation in Australia and address inequities. The results will guide targeted programs, including for particular school types such as those catering for special educational needs, schools in particular geographical locations, and schools with low attendance rates.
A RANDOMISED CONTROLLED TRIAL OF A MULTI-COMPONENT INTERVENTION TO IMPROVE SCHOOL-BASED HPV VACCINATION: IMPLEMENTATION AND IMPACT OUTCOMES


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5Women’s and Children’s Hospital and The University of Adelaide, Vaccinology and Immunology Research Trials Unit, Adelaide, Australia
6The University of Sydney, School of Public Health, Sydney, Australia
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8The Kirby Institute- University of New South Wales, Biostatistics and Databases Program, Sydney, Australia
9National HPV Vaccination Program Register, Medical Director, Melbourne, Australia
10Princess Margaret Hospital for Children and University of Western Australia and Telethon Kids Institute, General Paediatrics and Immunology- School of Paediatrics and Child health- Vaccine Trials Group-Wesfarmers Centre of Vaccines and Infectious Diseases, Perth, Australia
11The Royal Women’s Hospital and The University Melbourne and Murdoch Children’s Research Institute, Women’s Centre for Infectious Diseases, Melbourne, Australia
12The Kirby Institute- University of New South Wales, Public Health Interventions, Sydney, Australia
13The University of Adelaide, School of Public Health, Adelaide, Australia
14University of Technology Sydney, Faculty of Health, Sydney, Australia

Background and Aims

We evaluated a multi-component intervention to improve adolescent knowledge, vaccine-related psycho-social outcomes and HPV vaccine uptake. We previously reported no vaccine coverage increase, but significant improvements in adolescent knowledge, decisional involvement, and vaccine-related confidence and anxiety. Here we present process evaluation findings including implementation and impact of logistical components.

Methods

We recruited a stratified random sample of 40 schools (6,967 students) across two Australian states, and randomly allocated schools to intervention (21) or control (19) groups. Intervention schools implemented adolescent education and programmatic logistical strategies. Outcomes included vaccine uptake; student knowledge, decision-making involvement, vaccine-related confidence and anxiety; consent form return rates, time to vaccinate and a vaccination-room set up score, assessing compliance with best practice recommendations.
Results

In intervention schools, mean implementation score for vaccination room set-up was higher: 7.3 versus 6.0 (adjusted difference 1.3; 95%CI=0.02, 2.6) and average time to vaccinate 50 students was shorter: HPV dose 1 = 243 versus 354 minutes (adjusted difference -117; 95%CI=-244, 10), HPV dose 2 = 223 versus 281 minutes (adjusted difference -53; 95%CI=-179, 51), HPV dose 3 = 151 versus 271 minutes (adjusted difference -123; 95%CI=-208, 38). There was no significant difference in consent form return rates: 87.2% versus 87.9% (adjusted difference 3.2, 95%CI=-3.4, 9.8).

Conclusions

Education and effective logistic improvements can be successfully implemented in mass school-based vaccination. Our intervention improved adolescent HPV knowledge and vaccination experience and reduced time taken to vaccinate, suggesting an improved experience also for school and immunisation staff and a more efficient program.
POST-MARKETING SURVEILLANCE STUDY OF 2-DOSE QUADRIVALENT HPV VACCINE IN 6TH GRADE ELEMENTARY SCHOOL CHILDREN IN JAKARTA, INDONESIA: SAFETY AND IMPLEMENTATION OF SCHOOL-BASED HPV IMMUNIZATION PROGRAM

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Background and Aims

Quadrivalent human papillomavirus (HPV4) vaccine has been globally advised for routine vaccination of pre-adolescent girls, and a two-dose HPV4 vaccination schedule has been introduced in Indonesia to vaccinate 5th and 6th grade elementary school female students. This post-marketing surveillance study evaluated the possible adverse events following immunization with the two-dose HPV4 vaccine.

Methods

Girls studying in grade 6 of five designated elementary schools in Jakarta, receiving their 2nd dose of HPV4 vaccine and provided informed consent (represented by their parents), were included in the study. Local and systemic reactions noted 30 min, and 72 h to 28th day, after the immunization were recorded using a Children Symptom Dairy Card/Kartu Harian Anak Sekolah (KHAS).
Figure 1. Study Protocol

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<th>Second Visit (K2)</th>
<th>Third Visit (K3)</th>
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<tr>
<td>Kartu Harian Anak Sekolah (KHAS/Daily Cards) distribution</td>
<td>KHAS-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kartu Harian Anak Sekolah (Daily Cards) retrieval</td>
<td></td>
<td></td>
<td>KHAS-1</td>
</tr>
<tr>
<td>Anamnesis of Medical Treatment/ Medication Taken</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AE Observations</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

A total of 500 students from 20 schools were included. No serious adverse events were reported during the study period. Fever (systemic reaction) of mild intensity was noted in 1.6% of participants, which subsided after day 6. Local reactions such as pain, redness and swelling were noted in 59%, 23.6%, and 12.2% of participants, respectively. These resolved without any intervention in majority of the cases after day 5.
Figure 2. Details of local & systemic reactions noted 30 min to 28\textsuperscript{th} day after the 2\textsuperscript{nd} dose of HPV4 vaccine across all centers

<table>
<thead>
<tr>
<th>No</th>
<th>AEFI (Adverse Event Following Immunization)</th>
<th>Post Marketing Surveillance, Jakarta, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30’</td>
</tr>
</tbody>
</table>

A. Systemic Reaction

1. Fever (n=8; 1.6%)
   - Mild: 0 0.4% 0.4% 0.2% 0.4% 0.8% 0.6% 0
   - Moderate: 0 0 0 0 0 0 0 0
   - Severe: 0 0 0 0 0 0 0 0

2. Others: Malaise (n=1; 0.2%); Myalgia (n=2; 0.4%); Arthralgia (n=1; 0.2%)

B. Local Reaction

1. Pain (n=295; 59%)
   - Mild: 13.8% 15.2% 12.6% 14.2% 3% 1% 0.6% 0
   - Moderate: 18.4% 15.8% 14.4% 7.6% 1% 0 0 0
   - Severe: 12.4% 5.8% 4.4% 1% 0 0 0 0

2. Redness/Erythema (n=118; 23.6%)
   - Mild: 18.8% 11.5% 9.6% 9.2% 6.4% 4.0% 2.0% 2.0%
   - Moderate: 2.6% 2.4% 0.4% 0 0.2% 0 0 0
   - Severe: 0.4% 0.4% 0 0 0.4% 0 0 0

3. Swelling (n=62; 12.2%)
   - Mild: 11.6% 6.6% 8.6% 7.0% 4.4% 1% 0.6% 0.4%
   - Moderate: 2.4% 2.6% 0.4% 0 0.4% 0.4% 0.4% 0
   - Severe: 0 0 0 0 0 0 0 0

4. Others: local myalgia on the site of injection (n=9; 2%)

Conclusions
These results along with the safety data from the pre-licensure clinical trials confirm the favourable safety profile of HPV4 vaccine in pre-adolescent girls. The school-based two-dose HPV4 immunization program in Indonesia is an effective strategy for optimizing HPV vaccine coverage among pre-adolescent girls.
HIGH RESOURCE SETTINGS - VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

HPV IMMUNIZATION PROGRAMS: ENSURING THEIR SUSTAINABILITY AND RESILIENCE.
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¹University of Antwerp, Vaccine & Infectious Disease Institute, Antwerpen, Belgium

Background and Aims

Since 2016, Human Papillomavirus (HPV) immunization programs have been introduced in 74 countries, areas or territories using a variety of strategies such as school-based, healthcare professional (HCP)-based or community-based delivery programs. Despite its proven effectiveness, concerns about the safety of the vaccine and alleged side-effects led to significant decrease in vaccination coverage in a number of countries.

Methods

The HPV Prevention and Control Board has organized four technical and country meetings where international and local experts exchanged lessons learnt and experiences in order to strengthen countries’ efforts to secure HPV prevention and control. Based on these insights, the board has developed a checklist that can be used for countries with existing or soon to be introduced HPV vaccination programs.

Results

The checklist, which can also be applied to other vaccination programs, includes: 1) providing proper and timely support to Health Care Professionals (HCP) involved in implementing the programme, 2) elaboration of a communication plan, 3) talking about screening and prevention concomitantly, 4) reflecting on crisis prevention and mitigation from the start and 5) monitoring, follow-up and adjusting the immunization program.

Conclusions

It is clear that a programme starts well before the first vaccine is given. Taking the time to prepare is a necessary condition for success.
BACKGROUND AND AIMS

In Australia, adolescents are routinely offered both HPV and dTpa (diphtheria, tetanus, pertussis) vaccines simultaneously in the secondary school vaccination program. We identified schools where HPV initiation was lower than dTpa coverage and associated school-level factors across three states (Tasmania, New South Wales, and Western Australia).

METHODS

HPV vaccination initiation rates (first dose/total enrollments) and dTpa vaccination coverage (dTpa dose/ total enrollments) in 2016 were calculated using data from the National HPV Vaccination Program Register, state dTpa programs and school enrollments. A multivariate analysis assessed sociodemographic and school-level factors associated with HPV initiation being an absolute >5% lower than dTpa coverage.

RESULTS

Of 1,280 schools included, the median school-level HPV initiation rate was 85% (interquartile range [IQR]:75-90%) and the median dTpa coverage was 86% (IQR: 75-92%). Nearly a quarter (24%) of all schools had HPV vaccination initiation >5% lower than dTpa coverage and 11% had > 10% difference. School-level factors independently associated with >5% difference were: schools in remote areas (aOR 2.4, 95%CI=1.2-4.8) or schools located in major cities (aOR1.9, 95%CI=1.2-3.1), small schools (aOR 3.1, 95%CI=2.1-4.7), socioeconomic advantage (aOR 1.8, 95%CI= 1.2-2.7), and a
higher proportion of Language-background-other-than-English (LBOTE) (aOR 1.9, 95%CI=1.3-2.7). The final multivariable model was also adjusted for a five-level school affiliation variable.

Conclusions

This research has identified that schools which are located in remote areas or in major cities, smaller schools, schools that have higher socioeconomic advantage or a higher proportion of LBOTE have HPV vaccine initiation rates lower than dTpa. Research can now be prioritised to understand the reasons for differential uptake and develop interventions.
IMPACT OF HPV VACCINATION ON PENILE HPV PREVALENCE AMONG YOUNG MEN WHO HAVE SEX WITH MEN IN THE UNITED STATES

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3Centers for Disease Control and Prevention, Division of Viral Diseases- National Center for Immunization and Respiratory Diseases, Atlanta, USA
4University of Washington, Medicine, Seattle, USA
5Gay City Health Project, Gay City Health Project, Seattle, USA

Background and Aims

In the United States, HPV vaccination has been recommended since 2011 for males aged 11–12 years, with catch-up through age 21, and through age 26 for men who have sex with men (MSM). Our objective is to evaluate the real-world impact of HPV vaccination on penile HPV prevalence among young MSM.

Methods

During 2016–2018, a cross-sectional study enrolled 642 MSM (including transgender women) aged 18–26 years from clinics offering STI/HIV testing in Seattle, Washington. Participants submitted self-collected penile specimens for HPV DNA genotyping (37 types) by Linear Array. HPV vaccination status, sociodemographics, sexual behaviors, and health history were self-reported. Currently, results are available for 96 specimens. We compared quadrivalent vaccine-type (6/11/16/18) DNA prevalence among vaccinated participants versus participants with no/unknown vaccination history using Fisher’s exact test.

Results

Among 96 participants with genotyping results, median age was 23 years and median lifetime number of male sex partners was 25 (interquartile range:14–50). Forty-two (43.8%) self-reported HPV vaccination. Median lifetime partners did not differ by vaccination status. Any HPV was detected in 24 (26.4%) of 91 adequate specimens (beta-globin control positive). Quadrivalent vaccine-type HPV was detected among 0/40 vaccinated participants and 5/51 (9.8%) other participants (p=.07).

Conclusions

Vaccine-type penile HPV prevalence was lower among vaccinated participants compared to those with no/unknown vaccination history. Although non-statistically significant, these early results suggest a protective effect of HPV vaccination among MSM through age 26. Results presented at the conference will be updated to include additional penile HPV data from enrolled participants.
PERSPECTIVES OF YOUNG MEN WHO HAVE SEX WITH MEN FOR A MOBILE HEALTH TOOL DESIGNED TO FACILITATE HPV VACCINATION IN THE UNITED STATES

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²Boston College, WF Connell School of Nursing, Boston, USA
³Pennsylvania State University, Biobehavioral Health, University Park, USA
⁴Harvard Medical School, Fenway Health, Boston, USA

Background and Aims

Young men who have sex with men (YMSM) are at heightened risk for HPV-related diseases, but their vaccination rates lag. YMSM in the U.S. heavily utilize mobile application (app) technologies. The aim of this study was to understand YMSM’s preferences for an easy to use app designed to encourage HPV vaccination at a local health center.

Methods

We recruited YMSM (18 to 26 years old) for six online focus groups via pop-up advertisements on a popular app for men seeking social and sexual interaction with other men. The focus groups utilized a semi-structured script designed to elicit content and appearance preferences for an app related to health and HPV vaccination. Data were analyzed using conventional content analysis.

Results

48 YMSM participated. They had variable levels of HPV knowledge, with many unaware of male-associated cancers. Participants utilized mobile technology to stay engaged socially, and for travel, banking, gaming, news and entertainment. Few used apps related to health issues. They enthusiastically discussed the quality and content of an HPV vaccine app focused specifically for YMSM, desiring credible, relatable, secure, and easy to use interfaces that provided basic general and sexual health information in a positive context.

Conclusions

We identified an effective youth-driven approach to reach YMSM to elicit perspectives on an HPV vaccine app. Participants wanted credible, clearly presented information, and were interested in an app that addressed a broad range of sexual health issues, not just HPV vaccination. Their preferences subsequently were incorporated in development of the app, which is currently being evaluated.
WHEN WILL CERVICAL CANCER BE ELIMINATED IN AUSTRALIA?
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²Victorian Cytology Service, National HPV Vaccination Program Register, Melbourne, Australia
³Victorian Cytology Service, Victorian Cytology Service Registries, Melbourne, Australia
⁴University of Queensland, Faculty of Medicine, Brisbane, Australia

Background and Aims

In 2007, Australia was one of the first countries to introduce a national HPV vaccination program, and has achieved high gender-neutral coverage. Australia has also recently moved from two-yearly cytology-based screening to five-yearly primary HPV testing for women aged 25-74. We aimed to identify the earliest years by which cervical cancer incidence rates (currently ~7/100,000) could drop below the rare cancer threshold (6/100,000) and a putative ‘elimination’ threshold (4/100,000), as Australia is likely to be one of the first countries to reach these benchmarks.

Methods

We utilised Policy1-Cervix, an extensively validated dynamic model of HPV vaccination, natural history, and cervical screening, to estimate the age-standardised rate (ASR) of cervical cancer incidence out to 2099. We incorporated age-specific coverage rates, including the catch-up program, inclusion of boys from 2013 and the change to the nonavalent vaccine (‘HPV9’) from 2018 onwards. We also modelled the transition to five-yearly primary HPV screening. We considered two assumptions for screening recommendations for cohorts offered HPV9: (i) five-yearly HPV screening continues and (ii) no screening is offered.

Results

Cervical cancer will become rare by 2022 and will be ‘eliminated’ by 2021-2035, with the precise year depending on population structure assumptions. Cervical cancer incidence rates will drop below 1/100,000 by 2054-2077 if screening continues for cohorts offered HPV9 or below 3/100,000 if these cohorts are not screened; mortality is predicted to fall below 1/100,000 by 2025-2047.

Conclusions

If high-coverage vaccination and screening is maintained, cervical cancer could drop below a putative elimination threshold in Australia before 2035.
HIGH RESOURCE SETTINGS - ECONOMICS AND MATHEMATICAL MODELLING IN HIC

CLINICAL AND ECONOMIC IMPACT OF GENDER-NEUTRAL NINE-VALENT HPV VACCINATION IN SOUTH KOREA COMPARED WITH FEMALE-ONLY QUADRIVALENT OR BIVALENT HPV VACCINATION USING A TRANSMISSION DYNAMIC MODEL


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3Merck Sharp & Dohme, Global Medical Affairs, Seoul, Republic of Korea
4HCL America- Inc, Economic and Data Sciences, Sunnyvale- CA, USA
5Merck & Co.- Inc., Center for Observational and Real World Evidence, North Wales, USA
6Merck & Co.- Inc, Center for Observational and Real World Evidence, North Wales, USA

Background and Aims

The Korean national immunization program (NIP) of human papillomavirus (HPV) vaccines includes vaccination of 12-year-old girls with bi-valent vaccine (2vHPV; HPV-16/18) and quadri-valent vaccine (4vHPV; HPV-6/11/16/18). The nine-valent vaccine (9vHPV; HPV-6/11/16/18/31/33/45/52/58) covers approximately 90% of genital warts and about additional 20% of the cervical cancer (CC) burden. We assessed the incremental public health and economic impact of a gender neutral vaccination (GNV) program of 12-year old girls and boys with 9vHPV vaccine compared with girls-only vaccination with current NIP-included vaccines, and screening (without vaccination).

Methods

A transmission dynamic model was used to assess the public health impact of routine GNV among 12-year-olds compared with screening, girls-only 2vHPV vaccination, and girls-only 4vHPV vaccination, in preventing HPV-related cancers, lesions and genital warts in Korea. We assumed 70% coverage, 2-dose schedule, 100-year time horizon, and lifelong protection against vaccine types.

Results

9vHPV GNV resulted in fewer cases of HPV16/18/31/33/45/52/58-related cancers and cancer-related deaths including 39,495, 39,495, and 171,332, fewer cases of HPV16/18/31/33/45/52/58-related CC compared with girls-only 2vHPV, girls-only 4vHPV, and screening, respectively. In addition, it also resulted in 5,489,257, 894,962, and 5,489,257, fewer cases of genital warts compared with girls-only 2vHPV, girls-only 4vHPV, and screening, respectively, and cervical cancer-related and genital warts-related disease-management costs reductions of KRW91,109,648,511, KRW19,752,114,208, and KRW174,429,476,213 compared with girls-only 2vHPV, girls-only 4vHPV, and screening, respectively.

Conclusions

Model-based analysis suggests that 9vHPV-GNV in Korea will have the best public health impact due to reduced incidence of HPV-related diseases compared to girls-only 2vHPV or 4vHPV vaccination, or screening.
<table>
<thead>
<tr>
<th>HPV related disease/disease management cost</th>
<th>Cumulative Reduction in HPV-related Disease Incidence or Management Costs with 9vHPV GNV compared with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2vHPV female only</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>39,495</td>
</tr>
<tr>
<td>Cin 2/3</td>
<td>175,053</td>
</tr>
<tr>
<td>Cin 1</td>
<td>230,951</td>
</tr>
<tr>
<td>Genital warts</td>
<td>5,489,257</td>
</tr>
<tr>
<td>Cervical Cancer Deaths</td>
<td>9,267</td>
</tr>
<tr>
<td>HPV-related Disease management costs (cervical cancer-related and genital warts-related costs only) (KRW)</td>
<td>113,420,901,246</td>
</tr>
</tbody>
</table>
Background and Aims

The incidence of oropharyngeal cancer (OPC) is rising and the reason is an increase of cases caused by human papilloma virus (HPV). The aim of this study is to identify actual economic burden of OPC, with and without association to HPV, using a cost-of-illness approach.

Methods

123 patients with OPC (i.e., tonsillar cancer, cancer of the base of the tongue and of the soft palate), consecutively diagnosed in the Southern Health Care Region of Sweden (2011-2014), were identified from the Swedish Quality Registry for Head and Neck Cancer. Patients were classified according to tumour site, TNM-stage and HPV-status. Direct medical costs and indirect costs for morbidity and mortality, from 1 month prior to diagnosis to 3 years after treatment, were retrieved from care sites and from Statistics Sweden, and calculated using the human capital method.

Results

The mean cost per patient with OPC was €105,800. Tonsillar cancer represented the largest group, i.e., 62.6% of the cases, with a mean cost of €117,500. The mean cost for HPV-negative and HPV-positive OPC, respectively, was €127,000 and €107,400. As for cancer stage I-IVc the mean cost was €59,400, €57,000, €69,200, €114,100, €234,500, and €21,900, respectively.

Conclusions

The economic burden of OPC is substantial: e.g., €13,000,000 for the 123 patients in this study. HPV now inflicts 80% of the costs for OPC, of which 72% is represented by males. This data, retrieved using a bottom-up approach, may be used for cost-effectiveness analyses preceding policy decisions focusing on prevention of HPV-associated cancer.
IMPROVING CERVICAL CANCER SCREENING PARTICIPATION, DIAGNOSIS OR TREATMENT – WHICH WOULD HAVE THE BIGGEST IMPACT?

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Background and Aims

To help prioritize further investment in research and health services, we explored which improvements to aspects of the cervical cancer screening, diagnosis or treatment pathway would have the largest impact.

Methods

A well-established model of HPV natural history, and cervical cancer screening and treatment (Policy1-Cervix) was used. Idealised scenarios were modelled to evaluate the relative impact of i) perfect adherence to different screening pathways (routine/surveillance); ii) perfect colposcopy attendance; iii) perfect colposcopy performance (detection of CIN2+; unsatisfactory rate); and improvements in cancer treatment iv) effectiveness (10-80% reduction in mortality) or v) side-effect profile (no disutility).

Results

Considering life-years gained over the lifetime of 100,000 unvaccinated females aged 12, perfect screening adherence gained 251-929; perfect colposcopy attendance gained 108; perfect colposcopy gained 40-94; and 10-80% improvement in cancer treatment gained 184-1,463. The most effective improvement to screening participation was to ensure no women were unscreened. Relative gains from each pathway aspect were similar for QALYs and cancer cases prevented (except improving cancer treatment does not prevent cases). QALY gains from having no disutility associated with cervical cancer diagnosis and treatment were greater than those gained from perfect colposcopy attendance or performance, and similar to those from some (but not all) improvements to screening participation.

Conclusions

Ensuring no women are unscreened is one of the most effective improvements to the screening/diagnostic/treatment pathway, and generally more effective than treatment improvements that reduce mortality by 50%. Improvements in cancer treatment and side-effect profile could have an important effect if they are very substantial.
MAXIMIZING THE FUTURE IMPACT OF INTERVENTIONS ON CERVICAL CANCER IN AUSTRALIA THROUGH MODELLING: THE PATHWAYS-CERVIX PROGRAM


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4University of Sydney, Discipline of Obstetrics- Gynaecology and Neonatology, Sydney, Australia
5Victorian Cytology, Education and Liaison, Melbourne, Australia
6Victorian Cytology Service, Education and Liaison, Melbourne, Australia
7Chris O'Brien Lifehouse, Not applicable, Sydney, Australia
8Family Planning NSW, Not applicable, Sydney, Australia
9The University of Queensland, Diamantina Institute, Brisbane, Australia
10Royal Women's Hospital, Department of Microbiology and Infectious Diseases, Melbourne, Australia
11University of Western Australia, Division of Obstetrics and Gynaecology, Perth, Australia
12University of New South Wales, Kirby Institute, Sydney, Australia
13Scientific Institute of Public Health, Unit of Cancer Epidemiology, Brussels, Belgium
14Albert Einstein College of Medicine, Department of Epidemiology and Population Health, New York, USA
15University of Melbourne, Department of Obstetrics and Gynaecology, Melbourne, Australia
16University of Sydney, School of Public Health, Sydney, Australia

Background and Aims

Australia’s HPV-based cervical screening and vaccination programs are expected to reduce cervical cancer incidence and mortality over the next decades. To further increase the impact on cervical cancer burden, areas with the greatest potential to achieve future gains in cancer control need to be identified.

Methods

As part of a program of work called Pathways-cervix, interventions across the cervical cancer spectrum will be evaluated within a health economic framework to produce a list of best buys. Based on scientific evidence from the literature and relevance to the Australian context, a number of interventions were selected under the guidance of a multi-disciplinary Scientific Advisory.

Results

Selected interventions were: modification of vaccine uptake; vaccinating at older ages; increasing screening participation; methods for triaging HPV-positive women; improving the diagnosis of high grade squamous intraepithelial lesions (HSIL) and cancer; treating cervical abnormalities and cancer; and vaccinating women treated for HSIL to prevent recurrence. Evaluations will be performed using the Policy-1 Cervix model platform, previously used for policy evaluations in Australia. Idealised scenarios of interventions will be conducted in single birth cohorts to explore their potential impact. Interventions demonstrating a significant impact will be modelled further using more realistic
assumptions. Multi-cohort simulations predicting health outcomes, resource use and cost outcomes will then be conducted for the most promising strategies.

Conclusions

Pathways-cervix will assess the relative benefits of strategies providing evidence to underpin future research investment and new policy approaches in Australia, however, the applied methodology and flexibility of the modelling platform will enable applicability of this program internationally.
HIGH RESOURCE SETTINGS - PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

SYSTEMATIC LITERATURE REVIEW OF ADJUNCTIVE TESTING STRATEGIES TO DETECT INCIDENT CIN2+ AND LONGITUDINAL 3-YEAR RISK OF CIN2+ WITHIN HPV POSITIVE AND CERVICAL CYTOLOGY ATYPICAL CASES

D. Malinowski

1BD Life Sciences, Scientific Affairs, Durham, USA

Background and Aims

Advances in the screening and detection of cervical disease have been greatly aided by the inclusion of HPV testing along with cytology to identify patients at risk for CIN2+ disease. Various triage methods have been described in the literature to improve patient referral to colposcopy from HPV positive patients, as well as ASCUS and LSIL cases. We undertook a systematic review of literature to compare relative effectiveness of these triage methods.

Methods

The analysis included PubMed, PubMed Central, the Database for Abstracts of Reviews of Effects, and the Cochran Database of Systematic Reviews from 2000 through 2017 for relevant controlled clinical trials and observational studies. In addition, a supplemental review was conducted by searching retrieved article references. Metrics of clinical effectiveness included incident detection of CIN2+ and colposcopy referral rates.

Results

The following triage methods were evaluated in this systematic literature review: (i) protein biomarkers with immunocytochemistry assays; (ii) HPV mRNA testing; (iii) DNA methylation markers; and (iv) extended HPV genotyping. These methods were compared against a standard of HPV testing and cytology. All methods displayed varying degrees of incident CIN2+ detection with the potential to reduce colposcopy referral rates. Trade-offs in incident CIN2+ detection vs. specificity and colposcopy reductions were identified among these various triage options.

Conclusions

Published literature on the use of protein biomarkers, HPV mRNA and DNA methylation in triage applications focused on incident CIN2+ detection. Longitudinal 3-risk estimates were reported of the use of extended HPV genotyping, affording methods for risk stratification in patient management.
HIGH RESOURCE SETTINGS - PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

COMPARISON OF NEED FOR FOLLOW-UP TESTING AND RESULTS ACROSS THREE CURRENT SCREENING MODALITIES FOR CERVICAL CANCER

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²Johns Hopkins School of Medicine, Department of Gynecology and Obstetrics, Baltimore, USA
³Johns Hopkins School of Medicine, Department of Pathology, Baltimore, USA
⁴George Washington University, Department of Global Health, Washington DC, USA

Background and Aims

New screening guidelines being developed in the US recommend hrHPV for primary screening every 5 years in place of co-testing, while keeping the option of a triennial Pap test. This study aimed to compare the difference in need for any follow-up testing in each screening method.

Methods

Pap and hrHPV co-tests were performed during routine care for women ages 30-65 in a large academic institution between 2013-2015. Descriptive analyses were conducted to compare differences in need for any follow-up testing according to guidelines for co-testing vs. single screening options, and to examine the follow-up results under each scenario. Screening results requiring follow-up were: HPV-positive for hrHPV-only screening, ASCUS or worse for Pap-only screening, and any HPV-positive result or LSIL or worse on Pap for co-testing.

Results

Among 2,148 women, 14%, 10%, and 22% would require follow-up testing under the criteria for hrHPV only, Pap only, and co-testing screening modalities, respectively. To note, 68% of Pap-only screen positives were actually ASCUS/HPV-negative. At a follow-up, 34% of HPV-positives remained positive, while 24% of women who screened Pap-positive remained positive, and 33% of co-test positives remained positive.

Conclusions

This analysis demonstrates that truly single screening modalities require similar follow-up testing, both of which would be lower than co-testing. Our data suggest that following the draft guidelines may reduce the number of women initially referred for non-routine follow-up, but that more women remained positive in the hrHPV only screening modality than in the Pap only screening modality at subsequent follow-up.
Limited data are available on human papillomavirus (HPV) infections and associated cancers in the Central Asian countries, including Kazakhstan. The incidence and mortality rate of cervical cancer in these countries are higher than in most Western European countries. Studies showed that infection by specific genetic lineages of HPV 16 and 18 differ in their risks towards cancer development. The overall goal of this study was to obtain updated molecular epidemiological data regarding HPV and associated cancers, and to summarize recent information regarding the prevalence of HPV genotypes and genetic lineages within Kazakhstan and Central Asia.

Methods

A systematic review was performed with search terms that include cervical cancer, HPV genotypes, lineages and Kazakhstan.

Results

A 2012 prevalence study of HPV types in Kazakhstan detected total hrHPV infection in 28.5% of the cases; 29.4% of those infected with the virus had either HPV 16 or 18 types. Recent studies in Kazakhstan showed a high prevalence of with HPV 16, 18, 39, 51 and 31 and a statistically significant correlation between HPV 16 and HPV 33 positive samples and CIN grade II and III. HPV screening is conducted only once every five years and there is neither a sponsored program for testing HPV DNA, nor a vaccination program for HPV control in Kazakhstan.

Conclusions

The information could guide our ongoing research efforts to generate pertinent data regarding circulating HPV genotypes. We hope our research could help inform policies related to screening approaches and vaccination programs for prevention of HPV infection and cervical cancer in Kazakhstan.
INTERNATIONALLY, HUMAN PAPILLOMAVIRUS (HPV) VACCINATION UPTAKE IN YOUNG GIRLS IS 30-80%. WILL IT BE REASONABLE TO SCREEN – FOR CERVICAL CANCER - VACCINATED AND UNVACCINATED WOMEN ALIKE? NEXT TO FEASIBILITY ISSUES, THIS DEPENDS ON THE DIFFERENCE IN CERVICAL CANCER RISK BETWEEN THE TWO GROUPS. THE RISK IN UNVACCINATED WOMEN WILL BE DEPEND ON HERD IMMUNITY, AND THUS ON VACCINATION COVERAGE AND TIME SINCE VACCINATION STARTED. HOW MUCH HERD IMMUNITY IS EXPECTED AND WHEN?

METHODS

WE COMPARED THREE HPV TRANSMISSION MODELS AS PART OF THE CANCER INTERVENTION AND SURVEILLANCE MODELING NETWORK (CISNET) ON PREDICTED HPV16/18 INFECTION INCIDENCE REDUCTION AND RESULTING HERD IMMUNITY EFFECT, ASSUMING VACCINATION WITH 60% COVERAGE. HERD IMMUNITY EFFECT IS DEFINED AS THE CERVICAL CANCER INCIDENCE REDUCTION IN NON-VACCINATED WOMEN RELATIVE TO VACCINATED WOMEN (100% MEANS CERVICAL CANCER RISK IS EQUAL IN UNVACCINATED AND VACCINATED WOMEN).

RESULTS

IN THE STEADY STATE, HPV16 INCIDENCE REDUCTION WAS PREDICTED TO BE 80, 73 AND 65% IN ALL WOMEN FOR THE THREE INDEPENDENT MODELS. THIS WAS REACHED AFTER 70, 69 AND 37 YEARS RESPECTIVELY. FOR HPV18 THE RESULTS WERE SIMILAR. THE CORRESPONDING HERD IMMUNITY EFFECTS WERE 56, 32 AND 17% RESPECTIVELY.

CONCLUSIONS

ALTHOUGH HERD IMMUNITY IS IMPORTANT FOR DECISIONS CONCERNING CERVICAL CANCER SCREENING, THERE SEEMS TO BE UNCERTAINTY ABOUT ITS EXPECTED MAGNITUDE AND THE RATE AT WHICH IT WILL DEVELOP. MONITORING OF THE HPV PREVALENCE, ESPECIALLY IN UNVACCINATED WOMEN, IN VARIOUS POPULATIONS, COMBINED WITH COMPARATIVE MODELING, WILL ADD TO THE UNDERSTANDING OF THE DYNAMICS OF HERD IMMUNITY AND IMPROVE FURTHER PROJECTIONS.
Background and Aims

Men and transgender women (TGW) who are sex workers are an exposed and vulnerable population for Sexually Transmitted Infections (STI), of difficult access, resulting in a lack of information about prevalence and determinants of STIs in general and Human papillomavirus (HPV) in particular. To estimate the anogenital and oral HPV prevalence and determinants in men and TGW who report to be sex workers.

Methods

Men and TGW aged ≥18 residents in Barcelona are enrolled in a cross-sectional study conducted in collaboration with local non-governmental organizations, STOP SIDA. Demographic and behavioral characteristics are assessed by questionnaire, and anal, perianal, penis, urine and oral samples were collected for HPV testing and genotyping.

Results

From a total of 37 participants, 25 were TGW (recruitment is currently ongoing). Average age was 33 years and most participants were foreigners (97.4%), mainly from South America. 23% reported to be HIV-positive and 35.1% had another active STI. The prevalence of HPV was 91.6% in anal, 12.9% in oral and 6% in urine samples. Many participants were unfamiliar with HPV vaccination, but 87.1% expressed positive attitudes for vaccination. We estimate to collect a total of 450 samples from 90 participants until the end of the recruitment phase (July, 2018). HPV results from all patients and all locations will be presented at the IPVC 2018.

Conclusions

The prevalence of HPV infections is higher in this population than general population, mainly in anal and oral sites. Specific HPV vaccine programs addressed to this population should be considered.
THE HEALTH AND ECONOMIC IMPACT OF SCALING CERVICAL CANCER PREVENTION IN LOW-INCOME COUNTRIES, CASE FOR CONGO BRAZZAVILLE.

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Background and Aims

To estimate the health impact, financial costs, and cost-effectiveness of scaling-up coverage of human papillomavirus (HPV) vaccination (young girls) and cervical cancer screening (women of screening age) for women in countries that will likely need donor assistance.

Methods

We used a model-based approach to synthesize population, demographic, and epidemiological data from low-income countries. Models were used to project the costs, lifetime health impact (cervical cancer cases, deaths averted), and cost-effectiveness per disability adjusted life year averted) of: (1) two-dose HPV-16/18 vaccination of girls aged 10 years; (2) once-in-a-lifetime screening, with treatment when needed, of women aged 35 years with either HPV DNA testing or visual inspection with acetic acid (VIA); and (3) cervical cancer treatment over a 10-year roll-out.

Results

We estimated that both HPV vaccination and screening would be very cost-effective, and a comprehensive program could avert 5.2 million cases, 3.7 million deaths, and 22.0 million DALYs over the lifetimes of the intervention cohorts for a total 10-year program.

Conclusions

Investment in HPV vaccination of young girls and cervical cancer screen-and-treat programs in low-income countries could avert a substantial burden of disease while providing good value for public health dollars.
Background and Aims

With growing interest in 1-dose HPV vaccination, there has been an increasing number of post-vaccination surveillance studies assessing reduced-dose effectiveness. Although these studies suggest that reduced doses produce lower effectiveness, they are vulnerable to severe biases. Our aim is to quantify the impact of key biases in surveillance studies of reduced-dose HPV vaccination effectiveness against anogenital warts (AGW) and identify optimal methods to improve their validity/precision.

Methods

We reproduced, with an individual-based dynamic model (HPV-ADVISE), the 2 most common designs in the literature (Time-Dependent [TD], girls can contribute person-time to multiple doses & Final-Status-Last [FS-last], girls are categorised according to their last dose received and person-time/case counting begins after last dose), and a novel method (Final-Status-First [FS-1st], girls are categorised according to their last dose received and person-time/case counting begins after first dose). We examined the impact of buffer periods (delay between vaccination and start of person-time/case counting) to exclude prevalent infections at vaccination, different scenarios of vaccine efficacy and duration between infection-AGW consultations, and confounding by age/sexual activity.

Results
Conclusions

For TD and FS-last, effectiveness against AGW of 3 doses is 100% (IRR=theoretical value) as prevalent infections at vaccination are either cleared or AGW diagnosed prior to the 3rd dose. However, TD and FS-last bias towards lower effectiveness of reduced doses, unless there is a buffer sufficiently long to exclude all prevalent infections at vaccination. FS-1st underestimates effectiveness of 3,2,1 vs 0 in older age groups, but provides valid comparisons of reduced vs 3 doses, without a buffer. Confounding by age/sexual activity exacerbates biases.
IPVC8-0660
POSTER SESSION

PUBLIC HEALTH / EPIDEMIOLOGY - GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

HPV VACCINATION IN FRANCE: NUMBER NEEDED TO VACCINATE WITH 9-VALENT HPV VACCINE VS THE 4-VALENT HPV VACCINE TO PREVENT HPV-RELATED DISEASES, PRECANCEROUS LESIONS AND CANCERS

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Background and Aims

Simple and intuitive tools can help grasp the benefits of a vaccination programme. The Number of subjects Needed to Vaccinate to avoid a case of a given disease (NNV) helps in decision making process by combining the most recent immunization efficacy data, duration of protection and epidemiological data from a country.

Objective was to estimate the NNV for 9-valent (9vHPV) and 4-valent (4vHPV) vaccines in France to avoid HPV-related diseases as per indication in Europe.

Methods

NNV were calculated according to the following: inverse of absolute risk difference. Assumptions for risk calculations were: cohort of 12 years old girls (i.e. HPV-naïve individuals); vaccine efficacy as per EU’s label, lifetime duration of protection. Assumption of a lifetime vaccine protection for the type contained in the vaccine (no cross protection considered); no herd protection was considered; 2016 French epidemiology data was used.

Results

Overall, it is estimated: 6 girls vaccinated with 9vHPV and 7 with 4-valent HPV vaccine (4vHPV) are needed to avoid a case of HPV-related disease, lowering the NNV by about 14%. Likewise, it is estimated: 14 girls and 22 girls are needed to avoid a case of HPV-related pre-cancer and cancers respectively, lowering the NNV by about 36%. Summary in Table 1.

Conclusions

Vaccination with 9-vHPV reduced the NNV vs. 4-vHPV to avoid one HPV disease. These numbers could help communicate the importance of the benefits of HPV vaccination to prevent HPV-related diseases, including precancerous lesions and cancer. More research is needed to confirm NNV estimations, including using dynamic transmission models.
Background and Aims

The incidence of cervical cancer in 2012 was 527,624 and 265,672 women will die from their disease. The conundrum is how to control and prevent disease. Cervical cancer is a WHO priority for improving outcomes through planning, primary and secondary prevention and disease treatment and palliation.

Methods

The WHO NCD Country Capacity Survey (CCS) measures health system planning, services availability and coverage. Using questions related to cervical cancer control over 4 time points (2010, 2013, 2015, and 2017), a snapshot of the global evolution of cervical cancer was created. Monitoring of trends was done for variable time periods as the CCS was restructured in 2015.

Results

157 countries completed the surveys on all time points. Guideline based referral criteria was stable in 66% of countries. Registries improved from 28% (2010) to 88% (2017). HPV vaccination for girls increased from 49% (2015) to 56% (2017) with increase in coverage rates. Cervical screening was conducted in 78% of countries (2017), up from 71% (2010). The method of screening showed HPV testing increased from 3% (2015) to 8% (2017). Access to treatment through cancer surgery increased from 71% (2015)-76% (2017), subsidized chemotherapy from 64% (2010)-71% (2017) and radiation from 58% (2010)-62% (2017) of countries.

Conclusions

The CCS shows progress in a spectrum of activities related to cervical cancer control processes. Opportunities exist for increasing coverage in both vaccination and screening. The greatest opportunities for cancer care are in LIC. The CCS highlights at regional and income strata the specific areas for focused activity.
Background and Aims

Epidemiology of Human papillomavirus infection is evolving worldwide, therefore constant monitoring of circulating genotypes is a priority. Herein, we evaluated HPV genotypes prevalence in a cohort of women underwent HPV-DNA test in southern Calabria, Italy.

Methods

Overall, 1902 women (age range 16-78 years, mean age 38.5) underwent HPV-DNA diagnosis during routine microbiological practice at Microbiology laboratory of the “Azienda Sanitaria Provinciale 5” from January 2016 to December 2017. HPV genotypes were detected by Linear Array HPV Genotyping® (Roche) in cervical scrapes collected with a cytobrush in PCR Cell Collection Media (Roche)during clinical examination.

Results

A total of 650 (34.2%) women were HPV DNA positive for at least one (55.1%) or several (44.9%) HPV genotypes. Among single genotype HPV infections, 45.2% and 19.8 % were due to“high-risk” HPV (class I) categorized in human carcinogensand possibly/probably human carcinogens(class 2A/2B), respectively. Total HPV distribution showed the highest prevalence within the age range 30-39 years (35.8%). The most common high-risk (classes I and 2A/2B) HPV type detected in overall infection was HPV 16 (16.9%) followed by HPV53 (12.9%), HPV31 (9.8%) and HPV66 (9.4%). Moreover, in 495 women, we also evaluated HPV infection according to cervical status.

Conclusions

We provide epidemiological data on HPV types distribution over two years in a cohort of women living in southern Italy to check HR-HPV genotypes circulation. We found a higher prevalence of common HR-HPV genotype. Therefore, whether and how HPV vaccination may affect the circulation of HPV types in the next years is still unknown.
HUMAN PAPILLOMAVIRUS TYPE 73 A NON-VACCINE TYPE CAUSES CERVICAL CANCER

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Background and Aims

Human papillomavirus (HPV) type-specific oncogenicity is based on the prevalence of HPV types in cervix cancer (CxCa) tissues with supporting molecular evidence that includes presence of specific HPV spliced transcripts and integration of HPV DNA into the cancer cell genome. HPV73 is not routinely screened for in CxCa prevention programs nor is it covered by any of the existing HPV vaccines, thus we sought to evaluate the molecular evidence of HPV73’s oncogenicity in CxCa tissues.

Methods

Eight of 590 CxCa specimens referred to the National Cancer Institute (INCA), Rio de Janeiro, Brazil, were HPV73-positive (1.4%). DNA and RNA were isolated from CxCa biopsy specimens and cDNA was tested for transcriptional activity to detect spliced forms of HPV73. HPV integration was performed using a HPV73 DNA capture panel and next-generation sequencing assay. Exfoliated cells HPV73-positive from women without detectable cervical precancer were included as controls.

Results

The presence of HPV73 E1^E4 transcripts was observed in 4 of the CxCa cases, while HPV73 E6* transcripts were found in 7 specimens of the 7 CxCa cases with available cDNA. Twenty primary integrations (1-5 per sample) containing HPV73 sequences and human chromosomal DNA in single molecules were identified in all CxCa cases and localized to 12 human chromosomes. HPV73 integrations were found in genomic regions previously shown to contain viral integrations in HPV-associated cancers.

Conclusions

These results provide evidence that HPV73 is an oncogenic virus that can cause invasive cervix cancer. With current cervical molecular screening and HPV vaccination, not all cervix cancers will be prevented.
Background and Aims

Human papillomavirus (HPV) vaccination rates differ between regions of the United States, which lacks mandates for HPV vaccination in most states. The purpose of this study is to examine vaccine-type HPV by vaccination status within 4 regions of the US and to compare prevalence of genital HPV by gender.

Methods

We used National Health and Nutrition Examination Survey data collected in cross-sectional 2 year cycles between 2007 and 2014. These data include HPV results from cervical swab samples, and penile sample swabs from the 2013-2014 cycle among 14-59 year olds. We examined HPV prevalence between regions among vaccinated and unvaccinated women, 14-59 years of age. We also compared genital HPV prevalence by gender. Bivariate analyses using Rao-Scott chi-square statistics were used to compare weighted frequencies.

Results

Vaccine-type HPV (6, 11, 16, 18) did not vary across regions (p=0.27) among women. In analyses stratified by vaccination status, however, vaccine-type HPV varied by region among unvaccinated young women (p<0.05) with the South having the highest prevalence (8.3%) and the Northeast the lowest (5.5%). No significant regional variations in vaccine-type HPV were observed among vaccinated women. We found that there were significant differences in vaccine-type HPV between males and females in the South (p<0.05), but not in the other regions assessed.

Conclusions

Vaccination has the potential to reduce regional disparities in cervical cancer incidence. Further, low vaccination rates, particularly in the South, may contribute to regional and gender disparities in HPV prevalence.
Background and Aims

There are few studies on the perspective of gender equality in relation to Human Papilloma virus (HPV) infection, although it is well known as a sexually transmitted health problem in both sexes. This study assessed gender differences in HPV awareness (including knowledge) and health beliefs, and behavioral intentions to prevent HPV infection.

Methods

This study was a descriptive cross-sectional survey design and the structured questionnaires were used. Descriptive statistics including t-test and the multiple regression were used to analyze the data.

Results

The participants comprised 763 and 905 sexually active men and women living in Korea, respectively. Gender differences were measured in HPV knowledge, health beliefs, and sociodemographics that were significantly correlated with behavioral intentions to prevent infection. There were gender differences in the factors related to behavioral intentions to prevent HPV. In multiple regression analysis, HPV knowledge was not related to behavioral intentions, whereas perceived benefits were related to behavioral intentions consistently among men and women, while the effects of perceived barriers were inconsistent.

Conclusions

HPV awareness was very low regardless of gender. While HPV education is urgently required for men, enhancing HPV awareness, reinforcing positive perceptions of HPV prevention, and reducing unhealthy sexual behaviors are necessary for the entire Korean population.

Acknowledgement: This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (Grant No. 2018R1A2B2001231)
COMPARISON OF LIQUID-BASED CYTOLOGY AND CONVENTIONAL PAP SMEAR TESTS FOR CERVICAL CANCER DETECTION AMONG KAZAKHSTANI WOMEN

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Background and Aims

The incidence and mortality rates of cervical cancer in the Central Asia countries are much higher than those in the European region. Conventional Papanicolaou (pap) smear test and Liquid-based cytology (LBC) are screening methods that are commonly used for cervical cancer detection. The main objective of this study is to compare these two methods that were performed in Astana, Kazakhstan.

Methods

Samples were collected from women attending cervical cancer screening outpatient clinics. Conventional pap smear test was performed by one specialist at a private laboratory in Astana. The LBC was performed on the same samples by another specialist at a state laboratory also in Astana. Descriptive statistical analysis was conducted on the results obtained from 107 samples.

Results

Using LBC, 72.9% of samples were found to be negative for intraepithelial lesions and malignancy, and 18.7% were abnormal types of smear. Pap smear detected 21.5% of samples that were classified to be abnormal while 25.2% of samples were normal. The ratio of atypical squamous cells of undetermined significance was significantly less in LBC results compared to those analyzed by conventional Pap smear (9.3% and 13.1% of total samples respectively, p-value 0.002).

Conclusions

Our study found that conventional pap smear methodology generated statistically significant higher number of samples that were classified as abnormal when compared to LBC. Further evaluation of LBC and Conventional Pap smear results with increased number of samples can validate our finding. These future studies can help provide recommendations for an effective cervical cancer screening program in Kazakhstan.
Background and Aims

To assess the clinical impact of HPV vaccination, the causal HPV genotypes in CIN2+ must be identified. The hierarchical and proportional methods are widely used for this purpose, but these ignore the occurrence of multiple lesions and do not adjust for the genotype distribution in the general population. We aim to develop a new method for identifying the causal HPV genotypes in CIN2+ based on cervical screening samples.

Methods

Our model assumes that women may have multiple lesions caused by different HPV genotypes and that HPV genotypes have independent CIN2+ progression risks. We applied our method to 512 women with abnormal cytology who tested positive for at least one of the 25 HPV genotypes detected by SPF10-LiPA. We validated our method by means of laser-capture microscopy (LCM)-polymerase chain reaction (PCR).

Results

We predicted 271 type-specific lesion where 280 type-specific lesions, in 252 women, were observed by LCM. HPV16 and HPV33 had the highest estimated CIN2+ progression risk: 68% (95%CI: 61 – 75%) and 64% (44 – 81%), respectively. All low-risk HPV genotypes except HPV70 but including HPV53 had zero risk of CIN2+. The genotype attributable fractions( AFs) estimated by our method were closer to the AFs observed by LCM-PCR than those estimated by the proportional and hierarchical methods. HPV16 and HPV31 were estimated to attribute the most: 0.47 and 0.15, respectively.

Conclusions

Our new method estimates HPV genotype attribution in cervical lesions accurately without prior assumptions about type-specific oncogenicity. This method can play an important role in monitoring HPV vaccine effectiveness.
CERVICAL SCREENING AND HUMAN PAPILLOMAVIRUS GENOTYPING IN GRENADA: A NOVEL INVESTIGATION

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Background and Aims

The WHO estimates 70% of cervical cancer can be attributed to HPV 16 and 18. Growing evidence suggests a heterogeneity of non-16, -18 types outside of Gardasil-9 protection in Latin American and Caribbean populations. The pilot-study aimed to identify prevalence of circulating high-risk (HR) genotypes in the Caribbean tri-island state of Grenada.

Methods

Cervical samples from 114 women (20 – 72 years) seeking routine gynecological care in St. George’s, Grenada from 2013 – 2017 were preserved in PreservCyt® Solution and stored at -80°C until DNA extraction. Applied Biosystems®7500 RT-PCR and Stratagene Agilent Mx3005P Q-PCR were used to detect type-specific HPV E6/E7 DNA. Fourteen HR-strains were quantitatively tested using HPV Genotypes 14 Real-TM Quant kit.

Results

Of 125 samples, 110 were HPV positive. Thirteen HR-HPV genotypes were identified. Six non-16/18 HR-strains (39 (11.2%), 58 (8%), 66 (7%), 68 (7%), 52 (5%), 31 (5%)) were more prevalent than HPV 16/18 (4% each). Other genotypes were 35 (4%), 59 (4%), 51 (2%), 56 (1.6%) and 33 (0.8%). Twenty-four samples (19%) had multiple-genotypes detected. 59% of positive samples fell outside current vaccine coverage.

Conclusions

Our study provides insight into circulating HPV-strains in Grenada and suggest that non-16/18 types are more common than 16/18, similar to results from neighboring islands and in contrast to reports from other regions. Analysis via genotype-hybridization will verify results. Further investigations into HR-genotypes leading to cervical cancer are warranted given the implications for vaccine coverage. A follow up study using a larger sample, more representative of the general population is recommended.
HUMAN PAPILLOMAVIRUS PREVALENCE AMONG WOMEN FOLLOWING HPV VACCINE INTRODUCTION; A SYSTEMATIC REVIEW.

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Background and Aims

Worldwide efforts have been made by some countries to offer HPV vaccine introduction. Population effectiveness of HPV vaccines is presently an active area of research. We review available evidence on the effectiveness of HPV vaccine uptake among young women to prevent HPV infection.

Methods

A comprehensive search of published and grey literature was conducted. Data were pooled in a meta-analysis and stratified by continent considering vaccine type and cross protective HPV types as subgroups.

Results

Our search yielded 13 studies, with a total of 8332 vaccinated women aged 12 to 34 years from 3 continents. The pooled HPV (comprising types 6, 11, 16 and 18) prevalence was 7% (95% Confidence Interval (CI): 5% to 9%). By continent HPV prevalence for North America was 5% (95% CI: 3% to 7%); Europe, 14% (95% CI: 9% to 18) and Australia 5% (95% CI: 3% to 8%). We considered prevalence by cross protective types (31, 33, 45, 51 & 58), pooled prevalence was 9% (95% CI: 6% to 12%); by continent North America had 14% (95% CI: 12 to 17%), Europe 7% (95% CI: 6 to 8%) and Australia with 8% (95% CI: 5% to 11%).

Conclusions

This study showed an HPV prevalence of 7% in women vaccinated against HPV types 6,11,16 and 18, which represents a substantial difference to the 22% HPV prevalence in non-vaccinated women. There is however, still a dearth of information on vaccinated women and HPV prevalence, highlighting the need for further studies in this area.
IPVC8-0711
POSTER SESSION

PUBLIC HEALTH / EPIDEMIOLOGY - GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

PARENTAL ACCEPTANCE OF HUMAN PAPILLOMA VIRUS VACCINE FOR THEIR PRE-PUBERTAL AND TEENAGE DAUGHTERS

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Background and Aims

To determine the factors influencing parental acceptance of the HPV vaccine for pre-pubertal (age group 9-14 years) daughters

Four primary schools in Nairobi County in June 2017.

Methods

Girls in Standard five to eight selected for the study. A self explanatory one page questionnaire was given out to take to their mothers/guardian and returned in one week. Fifty mothers were then randomly selected from the returned questionnaires and an in depth telephone interview was conducted. The data entry and coding was done and analysed using SPSS version 15.

Results

In this study 68% of parents/guardians accepted that vaccination be done but only 58% agreed that their daughters should be vaccinated, majority of the respondents were females, (women 82% and men 18 %). This observed difference across the genders was not statistically significant p=0.078. The level of education of respondent (nil 2.7%, primary 6.6%, college /university 47.7% secondary 45.7%) the observed difference across the educational levels of agreeing vaccination was not statistically significant p=0.898. The knowledge/awareness on cervical cancer, its relationship to HPV infection correlated with the level of education was found to have been statistically significant. Parent/guardians suggested age of vaccination and HPV vaccine acceptance was significant correlated with the vaccination acceptance by the parents p=0.009. This study has shown that the recommended age of vaccination by parents is 11-13 years age group which was similar to findings done in many countries.

Conclusions

There was poor knowledge on the relationship between HPV infection and cervical cancer. The acceptable age of vaccine administration was 11-13 years
Background and Aims

Women living with HIV in Africa are at increased risk to be co-infected with Human Papilloma Virus (HPV), persistent high risk (HR) HPV infection and bacterial vaginosis (BV), which compounds HPV persistence, thereby increasing the risk for cervical dysplasia.

Methods

New guidance from WHO in 2014 advocating for a “screen and treat” approach in resource poor settings is becoming more widely recommended screening tool for cervical cancer prevention programs in such contexts. This summarizes risk factors considered when designing primary/secondary cervical prevention program in post-vaccination era HIV-infected women in Kenya.

This review article is based on prior research on the epidemiology of pHR/HR-HPV genotypes HIV-infected women and CIN 2+ in Kenya and other sub-Saharan contexts.

Results

In order to contextualize the findings, a literature search was carried out in March 2017 by means of four electronic databases: PUBMED, EMBASE, SCOPUS, and PROQUEST.

Risk factors for potential (pHR)/HR HPV acquisition, including CD4 count, HAART initiation, Female Sex Worker status (FSW) and BV need to be considered. Furthermore, there may be risk factors for abnormal cytology, including FSW status, multiple potential (p)HR/HR HPV genotypes, may require HIV-infected women be subjected to screening more frequent intervals than three year recommended by the WHO.

Conclusions

The quadruple synergistic interaction between HIV, HPV and BV and its related cervicitis may need be reflected within a larger prevention framework at the community level. The opportunities brought forth by the roll out of HAART could lead to task shifting of HIV-HPV-BV care to nurses may increase access in poorly-served areas.
PUBLIC HEALTH / EPIDEMIOLOGY - GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

UTILITY OF SELF-REPORTED HPV IMMUNIZATION HISTORY IN YOUNG-ADULT WOMEN
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Background and Aims

Little is known about the utility of self-reported HPV vaccine history in young-adult women. We aimed to assess concordance of self-reported immunization history of young-adult women with medical record verifications.

Methods

Vaccine eligible young-adult women in New Haven County, Connecticut were asked to complete a computer-based survey that included questions about immunization history, prior sources of care and sociodemographics. Medical records from all reported prior sources of care were reviewed for evidence of receipt of HPV vaccine.

Results

From 2013-2018, 201 women completed our survey (median age: 31 years, range 24-38). The sample was 53% White, 21% Black, 20% Hispanic and 6% Other. The accuracy, sensitivity and specificity of self-reported immunization status (yes/no) was 88% (95%CI: 83-93%), 89% (95%CI: 80-95%) and 88% (95%CI: 80-93%), respectively. Accuracy was not statistically significantly different when stratified by either income or racial group. The odds of being accurate varied significantly by age and education: older women were more likely to be accurate and women with no high school (HS) degree were less likely to be accurate (Table 1). Women with no HS degree were also more likely to over-report. Among those who accurately recalled whether they had received HPV vaccine, only 36% correctly recalled the number of doses received; most (53%) under-reported total number of doses. A
minority (38%) of those immunized correctly recalled the year of their first immunization.

### Table 1. Relationship of sociodemographic characteristics with over-reporting, under-reporting and accurate reporting of immunization status

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<td>&gt;$30k</td>
<td></td>
<td></td>
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<tr>
<td>&lt;$29k</td>
<td>0.72</td>
<td>0.47</td>
<td>0.88</td>
<td>0.80</td>
<td>5.28</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* Odds ratio using unadjusted logistic regression

**Conclusions**

Our study suggests that self-reported HPV immunization status by young-adult women is relatively accurate. However, self-reported number of doses received and year of immunization are often inaccurate.
Background and Aims

Among the barriers to HPV vaccine implementation are concerns that by offering adolescents the vaccine, young people will engage in riskier activities. We studied adolescent sexual behaviours before and after HPV vaccine implementation, using data from a large, serial population-level adolescent survey.

Methods

In British Columbia (BC), Canada, the school-based vaccination program was introduced in 2008. The BC Adolescent Health Survey (AHS) is a provincially representative survey administered in schools every 5 years on physical & emotional health. Demographic & sexual health behaviours from the AHS were compared between 2003, 2008, and 2013.

Results

Data from an estimated 298,265 girls (mean age 14.87 – 14.98 years), self-identified heterosexual or unsure, were included across all years. The proportion of girls reporting ever having sexual intercourse significantly decreased from 21.3% (2003) to 18.3% (2013) (adjusted odds ratio (AOR) 0.79, 95% CI 0.71-0.88). Self-reported intercourse before age 14 (AOR 0.76, 2008-2013), and substance use before intercourse (AOR 0.69, 2003-2013) also decreased significantly; while there was no significant change in the number of sexual partners. Contraception use (AOR 1.43, 2003-2013) and condom use (AOR 1.19, 2003-2013) also significantly increased, while pregnancy rates significantly decreased (AOR 0.56, 2003-2013).

Conclusions

Adolescent sexual risk behaviours at a population-level have decreased or remain unchanged from 2003-2013. Although these trends may not be directly attributable to the implementation of the school-based vaccination program in 2008; this large, provincial cohort found that a publicly funded HPV vaccine program did not increase prevalence of risky sexual behaviours in the province.
Background and Aims

Human papillomavirus (HPV) causes cervical and anogenital cancers. A large majority (around 85%) of the global burden occurs in the less developed regions. Vaccines are highly efficacious in preventing infection with virus types, but free HPV vaccine is not available for young women in Iran.

Methods

The following review article is developed using reference books and scientific networks among 47 articles between 2001 and 2018.

Results

A total of 851 women aged 18 - 65 years, attending regular gynecological visits, were retrospectively evaluated in 2014. HPV detection and genotyping was performed by use of PCR and RFLP. Nineteen different HPV types were detected in 265 of the 851 specimens (31.1%) from Iran. In 2018 prevalence of HR HPV infection was 10.3% in 2453 healthy sexually active women in Iran. Approximately, 5% of the study population had an abnormal cervical cytology (ASCUS or worse), of whom 34% were infected by HR HPV. Studies indicated that the burden of HPV infection among Iranian females was higher in comparison to previous estimates reported.

Conclusions

According to the results, there is an obvious need for continuous effective support from WHO and affiliated organizations for vaccination supply in low-income countries in order to reach global health development.
LATIN AMERICA DENTAL STUDENTS AND RESIDENTS KNOWLEDGE OF HUMAN PAPILLOMA VIRUS AND OROPHARYNGEAL CANCER

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²Universidad Autonoma de Baja California, School of Dentistry, Tijuana, Mexico
³University of Nevada, School of Dental Medicine, Las Vegas, USA
⁴Huntsman Cancer Institute, Nursing, Salt Lake City, USA

Background and Aims

The incidence of oropharyngeal cancer (OPC) associated with Human Papillomavirus (HPV) has dramatically increased. 25,000 new cases were reported in Latin America in 2008, 66% of those cases were among men. The countries with most cases were Brazil, Mexico, Argentina, Colombia and Cuba. Assuming that 50% of OPC cases were due to HPV; HPV will be responsible for about 12,500 new cases annually and 8,750-25,000 cases in a year. To assess the knowledge levels regarding HPV related OPC of last year dental students’ and residents from pediatric dentistry, endodontic, and orthodontic programs in Colombia and Mexico.

Methods

To assess student HPV, HPV-OPC, HPV vaccination, and overall knowledge levels, The Universidad de Antioquia and Universidad Autonoma de Baja California, Tijuana dental school programs were recruited to implement a 147 questions survey assessment tool. The acceptable knowledge threshold was set at 70%. Subsequently, results and research objectives were assessed.

Results

The results suggest overall adequate knowledge was poor for the dental students and residents (32% vs 38%). Adequate general HPV knowledge levels were lower for dental students compared to residents (52% vs 62%). Adequate HPV-OPC knowledge levels were greater proportionally for residents than for the dental students (30 % vs 20%). Adequate HPV vaccination knowledge levels were greater proportionally for residents than for the dental students (44 % vs 33%).

Conclusions

The results of this study suggest that dental students and residents have lower than expected knowledge about HPV and OPC. OHP education and dental curriculum changes are required to reduce this emerging cancer problem.
Background and Aims

Loop Electrical Excision (LEEP) and Cold knife conization (CKC) are excisional treatment options for the treatment of cervical intraepithelial neoplasia (CIN). CIN is caused by human papillomavirus (HPV), and CIN-2 and CIN-3 can potentially lead to cervical cancer. We aimed to estimate the annual proportion of mid-adult women in the US aged 27-45 years undergoing cervical conization from 2012-2016.

Methods

Mid-adult women aged 27-45 years undergoing CKC or LEEP procedures (CPT code 57520/22), and those who underwent cervical screening (HPV test and/or Pap test) and/or diagnostic procedure (colposcopy) were identified in the Truven MarketScan® database from calendar years 2012-2016. In a cross-sectional study, descriptive statistics were used to estimate the proportion of mid-adult women who undergo excisional procedures in the total population, and the screened population. Results were stratified by age and procedure type.

Results

Between 2012-2016, the annual proportion of mid-adult women undergoing conization in the total population and screened population was 1.7-1.8/1000 and 4.2-5.3/1000, respectively (Table 1). Proportions varied by age groups (2.1-1.2/1000 in 2016). About 77%-79% had LEEP, and 3% had both LEEP and CKC procedures.

Conclusions
Conization is a common treatment approach among mid-adult women of child-bearing age. The proportion of total women conized is about 15 times the incidence of cervical cancer (2014-SEER-incidence among 27-45 years-old=11.7/100,000). The proportion of screened mid-adult women who were conized increased from 2012-16. Attempt should be made to reduce the burden of conization by utilizing interventions such as HPV vaccination to reduce CIN2/3 burden.
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Mid-adult women aged 27-45 in the calendar year</td>
<td>7,952,055</td>
<td>6,567,762</td>
<td>7,144,086</td>
<td>4,355,250</td>
<td>4,317,934</td>
</tr>
<tr>
<td>Mid-adult women aged 27-45 undergoing HPV screening (HPV/Pap/Colposcopy)</td>
<td>3,064,246</td>
<td>2,345,226</td>
<td>2,330,227</td>
<td>1,415,068</td>
<td>1,380,980</td>
</tr>
<tr>
<td>Mid-adult women aged 27-45 undergoing conization during the calendar year</td>
<td>13,716</td>
<td>11,305</td>
<td>12,046</td>
<td>7,605</td>
<td>7,855</td>
</tr>
<tr>
<td>Mid-adult women aged 27-45 undergoing conization and had a HPV screening test in the calendar year</td>
<td>12,907</td>
<td>10,671</td>
<td>11,246</td>
<td>7,104</td>
<td>7,279</td>
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<tr>
<td>Proportion of mid-adult women aged 27-45 years who undergo cervical conization</td>
<td>1.7/1,000</td>
<td>1.7/1,000</td>
<td>1.7/1,000</td>
<td>1.7/1,000</td>
<td>1.8/1,000</td>
</tr>
<tr>
<td>Proportion of mid-adult women aged 27-45 years screened for HPV who undergo cervical conization</td>
<td>4.2/1,000</td>
<td>4.6/1,000</td>
<td>4.8/1,000</td>
<td>5.0/1,000</td>
<td>5.3/1,000</td>
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</table>
### Table 2: Number of cases of conization among mid-adult women

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cases of CKC or LEEP</th>
<th>Total population of mid-adult women identified (age 27-45)</th>
<th>Screened population of mid-adult women identified (age 27-45)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CKC</td>
<td>LEEP</td>
<td>Both</td>
</tr>
<tr>
<td>2012</td>
<td>2,753</td>
<td>(20%)</td>
<td>10,557</td>
</tr>
<tr>
<td>2013</td>
<td>2,194</td>
<td>(19%)</td>
<td>8,781</td>
</tr>
<tr>
<td>2014</td>
<td>2,287</td>
<td>(19%)</td>
<td>9,429</td>
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<tr>
<td>2015</td>
<td>1,433</td>
<td>(19%)</td>
<td>5,941</td>
</tr>
<tr>
<td>2016</td>
<td>1,440</td>
<td>(18%)</td>
<td>6,194</td>
</tr>
</tbody>
</table>
Globale Trends in HPV-related Awareness: An Updated Systematic Review

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2University of South Florida, Psychology, St. Petersburg- FL, USA
3Florida International University, Banyan Research Institute on Dissemination- Grants- & Evaluation, Miami- FL, USA
4Florida International University, Epidemiology, Miami- FL, USA

Background and Aims

High-risk HPVs can cause anogenital and oropharyngeal cancers. Low-risk subtypes can cause genital warts. Recent increases in oropharyngeal cancers, particularly in men, have spurred renewed interest in clinical and behavioral HPV research. Despite established evidence, many countries are hesitant to implement a vaccination program, possibly driven by low awareness and knowledge of the virus behind the diseases. We present findings from our updated global review of HPV-related awareness and knowledge. Our objectives were to 1) Update and improve our 2016 systematic review 2) Evaluate trends in HPV virus and vaccine awareness by geographical region 3) Frame the importance of HPV virus and vaccine awareness on reduction of HPV disease burden globally through global sub-group analyses.

Methods

Our updated search yielded over 6000 citations from five databases: PubMed, CINAHL, ASSIA, Embase, and PsycInfo. We systematically screened studies assessing binomial outcomes of HPV-related awareness or knowledge and analyzed trends over time by country or geographic region, gender, and other available sociodemographic variables.

Results

Over 400 literature citations were included in our review, representing over 30 countries. Publication frequency coincided with milestones in HPV policy. Increase in awareness were evident over time in most regions, with differences between sub-groups. College students, women, and high-income countries displayed higher awareness than their counterparts.

Conclusions

These preliminary results highlight the need for educational intervention among those vaccine-eligible and show how important policy can be in effecting change in population health. The implications of this review may be far-reaching for countries contemplating the addition of HPV vaccination to national programs.
NUMBER NEEDED TO VACCINATE (NNV) WITH THE NONAVALENT VACCINE TO PREVENT ONE HPV-RELATED DISEASE IN CANADA

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¹Merck Canada Inc., Medical Affairs, Kirkland, Canada
²Merck Canada Inc., Health Economics & Obs Research, Montreal, Canada
³Dalhousie University, Division of Infectious Diseases, Halifax, Canada

Background and Aims

In Canada, human papillomavirus (HPV) vaccination is recommended for females aged 9-45 and males up to 26 years. The HPV vaccine is funded in the school-based vaccination programs of all provinces and territories. Nonavalent HPV vaccine (HPV9) prevents HPV 6/11/16/18 and the five next most common cancer-causing HPV types (31, 33, 45, 52 & 58). Here we aimed to estimate the NNV to prevent a case of HPV disease by vaccinating 12-year-old girls and boys in Canada with HPV9.

Methods

NNV was defined as NNV = N ÷ P, where N is the size of the vaccinated cohort, and P is the predicted number of HPV-related events prevented in the vaccinated cohort over its lifetime. We estimate 90% vaccine coverage of a cohort of 12-years-old girls and boys and a lifetime vaccine protection. Vaccine efficacy, disease incidences, and proportion of cases attributed to the HPV-types included in the vaccine were retrieved from the literature.

Results

NNV estimates to prevent a case of cervical, vaginal, and vulvar cancer were 149, 3633 and 1975, respectively. Furthermore, NNV estimates were 4 and 8 respectively for CIN2+ and genital warts in women. In men, the NNV for genital warts is 8 and for anal cancer is 2061.

Conclusions

The NNV with HPV9 is illustrating the important benefits expected from the prophylactic use of the vaccine against 9 prevalent HPV types to reduce the burden of genital warts, cervical intraepithelial neoplasia and HPV related cancers in Canada.
Introduction: Information on the prevalence of specific human papillomavirus (HPV) types is needed among high-risk population such as HIV-infected women. Frequency and distribution of HPV genotypes among human immunodeficiency virus (HIV)-infected women have not been studied in Bolivia. In this study we report high-risk HPV (HR-HPV) prevalence and type distribution in HIV-infected bolivian women.

Methods

HR-HPV prevalence and genotyping was done using cervical samples from 197 HIV-infected women in a cross-sectional study between 2016 and 2017. Commercial® Anyplex II HPV14 test, which detects 14 genotypes, was used for the molecular detection and genotypes identification of HPV in cervical samples.

Results

The prevalence of HR-HPV infection was 46.97%. It decreased significantly with age: 74.3% (below < 20 years, n=35), 40.3% (20–29 years, n=62), 45.3% (30–99 years, n=64), 40.3% (40–49 years, n=27) and 33.3% (over 50 years, n=9). Frequency of single and multiple (between 2 to 7 genotypes) high-risk infections were 33.3% and 66.7%, respectively, infections with more than one genotype was observed commonly in young women. The most common HR-HPV genotype detected in HIV-infected women was HPV 16 (30.1%), followed by 52 y 58 (both 25.8%).

Conclusions

Our results show that the prevalence of HR-HPV in HIV-positive women is high especially in young women, nevertheless, this prevalence remains higher in each age strata when compared to the general population (17%). The frequency of multiple infections among the HIV-positive bolivian women is usually high.
Background and Aims

Studies are often designed to show that the immunogenicity of a candidate vaccine is non-inferior to the immunogenicity of an established vaccine. Such studies may conclude that the candidate vaccine is non-inferior if the ratio, $R=\text{GMT}_C/\text{GMT}_E$, between the Geometric Mean antibody Titers after the candidate ($\text{GMT}_C$) and established ($\text{GMT}_E$) vaccine exceeds a given threshold (i.e. $R>t$).

Methods

Here, we first use simulation and theory to demonstrate the relationship between the chosen non-inferiority threshold and the proportion of vaccine recipients who are protected against infection, as a function of the elicited GMTs and the titer level required for protection. We then introduce a new metric for defining non-inferiority that estimates the maximum change in the proportion protected over the plausible range of minimum levels required for protection and show how to calculate the confidence interval for that maximal change.

Results

We show that the efficacy of a candidate vaccine may not be adequately summarized by the ratio of GMTs and that the relative proportion of recipients protected by the vaccine depends on the ratio, the absolute values of the GMTs, and the level required for protection. We further show that an alternative metric, which can be used even when the exact titer levels required for protection is unknown may be an appropriate alternative and the estimated confidence intervals for this metric have valid statistical properties.

Conclusions

We show that using the ratio of GMTs to define non-inferiority may be a satisfactory metric for defining the efficacy of a candidate vaccine.
HPVCANCERFREE: FEASIBILITY OF A MHEALTH INTERVENTION TO INFLUENCE PARENT HPV VACCINATION DECISION-MAKING.

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¹University of Texas School of Public Health, Behavioral Science, Houston, USA
²Baylor College of Medicine, Pediatrics, Houston, USA
³Texas Children's Hospital, Texas Childrens Pediatric Clinics, Houston, USA

Background and Aims

In the United States, initiation of HPV vaccination lags behind other vaccines. Parents cite numerous reasons for refusing or delaying their child’s HPV vaccine initiation. mHealth technology represents a channel to potentially mitigate parental concerns and to persuade initiation. HPVCancerFree is a theory-based mobile app designed to 1) raise awareness of HPV and cancer prevention, 2) reduce perceived barriers to HPV vaccination using peer and professional role models, and 3) enable vaccination appointment scheduling. Our aim was to test the feasibility and perceived impact of HPVCancerFree among parents of vaccine eligible youth in a large urban pediatric clinic network.

Methods

Parents, recruited through flyers and e-mails from 12 community clinics, were invited to use HPVCancerFree within a 5-month period. Parents completed an online usability survey to rate the app’s features and its impact on their HPV vaccination intentions.

Results

Parents (n=21) were mostly female (95%), 44(±5) years old, and privately insured (86%). HPVCancerFree was accessed 204 times (1-21 visits/parent). Visit duration averaged approximately 2.5 minutes. Parents agreed that HPVCancerFree features were useful (62-81%), increased their knowledge (84%) of the HPV vaccine, were credible and trustworthy (68%), encouraged dialogue with their pediatrician (68%), and that HPVCancerFree was as much or more helpful than other apps (84%). HPVCancerFree increased parent intentions to vaccinate (47%) with some parents initiating vaccination “because of app” (5%). Study limitations include restricted sample size and study duration.

Conclusions

Feasibility and utility of HPVCancerFree in parent decision-making suggest that future efficacy testing is indicated.
Human papillomavirus (HPV) vaccine impact among populations with low vaccination coverage is unknown. In Tennessee, HPV initiation and completion among females aged 13-17 years in 2014 was 48% and 20%, respectively. We assessed trends in anogenital wart (AGW) incidence among low-income persons aged 15-39 years enrolled in TennCare, Tennessee’s Medicaid program, from 2006-2014.

Methods

We used diagnosis/pharmacy codes from TennCare billing claims to identify incident AGWs, defined by 12-months disease-free before meeting one of the following: 1) condyloma acuminatum diagnosis, 2) viral wart diagnosis and genital-specific code, or 3) AGW medication and genital-specific code. We calculated sex-specific annual AGW incidence and annual percent changes (APCs) by age group, race (White vs. Black), and urbanicity (metropolitan statistical area [MSA] vs. non-MSA).

Results

A total of 799,122 enrollees contributed to 2.7 million person-years of data. AGW incidence decreased among females 15-19 years (APC=-10.6%; P<0.01) and 20-24 years (APC=-3.9%; P=0.02). Incidence among females 25-39 years and males 15-39 years were stable or increased. Rates among males 15-19 years changed in 2010 from an increasing to decreasing trend but neither were significant. Age-
specific trends were similar by race and urbanicity.

Conclusions

We detected decreases in AGWs among age groups most likely to be vaccinated, even among a population with low vaccination coverage. Although not significant, decreasing incidence among young males after 2010 suggests possible early indirect effects; however, further follow-up is needed. Indication of population-level HPV vaccine impact supports continued adherence of current vaccination recommendations for preventing AGWs and other HPV-related diseases, such as cervical cancer.
A QUALITATIVE STUDY ON THE BARRIERS TO GETTING VACCINATED AGAINST HUMAN PAPILLOMAVIRUS AMONG MEN IN HONG KONG

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¹The Hong Kong Polytechnic University, Department of Applied Social Sciences- Faculty of Health and Social Sciences, Hung Hom, Hong Kong S.A.R.
²Hong Kong Baptist University, Department of Communication Studies- School of Communication, Kowloon Tong, Hong Kong S.A.R.

Background and Aims

Human papillomavirus (HPV) is clinically proven to cause different diseases. High risk strains can cause cervical cancer and cancer of vulva that exclusively involving women. However, HPV can infect men as well, such as cancers of penis, anus, and oropharynx. Other low risk strains can also lead to genital warts. Therefore, infection with HPV does not only involve women but men as well. However, past literature shows that the coverage of HPV vaccine on men population is far lower than women population. A majority of studies about the acceptance of HPV vaccine concerns women. There has been a paucity of literature about the perceptions and acceptance of HPV vaccine among men, in particular for Chinese communities. This study is conducted to investigate the non-acceptance of men about the HPV vaccine by using Hong Kong as an example.

Methods

This study adopted a qualitative approach with 39 in-depth individual semi-structured interviews with men who were purposively sampled, aiming at investigating the perceptions of HPV vaccine and the factors influencing the sampled men not to get vaccinated.

Results

The social construction of HPV as a consequence of promiscuity and HPV vaccine as an exclusively female issue are the major contributors of the low perceived needs of having HPV vaccine among the participants. HPV vaccine has been socially constructed as irrelevant to men, which is resulted from the patriarchal social and cultural values of Hong Kong.

Conclusions

To promote acceptance of HPV vaccine among men, attention should be given on the cultural values of a community.
IS THE POSITIVE PREDICTIVE VALUE OF HIGH-GRADE CYTOLOGY IN PREDICTING HIGH-GRADE CERVICAL DISEASE FALLING DUE TO HPV VACCINATION?

F. Sultana1, K. Winch1, M. Saville2, J. Brotherton1

1Victorian Cytology Service Ltd, Victorian Cytology Service Registries, Melbourne, Australia
2Victorian Cytology Service Ltd, VCS Pathology, Melbourne, Australia

Background and Aims

A fall in the positive predictive value (PPV) of high-grade squamous intraepithelial lesion (HSIL) and/or adenocarcinoma-in-situ (AIS) cytology in predicting histologically confirmed high grade cervical disease (HGD) has been predicted in the post HPV vaccination era due to the decrease in prevalence of significant cervical lesions.

Methods

Data was extracted from the Victorian Cervical Cytology Registry including cervical cytology tests taken between 2000 and 2016 and any subsequent histology performed within six months of the cytology. PPV was calculated for each age group (<20, 20-24, 25-29, 30-34, 35-39, 40-49, 50-59, 60-69, 70+ years) and calendar year. The x2 (chi-square) test was used to identify significant trends in PPV overtime in each age group in both the pre-vaccination (2000-2006) and the post-vaccination (2007-2016) periods.

Results

The overall PPV of HSIL/AIS cytology in predicting HGD was 75% and this was consistent across the different calendar years. When stratified by age group, there was a decreasing trend in the PPV in women aged <20 years (ptrend=0.0006) and 20-24 years (ptrend=0.0004) in the post-vaccination period but not in the pre-vaccination period (ptrend=0.82 and ptrend=0.73, respectively). No such decline in PPV was noted in either the pre-vaccination or the post-vaccination periods for any other age groups except age groups 60-69 years and 70+ years. Similar trends were observed when the analyses were restricted to HSIL cytology alone.

Conclusions

The decline in PPV of HSIL/AIS cytology in predicting HGD in age groups <20 and 20-24 years in the post-vaccination period could be an impact of the HPV vaccination.
DECLINING TRENDS IN HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN2+) BY BIRTH COHORT IN ALAMEDA COUNTY, CALIFORNIA, UNITED STATES OF AMERICA (U.S.A.)

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¹California Emerging Infections Program, HPV Vaccine Monitoring and Surveillance Unit, Richmond, USA
²Kaiser Permanente Northern California, Division of Research, Oakland, USA
³Centers for Disease Control and Prevention, Viral Vaccine-Preventable Diseases Branch- Division of Viral Diseases, Atlanta, USA
⁴University of California San Francisco School of Medicine, Department of Family and Community Medicine, San Francisco, USA

Background and Aims

In the U.S.A., HPV vaccine was introduced in 2006 for routine vaccination of females ages 11-12 years and through age 26; uptake gradually increased following adoption. We examined trends in high-grade cervical intraepithelial neoplasia (CIN2+) diagnoses by birth year to identify potential HPV vaccine impact in racially diverse (59.6% non-white) Alameda County, California.

Methods

Incident CIN2+ data were analyzed from population-based surveillance (HPV-Impact) of adult (18+) women, 2008-2015. Cervical cancer screening was estimated using Pap-screening rates from the county’s largest insurer, adjusted for uninsured status. County-wide Pap-screening rates by age-group (18-20, 21-24, 25-29, 30-34, and 35-39) were applied to age-specific population denominators and used to estimate CIN2+ incidence among screened women. We used Poisson regression to calculate incidence rate ratios (IRRs) among Pap-screened women for birth cohorts 1979-1994, using 1979, the youngest cohort not eligible for vaccination, as the reference year.

Results

4,018 women with CIN2+ born 1979-1994 were included. The youngest cohort with significant declines in CIN2+ incidence was born in 1990, aged ~16 years when vaccine introduced (IRR: 0.44; 95% CI: 0.34-0.57). Declines continued for subsequent cohorts, with the lowest incidence in the 1994
cohort; aged ~12 years when vaccine introduced (IRR: 0.18; 95% CI: 0.08-0.45) (Figure).

**Figure 1**: Relative change in incidence rates (per 100,000 screened women) of high-grade cervical lesions and 95% confidence intervals (CIs) by birth cohort 1980-1995, compared to 1979, Alameda County, CA, 2008-2015. Dot for each birth cohort indicates point estimate relative difference from 1979 (referent) birth cohort, and lines indicate 95% CIs.

**Conclusions**

CIN2+ incidence among Pap-screened women declined significantly starting with the 1990 birth cohort, who were eligible for catch-up vaccination from ages 16-25. Since this analysis evaluates CIN2+ incidence within the context of cervical cancer screening rates and gradually increasing vaccination coverage, it provides compelling evidence for progressive HPV vaccine impact in the U.S.A.
HUMAN PAPILOMAVIRUS 51 AND 58 ARE ASSOCIATED TO MULTIPLE INFECTIONS IN CERVICAL EPITHELIUM FROM MEXICAN WOMEN

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2Instituto Mexicano del Seguro Social, Centro Medico Nacional Siglo XXI, Mexico, Mexico

Background and Aims

Human papilomavirus infection (HPV) is the main factor for cervical cancer (CC). The HPV multiple infection (MI) and its possible role in CC is in study. Our aim was to investigate the HPV genotypes commonly associated to MI patterns in cervical epithelium from Mexican women.

Methods

HPV genotyping was performed in 54 cervical smears from women with and without cervical lesions (CL) including 34 low-grade squamous intraepithelial lesion (LSIL): 4 HSIL; and 1 cervical cancer (CC) and without cervical alterations (n=15) by using Genomica and/or linear array assays.

Results

Women HSIL+CC, LSIL and without cervical lesions (CL) mean ages were 35.6, 36.4 and 34.5 years. 57%(31/54) had HPV MI, a half with 2 or 3, the remaining with >3 genotypes. MI was in 67% without lesion, 56% LSIL, 40% HSIL. The Prevalence of HR-HPV and LR-HPV were 81.3% and 8.7%. The global HPV genotype distribution was 59(13.7%); 31(11.9%); 16(10.9%); 51(10%); 56(7.8%); 58(6.8%); 66(4.1%); 35,52,53,6 (3.2% each one), 61,33(2.7%). The more frequent genotypes associated to MI were HPV51,58,59 and 16. HPV16 and HPV59 were present in 31% and 69% single or MI, respectively. HPV51 was in 48% of woman with CL and only in 20% without lesion respectively. HPV58 was in 29% of woman with CL and in 10% without lesion. Interestingly, HPV51(clade A5) and HPV58(clade A9) were only present in MI.

Conclusions

High prevalence of HPV MI was found with HPV51 and HPV58. It may be important in the development of CL. The HPV51 (clade A5) should be taken in consideration in new vaccines schemes.
THE PREVALENCE AND GENOTYPE DISTRIBUTION OF MULTIPLE OR SINGLE CERVICAL HUMAN PAPILLOMAVIRUS IN MAINLAND CHINA: A META-ANALYSIS OF POPULATION-BASED STUDIES

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¹Cancer Institute/Hospital- Chinese Academy of Medical Sciences & Peking Union Med, Department of Cancer Epidemiology, Bei Jing, China

Background and Aims

We aimed to assess the prevalence and genotype distribution of multiple or single cervical human papillomavirus (HPV) in population-based women of mainland China by meta-analysis.

Methods

Literatures on HPV prevalence published between Jan 1995 and Dec 2016, were retrieved from PubMed, Medline and Chinese databases Information on study design, cytological or pathological diagnosis, assays for HPV DNA detection and other related data was collected. 14 population-based studies were left for final evaluation using Stata 12.0.

Results

A total of 77,197 women were included in the 14 studies. Overall single and multiple HPV prevalence were 10.74% (95%CI: 8.25-13.22) and 5.42 % (2.84- 8.01), respectively. As regards the type-specific HPV prevalence, single HPV infection was significantly higher than the corresponding multiple infection (all P<0.001), for the high-risk (hr-) HPV (5.51% vs. 3.19%), for the low-risk (lr-) HPV (2.38% vs. 1.79%), and for the single type-specific HPV prevalence covered in the nine-valent vaccine (5.85% vs. 3.15%).

The five most common types were HPV-16, -52, -58, -33 and -18 both for single and for multiple HPV infection across northern and southern China. The overall single hr- or lr- HPV infection, HPV-52 and HPV-6/-11 were more reported in the southern regions than the northern, while multiple hr- or lr- HPV infection and HPV-16/-35/-33/-59 was the opposite.

Conclusions

Mainland China presented unique type-specific infection both for single and for multiple HPV. Overall single or multiple HPV sharply varied across China regions, type-specific HPV infection also changed with relative small perturbation.
A CORRELATION STUDY BETWEEN ABNORMAL VAGINAL MICRO-ECOLOGY AND HR-HPV INFECTION BASED ON GENERAL WOMEN POPULATION IN YUNNAN PROVINCE, CHINA

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Background and Aims

To study the correlation between abnormal vaginal micro-ecology such as BV (bacterial vaginosis), TV (trichomonas vaginitis), VVC (vulvovaginal candidiasis), vaginal depuratory degree reduction (III~IV), pH value increase (pH>4.5) and HR-HPV infection among general women population in Yunnan province of China.

Methods

This is a cross sectional study. A total of 491 fertile women aged from 20 to 65 year-old (Mean age 45.2±6.7) were recruited from Yunnan Province. According to the HPV test, we divided the subjects into positive and negative groups. Chi-square test was used to compare inter-group rate, then explored the correlation between abnormal vaginal micro-ecology and HR-HPV infection.

Results

There were 28 cases with 45.5 ± 7.1 year-old on average age in HPV positive group and 463 cases with 45.2 ± 6.7 year-old on average age in HPV negative group. The positive rate of HPV was 5.7% (28/491). The proportions of patients with BV, TV, VVC, low vaginal depuratory degree and pH>4.5 in HPV positive and negative group were 28.6% (8/28), 10.7% (3/28), 10.7% (3/28), 21.4% (6/28), 78.6% (22/28) and 16.4% (76/463), 0.6% (3/463), 15.3% (71/463), 7.1% (33/463), 58.5% (271/463) respectively. Significant difference was found in TV, low vaginal depuratory degree and pH>4.5 in HPV positive group (P<0.05), and the OR (95%CI) were 18.400 (3.533~95.822), 3.554 (1.348~9.371), 2.598 (1.034~6.528). While BV and VVC have no correlation with HR-HPV infection.

Conclusions

The HPV infection rate in Yunnan general population is low. TV, low vaginal depuratory degree and pH >4.5 might have a positive correlation with HR-HPV infection.
Genital human papillomavirus (HPV) infection, the most common sexually transmitted infection among women, is potentially serious because of its associated high risk of cervical cancer. The aim of this study was first to determine the prevalence of carrying and second to characterize high-risk HPV genotypes among females sex workers in Ouagadougou.

Methods

During 1 months, 200 females sex workers voluntarily accepted endocervical swab collection. Real-time PCR was used to identify HPV genotypes.

Results

High-risk HPV carrying prevalence was 41.5%: 106 females sex workers were positive for at least one high-risk HPV genotype. Fourteen genotypes corresponding to 225 infections were characterized: HPV68 (33/225), HPV31 (27/225), HPV52 (21/225), HPV51 (20/225), HPV56 (17/225), HPV66 (17/225), HPV58 (16/225), HPV35 (16/225), HPV39 (14/225), HPV18 (14/225), HPV45 (13/225), HPV59 (7/225), HPV16 (6/225), HPV33 (4/225). Multiple infection, statistically associated with females sex workers’ age (p < 0.001), was detected in 53.8% of the infected females sex workers. While the number of sexual partners was statistically associated with carrying of HPV (p < 0.001; OR = 2.0; 95% CI : 0.56-7.14), the early beginning of the sexual intercourses and recent change of partners were not.

Conclusions

This study has shown that the prevalence of high-risk HPV genotypes is high and shows the need to strengthen the means of control against this disease. The genotypes here identified are different from those targeted in the currently available prophylactic vaccines. A broader study to chart the high-risk HPV genotypes circulating in West Africa is necessary to tailored vaccine.
Background and Aims

Unlike infection in women, less is known about HPV infection in men. HPV prevalence in men varies with sampling methods used, nature of tests applied and, anatomical site(s). There is a paucity of information on HPV prevalence in asymptomatic men who can be reservoirs of infection. We aimed to study HPV prevalence in asymptomatic men from the Indian subcontinent attending our urology clinic.

Methods

A prospective cross-sectional study of 140 men visiting the Urology clinic with symptoms unrelated to penile disease was done. Men with known HIV infection and other sexually transmitted infections (STI) were excluded. A questionnaire was administered to assess risk factors. Penile swabs were collected from the urethral meatus and the penile shaft. A WHO validated HPV PCR reverse-hybridization method (PGMY-CHUV assay) was used to identify the HPV infection and genotype. Presence of HPV was correlated with known risk factors.

Results

All samples were checked for sufficient DNA prior to analysis. Among the 140 participants, 12 (8.6%) were positive for HPV. Ten (83%) harboured established high risk genotypes (Figure). All were heterosexuals. There was no significant association of HPV with smoking, alcohol use, number of partners, phimosis, circumcision, penile warts and condom use.

Conclusions

HPV prevalence in “asymptomatic” men in the Indian subcontinent is low as in a Korean study. Low prevalence could be related to excluding men with HIV and STI. However, most of the HPV genotypes were high risk types. Large scale epidemiological studies are needed to assess the burden in symptomatic and asymptomatic men in India.
HUMAN PAPILLOMAVIRUS INFECTION AND CERVICAL INTRA-EPITHELIAL LESIONS AMONG FEMALE SEX WORKERS IN THE GREATER ACCRA REGION OF GHANA
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Background and Aims
As part of efforts to characterize the prevalent Human Papillomavirus (HPV) genotypes in order to predict the impact of prophylactic vaccination in reducing the incidence of cervical cancer in Ghana, we determined the prevalence and genotype distribution of genital HPV including abnormal Pap smear rate among Female Sex Workers (FSWs) in Greater Accra region (GAR).

Methods
This was a cross-sectional study where snowballing technique was used to identify and select FSW’s ≥18 years, working in GAR. Participants were interviewed and Pap smears taken from each. In addition, cervical swabs were collected for HPV-DNA detection, and genotyping by Nested Multiplex PCR.

Results
Hundred participants, age ranging from 18-45 years with a median of 22 years took part in the study. The prevalence of abnormal Pap smear was 18% comprising: 7% atypical squamous cells of undetermined significance, 8% Low-grade Squamous Intraepithelial Lesion, and 3% High-grade Squamous Intraepithelial Lesion. HPV prevalence was 26%. Eleven HPV genotypes were detected comprising: nine High-risk types and two Low-risk types. High-risk HPV detected in order of decreasing prevalence were: HPV-16 (8%), HPV-35 (5%), HPV-33/HPV-39/HPV-68 (3%), HPV-52/HPV-51 (2%) and HPV-18 (1%). HPV-42, was the commonest low-risk type (3%) followed by HPV-43 (1%). In addition, (3%) had HPV types that could not be genotyped by our method

Conclusions
We found a high HPV and abnormal Pap smear prevalence among FSWs in the Greater Accra Region. Majority of High-risk HPV genotypes seen are vaccine preventable, providing additional compelling argument for implementing a national cervical cancer prevention plan including vaccination.
Evidence in men for increased mortality from cancers of the lip, oral cavity and pharynx (oro-pharynx) among World War II birth cohorts from involved countries

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Background and Aims

An increase in oropharyngeal cancers linked with Human Papilloma Virus (HPV) as well as other HPV related cancers, has been attributed to changing sexual behaviours in birth cohorts. In this study we examine mortality due to squamous cell carcinoma of oro-pharynx across birth cohorts, with particular focus on cohorts born during World War II (WWII). Changes in sexual practices of parents of these children may have led to increase in vertical transmission of HR-HPV and subsequent increased mortality attributable to this cancer.

Methods

The International Agency for Research on Cancer (IARC) developed a cancer mortality database by extracting statistics from WHO mortality database, presenting it according to cancer type and sex, using five-year birth cohorts in 50 selected countries, until 2013. We performed a birth cohort analysis and examined trends in mortality due to cancers of oro-pharynx, rectum and anus, among men and women born between 1940-1945 in countries involved in WWII namely: United Kingdom, Australia, New Zealand, Japan, Germany and Italy and neutral countries (Denmark, Switzerland and Ireland).

Results

We observed a distinct peak in oro-pharyngeal cancer mortality in males <50 years among those born 1940-1945 in WWII countries. However, there were no obvious trends noted in women or in neutral countries.

Conclusions

Our analysis suggests a peak in male mortality from oro-pharyngeal cancer attributable to increased HPV vertical transmission. We suggest research on vertical transmission of High-Risk HPV (16 and 18) and its natural history. This would have implications for HPV vaccination of newborns.
Mortality from cancer of the lip, oral cavity and pharynx
United Kingdom: men

rate per 100,000 person-years

year of birth

International Agency for Research on Cancer (IARC) - 16.4.2018
Background and Aims

A significant proportion of mucosal squamous cell carcinomas of the head and neck (HNSCC; particularly of the oropharynx) are directly attributable to the human papillomavirus (HPV). The increase in incidence of HPV-related tumours has been postulated to be due to changing sexual practices.

Methods

We investigated HPV prevalence and associated characteristics among 136 patients with HNSCC (40 oral cavity and 96 oropharyngeal) at Princess Alexandra Hospital (Brisbane, Australia) who completed a detailed survey and for whom FFPE tumour tissue was also available. Samples were analysed using a combination of the mucosal HPV general primer GP+ PCR and sequencing; p16\(^{\text{INK4a}}\) expression was assessed by immunohistochemistry. Each patient completed a questionnaire detailing their lifestyle factors such as smoking, alcohol consumption, marital status, and sexual behaviour.

Results

HPV DNA prevalence was 72% in the oropharyngeal cancers compared with 5% in oral cavity cancers (\(p<0.0001\)). HPV-16 was the most commonly detected HPV type (found in 91% of all HPV-positive tumours). There was a strong correlation between HPV DNA positivity and positive p16\(^{\text{INK4a}}\) staining in oropharyngeal tumours (\(p<0.0001\)). Having a HPV-related tumour was associated with being married currently or previously (\(p=0.046\)), increasing number of passionate kissing partners (\(p=0.046\)), ever having given oral sex (\(p=0.0007\)) and with increasing number of oral sex partners (\(p=0.0015\)).

Conclusions

In summary, we found a higher prevalence of HPV in oropharyngeal than oral cavity tumours, with a strong association identified between oral sex behaviours and HPV-positive tumours. Further research is needed to establish that vaccines will reduce transmission and carriage of oropharyngeal HPV infections.
Background and Aims

The increasing incidence of oropharyngeal squamous cell carcinoma (SCC) is linked to oral human papillomavirus (HPV) infections. Despite recent dramatic increase in HNSCC in younger Australians, there is little published data on oral HPV prevalence in Australia.

Methods

We initiated the longitudinal Oral Health Study to investigate the natural history of oral HPV infection. Briefly, we recruited 627 participants aged 20 to 70 years in Greater Brisbane from June 2014 to November 2016, and asked them to complete a questionnaire about basic demographics, life-style factors, medical history and sexual behaviour. Saliva samples were collected from all participants for HPV testing and typing.

Results

73 of the 627 baseline saliva samples (11.6%) tested positive for oral HPV. Among the HPV-positive samples, HPV-33 was the most prevalent HPV type, followed by HPV-16. Compared to oral HPV-negative participants, participants infected with oral HPV reported a higher number of lifetime partners for passionate kissing (p=0.001), giving and receiving oral sex to more partners in a lifetime (p=0.016 and 0.002, respectively), more lifetime sexual intercourse partners (p=0.013), previously being diagnosed with a sexually transmitted infection (p=0.001) and wearing mouth jewellery (p=0.04). We found no associations with oral HPV status and gender, age, smoking, alcohol consumption, illicit drugs use, or preferred gender(s) of sex partners. Past history of a previous abnormal Pap smear result was not associated with oral HPV infection in women.

Conclusions

We found strong associations between multiple sexual partners and oral HPV infection.
MICROSPHERE-BASED METHOD FOR DETECTION AND GENOTYPING OF MUCOSAL HUMAN PAPILLOMAVIRUSES IN SOUTHERN GHANA

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²School of Public Health, Department of Applied Epidemiology and Disease Control, Accra, Ghana

Background and Aims

Among the general population of women at risk of cervical cancer in West Africa with Ghana inclusive, the prevalence of HPV is estimated to be 21.5%. High-risk HPV-DNA-based screening assays represent a group of qualitative or semi-quantitative multiplex assays in which the DNA of the targeted HPV types is detected using mixtures of probe cocktails for several HPV types with similar clinical characteristics. In this work we used a microsphere-based method to genotype HPV in Ghanaian women.

Methods

This study was a cross-sectional study that assessed human papillomavirus (HPV) genotype distribution in women using cervical specimens from Southern Ghana. Cervical specimens were obtained from women aged ≥18 Years. HPV DNA was amplified by PCR using general primers and typed by hybridization to HPV type-specific probes coupled to sortable microspheres based on a Luminex xMAP technology.

Results

HPV prevalence was 16.5% (n=97) and HPV genotypes detected were as follows, 16 (12.5%), 45 (12.5%), 66 (6.3%), 42 (18.8%), 31 (12.5%), 81 (6.3%), 62 (6.3%), 85 (12.5%), 90 (6.3%) and 67 (6.3).

Conclusions

The microsphere based genotyping method helped us characterize novel HPV genotypes such as HPV 81, 62, 85, 90 and 67 in Ghana for the first time. This work complements existing methods currently used in genotyping HPV in Ghana.
EXPLAINING THE DIFFERENT EFFECT OF AGE ON CIN2/3 AND CANCER RISK AFTER NEGATIVE CYTOLOGY AND HPV TEST: A MODEL-BASED EVALUATION

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3VU University Medical Center, Department of Epidemiology and Biostatistics, Amsterdam, The Netherlands
4University of Manchester, Institute of Cancer Sciences, Manchester, United Kingdom
5Aviano National Cancer Institute- IRCCS, Cancer Epidemiology Unit, Aviano, Italy
6Karolinska Institutet, Department of Laboratory Medicine, Stockholm, Sweden
7AO City of Health and Science, Centre for Epidemiology and Prevention in Oncology, Turin, Italy

Background and Aims

A pooled analysis of European RCTs observed that, at variance with the CIN2/3 decline, the risk of invasive cervical cancer (ICC) increased over age 50 after negative cytology and, less so, after negative HPV testing. We used a mathematical model to evaluate if low cytology sensitivity for a subset of precancerous lesions could explain such observations.

Methods

We predicted the difference between women aged 50-64 and 25-49 years in the risk of CIN2/3 and of ICC 3 years after normal cytology, under different scenarios concerning precancerous lesions poorly detectable (sensitivity 5%) by cytology.

Results

CIN2/3 risk decreased at age ≥50 under all scenarios. Likewise, assuming low sensitivity of cytology for some lesions, the predicted 3-year ICC risk increased above age 50. The older-minus-younger ICC risk difference increased from +0.8 to +2.5 and +7.4 per 100,000 if poorly detectable lesions represented 8% (overall cytology sensitivity 65%), 14% (overall sensitivity 65%) and 33% (overall sensitivity 55%) of precancerous lesions, respectively. In scenarios without cytologically poorly detectable lesions the risk difference was -1.4, -0.6 and +0.7 assuming 65%, 60% and 55% overall cytology sensitivity, respectively. The ICC risk increase at age ≥50 was mediated by an accumulation of lesions undetected from long time (>20 years).

Conclusions

Model predictions were consistent with observations. Of note, women in the HPV arm were at their first HPV screen and had plausibly already accumulated lesions undetected by cytology. Given increased HPV sensitivity, the observed effect is expected to disappear at subsequent HPV screens.
HRHPV POSITIVITY RATE DOES NOT CHANGE AFTER VACCINATION

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²University of Antwerp, AMBIOR- Laboratory for Cell Biology & Histology, Antwerp, Belgium
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Background and Aims

Since 2008, HPV vaccination in Belgium is reimbursed for girls aged 12-17. From 2010 onwards, free school-based HPV vaccination is offered to 12-year-old girls in Flanders. The purpose of this study is to investigate the effect of HPV vaccination in positivity and genotype distribution in young adults in Flanders.

Methods

Since 2006, AML routinely performs serial co-testing on all LBC samples including hrHPV genotyping. hrHPV genotype data of all screening LBC samples from women aged 20 to 22 in 2010 (non-vaccinated group: N= 2999) and 2017 (vaccinated group: N= 2249) were selected for analyses.

Results

Although no significant overall hrHPV positivity rate is observed between the vaccinated and non-vaccinated cohort (27.4% vs 28.6%; p= 0.35), the presence of HPV 16 and/or 18 is significantly lower (1.9% vs 10.5%, p<0.0001). For the individual HPV types, 6, 11, 16, 18 and 31 a significant reduction in positivity is detected (see table1). Additionally, in the vaccinated cohort, the presence of multiple
infections is significantly lower (10.3% vs 12.2%, p = 0.029).

<table>
<thead>
<tr>
<th></th>
<th>2010 Non vaccinated</th>
<th>2017 Vaccinated cohort</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N= 2999 %positive</td>
<td>N= 2249 %positive</td>
</tr>
<tr>
<td>hrHPV+</td>
<td>28.74%</td>
<td>27.43%</td>
</tr>
<tr>
<td>HPV 16/18</td>
<td>10.47%</td>
<td>1.91%</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td>12.2%</td>
<td>1.91%</td>
</tr>
<tr>
<td>P= 0.046</td>
<td></td>
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<tr>
<td>HPV 6</td>
<td>0.63%</td>
<td>0.13%</td>
</tr>
<tr>
<td>P= 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 16</td>
<td>8.70%</td>
<td>1.78%</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td></td>
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<tr>
<td>HPV 18</td>
<td>2.27%</td>
<td>0.13%</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td></td>
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<tr>
<td>HPV 31</td>
<td>5.74%</td>
<td>2.05%</td>
</tr>
<tr>
<td>P&lt;0.0001</td>
<td></td>
<td></td>
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<tr>
<td>HPV 33</td>
<td>1.20%</td>
<td>1.78%</td>
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<tr>
<td>P= 0.1</td>
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<td></td>
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<tr>
<td>HPV 35</td>
<td>1.00%</td>
<td>1.11%</td>
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<tr>
<td>P= 0.8</td>
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<tr>
<td>HPV 39</td>
<td>4.07%</td>
<td>4.94%</td>
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<tr>
<td>P= 0.1</td>
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<tr>
<td>HPV 45</td>
<td>0.80%</td>
<td>1.56%</td>
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<tr>
<td>P= 0.014</td>
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<tr>
<td>HPV 51</td>
<td>6.10%</td>
<td>6.63%</td>
</tr>
<tr>
<td>P= 0.47</td>
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<tr>
<td>HPV 52</td>
<td>4.70%</td>
<td>4.80%</td>
</tr>
<tr>
<td>P= 0.92</td>
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<tr>
<td>HPV 53</td>
<td>4.33%</td>
<td>5.42%</td>
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<tr>
<td>P= 0.08</td>
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<tr>
<td>HPV 56</td>
<td>3.70%</td>
<td>4.62%</td>
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<tr>
<td>P= 0.11</td>
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<tr>
<td>HPV 58</td>
<td>2.17%</td>
<td>2.71%</td>
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<tr>
<td>P= 0.24</td>
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<tr>
<td>HPV 59</td>
<td>3.83%</td>
<td>3.69%</td>
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<tr>
<td>P= 0.85</td>
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<tr>
<td>HPV 66</td>
<td>4.47%</td>
<td>4.00%</td>
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<tr>
<td>P= 0.44</td>
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<tr>
<td>HPV 67</td>
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</tr>
<tr>
<td>P= 0.0006</td>
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<td></td>
</tr>
<tr>
<td>HPV 68</td>
<td>3.50%</td>
<td>3.96%</td>
</tr>
<tr>
<td>P= 0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hrHPV single infection</td>
<td>16.51%</td>
<td>17.16%</td>
</tr>
<tr>
<td>P= 0.49</td>
<td></td>
<td></td>
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<tr>
<td>hrHPV multiple infection</td>
<td>12.24%</td>
<td>10.27%</td>
</tr>
<tr>
<td>P= 0.029</td>
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</tr>
</tbody>
</table>


Conclusions

Besides the expected reduction in the presence of HPV 6, 11, 16 and 18 in vaccinated adults, a reduction in HPV 31 positivity is detected. However, the overall hrHPV positivity in young adults is not changed after vaccination, suggesting type replacement and/or reduction of multiple hrHPV infections. The impact on future screening and triage algorithms needs further examination. It is too early to evaluate the effect in reduction of cervical lesions.
Oropharyngeal HPV among women with genital HPV

Background and Aims

HPV infection is the most prevalent sexually transmitted infection.

Its role as an obligatory event for cervical cancer is well established; other cancers are now associated with HPV infection, namely oropharyngeal cancer.

AIMS:
Determine frequency of oropharyngeal HPV infection in women with genital HPV.

Methods

Cross-sectional study evaluating frequency of oropharyngeal HPV infection among women with present or recent HPV cervical infection – at CUF Descobertas Hospital, Lisbon.

Women between 18 and 64 years old, attending the Colposcopy Unit for HPV lesion/infection, previous or present, since February 2016, where recruited. All participants were tested for HPV DNA in tonsils and cervix. Samples were analyzed using CLART HPV2® Test (Genomica) that allows the detection of 35 HPV genotypes. Demographic and behavioral variables were obtained.

Results

86 women, mean age of 35 (min. 24, max. 63); 55% (n=47) had a positive cervical HPV result (41% single infection, 14% multiple infections), all with at least one high risk (HR) genotype; only 7% (n=6) were HPV positive in the oropharynx. Three cases showed correspondence between cervical and oropharyngeal genotypes: 51,52/51,52 (HR), 53/53 (HR), 6/6 (LR).

From those who tested HPV positive (n=50), 60% had been vaccinated. It was not possible to establish associations between oral sex, vaccination or tobacco and oropharyngeal HPV infection or high risk cervical HPV infection.

Conclusions

This exploratory aims to generate evidence that could support further studies about epidemiology and natural history of HPV oropharyngeal infection.
From these results, oropharyngeal HPV infection is not frequent, but further research is needed.
CASE REPORT: CERVICAL TUBERCULOSIS DIAGNOSED AFTER TREATMENT FOR CERVICAL CARCINOMA

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Background and Aims

Tuberculosis has been shown to coexist with malignancy, but tuberculosis and cancer in the cervix is extremely rare. This is the first case of cervical tuberculosis diagnosed in a cervical cancer patient who has undergone concurrent chemoradiotherapy and brachytherapy.

Methods

Case Report

Results

This is the case of a 38 year old G2 P2 (2002) diagnosed with Squamous cell carcinoma, large cell non-keratinizing, Cervix, Stage IIIB. The patient underwent pelvic extended beam radiotherapy from February 3 to March 19, 2015. Concurrently, she was given 6 cycles of chemotherapy with Cisplatin. Brachytherapy with 4000 centi Grays was given in March 27-29, 2015.

On follow up one month after the last dose of brachytherapy, there was note of anodularity on the anterior lip of the cervix. A cervical punch biopsy was done which revealed: Chronic granulomatous inflammation with Langhan’s type multinucleated giant cells consistent with tuberculous infection. Negative for atypical/malignant cells.

This patient was started on Anti-Koch’s medication in the form of 2 months intensive treatment with Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol, then 10 months of Isoniazid and Rifampicin. She was seen on the 6th month of treatment at the Out Patient Clinic, there was note of decrease in the size of the nodularity and the rest of the cervix was noted to be smooth. Her Pap Smear was negative for intraepithelial lesion.

Conclusions

Cervical tuberculosis complicating cervical malignancy is curable with Anti-Koch’s therapy and has not been shown to adversely affect the course of the carcinoma.
Background and Aims

Seropositivity against HPV16E6 is a promising biomarker for HPV16-driven oropharyngeal cancer (HPV16-OPC) due to its early presence (10+ years before diagnosis) and high diagnostic accuracy (97%). In previous studies, ~0.7% of healthy controls were HPV16E6 seropositive of which only a minority will develop HPV16-driven cancer. We describe epidemiological risk factors for seropositivity to HPV16E6 and E7, and the cumulative exposure markers HPV16L1 and HPV18L1 in individuals without HPV-associated malignancy (prevalent/incident).

Methods

Using multiplex serology, serum antibodies were measured in a UK Biobank pilot study (n_pilot=9,695, n_UKB=500,000, recruitment 2007-2010, age 40-69y). Epidemiological risk factors for HPV seropositivity were determined by logistic regression models.

Results

Significant associations (ORs 2.7-14.5) of potential HPV-associated malignancies (n=113) with the HPV16 antibodies were observed. After excluding these malignancies, HPV16L1 and HPV18L1 seropositivity was associated with female gender (OR_{16L1} 2.1, 95%CI 1.7-2.7; OR_{18L1} 1.7, 95%CI 1.3-2.3) while HPV16 oncoprotein antibodies were more frequent in males (OR_{E6} 1.2, 95%CI 0.9-1.7; OR_{E7} 1.3, 95%CI 1.0-1.7). Seroprevalence of HPV16E6, HPV16L1 and HPV18L1 antibodies significantly increased with the number of reported lifetime sex partners (p-trend<0.005). All HPV antigens were significantly associated with ever having had same sex sexual intercourse (ORsmales 2.2-2.3).

Conclusions

The specificity of HPV16E6 antibody measurements in a large prospective cohort study of the general population is supported by their rarity, the observed associations with sexual behaviour and
overlapping risk factor profiles of HPV antigens. Additional risk stratification markers are needed to identify HPV16E6 seropositive individuals at highest risk of developing HPV16-OPC.
UPDATE OF GLOBAL ESTIMATES OF HPV PREVALENCE: META-ANALYSIS OF 2.4 MILLION WOMEN WITH NORMAL CYTOLOGY

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Background and Aims

Objective: to update global estimates on the HPV prevalence in women and provide more robust estimates by region, age, and HPV-type. Baseline HPV data is of relevance to support implementation and evaluation of programs of cervical cancer prevention and elimination.

Methods

PubMed was systematically searched for studies testing for HPV with a validated testing method (PCR or HC2) in health care provider collected cervical samples. We used random-effects models further standardized by the world’s population geographical structure to calculate HPV prevalences, and meta-regression and mixtures analysis to explore heterogeneity.

Results

In the period 1995-2015 we included 527 studies reporting from 2,361,528 women with normal cytology. Mean age was 36 years. Worldwide, the standardized HPV prevalence was 15.3% (95% CI 10.4–21.1%), with high heterogeneity between studies (Q test<0.001, I²:97-99% in most models). Compared to the worldwide average (see Figure), regional estimates ranged from 3-fold higher in the Caribbean (prevalence 50.7% (31.9-68.8%)) to a 0.6 lower in Southern-Asia (prevalence 8.5%(6.4-11%)). Age-specific analyses confirmed the first peak of infection at younger ages in all regions, except in Asia where the pattern was flatter. Type-specific analyses confirmed HPV16 (prevalence 3.5%) as the predominant and most prevalent HPV-type in all regions, and placed the rest of vaccine-preventable types among the most frequent ones.

Conclusions

These results confirm a high prevalence of HPV infection among women with normal cytology. In populations without local data, HPV prevention metrics could build on this frame of reference.
Figure. Ratio of HPV prevalences with reference to the World estimate
ORAL INFECTION WITH ALPHA-, BETA- AND GAMMA-PAPILLOMAVIRUSES IN AN URBAN ASIAN CHINESE POPULATION

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Background and Aims

Knowledge of the prevalence of and risk factors for oral human papillomavirus (HPV) infection, especially cutaneous types, is limited.

Methods

A population-based study using Next-Generation Sequencing consecutively recruited asymptomatic individuals aged 18-64 years from a proportional sampling of the general population of Hong Kong, according to age groups, gender and regions of residence. We examined associations of Alpha-, Beta- and Gamma-HPVs from oral rinse samples with participants' sociodemographics by logistic regression models.

Results

The prevalence of oral HPV infection among 1,426 ethnic Chinese was 15.5% (95% CI=13.7-17.5%), 2.5% (1.8-3.5%), 11.9% (10.3-13.6%) and 2.9% (2.1-3.9%) for any-type, Alpha-, Beta- and Gamma-HPV, respectively. Prevalence of any high-risk HPV was 0.8% (0.4-1.4%), and that of HPV16 was 0.4% (0.2-0.8%). HPV8 and HPV98 were the most common Beta-types detected, while HPV4 and HPVSD2R were the most common Gamma-types. Prevalence of Alpha- and Beta/Gamma-HPV infection showed a similar pattern of increase with age, and was higher in men than women. Smoking, drinking, oral sex and more sexual partners were associated with Alpha-HPV. Teeth brushing before sleep was protective for Beta/Gamma-HPVs.

Conclusions

The epidemiologic factors associated with oral infection with Alpha-HPVs are different from those of Beta/Gamma-HPVs, suggesting different modes of acquisition and persistence.
Background and Aims

Controversy remains towards high-risk HPV infection risk factors. We aimed to investigate the factors influencing HPV infection among women in mainland China.

Methods

We identified relevant studies through a search of relevant medical database. Stata 11.0 software was used for data analysis. If the value of $I^2$ was less than 50%, a fixed effects model was used to obtain risk estimates. If not, results were calculated using random effects models and reported as pooled odds ratios.

Results

Forty-two cross-sectional studies of 2355 articles from 1995~2017 were eligible for inclusion. Among the forty-two cross-sectional studies, total of 198643 women and 25214 hrHPV infection cases were included in the analysis, respectively. More than twenty factors were identified significantly, the pooled OR value and 95%CI for those factors were: pregnancy history:0.75(0.63~0.89), times of pregnancy: 1.30(1.12~1.52), parity history: 0.80(0.65~0.98), times of parity: 1.12(1.03~1.21), abortion history: 1.23(1.09~1.39), length of husband’s foreskin: 3.04(1.37~6.75), uterine cervical columnar ectopy: 1.61(1.44~1.80), trichomonas vaginitis: 1.33(1.04~1.69), tuberculosis: 1.71(1.32~2.23), urinary tract infection: 1.55(1.22~1.97), smoking: 1.32(1.10~1.58), marriage status: 0.62(0.48~0.79), number of times married: 1.47(1.25~1.73), number of sexual partners: 1.69(1.35~2.13), the husband’s extramarital sex: 1.61(1.23~2.12), husband’s number of sexual partners: 1.91(1.44~2.53), number of sexual partners during past five years: 2.33(1.25~4.33), sexual active years: 1.23(1.16~1.30), menopause: 1.68(1.03~2.76), the age of initial childbirth: 1.31(1.07~1.60), age at first sexual intercourse: 1.49(1.27~1.75), age of menarche: 1.19(1.03~1.38).

Conclusions

The influencing factors for HPV among women in mainland China are: times of pregnancy, marriage status, sexual activities and so on.
HIGH PREVALENCE OF ANAL HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTIONS AMONG 20-26 YEAR OLD UNVACCINATED MEN WHO HAVE SEX WITH MEN PRESENTING FOR A TARGETED VACCINATION PROGRAMME

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Background and Aims

The Victorian Government in Australia launched a targeted free quadrivalent human papillomavirus (4vHPV) vaccination programme for young men who have sex with men (MSM) in mid-2017. This study examined the proportion of anal HPV infections among unvaccinated MSM who were not covered by the national universal school-based programme.

Methods

496 unvaccinated MSM aged 20-26 years attending Melbourne Sexual Health Centre for the free 4vHPV vaccine were recruited in 2017. Anal swabs were taken as part of routine screening for gonorrhoea and chlamydia, and tested for HPV at their first vaccine dose using the Anyplex II HPV28 assay (Seegene) which simultaneously detects 19 high-risk and 9 low-risk HPV genotypes.

Results

The proportion of MSM with detected anal HPV genotypes was 75.2% (95% CI: 71.2-78.9%) (Table 1). More than half had at least one high-risk HPV genotype (64.5%; 60.1-68.7%) and any nonavalent (9vHPV) vaccine-preventable genotypes (53.4%; 48.9-57.9%); 43.1% (38.7-47.6%) had at least one 4vHPV vaccine-preventable genotype (6/11/16/18), but none had all four genotypes. Men with condomless anal sex in the last 12 months had higher odds of having at least one 9vHPV vaccine-preventable genotypes (OR:1.6; [1.0-2.5]). There was no association between 9vHPV vaccine-preventable genotypes positivity and demographic and sexual behaviours.
**Conclusions**

Almost half of these young men had at least one 4vHPV vaccine-preventable genotype, 26% of men had HPV 16 or 18 which are the common anal cancer associated genotypes. These men will receive an individual health benefit from vaccination, but the existing high HPV prevalence will limit herd protection from this targeted MSM programme.

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**Table 1. Anal human papillomavirus positivity among 496 unvaccinated young men who have sex with men.**

<table>
<thead>
<tr>
<th>HPV genotypes</th>
<th>Number of genotypes acquired</th>
<th>Positivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>112</td>
<td>22.6% (19.0-26.5%)</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>8.9% (6.5-11.7%)</td>
</tr>
<tr>
<td>16</td>
<td>104</td>
<td>21.0% (17.5-24.8%)</td>
</tr>
<tr>
<td>18</td>
<td>43</td>
<td>8.7% (6.3-11.5%)</td>
</tr>
<tr>
<td>Low risk vaccine-preventable genotypes (6 or 11)</td>
<td>144</td>
<td>29.0% (25.1-33.2%)</td>
</tr>
<tr>
<td>High risk vaccine-preventable genotypes (16 or 18)</td>
<td>131</td>
<td>26.4% (22.6-30.5%)</td>
</tr>
<tr>
<td>Quadrivalent vaccine-preventable genotypes (6, 11, 16 or 18)</td>
<td>214</td>
<td>43.1% (38.7-47.6%)</td>
</tr>
<tr>
<td>Nonavalent vaccine-preventable genotypes (6, 11, 16, 18, 31, 33, 45, 52, 58)</td>
<td>265</td>
<td>53.4% (48.9-57.9%)</td>
</tr>
<tr>
<td>Any high-risk genotypes(^\text{a})</td>
<td>320</td>
<td>64.5% (60.1-68.7%)</td>
</tr>
<tr>
<td>Any HPV genotypes(^\text{b})</td>
<td>373</td>
<td>75.2% (71.2-78.9%)</td>
</tr>
</tbody>
</table>

\(^{\text{a}}\)High-risk genotypes includes 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82
\(^{\text{b}}\)Any HPV genotypes includes 9 low-risk genotypes (6, 11, 40, 42, 43, 44, 54, 61, 70) and 19 high-risk genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82)
POOLED ANALYSIS OF HPV INFECTION IN WOMEN WITH PAIRED ANAL AND CERVICAL SAMPLES, BY HIV STATUS

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Background and Aims

In light of HPV16’s unique anal carcinogenicity, anal HPV16 prevalence may be a useful surrogate for stratifying groups of women at differing anal cancer risk based on routinely available cervical cancer screening outcomes.

Methods

49 studies including 14,000+ women with paired cervical and anal samples were identified in PubMed to March, 2018. Collaborators were invited to share individual-level data on at least age and type-specific HPV infection.

Results

The pooled dataset currently includes 7,007 HIV-negative and 2,420 HIV-positive women. Among HIV-negatives, anal HPV16 prevalence increased from 2% in 4,892 cervical HR-HPV-negative to 14% in 1,541 HR-HPV-positive women (PR=8.0, 6.4-10.1), and from 2% in 5,939 cervical HPV16-negative to 38% in 494 cervical HPV16-positive women (PR=17.7, 14.5-21.7). Among HIV-positives, anal HPV16 increased from 10% in 1,310 cervical HR-HPV-negative to 20% in 789 cervical HR-HPV-positive women (PR=2.0, 1.6-2.6), and from 11% in 1,909 cervical HPV16-negative to 40% in 190 cervical HPV16-positive women (PR=3.8, 3.1-4.7). Anal HPV16 also increased with severity of cervical cytology, but the association was not significant after adjustment for cervical HPV. Highest anal HPV16 prevalence was observed in 50 cervical HPV16-positive HIV-positive women with <350 CD4 (64%), and 83 women with HPV16-positive cervical cancer (74%).

Conclusions

HIV status and cervical cytology predict anal HPV16 prevalence, but do not offer much additional discrimination over cervical HPV, most notably HPV16, infection status. Of note, cervical HPV16-positive women, whether HIV-positive (40%) or HIV-negative (38%), show similar anal HPV16 prevalence to HIV-positive MSM (~35%), the population with highest known anal cancer risk.
LESION-SPECIFIC HUMAN PAPILLOMAVIRUS GENOTYPE PREVALENCE OF BASELINE ANAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS FROM THE STUDY OF THE PREVENTION OF ANAL CANCER (SPANC)

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Background and Aims

We report the prevalence of human papillomavirus (HPV) genotypes specifically associated with anal high-grade squamous intraepithelial lesions (HSIL) in a cohort of HIV-positive and -negative gay and bisexual men (GBM) in Sydney, Australia.

Methods

SPANC participants underwent high-resolution anoscopy-guided biopsy and histological assessment at baseline. Diagnosis of anal HSIL was according to the Lower Anogenital Squamous Terminology (LAST) project guidelines. Laser capture microdissection (LCM) was used to excise HSIL-specific tissue from biopsies of participants who gave extended consent, and for which tissue was available. DNA was extracted and genotyped using the RHA kit HPV SPF10-LiPA25, v1.0 and SPF+ strips. Multiple HSIL biopsies positive for the same genotype within the same individual were considered to represent a single HSIL.

Results

At baseline, 196/617 (31.8%) of SPANC participants had histologically-confirmed anal HSIL, of which 146 (74.5%) had HSIL-AIN3. LCM-genotyping was performed on 222 HSIL-AIN2 and HSIL-AIN3 biopsies from 160 participants. Of these 160 participants, 83 (52%) were HIV-positive. Following LCM-genotyping, 187 individual HSIL were identified. Quadrivalent vaccine types (HPV16,18) caused 45% and 28% of HSIL in HIV-negative and HIV-positive participants, respectively (p=0.016). Nonavalent vaccine types (HPV16,18,31,33,45,52,58) caused 68% and 75% of HSIL in HIV-negative and HIV-
positive participants, respectively (Figure 1).

**Conclusions**

HPV16/18 are significantly less likely to be the causative genotype of anal HSIL in HIV-positive GBM, which may have implications for future screening programs. The nonavalent HPV vaccine could protect against up to ~70-75% of anal HSIL in GBM irrespective of HIV status.
Background and Aims

We examined associations between the vaginal microbiome and persistent high-risk human papillomavirus (hrHPV) infection among HIV-negative and HIV-positive women.

Methods

We used 16S rRNA amplicon sequencing to characterize the vaginal microbiota in two serial samples taken approximately six months apart in 211 Nigerian women. We used generalized estimating equation logistic regression models to evaluate the association between the vaginal microbiota composition and persistent hrHPV infection; linear discriminant analysis effect size (LEfSe) to identify phylotype biomarkers of persistent hrHPV; Markov chain transition probabilities to evaluate transition patterns; and hierarchical clustering algorithms for community state (CST) assignments.

Results

Some 142 women were HIV-positive and 69 were HIV-negative. Of the 211 participants, 71 were persistently positive for hrHPV. Mean age (SD) of participants was 38 (8) years. High diversity, low Lactobacillus spp., CST-IV (A and B) were the most prevalent CSTs in HIV-negative (57% at baseline and 40% at follow-up) and HIV-positive (73% at baseline and 65% at follow-up) women. Among HIV-negative women, those who had a high relative abundance of Lactobacillus spp. were less likely to have persistent hrHPV (OR:0.35, 95% CI:0.14–0.89, p=0.03) compared to women with low relative abundance. In LEfSe analysis, Sneathia spp. was differentially more abundant in HIV-negative women with persistent hrHPV. Markov chain transition probabilities showed that most CST transitions were to CST-IV. In HIV-positive women, there was no significant association between the relative abundance of Lactobacillus spp and persistent hrHPV.

Conclusions

Our results suggest that persistent hrHPV is associated with a lack of Lactobacillus spp in the vaginal microbiota of HIV-negative women.
Background and Aims

To interpret the results of screening models we need to understand the influence of model structure and assumptions on cancer incidence and mortality predictions. Cancer cases and deaths after screening have three possible origins: 1) the lesion was not present at the time of screening, 2) lack of sensitivity of screening, or 3) treatment of the screen-detected lesion was not successful. We examined the relative contributions of these origins using three independently developed Cancer Intervention and Surveillance Modeling Network (CISNET) models.

Methods

To disentangle the impact of the three origins, the Maximum Clinical Incidence Reduction (MCLIR) method compares changes in the number of clinically-detected cervical cancers and cancer mortality between four simplified scenarios: 1) no-screening; 2) one-time perfect screening which detects all existing (pre-)cancers and perfect treatment of all lesions; 3) one-time realistic cytological screening and perfect treatment of all screen-detected lesions; 4) one-time realistic cytological screening and realistic treatment of all screen-detected lesions.

Results

In general, we found similar results when looking at the incidence and mortality reductions. The predicted mortality reduction within 15 years of follow-up ranged from 52% to 60% for one-time realistic screening (Figure). In contrast, the impact of imperfect sensitivity and treatment effect varied
Conclusions

Although the independently developed models showed similar reductions in cervical cancer incidence and mortality after one screening round, we found that these reductions stemmed from different model assumptions such as test sensitivity or by the treatment success rate.
THE EFFECT OF ANTIRETROVIRAL THERAPY ON ANAL HIGH-RISK HUMAN PAPILLOMAVIRUS, INTRAEPITHELIAL NEOPLASIA AND CANCER AMONG PEOPLE LIVING WITH HIV: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Aims

The effect of antiretroviral therapy (ART) on anal HPV and lesions in people living with HIV (PLHIV) are poorly understood.

Methods

We performed a systematic review and meta-analysis by searching Medline and Embase databases for cross-sectional or cohort studies from 1 January 1996 to 1 December 2017 that reported the associations of ART with prevalence of anal HPV or prevalence, incidence, progression or regression of histological/cytological anal abnormalities, or incidence of anal cancer. PROSPERO registration: CRD42018007271.

Results

We identified 3,538 publications through Medline and Embase searches, of which 114 articles matched the inclusion criteria; 87 among men who have sex with men (MSM), 15 among women and 12 among men who have sex with women (MSW), all of whom were HIV-positive.

There were 54 and 44 studies that evaluated the association of ART with prevalence of anal HPV and anal intraepithelial neoplasia (AIN), respectively. Sixteen prospective studies evaluated the association of ART with incidence of anal squamous intraepithelial lesion (SIL) or AIN, progression and regression of anal SIL/AIN and incidence of anal cancer. Pooled Odds Ratios and pooled Hazard Ratios for the association of ART with prevalence, incidence and progression of anal lesions and incidence of anal cancer will be presented, stratified by gender/sexual orientation.

Conclusions

It is expected that the impact of ART on anal lesions will be as relevant as has been shown for cervical precursor lesions and cancer. This data could help guide policy or practices on the management of anal HPV and related disease among PLHIV.
HPV-RELATED DISEASE AMONG RENAL TRANSPLANT RECIPIENTS IN DENMARK

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Background and Aims

To investigate the risk of HPV-related disease, including genital warts and moderate to severe anogenital dysplasia, among renal transplant recipients.

Methods

We identified all renal transplant recipients (RTRs) in Denmark between 1990 and 2015 from the Danish Nephrology Registry and the National Patient Registry (NPR). For each RTR, 50 population controls matched on age and sex were identified from the Civil Registration System. The unique personal identification number assigned to all Danish residents was used for unambiguous linkage between registries. Cases of genital warts (GWs) were identified through the NPR and by prescriptions for podophyllotoxin in the Danish Prescription Registry. Cases of moderate–severe dysplasia of the cervix, anus, vagina, vulva and penis were identified in the Danish Pathology Databank. Information on potential confounders was retrieved from several nationwide registries.

Separate Cox proportional hazard regression models with age as underlying time-scale were fitted for genital warts, cervical dysplasia, non-cervical female anogenital dysplasia and male anogenital dysplasia, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated comparing RTRs with controls, adjusting for age at index, sex, socio-economic position and HPV-vaccination.

Results

More than 4,000 RTRs and 200,000 population controls were included and followed until 2016. RTRs had increased risk of GWs (HR: 3.30, 95% CI: 2.76–3.93) and anogenital dysplasia (cervical dysplasia: HR: 2.16, 95% CI: 1.67–2.80; non-cervical female anogenital dysplasia: HR: 23.02, 95% CI: 16.32–32.46; male anogenital dysplasia: HR: 26.65, 95% CI: 15.77–45.05) compared with population controls.

Conclusions

RTRs have significantly increased risk of HPV-related disease.
Background and Aims

Persistent infection with oncogenic HPV confers the greatest risk for cervical cancer. Associations of HPV 16 DNA cervicovaginal detection and anti-HPV 16 antibodies were investigated in women followed longitudinally during adolescence and into mid-adulthood.

Methods

From a cohort of unvaccinated 146 adolescent women (Time-1), 30 mid-adult women with HPV 16 infection were re-recruited and tested for HPV 16 DNA (Time-2). Sixteen women returned for serum collection, and 15 had serological testing at Time-1. Anti-HPV 16 L1 antibodies were measured by competitive (cLIA) and total IgG luminex-based assays. Tests of association ($\chi^2$ and analysis of variance) between anti-HPV 16 antibodies and HPV DNA detection were performed.

Results

At Time-1, twelve (80%) and ten (66.7%) women had anti-HPV 16 antibodies by IgG and cLIA assays, respectively. At Time-2, HPV 16 DNA was detected in 43.8% (7/16) of women. All five women reporting vaccination before Time-2 had HPV 16 antibodies, and three of them had HPV 16 DNA detected at Time-2. Of 11 women who did not receive HPV vaccination, nine (81.8%) and six (54.6%) were positive at Time-2 for HPV 16 antibodies by IgG and cLIA, respectively. There was no association between IgG positivity and HPV 16 DNA at Time-2 ($p=0.229$). There was an association with cLIA positivity ($p=0.044$).

Conclusions

HPV 16 DNA was redetected in nearly half of mid-adult women with prior HPV 16 detection during adolescence. The presence of antibody against HPV 16 was not associated with lack of HPV 16 redetection, suggesting low-level HPV 16 persistence from infection acquired earlier in life.
SEQUENCE VARIANTS OF HUMAN PAPILLOMAVIRUS TYPE 16 IN HIGH GRADE CERVICAL INTRAEPITHELIAL LESIONS (CIN 2+) CASES IN HONDURAN WOMEN

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Background and Aims

Cervical cancer continues to be the leading cause of death among Honduran women. Persistent human papillomavirus type 16 (HPV16) is the major risk factor for cervical cancer. HPV 16 intratypic variants have been shown to differ in their geographical identity and oncogenic potentials. To assess the frequency of HPV 16 sequence variation in CIN 2+ cases in Honduran women.

Methods

A group of 52 women participating in a larger OncoE6 study (155 women), with HSIL cytology referred to colposcopy and confirmed by histology were tested with Hybrid Capture II (hC2) and LiPA (Genotyping kit HPV GP, primers GP5+/GP6+). A subset of 13 HPV16-positive cervical samples (1 CIN 2, 12 cancers) were analyzed by sequencing E6 and L1/MY genes and the variant distribution assigned into 4 major lineages: European-Asian (EAS), including the sublineages European (EUR) and Asian (As), African 1 (AFR1), African 2 (AFR2), and North-American/Asian-American (NA/AA).

Results

The identified variants were the EAS sublineage A1/2 (69.2%) and NA/AA sublineage D3 (30.8%). Variant EAS was uniformly distributed in all age ranges (30-64 years), unlike the NA/AA variant found only in women aged 36-50 years. Both variants were found with similar frequency in squamous carcinomas (EAS, 100% and NA/AA, 75%); only one NA/AA variant was detected in adenocarcinomas.

Conclusions

Preliminary results of the study suggest that most CIN 2+ infections belong to the EAS variants and corroborate previous data showing less frequency of NA/AA variants in cervical neoplasia among women of Honduran origin.
CANADIAN YOUNG ADULTS WHO HAVE DECLINED HPV VACCINATION: ATTITUDES, BELIEFS, AND HPV TRANSMISSION RISK BEHAVIORS

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Background and Aims

This research focuses on the attitudes, beliefs, and sexual risk behaviors of Canadian young adults who have not been vaccinated against HPV despite a publicly funded vaccination program for females and authoritative recommendation of vaccination for males.

Methods

Study I: 264 unvaccinated undergraduates (118 men, 146 women) completed measures of HPV vaccination-related attitudes, beliefs, and intentions. Study II: 507 Canadian undergraduates (154 men and 353 women) completed assessments of HPV vaccination status and sexual risk behaviors.

Results

Study I: Undergraduate men and women who do not intend to receive HPV vaccination consistently reported negative attitudes towards HPV vaccination, overestimated side effects of the vaccination, underestimated prevention effects of vaccination, and reported a lack of social and professional support for vaccination. Study II: Using validated sexual risk behavior cut-offs, in the female unvaccinated population (48.5% of respondents), the proportion at significantly increased risk for genital warts, cervical, anal, and oropharyngeal cancer was 11.0%, 30.0%, 6.5%, and 49.2% respectively. In the male unvaccinated population (89.6% of respondents), the proportion at significantly elevated risk for genital warts and anal cancer was 27.2% and 2.9% respectively.

Conclusions

A substantial proportion of Canadian undergraduates sampled remained unvaccinated. Those who decline vaccination have negative attitudes and beliefs about vaccination that are potentially modifiable. Critically, unvaccinated young adult Canadians are already at significantly elevated risk of HPV related morbidity, at a very early point in their sexual careers, underscoring the need for focused HPV vaccine education and catch-up vaccination programs.
Background and Aims

Human papillomavirus (HPV) vaccines which target HPV-associated cancers and genital warts have just been approved for marketing in mainland China. Our study aimed to estimate the present HPV prevalence and type-distribution among mainland Chinese women.

Methods

Literature regarding HPV prevalence among the general female population in mainland China published in Chinese and English between 1995 and 2016 was retrieved. To be included, studies should have used polymerase chain reaction for HPV DNA detection for cervical samples. Meta-analysis was performed.

Results

The analysis included 58 studies comprising 504,318 asymptomatic women. The estimated overall HPV prevalence was 12.4% (95% confidence interval, 11.4%-13.4%). Central China (16.3%, 11.2%-

Figure 1. Flow-chart of the study selection process and specific reasons for exclusion from meta-analysis
22.2%) and East China (14.0%, 13.0%-15.1%) ranked first two among all the seven geographical regions while Northwest China was the lowest one (9.9%, 8.4%-11.6%). Infection rates of HPV-16, HPV-52, HPV-58, HPV-18 and HPV-33 were 2.5% (2.2%-2.7%), 2.0% (1.7%-2.3%), 1.6% (1.4%-1.8%), 0.8% (0.7%-0.9%) and 0.7% (0.6%-0.8%), respectively, followed by the other nine high-risk types. Low-risk HPV-6 and HPV-11 had the prevalence of 0.4% (0.3%-0.4%) and 0.3% (0.3%-0.4%). HPV-16 was the most frequent type in Northwest, North, Central and Northeast China, while the prominent type was HPV-52 in East, Southwest and South China. Besides, Northwest China saw the highest prevalence of HPV-6 (0.5%, 0.2%-1.0%) and HPV 11 (0.6%, 0.0%-1.7%), which was followed by South and East China.

### Table 1. HPV type-specific prevalence (95%CI) by region among mainland Chinese women (%)^a^

<table>
<thead>
<tr>
<th>Overall HPV</th>
<th>Overall</th>
<th>North</th>
<th>Northeast</th>
<th>East</th>
<th>Central</th>
<th>South</th>
<th>Southwest</th>
<th>Northwest</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV-16</td>
<td>2.48 (2.24, 2.73)</td>
<td>3.31 (2.25, 4.55)</td>
<td>2.02 (1.96, 2.92)</td>
<td>2.10 (2.18, 2.84)</td>
<td>2.72 (2.22, 4.77)</td>
<td>1.70 (1.45, 1.97)</td>
<td>2.05 (1.80, 2.67)</td>
<td>5.53 (3.65, 7.62)</td>
</tr>
<tr>
<td>HPV-52</td>
<td>2.01 (1.77, 2.23)</td>
<td>0.99 (0.33, 1.58)</td>
<td>1.97 (1.56, 2.43)</td>
<td>2.63 (2.35, 2.94)</td>
<td>2.63 (1.55, 3.97)</td>
<td>2.30 (1.76, 3.11)</td>
<td>2.36 (1.59, 3.38)</td>
<td>0.25 (0.08, 0.49)</td>
</tr>
<tr>
<td>HPV-58</td>
<td>1.60 (1.43, 1.77)</td>
<td>1.74 (1.22, 2.34)</td>
<td>1.30 (1.05, 1.72)</td>
<td>1.90 (1.74, 2.06)</td>
<td>2.58 (1.54, 3.68)</td>
<td>1.26 (1.03, 1.51)</td>
<td>1.67 (1.04, 2.46)</td>
<td>0.92 (0.27, 1.59)</td>
</tr>
<tr>
<td>HPV-18</td>
<td>0.80 (0.71, 0.89)</td>
<td>0.77 (0.45, 1.16)</td>
<td>0.74 (0.50, 0.95)</td>
<td>0.96 (0.86, 1.07)</td>
<td>0.98 (0.87, 1.09)</td>
<td>0.87 (0.65, 1.13)</td>
<td>0.43 (0.31, 0.63)</td>
<td>0.80 (0.39, 1.26)</td>
</tr>
<tr>
<td>HPV-33</td>
<td>0.71 (0.63, 0.83)</td>
<td>0.79 (0.66, 1.05)</td>
<td>0.50 (0.40, 0.64)</td>
<td>0.96 (0.87, 1.09)</td>
<td>0.98 (0.87, 1.09)</td>
<td>0.87 (0.65, 1.13)</td>
<td>0.43 (0.31, 0.63)</td>
<td>0.80 (0.39, 1.26)</td>
</tr>
<tr>
<td>HPV-31</td>
<td>0.54 (0.45, 0.64)</td>
<td>0.52 (0.39, 0.67)</td>
<td>0.62 (0.34, 0.99)</td>
<td>0.74 (0.63, 0.86)</td>
<td>0.51 (0.34, 0.77)</td>
<td>0.36 (0.28, 0.44)</td>
<td>0.61 (0.22, 1.16)</td>
<td>0.28 (0.05, 0.65)</td>
</tr>
<tr>
<td>HPV-39</td>
<td>0.54 (0.45, 0.63)</td>
<td>0.40 (0.20, 0.66)</td>
<td>0.50 (0.22, 0.89)</td>
<td>0.53 (0.39, 0.69)</td>
<td>0.53 (0.39, 0.69)</td>
<td>0.56 (0.40, 0.76)</td>
<td>0.75 (0.38, 1.04)</td>
<td>0.52 (0.12, 1.09)</td>
</tr>
<tr>
<td>HPV-68</td>
<td>0.50 (0.37, 0.63)</td>
<td>0.31 (0.13, 0.71)</td>
<td>0.50 (0.37, 0.66)</td>
<td>0.34 (0.22, 0.97)</td>
<td>0.28 (0.15, 0.43)</td>
<td>0.28 (0.15, 0.43)</td>
<td>0.18 (0.04, 0.39)</td>
<td>0.05 (0.00, 0.20)</td>
</tr>
<tr>
<td>HPV-66</td>
<td>0.49 (0.42, 0.56)</td>
<td>0.42 (0.31, 0.64)</td>
<td>0.48 (0.39, 0.58)</td>
<td>0.48 (0.39, 0.58)</td>
<td>0.86 (0.28, 1.72)</td>
<td>0.49 (0.34, 0.66)</td>
<td>0.16 (0.01, 0.81)</td>
<td>0.18 (0.04, 0.40)</td>
</tr>
<tr>
<td>HPV-56</td>
<td>0.43 (0.36, 0.52)</td>
<td>0.50 (0.27, 0.80)</td>
<td>0.34 (0.18, 0.74)</td>
<td>0.57 (0.42, 0.73)</td>
<td>0.39 (0.08, 0.59)</td>
<td>0.34 (0.22, 0.49)</td>
<td>0.41 (0.12, 0.67)</td>
<td>0.27 (0.03, 0.69)</td>
</tr>
<tr>
<td>HPV-51</td>
<td>0.41 (0.32, 0.51)</td>
<td>0.36 (0.09, 0.69)</td>
<td>0.17 (0.08, 0.37)</td>
<td>0.42 (0.39, 0.71)</td>
<td>1.12 (0.49, 1.99)</td>
<td>0.47 (0.29, 0.68)</td>
<td>0.71 (0.30, 0.75)</td>
<td>0.24 (0.04, 0.57)</td>
</tr>
<tr>
<td>HPV-59</td>
<td>0.23 (0.27, 0.39)</td>
<td>0.23 (0.16, 0.56)</td>
<td>0.27 (0.10, 0.51)</td>
<td>0.38 (0.30, 0.47)</td>
<td>0.78 (0.10, 2.04)</td>
<td>0.27 (0.18, 0.37)</td>
<td>0.17 (0.04, 0.38)</td>
<td>0.35 (0.04, 0.51)</td>
</tr>
<tr>
<td>HPV-45</td>
<td>0.26 (0.20, 0.32)</td>
<td>0.17 (0.08, 0.30)</td>
<td>0.18 (0.05, 0.37)</td>
<td>0.24 (0.18, 0.31)</td>
<td>0.18 (0.03, 0.21)</td>
<td>0.40 (0.15, 0.63)</td>
<td>0.09 (0.03, 0.18)</td>
<td>0.20 (0.04, 0.47)</td>
</tr>
<tr>
<td>HPV-35</td>
<td>0.21 (0.15, 0.27)</td>
<td>0.12 (0.01, 0.32)</td>
<td>0.15 (0.06, 0.33)</td>
<td>0.26 (0.15, 0.38)</td>
<td>0.17 (0.07, 0.30)</td>
<td>0.22 (0.15, 0.29)</td>
<td>0.05 (0.02, 0.09)</td>
<td>0.27 (0.00, 1.01)</td>
</tr>
<tr>
<td>HPV-5</td>
<td>0.35 (0.28, 0.42)</td>
<td>0.24 (0.07, 0.49)</td>
<td>0.37 (0.14, 0.68)</td>
<td>0.34 (0.27, 0.43)</td>
<td>0.18 (0.02, 0.44)</td>
<td>0.46 (0.30, 0.66)</td>
<td>0.13 (0.04, 0.26)</td>
<td>0.49 (0.15, 0.59)</td>
</tr>
<tr>
<td>HPV-11</td>
<td>0.32 (0.26, 0.38)</td>
<td>0.30 (0.12, 0.52)</td>
<td>0.15 (0.00, 0.26)</td>
<td>0.40 (0.29, 0.53)</td>
<td>0.14 (0.00, 0.41)</td>
<td>0.28 (0.20, 0.38)</td>
<td>0.23 (0.12, 0.37)</td>
<td>0.55 (0.01, 1.72)</td>
</tr>
</tbody>
</table>

*The five most common HPV types are highlighted by red, orange, yellow, green and blue in sequence.

**Conclusions**

Despite the varied prevalence in different regions across mainland China, HPV-16, HPV-52, HPV-58, HPV-18 and HPV-33 are the five most common genotypes. The results indicate a foreseeable preventive effect of HPV vaccines in China.
EVIDENCE OF MINIMAL RACIAL/ETHNIC HETEROGENEITY OF HPV GENOTYPES FOUND AMONG INVASIVE CERVICAL CANCER CASES IN THE UNITED STATES

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⁶University of Oklahoma Health Sciences Center, Section of Gynecologic Oncology, Oklahoma City, USA

Background and Aims

To describe the distribution of human papillomavirus (HPV) genotypes among cervical squamous intraepithelial neoplasia 3 (CIN3), cervical adenocarcinoma in-situ (AIS), and invasive cervical cancer cases by race/ethnicity.

Methods

HPV genotype results for 4,305 CIN3/AIS and 1,471 invasive cervical cancer cases diagnosed from 1997-2014 were obtained from five US studies funded by the National Cancer Institute or Centers for Disease Control and Prevention. HPV testing was performed on the histopathology diagnostic sample or cervical cytology screening sample taken at, or immediately preceding, the time of diagnosis. HPV detection methods included linear array, line blot assay, and PCR. HPV genotypes were analyzed individually, and grouped by the oncogenic types present in the first generation HPV vaccines (bi/quadrivalent or HPV16/18) and the current nonavalent (HPV16/18/31/33/45/52/58) vaccine. Results were stratified by race/ethnicity.

Results

Among all CIN3/AIS cases, 61.9% tested positive for HPV16/18 and 87.1% tested positive for HPV16/18/31/33/45/52/58. Non-Hispanic whites had the highest HPV16/18 positivity (66.8%, p<0.0001), followed by Hispanics (58.0%), non-Hispanic Asian (53.0%) and non-Hispanic blacks (48.6%). Non-Hispanic whites also had the highest HPV16/18/31/33/45/52/58 positivity (88.4%, p=0.0009), followed by non-Hispanic Asians (88%), Hispanics (85%) and non-Hispanic blacks (80.9%). Among all invasive cervical cancers, 69.8% tested positive for HPV16/18 and 83.6% tested positive for HPV16/18/31/33/45/52/58; no significant differences were observed by race/ethnicity.

Conclusions
Although HPV genotypes vary by race/ethnicity in CIN3/AIS cases, the difference is not observed in invasive cervical cancer cases in the US, suggesting that for all race/ethnicity groups the current, nonavalent HPV vaccination will prevent most invasive cervical cancer cases.
IPVC8-0157
POSTER SESSION

PUBLIC HEALTH / EPIDEMIOLOGY - EPIDEMIOLOGY: NATURAL HISTORY/GLOBAL BURDEN/RISK FACTORS

HIGH-GRADE PAP ABNORMALITIES AND HPV INFECTION IN PARTICIPANTS IN HPV VACCINE TRIALS
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²Duke University, Research, Durham, USA
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Background and Aims

The purpose of this analysis was to describe the burden of high-grade Pap abnormalities associated with specific HPV types targeted by HPV vaccines in women participating in 3 worldwide HPV vaccine trials (FUTURE I, II, and III).

Methods

Prevalence of HPV infection was assessed in anogenital swab samples collected from all women with high-grade Pap abnormalities at baseline: 157 of 16,949 young women (YW) age 15-26 years (FUTURE I & II) and 30 of 3,674 adult women (AW) age 24-45 (FUTURE III). Cumulative incidence (over 48 months of follow-up) of high-grade abnormalities was estimated among all 1,481 YW and 1,701 AW with normal Pap at baseline who received placebo. HPV infection was measured by PCR for 14 types.

Results

Among women with high-grade abnormalities at baseline, prevalence of any 9-valent (9v) HPV vaccine type (6/11/16/18/31/33/45/52/58) was 89% (YW) and 93% (AW). Prevalence of any non-vaccine HPV type (35/39/51/56/59) was 47% (YW) and 38% (AW). Cumulative incidence of high-grade abnormalities during follow-up of YW and AW, respectively, by HPV detection at baseline was: 8% and 6% (if any 9v type at baseline); 5% and 3% (if only any non-vaccine type); and 2% and 0.4% (if no HPV at baseline).

Conclusions

While the 9v vaccine will substantially reduce high-grade Pap abnormalities associated with HPV types that cause 90% of cervical cancers, some non-vaccine HPV types also contribute to Pap abnormalities. These findings underscore the need to protect against 9v types with vaccination, as well as the ongoing need for cervical screening.
PROJECTED CERVICAL CANCER INCIDENCE IN SWAZILAND USING THREE METHODS AND LOCAL SURVEY ESTIMATES

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¹University of KwaZulu-Natal- Howard College, Public Health Medicine, Durban, South Africa

Background and Aims

The scarcity of country data for the burden of cervical cancer (CC) in low-income countries (LCIs) such as Swaziland remains a huge challenge. We aimed to estimate likely cervical cancer incidence in Swaziland using three different methodologies (triangulation), to help better inform local policy guidance regarding likely higher “true” burden and increased resource allocation required for treatment, CC screening and HPV vaccine implementation.

Methods

Three methods were applied to estimate CC incidence, namely: 1) application of age-specific CC incidence rates for Southern African region from GLOBOCAN-2012 extrapolated to the 2014 Swaziland female population; 2) a linear regression based model with transformed age-standardised CC incidence against hr-HPV (with & without HIV) prevalence among women with normal cervical cytology; and 3) a mathematical model, using a natural history approach based on parameter estimates from various available literature and local survey estimates. We then triangulated estimates and uncertainty from the 3 models to estimate the most likely CC incidence rate for Swaziland in 2015.

Results

The projected incidence estimates for models 1-3 were 69.4 (95%CI:66.7-72.1), 62.6/100 000 (95%CI:53.7-71.8) and 44.6/100 000 (41.5 to 52.1) respectively. Model 2 with HIV prevalence as covariate estimated a higher CC incidence rate estimate of 101.1/100 000 (95%CI:90.3-112.2). The triangulated (‘averaged’) age-standardized CC incidence based across the 3 models for 2015 was estimated at 69.4/100,000 (95% CI:63.0-77.1) in Swaziland.

Conclusions

It's widely accepted that cancer incidence is underestimated in settings with poor and lacking registry data. Our findings suggest higher projected burden of CC than that suggested from other sources. Local health policy decisions and decision-makers need to re-assess resource allocation to prevent and treat CC effectively.
Background and Aims

Although seroprevalence can be used as a crude estimate of cumulative HPV exposure in a population, there are relatively few studies of type-specific HPV seroprevalence in males. We studied HPV seropositivity and anogenital detection at baseline in 602 MSM 17-27 years old participating in a multinational clinical trial of the quadrivalent HPV vaccine.

Methods

A highly specific and sensitive competitive luminescence immunoassay (cLIA) was used to measure baseline seropositivity for the HPV types targeted by the 9-valent (9v) vaccine (6/11/16/18/31/33/45/52/58). Intra-anal, scrotal, perineal/perianal, and penile (“anogenital”) swabs were collected at baseline and analyzed for 14 HPV types, including the 9v vaccine types.

Results

At baseline, 228 MSM (38%) had HPV detection of any 9vHPV vaccine type, of whom 41% were seropositive to the same HPV type and 64% were seropositive to any 9vHPV type. Seropositivity concordant with the same HPV type was: HPV6 (56%), HPV11 (35%), HPV16 (36%), HPV18 (23%), HPV31 (27%), HPV33 (11%), HPV45 (11%), HPV52 (17%), HPV58 (20%). HPV type concordance between anogenital swab and seropositivity varied by swab anatomic location (penile, 31%; perineal/perianal, 47%). In a sub-analysis of all 335 trial MSM from the US, EU, and Canada without HPV detection at baseline, 34% were seropositive for any 9vHPV type.

Conclusions

Young MSM had evidence of past HPV exposure, even without anogenital HPV detection. Approximately 2/3 of MSM with current anogenital HPV detection were seropositive to any 9vHPV type. HPV exposure in young MSM was common, emphasizing the need to vaccinate prior to sexual debut.
HUMAN PAPILLOMAVIRUS INFECTION AND OTHER CO-FACTORS IN THE AETIOLOGY OF HEAD AND NECK CANCER


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Background and Aims

Human papillomavirus (HPV) is responsible for approximately 25% of head and neck (H&N) cancer cases worldwide. As part of HPV-AHEAD, a multicountry, FP7 funded collaborative network, the HPV prevalence in H&N cancer in Belgium was determined.

Methods

Retrospective patient information and paraffin blocks were collected with a sampling period from 2000 to 2016. Approximately 1039 cases diagnosed with invasive tumours of oral cavity, oropharynx, hypopharynx and larynx were collected. H&E staining, immunohistochemistry, extraction of DNA and RNA, and HPV genotyping (multiplex PCR-Luminex) were performed.

Results

Currently, 1039 patients have been analyzed by the IARC for their HPV DNA status showing a prevalence of 8.8%. 82.8% of all HPV positive tumours were HPV16 and/or HPV18 positive. Only 2.2% showed multiple infections, while 73.1% were HPV16 single infections. 64% of all HPV DNA positive samples were tested positive for HPV16 RNA. p16 diffuse staining pattern showed excellent prediction accuracy for HPV16 RNA positivity including sensitivity of 95% and specificity of 90.6%. Most frequently detected HPV16 RNA was located in the primary site of the tonsils, base of the tongue.

Conclusions

These results show an HPV DNA prevalence of 8.8% in invasive H&N tumours. 82.8% of them were HPV16 and/or HPV18 positive. 64% of all HPV DNA positive samples were positive for HPV16 RNA. The most frequently detected HPV16 RNA is located in the primary site of the tonsils and the base of the tongue.
Despite the great diversity of HPV types associated with genital infections, the real role of different molecular variants of HPV in this persistence still needs further clarification. The present work determined the molecular variants of HPV-16 involved in persistent infections detected in a molecular study consisting of 1,642 women aged 15-50 years attended at Botucatu Health Units.

Methods

HPV-16 positive samples were amplified by a specific LCR PCR reaction, sequenced and analyzed for the genetic variants.

Results

Prevalence of 33% in HPV infection was observed, and 20% belonged to the HPV16 genotype. The mean age of women who participated in the cohort and had the HPV16 genotype was 22 years, the most common ethnic variable was white in both persistent infections 53.6% and transient 61.2% due to sexual behavior. General prevalence analysis showed that the European and Asian-American variants were the most frequent in the analyzed groups, 1st visit E 89%, Aa 4.5%; 2nd visit E 89%, Aa 8.3%; 3rd visit E 84.6%, Aa 5.2%; 4th visit E 87.1%, Aa 3.3%; 5th visit E 90%, Aa 10%. Regarding the persistence analysis, women with transient infection in the European branch were more prevalent, 79%, followed by the African branch 2 13.5%, and in the persistent infection the European branch 90.2%.

Conclusions

Among HPV-16 positive women the majority were less than 35 years of age. Descriptive analysis suggests higher prevalence of HPV16 in white women, single and with more than two partners. The most prevalent HPV16 variable in the study group was European, prototype lineage.
We report the incidence and predictors for anal HSIL, the presumed precursor to anal cancer, in a cohort of gay and bisexual men in Sydney, Australia.

Methods

SPANC participants underwent cytological and histological assessments and HPV genotyping (Roche Linear Array) at all study visits. Composite HSIL was defined as detection of cytological and/or histological HSIL.

Results

Of 617 men recruited, 377 men attended all annual follow-up visits by February 2018. Among them, 226 men (median age: 51, 29.7% HIV-positive) did not have composite HSIL at baseline. By 36 months, 64 developed HSIL, an incidence of 10.3 per 100 person-years (95%CI: 8.1-13.2). Neither age, HIV status, nor lifetime sexual behaviours were associated with HSIL development, but HSIL incidence was significantly higher in those who reported a higher number of recent sexual partners (p=0.026) and receptive condomless anal intercourse (p=0.002) in the last 6 months. Testing positive to HPV16 at baseline (HR=2.88, 95%CI 1.60-5.08), but not HPV18 was associated with incident HSIL. HSIL incidence was lowest in those who tested negative to HRHPV consistently at baseline and 12-month visits (3.2 per 100 person-years), compared with those who had persistent HPV16 infection (33.6 per 100 person-years, HR=10.10, 95%CI 4.21-24.3) and persistent infection of other HRHPV types (21.4 per 100 person-years, HR=6.60, 95%CI 2.92-15.0).

Conclusions

Incident anal HSIL was common in sexually active GBM and was strongly associated with persistent HRHPV infection. Among men without HSIL, repeat HRHPV testing identifies those who were likely to develop this condition.
Post-treatment HPV infection in women treated for CIN is an important indicator of disease cure, persistence or recurrence. We are reporting post-treatment HPV infection in HIV-infected women who were treated for any CIN either by thermo-coagulation (aka cold coagulation) or by LEEP.

Methods

HIV-infected women treated for any CIN were called for the initial follow-up visit between 6 weeks to 3 months, then at month 6 and then every year thereafter. Women with any grade of CIN have been followed up to a maximum of 6.4 years. At the follow-up visits, women were screened with VIA and then all women underwent colposcopy, followed by biopsy and treatment if indicated. A repeat HPV DNA testing using HC2 test was performed after 3 or more years from treatment.

Results

Of the 101 women treated for any CIN, 33/45 (73.3%) with CIN 1 and 35/56 (62.5%) with CIN 2/3 disease have been followed. Among the 33 women with CIN 1 at baseline, 11 (33.3%) were HPV negative, 4 (12.1%) had incident HPV infection, 14 (42.4%) cleared HPV infection and 4 (12.1%) had persistent HPV infection following treatment. Among 35 women with CIN 2/3 disease, 2 (5.7%) were HPV negative, 1 (2.9%) had incident HPV infection, 17 (48.6%) cleared and 15 (42.9%) had persistent HPV infection following treatment.

Conclusions

A substantial proportion of HIV-infected women treated for high-grade CIN have persistent HPV infection and thus need long-term surveillance for prevention of cervical cancer among them.
THE PREVALENCE OF HIGH-RISK HUMAN PAPILLOMAVIRUS, AND ASSOCIATION WITH OROPHARYNGEAL CANCER AMONG INDIGENOUS AND NON-INDIGENOUS/ GENERAL POPULATION: A SYSTEMIC REVIEW AND META-ANALYSIS

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²Cancer Council of NSW, Cancer Research Division, Sydney, Australia

Background and Aims

To estimate the prevalence of genital high-risk human papillomavirus (HR-HPV) infection, and the proportion of HR-HPV-related oropharyngeal cancer (OPC) among Indigenous and Non-Indigenous/general populations.

Methods

PubMed, Embase and MEDLINE were searched from Jan 2000 until March 2018, for studies with a minimum of 100 cases assessing HR-HPV in population samples or oropharyngeal cancer tumour series. Meta-analysis was performed to calculate the prevalence of HR-HPV infection by adjusting for the broad age group in primary studies, and the proportion of HR-HPV-related OPC in Indigenous people and Non-Indigenous/general populations.

Results

We identified 131 studies from 3045 papers: 9/27 assessing genital HR-HPV infection among Indigenous women and 3/27 comparing with Non-Indigenous women; 7/21 population-based and 11/83 hospital-based HR-HPV-related OPC studies for meta-analyses. The prevalence of genital HR-HPV infection among Indigenous women was 34% (95%CI: 27%-41%, $I^2$=96.01%; p<0.0001), compared with 32.1% (32.0%-32.1%) in the general population. Based on the three comparison studies, genital HR-HPV prevalence was 50% (95%CI: 31%-70%; $I^2$=96.15%; p<0.0001) and 41% (95%CI: 29%-54%; $I^2$=98.35%; p<0.0001) among Indigenous and Non-Indigenous women, respectively. The proportion of HR-HPV-related OPC was 61% (95%CI: 57%-65%, $I^2$=73.06%; p=0.0001) and 67% (95%CI: 61%-73%, $I^2$=88.51%; p<0.0001) based on population and hospital studies, respectively. Limited information on oral HR-HPV infection, and HR-HPV-associated OPC among Indigenous populations was reported.

Conclusions

Although the prevalence of genital HR-HPV infection among Indigenous people was higher than that in the Non-Indigenous or general populations, these differences were not substantial. There is limited evidence on the prevalence of HPV in OPC in Indigenous vs. non-Indigenous populations.
WHEN WILL WE ELIMINATE GENITAL WARTS IN AUSTRALIA?
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Background and Aims

In Australia, high and widespread quadrivalent HPV vaccine uptake has resulted in dramatic declines in genital warts (GW) among young people, but it is unknown when elimination will occur. We estimated new GW cases in Australia from baseline (2006) to year 2060.

Methods

We used modelling and epidemiological calculations to estimate the number of new GW cases per year in Australian resident heterosexuals, men who have sex with men (MSM), and international travellers (students, backpackers, female sex workers and immigrants). Parameters considered: Population size, baseline GW incidence, sexual behaviour and mixing, and vaccination coverage in Australia and home countries. Population-specific GW incidence and modelled relative reductions were calculated for years 2021, 2030 and 2060.

Results

New GW cases will decline from ~22 per 10,000 population in 2006 (n=44,000) to ~1 per 10,000 population by 2060 (n=4,600): a 95% reduction (Table1). The fastest reductions will occur in Australian resident heterosexuals (Figure1). Reductions in MSM will be slower initially but catch-up by 2060. Among international travellers, reductions will be slower due to lower vaccination coverage in home countries, with nearly half of the cases attributable to students (n=11,000). By 2060, the proportion of new GW cases related to international travellers will increase from 3.6% in 2006 to ~49% (Figure2).

Conclusions

Our results indicate that in Australia the current vaccination program will minimise endemic transmission, but importation will continue (if global vaccine coverage remains stable). These findings have informed an expert consultation aimed at reaching national consensus on HPV elimination targets.
Table 1: Estimates of overall number of new genital warts cases and relative reduction in genital warts incidence in Australia, 2006-2060

<table>
<thead>
<tr>
<th>Year</th>
<th>Australian population</th>
<th>Total number of new genital warts cases/year nationally (95% CI)</th>
<th>Rate per 10,000 persons (95% CI)</th>
<th>Relative reduction (%) in new genital warts from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (2006)</td>
<td>20,091,504</td>
<td>43,937 (38,815-50,086)</td>
<td>21.9 (19.3-24.9)</td>
<td></td>
</tr>
<tr>
<td>2021</td>
<td>26,110,176</td>
<td>18,752 (17,876-21,828)</td>
<td>7.2 (6.8-8.4)</td>
<td>67.2 (66.6-67.7)</td>
</tr>
<tr>
<td>2030</td>
<td>29,748,172</td>
<td>11,461 (10,567-12,554)</td>
<td>3.9 (3.6-4.2)</td>
<td>82.4 (82.0-82.7)</td>
</tr>
<tr>
<td>2060</td>
<td>40,703,739</td>
<td>4,684 (4,206-5,254)</td>
<td>1.2 (1.0-1.3)</td>
<td>94.7 (94.6-94.9)</td>
</tr>
</tbody>
</table>

Figure 1: Estimates of relative reduction in genital warts incidence in Australia in all populations considered, by time period.
Figure 2: Estimated number of new genital warts cases in Australia, 2006-2060, by population type
Background and Aims

To assess availability of recent type-specific data on human papillomavirus (HPV) infection in oropharyngeal squamous cell carcinoma (OPSCC) and report on type-specific HPV prevalence in OPSCC in Europe.

Methods

PubMed/Medline and EMBASE databases were systematically searched for full publications reporting type-specific HPV DNA detection in histologically confirmed OPSCC. Bibliographies were also searched. Original studies reporting on HPV 16 and 18 and ≥1 other high-risk type were included. Exclusion criteria: publication before 2012, not English, special populations (e.g., HIV-infected only), N<25. Key information, including study type, country, population characteristics, sample type, HPV assay, HPV types detected, p16INK4a expression, E6/E7 mRNA detection was extracted.

Results

26 publications were included: 19 reporting data on OPSCC overall, 6 on tonsillar SCC, 5 on base of tongue SCC, and 3 studies on other OPSCC sites. Ten studies originated from Northern Europe, 8 from Western Europe, 6 from Southern Europe, 1 from Eastern Europe, and 1 study reported across European regions. Most studies originated from Italy (5), Germany and Sweden (4 each), and France (3). Across Europe, HPV was detected in 50.4% of 3,302 oropharyngeal SCC cases overall, 66.9% of 650 tonsillar SCC, and 59.3% of 275 base of tongue SCC cases. HPV 16 was detected in 88% of HPV-positive OPSCC and was the dominant type across all subsites.

Conclusions

There is a growing body of evidence on HPV in OPSCC in Europe. HPV is detected in over half of all European OPSCC cases; the predominant type is HPV 16 across all subsites investigated.
DISTRIBUTION OF HUMAN PAPILLOMAVIRUS GENOTYPES AMONG INVASIVE CERVICAL CANCER CASES IN LATIN AMERICA AND THE CARIBBEAN

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Background and Aims

To compile published information on HPV genotype distribution among invasive cervical cancer (ICC) cases in Latin America and the Caribbean (LAC), at country, sub-region and region levels.

Methods

Systematic literature searches were conducted to identify publications from January 2000–October 2017 reporting type-specific HPV prevalence in histologically-confirmed ICCs in LAC. Original studies reporting HPV DNA detection of types 16, 18 and ≥1 of 31, 33, 45, 52, 58 were included. Key exclusion criteria: not English, special populations (e.g., immunocompromised), N<50. Data extracted included country, histology, HPV type distribution.

Results

31 publications were identified, reporting on 11,127 cases from 13 countries. 1,881/11,127 were squamous cell carcinomas (SCC); 218/11,127 were adenocarcinomas/adenosquamous carcinomas (AC/ASC). Brazil (2,035) and Mexico (1,052) contributed the largest number of cases. Among SCCs, 84.0% were HPV-positive; type 16 was most common (56.1%), followed by 18 (6.8%), 31 (5.0%), 45 (4.6%), 33 (3.6%), 52 (3.2%), 35 (2.9%), 58 (2.1%). Prevalence of other high-risk (HR) HPV types was <2%. Type distribution was similar among ICCs (N=8,991) for which histological subtype was not specified. Among AC/ASC, 78.0% tested HPV-positive, HPV 16, 18 and 45 were detected in 50.0%, 22.0% and 8.5% of cases, respectively and other HR types in <2%. HPV 16, 18, 45 and 31 were the leading types across LAC sub-regions, including Central and South America and the Caribbean.

Conclusions

HR HPV 16/18/31/33/45/52/58 prevalence was consistent with other international reports. These findings suggest a 9-valent HPV vaccine could have a significant impact on ICC burden of disease in LAC countries.
Background and Aims

Cervical cancer, which is principally caused by high-risk HPV types, is the second-most frequent cancer among women in Africa, associated with more than 60,000 deaths annually. This study aims to collate published information on HPV genotype distribution among invasive cervical cancer (ICC) cases in Africa.

Methods

Systematic literature searches were conducted in PubMed/Medline and EMBASE databases to identify publications reporting type-specific prevalence of HPV infections in histologically confirmed ICC among women in Africa. Original studies published from January 2000–October 2017, reporting on types 16 and 18 and ≥1 of types 31, 33, 45, 52, 58 were included. Key exclusion criteria were special populations (e.g., immunocompromised), not English, population <50. Study design, country, population characteristics, sample type, HPV assay and HPV data were extracted.

Results

Thirty eligible publications were identified reporting on HPV prevalence in 6,134 histologically confirmed ICC cases. Eastern/Middle Africa contributed the largest number of studies (12), followed by Western Africa (8), reporting on 2,289 and 809 cases, respectively. Across all studies, 5,195 (89.8%) ICC tested positive for HPV, varying from 75.3% in Uganda to 96.9% in Zimbabwe. HPV prevalence was lower in 204 adenocarcinoma/adenosquamous carcinoma cases (80.4%) than 3,203 squamous cell carcinoma cases (92.0%). Throughout Africa, HPV16 was the most commonly identified type (50.4%), followed by HPV18 (20.4%), HPV45 (11.3%), HPV35 (6.2%) and HPV33 (4.6%); prevalence of other types was <4.0%.

Conclusions

Overall HPV prevalence in ICC varied between African countries and by histology. HPV types 16, 18, 45, 35, and 33 were the most frequently detected in ICC in Africa.
Background and Aims

Cross-protective efficacy against infection and CIN 2+ has been assessed for the bivalent and the quadrivalent HPV vaccines. We performed a systematic review of available clinical trial and real-world evidence to investigate the consistency and durability of the cross-protective effect of the bivalent vaccine.

Methods

PubMed/Medline and EMBASE were searched for peer-reviewed, full-text publications (published January 2007-2018) from interventional or observational studies on prophylactic efficacy or effectiveness of the bivalent HPV 16/18 vaccine against infection with other high-risk HPV types in healthy females. Searches were supplemented by bibliographies and publicly accessible reports.

Results

Six RCTs were identified; enrollment ranged from 506 to 18644 subjects. Among fully vaccinated, HPV-naive subjects, statistically significant efficacy against 6-month persistent infection was reported from four RCTs for type 31 (point estimates 64.7-79.1%), one RCT for type 33 (44.8%) and three RCTs for type 45 (73.0-76.9%). Across three RCTs with mean follow up ≥ 5.9 years, only one, enrolling women > 25 years, observed cross-protective efficacy (types 31 and 45). Cross-protective effectiveness was reported from two real-world RCTs (31/33/45 combined), one prospective cohort study (31 only), Scottish (31, 33 and 45) and Dutch (31, 35, 45, 52) cross-sectional surveys. No significant reductions in HPV-type 31/33/45 prevalence since the pre-vaccine era were seen in two UK surveillance studies.

Conclusions

Cross-protective efficacy against persistent infection appears to be lower and less durable than against HPV types targeted by the vaccine. Real-world evidence for cross-protective effectiveness against infection is inconsistent and its long-term durability remains to be determined.
WHOLE-GENOME ANALYSIS OF HPV52/58 ISOLATED FROM JAPANESE WOMEN WITH CERVICAL INTRAEPITHELIAL NEOPLASIA AND INVASIVE CERVICAL CANCER

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Background and Aims

HPV52/58 are frequently detected in patients with cervical intraepithelial neoplasia (CIN) and invasive cervical cancer (ICC) in East Asian countries including Japan. HPV52/58 consist of multiple lineages of genetic variants harboring less than 10% differences between complete genome sequences of the same HPV genotype. The aim of this study was to investigate genetic variations of HPV52/58 prevalent among Japanese women by analyzing the viral whole-genome sequences.

Methods

The entire genomic region of HPV52/58 was amplified by long-range PCR with total cellular DNA extracted from cervical exfoliated cells isolated from Japanese patients with CIN or ICC. The amplified DNA was subjected to next generation sequencing to determine the complete viral genome sequences. Phylogenetic analyses were performed with the whole-genome sequences to assign variant lineages/sublineages to the HPV52/58 isolates.

Results

Among 52 isolates of HPV52 (CIN1, n = 20; CIN2/3, n = 21; ICC, n = 11), 50 isolates belonged to lineage B (sublineage B2) and two isolates belonged to lineage A (sublineage A1). Among 48 isolates of HPV58 (CIN1, n = 21; CIN2/3, n = 19; ICC, n = 8), 47 isolates belonged to lineage A (sublineages A1/A2/A3) and one isolate belonged to lineage C. The distribution of HPV58 variants showed a trend of a higher prevalence of A3 in ICC in Japan.

Conclusions

Among the HPV52/58-positive specimens from Japanese women with CIN/ICC, the variant distributions were strongly biased toward lineage B for HPV52 and lineage A for HPV58 across all histological categories.
PREVALENCE AND RISK FACTORS OF HUMAN PAPILLOMAVIRUS INFECTIONS IN MEN WHO HAVE SEX WITH MEN RESIDING IN NORTH WEST OF PRETORIA, SOUTH AFRICA

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²University of Antwerp, Laboratory for Cell Biology and Histology, Antwerp, Belgium
³Sefako Makgatho Health Sciences University, Mecru Research Unit, Pretoria, South Africa
⁴Sefako Makgatho Health Sciences University, Microbiological Pathology and Mecru Research Unit, Pretoria, South Africa

Background and Aims

Men who have sex with men (MSM) population face many challenges in the community at large including identity stigma. This may increase the risk of acquiring a number of sexually transmitted diseases due to limited access to health care facilities. The prevalence of Human papillomavirus (HPV) and risk factors that could be associated with acquisition of HPV infection were investigated.

Methods

One hundred and ninety nine MSM aged ≥18 years were recruited from March 2016 through to July 2017 from the neighbouring townships, rural areas of North West of Pretoria. Participants completed a questionnaire, for the purpose of this report, samples from the anorectal canal were collected using Anex brush and preserved in ThinPrep PreserveCyt solution and tested for HPV DNA using Linear Array genotyping assay.

Results

Median age was 31.6 years (95% CI 26.6-38.7), age ranged from 18 to 61 years with majority (98.0%) been black Africans. Almost 90% considered themselves as gays. HPV prevalence was very high (78.3%) with HR HPV types 16 (16.6%), 51 (16.6%) and 35 (15.6%) in majority. Having more than three sexual partners (p-value 0.05), receptive anal sex (p-value 0.054), and level of education (p-value of 0.068) were significantly associated with acquisition of HPV infection with 36.2%, 57.3% and 40.4% with matric only been positive for HPV respectively.

Conclusions

There is a high prevalence of HPV infection among South African MSM residing at North West of Pretoria. The study observed strong associations between HPV infections and multiple sexual partners, receptive anal sex and level of education.
MESSENGER RNA TRANSCRIPTION AND HPV PREVALENCE IN ANORECTAL ABNORMAL LESIONS OF MEN WHO HAVE SEX WITH MEN RESIDING IN NORTH WEST OF PRETORIA, SOUTH AFRICA

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²Sefako Makgatho Health Sciences University, Mecru Clinical Research Unit, Pretoria, South Africa
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Background and Aims

Persistent high-risk Human papillomavirus (HPV) infection has been established as a strong risk factor for progression of precursor lesions to cancer. However, the presence of HPV DNA does not necessarily indicate active HPV infection and development of abnormal lesions. HPV E6/E7 mRNA testing allows for the detection of transient and potentially transforming HPV infections. In this cross sectional study the prevalence of abnormal anorectal lesions and expression of HR HPV mRNA was evaluated.

Methods

One hundred and ninety nine MSM aged ≥18 years were recruited from March 2016 through to July 2017. Anorectal samples were collected using Anex brush in ThinPrep PreserveCyt solution. HPV DNA was tested using Linear Array Genotyping assay and HR HPV mRNA tested with Aptima HPV assay. Liquid based cytology slides were prepared with automated ThinPrep T5000 system and stained with Pap stains manually.

Results

About 97/199 were deemed unsatisfactory due to poor sample collection, of these 61.9% were HPV DNA positive. HPV prevalence was very high 78.3% and only 26.5% of the HPV positive expressed HR mRNA. Abnormal lesions were detected in 47/102 (46.1%) participants, 2.9% with ASIL, 10.8% with ASCUS, 0.9% with ASC-H, 26.5% with LSIL, and 4.9% with HSIL. Of the abnormal lesions, only 40/47 (85.1%) were HPV DNA positive and almost half (46.8%) showed the presence of mRNA.

Conclusions

LSIL was common among the MSM population and most the LSIL cases were positive for HPV DNA however only half of them were positive for mRNA. Collection of sample is evidently important for cytology.
Background and Aims

Differences in human papillomavirus (HPV) seroprevalence by sex have been observed, likely due to differences in the anatomic site of HPV exposure. Seroconversion may be more likely after exposure at non-keratinized (mucosal) compared to keratinized epithelium. We compared seroprevalence among gay/bisexual men who have sex with men (MSM) and females, two groups more likely exposed at mucosal epithelium, and men who only have sex with women (MSW), a group likely exposed primarily at keratinized epithelium, using data from the National Health and Nutrition Examination Survey from 2003-2010.

Methods

HPV 6/11/16/18 serum antibody was detected using a multiplexed, competitive luminex immunoassay. Weighted seroprevalence was estimated among unvaccinated sexually experienced 18-59 year-old MSM, MSW, and females, overall and by demographic and sexual behavioral characteristics. Seroprevalences were compared using prevalence ratios adjusted for sexual behavior (aPRs).

Results

Overall, seroprevalence in MSM, MSW, and females was 46.2%, 13.2%, and 37.1%, respectively. Seroprevalence in MSM was comparable to females (aPR: 0.85, 95% CI: 0.68-1.08) and higher than MSW (aPR: 2.72, 95% CI: 2.19-3.38). MSW had a significantly lower seroprevalence than females (aPR: 0.31, 95% CI: 0.28-0.34). Similar associations were seen in all sociodemographic subgroups. Seroprevalence increased with number of lifetime sex partners in all groups.

Conclusions

In this population-based survey, HPV seroprevalence among groups likely exposed at mucosal epithelium (MSM, females) was comparable; seroprevalence in both groups was higher than in MSW. Variations in seroprevalence among these groups may indicate differences in susceptibility to future infection, if naturally acquired antibodies provide protection.
THE INFLUENCE OF THE VENUE-BASED NETWORK TO THE HUMAN Papillomavirus INFECTION OF MEN WHO HAVE SEX WITH MEN IN SOUTHERN TAIWAN

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Background and Aims

The role of social network among men who have sex with men (MSM) in association with HIV transmission has received increasing attention, yet little is known regarding other sexually transmitted infections, such as HPV detection. We investigated anogenital human papillomavirus (HPV) infection in association with connections formed from going to same sex-seeking venue in a sample of MSM.

Methods

A total of 253 adult MSM were recruited from Southern Taiwan in 2015-2016 and 182 were followed at the 6th month after baseline. In the follow-up survey, each man completed a self-reported questionnaire to indicate where they used to meet potential sexual partners in the past six months from a list of popular socialization venues. Those who reported visiting the same venues were potentially linked, and a venue-based network was created by these connections. Also, anogenital swabs were collected for HPV testing.

Individual characteristics and network centrality measures were tested for the association with HPV infection. Regression analysis and autologistic actor attribute model (ALAAM) were used to address network dependencies between observations.

Results

ALAAM results show that betweenness was significantly associated with anal HPV infection in MSM (b=0.0008, 95% C.I. = (0.0002, 0.0013), p<.01), but not other centrality measure, such as degree or eigenvector centrality.

<table>
<thead>
<tr>
<th>Response Centrality</th>
<th>Anal HPV Infection</th>
<th>Penile HPV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>Betweenness</td>
<td>0.0008</td>
<td>(0.0002, 0.0013)</td>
</tr>
<tr>
<td>Degree</td>
<td>0.0043</td>
<td>(-0.0064, 0.0150)</td>
</tr>
<tr>
<td>Eigenvector</td>
<td>0.1146</td>
<td>(-0.9285, 1.1577)</td>
</tr>
</tbody>
</table>

Conclusions
The bridging population who goes to several popular venues for sex-seeking possibly facilitates the transmission of anal HPV infection and thus act as crucial roles. Venue-based social connection plays a role in MSM’s anal HPV infection. Identifying one’s sex-seeking venue may be important in the interventions.
DISTRIBUTION AND ASSOCIATED FACTORS OF HIGH-RISK HUMAN CERVICAL PAPILLOMAVIRUS GENOTYPES INFECTION IN SHENZHEN, CHINA

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Background and Aims

To analyze the epidemiological distribution and associated factors of high-risk human papillomavirus (HPV) in cervical infection among women in Shenzhen area.

Methods

The information on sociodemographic characteristics and HPV genotypes of HPV-positive women who participated cervical screening test during January, 2014 to December, 2016 was downloaded from the Shenzhen Maternity and Child Healthcare Management Information System.

Results

In total, 10 624 women received HPV genotyping from 2014 to 2016 in Shenzhen area. The proportions of high-risk HPV infection in each year were 91.5%, 93.8%, and 95.6%, increasing with the screening year (P<0.001). The 5 most common HPV genotypes were HPV52 (25.1%), followed by HPV16 (19.2%), HPV58 (13.3%), HPV18 (9.9%), and HPV51 (9.3%). Multivariate logistic regression analysis showed that compared with women younger than 25 years old, women in older age groups (26~30, 31~35, 36~40, 41~45, and 50 years or older) had increased risks of high-risk HPV infection, with OR (95%CI) of 1.67 (1.20-2.31), 1.49 (1.09-2.03), 1.71 (1.23-2.37), 1.65 (1.19-2.31), and 1.84 (1.26-2.67); single women had a decreased risk of high-risk HPV infection than women who got married (OR (95%CI): 0.71 (0.50-1.00)); women received HPV testing in 2015 and 2016 showed a higher risk of high-risk HPV infection than those in 2014 (OR (95%CI): 1.43 (1.17-1.74) and 2.03 (1.68-2.46)).

Conclusions

Age, marital status, and screening year were associated with high risk HPV infections. Except for HPV16 and HPV18, the prevention and control on HPV infections for HPV52, HPV58, and HPV51 should be prioritized in Shenzhen area.
Background and Aims

Our aim was to analyze the incidence of HPV-associated anogenital lesions in Russia and in Moscow over the past few years.

Methods

We analyzed retrospective data with diagnostic codes related to anogenital warts and cancers of cervix, anus, penis, vulva and vagina from the official statistic using incidence in 2011–2016 in Russia and Moscow. The world standard for the age distribution of the population was used to calculate the standardized incidence rates.

Results

Incidence rates of cervical cancer in Moscow did not change significantly – 9.3 (in 2011) and 9.1 (in 2016) per 100,000. In Russia incidence rates of cervical cancer significantly increased from 13.7 to 15.5 per 100,000 (by 12.8%). Incidence rates of anal cancer in Moscow and Russia did not change significantly and averaged at 0.26 and 0.35 per 100,000 population, respectively. Incidence rates of penile cancer were on average – 0.39 and 0.58 per 100,000 in Moscow and in Russia. Incidence rates of vulvar cancer averaged 0.93 and 1.09 per 100,000 in Moscow and in Russia; vaginal cancer – 0.22 and 0.31 per 100,000. Incidence rates of anogenital warts averaged 31.7 and 23.7 per 100,000 (both sexes) in Moscow and in Russia.

Conclusions

HPV-associated anogenital lesions take an important place in pathology of women and men. One possible reason for the observed differences in incidence of the HPV-associated lesions in Moscow and Russia can be the preventive measures used throughout the city and the whole country. Optimizing the prevention of HPV infection, and especially vaccination, can change the current situation.
IPVC8-0289
POSTER SESSION

PUBLIC HEALTH / EPIDEMIOLOGY - EPIDEMIOLOGY: NATURAL HISTORY/GLOBAL BURDEN/RISK FACTORS

DESCRIPTIVE ANALYSIS OF A PRE-VACCINE POPULATION OF OROPHARYNGEAL CANCER PATIENTS IN NEW ZEALAND

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Background and Aims

HPV-positive oropharyngeal cancer is consistently linked to sexual behaviours whereas HPV-negative cases tend to be associated with tobacco and alcohol consumption. There is currently no description of risk factors for oropharyngeal cancers in the New Zealand population. This study aimed to describe the demographics and exposures of a pre-vaccine population of oropharyngeal cancer patients.

Methods

Participants who had been recently diagnosed with oropharyngeal cancer were recruited prospectively (2016-17) through ENT surgeons. Additional participants from previous research (diagnosed 1997-2012) were retrospectively recruited by an invite to participate when sent a requested summary of results from the prior study. Each participant completed a questionnaire covering demographics, lifestyle factors, sexual behaviours, and medical history. A section for free text additional information was provided.

Results

The study population consisted of 89 completed questionnaires of which 89% were p16 positive. There was a significant association between a p16 positive result and having ever had oral sex (Adjusted OR: 15.9, 95% CI: 1.4-230.5). Analysis of the 32 free text comments generated three themes: hypothesized contributors to the patient's cancer, an increased recall of probable symptoms, and concern over the time taken between onset of symptoms and diagnosis. Further analysis is pending.

Conclusions

The association between oral sex and HPV positivity is consistent with international data. The themes identified may suggest an increased awareness of oropharyngeal cancer in the primary care setting could facilitate an earlier diagnosis for patients.
Cervical cancer (CC) studies report strong associations with human leukocyte antigen (HLA) alleles. We assessed risk of HPV16+ vulvar intraepithelial neoplasia (VIN3)/vulvar cancer (VC) with HLA alleles compared to population controls and HPV16+ CC.

Methods

Participants were 18-74 year old Caucasian women residing in Seattle. DNA from lymphocytes was typed using high-resolution molecular methods to identify Class I (A, B, C) and Class II (DRB1, DQB1) HLA polymorphisms. HPV typing of tumor blocks used MY09/11 L1 primers and HPV16/18 E6 type-specific primers. We restricted this analysis to 238 women with HPV16+ VIN3/VC, 238 HPV16+ CC, and 637 population-based controls without a history of CC. We estimated odds ratios using logistic and polytomous regression models. There was no measure of HPV for controls.

Results

Risk of VIN3/VC was increased for seven (A*2902, B*0702, B*4403, B*5501, C*0602, C*0702, and C*1601) and decreased for two (B*1501 and B*3501) class I alleles. Likewise, there were elevated risks of VIN3/VC associated with six (DRB1*0701, DRB1*1101, DRB1*1501, DQB1*0202, DQB1*0301, DQB1*0602) and decreased risks associated with six (DRB1*0101, DRB1*0301, DRB1*1301, DQB1*0201, DQB1*0501, DQB1*0603) class II alleles. Only B*5501 and DRB1*1101 were significantly different for vulvar vs. cervical cancer (p value for equal ORs: 0.046 and 0.028, respectively).

Conclusions

These data suggest that associations between HLA alleles and HPV16+ cancers of the vulva and cervix are largely similar, supporting an underlying uniformity in HPV16 antigen recognition or non-recognition across anatomic sites. Further, T helper and cytotoxic T cells are important cofactors with HPV for both vulvar and cervical cancers.
Background and Aims

Hand-to-genital contact is a hypothesized mode of HPV transmission, but its importance remains uncertain. We quantified hand-to-genital and genital-to-genital transmission between heterosexual partners.

Methods

The HITCH Cohort Study followed 18-24 year-old female university students and their male partners in Montréal, Canada (2005-2011). Hand and genital samples were tested for 36 alpha HPV types using PCR. We assessed risks for incident hand and genital type-specific HPV detection according to one’s own and one’s partners hand and genital type-specific infection using Cox proportional hazards models with mixed effects; we report these as hazard ratios (HR) with 95% confidence intervals (CI).

Results

There were 479 female and 489 male valid hand samples; HPV was present in 35.5% and 36.4%, respectively. The HR for incident female genital HPV infection was 5.0 (CI 1.5-16.4) if her male partner’s hand was positive vs negative; adjustment for her partner’s genital infection reduced the HR to 0.5 (CI 0.1-1.8). Similarly, incident male genital HPV infection had a HR of 20.3 (CI 8.8-46.9) if his female partner’s hand was positive vs negative; adjustment for female genital infection reduced the HR to 2.6 (CI 0.9-7.7). Conversely, even after adjustment for hand positivity of the individual and their partner, the HRs for female and male incident genital HPV detection were respectively 19.3 (CI 11.8-31.8) and 36.2 (CI 18.4-71.2) if their partner was genital HPV positive vs negative.

Conclusions

Hand-to-genital HPV transmission is unlikely to be an important mode of sexual transmission. The vast majority of genital HPV infections are likely acquired via genital-to-genital transmission.
STUDY OF PREVALENCE OF HPV IN MSM WITH NEGATIVE CYTOLOGY

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³GAT Portugal, CheckpointLX, Lisbon, Portugal

Background and Aims

Persistent HPV infections with HR types, especially with HPV16, are associated with anal cancer. Anal cancer is rare, however, his incidence is increasing in men who have sex with men (MSM) population mainly in HIV seropositive men.

The objective of this study was the characterization of anal HPV infection and other microorganisms in MSM with negative anal cytology.

Methods

Anal cytology and HPV screening (in house HPV test) follow by genotyping (if positive) were performed in MSM who attended to a community based STI clinic for MSM in Lisbon, Portugal – Checkpoint LX.

664 men with negative cytology where included in this study, with an average age of 32.6 years (range 16-81 years). Samples were collected for PreservCyt Solution and processed in the ThinPrep processor. All slides were stained with Papanicolaou and evaluated according to the Bethesda 2001 ed, and quality control was performed. HPV was screened by an in house qPCR (SFP primers), and positive samples were typed.

Results

Of the 679 samples analyzed 67.3% were positive for HPV. Multiple infections were very common representing more than 58.1% and at list one HR types was detected in 69.1% of positive samples.

Other cytological alterations were observed, being candida albicans the most frequented detected.

Conclusions

Follow up of HPV positive men can give us more data to predict men that have higher risk for disease progression.

Many anal HPV infections were with types targeted by the vaccine. MSM would benefit from HPV vaccination, due to high rates of HPV infections resulting in increasing HPV disease.
Background and Aims

Human papillomavirus (HPV) vaccination, introduced in 2006, is expected to reduce racial/ethnic disparities in cervical cancer in the United States by targeting the most common cancer-causing HPV types. Using data from the National Health and Nutrition Examination Survey in pre-vaccine (2003-2006) and vaccine (2011-2014) eras, we assessed declines in quadrivalent HPV vaccine (4vHPV)-type prevalence by race/ethnicity.

Methods

In 14-34 year-old females, we analyzed HPV DNA in self-collected cervicovaginal specimens and self/parent-reported demographic characteristics, sexual behaviors, and HPV vaccination. We compared vaccine to pre-vaccine era 4vHPV-type prevalence and calculated prevalence ratios (PR) [95% confidence intervals (CI)] using logistic regression in non-Hispanic white (NHW), non-Hispanic black (NHB), and Hispanic females.

Results

HPV typing results were available from 1,586 NHW, 1,260 NHB, and 1,346 Hispanic females. 4vHPV-type prevalence decreased from pre-vaccine to vaccine eras in 14-19 year-olds of all race/ethnicities: 11.3% to 2.2% NHW (PR=.20 [.08-.47]); 17.1% to 8.4% NHB (PR=.49 [.25-.97]); 9.6% to 1.7% Hispanic (PR=.17 [.06-.50]). A statistically significant decline from 21.1% to 4.8% (PR=.23 [.09-.56]) was also observed in NHW 20-24 year-olds. In 2011-2014, >1 dose vaccine coverage among 14-19 and 20-24 year-olds was 57% and 50% in NHW, 49% and 40% in NHB, and 58% and 28% in Hispanic females.

Conclusions

Since HPV vaccine introduction, 4vHPV-type prevalence declined 51-83% among 14-19 year-old NHW, NHB, and Hispanic females. The variation in declines by race/ethnicity may be explained by vaccination coverage differences. Increases in coverage in all races/ethnicities are expected to lead to declines in disparities in cervical cancer.
PROSPECTIVE MONITORING FOR JUVENILE ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS (JORRP) IN THE UNITED STATES, 2015–2018

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³Division of High-Consequence Pathogens and Pathology - National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta GA, USA

Background and Aims

Juvenile onset recurrent respiratory papillomatosis (JORRP) is a rare but serious disease most often caused by human papillomavirus (HPV) types 6 or 11, presumably acquired through vertical transmission. In the United States, HPV vaccination is routinely recommended for adolescents; quadrivalent and 9-valent HPV vaccines, introduced in 2006 and 2015, protect against these types. We are monitoring JORRP burden to evaluate potential impact of HPV vaccination.

Methods

Since January 2015, we have enrolled patients aged <18 years with JORRP from U.S. pediatric otolaryngology clinics. Clinical history is abstracted from medical records, patient demographics and maternal characteristics are reported by mothers, and tissue from papillomas are tested for HPV DNA (37 types). We calculated descriptive statistics including interquartile ranges (IQRs) and report maternal vaccination status.

Results

Through March 2018, 138 prevalent JORRP cases were reported from 17 participating clinics. Median diagnosis age was 4 years (IQR:2–6), birth year ranged from 1997 to 2015. The majority (90, 65.2%) were first-born children and (126, 91.3%) were delivered vaginally. Median maternal age at delivery was 21.5 (IQR:19–26) years; none reported HPV vaccination before delivery. Among 86 case-patients with available typing, HPV 6 was detected in 70 (81.4%), HPV 11 in 11 (12.8%), HPV 16 in 1 (1.2%), and none were detected in 4 (4.7%).

Conclusions

JORRP case-patients were commonly first-born children delivered vaginally by unvaccinated young mothers. HPV types 6 or 11 were detected in nearly all case-patients. Increasing vaccine uptake in the target age group could reduce and even eliminate JORRP.
Human papillomavirus (HPV) infection can be prevented through a vaccination program. The nonavalent vaccine (HPV9) is active against HPV6/11/16/18/31/33/45/52/58. Currently, HPV vaccination coverage rate (VCR) in France is 20% in 11-14 year-old girls. The aim of this study was to evaluate the health benefits of a gender neutral vaccination (GNV) program with HPV9 using different VCR assumptions in France.

Methods

A published HPV disease transmission dynamic model accounting for herd protection effects with a 100-year time horizon was adapted and calibrated for France. The impact of different strategies of vaccination on the reduction of HPV prevalence compared to no vaccination was estimated among HPV types covered by HPV9. We assessed the effectiveness of alternative vaccination scenarios including GNV and compared them to the current VCR in girls. Several scenarios for VCR were performed.

Results

A 60% VCR in boys and girls with HPV9 vaccination versus no vaccination resulted in reductions of 58%, 87% and 97% in HPV6/11, HPV16/18 and HPV31/33/45/52/58 prevalence, respectively. This scenario would achieve 4-fold, 3-fold and 2.5-fold reduction in prevalence of HPV6/11, HPV16/18 and HPV31/33/45/52/58 prevalence, respectively compared with a scenario with 20% VCR among girls (Table). Using a VCR of 60% in girls and 20% in boys, reductions were respectively of 47%, 81% and
95% in HPV6/11, HPV16/18 and HPV31/33/45/52/58 prevalence.

<table>
<thead>
<tr>
<th>Relative reduction of HPV prevalence</th>
<th>HPV9 F20 (base case)</th>
<th>HPV9 F60 M20 (scenario 1)</th>
<th>HPV9 F60 M60 (scenario 2)</th>
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<tbody>
<tr>
<td><strong>Females (F)</strong></td>
<td></td>
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<tr>
<td>HPV 16</td>
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<td>HPV 18</td>
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<td>97%</td>
</tr>
<tr>
<td>HPV 16/18</td>
<td>34%</td>
<td>78%</td>
<td>84%</td>
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<tr>
<td><strong>Males (M)</strong></td>
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</tr>
<tr>
<td>HPV 16</td>
<td>25%</td>
<td>72%</td>
<td>80%</td>
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<tr>
<td>HPV 18</td>
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<tr>
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<td>85%</td>
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<tr>
<td>F+M HPV 16/18</td>
<td>31%</td>
<td>81%</td>
<td>87%</td>
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<td><strong>Females (F)</strong></td>
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<tr>
<td>HPV 6/11</td>
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<td>61%</td>
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<tr>
<td><strong>Males (M)</strong></td>
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<tr>
<td>HPV 6/11</td>
<td>12%</td>
<td>41%</td>
<td>55%</td>
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<td>F+M HPV 6/11</td>
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<td>3.94</td>
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<tr>
<td><strong>Females (F)</strong></td>
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<td>HPV31/33/45/52/58</td>
<td>42%</td>
<td>95%</td>
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<tr>
<td><strong>Males (M)</strong></td>
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<tr>
<td>HPV31/33/45/52/58</td>
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<td>94%</td>
<td>98%</td>
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<td>2.45</td>
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</table>

**Conclusions**

The HPV9 GNV has a greater impact in terms of public health benefits compared to a girls’ only vaccination program. In our analyses, GNV vaccination strategy is the most effective to obtain greater reduction in HPV9 type prevalence.
GENOME-WIDE PROFILING OF HUMAN PAPILLOMAVIRUS (HPV) DNA INTEGRATION IN LIQUID-BASED CYTOLOGY SPECIMENS FROM A GABONESE URBAN FEMALE POPULATION USING HPV CAPTURE TECHNOLOGY

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Background and Aims

Human papillomavirus (HPV) is recognised as the cause of precancerous and cancerous cervical lesions. Furthermore, in high-grade lesions, HPV is frequently integrated in the host cell genome and associated with the partial or complete loss of the E1 and E2 genes, which regulate the activity of viral oncoproteins E6 and E7

Methods

In this study, using a double-capture system followed by high-throughput sequencing, we determined the HPV integration status present in liquid-based cervical smears in an urban Gabonese population. The main inclusion criteria were based on cytological grade and the detection of the HPV16 genotype using molecular assays

Results

The rate of HPV integration in the host genome varied with cytological grade: 85.7% (6/7), 71.4% (5/7), 66.7% (2/3) 60% (3/5) and 30.8% (4/13) for carcinomas, HSIL, ASCH, LSIL and ASCUS, respectively. For high cytological grades (carcinomas and HSIL), genotypes HPV16 and 18 represented 92.9% of the samples (13/14). The integrated form of HPV16 genotype was mainly found in high-grade lesions in 71.4% of samples regardless of cytological grade. Minority genotypes (HPV33, 51, 58 and 59) were found in LSIL samples, except HPV59, which was identified in one HSIL sample. Among all the HPV genotypes identified after double capture, 10 genotypes (HPV30, 35, 39, 44, 45, 53, 56, 59, 74 and 82) were detected only in episomal form.

Conclusions
Our study revealed that the degree of HPV integration varies with cervical cytological grade. The integration event might be a potential clinical prognostic biomarker for the prediction of the progression of neoplastic lesions.
INCIDENCE OF AND MORTALITY/SURVIVAL FROM PENILE SQUAMOUS CELL CANCER IN DENMARK – 1978-2016
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¹Danish Cancer Society Research Center, Unit of Virus- Lifestyle and Genes, Copenhagen, Denmark

Background and Aims

Penile cancer is a rare cancer with the highest incidence in developing countries. The trends in incidence in developed countries have been unclear. We present an update of a previous incidence report from Denmark with 8 years and add data on mortality and relative survival for an almost 40-year period.

Methods

We used data from the Danish Cancer Registry and the Danish Pathology Registry in the period 1978-2016 on all incident penile cancers. From both registries, we extracted data on patients' date of birth, vital status, date of diagnosis, morphology, and stage. We calculated age-standardized incidence rates per 100,000 person-years using the World Standard Population.

Results

Altogether, 2,125 cases of penile cancer were identified during the 39-year study period. Of those, 1,887 (88.8%) were squamous cell carcinomas (PeSCC). Approximately, 56% had localized disease, 14% had regional disease and 3% had distant metastases at diagnosis; the remainder had no information about stage at time of diagnosis. The age-standardized incidence rate of PeSCC was e.g., 0.98/100,000 person-years in 1984-85 and 1.25/100,000 person-years in 2014-16 (Figure 1).

Figure 1. Age-standardized incidence rate of penile squamous cell carcinomas in Denmark, 1978-2016.
The age-specific incidence rates of PeSCC increased with increasing age from 1.35/100,000 person-years in men aged 45-49 years to 14.3/100,000 person-years in men ≥80 years of age.

**Conclusions**

Results on incidence trends over time and results for mortality and relative survival will be presented at the conference.
Background and Aims

To cluster anal microbiota and determine microbial signatures associated with oncogenic HPV among Nigerian men who have sex with men (MSM) living with or at risk for HIV.

Methods

The relative abundances of the top 15 genera in the anal microbiota of 113 MSM were analyzed using hierarchical clustering in this cross-sectional study. Compositional differences among clusters were evaluated by converting relative abundances to Z-scores. Differences in demographics, clinical characteristics, sexual behavior and sexually transmitted infections (STIs) by cluster membership were evaluated with Fisher’s exact and Kruskal-Wallis tests.

Results

Four clusters were generated using hierarchical cluster analysis. Cluster 2 was significantly overrepresented with Sneathia in anal microbiota of MSM who had a high prevalence of HPV-16 (p=0.01), a high adherence to ART regimens (p<0.01), and used non-water based lubricants (p<0.01). HPV-35, the most dominant oncogenic HPV in our prior work, did not co-infect MSM with HPV-16 and a cluster 2 microbiota (p=0.07). Participants with a microbiota enriched with Sneathia also trended towards reporting more strictly male sexual partnerships (p=0.07). Prevalent and incident bacterial STIs were similar across all clusters (all p>0.05).

Conclusions

Sneathia spp. are associated with a variety of genitourinary tract conditions in both men and women, including STIs and cervical cancer. The enrichment of Sneathia in the anal mucosa for MSM with HPV-16 warrants prospective evaluation with persistent HPV-16 and progression to precancerous lesions.
IPVC8-0206
POSTER SESSION

PUBLIC HEALTH / EPIDEMIOLOGY - EPIDEMIOLOGY: NATURAL HISTORY/GLOBAL BURDEN/RISK FACTORS

OBESITY AND OVERWEIGHT ARE ASSOCIATED WITH SIX-MONTH PERSISTENT ANAL HPV AMONG MEN HAVING SEX WITH WOMEN: THE HIM STUDY

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Background and Aims

Factors associated with anal cancer among men having sex only with women (MSW) are unknown. After previously finding an association between obesity and prevalent anal HPV among MSW, we aimed to assess the association between overweight/obesity and sixth-month anal HPV persistence among MSW. We then estimated the same association among men having sex with men (MSM).

Methods

Genotyping of anal specimens was conducted at the baseline and 6-month visits of 18-70 year-old men recruited in Brazil, Mexico, and the USA. Eligibility included no history of genital warts or HIV. Among 1226 MSW and 310 MSM we derived the prevalence of persistence and odds ratios (OR) for the association between BMI and persistence.

Results

Among MSW, persistence was rare (1.0% for any 9-valent type) but increased by BMI (normal=0.4%; overweight=1.2%; obese=1.7%) (graph). Among MSM, persistence declined by BMI (normal=19.1%; overweight=14.6%; obese=4.9%). BMI was not associated with number of sexual partners among MSW; however, there was a strong inverse association between BMI and number of sexual partners among MSM (p for trend=0.007). Overweight and obese MSW had 3.1 and 4.2 times higher odds of persistent infection with any 9-valent type, respectively (95% CI 0.6-15.5 for overweight and 0.8-23.3
Conclusions

Overweight and obesity were associated with persistent anal HPV among MSW; however, the rarity of persistence among MSW requires larger sample sizes for more stable estimates. Fewer sexual partners among obese MSM compared to normal weight MSM likely limits their persistence.
THE INCIDENCE OF JUVENILE-ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS IN REPUBLIC OF KOREA
M. Han¹, J.K. Oh¹, H.Y. Choi¹, M. Ki¹
¹National Cancer Center, Cancer Control and Population Health, Goyang, Republic of Korea

Background and Aims

Recurrent respiratory papillomatosis (RRP), a rare disease caused by human papillomavirus (HPV) types 6 and 11, is preventable through vaccination. This study examined the incidence and demographics of juvenile-onset RRP cases in the era before implementation of a national HPV vaccination program in Korea.

Methods

The claims data provided by the National Health Insurance Service (NHIS), a mandatory insurance program, were used to estimate the incidence of RRP and their healthcare utilization. Patients with juvenile RRP were defined as those aged 13 years and younger with more than one visit/admission during which they were assigned the International Classification of Diseases (ICD) code of benign neoplasms of the larynx (D14.1).

Results

Between 2002 and 2015 (mean 6 person-years of follow-up), 184 (104 boys and 80 girls) children were diagnosed with RRP. The incidence was 0.5/100,000 population/year. The median age of the patients at diagnosis was 3 (mean 3.6) years. Fifty-six (30.4%) patients had undergone surgical treatment, and 19 (10.3%) patients underwent surgical treatment 2 or more times. The interval between repeated surgical treatments ranged from 5 to 3620 days. The median age at surgical treatment was 4 (mean 4.3) years. The healthcare costs per patient were 3.3 million Korean won (~$3,000 USD) and 287,000 Korean won (~$260 USD) in inpatients and outpatients, respectively.

Conclusions

To our knowledge, this is the first report on epidemiological features of juvenile RRP in Korea. The RRP burden can be monitored after implementation of the national HPV vaccination program using the NHIS claims data.
The prevalence of human papillomavirus and p16 in penile cancer and penile intraepithelial neoplasia – a systematic review and meta-analysis

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³Copenhagen University Hospital- Rigshospitalet, Department of Pathology, Copenhagen, Denmark
⁴University of Copenhagen, Department of Cellular and Molecular Medicine, Copenhagen, Denmark
⁵Rigshospitalet- University of Copenhagen, Department of Gynecology, Copenhagen, Denmark

Background and Aims

In this meta-analysis, we examine the overall and type-specific prevalence of HPV DNA and assess the expression of p16 in penile cancer and penile intraepithelial neoplasia (PeIN).

Methods

PubMed, Embase and Cochrane were searched until 24 July 2017. English-language articles reporting the prevalence of HPV and/or p16 expression in ≥5 cases of penile cancer or PeIN were included. Using random effects models, we estimated the pooled prevalence and 95% confidence intervals (CI) of HPV and/or p16 expression in penile cancer and PeIN stratifying by e.g., histological subtype and HPV DNA and/or p16 detection method. Type-specific prevalence of HPV6, 11, 16, 18, 31, 33 and 45 in penile cancer was estimated.

Results

Altogether, 73 articles were included. The pooled HPV prevalence in penile cancer (N=4198) was 50.8% (95% CI: 44.9-56.8). A particularly high pooled HPV prevalence was seen in basaloid squamous cell carcinomas (SCC) (84.0%) and in warty-basaloid carcinoma (75.7%). The predominant HPV type in penile cancer was HPV16 (73.1%), followed by HPV18 (3.1%) and HPV6 (2.2%). The pooled HPV prevalence in PeIN (N=445) was 79.8% (95% CI: 69.3-88.6). The pooled p16 prevalence in penile cancer (N=2196) was 42.3% (95% CI: 36.8-47.9), with a high pooled p16 prevalence in HPV-related SCC including basaloid/warty-basaloid SCC (85.8%) as compared to non-HPV-related SCC (17.1%). Moreover, among HPV-positive cases the pooled p16 prevalence was 79.6%.

Conclusions

A large proportion of penile cancers and PeIN are associated with infection with HPV (predominantly HPV16) emphasising the possible benefits of HPV vaccination in males.
Background:

HPV causes 10% of cancers among HIV-infected people in the United States (US). Given that Hispanics are disproportionally impacted by the HIV epidemic, and by infection-related cancers, we compared incidence rates and survival of HPV-related cancers among Hispanics to non-Hispanic whites (NHWs) and non-Hispanic Blacks (NHBs) in the HIV-infected US population.

Methods:

Using data from the HIV/AIDS Cancer Match Study, standardized incidence ratios (SIRs) were used to estimate cancer risk in HIV-infected Hispanics compared with the general US Hispanic population. Among HIV-infected people, cancer rates were compared with incidence rate ratios (IRRs) and survival was compared with hazard ratios between Hispanics and NHWs and NHBs.

Results:

Except for oropharyngeal cancer, risk of HPV-related cancers was higher among HIV-infected Hispanics than in the general population (range: SIR=3.59 [cervical cancer] to SIR=18.7 [anal cancer in men]). Among HIV-infected females, Hispanics had higher cervical cancer rates than NHWs (IRR=1.70, 95%CI=1.19-2.43), but lower vulvar cancer rates than NHWs (IRR=0.40, 95%CI=0.24-0.67) and NHBs (IRR=0.62, 95%CI=0.41-0.95). Among HIV-infected males, Hispanics had higher penile cancer rates than NHWs (IRR=2.60, 95%CI=1.36-4.96), but lower anal cancer rates than NHWs (IRR=0.54, 95%CI=0.46-0.63) and NHBs (IRR=0.65, 95%CI=0.56-0.77). Among HIV-infected Hispanics, 5-year survival was >50% across HPV-related cancer types, with no major differences by racial/ethnic group.

Conclusions:
HIV-infected Hispanics have elevated risk for HPV-related cancers. Similar to the general population, HIV-infected Hispanics have higher rates of cervical and penile cancer than NHWs and NHBs. HPV vaccination should continue to be promoted among HIV-infected individuals to reduce the burden of HPV-related cancers.

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HUMAN PAPILLOMAVIRUS (HPV) TYPE DISTRIBUTION IN ANAL LESIONS IN MEN WHO HAVE SEX WITH MEN (MSM)
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Background and Aims

HPV causes the majority of anal lesions that lead to anal cancer in men and women. Standard screening for early anal cancer detection is not available, and limited data are available on HPV types found in anal lesions. In this analysis, we report the type-specific HPV prevalence in anal lesions occurring during follow-up in MSM enrolled in the placebo group of a multinational clinical trial of the quadrivalent HPV vaccine.

Methods

Clinical visits occurred at 6-month intervals for up to 48 months during the study follow-up. Low- and high-grade anal intraepithelial neoplasia (AIN1, AIN2/3, respectively) and anal condyloma (AC) were diagnosed by a panel of expert pathologists. Anal lesions were tested by PCR for 14 HPV types.

Results

Of 301 MSM 17 to 27 years old and HIV negative at enrollment who received placebo, 103 were diagnosed with a total of 159 anal lesions during the trial follow-up period (67 AIN1, 59 AIN2/3, and 33 AC). At least 1 HPV type targeted by the 9-valent HPV vaccine (6/11/16/18/31/33/45/52/58) was identified in 73% of AIN1, 80% of AIN2/3 and 94% of AC. HPV6 was detected in all lesion types (52% AIN1, 31% AIN2/3, 61% AC). HPV11 was found in 36% of AC. Non-vaccine HPV types (35/39/51/56/59) were found in 25% of AIN1, 22% of AIN2/3 and 6% of AC.

Conclusions

A substantial proportion of HPV types found in pre-cancerous anal lesions are targeted by the 9v HPV vaccine, including HPV6 and 11.
Background and Aims

HPV prevalence in the general female population varies by age and region. We compiled published information on the prevalence of vaccine-targeted HPV types in mid-adult women in the Asia-Pacific region.

Methods

PubMed/EMBASE were systematically searched for original studies, published from January 2013–October 2017, reporting on type-specific cervical HPV prevalence among the general population of mid-adult women in the Asia-Pacific region. Studies reporting DNA detection of HPV 16, 18 and ≥1 of 31, 33, 45, 52, or 58 in populations screened for cervical cancer with a mean or median age between 30 and 40 years were included. Key exclusion criteria were age <25 or >45 years only, small study (N<300), not English, and diseased or high-risk population. Data extracted included country, type of population, age information, HPV typing and sample collection methodology.

Results

46 publications were identified: 30 (N=323,336 women) for East Asia, eight (N=11,664) for Western Asia, five (N=5,713) for Southern Asia, two (N=3,515) for Oceania and one (N=11,224) for South-Eastern Asia. Reported prevalences varied substantially on study and country levels. Pooled prevalences ranged from 1.5% in South-Eastern Asia to 7.6% in Western Asia for HPV 16; 1.0% in East Asia to 3.0% in Western Asia for HPV 18; 0.9% in Western Asia to 2.9% in East Asia for HPV 52; and 0.4% in Western Asia to 2.2% in East Asia for HPV 58. Prevalences of HPV types 33 and 45 ranged within 0.3–1.0% across sub-regions.

Conclusions

Although estimates vary, a sizeable proportion of Asia-Pacific mid-adult women are infected with vaccine-targeted HPV types.
PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) INFECTION AND RELATED FACTORS AMONG FEMALE STUDENTS IN HANOI AND HUE CITIES- VIETNAM

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Background and Aims

Human papillomavirus (HPV) is the major cause of anogenital cancers including cervical, vaginal and vulvar cancers. HPV infection among adolescents in resource-limited countries including Vietnam has not been widely investigated. This study aimed to assess the prevalence of HPV among female students aged 18-25 in Vietnam.

Methods

In this cross-sectional descriptive study, students from 2 universities in Hanoi and Hue cities were asked to answer a structured questionnaire on demographic characteristics, sexual behaviours, knowledge about HPV, HPV-related diseases and preventive methods. At the same time, students were instructed to take vaginal swabs (self-collected or with the assistance). Samples were screened for HPV by PCR using the primer set PGMY9/11, then genotyped for 33 different high- and low-risk HPV types.

Results

Among the 984 registered students available for analysis, the overall HPV prevalence among these students (age 17.9-24.6 years) was 5.3% in Hanoi (95%CI: 3.5-7.6%) and 6.5% (95%CI: 4.6-9.1%) in Hue city, of which 75-81% of cases were caused by high-risk HPV types. The most common HPV types are 16,18,39,51,52,58 in Hanoi and 11,39,52,56,66/68 in Hue city. In both cities, the HPV prevalence among students with reported sexual activities was 17.2-18%, which was significantly higher compared to 3.5-3.8% among those without.

Conclusions

This is the first study of HPV prevalence among the 18-25 age group in Viet Nam, which emphasises the need for more effective communication on HPV disease prevention among young people. Introduction of HPV vaccine which covers multiple low and high-risk types will have significant impact to reduce the HPV-related disease burden.
HUMAN PAPILLOMAVIRUS AND P16 EXPRESSION IN SQUAMOUS CELL CARCINOMA AND PRECANCEROUS LESIONS OF THE VAGINA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Aims

Our aim was to estimate the overall and type-specific prevalence of human papillomavirus (HPV) and evaluate p16 expression in vaginal squamous cell carcinoma (VaSCC) and vaginal intraepithelial neoplasia (VaIN) by means of meta-analysis.

Methods

We conducted a systematic search of PubMed, Embase and Cochrane Library to identify all studies published between 1986 and 2017 using a PCR-based or Hybrid Capture test to evaluate the presence of HPV DNA, and/or detection of p16 expression (using any method) in VaSCC and VaIN. Applying a random effects model, we estimated the pooled prevalence of HPV and p16 expression along with 95% confidence intervals (CIs). The I² statistic was used to assess heterogeneity.

Results

We identified 30 relevant studies; of these, 27 reported HPV prevalence in VaIN and/or VaSCC and five evaluated p16 expression in VaSCC. One study reported p16 expression in VaIN. The pooled HPV prevalences in VaSCC (total no. of samples=593) and VaIN (total no. of samples=1374) were 66.7% (95% CI: 54.7-77.8) and 85.2% (95% CI: 78.2-91.0), respectively. In pooled analyses of p16 expression, 89.9% (95% CI: 81.7-94.6) of HPV positive and 38.9% (95% CI: 0.9-90.0) of HPV negative VaSCC samples were positive for p16. Substantial inter-study heterogeneity was observed. The most predominant HPV type among the HPV positive cancers and VaIN cases was HPV16, followed by HPV33 and HPV18.

Conclusions

Approximately 67% of VaSCC and 85% of VaIN lesions were associated with HPV – predominantly HPV16. Prophylactic vaccines against HPV may thus prevent a substantial number of vaginal cancers and precancerous lesions.
HPV-RELATED ANOGENITAL DYSPLASIA AND CANCER AMONG DIABETES PATIENTS IN DENMARK

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2Steno Diabetes Center Copenhagen, clinical epidemiology, Gentofte, Denmark

Background and Aims

Diabetes patients may be susceptible to infections due to an altered immune system. Certain immunocompromising conditions are associated with an increased risk of developing human papillomavirus (HPV)-related anogenital dysplasia and cancer. However, little is known about HPV-related disease in diabetes. The aim of this nationwide cohort study is to assess the risk of HPV-related anogenital dysplasia and cancer among diabetes patients compared with controls without diabetes.

Methods

A cohort including all diabetes patients in Denmark between 1995-2016 will be identified in registries and clinical databases. A comparison cohort matched on age and sex will be identified in the population registry among individuals without DM using risk set sampling. The study population will be linked to the Danish Cancer Registry and Danish Pathology Databank and followed for development of HPV-related anogenital dysplasia/cancer until August 2017. Potential confounders or risk modifiers (e.g. HPV vaccination, body mass index, comorbidity, medication use, and educational level) will be taken into account. Within the diabetes cohort, we will assess the risk of HPV-related anogenital dysplasia/cancer in relation to diabetes type (type 1 versus type 2), age at diagnosis, and duration of DM.

Results

Approximately 270,000 individuals in Denmark have diabetes. Registry linkages to assess the burden of HPV-related dysplasia and cancer among DM patients are currently performed. Results will be ready for presentation at the conference.

Conclusions

This study will provide results that can inform recommendations for HPV vaccination and screening strategies among diabetes patients.
A SYSTEMATIC REVIEW OF THE HPV-ATTRIBUTABLE FRACTION OF OROPHARYNGEAL SQUAMOUS CELL CANCERS IN GERMANY

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Background and Aims

Wide variations in the proportion of oropharyngeal squamous cell cancers (OPSCC) attributable to HPV have been reported. The objective of the present study was to summarize the HPV-attributable fraction of OPSCC in Germany as a source for future estimations of HPV disease burden.

Methods

A systematic literature review was conducted in Medline. Inclusion criteria were 1) patients with SCC localized in the oropharynx (or oropharyngeal sublocations such as tonsil), 2) treated at a German medical center and 3) results of HPV DNA PCR combined with p16INK4a immunohistochemistry were reported to determine the HPV status.

Results

Out of 287 screened publications, 12 were identified that fulfilled the inclusion criteria. The HPV-attributable fraction in OPSCC ranged from 11.5% (12/104, Frankfurt, diagnosis between 1988-2008) to 47.5% (28/59, Münster, <2013) (see Table 1 for all results). While most studies reported the result for a broad calendar period, two studies analyzed changes over time and reported an increase in the HPV-attributable fraction of OPSCC: Latest results were reported from Gießen for the year 2015 with 53.1% (17/32) HPV prevalence in OPSCC and from Berlin (Charite) for 2012/2013 with 59% HPV
prevalence in OPSCC (not detailed in Table 1).

Conclusions

Reported HPV prevalence in OPSCC in Germany varies widely (11.5\%-47.5\%). Sub-analyses from single studies including patients diagnosed after 2012 point towards an HPV-attributable fraction in OPSCC of >50% in Germany.

<table>
<thead>
<tr>
<th>City of medical center</th>
<th>Calendar period of diagnosis</th>
<th>Localization</th>
<th>N</th>
<th>n HPV+</th>
<th>% HPV+</th>
<th>Author, year</th>
</tr>
</thead>
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<tr>
<td>Münster</td>
<td>&lt;2013</td>
<td>Oropharynx</td>
<td>59</td>
<td>28</td>
<td>47.5</td>
<td>Weiss, 2013</td>
</tr>
<tr>
<td>Berlin (Charite)</td>
<td>2004-2013</td>
<td>Oropharynx</td>
<td>227</td>
<td>91</td>
<td>40.1</td>
<td>Tinhofer, 2014</td>
</tr>
<tr>
<td>Kiel</td>
<td>2002-2010</td>
<td>Palat. tonsil</td>
<td>126</td>
<td>48</td>
<td>38.1</td>
<td>Hoffmann, 2017</td>
</tr>
<tr>
<td>Berlin (UKB)</td>
<td>1997-2011</td>
<td>Oropharynx</td>
<td>122</td>
<td>42</td>
<td>34.4</td>
<td>Hauck, 2015</td>
</tr>
<tr>
<td>Hamburg</td>
<td>2011-2013</td>
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<td>12</td>
<td>34.3</td>
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</tr>
<tr>
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<td>Oropharynx</td>
<td>102</td>
<td>30</td>
<td>29.4</td>
<td>Maier, 2013</td>
</tr>
<tr>
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<td>5</td>
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<td>Gießen</td>
<td>2000-2015</td>
<td>Oropharynx</td>
<td>599</td>
<td>150</td>
<td>25.0</td>
<td>Würdemann, 2017</td>
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<tr>
<td>Heidelberg</td>
<td>1990-2008</td>
<td>Oropharynx</td>
<td>178</td>
<td>42</td>
<td>23.6</td>
<td>Holzinger, 2012</td>
</tr>
<tr>
<td>Frankfurt</td>
<td>1988-2008</td>
<td>Oropharynx</td>
<td>104</td>
<td>12</td>
<td>11.5</td>
<td>Tahtali, 2013</td>
</tr>
</tbody>
</table>

*Table 1: HPV-attributable fraction (column %HPV+) of OPSCC in German medical centers. Listed are all 13 studies identified via a systematic literature search. HPV DNA PCR combined with p16INK4a immunohistochemistry was used in all studies to determine the HPV status.*
HPV16 INFECTION NATURAL HISTORY AT THE ISOLATE LEVEL

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Background and Aims

An apparently persistent HPV16 infection at the type level could, in fact, represent a sequence of successive different HPV16 viruses if examined at a finer level. This would affect our view of clearance, persistence and progression.

We investigated the frequency of HPV16 infection changes over time, at the isolate level, using HPV16 whole-genome sequencing at deep coverage data among women who did or did not develop CIN3 or worse lesions.

Methods

93 HPV16 persistent (10+ months) infections from women enrolled in the 7-year follow-up of the Guanacaste Costa Rica cohort were included. For each woman, among serial samples, we identified concurrent HPV16 co-infections and sequential changes in isolates. A 3+ nucleotide sequence difference was considered a different “HPV16 isolate”. The proportions of infections having 1+ HPV16 isolate sequentially or as co-infections, prior to CIN3+ development, were investigated.

Results

On average HPV16 infections were sequenced at 3.3 [range 2–9] times. Regardless of CIN3+ development, two-thirds of infections were unchanged over time. Perhaps due to small numbers, there were no significant differences, but no women developing CIN3+ had more than 2 different HPV16 isolates while up to 4 isolates were found among controls (graph 1). Coinfections were slightly less frequent among women with CIN3+ lesions (3 out of 18) than among women without CIN3+ lesions (21 out of 75).

Conclusions

Many different HPV16 isolates circulate when measured at the isolate level. HPV16 infections with CIN3+ lesions were non-significantly less likely to have isolate changes or co-infections over time. Further analyses with larger datasets are needed.
Background and Aims

While the overall incidence of cervical cancer is known to be higher in HIV-infected women, there are no data on the incidence of cervical adenocarcinoma (ADC), a histologic subtype that is increasing in the general population (GP). Therefore, we aim to establish the epidemiology of ADC in HIV-infected women.

Methods

Data from the HIV/AIDS Cancer Match Study, a linkage of 10 cancer and HIV registries from 1996-2014, were used to determine the incidence of ADC compared to cervical squamous cell carcinomas (SCC) in HIV-infected women and the GP. The relative risk of ADC in HIV-infected compared to GP women was assessed using standardized incidence ratios (SIRs).

Results

Of 51,048 cervical cancer cases, 478 occurred among HIV-infected women (0.94%). The mean age of HIV-infected women was 43.7 years at diagnosis and 61.4% were black. Among HIV-infected women, ADC accounted for 5.4% of all cervical cancers compared to 18.0% in the GP (p<0.05). The crude incidence rates of ADC and SCC were 2.6 and 39.0 per 100,000 HIV-infected women. Cervical ADC rates in HIV-infected women were modestly, but not significantly, higher than the GP (SIR: 1.4; 95% CI: 0.9-2.0), whereas SCC incidence was strongly associated with HIV (SIR: 3.6; 95% CI: 3.2-3.9).

Conclusions

Although SCC and ADC share a common etiology in human papillomavirus infection, SCC incidence is significantly increased in HIV-infected women whereas ADC incidence is similar to the GP. Time trends in the ADC rates in HIV-infected and GP women in the United States will also be presented.
RISK FACTORS FOR ORAL HPV AMONG SEXUALLY-ACTIVE INNER-CITY ADOLESCENT WOMEN

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Background and Aims

Sexual activity – not only oral – is an important risk factor for oral HPV. We characterized risk-profiles for oral HPV in a population of high risk sexually-active inner-city adolescent women.

Methods

We conducted a longitudinal study involving oral rinse specimens, anal and cervical swabs from 1,259 sexually-active women from a large adolescent-health clinic in NYC. Demographic and behavioral data were obtained by a risk-factor survey. Specimens were collected every six months and tested for HPV-DNA using a MY09/MY11-PCR system. Risk factors for oral HPV were analyzed using multivariate regression analyses for repeated measurement data.

Results

The median age of participants was 18 years (range: 13-21) and most (96%) were of African-American and/or Hispanic origin. All had practiced vaginal sex with a median number of lifetime sex partners of 4 at time of enrollment. Most (92%) had also practiced oral sex and a third (31%) had practiced anal sex. Prevalence of oral HPV (14%), including high-risk types (2%), was higher than the general population. Dose-response relationships between oral HPV and increased sexual activity (including oral sex) was not evident, although we observed a 30% lower relative risk with marijuana use (OR=0.68, 95%CI:0.5-0.9), which remained unchanged after adjusting for age, sexual activity, tobacco, and alcohol use. The strongest predictor of oral HPV was the detection of the same HPV type in the cervix six months prior (p<0.0001), especially if a high-risk type was involved (OR=2.7, 95%C.I:2.4-3.2).

Conclusions

Concomitant cervical HPV positivity is a strong predictor of oral HPV in sexually-active adolescent women.
Background and Aims

This study was to identify the persistence and clearance of cervical human papillomavirus (HPV) infection among Korean women by age.

Methods

During 2010-2016, a total of 1,325 women aged 20-60 years with HPV were enrolled by five hospitals in Korea as the Korea HPV cohort study. Their cervical cytology and HPV DNA testing were undergone every six months. We selected 472 women who were followed during 20-30 months. The genotyping results were described the persistence and clearance according to the change from baseline HPV genotype to followed HPV genotypes. Epidemiological factors associated with HPV genotype were explored using a logistic regression model.

Results

The mean age of the 472 women was 41.0 years. During follow-up of mean 24 months, HPV persistence and clearance were 17.1% (82/479) and 42.4% (203/479), respectively. For HPV persistence, there was a significant increase by age (Ptrend<0.002). HPV persistence in the old women over fifty increased significantly as compared with the young women aged 20-29 years (adjusted relative risk (aRR)=2.577; 95% confidence interval (CI)=1.079-6.154). For women with HPV 16/18/52/56/58, which were main high risk genotypes in Korean women, their persistence was higher than women with other HPV genotypes (aRR=1.851; 95% CI=1.139-3.009). For HPV clearance, there were associated with HPV 16/18/52/56/58(aRR=0.579; 95% CI=0.395-0.848).

Conclusions
We found there were some association with age and high risk genotypes in persistence and clearance of HPV infection among Korean women. Our study showed that women over fifty could be high the persistence of HPV infection.
THE PREVALENCE AND MULTI-INFECTION PATTERNS OF 27 HPV VIRUSES’, HIGH CONSISTENCY BETWEEN THE HPV16/18 CO-INFECTION PREFERENCE PATTERN AND THE CROSS-PROTECTIVE EFFICACY OF HPV16/18 VACCINE

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Background and Aims

This multi-center study was organized to delineate the national prevalence and multi-infection patterns of 27 HPVs among gynecological outpatients (GOP), and to evaluate the cross-protective efficacy of HPV16/18 vaccine.

Methods

 GOP were recruited from 8 hospitals cross China. Cervical exfoliated cells were collected for HPV genotyping using Tellgenplex™ 27 HPV DNA Assay. Odds ratio was calculated to evaluate the co-infection(AB) preference: the observed infection rate of AB divided by the multiplication of the single infection rate of A and B.

Results

Among 137,949 samples from GOP, the total prevalence of 27 HPVs (17hr/10lr) was 23.5%. Age-specific prevalence showed a flat “U-formed” pattern. The most prevalent hrHPVs were all from α9: HPV16(3.3%)/HPV52 (2.3%)/HPV58 (1.9%). The most prevalent lrHPVs were both from α3: HPV81(0.9%)/HPV61(0.9%). Multi-infection was identified in 25.8%. HPV16 consisted of 66.51% single infection, the highest, followed by HPV52(60.2%), HPV58(59.81%), while HPV26(33.3%) as the lowest. The HPV16+58(283) and HPV16+52(265), HPV52+58(242), HPV16+18(195) were the most common multi-infections. The co-infection preference of 13 hrHPVs to HPV16/18 calculated by odds ratio revealed that HPV31 was the most involved in HPV 16/18 co-infection, while HPV52/58 had less co-infection preference to HPV16/18.

Conclusions
These co-infection (AB) preference patterns are highly consistent with cross-protective efficacy of HPV16/18 vaccine against HPV31, but almost negative vaccine efficacy against HPV52/58. This finding may explore the mechanism of cross-protection of HPV vaccines. On another side, it indicates that it is urgently needed to evaluate the efficacy of HPV16/18 vaccines and the influences to the HPV epidemic in China, where with high prevalence of HPV52/58.
Prevalence and Risk Factors for Genital HPV in Young Australian Men in the HPV in Young Males (HYM) Study

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Background and Aims

To identify prevalence and risk factors for HPV detection in a community-recruited study of young Australian men.

Methods

Part of the National HPV Monitoring Program, the HYM utilised Facebook’s ad-targeting mechanism to recruit Australian men aged 18-35, for HPV surveillance research. Participants completed a survey, and self-collected a penile sample for HPV genotyping (Roche Linear Array), returned via post.

Results

By April 2018, genotyping data were available for 634 participants (median age 27, range 23-30 years), 3% of whom received ≥1 dose of 4vHPV vaccine. Prevalence of any HPV was 17.8% (95% CI: 14.8-20.7), and 3.6% (95% CI: 2.2-5.1) for 4vHPV-targeted types. In univariate analyses, detection of any penile HPV was associated with having only heterosexual contact in the previous year (p=0.007), being Australian-born (p=0.02), being a smoker (p=0.009), having more lifetime sexual partners (p-trend<0.001), having two or more sexual partners in the previous year (p=0.003) and lifetime diagnosis of any STI (other than HPV) (p=0.02). In adjusted analyses, only heterosexual contact (p<0.001), being Australian-born (p=0.009), lifetime sexual partners (p-trend=0.001), and non-HPV STI diagnosis (p=0.047) remained independently associated. Prevalence was not associated with age or circumcision.
Table 1: univariate and multivariate analyses of factors associated with penile HPV detection among study participants.

<table>
<thead>
<tr>
<th></th>
<th>Any HPV type</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=634</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-21 years</td>
<td>61 (14)</td>
<td>15 (16)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>22-24 years</td>
<td>120 (19)</td>
<td>19 (16)</td>
<td>0.95 (0.45-2.00); 0.90</td>
</tr>
<tr>
<td>25-29 years</td>
<td>225 (35)</td>
<td>46 (20)</td>
<td>1.30 (0.69-2.47); 0.42</td>
</tr>
<tr>
<td>30-35 years</td>
<td>423 (31)</td>
<td>33 (17)</td>
<td>1.01 (0.52-1.98); 0.97</td>
</tr>
<tr>
<td><strong>Risk group</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MSW</td>
<td>365 (58)</td>
<td>78 (21)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>MSM</td>
<td>269 (42)</td>
<td>35 (13)</td>
<td>0.55 (0.36-0.85); 0.007</td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>343 (84)</td>
<td>104 (19)</td>
<td>2.21 (1.11-4.39); 0.024</td>
</tr>
<tr>
<td>Other</td>
<td>202 (16)</td>
<td>10 (10)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Secondary</td>
<td>324 (20)</td>
<td>23 (10)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Tertiary</td>
<td>298 (83)</td>
<td>90 (18)</td>
<td>0.95 (0.57-1.57); 0.87</td>
</tr>
<tr>
<td><strong>Area of residence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Cities</td>
<td>516 (82)</td>
<td>91 (18)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Regional and remote</td>
<td>116 (18)</td>
<td>21 (18)</td>
<td>1.03 (0.61-1.74); 0.91</td>
</tr>
<tr>
<td><strong>Socioeconomic status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>More disadvantaged</td>
<td>449 (71)</td>
<td>63 (18)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Less disadvantaged</td>
<td>383 (29)</td>
<td>29 (16)</td>
<td>0.83 (0.52-1.32); 0.43</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>539 (85)</td>
<td>87 (16)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>55 (15)</td>
<td>26 (27)</td>
<td>1.96 (1.38-3.25); 0.009</td>
</tr>
<tr>
<td><strong>Circumcised</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>556 (73)</td>
<td>85 (19)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>178 (28)</td>
<td>28 (16)</td>
<td>0.84 (0.53-1.34); 0.67</td>
</tr>
<tr>
<td><strong>Age at first sex</strong></td>
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<td></td>
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</tr>
<tr>
<td>Under 16</td>
<td>304 (17)</td>
<td>23 (22)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>≥16 or older</td>
<td>330 (82)</td>
<td>95 (36)</td>
<td>0.69 (0.41-1.96); 0.28</td>
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<tr>
<td><strong>Lifetime number of sexual partners</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≤5</td>
<td>217 (27)</td>
<td>13 (7)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>6-15</td>
<td>240 (31)</td>
<td>36 (10)</td>
<td>2.77 (1.42-5.42); 0.003</td>
</tr>
<tr>
<td>≥16</td>
<td>204 (41)</td>
<td>101 (43)</td>
<td>4.32 (2.03-9.19); 0.001</td>
</tr>
<tr>
<td><strong>Number of sexual partners in previous 12 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>440 (56)</td>
<td>76 (22)</td>
<td>1.95 (1.26-3.03); 0.003</td>
</tr>
<tr>
<td>&gt;1</td>
<td>316 (24)</td>
<td>31 (12)</td>
<td>0.64 (0.39-1.09); 0.11</td>
</tr>
<tr>
<td><strong>STI diagnosis ever (non-HPV)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>488 (77)</td>
<td>77 (16)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>346 (23)</td>
<td>36 (25)</td>
<td>1.75 (1.12-2.73); 0.02</td>
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<tr>
<td><strong>Use of condom at last sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>437 (70)</td>
<td>82 (19)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>287 (30)</td>
<td>29 (15)</td>
<td>0.79 (0.50-1.25); 0.31</td>
</tr>
<tr>
<td><strong>Identifies as Aboriginal or Torres Strait Islander</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36 (3)</td>
<td>5 (31)</td>
<td>2.18 (0.74-6.41); 0.156</td>
</tr>
<tr>
<td>No</td>
<td>615 (97)</td>
<td>106 (17)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td><strong>Dose of HPV vaccine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>618 (97)</td>
<td>111 (18)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>≥2</td>
<td>26 (3)</td>
<td>2 (13)</td>
<td>0.85 (0.15-2.91); 0.756</td>
</tr>
</tbody>
</table>

1Total dose not always equal 634 due to missing data
2Only variables which were associated with detection on penile HPV (p<0.1), and age, in univariate analysis were included in adjusted analysis.
3Risk group was determined by self-reported number of partners of each sex in the last year – if any male partners in the last year participant classified as MSM.
4Vaccination status of all participants was checked against the National HPV Vaccination Program Register. Abbreviations: HPV, human papillomavirus; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence intervals; MSM, men who have sex with men; MSW, men who have sex with women; STI, sexually transmitted infection.

Conclusions
In this community-based study of young Australian men, one in five participants had any genital HPV detected; lower than reported in published clinic-based studies. Risk factors for detection were related to sexual behaviour. Prevalence of vaccine HPV types was low, which may reflect herd effects achieved by high coverage of the female-only vaccination program. Further reductions in prevalence could be achieved by sustained vaccination of males.
BACKGROUND AND AIDS

Adding the human papillomavirus (HPV) vaccine to cervical cancer screening programs provides a powerful tool in cancer prevention. However, public health benefits will only be realized if vaccines reach those most at risk—unscreened women. Vaccinating well-screened women alone is unlikely to impact cervical cancer mortality. We use data from a nationally represented sample of US adults to assess the association between HPV vaccine status and cervical cancer screening behavior.

METHODS

Data from the Behavioral Risk Factor Surveillance System were collected between 2012 and 2016 from states that included the optional Adult HPV Vaccination module. Analysis was restricted to women ages 21-49 years. Analyses used survey weights to account for complex sampling design.

RESULTS

Youngest women were 60% less likely to be up to date on screening (aOR: 0.39, 95% CI:0.28-0.53), but over 13 times more likely to be vaccinated (aOR: 13.75, 95% CI:10.48-18.04) than older women. Uninsured women were less likely to be vaccinated (aOR: 0.49, 95% CI:0.38-0.62) and less likely to be screened (aOR: 0.39, 95% CI:0.29-0.54) than insured women. Vaccinated women were 75% more likely to be up to date on screening than unvaccinated women (aOR: 1.75, 95% CI:1.22-2.50).

CONCLUSIONS

Unvaccinated, unscreened women are at continued risk for cervical cancer. Uninsured women were most likely to be in this group. Concerted efforts should be focused on increasing vaccination and screening in this population. Cancer prevention innovations, like the HPV vaccine, must reach at risk populations in order to avoid further protecting the protected and failing to reduce existing health disparities.
HISTORICAL AND PROJECTED HYSTERECTOMY RATES IN THE USA: IMPLICATIONS FOR FUTURE OBSERVED CERVICAL CANCER RATES AND EVALUATING PREVENTION INTERVENTIONS

**Background and Aims**

Cervical cancer incidence rates that account for hysterectomy prevalence are higher than routinely-reported SEER rates that are not adjusted for hysterectomy. Hysterectomy rates have been declining, and this trend may continue as alternative treatments become more widespread. We therefore aimed to (i) evaluate historical trends in hysterectomy incidence; (ii) project hysterectomy incidence rates out to 2035; (iii) convert hysterectomy incidence rates into cross-sectional prevalence for each year, and (iv) predict the impact on cervical cancer rates.

**Methods**

We performed a systematic search of Medline, Embase, Premedline, Cochrane Central databases for articles on hysterectomy in the USA. We then projected hysterectomy incidence rates out to 2035, converted rates into prevalence, and predicted the impact on cervical cancer.

**Results**

Age-specific hysterectomy incidence rates increased from 1.5 per 1,000 women in 1935 to a peak of 10.6 per 1,000 by 1975. Thereafter, rates declined steadily and are predicted to fall to 3.2 per 1,000 by 2035. Consequently, in the absence of other changes, SEER reported cervical cancer rates would be expected to increase by 25% in women aged 55-84 from 2009-2035.

**Conclusions**

Declining hysterectomy rates have implications for the evaluation of cervical cancer prevention for the next 15-years as a background apparent increase in cervical cancer rates will to some extent work against expected decreases due HPV-based screening. This will be particularly apparent for women aged 55-84 years, who will also be unlikely to benefit from vaccination before 2035. Modelled evaluations should consider historical and projected hysterectomy rates when evaluating the impact of prevention efforts.
Prevalence of high-risk human papillomavirus associated with predictor factors to cervical cancer in unimmunized Brazilian women without cytological abnormalities

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¹Oswaldo Cruz Institute- Oswaldo Cruz Foundation, Virology- Helio and Peggy Pereira Building, Rio de Janeiro, Brazil
²Oswaldo Cruz Institute- Oswaldo Cruz Foundation, Virology- Helio and Peggy Pereira Building, Rio de Janeiro, Brazil

Background and Aims

The Brazilian Immunization Program recommended the HPV vaccine to be administered at 9 to 11 years of age before sexually activity. The aim of this cross-sectional design study was to evaluate HPV prevalence among unimmunized women and co-factors related to cervical cancer.

Methods

About 100 clinical samples were collected with a cervical cytobrush. DNA extraction and HPV detection were performed by molecular techniques. Restriction fragment length polymorphism (RFLP) patterns of L1 PCR products were used for genotyping. Statistical analysis was applied in 18 socio-demographic variables.

Results

HPV prevalence was of 20%. HPV 18 and 45 were the most frequently detected HPV types. Most women were currently not married (56%) and married or cohabitating (44%) (p<0,05). Psychosocial and psychosexual issues demonstrated that six percent of the women exhibit history of sexually transmitted diseases, except HIV, with 85% of women having sex with until to five partners (p<0,03). The 3% who have had the both types of HPV infection had more than five sexual partners. A highly significant factor associated with HPV infection was who did not use the condom and had an income between one to four minimum wages, both with 87.5%. About the employment status of all the participating women, 90% reported having had at least one until four basic salaries.

Conclusions

Sociodemographic characteristics related to sexual health were relevance significantly in women without cytological abnormalities. A large challenge to public health is cancer prevention in populations from developing countries with high risk exposure associated with the history of other sexually transmitted diseases.
ANOGENITAL HUMAN PAPILLOMAVIRUS (HPV) INFECTION IN HIV-INFECTED AND HIV-UNINFECTED MEN WHO HAVE SEX WITH MEN (MSM) IN RWANDA

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1Rwanda Military Hospital, Clinical Education and Research Division, Kigali, Rwanda
2Albert Einstein College of Medicine, Epidemiology and Population Health, New York, USA
3Albert Einstein College of Medicine, General Internal Medicine, New York, USA
4New York Medical College, Public Health, New York, USA
5Rutgers University, Department of Statistics-, New York, USA
6New York Medical College, Epidemiology and Community Health, New York, USA
7University of Rwanda, Human Genetics, Kigali, Rwanda
8University of California San-Francisco, Medicine, California, USA

Background and Aims

Men who have sex with men (MSM) have high prevalence of anal and penile human papillomavirus (HPV) infection; HIV-infected MSM have the highest rates. Nearly all anal cancers, and approximately half of penile cancers, are HPV-associated. Few data exist on HPV in MSM from Sub-Saharan Africa or Rwanda.

Methods

We recruited 350 self-identified MSM, including 50 recruited because of known HIV + status, from community-based associations and health facilities providing HIV care within Kigali city using respondent-driven sampling. Participants were aged >18. Participants completed a 45-minute questionnaire using audio-computer assisted survey interview. Penile and anal swabs were collected. For this analysis, 150 samples from 75 participants contributing one penile and one anal specimen were sent to San Francisco for HPV testing and genotyping.

Results

Of the 75 participants, 30 were HIV+. HIV+ were older than HIV-negative participants (30.7 vs. 25.6 years). Penile and anal HPV prevalences were 46.7% and 40% respectively. HIV+ and HIV-negative participants had similar rates of penile (22.6% and 24.2%, P=0.48) and anal (20.0% and 20.0%, P=0.16) HPV. HPV-6/11 (8.6%) and HP-16 (5.7%) were the most common anal types; HPV-6/11 (8.1%) and HPV 62 (6.5%) were the most common penile types.

Conclusions

We found a lower anal and penile HPV prevalence than in other MSM studies. HIV+ and -negative participants had similar HPV penile prevalence. To provide a better epidemiological picture and better inform policies, all samples from baseline are being tested and results will be presented during the HPV2018 conference.
Optimal HPV sampling in the male urogenital tract is important in extending knowledge on HPV epidemiology and future studies on assessment of HPV vaccination effect in men. Expressed prostate secretion (EPS), obtained during a routine urological visit, may represent informative sampling material for the study of HPV epidemiology in the male. However, most of the current studies on HPV in men employ "standard" urogenital (penile/urethral) and anal samples only.

Using a reference method from the WHO HPV LabNet global reference laboratory, the HPV prevalence in the ano-urogenital and EPS samples and risk factors were analysed.

Methods

Beta-globin-positive penile, urethral, anal swabs and EPS were obtained from 965 HIV-negative men (average: age 31.8 years; age at sexual debut 17.5 years; number of life-time sexual partners 34) attending the urology unit of a STI clinic in St. Petersburg. HPV DNA testing for 26 (13 oncogenic) types was conducted, using a Luminex assay.

Results

The overall/oncogenic/nonavalent-vaccine HPV prevalence for penile, urethral, anal samples and EPS was 25.6/16.7/14.4%, 24.7/17.0/15.4%, 32.4/19.2/17.8% and 18.6/11.6/11.0% respectively. Studying EPS resulted in increased HPV diversity and additional detection of 14.1% HPV-positive men compared to testing ano-urogenital (15.5% in urogenital) samples only. HPV was significantly more commonly detected in: anal samples of MSM (OR=3.8, 95%CI:1.2-11.5), EPS of men with >20 life-time sexual partners (OR=1.5, 95%CI:1.0-2.2), and urethral samples of men reported chlamydia infection in the past (OR=1.4, 95%CI:1.0-
Conclusions

The analysis of EPS increases both prevalence and diversity of HPV and should be in focus for HPV studies.
Background and Aims

Data regarding the anal genera-specific concordance for mucosal α- and cutaneous β- and γ-HPVs and their determinants in men are limited and geographically narrow. Knowledge of determinants of anal detection of HPVs in different regions is needed for better understanding of the natural history, transmission dynamics of HPVs, and their role in the development of anogenital diseases.

Methods

β-globin-positive anal canal samples, obtained from 514 men (average: age 31.8 years; age at sexual debut 17.5 years; number of lifetime sexual partners 34) attending the urology unit of a STI clinic in St. Petersburg, were screened for 36 α-, 43 β- and 29 γ-HPVs, using Luminex assays.

Results

Cutaneous β- or γ-HPV-genera were also more prevalent in the anal samples positive for mucosal α-HPVs than in the α-HPV-negative samples (p=0.034 and p=0.017, respectively). All three genera were overrepresented in HIV-positive men. This effect was even more remarkable in mucosal-cutaneous HPV genera combinations: α and β (crude OR=32.4, 95%CI: 10.1-103.8) as well as in α and γ (OR=19.3, 95%CI: 6.6-56.0) HPV genera.

In the multivariate analysis for genera-specific concordance, practicing sex with men (MSM) resulted in more significant prevalence of α-HPVs (OR=6.0, 95%CI: 1.7-21.4) and γ-HPVs (OR=4.9; 95%CI: 1.1-22.1).

Conclusions

In HIV-positive men, α, β and γ HPV genera are overrepresented. In MSM, this applied to α and γ genera. As HIV-positive status may favor the anal acquisition or modify the natural history of HPVs, future study should analyse the type-specific concordance in men.
NO SIGNIFICANT GENERA-SPECIFIC CONCORDANCE BETWEEN ALPHA, BETA AND GAMMA HUMAN PAPILLOMAVIRUS (HPV) IN PENILE-URETHRAL SAMPLES

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²International Agency for Research on Cancer - World Health Organization, Infections and Cancer Biology Group, Lyon, France
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⁵St. Petersburg State University, Faculty of Medicine, St. Petersburg, Russia
⁶Clinical Infectious Diseases Hospital named after S.P. Botkin, Clinical Infectious Diseases Hospital named after S.P. Botkin, St. Petersburg, Russia

Background and Aims

Data regarding the penile-urethral genera-specific concordance for mucosal α- and cutaneous β- and γ-HPVs and their determinants in men are limited and geographically narrow. Such knowledge obtained from different regions is needed for better understanding of the natural history, transmission dynamics of HPVs, and their role in the development of HPV-related morbidity.

Methods

β-globin-positive anal canal samples, obtained from HIV-negative 372 men (average: age 31 years; age at sexual debut 17 years; number of life-time sexual partners 34) attending the urology unit of a STI clinic in St. Petersburg, were screened for 36 α-, 43 β- and 29 γ-HPVs, using Luminex assays.

Results

Although cutaneous β- but not γ-HPV-genera were slightly more prevalent in the penile-urethral samples positive for mucosal α-HPVs than in the α-HPV-negative samples (p=0.041 and p=0.678, respectively), no overrepresentation of mucosal-cutaneous HPV genera combinations was observed for bi-, quadri- and nine-valent vaccinated α-HPVs (p=0.506-0.912).

Conclusions

There are α, β and γ HPV genera overrepresentations in penile-urethral samples in HIV-negative heterosexual men but no genera-specific concordance. Future studies should analyse the type-specific concordance in men from key high-risk populations (i.e., in HIV-positive men).
Previous studies have reported that anal cancer incidence has increased in individual countries; however, age-specific trends were not examined in detail. This study describes pooled and country-specific anal cancer incidence trends by sex, age (all ages, <60 and 60+ years) and histological subtype (all subtypes, squamous cell carcinoma [SCC] and adenocarcinoma [ADC]).

Methods

Five-year incidence and population-at-risk data were obtained from IARC’s Cancer Incidence in Five Continents for the years 1988-1992 to 2003-2007. The standardised rate ratios (SRRs) for 2003-2007 vs 1988-1992 and the 5-year average percent change (AvPC) during the period were used to assess changes in the age-standardised incidence rates.

Results

During the study period, there were significant increases in the incidence of SCC in both men (SRR=1.67 [95%CI: 1.55-1.80]) and women (SRR=1.60 [95% CI:1.51-1.69]). In both men and women, these increases were highest in those aged <60 years (SRR=1.96 [95% CI: 1.77-2.18] and SRR=2.12 [95% CI: 1.94-2.31], respectively). By contrast, there were significant decreases in the incidence of ADC in men (SRR=0.76 [95%CI: 0.68-0.84]) and women (SRR=0.71 [95% CI: 0.63-0.80]), with similar decreases in those aged <60 years and 60+ years. These competing trends still resulted in significant increases in the overall incidence of anal cancer in men and women of all ages (25%; SRR=1.25 [95% CI: 1.18-1.33]; AvPC=9% in men, and 38%; SRR=1.38 [95% CI: 1.32-1.45]; AvPC=13% in women).

Conclusions

Increases in the incidence of anal SCC may be associated with changing sexual behaviours and increasing levels of HPV exposure in younger cohorts.
Human papillomavirus genotype distribution in the north region of Portugal: data from regional cervical cancer screening

Background and Aims
Currently, High-Risk Human papillomavirus (HR-HPV) detection is considered the best cervical cancer screening method. Genotyping methods add important information about epidemiology and future HPV-approach strategies.

Methods
We determined the prevalence and distribution of HR-HPV genotypes in cervical samples collected within Regional Cervical Cancer Screening Program from the Northern Region of Portugal, (August 2016 to December 2017). HR-HPV detection and genotyping were performed using Anyplex™ II HPV-HR Detection kit (Seegene®).

Results
A total of 105,546 women were enrolled (median age: 45, range: 24-66): 465 (0.44%) had insufficient sampling and 10,568 (10.06%) were HR-HPV positive. Multiple infections (two or more HR-HPVs) were detected in 2703 (26.4%) women. HR-HPV infection varied according to age (16.8% at age 25 to 6.3% at age 60), with multiple infections ranging from 30.8% (age 25) to 17.0% (age 65) (figure1a). HR-HPV prevalence varied geographically ranging from 8.7% to 10.7% (multiple infections; 21.1% - 26.8%) (figure1b). HPV-16 (17.6%), HPV-39 (16.8%), HPV-31 (15.1%), HPV-68 (13.3%), HPV-52 (10.8%) and HPV-51 (10.7%) genotypes predominated, while HPV-18 corresponded only to 5.19% (figure2). Concerning age distribution, HPV-16 predominated in women 30-45 years whereas HPV-39 predominated in women 50-65 years (figure3a). The four most common HR-HPV genotypes were the same in all geographic locations (figure3b).
Figure 2

High-Risk HPV genotype prevalence in Population

- HPV16: 17.65%
- HPV18: 5.19%
- HPV31: 15.14%
- HPV33: 4.40%
- HPV35: 5.18%
- HPV39: 16.86%
- HPV45: 3.33%
- HPV51: 10.66%
- HPV52: 10.80%
- HPV56: 9.44%
- HPV58: 8.44%
- HPV59: 6.35%
- HPV66: 9.05%
- HPV68: 13.35%
Figure 3

(a) HR-HPVs genotype distribution by age groups

(b) HR-HPVs genotype distribution by region
Conclusions

This is the largest study on HR-HPV genotyping for Cervical Cancer Screening in Western populations, disclosing the HR-HPV genotype pattern in a particular population. These results forecast HR-HPV infection dynamics and provide critical data for program management as well as obvious implications regarding vaccine policy.
HPV INFECTION PATTERNS IN ONE HUNDRED AND THIRTY THOUSAND CHINESE WOMEN
Z. Su1, B. She2, W. Chen1
1Chinese Academy of Medical Sciences- Peking Union Medical College, Cancer Hospital, Beijing, China
2Tellgen Corporation, Academic Development, Shanghai, China

Background and Aims
To explore the coinfection patterns of any two types of 12 high risk HPVs and HPV6/11 by different age groups based on a multi-center and big sample size study.

Methods
137,943 female outpatients aged 15-70 years old from 7 central hospitals were recruited. Tellplex® HPV27 genotyping assay, which can detect HPV16, 18, 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 6, 11, was used. Based on Poisson distribution, observed/expected ratios were calculated in <30 and >30 years old women respectively, to assess the patterns for any two HPV coinfections. For the case with more than two HPV types, the observed number was weighted by one divided by all possible pairs. The level of statistical significance was adjusted by Bonferroni method.

Results
The rates of single infection and multiple infection are 17.7% and 5.7% in >30 group, 16.5% and 7.5% in <30 group respectively. Of the 91 two-HPV type coinfection pattern, no significant difference were found between the observed and the expected in >30 group. However, in the group of <30 years old, 58 HPV pairs showed statistical significance. For example, HPV16 and HPV18 with other 11 HR-HPV types showed statistical correlation; The possibility of pairs between HPV 51/52/56/58, HPV11/59, HPV11/16 and HPV6 with HPV16/51/52/56/59/66 were also found significantly higher than the expected.

Conclusions
Age is not only associated with multiple infection, but also with the pattern of HPV coinfections.
Background and Aims

Cervical cancer is the most common malignancy in women in rural Eastern Cape. Despite this, information on HPV prevalence is scarce. This is the first study to report the prevalence of high-risk (HR)-HPV and associated risk factors among women from rural Eastern Cape.

Methods

Women aged ≥30 years were recruited from a community health clinic within OR Tambo district in Eastern Cape Province of South Africa. Sociodemographic data and information on risk factors were obtained through interviews. Cervical specimens were examined for high-risk HPV genotypes (16,18,31,33,35,39,45,51,52,56,58,59,68) using the Hybrid Capture-2 (HC2) assay and Papanicolaou testing.

Results

The median age of the 152 women enrolled was 47 years (range 30-76). Overall, the prevalence of HR-HPV was 24%. Cytology results were available for 132 women with 118 reported to have normal cytology. HPV infection was 2.5 times significantly higher (p=0.035) in younger (aged 30-49 years) than older women (aged ≥50 years). Although not significant, HR-HPV prevalence was high in HIV-positive women (33%) compared to HIV-negative women (19%), p=0.068. HPV infection increased with number of lifetime partners (p=0.146). There was no association of HPV infection with the level of education and annual household income.

Conclusions

The prevalence of HR-HPV in women with normal cytology was high compared to that reported in similar studies worldwide. This high HPV burden should be considered when examining the feasibility of HPV-based screen-and-treat approaches for this region. This data will be crucial in developing preventive strategies to reduce the cervical cancer burden.
PROGNOSTIC VALUE OF CERVICAL CYTOKINES LEVELS IN HPV-HR CLEARANCE

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Background and Aims

Alterations in the host cellular immune response allow persistent infections with High-Risk Human Papillomavirus (HR-HPV) and development of premalignant cervical lesions and cervical cancer (CC). Variations of immunosuppressive cytokine levels in cervix are associated with the natural history of CC. Objectives. To evaluate the prognostic value of the detection of immunological markers (IL-10, IL-4, TGFβ1, IFNγ, IL-6 and TNFα) in the cervix with the persistence or elimination of HR-HPV infection.

Methods

A cohort of women over 30 years old with normal cytology at baseline was followed every 12 months for an average of 3 years. Cervical swabs were used for HPV typing and evaluation of mRNA cytokines. The Wilcoxon rank-sum test was used for measuring the difference of medians for all cytokines and estimated differences in means of cytokine expression levels in the cervix was evaluated by linear regression adjusting for potential confounders, according to the state of infection (cleared or persistent) at one year of follow-up.

Results

The genotype-specific HPV persistence at one year of follow-up was 18.6%, with the genotype of HPV 58 being the most persistent genotype. The virus genotype that was most eliminated was HPV 53. When evaluating the association between the level of IL-6 mRNA expression at the cervix level with viral elimination, the estimated difference in URE means of IL-6 between clearance vs non-clearance adjusted by age and hormonal contraception was 1.16 units (CI 0.149-2.183, p = 0.025).

Conclusions

Findings suggest that the cervical cytokines levels can be determinants of clearance and risk of HPV persistence.
BACKGROUND AND AIMS

HPV-positive oropharynx cancer (OPC) incidence has increased rapidly in cohorts of white US men born around 1940s. We investigated whether increases continued into recent birth-cohorts and forecasted the future burden.

METHODS

OPC incidence (1992-2015, ages 33-84) was obtained from 18 US NCI-SEER registries. Log-linear Joinpoint regression and age-period-cohort models were used to evaluate incidence trends and projections.

RESULTS

Among white men, OPC incidence increased most rapidly in the 1939-1955 birth-cohorts (5.2% per year, 95%CI=4.8%-5.7%), but this increase moderated considerably (p-value<0.05 for incidence change in 1955) in subsequent birth-cohorts (1955-1981=1.5% per year, 95%CI=0.8%-2.3%). Ageing of the 1939-1955 birth-cohorts and the moderation in subsequent birth-cohorts has resulted in a shift in OPC incidence from young to older individuals. Through 2030, we forecast that incidence would increase substantially (35.9 in 2015 to 54.0/100,000 in 2030) among older (≥59 years) white men, but only modestly in young white men (11.4 in 2015 to 11.8/100,000 in 2030). This translates to a 75% increase in the annual number of OPCs (8,534 to 14,980) among older white men and 73% decline (5,091 to 1,343) among younger white men.

CONCLUSIONS

The wave of exponential rise in OPC incidence in young white US men has ebbed, and only modest increases are occurring/anticipated in cohorts born after 1955. Continued robust increases in incidence in cohorts born before 1955, and an approximate doubling of the size of these cohorts through 2030, portend a significant shift in the burden to elderly white men. These observations have key implications for screening and treatment of HPV-positive OPC.
Social determinants of health as risk factors for high-risk HPV infection in midlife


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Background and Aims

Social determinants of health (SDH) are features of the environments in which people live/work that affect health, functioning, outcomes, and risks. Five SDH indicators have been identified: economic stability, education, social and community context, health and health care, and neighborhood and built environment.

Methods

Data from the HPV in Perimenopause Study were used to evaluate the extent to which negative SDH indicators were associated cumulative high-risk HPV (hrHPV) infection over a 2 year period.

Results

Among 487 women completing follow-up, mean age of respondents was 49.6 years (SD=6.6) at study exit. Cumulative 24-month hrHPV prevalence was 18.3%. Negative SDH indicators for economics (low income), health (current smoker), social context (married or black race or lifetime sexual partners >=5), and education (HS graduate or less) were derived from proxy variables. In simple regression analyses, odds of hrHPV infection was associated with negative SDH indicators for economics, health, and social context. In multivariable models, negative SDH indicators for economics (low-income) and social context (not married, >= 5 lifetime sexual partners) were associated with increased risk of hrHPV infection among women without new sexual partners.

<table>
<thead>
<tr>
<th>SDH</th>
<th>Odds Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Economics</td>
<td>2.00 (1.19-3.36)</td>
</tr>
<tr>
<td>Health</td>
<td>2.65 (1.36-5.19)</td>
</tr>
<tr>
<td>Social context</td>
<td>4.41 (2.16-8.99)</td>
</tr>
<tr>
<td>Education</td>
<td>.731 (0.389-1.38)</td>
</tr>
</tbody>
</table>
Conclusions

Results from these analyses suggest that negative SDH increases risk of hrHPV infection. One hypothesis for the biological pathway by which negative SDH affects hrHPV infection is through the effect of chronic stress on immune functioning. Future studies should directly assess the association between negative SDH, stress, immune functioning, and hrHPV as a disease outcome.
Background and Aims

The Advisory Committee on Immunization Practices (ACIP) recommends routine administration of the quadrivalent human papillomavirus (HPV4) vaccine for males aged 11-21 years. Despite this recommendation, HPV4 vaccine uptake and completion in the United States has been very low; nationally, coverage rates are approximately 27% among 13-15 year old males.

Methods

Electronic health record data for males receiving care at University of Maryland Medical System outpatient practices were used to examine disparities in HPV vaccine uptake and completion. The sample included data from males between the ages of 11-21 years with medical encounters from 2011-2017, inclusive.

Results

Valid data were available for N=71,077 males. Overall, 6.2% of the sample initiated vaccination. HPV4 vaccine initiation rates increased from 4.6% to 7.5% from 2011 to 2017, respectively; completion rates ranged from 51-58%. Of those who initiated vaccination, 50.3% received 3 doses; however, only 16.3% received all doses within the recommended 12 months. Males who initiated vaccination were younger (p<0.01), more likely to be black (p<0.01), and more likely to reside in Baltimore City (p<0.01). Those who completed the full HPV4 series were older (p<0.01) and more likely to be white (p<0.01).

Conclusions

Data from this study suggest that for some populations and geographic regions, HPV4 vaccine coverage is significantly lower than what is reported by national surveys. Disparities in patterns of uptake and completion may contribute to differential protection against strains of HPV targeted by the HPV4 vaccine among males. Future research should identify barriers to uptake and completion in US males.
Background and Aims

Trends in human papillomavirus (HPV) prevalence among population-based samples have been used to monitor HPV vaccine impact. Evaluating trends among those age-ineligible for vaccination provides a needed context for interpretation.

Methods

We analyzed data from women in the National Health and Nutrition Examination Survey (NHANES), 2003 through 2014. Self-collected cervicovaginal swabs from 5885 NHANES participants aged 35-59 years tested for 37 HPV types by PCR were included. Weighted prevalence and 95% confidence intervals were estimated for any HPV, 14 high risk (HR) types, HPV 16/18 and five additional HR types in 9-valent vaccine in three 4-year time periods (2003-2006, 2007-2010 and 2011-2014) for women ages 35-39, 40-49, and 50-59. Trends in prevalence were evaluated using the stratum-adjusted Cochran-Mantel-Haenszel test for trend.

Results

HPV 16/18 prevalence was unchanged in all age groups during the 3 time periods (Table). Among 35-39 year-olds there were no significant changes in any HPV type category. Prevalence of five additional HR types decreased among 40-49 and 50-59 year olds (p_trend<.05). Prevalence of any HPV and HR HPV decreased among 50-59 year olds (p_trend<.05). There were no deceases in number of
Conclusions

The stability of HPV 16/18 prevalence in women older than age for HPV vaccination supports the interpretation that decreases noted previously in younger age groups in NHANES are due to vaccine impact. Further exploration of cohort differences in sexual behaviors or demographics is needed to understand the decreasing HR type prevalence in women who were age-ineligible for vaccination.
IPVC8-0410
POSTER SESSION

PUBLIC HEALTH / EPIDEMIOLOGY - EPIDEMIOLOGY: NATURAL HISTORY/GLOBAL BURDEN/RISK FACTORS

GENITAL HPV POSITIVITY AND TYPE-SPECIFIC CONCORDANCE IN A GROUP OF WOMEN WITH CYTOLOGICAL ABNORMALITIES AND THEIR SEXUAL PARTNERS FROM BOGOTA, COLOMBIA

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Background and Aims

HPV is one of the most common sexually transmitted infections. However, little is known about its prevalence in the male population and the type-specific concordance with their female partners. Objective: To characterize HPV positivity and type-specific concordance in 25 sexual partners, as well as the possible risk factors associated with viral infection.

Methods

We include 25 sexual partners of women with cytological abnormality. Detection of 37 viral types was carried out using linear array - Roche.

Results

56% (14/25) of men and 80% (20/25) of women were positive for at least one viral genotype. HPV16 was the most common high-risk viral type in men (21.4%) and women (25%). The type-specific concordance for HPV infection between couples was 28%. Only one couple had 100% agreement, showing HPV16 infection.

Conclusions

We found a high prevalence of HPV positivity in men and women as well as low type-specific concordance of HPV infection in couples from the city of Bogota, Colombia, whose female partners presented some type of cytological abnormality.
Background and Aims

The early identification of cellular atypia and lesions such as ASC-US, AG-US and low- and high-grade intraepithelial lesions provides a good opportunity for the diagnosis, treatment and monitoring of cervical disease, reducing its social and economic impact. **Objective:** To estimate the prevalence of HPV types in a group of women with cytological diagnosis of ASC-US from the Gynecology and Colposcopy Service of Engativá Hospital, Bogotá, Colombia.

Methods

Cervical samples from 200 women with an ASC-US Pap smear were analyzed for the presence of HPV DNA and genotype distribution using a commercial molecular technique (Linear Array®; Roche Molecular Systems, USA).

Results

Overall prevalence of HPV infection was 70%; of this, 46.4% represented high risk viral types, 16.4% low risk genotypes and 37.1% high and low risk genotypes. The HPV types most commonly detected were 16, 53, 52, 58, 59 and 39, with prevalences of 26.4, 16.4, 13.6, 12.9, 12.1 and 10.7%, respectively.

Conclusions

The epidemiological characterization of HPV infection obtained in the present study could guide the actions of epidemiological surveillance and contribute to strengthening the cervical cancer preventing program “Early detection of cervical cancer” in Bogotá.
PREVALENCE OF HPV INFECTION IN THE ANAL REGION OF SEXUALLY ACTIVE WOMEN FROM BOGOTA, COLOMBIA

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Background and Aims

HPV can infect different anatomical areas having transitional epithelial tissue. A high percentage of anogenital cancers are associated with HPV infection. However, this issue has not been widely studied in Colombia. **Objective:** To estimate HPV infection prevalence in the anal region in a group of sexually active women from Bogota, Colombia.

Methods

A total of 253 anal smears obtained from women aged 18-88 years was analyzed for the presence of HPV DNA and genotype distribution using a commercial molecular technique (Linear Array ® ; Roche Molecular Systems, USA).

Results

Overall HPV prevalence was 60.08%, represented by 36.84% high risk viral types, 26.97% low risk HPV types and 36.18% both high and low risk HPV types. Moreover, 64.35% of patients with negative anal cytology were positive for some viral genotype. The age group with the highest positivity (63.82%) was 25-44 years.

Conclusions

The high prevalence of HPV in the anal region found in Colombian women aged 25-44 years should encourage the implementation of public health actions for the early identification of high-risk virus in order to avoid the development of precursor lesions and anal cancer.
HUMAN PAPILLOMAVIRUS (HPV) SEROPREVALENCE AND ANOGENITAL HPV DETECTION AMONG YOUNG HETEROSEXUAL MEN

Background and Aims

HPV seroprevalence is a marker of cumulative HPV exposure, and though imperfect, can provide a simple measure of HPV exposure in a population. We studied HPV seroprevalence and anogenital detection at baseline in 3,463 heterosexual men (HM) 17-27 years old participating in a multinational clinical trial of the quadrivalent HPV vaccine.

Methods

Intra-anal, scrotal, perineal/perianal, and penile (“anogenital”) swab samples were collected at baseline and analyzed for 14 HPV types, including types targeted by the 9-valent (9v) HPV vaccine (6/11/16/18/31/33/45/52/58). Seropositivity was measured for the 9v types with a highly specific and sensitive competitive luminescence immunoassay (cLIA).

Results

At baseline, 457 (13%) HM had HPV anogenital detection of at least one 9vHPV type; of these, 13% were seropositive to the same HPV type and 34% were seropositive to any 9v type. Among these 457 men, seropositivity concordant with the same HPV type was: HPV6 (34%), HPV11 (20%), HPV16 (7%), HPV18 (3%), HPV31 (4%), HPV33 (9%), HPV45 (5%), HPV52 (5%), HPV58 (11%). Concordance between anogenital detection at baseline and seropositivity to the same HPV type varied by anatomic location of swab sample (highest for perineal/perianal swabs). In a subanalysis of a random sample of 208 HM from the US with no HPV detected at baseline, 13% were seropositive to at least one 9vHPV type.

Conclusions

Young HM showed evidence of past and current exposure to 9vHPV types. These findings support early age at HPV vaccination in males to maximize vaccine preventive benefit prior to sexual debut.
LOW-GRADE PAP ABNORMALITIES AND HPV INFECTION IN PARTICIPANTS IN HPV VACCINE TRIALS

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²The Women's Hospital, Research, Melbourne, Australia
³Moffitt Cancer Center, Research, Tampa, USA
⁴Duke University, Research, Durham, USA

Background and Aims

Cervical screening guidelines typically call for repeat cytology testing, HPV testing, and sometimes additional follow-up measures for women with low-grade Pap abnormalities. Few studies have reported the burden of low-grade Pap abnormalities associated with specific HPV types targeted by HPV vaccines. The purpose of this analysis conducted in women participating in 3 worldwide HPV vaccine trials was to describe HPV infection prevalence in women with low-grade Pap abnormalities at baseline.

Methods

At baseline, atypical squamous cells of undetermined significance (ASC-US) was found in 781 of 16,949 young women (YW) age 15-26 years (FUTURE I, II) and in 115 of 3,674 adult women (AW) age 24-45 years (FUTURE III); low-grade squamous intraepithelial lesion (LSIL) was found in 993 (YW) and 113 (AW) women. HPV infection was measured by PCR for 14 HPV types.

Results

Prevalence of any 9-valent (9v) vaccine type (6/11/16/18/31/33/45/52/58) among women with ASC-US or LSIL at baseline was 47% and 67%, respectively in YW, and 29% and 55%, respectively in AW. Prevalence of any non-vaccine HPV types (35/39/51/56/59) among women with ASC-US or LSIL at baseline was 32% and 64%, respectively in YW, and 24% and 54%, respectively in AW.

Conclusions

HPV types targeted by the 9-valent vaccine, as well as non-vaccine types, were commonly found in women with low-grade Pap abnormalities. These data suggest that, even when HPV vaccination programs achieve high population coverage, cervical screening will still be needed, as high-risk HPV types not targeted by the vaccine may cause cytological and histological abnormalities.
HIGH RISK HUMAN PAPILLOMAVIRUS IN A GROUP OF PORTUGUESE WOMEN

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Background and Aims

Human Papillomavirus (HPV) is the etiological agent for cervical cancer and genital warts. Worldwide, cervical cancer is the fourth most common cancer in women and the high risk HPV (HR-HPV), namely HPV 16 and 18 are responsible for the most of the cases. The objective was to analyze the HR-HPV frequency in a group of women referred for HR-HPV testing.

Methods

Clinical samples from 3117 women were perform by Cobas® HPV test (Roche Molecular Systems, CA, USA), this assay detected HPV 16 and HPV 18 and ‘Other HR-HPV’ (-31,-33,-35,-39,-45,-51,-52,-56,-58,-59,-66 and 68). Positive samples for ‘Other HR-HPV’ were sequenced for genotyping using MY09/11 primer’s.

Results

HR-HPV frequency was 20.8% (649/3117). Among the positive samples, ‘Other HR-HPV’ was the most common (72.8%; 473/649). HPV 16 and 18 were detected only in 22.8% (148/649) and 7.4% (48/649) of the cases, respectively. 7.4% (48/649) of the positive women were infected with more than one HPV (34 with ‘Other HR-HPV’ + HPV 16; 8 with ‘Other HR-HPV’ + HPV 18; 5 with ‘Other HR-HPV’ + HPV 16 + HPV 18 and 1 with HPV 16 + HPV 18). Sequencing of ‘Other HR-HPV’ is ongoing and preliminary results shown the majority frequency for HPV 31 (11.7%) followed by HPV 56 (9.1%) and 8.9% for the HPV 66.

Conclusions

The HR-HPV frequency is high (20.8%), 30.4 % of these women were infected with HPV 16 or HPV 18 which is a high frequency. This study reveals the importance of the implementation of screening programs, and the use of HPV detection.
HEAD AND NECK CANCERS ATTRIBUTABLE TO HPV IN NORTH AMERICA
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⁴Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Canada

Background and Aims

The presence of human papillomavirus (HPV) in cancer tissue can indicate that the cancer is attributable to HPV. On behalf of the ComPARE Study Group, we estimated the proportion of head and neck cancers (HNCs) attributable to HPV in North America via different HPV detection methods.

Methods

We systematically searched the literature and reviews for studies published after 1994 reporting on HPV prevalence in primary tumours of the oropharynx, oral cavity, or larynx. Data were pooled with random effects, 95% confidence interval (CIs) were calculated, and heterogeneity was assessed with the index of consistency.

Results

We included 37 studies in the analysis. Estimates of the attributable fraction of HPV in oral cavity cancers ranged from 5% to 11%, in oropharyngeal cancers from 54% to 69%, and in laryngeal cancers from 8% to 19%. Heterogeneity was significant for all endpoints.

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>HPV DNA via PCR</th>
<th>HPV-16 via PCR</th>
<th>HPV-16 via E6/7</th>
<th>p16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>64 (53–73)</td>
<td>57 (45–70)</td>
<td>54 (45–63)</td>
<td>69 (60–77)</td>
</tr>
<tr>
<td>Larynx</td>
<td>19 (11–28)</td>
<td>19 (10–29)</td>
<td>8 (0–22)</td>
<td>9 (1–24)</td>
</tr>
</tbody>
</table>

Conclusions

The gold standard detection technique, HPV-16 E6/7, produced lower but not significantly different HPV prevalence estimates from the other detection methods. This analysis indicated that if HPV were eliminated, 5% of oral cavity, 54% of oropharyngeal and 8% of laryngeal cancers could have potentially been prevented in North America.
PUBLIC HEALTH / EPIDEMIOLOGY - EPIDEMIOLOGY: NATURAL HISTORY/GLOBAL BURDEN/RISK FACTORS

A HIGHER CONTRIBUTION OF HPV 52 AND 58 IN CERVICAL DISEASE IN SELECT ASIAN COUNTRIES AS COMPARED TO USA

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Background and Aims

HPV 16 & 18, followed by types 31,33,45,52 & 58, are the most common HPV types causing diseases & cancers in females.

Methods

We extracted type-specific HPV prevalence in cervical cancers & precancers for HPV types 52 & 58 from the ICO/IARC Information Centre for HPV & Cancers (updated till 2015) by individual Asian country (China, Korea, Thailand, Singapore, Malaysia) & compared to US & Australian data.

Results

- HPV 52 & 58 infections in LSIL patients in China, Korea, Thailand, & Malaysia were 8-19.2% higher than USA. Using 9vHPV (9 valent HPV vaccine) instead of 4vHPV (9valent HPV vaccine) could possibly give an additional protection against LSIL by 21.7%-35.8% in these countries compared to 17.2% in USA & 27.5% in Australia.
- HPV 52 & 58 infections in HSIL patients in China, Korea, Thailand, Singapore & Malaysia were 11.3-26.9% higher than USA. Using 9vHPV instead of 4vHPV vaccine could possibly give an additional protection against LSIL by 35.5%-51% in these countries compared to 33.2% in USA & 33.6% in Australia.
- HPV 52 & 58 infections in CC patients in China, Korea, Thailand, Singapore & Malaysia were 1.2-15.6% higher than USA. Using 9vHPV instead of 4vHPV vaccine could possibly give an additional protection against CC by 14.4%-38.6% in these countries compared to 16.3% in USA.

Conclusions

- HPV 52 & 58 seem to occur in higher proportions of cervical cancer & precancerous lesions in some Asian countries compared to US/Australia.

*Xavier Bosch and Laia Bruni did not receive any funds to do this work. They both only contributed to the data.*
Recurrent respiratory papillomatosis (RRP) is caused by human papillomavirus types 6 and 11, and two forms are recognized: juvenile onset (JoRRP) and adult onset (AoRRP). RRP patients suffer from high morbidity and poor quality-of-life. In previous US studies, incidence was 4.3 /100,000 children and 1.8 /100,000 adults, estimating 80-1,500 new cases each year. Children with RRP undergo an average of 4.4 to 19.7 procedures per year, equivalent to more than 10,000 surgical procedures annually for children with RRP in the US. This systematic literature review (SLR) aimed to identify the latest evidence on RRP incidence.

Methods

A systematic literature search was performed using Medline and EMBASE. Studies containing original incidence data published between January 1st, 2008 and March 23rd, 2018 in English were included.

Results

We identified six studies from Africa, Australia, Europe, and North America. Incidence varies by year, country, age of onset and sex (Table 1 and Figure 1). Following the implementation of HPV vaccination programs, a low incidence rate (0.022 /100,000 in 2016) is reported in Australia. Pre-HPV vaccination incidence rates for the US (1.03 /100,000) and South Africa (1.34 per 100,000) were higher.
Table 1 RRP incidence rates by age and sex

<table>
<thead>
<tr>
<th>Study</th>
<th>Country/region</th>
<th>Year(s) data collected</th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRP</td>
<td>South Africa/Free State province</td>
<td>2011-2015</td>
<td>0.51</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>JoRRP</td>
<td>Canada</td>
<td>1994-2007</td>
<td>0.24 (≤14 yrs)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Norway/Oslo and Akershus</td>
<td>1997-2009</td>
<td>-</td>
<td>0.26 (≤17 yrs)</td>
<td>0.09 (≤17 yrs)</td>
</tr>
<tr>
<td>Marsico 2014</td>
<td>USA (privately insured)</td>
<td>2006</td>
<td>-</td>
<td>0.58 (≤17 yrs)</td>
<td>0.43 (≤17 yrs)</td>
</tr>
<tr>
<td>Marsico 2014</td>
<td>USA (publicly insured)</td>
<td>2006</td>
<td>-</td>
<td>0.89 (≤17 yrs)</td>
<td>1.19 (≤17 yrs)</td>
</tr>
<tr>
<td>Seedat 2014</td>
<td>Lesotho</td>
<td>2011-2013</td>
<td>0.49 (≤14 yrs)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Seedat 2017</td>
<td>South Africa/Free State province</td>
<td>2011-2013</td>
<td>1.34 (≤14 yrs)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Novakovic 2018</td>
<td>Australia</td>
<td>2012-2015</td>
<td>0.045-0.16* (≤14 yrs)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AoRRP</td>
<td>Norway/South East</td>
<td>1997-2009</td>
<td>-</td>
<td>0.88 (≥18 yrs)</td>
<td>0.23 (≥18 yrs)</td>
</tr>
<tr>
<td>Seedat 2017</td>
<td>South Africa/Free State province</td>
<td>2011-2015</td>
<td>0.18 (≥15 yrs)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Range from 2012-2015

Figure 1 RRP incidence rates by country, onset type and year
Conclusions

RRP does not have an ICD code making it difficult to identify cases and measure incidence. A consistent, validated method of identifying incidence of JoRRP and AoRRP, in males and females, across ages and years is lacking. While there is no post-vaccination incidence data for the US, recent Australian data suggests a decline in burden of RRP possibly due to reduction in vertical transmission.
SEX DIFFERENCES IN PREVALENCE, INCIDENCE AND CLEARANCE OF ANAL HUMAN PAPILLOMAVIRUS INFECTION IN HETEROSEXUAL POPULATION: AN OBSERVATIONAL PROSPECTIVE STUDY

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2Liuzhou Center for Disease Control and Prevention, Central office, Liuzhou, China

Background and Aims

Anal cancer is mainly caused by human papillomavirus (HPV) infection. Cross-sectional data suggested that prevalence of anal HPV infection in men is lower than that in women, whereas sex differences in natural history of anal HPV infection remains unknown.

Methods

From May 2014 to March 2016, anal swab samples were collected semiannually from 2302 men and 2371 women aged 18-55 years in Liuzhou, China. Specimens were genotyped for 13 oncogenic HPV types by PCR. Cumulative risk of acquisition and clearance of HPV infection by age groups were assessed with Kaplan-Meier method. Cox and WLW Cox proportional hazard models were used to estimate the factors associated with incidence and clearance, respectively.

Results

The prevalence (3.3% vs 8.0%) and incidence (3.4 vs 7.8 per 1000 person-months) of anal HPV were lower in men than that in women (all \( P < .0001 \)). The clearance rates were higher among men than women for both incident (143.0 vs 100.2 per 1000 person-months, \( P = 0.0820 \)) and prevalent (97.4 vs 62.3, \( P = 0.0222 \)) infections, respectively. Incidence of oncogenic HPV infection decreased with age in women (\( P = .0001 \)), but did not vary by age in men (\( P = 0.4279 \)). Clearance was stable across age groups in both sexes (all \( P > 0.05 \)). Besides sex behavior, hygiene behavior was also associated with incidence or clearance of HPV infection in both sexes.

Conclusions

Both higher incidence and slower clearance of anal carcinogenic HPV infection in women may lead to higher burden of anal cancer among women than that among heterosexual men.
Prevalence of HPV and Other STI Co-Infection and Associated Risk Factors: Results of POP-Brazil Study

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4Brazilian Ministry of Health, Department of Surveillance- Prevention and Control of Sexually Transmitted Infections- HIV/AIDS and Viral Hepatitis, Brasília, Brazil

Background and Aims

Studies establishing an association between HPV and others sexually transmitted infections (STI) may help to better understand the role of these viruses in developing cervical cancer. Although co-infection is common, precise estimates are unavailable, especially in the general population. The objective of the study was to analyze the prevalence of HPV and other STI co-infection and associated risk factors among women and men aged 16 to 25 years from 26 Brazilian capitals and the Federal District.

Methods

POP-Brazil is a nationwide HPV prevalence study with participants enrolled in 119 public primary care units by trained health care professionals. Cervical and penis samples were collected for HPV detection. To characterize others STIs, we asked participants if they had ever been diagnosed with syphilis, gonorrhoeae, HIV and/or genital herpes.

Results

Among 6,258 participants with valid data, the prevalence of HPV with other STI co-infection was 5.39% (n = 275), 26 participants (0.66%) presented two other STI besides HPV and only one had three other self-reported STIs. The most frequent association was HPV-HIV co-infection, followed by gonorrhea (Figure 1). Although a univariate model had shown that male gender was associated with HPV co-infection, when adjusted for sociodemographic and behaviors characteristics, only smoke, drug use, ever had same-sex experience and have more than 2 partners in the past year were
significantly associated with HPV co-infection.

Figure 1. HPV and STI coinfection among the participants aged 16-25 years.

<table>
<thead>
<tr>
<th>Coinfection</th>
<th>Total</th>
<th>Count</th>
<th>Prevalence</th>
<th>Prevalence and 95% IC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis,HPV</td>
<td>163</td>
<td>104</td>
<td></td>
<td>59.56 49.07 70.05</td>
</tr>
<tr>
<td>Gonorrhea,HPV</td>
<td>113</td>
<td>76</td>
<td></td>
<td>62.77 46.66 78.88</td>
</tr>
<tr>
<td>Herpes,HPV</td>
<td>133</td>
<td>67</td>
<td></td>
<td>62.23 46.54 77.92</td>
</tr>
<tr>
<td>HIV,HPV</td>
<td>33</td>
<td>25</td>
<td></td>
<td>85.41 69.89 100</td>
</tr>
</tbody>
</table>

*Weighted by sex and size of population in each capital

Conclusions
Presence of HPV and STI co-infection is common in the Brazilian population. The associated factors reinforces the importance of implementing global STI preventive and behavioral strategies.
PREVALENCE OF HPV INFECTION IN BRAZIL: A NATIONWIDE STUDY
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Background and Aims

HPV infection is the most common sexually transmitted infection and is strongly associated with cervical, anogenital and oropharyngeal cancers. The aim of this project was to have a nationwide baseline HPV prevalence in Brazil given that there is no information so far.

Methods

Participants from 16-25 years old were recruited in primary care units of the 26 states and Federal District. Participants answered to a questionnaire including sociobehavioral data. Trained nurses collected cervical sample and for men self-collect samples were performed using a saline-wetted Dacron swab, under supervision. DNA was extracted using MagNA Pure (Roche) automated method and genotyping done with the Roche's PCR-based Linear Array Genotyping Test. Sampling weights by age-structure of Brazil were applied to estimate population based prevalence.

Results

The prevalence of overall HPV was 53.56% (95% IC 51.37-55.75) among the 6,387 valid samples, with no differences according to sex (p=0.31). High-risk HPV was detected in 38.62%, with higher prevalence in females (38.62%) than males (29.18%; p=0.0003). There was a higher prevalence of infection in the 16-21 years old group (56.65%, 95% CI 53.61-59.70) comparing to 22-25 (50.03%, 95% CI 46.86-53.19). Declare himself as brown/mixed, not be married, smoke, and have 2 or more sexual partners in past 5 years are characteristics independently associated with overall HPV.
Figure 1. Prevalence of high-risk HPV according to age-range: POP-Brazil Study.

$X^2$ difference between weighted age ranges.

**Conclusions**

There was a very high prevalence of HPV infection in not vaccinated Brazilian population. These data provide a nationwide baseline against which trends in HPV type distribution can be measured, in order to monitor the impact of HPV vaccination.
Background and Aims

The vaccine against Human papillomavirus (HPV) is an effective and safe method to prevent HPV infection. Although vaccination is provided by public funded programs in many countries, almost all reported low coverage. For this reason, measure knowledge becomes essential to provide information for developing effective programs for encouraging HPV vaccination. The aim of the study was to adapt a questionnaire about knowledge, beliefs, and behaviors about HPV to Brazilian Portuguese.

Methods

The original instrument had been submitted to translation and back-translation. Experts assessed the validity content and cross-cultural adaptation during a pilot study and then it was applied to the participants of POP-Brazil study. To test the construct validity and reproducibility we split the results in two halves randomly and compared it each other to obtain the absolute agreement. We restricted the original instrument to questions about HPV knowledge and vaccination to create a score, categorizing the answers as adequate or not.

Results

The instrument composed by 30 questions was applied to 8,580 male and female Brazilians (16 and 25 years) and presented a good absolute agreement (61.16 ± 9.97). The preventive behavior section presents the lowest agreements (Figure 1). Men and women had different scores concerning their knowledge about HPV (men 0.48 (± 8.93) vs. women 0.55 (± 4.51) p<0.001) (figure 2).
Figure 1. Absolute agreement between two halves - POP-Brazil Study score

<table>
<thead>
<tr>
<th>Questions</th>
<th>Absolute Agreement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV infection and presence some symptom</td>
<td>54.76</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>71.52</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>63.77</td>
</tr>
<tr>
<td>Cystitis</td>
<td>60.26</td>
</tr>
<tr>
<td>Genital warts</td>
<td>55.67</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>55.01</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>52.43</td>
</tr>
<tr>
<td>Anus cancer</td>
<td>52.25</td>
</tr>
<tr>
<td>Mouth cancer</td>
<td>51.72</td>
</tr>
<tr>
<td>Have you known about HPV vaccination?</td>
<td>68.79</td>
</tr>
<tr>
<td>When do you believe a HPV vaccine should be had?</td>
<td>55.88</td>
</tr>
<tr>
<td>Who should be vaccinated?</td>
<td>71.71</td>
</tr>
<tr>
<td>When you have sexual relations do you use a condom?</td>
<td>52.95</td>
</tr>
<tr>
<td>Did you or your partner use a condom in the last intercourse?</td>
<td>52.99</td>
</tr>
<tr>
<td>Do you know Papanicolaou test?</td>
<td>73.78</td>
</tr>
<tr>
<td>After Vaccine what would be the attitude towards the Pap smear?</td>
<td>87.37</td>
</tr>
</tbody>
</table>

Caption: The table shows the absolute agreement in Pop-Brazil following the questions from the score (range 0-14 for men and 0-16 for women). The variables were categorized like a dichotomous measure (adequate and not adequate answers) for creating the score. The absolute agreement was obtained from two halves from total sample. Data were analyzed using SAS software (Statistical Analysis System, SAS Institute Inc., Cary, N.C.), version 9.4.
Conclusions

The proposed questionnaire is the first instrument able to describe knowledge, beliefs, and behaviors about HPV in Brazilians male and female. The instrument can be used in futures research about HPV.

Caption: The figure shows the percentage of participants who answered correctly the questions following the score. The horizontal axis corresponds to the number of correct answers according to score (range 0-14 for men♂ and 0-16 for women♀). Data were analyzed using SAS software (Statistical Analysis System, SAS Institute Inc., Cary, N.C.), version 9.4.
PUBLIC PERCEPTION OF HPV AS A WOMEN’S HEALTH ISSUE IN THE UNITED STATES: AN ANALYSIS OF THE HEALTH INFORMATION NATIONAL TRENDS SURVEY

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Background and Aims

The promotion of HPV vaccination has almost exclusively focused on cervical cancer prevention, despite that more than 25% of all HPV-related cancers in the U.S. occur in men. The purpose of this study is to: (1) Estimate HPV-awareness and -cancer knowledge among adults and across subgroups who are vaccine eligible; (2) Estimate changes in awareness/knowledge between 2014 and 2017.

Methods

We used data from the Health Information National Trends Survey (HINTS). HINTS is a cross-sectional nationally-representative survey of civilian adults in the U.S. HPV-awareness was assessed with one item indicating aware or never heard of HPV. HPV-cancer knowledge was assessed with four items asking if HPV can cause cervical, anal, oral, or penile cancer (e.g., “Do you think HPV can cause anal cancer?”). Responses were coded yes/no or not sure. Vaccine eligible were 18-26-year olds, as well as respondents with an immediate family member between 9 and 26 years old.

Results

64% (SE=1.4) of the population was aware of HPV. Awareness was higher among women and the vaccine eligible subpopulation. No change in awareness was observed between 2014-2017. Knowledge of cervical cancer was high (78%), but low for anal (26%), oral (30%), and penile (30%) cancers (SEs<2). Cervical cancer knowledge increased among women, but no other increases in HPV-cancer knowledge were observed.

Conclusions

The general public is aware of HPV and largely associate HPV with cervical cancer. Knowledge of non-cervical HPV-related cancers is low, even among vaccine eligible subgroups. Public health education is needed to raise awareness of non-cervical HPV cancers.
PREVALENCE AND DETERMINANTS OF BETA HUMAN PAPILLOMAVIRUS DETECTION IN ORAL SAMPLES FROM HEALTHY MID-ADULT WOMEN

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²International Agency for Research on Cancer - World Health Organization, Infections and Cancer Biology Group, Lyon, France
³University of Washington, Global Health, Seattle, USA
⁴FIDALAB, Fidalab, Seattle, USA

Background and Aims

To inform the epidemiology of oral β human papillomaviruses (β-HPVs) in women, we estimated prevalence and determinants of β-HPVs in stored samples from healthy mid-adult women (aged 30-50 years).

Methods

We performed multiplex PCR for 46 β-HPV genotypes on 403 oral rinse samples. β-HPV genotyping results in paired fingernail samples were also available for a subset of 184 women. We used log-binomial regression to estimate prevalence ratios (PRs) for associations between demographic, health, and sexual behavior risk factors (lifetime numbers of vaginal and oral sex partners and open-mouth kissing partners) and oral β-HPV detection. We also evaluated whether detection of β-HPV in fingernails was associated with concurrent detection of the same type in the oral cavity.

Results

Oral HPV prevalence was 20.6% for any β-HPV; the most common types were HPV-23 (3.5%) and HPV-38 (3.0%). In multivariate analysis, oral β-HPV detection was associated with increasing age (adjusted prevalence ratio (aPR) for each 5-year difference=1.34, 95%CI:1.06-1.71) and race (aPR for non-white versus white race=0.44, 95%CI:0.21-0.90) and borderline statistically-significantly associated with current smoking (aPR versus never smoked=2.03,95%CI:0.90-4.61). In the subset with fingernail results, concurrent detection of the same β-HPV type in fingernails was strongly associated with oral β-HPV detection (PR=44.17, 95% CI:29.36-66.44 ). We did not identify any significant sexual behavior predictors of oral β-HPV detection.

Conclusions

Oral β-HPV was detected in one out of five healthy mid-adult women. Our results support the hypothesis that fingers may serve as a source of transmission or autoinoculation of β-HPVs to the oral cavity.
VACCINATION STATUS AND HPV TRANSMISSION IN YOUNG, RECENTLY FORMED HETEROSEXUAL COUPLES IN MONTREAL, CANADA

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³McGill University, Family Medicine, Montréal, Canada
⁴Université de Montréal, Microbiology and Immunology, Montréal, Canada

Background and Aims

Vaccination against HPV prevents HPV infections and cervical lesions. However, the effect of vaccination on HPV transmission within couples is unknown.

Methods

We used data from HITCH, a prospective cohort of heterosexual couples in Montreal, Canada (women aged 18-24). Genital samples were tested for HPV DNA by PCR (Linear Array HPV genotyping assay). Type-specific viral loads were quantified using real-time PCR. Odds and hazard ratios (OR/HR) of HPV transmission associated with self-reported vaccination history were estimated using multi-level mixed-effects logistic regression and mixed-effects parametric survival-time models, respectively. Viral load differences were evaluated using Wilcoxon rank-sum tests.

Results

Among 497 couples, 12, 16, and 34 women had received 1, 2 and 3 vaccination doses before enrollment, respectively; no men were vaccinated. Median age at vaccination was 19 years. All women had been sexually active before vaccination. Sexual behavior of vaccinated and unvaccinated women was similar. At baseline, concordance of HPV6/11/16/18 was significantly lower in vaccinated couples (OR 0.19, 95%CI 0.05-0.75) but concordance of other HPV types was similar between groups (OR 1.11, 95%CI 0.54-2.25). Incidence rates of HPV6/11/16/18 in women were inversely correlated to the number of vaccination doses (HR 0.64, 95%CI 0.45-0.91); however, they were similar in women who received 1 dose or none. Mean HPV16 viral loads were lower in vaccinated than unvaccinated women (0.01 versus 1.24 copies/cell, p=0.001). In men, 0.5% and 1.7% had incident HPV6/11/16/18 infections at follow-up when having vaccinated or unvaccinated partners, respectively.

Conclusions

Vaccination of sexually active women significantly reduced HPV transmission in heterosexual couples.
THE EFFORTS OF ELIMINATION OF CERVICAL CANCER IN MACAU
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Background and Aims

Cervical cancer is an important disease burden worldwide. A well-established cervical screening program is crucial in the prevention of cervical cancer. Since 1985, the Macau government has offered free pap smear screening for residents of Macau and further strengthened in 2009. This study provides the evidences to assess the impact of the national quadrivalent HPV vaccine program since 2013 and initiation of nonavalent HPV program in 2017.

Methods

The incidences of cervical diseases have been collected and served as HPV disease registry to examine the current epidemiology of cervical cancer and cervical screening impact.

Results

Cervical cancer ranked #5 in 2007, whereas in 2015 the rank has decreased to #8 in female malignancy tumor, with the per 100,000 crude incidence rate of cervical cancer dropping to 7.7 in 2015 from 11.3 in 2007.

Conclusions

Considering the limitation of cytology screening, introduction of HPV co-testing (Roche-4800) in 2018 for women aged 30 or above could generate synergy in prevention. In addition, it is also important to consider HPV vaccination for boys, not only to enhance the rate of decline in HPV infection and cervical cancer incidence by reducing HPV transmission, but also for direct protection in males. No regular screening program is available for males who are susceptible to a number of HPV-related diseases such as anal, penile and oropharyngeal cancers. A gender neutral approach to vaccinate both boys and girls is crucial for the protection of both females and males against HPV cancers.
Background and Aims

HPV E6/E7 mRNA and E6-protein are associated with cervical carcinogenesis, but very few epidemiologic data have been obtained. We investigated the relation between E6/E7 expression and cervical cancer in HPV-positive population.

Methods

This case-control, multicenter study was performed between 2013 and 2017 in five hospitals of China. Women were tested for presence of 14 types of high-risk HPV DNA, E6/E7 mRNA and HPV16/18 E6-protein. HPV16/18 DNA positive women were included into final analysis.

Results

Of 2,016 recruited subjects, 33 women with normal histopathology, 176 precancer and 422 cancer were HPV16/18 DNA positive. The presence of HPV16 mRNA and E6-protein significantly associated with the risk of precancer (OR\textsubscript{mRNA}=6.67, 1.86-23.85; OR\textsubscript{E6-protein}=2.70, 1.07-6.80) and cancer (OR\textsubscript{mRNA}=11.56, 3.47-38.56; OR\textsubscript{E6-protein}=26.88, 10.47-69.05). For HPV18, the only significant association was observed between E6-protein and the risk of cancer (OR\textsubscript{E6-protein}=7.19, 1.58-32.67). The positivity rate of multiple infections in cancer cases was significantly lower than single infection for HPV16 E6/E7 mRNA (88.6% vs. 99.1%), HPV16 E6-protein (72.7% vs. 93.7%), HPV18 E6/E7 mRNA (69.2% vs. 100.0%) and HPV18 E6-protein (53.8% vs. 95.1%). There were three cancer cases with HPV16/18 coinfection transcribed both HPV16 and HPV18 mRNA, but none of the cases expressed HPV16 and HPV18 E6-protein simultaneously. E6-protein of each genotype expressed in 50% of HPV16/18 coinfection cancer cases.

Conclusions

E6/E7 mRNA and E6-protein were associated with different risk of cervical precancer and cancer in HPV-positive population. Cervical cancer could be caused by single HPV genotype—the E6-protien expressing genotype, in multiple infections.
Background and Aims

Exploring HPV distribution in Xinjiang women and analyzing the possible related risk factors are of great importance to conducting the more appropriate cervical cancer prevention and control program in Xinjiang.

Methods

Rural women in the Xinjiang Uygur Autonomous Region in western China aged 35-64 years old were screened for cervical cancer by gynecological examination, vaginal secretions smear microscopy examination, cytology and HPV testing. The women with suspicious or abnormal results were examined by colposcopy and biopsy if necessary.

Results

710122 women were screened from 2015 to 2017, 55508 of them received HPV testing. HPV positive rate was 6.95%. Compared to 35-45 age group, the OR (95%CI) of HPV infection rates in 45-55 and 55-64 age groups were 1.10 (1.02-1.18) and 1.59 (1.44-1.76). Compared to women with elementary and junior high school education level, the OR (95%CI) for the women with education level of middle school, high school or secondary school and above were 1.10 (1.02-1.19), 1.66 (1.49-1.86) and 1.74 (1.50-2.01). Compared to the Han nationality, the OR (95%CI) for the Uyghur women were 1.09 (1.01-1.18). The main prevalent HPV types are 16 (24.00%), 33 (12.70%) and 52 (11.80%). The detection rate and the early diagnostic rate of cervical cancer were 0.13% and 90.67%. Proportion of cervical cancer and precancerous lesions patients were higher among women aged 45-55 and 35-45, Uyghur nationality, primary school education level.

Conclusions

The HPV infection rate among rural women in western China was lower than the national average level and showed a slowly increasing trend with increasing female education level and age. Cervical cancer and precancerous lesions have high prevalence in western China.
HUMAN PAPILLOMAVIRUS PREVALENCE AND RISK FACTORS IN ORAL SCRAPES FROM HEALTHY MEXICAN INDIVIDUALS

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3Instituto Mexicano del Seguro Social, Centro Medico Nacional Siglo XXI, Mexico, Mexico

Background and Aims

Oral human papillomavirus (HPV) infection is associated with oral cancer (OC) development. However, few epidemiologic investigations have focused on oral HPV prevalence in healthy individuals. The objective was to investigate the HPV prevalence in oral scrapes from healthy individuals from a Central Region of Mexico and to describe the risk factors (RF) associated.

Methods

HPV DNA was identified by PCR using degenerated oligonucleotides. Demographic and sexual behavior data were obtained from the patients by using a survey. This is a pilot, descriptive and experimental design. The individuals were attended in a Dentistry Clinic to routine review.

Results

Fifty samples were collected from oral cavity from adult healthy Mexican subjects ranged from 22-64 years (mean of 41.8 years); 35(70%) were female and 30% male. Overall, in 16% of the cases HPV sequences were detected. Regarding to the RF we observed: first sexual intercourse at 19.6 years (14-28), oral sex practice (54%), smoking (30%), and alcohol consumption (38%). From the cases HPV+ 87.5% were women, the age at first sexual intercourse was 22 years (18-28), 75% were married, 50% with high educational level, 50% with oral sex practice, 37.5% with smoking, and 25% with alcohol consumption.

Conclusions

The presence of HPV DNA in oral cavity of the healthy Mexican individuals studied was higher than other reports, being most commonly found in women. In order to prevent future oral lesions or viral transmission, a periodical review should be performed, and re-educative plans and health campaigns are necessary.
INCIDENCE AND ASSOCIATED FACTORS OF ANOGENITAL HUMAN PAPILLOMAVIRUS INFECTION IN A COMMUNITY SAMPLE OF MEN WHO HAVE SEX WITH MEN IN TAIWAN

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²Sun Yat-sen University, School of Public Health, Guangzhou, China
³Taipei Veterans General Hospital, Division of Infectious Diseases, Taipei, Taiwan R.O.C.

Background and Aims

We aimed to estimate the incidence of anogenital HPV infection in men who have sex with men (MSM) and identify risk factors associated with HPV incidence.

Methods

We recruited 253 MSM (aged 20-56 years) from community health center and LBGT-friendly venues in South Taiwan in 2015-2016 and followed in 6 and 12 months after baseline. At each visit, participants received HPV screening at the anal and penile sites and 37 HPV genotypes were detected. Definite HPV infection is defined as being detected with HPV infection twice at the same site in men not detected with HPV in the baseline. Possible HPV infection is defined as only one positive HPV test in the same site in men with a negative test at baseline. Poisson regression was used to examine associated behavioral risk factors.

Results

Definite incidence rate per 100 person-years for anal and penile site were 5.13 (95% CI 1.65-15.9) and 15.34 (95% CI 7.67-30.67) respectively. Having three or above sexual partners with receptive anal sex is significantly associated with new definite or possible HPV detected in the anal site (Incidence rate ratio (IRR)=3.06, 95% CI 1.21-7.70). Any definite HPV infection in the anal site is also associated with education level (IRR=0.27, 95% CI 0.08-0.94, high school graduate or below vs university graduate or above) and having at least one sexually transmitted infection in the past year (IRR=4.12, 95% CI 1.09-15.54).

Conclusions

High HPV incidence in the MSM community suggests a potential need to raise awareness and uptake of HPV vaccine in men.
Men who have sex with men (MSM) are at high risk of anogenital human papillomavirus (HPV) infection which can lead to cancers. Existing research had conflicting findings on the role of circumcision in HPV infection among MSM.

Methods

We conducted a systematic review and meta-analysis by searching MEDLINE, Web of Science, BioMed Central, Scopus, Research Gate, Cochrane Library, EMBASE, PsycINFO, Google Scholar, and websites of international HIV/STI conferences through March 2018. Studies containing original quantitative data representing the association between circumcision and HPV infection among MSM were included. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effect models.

Results

A total of 12 observational studies including 29,842 MSM met inclusion criteria. We found circumcision was not associated with HPV infection among MSM overall (OR=1.01; 95% CI, 0.87-1.17). However, in subgroup analyses, circumcision was significantly associated with reduced odds of HPV infection in studies adjusted for potential confounders (0.67; 0.48-0.94). We found a non-significant protective
association between circumcision and penile HPV infection among MSM overall (0.83; 0.66-1.05), but this protective association was significant among MSM living with HIV (0.71; 0.51-0.99).

Conclusions

Circumcision is likely to protect MSM from HPV infection. Further research is warranted to investigate circumcision for penile HPV prevention among MSM, particularly among those infected with HIV.
Background and Aims

Little data exists on transfer and clearance of maternal HPV antibodies in newborns and children. This study aimed to analyze the correlation of mother and newborn anti-HPV antibodies and to describe the dynamics of anti-HPV antibodies levels in children from birth until two years of age.

Methods

The HERITAGE study aims to describe perinatal transmission of HPV. We analysed data and samples from 58 HPV-positive pregnant participants and their children, recruited in Montreal (Canada) between 2009-2012. Dried blood spots were collected from the women during the first trimester of pregnancy and from their infants at birth, 6, 12 and 24 months. Luminex immunoassay was used to analyze total immunoglobulin G levels in normalized median fluorescence intensity (NMFI) against HPV types 6-11-16-18. Scatter-plots and Spearman's coefficients were used to compare pregnant women and
newborn anti-HPV levels. Dynamics in children were described using panel graphics and survival analysis.

**Results**

Anti-HPV levels from mothers and newborns were significantly correlated: \( r=0.81 \) (95%CI:0.70-0.88), \( r=0.68 \) (95%CI:0.50-0.80), \( r=0.90 \) (95%CI:0.83-0.94) and \( r=0.85 \) (95%CI:0.76-0.91) for anti-HPV-6-11-16-18, respectively. Anti-HPV antibodies detected at birth cleared before 24 months in all children, approximately 80% before 12 months. In one child, anti-HPV-16-18 antibodies were redetected at 24 months. In another child, anti-HPV-6-11 were detected for the first time at 12 months, and persisted at 24 months.

**Conclusions**

This study has been the first to document the waning of maternally transmitted HPV antibodies and dynamics in early childhood. Further research could improve knowledge on the influence of maternally and naturally acquired immunity on HPV infection in children.
Background and Aims

Vaccination against human papillomavirus (HPV) and screening coverage for HPV-induced cervical and anal cancers are low in the Chinese population. We aim to assess the demographic characteristics, temporal and geographical trends of HPV in heterosexual men, women, men who have sex with Men (MSM) in China.

Methods

This meta-analysis searched literatures published from January 2000 to May 2017 in Pubmed, Web of Science, China National Knowledge Infrastructure, and Wanfang Data. Two hundred and seventy-four articles targeting heterosexual women, men and MSM were collected for synthesis. Meta-analysis was used to estimate pool HPV. Meta-regression was conducted to identify the underlying factors for HPV heterogeneity in different populations.

Results

The national HPV prevalence in heterosexual women stabilised at 15.6% (14.4-16.9%) in the past decade. The highest prevalence was reported in Central China (20.5% [15.2-25.8%]). HPV prevalence in heterosexual men with normal cytology (14.5% [11.3-17.7%]) was comparable to that of heterosexual women (OR=1.1 [1.0-1.1]), but MSM (59.9% [52.2-67.6%]) was far more prevalent than heterosexual men (OR=8.8 [8.0-9.7]). HIV significantly increased the risk of HPV infection, HIV+ MSM (87.5% [82.3-90.9%]) and women (45.0% [38.4-51.6%]) were at 6.4 [5.2-8.0] and 4.6 [3.6-6.0] higher odds of HPV infection than their HIV- counterparts. Women with low-grade (69.8% [61.9-77.7%]), high-grade (86.0% [84.2-97.8%]) and cervical cancer (88.7% [86.7-90.6%]) had significantly high prevalence for HPV.

Conclusions

HPV is more prevalent in the general Chinese population, particularly in Central China. MSM is highly at risk of HPV infection. HIV significantly increase HPV acquisition in both females and MSM population.
To explore the availability and extent of research evidences on economic burden of cervical cancer in China from 1996 to 2014.

Methods

Based on PubMed and two Chinese publication databases (CNKI and Wangfang), using a systematic review approach, literatures on economic burden of cervical cancer in China between January 1996 and December 2014 were searched. Expenditure data were converted to 2013-value Chinese Yuan (CNY) using China’s health care CPI, and average annual growth rates (AAGR) were analyzed.

Results

A total of 19 literatures were included, 9 of which published after 2010. Only 3 studies at population level were confirmed (1 conducted at provincial level and 2 at prefecture level), the methodologies varied and results were less comparable among studies. Of 16 individual-level studies, 15 studies only reported data on direct medical expenditure, and three commonly used indicators were expenditure per patient (one or more clinical visits/admissions, 12 studies), expenditure per clinical visit (4 studies) and expenditure per inpatient day (9 studies). The corresponding median expenditures of the three indicators were estimated at 11,063 CNY (range: 3,814~15,594), 14,386 CNY (7,778~19,615) and 398 CNY (204~909), respectively. The corresponding AAGRs were estimated at 6.3%, 4.5% and 8.7%, respectively.

Conclusions

In China, evidence on economic burden of cervical cancer was increasing, 1996-2014, but results on per-patient expenditure likely under-estimated the real burden and should be interpreted cautiously. Evaluations at population-level, on direct non-medical and indirect medical expenditures should be addressed in the future.
BACKGROUND AND AIMS

Cervical cancer is a leading cause of morbidity and mortality in women especially in sub-Saharan African countries. It can be prevented by providing widespread and regular cervical screening services for all women who have been sexually active. This is an insight into women’s understanding of cervical cancer risk factors, symptomatology, prevention and screening.

METHODS

The study was cross-sectional in design. Quantitative Data was collected using questionnaires administered to 2000 women (aged 20 to 64 years) who were selected by multi-stage sampling technique across the 20 local government areas in Ogun State, Nigeria.

RESULTS

The study showed that the awareness of cervical cancer and screening was very low (6.5% and 4.8% respectively). The knowledge about cervical and screening was very poor. Only 2.3% of the women could identify a virus as the cause of cervical cancer while 4.1% identified cervical screening as a way to prevent cervical cancer. 97.7% and 97.9% had no or poor knowledge of risk factors and knowledge of symptoms of cervical cancer. 90.5% identified lack of awareness as the barrier to uptake of cervical screening. 1.4% of the women have had cervical screening done.

CONCLUSIONS

In order to step up the campaign for the control of cervical cancer in Nigeria, it is very important to concentrate much of the effort on creation of awareness and enhancing the knowledge of women about cervical cancer and screening.
AN INDICATION OF THE IMPACT OF KNOWLEDGE OF HPV POSITIVITY ON CYTOLOGY TRIAGE IN PRIMARY HIGH-RISK HPV SCREENING

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Background and Aims

Several studies have shown that there is an upward shift in the classification of cervical cytology by cytotechnicians and pathologists when high-risk HPV (hrHPV) status is known to be positive. The Netherlands implemented primary hrHPV screening with reflex cytology as the primary screening test in 2017. Prior to implementation of the new programme, we aimed to investigate whether knowledge of hrHPV status influences cytology rating.

Methods

Using a set of 200 cytology slides blinded for previously tested HPV, two pairs of cytotechnicians rated 100 slides per pair twice; first without knowledge of hrHPV status and then, after a wash-out period of two months, with knowledge of hrHPV status. Upgrades and downgrades in the rating of cytology were identified for each pair of observations.

Results

Our results show that hrHPV positive slides were more often rated upwards than hrHPV negative slides (hrHPV positive 22 times (12.4%) vs. hrHPV negative 7 times (3.9%)). Most uprated hrHPV positive slides were rated upwards from negative to 'atypical squamous cells of undetermined significance' (9.0%), and therefore over the threshold for referral in the renewed Dutch screening programme. No clear patterns were found for the impact of upgrading or downgrading slides on detection of clinically relevant lesions due to a lack of follow-up data.

Conclusions

If an upward rating trend were observed in the national programme, it may impact numbers of referrals and overtreatment of low-grade lesions. Whether this upward rating results in more false or true positives needs to be explored.
EVALUATION OF ACCEPTABILITY OF SELF-COLLECTED VAGINAL SWAB TO DETECT HPV INFECTION AMONG YOUNG WOMEN IN MONGOLIA

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Background and Aims

Self-collected vaginal samples is a new approach to detect sexually transmitted diseases. The aim of the study was to evaluate acceptability of self swabbing technique in Mongolia.

Methods

365 young women (18-22 years old) were offered self vaginal sampling using flocked self vaginal swabs (FLOQSwab, Copan, Italy) at hospital following swab instructions in December 2017 - January 2018. Participants completed a Questionnaire to assess acceptability and feasibility of self swabbing technique. Swabs were placed in PreservCyt solution and processed for detection of HPV.

Results

86.8% of participants found that FLOOQSswabs were easy to use and 97.8% found instructions clear and comprehensive. Most of the participants preferred standing position with the legs apart (56.7%), with less preference of sitting forward on a toilet with the legs apart position (25.5%) and one foot resting on the toilet rim position (15.5%). 73.2% indicated that they did not experienced pain during sampling. Majority of participants (65.7%) preferred to provide self swabbing rather than collected by physician. The reason for preference of vaginal self sampling, was greater privacy (38.6%), time saving (22.7%), less anxiety (21.9%) and all these 3 reasons (15.6%).

Conclusions

The vaginal self sampling is new method in Mongolia and has shown as an acceptable method to collect vaginal swabs. Most of participants preferred standing position to collect samples and expressed preference of this method due to provision of greater privacy, time savings and reduction of anxiety. This method could increase the uptake of HPV and other STD testing among young women in Mongolia.
Background and Aims

Mongolia has a high documented cervical cancer disease burden. In 2012 the Mongolian Government received a donation of quadrivalent HPV vaccines and initiated a HPV pilot vaccination program in school-aged girls. Currently no HPV vaccination is taking place in Mongolia. We aimed to describe HPV detection rates in girls vaccinated with 3 HPV doses and age-matched controls 6 years following the campaign, as well as risk factors for infection.

Methods

A sample of 1903 (928 randomly chosen cases and 975 controls) young women (18-22 years old) from Ulaanbaatar and two provinces were recruited from August 2017 - January 2018. Participants completed a questionnaire and provided self-administered vaginal swabs (FLOQSwab, Copan Italy) which were tested using an Xpert HPV Assay (Cepheid).

Results

Of a total of 1624 women who provided vaginal swabs, 1518 had conclusive results. There was no significant difference in the detection rates of high risk HPV genotypes not in the vaccine, between the vaccinated (237/727, 33%) and control group (193/791, 24%, p=0.07). The rate for HPV 16/18_45 infection was significantly lower in the vaccinated group (35/727, 5% vs 136/791, 17%, p<0.001). Risk factors for HPV16/18_45 positivity included alcohol use, smoking, a higher number of previous partners and previous pregnancy.

Conclusions

We have shown lower rates of vaccine-targeted HPV genotypes in vaccinated women 6 years following a pilot HPV vaccine program in Mongolia. It is hoped that this data will assist in restarting the discussion on HPV vaccination in Mongolia.
Background and Aims

To evaluate the 9-year incidence of intraepithelial cervical neoplasia grade 2 or worse (CIN2+) in a cohort of underscreened women after baseline cervical cytology and HPV tests.

Methods

In Catalonia, Spain, co-testing with cervical cytology and HPV test (HC2) has been recommended at the Public Health level since 2006 for underscreened women, defined as women aged 40+ years with no screening history in the last 5 years. We followed-up 1,594 women identified as underscreened in 2007 up to 2016 through pathological department’s records. Nine year cumulative incidence of CIN2+ was estimated using Kaplan Meier statistics.

Results
Follow-up was available for 1,009 women (63.3%). Most of the follow-up losses were from women with both tests negative rather than women with a positive result (38.7% vs 15.8%, p-value <0.001). 2.3% (N=23) of women developed CIN2+ lesions. Of them, 82% (19) had either a positive HPV or an abnormal cytology, 48% (11) had a negative cytology but a positive HPV (6 CIN2 and 5 CIN3) and 17% (4) had both tests negative at baseline (3CIN2 and 1CIN3). 9-year cumulative incidence of CIN2+ was 0.09% in women with both tests negative at baseline, 13.5% when both tests were positive and 4.1% if only HPV was positive. The negative predictive value of double negatives was 99.6%.

**Conclusions**

HPV testing improves the long term negative predictive value to develop CIN2+. However, it is necessary to establish mechanisms to avoid long term loss of adherence to cervical cancer screening among women with negative tests.
HPV primary cervical cancer screening in Tuscany in 2017: data of HPV positivity, triage cytology and partial genotyping

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Background and Aims

Tuscany Region has started HPV primary cervical cancer screening in 2013 centralizing all HPV tests in one lab at Regional Laboratory for Cancer Prevention (LRPO). The process started gradually, by Local Health Units (LHU) and by age (3 LHUs, Firenze, Viareggio and Grosseto, age class 55-64 yo). In 2017, a total of 8 on 12 LHUs enrolled the whole cohort 34-64 yo. Our objective is to describe 2017 data related to HPV positivity, HPV 16/18 genotyping by area and correlation with triage cytology of a large screening population (not available before June 2018).

Methods

In 2017 samples were processed by COBAS 4800 HPV test that is able to perform partial genotyping (HPV16, HPV18, other HR-HPV).

Results

In 2017, LRPO performed 69,834 HPV tests (primary screening +12-months recall) with a row adhesion of 43.8% (invited women: 159,504). HPV positivity at baseline was 7.8% (5,266/67,317), ranging from 6.5 of Prato to 9.9% of Viareggio, and at 12-months recall was 52.8% (1,329/2,517). At baseline and at 12-months recall HPV16, HPV18 and HR-HPV other positivity were 14.6% vs 14.2%, 4.1% vs 4.4 and 72% vs 72.2, respectively; co-infections HPV16+other HR HPV and HPV18+other HR HPV were 6.1% vs 6.3% and 2.1% vs 2%, respectively, without significative variations among LHU. Results of cytology showed 25.2% (1,634/6,491) of LSIL+, 62% HPV other, 17.6% HPV16, 4.9% HPV18, 7% HPV16+other and 3% HPV 18+other.

Conclusions

Centralization of HPV test and triage cytology in one laboratory represents a very high organizational model able to reach screening indicators guaranteeing high quality.
FACTORS ASSOCIATED WITH CERVICAL CANCER SCREENING BEHAVIORS AMONG MARRIED FEMALE IMMIGRANTS IN KOREA

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Background and Aims

The purpose of this study was to identify factors associated with the national cervical cancer screening behaviors of married female immigrants living in South Korea.

Methods

The present study dataset was collected by the National Health Insurance Services in 2014–2015. A final study population of 15,935 were considered eligible for inclusion in this study if they met the criteria for participation in the national cervical cancer screening program in the 2014–2015.

Results

Of the 15,935 subjects, 7,837 (49%) participated in cervical cancer screening. Based on the results of the logistic regression analysis of the association between cervical cancer screening behaviors and related factors, the odds ratio (OR) for participation in cervical cancer screening among individuals older than 50 years was the highest [OR=2.134; 95% confidence interval (CI): 1.819–2.505], and the OR increased as their duration of stay in Korea decreased. The OR of Chinese women for cervical cancer screening participation was higher than that of non-Chinese women (OR=1.832; 95% CI: 1.686–1.991). The OR value was 29.384 (95% CI: 25.945–33.344) among those who participated in the general health screening compared with those who did not participate.

Conclusions

To improve awareness about cervical cancer screening and reduce disparities in access to healthcare, appropriate programs should be developed to promote cervical cancer screening participation to socially vulnerable classes. Continuous social attention is needed to address these issues and encourage participation in general health screening to improve the rate of cervical cancer screening.
Background and Aims

The aim of this study is to detect HPVs in oral and anal sites, and to explore the correlation between these 2 sites among men who have sex with men (MSM) and HIV in Taiwan.

Methods

Between 2015 and 2016, HIV-infected men who attended the outpatient clinics of Taoyuan General Hospital, Taiwan, had been enrolled. Oral gurgling and anal swabs were collected for thin-preparation cytology and linear array HPV genotyping tests.

Results

Totally 208 subjects were enrolled, and 196 were eligible for analysis. Their mean ages (±SD) were 32.13 (±7.02) years, and >90% were MSM. Their recent mean (±SD) CD4 T+ cell counts were 588 (±267) cells/µL, and 73% of their viral load were fully suppressed. Anal HPV could be detected in 186 subjects (94.9%), and 82.7% have oncogenic HPVs; whereas oral HPV could be detected in only 20 cases (10.2%), and 30% have oncogenic types. Further, 41.1% (14/34) of oral genotypes could be found on the subjects’ anal sites. But, only 30.1% of subjects used condom in oral sex. Subjects who had oral HPV have statistically significant number of anal HPV genotypes (odd ratio 1.22, 95% CI 1.02-1.46, p=0.03) after adjusting the number of lifetime sexual partners and new partners in 6
months, history of sexually transmitted diseases, and recreational drug use.

**Conclusions**

Above data indicates that of 94.9% and 10.2% of anal and oral HPV prevalence, respectively; and 41.4% of genotypic similarity between 2 sites. Promotion of condom use during oral sex might be helpful for HPV prevention.
Background and Aims

We describe trends in human papillomavirus (HPV) test utilization preceding diagnosis of precancerous cervical lesions during a time of changing screening recommendations in the United States.

Methods

We analyzed data on women aged 21-39 years diagnosed with cervical intraepithelial neoplasia grade 2 or higher (CIN2+) identified through population-based surveillance in five U.S. locations. Screening history was abstracted from medical records, and classified as cytology+HPV, cytology only, HPV only, or unknown. We used the Cochran Armitage test to evaluate trends in screening tests among two screening-eligible age groups (21-29, 30-39 years), and Chi-square to examine HPV test utilization by cytology results.

Results

From 2008–2015, CIN2+ was identified in 16,041 women (n=9,487 21-29, n=6,554 30-39). The use of an HPV test, either as adjunct with cytology or as primary screen, increased from 36.2% in 2008 to 64.7% in 2015 (p<0.001, Figure); testing increased in both age groups (21-29: 31.9% to 54.3%, p<0.001; 30-39: 44.3% to 74.4%, p<0.001). In 2015, most screening was cytology+HPV (63.7%); use of HPV test alone was rare (1%). Adjunctive HPV testing varied by cytology results for both age groups (p<0.001, Table). For example, among 21-29 year-olds, 23.6% of LSIL and 91.5% of ASCUS cytology had an HPV test. Over half (n=2,248/3,874) of HPV tests in 21-29 year-olds were among cases with ASCUS.
Conclusions

Increasingly, the cervical cancer screening method leading to detection of CIN2+ includes HPV testing. Trends in screening, methods, and population screened, need to be considered when interpreting trends in CIN2+.
A STUDY OF HPV CERVICAL SCREENING IN HPV IMMUNISED WOMEN AS FIRST TEST (SHIFT)

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Background and Aims

Women who were offered HPV vaccine in the Scottish programme entered the national cervical screening programme from 2010. The provision of cervical screening needs to evolve to reflect the changes in the extent and nature of HPV infection and disease following immunisation. This study (SHIFT) is part of the programme of work that aims to inform our understanding of the performance of cytology and HPV testing to screen for cervical intraepithelial neoplasia (CIN) post-vaccination.

Methods

Co-testing of cytology and high-risk HPV (hrHPV) DNA testing was applied to women in the HPV immunisation catch-up cohort. Residual LBC reported as borderline/low-grade and 2 subsets of women with high grade or negative cytology were tested with a clinically validated HR-HPV test (the Hybrid Capture 2 test). Women with a positive HPV test were invited for colposcopy. Outcome data was collected from the national cervical screening (SCCRS) and colposcopy (NNCIAS) databases linked to HPV result and vaccine status.

Results

10,000 women had samples tested. The rates of hrHPV infection were 27% in cytology negative women and 86% with low grade. Most had normal colposcopy findings/HPV changes. Results from 4871 women who tested hr HPV+, including vaccination status, HPV DNA results, colposcopy findings, histology and treatments and subsequent cytology for women who decline to attend for colposcopy will be presented.

Conclusions
These results will provide information in terms of how cervical screening services are offered in the future and provide early insight into the impact of HPV immunisation on the performance of cervical screening and cervical cancer prevention.
A DEMONSTRATION STUDY OF POPULATION-BASED CERVICAL CANCER SCREENING FROM 2015 TO 2017 IN REAL-WORLD IN RURAL CHINA

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Background and Aims

To evaluate the efficacy of cervical cancer screening performed by local doctors in high-risk areas of China.

Methods

A population-based study was conducted in Shanxi Province from 2015 to 2017. 4526 eligible women aged 35-64 years were enrolled and divided into careHPV (1503) testing, visual inspection with acetic acid/Lugol's iodine (VIA/VILI, 1506) and cytology (1517) groups randomly and equally; women with positive careHPV results were randomly referred by VIA/VILI, cytology or directly colposcopy. Biopsy was performed if necessary. All women would be followed-up at the third year and screened by the three approaches simultaneously.

Results

At baseline, the positive rate of careHPV testing, VIA/VILI and cytology were 16.50%, 5.98% and 11.02% ($P<0.05$). 38 (0.84%) cervical precancer or worse (CIN2+) were detected. The positive predictive value (PPV) for these groups were 8.87%, 13.79% and 10.49%. 3,687 (81.46%) women were followed-up. Taking cumulative CIN2+ as the outcome, careHPV testing had a higher sensitivity and negative predictive value than VIA/VILI and cytology (75.56% vs. 50.00% vs. 56.67%; 96.93% vs. 95.48% vs. 95.81%). The specificity were 63.89%, 81.49%, and 69.72%. The PPV were 14.88%, 17.24% and 11.64%. Of the 55 new CIN2+ cases, 40.00%, 32.73% and 27.27% were in these groups at baseline, and 54.54% new CIN2+ cases were persistent infection in careHPV testing group, 21.43%, 28.57% and 50.00% new CIN2+ cases in careHPV testing with triage of VIA/VILI, cytology and colposcopy directly.

Conclusions

In low resource areas, the careHPV testing is feasible, and careHPV testing with VIA/VILI triage might be better when healthy providers are well-trained.
Background and Aims

The EU-TOPIA project aims to decrease the cervical cancer burden across Europe, by systematically monitoring and evaluating screening programmes in all European countries.

Methods

An indicator-set to collect information on screening practices and (short-term) effects of a screening programme was developed, partly based on the set used in the EU guidelines for quality assurance of cervical cancer screening. An online monitoring tool was developed to measure these indicators. To estimate the long-term effects of different screening protocols, an online version of the microsimulation model MISCAN was developed (i.e. the evaluation tool). This tool automatically uses data collected in the monitoring tool. Both tools were first tested in 4 exemplary countries, before they will be used by delegates of all European countries.

Results

We have collected data for 9 demographical/epidemiological and 12 screening indicators, for Slovenia, Italy, Finland and the Netherlands. Based on the data collected, we have developed 4 different regional MISCAN models that fitted the data well and are now incorporated in the evaluation tool. Currently, participants in all European countries are using the monitoring tool to collect data. In September 2018, delegates of all European countries will work with the evaluation tool to simulate the long-term impact of different screening programmes in their country.

Conclusions

We were able to develop two innovative tools that can be used to monitor and evaluate cervical cancer screening practices and effects in all European countries. This is a crucial step towards improved cervical cancer screening programmes in Europe.
Background and Aims

The vaccination of HPV naive women against HPV 6/11 protects sufficiently from genital warts and may even lead to protection of non-vaccinated men and women in the same population (herd protection). However, it is uncertain what level of vaccine coverage is required to achieve herd protection.

Methods

WOLVES (Wolfsburg HPV epidemiological study) invited all women born 1983/84, 1988/89 and 1993/94 with first residency in Wolfsburg to participate. All recruited women attended for annual visits with HC2-HPV testing and genotyping with SPF-10 PCR of all HPV positive and 10% of HC2 negative samples.

Results

2,477 women were included between Oct 2009 and Jan 2018. The HPV vaccination coverage rate rose from 6.1% to 18.4% among 26 years old women. The corresponding rates for 21 years old women increased from 23.7% to 48.7%. Simultaneously the life risk to suffer from at least one episode of genital warts before age 27 dropped from 4.7% to 2.5% and before age 22 from 1.8% to 0.4%. The near-disappearance of genital warts was underlined by a decline in the prevalence of HPV 6 from 2.1% to 0.2% among 26 years old women and from 2.0% to 0.0% among 21 years old women.

Conclusions

We observed the unexpected decline of genital warts and almost complete disappearance of HPV 6 in a population with low HPV vaccine coverage.
MAGNITUDE OF PRECANCEROUS CERVICAL LESIONS AND ITS ASSOCIATED FACTORS USING VISUAL INSPECTION WITH ACETIC ACID (VIA) AT A REFERRAL HOSPITAL IN ETHIOPIA

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Background and Aims

Ethiopia has over 29 million women aged 15 years and older who are at risk of cervical cancer. The aim of this study was to provide prevalence of precancerous cervical lesions and its associated factors among women visiting gynecology department of Felege Hiwot referral Hospital.

Methods

A cross sectional study was conducted from December 2016-June 2017 on 428 women. Relevant socio-demographic and data on visual inspection using 5% acetic acid (VIA) for abnormal cervical presentation were collected for analysis. The screening result was documented based on the national VIA screening record format; ‘No acithowhite lesion’, ‘Acithowhite lesion eligible for cryo’, ‘Acithowhite lesion non-eligible for cryo’ or ‘Suspicious for cancer’. Statistical significance was set at \( p \text{ value} < 0.05 \).

Results

Of the participants, 247 (57.7%) and 194 (45.3%) used long term contraceptive and were HIV positive, respectively. Majority, 242 (56.5%) were in the age group of 39-49 years with the median age at 35.0 years. The median age during first sex was at 16. On top of this, >half of the participants at 268 (62.6%) exercised multiple sexual partner. Majority, 367 (85.7%) were negative for precancerous lesions. The rest, at 61 (14.3%) had abnormal cervical lesion of which some 23% (14/61) were suspicious for cervical cancer. Among VIA positive participants, 46 were eligible for cryotherapy and got the treatment. The odds of having VIA positive result was lower by 24% among women engaged in private business than government employees [Adjusted OR: 0.24, 95%CI (0.07-0.85)].

Conclusions

The observed VIA screening result calls stakeholders to strengthen the primary cervical cancer prevention strategies in the studied area.
PUBLIC HEALTH / EPIDEMIOLOGY - SCREENING FOR HPV RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

HPV PRIMARY SCREENING: VIEWS FROM SCREENING AGED WOMEN IN AUSTRALIA

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Background and Aims

In December 2017, the Australian National Cervical Screening Program (NCSP) reduced screening from two yearly to five yearly, implemented primary human papillomavirus (HPV) screening and increased the start age from 18 years to 25 years. This study aimed to gain insight into women's attitudes towards these changes.

Methods

Six focus groups were conducted in November 2017 in the Sydney area, with 49 women aged 18-74. Focus groups were structured around a presentation of information about the changes to the NCSP, with discussions of the information facilitated throughout. The focus groups were analysed thematically.

Results

Only a third of women had heard something about the changes, mainly either the increased interval between tests or the increased starting age. Questions were raised about the test, with awareness of HPV evidently limited. Explaining clearly the difference between the two tests (Pap smear vs HPV test), and that the procedure is exactly the same for both tests, was important to women. Understanding of the new test was key to alleviate concerns about the extended screening interval. Communicating the rationale of the changes to women, in a clear and coherent way, was paramount for acceptance of the new program.

Conclusions

Communicating the rationale behind the implementation of a new test, the primary HPV test, needs to be clear and coherent to limit negative concerns from the public. The findings of this study contribute to an understanding of what information women seek about changes to the Australian NCSP, in particular the primary HPV test.
HIGH PREVALENCE OF ANAL HUMAN PAPILLOMAVIRUS INFECTION AMONG HIV INFECTED AND HIV UNINFECTED MEN WHO HAVE SEX WITH MEN. FINDINGS FROM URBAN KARACHI PAKISTAN

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Background and Aims

Anal HPV infection is very common worldwide among men who have sex with men (MSM) in general and HIV+ MSM in particular. Given the high prevalence of HIV among MSM in Pakistan, it is imperative to know the disease burden. Therefore, the aim of the study was to determine prevalence, types and associated risk factors of HPV among HIV+ and HIV- MSM in Karachi Pakistan.

Methods

A cross-sectional study from March 2016 to November 2017 was conducted in Karachi Pakistan. Study participants were recruited from ART center of National AIDS Control program and a local NGO. Anal swabs were collected for HPV DNA detection and typing.

Results

A total of 320 MSM were recruited and lab data were available for 298 MSM (HIV+ n=131; HIV- n=167). Overall HPV DNA prevalence was 65.1% and was higher in HIV+ MSM than HIV- MSM (87% versus 48%). The most frequently HR-HPV types identified were HPV6/11 (46.9%), HPV16 (35.1%), HPV18 (23.2%), HPV35 (21.1%). HIV+ MSM identified with HPV type 16 and HIV- MSM with HPV types 6/11. A strong dose-response relationship was found between HIV seropositivity and multiplicity of HPV types (p<0.001). HIV status (PR: 1.81 95% CI 1.16-2.82) never condom use (PR: 2.31 95% CI 1.03-5.20) were independently associated with prevalence of any anal HPV infection.

Conclusions

High prevalence of HPV indicates future risk of anal cancer in MSM in general and HIV infected MSM in particular. Current findings support HPV vaccination efforts to this vulnerable high-risk population.
Background and Aims

In sexually active men who have sex with men (MSM) the incidence of HPV related anal cancer and its intraepithelial neoplasia is increasing in recent decades. HPV induced dysplastic changes in the anal epithelium can be identified through anal pap smear and subsequent cytological analysis. The aim was to evaluate the prevalence and epidemiological associates of anal cytological abnormalities among HIV+ and HIV- MSM.

Methods

A cross-sectional study from March 2016 to November 2017 was conducted among MSM ≥18 years having had anal sex in the last preceding at least 6 months. Recruitment was done from Sexual Health Clinic and ART center run by National AIDS Control Program. Anal sample were collected for both cytology and HPV testing.

Results

Mean age of 298 recruited MSM was 28 years. Overall 65% of MSM had HPV DNA detected, 35% of them had any anal abnormal cytology with LSIL the most prevalent (24.5%), followed by ASCUS (6.7%). HIV infected MSM were significantly more infected with HPV, having detected more oncogenic and multiple types and bore more proportion of any anal abnormal cytology. Any oncogenic HPV type (PR 3.04; 95% CI 1.75-5.26), concurrent STI (PR; 2.13, 95% CI 1.28–3.55).and HIV+/HPV+ coinfection (PR 1.75; 95% CI 1.07-2.88) appeared as independent factors for the prevalence of anal abnormal cytology.

Conclusions

One third of the recruited MSM showed presence of any abnormal cytology and their strong association with any oncogenic type in general and HPV 16 in particular. These findings support the introduction of vaccination program for this high-risk group.
IPVC8-0330
POSTER SESSION

PUBLIC HEALTH / EPIDEMIOLOGY - SCREENING FOR HPV RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

PREDICTIVE VALUE OF HPV SELF-SAMPLING COMPARED TO CLINICIAN HPV SAMPLING AND CYTOLOGY IN DETECTING HIGH-GRADE CERVICAL LESIONS

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Background and Aims

Self-sampling has become an attractive proposition now that HPV primary testing is being incorporated into cervical cancer screening programs worldwide. We compared predictive values of HPV testing based on self- and physician-collected samples, and cytology, in detecting high-grade cervical intraepithelial neoplasia (CIN).

Methods

The Cervical And Self-Sample In Screening (CASSIS) study enrolled 1217 women aged 16-70 years prior to scheduled colposcopies in three university clinics. Vaginal specimens were self-collected using the validated HerSwab™ device. Cervical specimens were collected by gynecologists. Specimens were transferred to PreservCyt solution and tested for presence of high-risk (HR) HPV (cobas® 4800 HPV Test). Conventional cytology and biopsies were taken if indicated by colposcopy. We estimated positive and negative predictive values (PPV,NPV) and 95% confidence intervals (in parentheses below) for a subset of women (n=700) who underwent cervical biopsy and cytology at CASSIS visit.

Results

Among the 700 women, HR-HPV was detected in 329 women (47.0%) with HerSwab™ and in 327(46.7%) with physician sampling. Respective values for HPV16/18 were 119(17.0%) and 121(17.3%). On histology, 134 women had CIN1, 49 CIN2, 48 CIN3, 5 CIN2/CIN3 and 3 cancers. PPVs for CIN2+ of any HR-HPV were 28.0%(23.2-33.1) and 29.7%(24.8-34.9) for HerSwab™ and physician-samples, respectively. Corresponding values for HPV16/18 were 43.7%(34.6-53.1) and 43.8%(34.8-53.1). PPV of ASC-US+ cytology was 26.6%(21.6-32.0). NPVs (same order as above) were: 96.4(93.9-98.1), 97.8(95.6-99.0), 90.9%(88.2-93.1), 91.0%(88.4-93.2) and 94.7%(91.8-96.8).

No difference was observed by age group.

Conclusions
Our results confirm that HPV self-sampling has comparable performance to a physician-collected sample in detecting cervical lesions, and may ultimately increase screening coverage.
To determine if the detection of histologically confirmed cases of cervical intraepithelial neoplasia or worse (CIN2+) can be increased by having each liquid-based cytology (LBC) slide read by two cytologists.

Methods

Over 36,212 women aged 30 to 64 years participated in the FRIDA study in Tlaxcala, Mexico, between 2013 and 2016. For each participant, two cervical samples were collected at the same clinic visit to test for high-risk human papillomavirus (hrHPV), and LBC to triage the women with a positive hrHPV result. LBC slides were distributed among seven cytologists, with each slide read independently by two blinded cytologists. All women with ASCUS+ results were sent to colposcopy for further evaluation and diagnosis. A panel of three pathologists evaluated the biopsy specimens to confirm the final CIN2+ diagnosis. The CIN2+ detection rate for single reading versus double reading were estimated and compared.

Results

A total of 3,896 women with a positive hrHPV test result were followed up with LBC. The first and second cytology readings resulted in 40 and 42 CIN2+ cases detected, respectively, with an average of 41 CIN2+ cases identified by each single cytology reading. The double reading strategy detected an
additional 8 CIN2+ cases, resulting in a total of 49 CIN2+ cases. The CIN2+ detection rate increased from 10.52% with a single reading to 12.58% with a double reading (p-value = 0.005).

Conclusions

An 19.5% increase in CIN+ cases detected was achieved with a double reading of the LBC slides in this sample of hrHPV positive women.
SCREENING OF CERVICAL PRECURSOR LESIONS USING HPV AND PAPANICOLAOU TEST.
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Background and Aims

The main objective was the comparison between HPV and Papanicolaou tests in the detection of cervical precursor lesions and patient’s referral to colposcopy as a pilot study for its implementation at the National Cervical Cancer Prevention Program.

Methods

Recruitment involved asymptomatic, not hysterectomized, non pregnant and without a history of cervical cancer females, between 30 and 64 years old, from Centro de Salud de la Costa and Pando (ASSE). Simultaneous screening using HC2 HPV Hybrid Capture test (Qiagen) and conventional Papanicolaou test was performed from 1st Jan 2015 to 31st Aug 2017. The follow-up was considered until 31st Dec 2017.

Results

Of the 1010 women enrolled, 123 (12.8%) were HPV positive and 167 (16.53%) had abnormal PAP test. Both groups of women presenting HPV positive tests and/or abnormal PAP test results were referred to colposcopy. 13 women with high-grade intraepithelial lesions (4 CIN 2 and 9 CIN 3) were diagnosed by colposcopy-guided biopsy. HPV test was positive in all cases (100%) while cytology was positive in 6 cases (46%) being 1 of 4 CIN 2 and 5 of 9 CIN 3 detected by this later method.

Conclusions

The HPV test was more effective than conventional Papanicoalou Test for the diagnosis of precursor lesions of cervical cancer and more efficient because it needed less diagnostic colposcopies to detect more cervical lesions.
WILLINGNESS TO UNDERGO AND BELIEFS REGARDING ANAL CANCER SCREENING AMONG MEN LIVING WITH HIV RECEIVING HIV SPECIALTY CARE IN ONTARIO, CANADA

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Background and Aims

Despite anal cancer rates up to 100-fold higher in HIV-positive men than the general population, the most acceptable approach to anal cancer screening is unknown. Our objective is to assess HIV-positive men's willingness to undergo anal cancer screening.

Methods

A quantitative questionnaire, developed using Theory of Planned Behaviour, examining knowledge and beliefs regarding HPV-associated diseases and prevention was administered between 04/2016-06/2017 to men in the Ontario HIV Treatment Network Cohort Study attending HIV clinics. We used logistic regression to assess factors associated with men's willingness to undergo screening. Results reported as adjusted odds ratios(aOR) with 95% confidence intervals(CI).

Results

1688 men completed the questionnaire; 69% had experience with digital rectal exams(DRE), 36% with anal Pap, 23% with anoscopy. Majority would be likely/very likely to undergo anal cancer screening via DRE (89%), anal Pap (90%) or anoscopy (83%). The following were associated with increased odds of being likely/very likely to undergo anal cancer screening: knowing someone with HPV-associated cancer (aOR=2.11;CI=1.07,4.15); previous diagnosis of genital warts/HPV/anal pre-cancer (aOR=1.53;CI=1.02,2.30); experience with DRE (aOR=1.82;CI=1.28,2.58); comfort discussing anal health with doctor (aOR=2.32;CI=1.58,3.41); confident one would be offered treatment (aOR=2.48;CI=1.51,4.06); and identifying as gay (aOR=2.11; CI=1.43,3.11). Age, race and HPV awareness were not associated with willingness.

Conclusions

Although men's stated willingness was high, particularly among those with personal experience with HPV-associated disease and prevention, comfort discussing anal health and confidence in treatment, actual acceptance of invitation into a Canadian anal cancer screening study, recruited from HIV clinics, has been quite low (approximately 25%). We continue to investigate such discrepancies.
EXAMINING HIV-POSITIVE MEN’S PERSONAL AND PAST EXPERIENCE WITH HPV-ASSOCIATED DISEASE AND ANAL CANCER SCREENING AMONG MEN ATTENDING HIV SPECIALTY CLINICS IN ONTARIO, CANADA

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Background and Aims

Men living with HIV are at increased risk for HPV-associated anal cancer with incidence rates estimated at 46-131 per 100,000 person-years. Our objective was to establish rates and correlates of anal cancer screening among men living with HIV.

Methods

A questionnaire assessing knowledge, attitudes, and experience with HPV-associated diseases and their prevention was administered in 2016-17 to 1,688 men in the Ontario HIV Treatment Network Cohort Study, a multi-site clinical HIV cohort. We used logistic regression to identify factors associated with men’s past experience with anal cancer screening (anal cytology and/or anoscopy). Results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI).

Results

Overall, 69% of men reported past experience with digital anorectal exams, 35% with anal cytology, and 23% with anoscopy. 12% reported knowing someone who had been diagnosed with an HPV-associated cancer. Older age, identifying as gay or bisexual, previous diagnosis with an AIDS-defining illness, comfort discussing anal health with their doctor, and knowing someone with HPV-associated cancer were positively correlated with self-reported past screening for anal cancer (Table 1). 14% of men reported being told that they had HPV, 28% reported a history of genital/anal warts and 7% a history of anal pre-cancer.
Conclusions

In this cohort of men engaged in HIV specialty care, 40% had undergone anal cancer screening (cytology and/or anoscopy). These results advance our understanding of screening among men at highest risk for anal cancer and may help inform future screening programs, as currently no formal screening programs exist in Ontario, Canada.
Background and Aims

In response to emergent evidence, many countries are transitioning from cytology-based to HPV screening. We evaluated the impact of a 2019 transition on health outcomes and resource utilisation in New Zealand.

Methods

An extensively validated model of HPV transmission, vaccination, natural history and cervical screening ('Policy1-Cervix') was utilised to simulate a transition from three-yearly cytology for women 20-69 years to five-yearly HPV screening with 16/18 genotyping for women 25-69 years, accounting for HPV immunisation in New Zealand. Cervical disease rates, resource-use volumes, test positivity rates and costs from 2015-2035 were estimated, accounting for population change.

Results

By 2035, cervical cancer incidence and mortality rates are predicted to decline by 32% and 25%, respectively, compared to 2018. A 5% apparent increase in cervical cancer due to earlier detection is predicted for the year of transition. Annual numbers of women screened will reduce following transition, fluctuating with the five-year screening interval; volumes of follow-up procedures are not expected to be substantially altered. Primary HPV test positivity rates are expected to be ~9% during the first round of HPV screening (2019-2023), and 2.7% of women referred for colposcopy based on their primary or triage test.

Conclusions

Primary HPV screening and vaccination will reduce disease, resource-use, and program costs. A small transient increase of invasive cancer rates due to earlier detection may be detectable at the population level after transitioning, reflecting the introduction of a more sensitive screening test. These findings can be used to inform health services planning and public communications surrounding program implementation.
Background and Aims

While cytology-based screening programs have significantly reduced mortality and morbidity from cervical cancer, the global consensus is that primary human papillomavirus (HPV) testing for cervical screening increases detection of high-grade cervical intraepithelial neoplasia (CIN) and invasive cancer. However, the optimal triage strategy for HPV-positive women to avoid over-referral to colposcopy may be setting specific. Since Japan requires data that has been generated domestically to modify screening guidelines, we conducted a 3-year prospective study COMparison of HPV genotyping And Cytology Triage (COMPACT) to evaluate the potential role of HPV16/18 partial genotyping and cytology for primary HPV screening.

Methods

Totally, 14,642 women aged 20-69yrs undergoing routine screening at three centers in Hokkaido were enrolled. Conventional cytology and HPV testing (Cobas 4800, Roche®) were performed. Women with abnormal cytology or HPV16/18 positive underwent colposcopy. Those with 12 other high-risk (hr) HPV types underwent repeat cytology after 6 months. Primary study endpoints were detection of high-grade cervical disease defined as CIN2/CIN3 or greater as determined by consensus pathology.

Results

Prevalence of cytologic abnormalities was 2.4%. hrHPV, HPV 16, and HPV 18 were detected in 4.6%, 0.9%, and 0.3% of women, respectively. HPV16/18 were detected in all (8/8) invasive cervical cancers and all (2/2) adenocarcinomas in situ. Both cytologic abnormalities and hrHPV positivity declined with increasing age.

Conclusions
This is the first Japanese study to investigate the role of partial genotyping and cytology in an HPV based screening program. Results should help policy-makers develop guidelines for future cervical screening programs and management of cervical abnormalities based on HPV genotype.
Background and Aims

Increased efficacy at detecting high-grade cervical intraepithelial neoplasia or worse (≥CIN3) has prompted many countries to consider shifting to a human papillomavirus (HPV) primary screening programme. However, effective triage to ensure women are not subjected to unnecessary follow-up is critical. HPV screening that distinguishes HPV16/18 from other high-risk (hr) HPV types may identify women at greatest risk of ≥CIN3 and permit less aggressive management of women with other hrHPV infections. We compared baseline and relative risk of ≥CIN2/3 within 12m of a negative cytologic result in women HPV16/18+ compared to those with one or more of 12 other pooled hrHPV genotypes.

Methods

Participants were 14,160 women aged 25-69yrs with negative cytology participating in the 3-year prospective COMparison of HPV genotyping And Cytology Triage (COMPACT) study. Women who were HPV16/18+ were referred to colposcopy. Those with a 12 other hrHPV type underwent repeat cytology after 6m and those with ≥ASC-US went to colposcopy.

Results

Baseline risk of ≥CIN2 in HPV16/18+ women was 19.5% (95%CI:12.4%-29.4%). In women 25-29yrs and HPV16+ it was 40.0% (95%CI:11.8%-76.9%). Baseline risk of ≥CIN3 in women HPV16/18+ was 11.0% (95%CI:5.9%-19.6%). For women 30-39yrs and HPV16+ it was 23.1% (95%CI:5.0%-53.8%). Overall risk of ≥CIN2, ≥CIN3 in women with a 12 other hrHPV type was 5.6 (95%CI:3.1%-9.7%) and 3.4% (95%CI:1.6%-7.2%) respectively. Relative risk of ≥CIN2, ≥CIN3 in HPV16/18+ vs. 12 other hrHPV was 3.5 (95%CI:1.7-7.3, p<0.01) and 3.3 (95%CI:1.2-8.8, p<0.02), respectively.

Conclusions

HPV screening with HPV16/18 partial genotyping might be an effective strategy to identify women at high current or future risk of ≥CIN3 in Japan.
DETECTION OF HIGH- RISK HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL SCRAPES FROM TRIBAL POPULATION
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Background and Aims

India with geographically diverse populations and cultural practices demonstrates an extremely variable prevalence of HPV infection in different regions. Despite variation in prevalence of HPV infection, two major high risk HPVs, HPV16 and HPV18 is the highest in cervical cancers of India ranges upto 98%. Nothing is known about the prevalence of HPV infection in the Andaman and Nicobar population, which is geographically isolated and completely different lifestyle. To determine the prevalence of HPV infection in the tribal population of A&N and to find out the most dominant HPV types present in this population.

Methods

A total of 50 cervical scrapes were collected, DNA extracted and analyzed for HPV infection by HPVL1 and type-specific PCRs.

Results

Out of 50 cervical scrapes tested, 3 (6.0%) cases were found positive for L1 consensus sequences in preliminary screening. Analysis of these samples by HPV16/18 type-specific PCR revealed a positivity of HPV16 in all the 3 cases and co-infection of HPV16 and HPV18 was detected in one case. Adequacy of the samples and the quality of the assay was controlled by PCR for b-globin gene which was used as an internal control. Study shows an overall 6% prevalence of HPV in A&N population and HPV16 was found to be the leading HR-HPV types.

Conclusions

Though the data is based on a small sample size which is being improved further, it the maiden report indicating a moderate HPV prevalence and a similar HPV type distribution in this geographically and culturally distinct population as in main land of India.
COMPARING STRATEGIES FOR CERVICAL CANCER SCREENING USING HPV ASSAYS IN AUSTRALIA: A HEALTH ECONOMIC ANALYSIS

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Background and Aims

Cervical cancer screening programs continue to evolve the use of HPV testing as the primary screening method and there is now the potential to add extended genotyping (XGT) with the aim of improving detection while avoiding over treatment. To help with decision making this model based analysis aims to estimate the relative clinical impact of these different strategies.

Methods

An excel based health economic model was developed using disease and genotype specific prevalence information from Australia. The model estimates the clinical outcomes of using three primary screening methods, cytology, HPV primary XGT and the new Australian National Cervical Screening Program (The Program). Endpoints include number of cancer and CIN detected and number of referrals for colposcopy.

Results

Preliminary results indicate that primary screening with HPV XGT and The Program detect similar amounts of CIN 2 and substantially more disease than primary screening with cytology. Compared with cytology, The Program and HPV XGT were both found to lead to a substantial increase in the numbers of referrals for colposcopy, but there could be an over 10% reduction in referrals with HPV XGT compared with The Program.

Conclusions

The adoption of The Program is a substantial improvement on cytology for detecting disease when screening for cervical cancer. HPV XGT provides additional information that could be used to modify the screening algorithm and partially mitigate the increase in colposcopy referrals that could be associated with the Program while achieving similar levels of disease detection.
HIV-INFECTED WOMEN TREATED FOR CERVICAL INTRA-EPITHELIAL NEOPLASIA (CIN): FOLLOW-UP DISEASE OUTCOME FROM A STUDY FROM MAHARASHTRA, INDIA

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Background and Aims

Women treated for CIN remain at an elevated risk of recurrent CIN or cervical cancer and need long-term follow-up. We report the follow-up disease status among HIV-infected women treated for CIN.

Methods

HIV-infected women treated for any CIN were called for the initial follow-up visit at 6-12 weeks, at month 6 and then every year. Women with any grade of CIN have been followed up to a maximum of 6.4 years. At the follow-up visits, women were screened with VIA and all women underwent colposcopy, cervix biopsy if required. Treatment was offered by thermo-coagulation (aka cold coagulation) following colposcopy and biopsy but prior to the histopathologic confirmation if the lesion was eligible for the ablative treatment or else by LEEP at a later date.

Results

Of the 101 HIV-infected women treated for any CIN, 77 (76.2%) have been followed. Of the 37/45 women treated for CIN 1, complete regression was seen in 30 (81.1%) women, 5 (13.5%) had persistent disease and 2 (5.4%) progressed to a higher grade. Of the 40/56 (71.4%) women treated for CIN 2/3 disease, 25 (62.5%) completely regressed, 6 (15.0%) partially regressed (to a lower grade), 6 (15.0%) persisted and 3 (7.5%) progressed.

Conclusions

There is limited knowledge about the long-term outcome of treatment of CIN in HIV-infected women. Although persistence and progression were seen, complete regression was observed in more than 60% of the HIV-infected women with high-grade CIN treated in a screen and see and treat programme.
Performance of vaginal self-sampling for HPV testing among women living with HIV in Botswana

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Background and Aims

We conducted the first assessment of self-collected vaginal samples compared to provider-collected cervical samples in Botswana, and report the prevalence of hr-HPV in an HIV-positive population.

Methods

We recruited women ≥25 years attending an HIV clinic in Gaborone. Participants self-sampled using flocked swabs and also had a provider-collected cervical sample for comparison. All samples were tested within 24 hours using the Cepheid GeneXpert HPV assay. Women with any hr-HPV returned to the clinic for colposcopy. Unweighted κ statistics were used to determine agreement.

Results

A total of 103 eligible women were recruited with a median age of 44 (IQR: 40-51). All participants were on ART with a median CD4 count of 651 (IQR: 451-893), and 97 (94.2%) reported previous cervical screening. Thirty-one (30.1%) women tested positive for any hr-HPV (Table 1), and of these 10 tested positive for more than one genotype. The most common genotypes were HPV 31/35/52/58 (self 16.5%; provider 13.6%). Overall agreement for detection of hr-HPV between self and provider samples was 91% with a κ of 0.79. Excluding three inadequate self-samples, agreement of paired
samples was 94% with a κ of 0.84.

### Table 1. Characteristics of women attending HIV clinic by HPV result

<table>
<thead>
<tr>
<th></th>
<th>Positive for any hr-HPV (%)</th>
<th>Negative for any hr-HPV (%)</th>
<th>Total (n, %)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td><strong>Socio-demographic characteristics</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Age, median (IQR)</td>
<td>44 (37.48)</td>
<td>44 (40.53)</td>
<td>44 (40.51)</td>
<td>0.24</td>
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<tr>
<td>Single, never married</td>
<td>24 (77.4)</td>
<td>49 (68.1)</td>
<td>73 (70.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Rural residence</td>
<td>17 (54.8)</td>
<td>28 (38.9)</td>
<td>45 (43.7)</td>
<td>0.13</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td>0.41</td>
</tr>
<tr>
<td>None/Primary</td>
<td>9 (29.0)</td>
<td>27 (37.5)</td>
<td>36 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Secondary/Tertiary</td>
<td>22 (71.0)</td>
<td>45 (62.5)</td>
<td>67 (65.1)</td>
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</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Professional/skilled/service/clerical</td>
<td>11 (35.4)</td>
<td>23 (31.9)</td>
<td>34 (33.0)</td>
<td></td>
</tr>
<tr>
<td>Manual/unskilled/self-employed</td>
<td>8 (25.8)</td>
<td>27 (37.5)</td>
<td>35 (34.0)</td>
<td></td>
</tr>
<tr>
<td>Not working/student</td>
<td>12 (35.3)</td>
<td>22 (64.7)</td>
<td>34 (33.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical and behavioral risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 count, median (IQR)</td>
<td>659 (416-909)</td>
<td>638 (454-881)</td>
<td>651 (451-893)</td>
<td>0.72</td>
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<tr>
<td>Duration of ART use (yrs), median (IQR)</td>
<td>12 (7-13)</td>
<td>12 (11-14)</td>
<td>12 (9-14)</td>
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<tr>
<td>Age at sexual debut</td>
<td>18 (17-20)</td>
<td>19 (17-20)</td>
<td>18 (17-20)</td>
<td>0.55</td>
</tr>
<tr>
<td>Lifetime sexual partners, median (IQR)</td>
<td>5 (4-10)</td>
<td>4.5 (3-8)</td>
<td>5 (3-8)</td>
<td>0.07</td>
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<tr>
<td>Concurrent sexual partners</td>
<td>4 (12.9)</td>
<td>2 (2.8)</td>
<td>6 (5.8)</td>
<td>0.04</td>
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<tr>
<td>Prior screening history</td>
<td>28 (90.3)</td>
<td>69 (95.8)</td>
<td>97 (94.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Previous abnormal smear</td>
<td>3 (9.7)</td>
<td>7 (9.7)</td>
<td>10 (9.7)</td>
<td>0.99</td>
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</table>

Notes: hr-HPV, high-risk human papillomavirus; IQR, interquartile range; ART, antiretroviral therapy

### Conclusions

In this well-managed HIV-positive population, hr-HPV prevalence was 30%, and detection was comparable between self and provider samples. Despite a few inadequate samples, self-sampling is a feasible and accurate alternative to provider screening in Botswana.
An organised cervical cancer screening (CCS) program in Germany and co-testing with cytology and HPV test is planned. We aim to determine the stand-alone and combined screening accuracy of cytology and HPV-DNA testing within a population-based cohort study in the German opportunistic screening system.

Methods

A randomised prospective cohort study on CCS was conducted between 2005-2012 in Mainz, Germany (MARZY). Women aged 30-65 years (n=7,758) were invited by post to undergo routine Pap smear, liquid-based cytology (LBC, ThinPrep) and HPV-DNA test (Hybrid Capture 2, HC2) and approximately 3 years later. All test positive (≥ASC-US or equivalent / HPV high-risk type positive) and 5% of test negative women were invited to colposcopy. Biopsies were taken for histological verification. Key values of stand-alone and co-testing include sensitivity, specificity, negative predictive value, positive predictive value and detection rate.

Results

At baseline, 5,275 women were eligible for CCS and 2,627 underwent screening. 228 women tested positive and 620 women in total were invited to expert colposcopy, of which 194 histologically confirmed results were derived. The mean time from screening to colposcopy was 4.9 months (SD ±4.9). Preliminary analyses highlight lower sensitivity but higher specificity of cytology stand-alone (≥CIN2) and higher specificity of HC2 stand-alone compared to cytology. Co-testing with LBC also revealed greater specificity than co-testing with Pap.

Conclusions

Results of this study can help guide implementation of the organised screening program, highlighting the benefit of co-testing with LBC in detecting cervical dysplasia.
RISK STRATIFICATION OF TYPE-SPECIFIC HUMAN PAPILLOMAVIRUS FOR CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2/3 AND INVASIVE CERVICAL CANCER: EVIDENCE FROM A CROSS-SECTIONAL STUDY IN SHENZHEN

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²Shenzhen Maternity and Child Healthcare Hospital, Department of Health Care, Shenzhen, China

Background and Aims

To analyze the epidemiological genotype features of human papillomavirus (HPV) in cervical infection and their risks for cervical intraepithelial neoplasia grade 2/3 and invasive cervical cancer (CIN2+) among urban women.

Methods

A total of 2717 individuals ranging in age from 30~59 years were recruited in 18 community health centers of Shenzhen city by a cluster sampling method. Clinical sensitivity and specificity as well as positive (PPV) and negative (NPV) predictive values for CIN2+ were estimated.

Results

The HPV infection rate in Shenzhen area was 15.9% (432/2717). The 5 most common HPV genotypes were HPV52 (22.9%), followed by HPV16 (12.7%), HPV53 (10.0%), HPV51 (8.6%), and HPV58 (8.1%). According to PPV for CIN2+ in a decreasing order, high-risk HPV genotypes were divided into four groups, which were group A (HPV33/16), group B (HPV58/56/68), group C (HPV18/52/39) and group D (HPV35/31/59/51/53/66/45). Compared to HPV16/18 genotyping, group A HPV genotyping had a higher sensitivity (57.14% vs. 42.86%, \(P<0.05\)) and an acceptable specificity (87.27% vs. 86.89%, \(P>0.05\)). Compared to only liquid based cytology testing (LBC, ASCUS+), LBC LSIL+ combined with group A HPV genotyping had a higher sensitivity (75.00% vs. 64.29%, \(P<0.05\)) and an acceptable specificity 83.46% vs. 89.23%, \(P>0.05\), demonstrating a good clinical performance for cervical screening among urban females.

Conclusions

In the present study, the top five risks for CIN2+ of HPV genotypes were HPV33, 16, 58, 56, and 68. Triaging HPV-positive women by LBC LSIL+ combined with HPV33/16 genotyping may be a potential strategy for cervical cancer screening in Shenzhen area.
Background and Aims

Māori (Indigenous) women experience substantially higher rates of cervical cancer than New Zealand European women. Cervical screening rates are significantly lower for Māori. He Tapu Te Whare Tangata RCT study is testing whether offer of a self taken vaginal swab for HPV increases cervical screening in under-screened Māori women. The aim of this presentation is to identify issues around engaging community and primary care to lead this research in semi-rural New Zealand – Te Tai Tokerau.

Methods

A team of researchers, clinicians and Māori advisors was assembled. Face to face meetings were held with community members, Kaumātua (elders) and primary care clinicians to garner interest. Contact was also started with the district hospital colposcopy team. Suggestions from these groups were incorporated into design of the study. Following consultation, 6 primary health clinics were randomised (3 per arm): control arm – standard offer of smear; intervention arm – offer of HPV self-test. A community based research nurse acts as a clinician champion liaising with clinics and research team. Women with hrHPV positive results are supported to attend colposcopy.

Results

Clinicians and community members were enthusiastic about the study and although engagement took over a year, it enabled us, once funding was secured, to move forward in a timely way. Thus, we obtained consent from well informed clinics to enroll in this RCT. Recruitment of women commenced in March 2018.

Conclusions

We will present the challenges of working with community to design and implement an RCT including: consultation, ethics, managing expectations, unforeseen problems, and solutions.
Background and Aims

There is limited empirical evidence to inform the age at which to stop cervical cancer screening. We used a Markov model of cervical cancer screening to estimate remaining lifetime risks at different ages.

Methods

We calibrated our model to Canadian cervical cancer incidence data and simulated the impact of stopping screening at different ages. We estimated remaining lifetime risks of cervical cancer diagnosis for women who stop screening at different ages with different screening tests, excluding women who have undergone hysterectomies.

Results

The model predicted that regular cytology screening between the ages of 25-69 reduces the lifetime risk of cervical cancer from 1/45 women without screening to 1/532 women. Most of this reduction came from screening below the age of 55, but delaying the age at which women stop screening in 5-year increments still led to incremental decreases in cancer risk later in life. A 70-year old woman whose screening history is unknown had an average remaining lifetime risk of 1/588 if she stopped screening. Her remaining lifetime risk at age 70 was reduced to 1/1206 (2.0 times lower) if she had a negative cytology test, 1/6525 (12.9 times lower) if she had a negative HPV test, and 1/9550 (18.1 times lower) if she had a negative co-test.

Conclusions

Current Canadian recommendations to screen until age 65-69 are supported by model projections. If a woman’s screening history is unknown, an exit HPV test may provide reassurance of a low remaining lifetime cervical cancer risk.
Every year there are approximately 16,000 new cases of cervical cancer in Brazil. New technologies may lead to a reduction of this number by allowing an expansion of the screening covered population but also by improving the detection rate of precursor lesions.

Methods

Women participating in a routine CC primary screening program were invited to enroll in this study. An LBC sample was collected in SurePath medium and transported to Fundação Oncocentro where BD Totalys prepared, in parallel, slides for cytology and an aliquot for the BD Onclarity™ HPV Assay. A positive high-risk HPV test and/or cytology class ASC-US + referred the patient to colposcopy and biopsy, if necessary.

Results

Between December 2014 and March 2016, 15,991 women enrolled. HPV DNA testing showed 2,398 (15%) positive samples, twice than more cytology (7.2%). HPV testing identified two squamous carcinomas, in addition to 88% of the 87 HSIL cytologies. Per protocol, 2,309 (14.4%) were referred to colposcopy and 1,287 (55.7%) submitted to the procedure. Of these, 334 women were biopsied, revealing 72 CIN2+ and 13 CIN3+ cases. HRHPVs were detected in 98.6% (71/72) of CIN2+ and 100% of CIN3+. Cytology called 18/72 CIN2+ and 2/13 CIN3+ negative. Among CIN3+ cases, HPV 16 was the most frequent type, found in 53.8%.
Conclusions

The higher case detection of HPV testing vs. cytology suggests improved CIN rate may allow a thorough evaluation of the assays and management strategies, hopefully improving the rate of detection of precursor lesions (CIN2+) and sparing resources. **Support**: BD, USA; CNPq 573799/2008-3, FAPESP 2008/57889-1.
FOCALPOINT COMPUTER-ASSISTED PAP TEST SCREENING IN A PUBLIC HEALTH SERVICE

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¹⁰Fundação Oncocentro de São Paulo, Director President, São Paulo, Brazil

Background and Aims

In the last decade, new and more effective technologies for cervical cancer control are now available; liquid-based cytology (LBC) was designed to reduce the overlapping of cells and automated systems facilitate the detection of abnormalities during manual reading, thus reducing false-negative results. The use of computer-assisted technology for Pap test reading was evaluated in a public health service.

Methods

We prospectively processed and read 15,991 LBC samples from women examined at Fundação Oncocentro de São Paulo. The cervical samples were preserved in BD-SurePath liquid medium and prepared using BD Totallys equipment. Slides were first read by the FocalPoint system (BD, Burlington, USA) that identified the 10 most concerning locations per slide and assigned slides to a risk quintile. Well-trained cytotechnologists and cytopathologists read slides with attention to fields.

Results

Manual slide reading with FocalPoint read 119 (0.7%) ASC-H, 392 (2.5%) LSIL, 87 (0.5%) HSIL and 2 (0.00%) invasive squamous cell carcinoma. FocalPoint’s quintile classified the two invasive cancers in Q1 and almost 90% of HSILs and 82% of ASC-Hs in Q1 and Q2. Negative Pap test results were similarly distributed among all quintiles. FocalPoint analysis was not possible in 1,247 (7.8%) of slides, mainly due to broken coverslips, cracked, obscured or bubbled.

Conclusions
Our findings demonstrate that the FocalPoint system successfully classified high grade Pap results into the two top quintiles, which suggests computer-assisted Pap reading in daily routine, may safely increase productivity avoiding false negative results. Attention is required to limit challenges when preparing slides. **Support:** BD USA; CNPq 573799/2008-3, FAPESP 2008/57889-1.
Background and Aims

High-risk human papillomavirus (hrHPV) is the primary cause of cervical cancer. We systematically reviewed the literature on screening with hrHPV testing (alone or cotesting) compared to cytology alone.

Methods


Results

8 RCTs (n=410,556), 5 cohorts (n=402,615), and 1 individual participant data (IPD) meta-analysis (n=176,464) were included. Trials were heterogeneous for screening intervals, follow-up protocols for abnormal results, number of screening rounds, and second round screening strategy. Evidence was consistent that hrHPV testing alone in Round 1 screening increased detection of CIN3+ compared to cytology alone; relative risk (RR) range 1.61 (95% CI, 1.09-2.27) to 7.46 (95% CI, 1.02-54.66) (4 trials). Co-testing trials did not demonstrate significantly higher CIN3+ detection in Round 1. No trial sustained intervention and control group protocols beyond two screening rounds. In the IPD meta-analysis, ICC incidence was lower with HPV testing. False positive and colposcopy rates were 2-3 times higher for hrHPV testing. Limited evidence suggested that positive hrHPV screening was associated with more anxiety and sexual concerns compared to abnormal cytology.

Conclusions

4 RCTs suggested hrHPV screening alone results in higher CIN3+ detection at initial screening, but also leads to more false-positives and followup testing compared to cytology. Research is needed on outcomes over multiple screening rounds, longer hrHPV screening intervals, and interventions to reach under-screened women.
CONCORDANCE OF CERVICAL CYTOLOGY (PAP SMEAR) WITH HISTOPATHOLOGY IN HIGH-RISK WOMEN FROM THE WESTERN CAPE, SOUTH AFRICA

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Background and Aims

This study estimates the concordance of cytology, specifically low-grade and high-grade intraepithelial lesions (LSIL & HSIL) with corresponding histopathology of CIN1 and CIN2+ among high-risk, HIV-infected and -uninfected South African women receiving care at a colposcopy clinic in Cape Town, South Africa.

Methods

Data were abstracted from 213 charts of women receiving care at the colposcopy clinic, Tygerberg Hospital, Cape Town, South Africa from January 1, 2013 to December 31, 2014. Among 208 women with initial cervical cytology results, 171 had adequate histopathology specimens. Concordance between LSIL and HSIL and corresponding CIN1 and CIN2+ (N=149) was assessed using the one sample binomial test.

Results

Demographically, median age of women was 34 (range, 19-76) years; median age of sexual debut was 18 (range, 13-28) years; 27% were currently married; and 70% were HIV-infected. Initial cytology findings among women with paired histology results were ASC-US 3.5% (6/171), LSIL 39.2% (67/171), and HSIL 53.2% (91/171). Histopathology results showed HPV changes/CIN1 in 27/171 women, CIN2+ in 136/171 women. All six women with ASC-US were CIN2+. Concordance between HSIL and CIN2+ was high at 94% (p<0.001); while LSIL and CIN1 was 30% and LSIL and CIN2+ was 70% (p=0.002).

Conclusions

Although there was a high concordance between HSIL and CIN2+, most ASC-US and LSILs were concordant with CIN2+ in this high-risk population. In low-resource, urban settings, high-risk women with either low- or high-grade cervical cytology findings may benefit from early treatment when HPV testing and/or colposcopy are not available and to prevent loss to follow-up.
Background and Aims

Cervical cancer is still a big problem for Lao PDR Health section due to limited resources to set up cervical cancer screening program. We previously reported the cervical cytology and presence of high-risk (HR) human papilloma virus (HPV) among 1422 healthy women in Vientiane, the capital city of Lao PDR. Oudomxay is one of rural provinces in the north of Lao PDR. In this study, we report the status of cervical cytology and HR-HPV in volunteer healthy women in Oudomxay, because it is unavailable for cervical cytology in ordinary.

Methods

We collected cervical samples from 300 volunteer and asymptomatic healthy women in Oudomxay, 297 sufficient samples were examined for cervical cytology and HR-HPV used by the hybrid capture 2 (HC2) and the polymerase chain reaction (PCR) for genotypes.

Results

The overall rate of abnormal cytology was 9.8% (29/297), and HR-HPV positive rates in HC2 and PCR were 22.9% (68/297) and 9.1% (27/297), respectively. The most common type of HR-HPV in samples with abnormal cytology was HPV 16, followed HPV33 and HPV 58.

Conclusions

Healthy women even in rural district, Oudomxay, have high rates of abnormal cytology and HR-HPV infection as same as urban Vientiane’s data. To consider together with our last data in Vientiane, HPV 58 is relatively common in Lao PDR.
Invasive cervical cancer (ICC) is common in areas where human immunodeficiency virus (HIV) is also prevalent. Currently, HIV seroprevalence as well as acceptability of HIV testing in ICC patients in Kenya is unknown. The objective of this study was to determine the acceptability of HIV testing among patients with ICC.

Methods

Women with histologically verified ICC at Kenyatta National Hospital participated in the study. A structured questionnaire was administered to patients who gave informed consent. HIV pre- and posttesting counseling was done. Blood was tested for HIV using enzyme-linked immunosorbent assay. Overall, 11% of ICC patients were HIV seropositive. The acceptance rate of HIV testing was 99%; yet, 5% of the patients did not want to know their HIV results.

Results

Patients less than 35 years old were two times more likely to refuse the result of the HIV test (odds ratio [OR] 2.2). Patients who did not want to know their HIV results were three times more likely to be HIV seropositive (OR 3.1). Eighty four percent of the patients were unaware of their HIV seropositive status.

Conclusions

The HIV-1 seroprevalence in ICC patients was comparable to the overall seroprevalence in Kenya. ICC patients were interested in HIV testing following pretest counseling. Offering routine HIV testing is recommended in ICC patients.
In 2017, Australian cervical screening changed from two-yearly Pap smears from ages 18-69, to five-yearly HPV primary screening from ages 25-74. Women who perceive they are at increased risk may be concerned by less frequent screening. This study investigated attitudes towards the changes of women previously affected by cervical abnormalities/cervical cancer, personally or through a friend/relative.

Methods

Thematic analysis of 426 comments expressing personal experience or family/friend experience with cervical abnormalities/cervical cancer as reason for opposing screening changes. These comments were taken from a random sample of 2000 comments, 10% of the 19,633 comments posted on the “Change.org” petition ‘Stop May 1st Changes to Pap Smears - Save Women’s Lives’ over February-March 2017.

Results

292 (14.6%) comments expressed personal experience and 145 (7.3%) expressed family/friend experience with cervical abnormalities (11 comments fitted both categories). Many believed their cervical abnormality or that of their friend/relative may have been missed by HPV screening, due to increased screening interval or later age of first screening. Women preferred to keep a tried and tested screening system, believing the HPV program to be less effective, with less extensive testing than the Pap smear program. Misconceptions about the rationale for screening program changes were identified.

Conclusions

Women previously affected by cervical abnormalities or cervical cancer, personally or through a friend/relative may be concerned about changes to cervical screening programs, particularly increased screening intervals and later age of first screening. Specific education campaigns may be required to accurately communicate risk for these women and the rationale for screening program changes.
PREVALENCE AND DETERMINANTS OF HUMAN PAPILLOMAVIRUS INFECTION AND CERVICAL INTRAEPITHELIAL NEOPLASIA AMONG FEMALE SEX WORKERS IN MUMBAI, INDIA: IMPLICATIONS FOR INTERVENTIONS.

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Background and Aims

Women having multiple sex partners have high rates of sexually transmitted infections (STIs) and are likely to be at an increased risk of Human papillomavirus (HPV) infection and thereby cervical neoplasia. This study aimed to determine the prevalence and determinants of HPV infection and cervical intraepithelial neoplasia (CIN) among female sex workers (FSWs) in Mumbai.

Methods

Total 448 FSWs between the ages of 18-50 yrs were recruited from designated red light districts in Mumbai, India. Information on socio demographic and sexual behavioral characteristics were obtained via structured pretested questionnaire. All FSWs were screened for HPV DNA by Hybrid Capture II and VIA (visual inspection with acetic acid) followed by colposcopy and cervical biopsy.

Results

The overall high risk HPV prevalence was 35.5% and 12.5% of them were tested positive on VIA. The prevalence of CIN II and above lesions was 1.3%. HPV prevalence was higher among FSWs in age group less than 25 yrs (p<0.001), had no formal education (p=0.002), not exposed to the STD/HIV/AIDS education program (p=0.043), currently single (p<0.001), with first sexual experience at less than 18 years (p=0.028), had never or rarely uses barrier contraception (p=0.026), with more than 2 pregnancies (p<0.001) and those with STI symptoms in the recent 12 months (p=0.005).

Conclusions

FSWs have a high prevalence of HPV infection and are at increased risk of cervical cancer. Study findings have important implications for developing cervical cancer prevention programs including HPV vaccination along with STD/HIV/AIDS to decrease the burden of cervical cancer among FSW.
Background and Aims

Cervical cancer mortality remains high in North, Northeast and Midwest Brazil, despite the Universal Health Care System (SUS) that provides free cytology-based cervical cancer screening and treatment. In 2014, Brazil started nationwide HPV vaccination among girls aged 9-14. Cytology performance is inferior to HPV testing and even worse among vaccinated women, pressing for a change in cervical screening strategy. Since HPV testing may be introduced soon, the challenges to the current screening program were identified in three cities with an elevated burden of cervical cancer.

Methods

Barriers to implementing a successful comprehensive screening program were identified through visits and interviews with personnel at primary screening clinics, laboratories, and referral hospitals.

Results

Several unique challenges were found in some cities. Access to screening was limited by excessive travel required to access clinics, inconvenient service hours, and lack of public education. Cytology had many unsatisfactory results and low positivity. Follow-up was incomplete at all steps. Laboratories provided delayed cytology and biopsy results (3+ months). Screening clinics did not arrange or track colposcopy referrals; colposcopy clinics received no information from referring clinics. Queues for colposcopy and treatment were long. Treatment services were offered in tertiary hospitals. Electronic medical records have not yet replaced paper recordkeeping, leading to errors and loss of medical records. Some services were excessive with women outside targeted age range and over-referral to colposcopy (i.e. minor abnormalities).

Conclusions

Cities are already improving program with additional clinic hours, educational campaigns and improved coordination. Further consideration of HPV testing will require consideration of these barriers.
BACKGROUND AND AIDS

HIV-infected women are at heightened risk for cervical cancer due to HPV co-infection. In our safety-net healthcare setting, 50% of HIV-infected women are under-screened for cervical cancer. Of those screened, only 50% received follow-up colposcopies when indicated. This study aimed to assess barriers to optimal care delivery and opportunities to improve cervical cancer screening and follow-up care for HIV/HPV co-infected women in a safety-net healthcare setting in Dallas, Texas.

METHODS

We conducted interviews with twenty providers and staff in HIV and gynecology specialty clinics. Topics included cervical cancer screening protocols for HIV/HPV co-infected patients, provider-patient communication, transition to specialty care for patients with abnormal Pap results, and suggestions for systems-level improvements. We transcribed interviews; coders identified care pathways, system-level barriers, and opportunities for interventions. We also conducted patient surveys to assess perceived barriers to care and solutions.

RESULTS

Data were synthesized into process maps (Figures 1-2) illustrating cervical cancer screening, follow-up care, barriers to optimal care delivery, and interventions to improve care for HIV/HPV co-infected women. System-level barriers included bottlenecks for financial counseling, logistics (e.g., scheduling, staffing, equipment), and lack of communication between referring providers and specialty clinics. Patient-level barriers included competing family, work, and medical demands. Intervention opportunities included adaptations to electronic health record (EHR) documentation, systematized communication between clinics using EHR alerts, and streamlined financial counseling processes to decrease patient wait times.
Conclusions

Systemic barriers rather than patient level barriers were primary challenges in care delivery for HIV/HPV co-infected women in a safety net setting, and system-level interventions are needed.
Background and Aims

Evidence shows that mHealth interventions using SMS messages are effective to improve several health outcomes. But little information is available about using SMS messages to increase HPV+ women adherence to follow-up. We describe results of formative research carried out to design SMS messages to be sent to HPV+ women with self-collected tests to increase their adherence to cytology triage. This research is part of the ATICA study (Application of Communication and Information Technologies for Self-Collection) carried out in Jujuy, Argentina, and funded by the NCI/NHI through a R01 grant.

Methods

Six focus group discussions (FGD) were carried out with 48 women aged 30 and over, who performed HPV self-collection offered by community health workers during home visits in the last 12 months. We used different participatory techniques that included brainstorming, card-sorting, and plenary discussion about advantages and pitfalls of proposed messages.

Results

Research showed that women highly valued receiving SMS as reminders to increase triage. FGD participants also signaled the importance of SMS content to strengthen their communication with health providers, that it has a formal but warm tone, it does not include information on their HPV status, and protects their privacy, especially when phones are shared by family members.

Conclusions

SMS as reminders have a great potential to increase adherence to triage by HPV+ women. However their content must be designed taking into account women’s perspectives on privacy and confidentiality; they should also reinforce the link between HPV+ women and the health system.
PERFORMANCES OF TRIAGE TESTS IN PRIMARY HPV SCREENED POSITIVE WOMEN: A POOLED ANALYSIS

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¹International Agency for Research on Cancer, Screening, Lyon, France

Background and Aims

The low specificity of HPV testing implies the need of triaging method of HPV positive women in order to avoid high referral rate to colposcopy and overtreatment.

We aimed at comparing the colposcopy referral rate of HPV screened positive women and the detection rate of CIN2+ lesions of the different triaging tests.

Methods

We performed an electronic literature search (PubMed, Web of Science and Cochrane database). Publications from January 2005 to January 2018 were considered without language limitation. A total of 2320 articles were retrieved from which the title was reviewed for eligibility. Secondarily, the full text was assessed (n=320), and a total of 89 papers were included in a pooled analysis.

Eligibility criteria included a primary HPV test in the context of a cervical cancer screening setting (with or without co-testing); women screened positive should undergo triage by a second test and the data should be original.

Results

Colposcopy referral rate (defined as the number of triage+ among HPV+), with conventional cytology (CC) was 26.7%, liquid-based cytology (LBC):31.1%, other cytology tests (p16/Ki-67, BD ProX):34.1%, visual inspection with acetic acid (VIA):24.7%, colposcopy impression:16.4%, and HPV test (repeat HPV test or HPV genotyping):40.1%.

Detection rate of CIN2+ with CC was 6.2‰ women screened, LBC:11.5‰, other cytology tests:13.9‰, VIA:7.9‰, colposcopy impression:6.9‰, and HPV test:14.4‰.

Co-testing did not modify the results.

Conclusions

Cytology-related triage tests (CC, LBC, other tests) had a lower colposcopy referral rate than HPV triage tests while HPV triage tests detected more CIN2+ lesions, followed by p16/Ki-67 tests.
APPLICATION OF DH2 AND HPV16/18 GENOTYPING IN CERVICAL CANCER SCREENING: A POOLED ANALYSIS OF 338,467 RURAL CHINESE WOMEN

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1Maternal and Child Care Service Centre of Cixi City, Gynecology, Cixi, China

Background and Aims

To compare the performances of DH2, a new generation of hybrid capture based HPV assay by DALTONbio, and Pap smear in cervical cancer screening. To evaluate the clinical significance of HPV16/18 genotyping in triage management of DH2 positive patients.

Methods

In 2013, 2014, 2015, 2016 and 2017, 79847, 81702, 61072, 59634 and 56212 women aged 30 to 55 were screened for cervical cancer by traditional Pap smear in a rural Chinese city of Cixi. In 2015, 2016 and 2017, 35657, 59225 and 54607 women of the above populations were additionally screened by a new generation of hybrid capture based 14 high-risk HPV assay (DH2). DH2 positive samples were further assayed by hybrid capture based HPV16/18 genotyping (DALTONbio). Finally, pathology results of Low-grade Squamous Intraepithelial Lesion (LSIL) or above were recorded and analyzed.

Results

From 2013 to 2017, the detection rates of LSIL or above for total tested population were 0.048%, 0.105%, 0.134%, 0.201% and 0.144% by Pap smear. In comparison, the detection rates of LSIL or above were 0.415%, 0.554% and 0.504% by DH2 HPV test in 2015, 2016 and 2017, respectively. The detection rates of LSIL or above in DH2 positive and HPV16/18 positive patients in 2016 were 6.358% and 22.430%, whereas the corresponding results in 2017 were 5.877% and 26.031%.

Conclusions

Compared with Pap smear, high-risk HPV test DH2 is highly sensitive for the detection of cervical precancerous lesions. DH2 positive samples followed by HPV16/18 genotyping DH assay provide a useful tool for future cervical cancer screening in Chinese rural areas.
THE ADDED VALUE OF RESCREENING CYTOLOGY NORMAL SAMPLES WITH POSITIVE HPV MRNA TEST FOR THE DETECTION OF CIN2+ IN PRIMARY SCREENING

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Background and Aims

To estimate the increased detection rate of CIN2+ in women with normal Pap-smears by rescreening Pap-smears from HPV mRNA positive samples.

Methods

From April 4th, 2013, the Department of Pathology, Ålesund Hospital, introduced a study by rescreening all normal Pap-smears that had a positive HPV mRNA test (PreTect SEE E6/E7) (types 16, 18 and 45) in women younger than 40 years. Within the SymPathy database, a study population of 4 366 women aged 23–39 years with no prior history of CIN1+ was established.

Results

38% of women with normal cytology were tested via HPV mRNA (1444/3851), and 28 samples were positive (1.9%). After re-evaluation of the index cytology and subsequent follow-up smears, 15 women had colposcopy, resulting in five diagnoses of normal biopsies, 6 CIN1 and 9 CIN2+. The detection rate of CIN2+ among rescreened normal Pap-smears was 0.62% (95% CI: 0.60–0.65). In the ASC-US+ arm (n=515), 138 CIN2+ were detected. If we apply the CIN2+ detection rate among cytology normal / HPV mRNA-positive women (0.62%) to the arm of women with normal cytology without HPV testing, a 17-18% increase in CIN2+ detection rate was estimated. Four cancers were detected in the ASCUS+-arm, none among rescreened SEE-positives.

Conclusions

By testing all women with normal cytology with a specific HPV mRNA test, a significant increase in screening program sensitivity can be achieved. The volume of rescreened smears (1.9%) is very low. In addition, the study adds quality to educating the screeners by rescreening presumably false negative Pap-smears.
EVALUATION OF P16/KI-67 DUAL STAINING IN DETECTION OF CERVICAL PRECANCER AND CANCER IN CHINA

X. sun

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Background and Aims

This study evaluated the clinical performance of p16/Ki-67 dual staining in detection of cervical intraepithelial neoplasia 2 or worse (CIN2+) or CIN3+ in Chinese women.

Methods

Specimens of cervical exfoliated cells were collected from 537 eligible women who visited department of gynecology for colposcopy, which were used for PreservCyt® liquid-based cytology (LBC) diagnosis, p16/Ki-67 dual staining and HPV DNA testing. Biopsies were performed on women with any abnormal sites under colposcopy.

Results

Positive rate of p16/Ki-67 dual staining increased significantly with histology severity, with 13.09% in normal, 33.33% in CIN1, 77.55% in CIN2, 89.19% in CIN3, 97.67% in squamous cell carcinoma and 85.71% in adenocarcinoma. Expression of p16/Ki-67 in HR-HPV infected women (70.17%) was significantly higher than in HR-HPV negatives (11.16%) (p<0.001). Sensitivities of p16/ki-67 dual staining for detecting CIN2+ and CIN3+ were 88.10% and 91.30%, respectively. Compared to HR-HPV, sensitivities of p16/ki-67 dual staining was lower for detecting CIN2+ (95.71%, p<0.05) and had similar performance where CIN3+ as the endpoint (96.27%, p>0.05). Specificities of p16/Ki-67 were 85.02% for detecting CIN2+ and 76.86% for detecting CIN3+, which were similar with LBC (84.71%, 80.05%, p all>0.05), but higher than HR-HPV (62.77%, 71.25%, p all <0.05). With respect to the performance of triage women with ASC-US, the sensitivity of p16/ki-67 was 86.36% for detecting CIN2+ and 83.33% for detecting CIN3+, similar with HR-HPV (95.45%, 100.00%, p>0.05). However, the specificities were both higher than HR-HPV.

Conclusions

p16/Ki-67 dual staining could detect most cervical precancer, and had similar specificities for CIN2+ and CIN3+ compared to LBC. It also could be considered as an efficient triage method for women diagnosed with ASC-US.
PUBLIC HEALTH / EPIDEMIOLOGY - SCREENING FOR HPV RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

OUTCOME OF FIRST FOLLOW-UP OF HIGH-RISK HPV POSITIVE CASES 12-MONTHS AFTER THE INITIAL ROUND OF SCREENING AMONG WOMEN AGED 25 TO 69 YEARS OLD.
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**Background and Aims**

This study investigated the participation rate and outcome of follow-up screening for women, between 25 and 69 years old, who were test positive for 12 high-risk HPV (12-hrHPV), excluding HPV-16/18, during the initial round of routine cervical screening 12 months previously.

**Methods**

The subjects were women on 12-month follow-up by screening protocol. Their initial HPV-DNA screening with partial genotyping for HPV-16/18 (Roche USA, Cobas 4800 system) showed 12-hrHPV-positive/cytology-negative (Figure-1). The attendance of the women for the repeat test between 9 and 15 months after the initial test was traced and the outcome of repeat screening test recorded. The main measures of the study were the follow-up attendance rate, rate of repeat test, and persistence and regression rates of HPV infection.

**Results**

Of 254 women analyzed, 36 (14.2%) defaulted follow up, 35 (13.8%) did not take a repeat screening, 24 (9.4%) took cytology alone, and 159 (62%) took the recommended HPV and cytology screening. At 12-months, persistence rate of 12-hrHPV infection was 57.2% (91/159) while regression rate was 42.8% (68/159). Eight women with persistent 12-hrHPV infection acquired additional HPV-16 (n=4) and HPV-18 (n=4) infection. Cytology outcome of 91 HPV positive women was normal in 66, ≥ASC-US (abnormal) in 23, and unsatisfactory in 2. Overall, 23 (14.5% or 23/159) were referred to colposcopy.

**Conclusions**

Women whose cervical screening showed 12-hrHPV+/Cytology- represent a high-risk population for intensive surveillance. Improving the compliance of follow-up screening at 12-months may increase the overall success rate of cervical cancer control.
IMPACT OF HPV-VACCINATION ON CERVICAL SCREENING CYTOLOGY OUTCOMES IN DENMARK

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Background and Aims

In Denmark, girls have been offered free vaccination against human papillomavirus (HPV) since 2008. Women are first invited for cervical screening at age 23 and the program is based on liquid-based-cytology (LBC). The objective of this study was to examine the impact of HPV-vaccination on cervical screening cytology outcomes in Denmark.

Methods

The study is an observational register-based study. Outcomes from birth cohorts of women with different exposure to HPV-vaccination were compared. Women born in 1983 have never been offered free HPV-vaccination. Women born in 1993 were the first birth cohort to be offered free HPV-vaccination and entered the cervical screening program in 2016.

Results

No difference in atypical squamous cell of undetermined significance and worse (ASCUS+) RR = 1.04 (0.96-1.12), but an increase in ASCUS RR = 1.4 (1.2-1.6), and a decrease in high grade squamous intraepithelial lesion HSIL RR = 0.6 (0.5-0.7) was observed. Stratification by age at first cytology showed that the increase in ASCUS was predominately in women < age 23 years while the decrease in HSIL was seen in women ≥ age 23 years RR = 0.49 (0.38-0.63). When stratifying the 1993 cohort by HPV-vaccination status ASCUS+ was lower in women vaccinated at an early age than unvaccinated RR = 0.78 (0.65-0.93). However, unvaccinated women were a minority and therefore a selected group.

Conclusions

The finding of a decrease in HSIL is encouraging because fewer women need referral for further examination. The puzzling increase in ASCUS is most likely due to a shift from conventional cytology to LBC.
Background and Aims

Since 2015, human papillomavirus (HPV)-based cervical cancer screening was randomly implemented among 34 to 69 year old Norwegian women. The aim of this study is to evaluate the risk of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) among women after stratifying by high-risk HPV genotypes and cytology diagnosis.

Methods

A total of 168,201 women were randomly allocated to primary HPV or routine liquid-based cervical cytology during the period of 2015-2017 in four Norwegian counties. We estimated absolute risks and three-year cumulative risk ratios for HPV-type-specific (HPV-16/HPV-18/other high-risk) genotype for women with CIN3+.

Results

A total of 1,335 women were diagnosed with CIN3+; 225 (16%) had atypical squamous cells of undetermined significance (ASCUS) and 159 (12%) low-grade squamous cell intraepithelial (LSIL) lesions as indication for the follow-up. Three-year risks of CIN3+ were lower for HPV 16/18-negative women for normal (0.12%), ASCUS/LSIL (0.43%), and (high-grade squamous intraepithelial (HSIL) (33%) cytology, while for HPV16/18-positive women had risks of 10% for normal, 32% for ASCUS, 38% for LSIL, and 70% for HSIL cytology. Women with HPV16/18-negative test results and normal cytology in the primary HPV testing arm had a lower CIN3+ cumulative risk (CR=0.002; 95% Confidence Interval (CI): 0.000-0.02) than women with the same results in the primary cytology arm (CR=0.01, 95% CI: 0.01-0.04).

Conclusions

Follow-up algorithms based on HPV16/18-positivity in women 34 to 69 years resulted in better discrimination of those with high- and low- CIN3+ risk. The Norwegian cervical cancer screening algorithm has been updated to include HPV genotyping.
IMPACT OF THE NEW CERVICAL SCREENING TEST (CST) ON COLPOSCOPY REFERRAL RATES TO A TERTIARY HOSPITAL ON THE GOLD COAST.

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Background and Aims:

Following the introduction of the Cervical Screening Test (CST) on 1 December 2017, there has been a significant increase in the number of referrals to Colposcopy at our service. This was contrary to what was predicted under the new guidelines. Our aim is further characterise the new referrals for Colposcopy with a positive CST.

Methods:

This is a retrospective audit on all new case referrals to Colposcopy at Gold Coast University Hospital between 1 December 2017 and 28 February 2018. Cases were excluded if they did not have CST results available in the referral.

Results:

As demonstrated in Figure 1, there has been an exponential rise of over 200% in the number of referrals to Colposcopy.
Within the study period, there were a total of 143 new referrals with a positive CST. Of these, 98 (68.5%) were HPV positive cytology negative and 45 (31.5%) were HPV positive cytology positive. There were 50 (35.0%) HPV 16, 18 (12.6%) HPV 18, 55 (38.5%) HPV 'other,' and 20 (14.0%) with HPV 16 or 18 and HPV 'other.'

Conclusions

Conclusion:

The change in guidelines has had a dramatic impact on our service with the rate of referrals increasing by over 200%. This has implications for service provision, resources and cost. Importantly, 98 of the referrals with HPV positive and normal cytology would not have been referred to colposcopy under the old guidelines.
ASSOCIATION BETWEEN KNOWLEDGE AND ATTITUDE TOWARD CERVICAL CANCER SCREENING AMONG WOMEN IN PASAR REBO HEALTH CENTER, INDONESIA
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Background and Aims

Every sexually active women are in risk for having cervical cancer. About 40,000 new cases are reported each year. Unfortunately, despite the evidence of methods for prevention, most of the women remain unscreened. Some barriers include unawareness of risk factor and lack of knowledge about the disease among women. This study attempts to assess the knowledge and attitude related to cervical cancer and its screening among women in Pasar Rebo Health Center, Indonesia.

Methods

This cross-sectional study was conducted among women patient who already married in Pasar Rebo Health Center. Menopausal women was excluded. Structured questionnaire consisting 8 knowledge items and 4-items for attitude and history of Inspection with Acetid Acid (VIA) for screening were questioned by interviewer after informed consent on March 2017.

Results

A total of 65 patients were included in this study of which 46 patients had bad level of knowledge, 35 patients had good attitude, and 3 patients had underwent screening test for cervical cancer. From statistical analysis shows association between knowledge and cervical cancer screening (p= 0.02) but no association between attitude and cervical cancer screening.

Conclusions

There was association between level of knowledge and awareness to do cervical cancer screening but no association between attitude and awareness to do cervical cancer screening. Further study needs to be done for identifying factors that promotes womens awareness to do cervical cancer screening.
Background and Aims

Expanding accessibility of cervical cancer screening will depend on the acceptability to high-risk women. We thus investigated the acceptability of a new “screen-and-treat” strategy combining self-sampling HPV testing and thermocoagulation to help prevent cervical cancer in low-income setting, China.

Methods

In 2017, a total of 9526 women aged 29–65 years were recruited from rural regions of Inner Mongolia and Shanxi Province in China. All participants performed HPV self-sampling for HPV testing. Women with positive HPV results were called back for colposcopy and treated with thermocoagulation if eligible. Questionnaire items inquired about acceptability of self-sample HPV testing and thermocoagulation.

Results

Most women (70.6%, 6707/9508) had “mostly positive” overall thoughts about the self-test mainly because of the convenience for self-sampling procedure (70.2%), followed by protecting privacy (34.1%) and home-based testing (14.3%). And primary concern expressed by women was that the sampling may not be done correctly (97.3%, 2725/2801). 96 women were eligible for thermocoagulation, and 100.0% underwent thermocoagulation immediately. 21.9% and 63.5% of women reported nervousness and mild pain respectively mainly because of the pretreatment cervical punch biopsies. Besides, no other serious adverse effects were observed during the treatment.

Conclusions

Self-sample HPV testing followed by thermocoagulation within a single visit to hospital is acceptable to women who seeking care in low-recourse areas in China, however, further education should be conducted to increase knowledge. It offers a unique strategy to improve cervical cancer screening among high-risk women who otherwise do not attend for regular screening.
PERFORMANCE OF COMBINED P16/KI-67 WITH EXTENDED HPV GENOTYPING IN DETECTION OF CERVICAL PRECANCER AND CANCER AMONG HPV-POSITIVE WOMEN: A MULTICENTER STUDY

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Background and Aims

To explore the risk stratification capability of p16/Ki-67 for different HPV genotype positive women, and to evaluate triage algorithms where combined p16/Ki-67 with extended HPV genotyping for detecting cervical precancer and cancer.

Methods

In total 1839 participants from screening population or colposcopy clinics were recruited for HPV Onclarity assay, p16/Ki-67 dual stain and cytology. Screening women with any of test positive were called back for colposcopy with biopsies. HPV genotypes were divided into 4 strata according to the risk of each HPV type channel for CIN3+.

Results

Dual stain positive rates increased with HPV strata from 64.4% in HPV51/39/68/35 positive women to 88.3% in HPV16/18 positive women (P\textsubscript{trend}<0.05). Increasing trend of p16/Ki-67 positivity with the raising grade of histology was observed, 18.6%, 53.9%, 69.8%, 87.5% and 87.2% for normal women, CIN1, CIN2, CIN3 and cancer, respectively (P\textsubscript{trend}<0.05). For 8-type HPV-positive women (HPV31/33/58/52/45/59/56/66), p16/Ki-67 was an effective triage tool [HPV31/33/58/52: OR\textsubscript{Dual-Stain+}=24.7 (95%CI: 15.9-38.4) and OR\textsubscript{Dual-Stain-}=4.38 (95%CI: 2.24-8.58); HPV45/59/56/66: OR\textsubscript{Dual-Stain+}=9.46 (95%CI: 4.70-19.0) and OR\textsubscript{Dual-Stain-}=1.24 (95%CI: 0.372-4.15)]. The sensitivity and specificity for p16/Ki-67 triage for 8-type positive-women combined with HPV16/18 genotyping [87.3% (95%CI: 84.7%-89.7%), 89.0% (95%CI: 87.0%-90.8%)] was better than p16/Ki-67 triage for HPV positive-women [81.2% (95%CI: 78.1%-84.0%), 88.9% (95%CI: 86.9%-90.7%)].

Conclusions

The combination of HPV16/18 genotyping with p16/Ki-67 triage of 8-type HPV was a promising triage strategy for HPV-positive women.
Clinical evaluation of INNO-LiPA HPV Genotyping EXTRA II assay using the VALGENT framework

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Background and Aims

To evaluate the clinical accuracy and HPV genotyping performance of the INNO-LiPA HPV Genotyping Extra II (INNO-LiPA) within the VALGENT-3 framework.

Methods

The VALGENT-3 panel comprised 1,300 consecutive cervical cell specimens enriched with 300 samples with abnormal cytology obtained from women attending the Slovenian cervical cancer screening programme. The INNO-LiPA allows type-specific detection of 32 HPV types; however, for the clinical accuracy assessment we considered it as high-risk (hr)HPV positive when at least one of the 13 hrHPV types targeted by Hybrid Capture 2 (HC2) was present. Clinical accuracy for detection of CIN2+ was compared between INNO-LiPA and HC2, which is a standard comparator test for HPV tests used in cervical cancer screening. In addition, hrHPV and type-specific detection HPV types was compared between INNO-LiPA and Linear Array HPV Genotyping Test (Linear Array).

Results

The prevalence of hrHPV determined by INNO-LiPA was 17.1% (95%CI: 15.0-19.2%) in the screening population. HrHPV testing with INNO-LiPA had a sensitivity for CIN2+ of 96.9% (95%CI: 92.1-99.1%) which was non-inferior to HC2 (relative sensitivity of 1.01; 95%CI, 0.97-1.04; p_{n.inf} =0.0002)) and a specificity for ≤CIN1 of 85.3% (95%CI: 83.2-87.3%) which was inferior to HC2 (relative specificity of 0.95; 95%CI, 0.93-0.97; p_{n.inf} =0.9998). Genotyping agreement between INNO-LiPA and Linear Array was excellent for hrHPV, HPV16, HPV18, HPV35, HPV45, HPV58 and HPV59, but good or fair for other HPV types.

Conclusions

INNO-LiPA demonstrated non-inferior clinical sensitivity but lower specificity compared to HC2 in addition to excellent concordance compared to Linear Array for hrHPV and some genotypes.
ANALYSIS OF OPTIMAL CUT-OFF ON SELF-TAKEN CAREHPV AS A CERVICAL CANCER PRIMARY SCREENING METHOD IN CHINESE RURAL AREAS

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Background and Aims

Inferior clinical performance of self-taken samples versus clinician-taken samples was indicated when using careHPV. We assessed feasibility on improving clinical performance of self-collected careHPV through adjusting cut-off values.

Methods

9,526 women were recruited in 2017 for a five-year project in 3 Chinese rural areas. At baseline, all participants collected cervicovaginal samples prior to detailed instructions on how to obtain a high-quality self-samples. High-risk HPV positivity is considered on careHPV according to recommended standard when relative light units (RLU)/cutoff (CO)≥ 1.0. In this study, optimal cut-off values on self-taken samples were re-analyzed with baseline careHPV results using receiver operating characteristic curves (ROC).

Results

RLU/CO cut-off at 0.578 pg/mL indicates better performance versus cut-off at 1 pg/mL on cervical intraepithelial neoplasia grade two or higher (CIN2+) with an increased sensitivity (74.3% to 88.2%, p=0.025). There is also decreasing trend observed for optimal cut-offs balancing sensitivity and specificity with increasing of age groups. Positive RLU/CO cut-off at 0.764 pg/ml indicates optimal validity for CIN2+ (sensitivity at 91.7%, specificity at 84.8%) in 30-39 age groups; 0.632 pg/ml in 40-49 age groups(86.1%, 79.2%); 0.563 pg/ml in 50-59 age groups(87.5%, 75.5%) and 0.442 in 60-65 age groups(100.0%, 66.2%) respectively. However, there is no significance in the area under ROC among different age groups.

Conclusions

Clinical performance of careHPV was improved with lower cut-off values on self-taken samples, with much lower cutoff required among the older group. More evidence on improving clinical performance of self-taken careHPV through updated cut-off might be accumulated.
PUBLIC HEALTH / EPIDEMIOLOGY - SCREENING FOR HPV RELATED DISEASE:
IMPLEMENTATION, EVALUATION AND IMPACT

COST-EFFECTIVE ANALYSIS OF COMBINED HPV VACCINATION FOR SCHOOLGIRLS WITH
EXISTING CERVICAL SCREENING PROGRAM IN CHINESE WOMEN: A MODELING STUDY
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Background and Aims

Three-year cervical cancer (CC) screening coverage is about 20% in China but vaccination is rare due
to high cost (quadrivalent HPV: $400/3-dose). We forecasted the population impact and cost-
effectiveness of universal schoolgirls vaccination program and CC screening in the Chinese women
based on a mathematical model.

Methods

We constructed a deterministic compartmental model to project HPV epidemic. By comparing different
HPV vaccination and scale-up CC screening scenarios, we assessed the population benefits and
cost-effectiveness of combined interventions over the period 2018-2037.

Results

We projected that the status quo will result in about 77,000 cancer cases with 2,400 cancer mortality
and 461,000 cases of genital warts (GW) during 2018-2037. Vaccinating 90% schoolgirls annually will
require an annual investment of US$1.8 trillion, resulting in 57% overall population coverage by 2037.
Vaccination (90%) alone will reduce two-third of the 461,000 GW cases but avert only 1,900 cervical
cancer cases and 600 cancer deaths. The cost of averting one Disability-adjusted Life Year (DALY)s
would be $223,550. In comparison, scaling-up CC screening from 20% to 70% will require an annual
investment of $0.5t and reduce 24,580, 40,120, and 7,480 GW, cancer cases and deaths,
respectively. Averting one DALYs will cost $10,448. Combined vaccination and CC screening scenario
will reduce 85% DALYs compared with status quo ($48,325/DALY averted) but still fall short of cost-
effectiveness threshold.

Conclusions

Scale-up cervical screening program will be cost-effective for Chinese women but HPV vaccination will
not due to high price. Reduction of vaccination price is necessary for a universal roll-out.
PUBLIC HEALTH / EPIDEMIOLOGY - SCREENING FOR HPV RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

CLINICAL PERFORMANCE OF HPV E6/E7 MRNA TEST TO DETECT CERVICAL HIGH-GRADE INTRAEPITHELIAL NEOPLASIA AND CANCER: A HOSPITAL-BASED STUDY IN CHINA

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Background and Aims

This study aims to evaluate the clinical performance of HPV E6/E7 mRNA test for detection of cervical high-grade intraepithelial neoplasia and cancer in China.

Methods

A hospital-based study was conducted in Henan province with mRNA, DNA and liquid-based cytology (LBC) as the primary screening tools. Each woman received a colposcopy with biopsies taken at abnormal sites. The histopathological diagnoses were used as the gold standard. The absolute estimates and 95% confidential intervals (95%CI) of positive rates, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Results

The positive rates of HPV DNA, mRNA and LBC increased with the severity of histopathology diagnosis, from 25.5%, 19.1% and 11.4% in normal to all 100.0% in SCC, respectively. The sensitivities for mRNA to detect CIN2+ and CIN3+ were 93.8% (95%CI: 89.7-96.4) and 95.7% (95%CI: 91.3-97.9), respectively, which were not different from those detected by DNA (95.7% [95%CI: 92.0-97.7] for CIN2+, 96.3% [95%CI: 92.1-98.3] for CIN3+), but higher than those detected by LBC (80.4% [95%CI: 74.5-85.2] for CIN2+ and 88.8% [95%CI: 83.0-92.8] for CIN3+). The specificities for mRNA to detect CIN2+ (79.0% [95%CI: 74.2-83.0]) and CIN3+ (70.5% [95%CI: 65.7-74.9]) were higher than those detected by DNA (71.0% [95%CI: 65.9-75.7] for CIN2+, 62.8% [95%CI: 57.8-67.5] for CIN3+), but lower than those detected by LBC (84.5% [95%CI: 80.1-88.0] for CIN2+, 79.8% [95%CI: 75.4-83.6] for CIN3+).

Conclusions

It is promising that mRNA could be used in China’s national cervical cancer screening to decrease the false positives without losing any sensitivities.
SAFETY OF HUMAN PAPILLOMA VIRUS VACCINES IN MALE AND FEMALE HIV-INFECTED PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background and Aims

Human immunodeficiency virus (HIV) infected patients are highly susceptible to human papilloma virus associated cancers. The issue of vaccine safety is one of the major causes of apprehensions linked with vaccine hesitancy and acceptance of HPV vaccination. A systematic review and meta-analysis was conducted to assess the safety of HPV vaccines in both female and male HIV-infected patients.

Methods

Studies on HPV vaccines were identified from MEDLINE, Cochrane Central Register of Controlled Trials, Scopus, Web of Science and references of identified studies. The identified studies were assessed by two independent reviewers. Safety data were synthesised using fixed-effect models, and evaluated for heterogeneity using $I^2$ statistic.

Results

Seven trials enrolling 951 participants with age range of 7-65 years were included. Three studies reported studies involving quadrivalent human papillomavirus vaccine (qHPV) and control vaccines. Two studies are single-arm trials involving only qHPV while the two other studies had qHPV on both arms. Three studies were included in meta-analysis for total adverse events (AEs) with fixed-effect odds ratio (OR) and 95% confidence intervals been 0.38 (0.23-0.62). The corresponding OR for injection site pain was 0.53 (0.32-0.90). None of the studies recorded any discontinuation due to AEs and mortality while Grade 3-4 AEs were minimal.

![Figure 1: Assessment of adverse events - Total adverse events](image-url)
Conclusions

HPV vaccines are well tolerated and safe in HIV-infected female and male patients of different age groups. However, there is need for more studies to be done in sub-Saharan African countries that has high prevalence of HIV, cervical and anal cancers. There are also need to do long-term safety studies.
ASSESSING VARIABLES AFFECTING HPV VACCINATION PERCEPTIONS BETWEEN VACCINATED AND UNVACCINATED WOMEN

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Background and Aims

Many of the women who did not receive the full HPV vaccine series following the CDC's endorsement in 2007 are still within the guidelines to begin the vaccination series.

The objective of this study is to gather information from this population of women in order to inform the development of a health campaign for HPV vaccination. The following goals were investigated: assessing the levels of HPV knowledge between women who received a 3-dose series of an HPV vaccine and those who did not; assessing the association between HPV knowledge and health beliefs related to HPV.

Methods

The protocol was adapted from a previously conducted study by H.W. Kim (2011). Data were collected from October 18, 2016 through December 18, 2016. Categorical variables are represented as frequencies and percentages. Continuous variables are expressed as mean and standard deviation. Associations between sociodemographic variables, HPV knowledge, and health beliefs in relation to intentions to recommend HPV vaccination were analyzed using Chi-square and/or Fisher’s exact test. From the univariate analysis with statistically significant associations at p < 0.05, variables were selected to include in a logistic regression between the independent variables and the significant dependent variables analyzed. P-values < 0.05 are considered statistically significant. Statistical analyses were conducted using SPSS 24.0 (IBM; Chicago, IL).

Results
<table>
<thead>
<tr>
<th>Health Beliefs and Intentions</th>
<th>Not Vaccinated (n = 47)</th>
<th>Not Fully Vaccinated (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perceived benefits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) How much more/less likely would you be to get the HPV vaccine if you knew the HPV vaccine can prevent genital warts and genital cancer?</td>
<td>5.00 ± 1.82</td>
<td>6.43 ± 0.84</td>
</tr>
<tr>
<td>2) How much more/less likely would you be to get the HPV vaccine if you knew the HPV vaccine can prevent cervical cancer?</td>
<td>5.21 ± 1.72</td>
<td>6.56 ± 0.77</td>
</tr>
<tr>
<td>3) How much more/less likely would you be to get the HPV vaccine if you trust the safety and efficacy of the HPV vaccine?</td>
<td>5.77 ± 1.32</td>
<td>6.36 ± 0.77</td>
</tr>
<tr>
<td><strong>Perceived susceptibility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) How much more/less likely would you be to get the HPV vaccine if you knew the likelihood of getting genital warts is high if one is not vaccinated against HPV?</td>
<td>5.47 ± 1.61</td>
<td>6.41 ± 0.92</td>
</tr>
<tr>
<td>2) How much more/less likely would you be to get the HPV vaccine if you knew the likelihood of getting cancer is high (girl, cervical cancer; boy, anal or penile cancer) if they are not vaccinated against HPV?</td>
<td>5.43 ± 1.73</td>
<td>6.43 ± 0.94</td>
</tr>
<tr>
<td><strong>Perceived severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) How much more/less likely would you be to get the HPV vaccine if you knew that HPV infection is a serious disease that can disturb school life?</td>
<td>5.45 ± 1.67</td>
<td>6.35 ± 1.10</td>
</tr>
<tr>
<td>2) How much more/less likely would you be to get the HPV vaccine if you knew that HPV infection can cause death?</td>
<td>5.81 ± 1.72</td>
<td>6.57 ± 0.98</td>
</tr>
</tbody>
</table>
Conclusions

The strongest correlation was found between perceived susceptibility and severity of HPV (0.92). Development of a health campaign constructed to be Instructional or Persuasive would result in increased intention to vaccinate.

Limitations: convenience sampling, lack of post hoc focus groups
CHARACTERISTICS OF PARENTS INDICATING SPECIAL HEALTH CARE NEEDS FEMALE ADOLESCENT AS THE REASON FOR NON-INTENT TO VACCINATE AGAINST HUMAN PAPILLOMAVIRUS: THE NATIONAL IMMUNIZATION SURVEY-TEEN, 2008-2016

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Background and Aims

While in 2016, over 60% of general population adolescent females aged 13-17 years in the U.S. had received at least a single dose of human papillomavirus (HPV) vaccine, not much is known about the vaccine coverage and related issues in adolescents with special health care needs. We describe the characteristics of the parents who indicated “handicapped/special needs/illness” as the reason for non-intent to vaccinate the female adolescent against HPV.

Methods

2008-2016 data from the National Immunization Survey-Teen (NIS-Teen), a nationally representative sample of U.S. households, were analyzed for the study. The present analysis was limited to unvaccinated adolescents whose parents indicated they did not intend to have the adolescent vaccinated in the next 12-months and provided adolescent as having “handicapped/special needs/illness”, termed having special health care needs (SHCN), as the reason for non-intent.

Results

Of the 17,373 respondents in the sample, 173 (weighted proportion: 0.83%) indicated the female adolescent being SHCN child as the reason for non-intent to vaccinate against HPV. Of the 173 parents, the majority were non-Hispanic black (74.5%; 95% confidence interval [95% CI: 65.4-83.5%), and married (77.5%; 95% CI: 68.5-86.5%), and 40% (95% CI: 28.2–51.8%) reported annual household income over $75,000. Only 32.5% (95% CI: 22.8-42.2%) reported a health care provider having recommended the HPV vaccine for their SHCN female adolescents.

Conclusions

Non-Hispanic black parents were disproportionately represented among the parents who gave having a SHCN female adolescent as the reason for non-intent to vaccinate their female adolescent in the next 12-months.
HEALTHCARE PRACTITIONERS’ HPV VACCINE PROMOTION PRACTICES AMONG HIV-POSITIVE PATIENTS

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2Arizona State University, College of Health Solutions, Phoenix, USA

Background and Aims

HPV is the most common sexually transmitted infection. Oncogenic HPV strains (16 and 18) are responsible for several types of HPV-related cancers (e.g. cervical, anal) which disproportionately affect HIV-positive individuals. The HPV 4-valent and 9-valent vaccines can protect against some cancerous HPV strains and strains which cause non-cancerous genital warts. The strongest influence on patients’ HPV vaccine uptake is provider recommendation. Little is known about the perceptions and behaviors related to HPV vaccine promotion and administration among practitioners who provide care to HIV-positive individuals.

Methods

To explore practitioner’s HPV vaccine promotion practices, we conducted 25 in-depth interviews with a variety of healthcare providers (e.g., nurse practitioners, primary care physicians, physician assistants) who provide care to HIV-positive individuals. All data was hand-coded using qualitative content analysis and organized into ATLAS.ti software.

Results

Most providers (n=21) indicated individuals within the CDC’s guidelines should receive the HPV vaccine. Seven providers indicated having patients over age 26 wanting the HPV vaccine; some providers thought it might benefit these individuals (n=4) while others were unsure or thought there was no benefit in vaccinating over age 26 (n=4). Many providers mentioned that the vaccine is safe (n=10); however, several mentioned that they may wait to vaccinate a patient who is newly diagnosed with HIV, not adherent to antiretroviral therapy, or has a low CD4 count.

Conclusions

This study will inform future provider education about administering the HPV vaccine for HIV-positive patients. Future research could assess the effectiveness of administering the HPV vaccine to HIV-positive patients over age 26.
Background and Aims

Cervical cancer is the second common cancer among women with high incidence in urban settings. Female driven factors for HPV vaccine acceptability and cervical cancer screening are important predictors for implementing cervical cancer preventing strategies, in urban areas.

Methods

A descriptive cross sectional study was carried out among mothers of female students in urban settings in Colombo district, Sri Lanka. Cluster sampling selected 620 mothers for the study.

Results

The response rate was 97%; 95% Buddhists; 97.4% Sinhalese; mean age 42 years. Majority (99.7%) attended schools and 36% were employed.

Nearly 96% knew about cervical cancers and its spread; Majority (76%) received knowledge through media and public health staff. Only 34% knew the causative factor as HPV, of which 53% were knowledgeable on transmission of HPV. Most respondents (93%) intended to get their daughters vaccinated against HPV and to undergo cervical cancer screening (92%). Higher knowledge level was significantly associated (P<0.01) with education, income, being employed, undergoing cervical cancer screening and internet literacy.

Higher intentions to vaccinate an adolescent daughter against HPV were significantly associated (p=0.03) with higher knowledge on HPV and cervical cancers, positive attitudes to receive HPV vaccination to their daughters and belief that HPV vaccine prevents cervical cancers.

Conclusions

Knowledge on cervical cancers is satisfactory while identifying inadequate knowledge on causative HPV. However, acceptability for cervical cancer screening and HPV vaccination for their daughters is high. Researchers recommended a well-organized advocacy programme on HPV vaccine introduction which was due after the study in 2017.
Public Health / Epidemiology - Vaccine Safety: New Evidence and Public Perception


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Background and Aims

In the United States, the Food and Drug Administration (FDA) approved quadrivalent human papillomavirus vaccine (4vHPV) for use in females and males aged 9-26 years, since 2006 and 2009 respectively. We characterized reports to the Vaccine Adverse Event Reporting System (VAERS), a US spontaneous reporting system, in females and males who received 4vHPV vaccination.

Methods

We searched VAERS for US reports of adverse events (AEs) following 4vHPV from January 2009 through December 2015. Signs and symptoms were coded using Medical Dictionary for Regulatory Activities (MedDRA). We calculated reporting rates and conducted empirical Bayesian data mining to identify disproportional reports. Clinicians reviewed available information, including medical records, and reports of selected pre-specified conditions.

Results

VAERS received 19,760 reports following 4vHPV; 60.2% in females, 17.2% in males, and in 22.6% sex was missing. Overall, 94.2% of reports were non-serious; dizziness, syncope and injection site reactions were commonly reported in both males and females. Headache, fatigue and nausea were commonly reported serious AEs. More than 60 million 4vHPV doses were distributed during the study period. Crude AE reporting rates were 327 reports per million 4vHPV doses distributed for all reports, and 19 per million for serious reports. Among 29 verified reports of death, there was no pattern of clustering of deaths by diagnosis, co-morbidities, age, or interval from vaccination to death.

Conclusions

No new or unexpected safety concerns or reporting patterns of 4vHPV with clinically important AEs were detected. Safety profile of 4vHPV is consistent with data from pre-licensure trials and post-marketing safety data.
Background and Aims

There is currently a discussion about including boys in the national school-based HPV vaccination program in Sweden. There is limited knowledge about boys’ beliefs about the vaccine. Thus the aim was to explore young males’ beliefs, views and awareness about HPV and HPV vaccination.

Methods

We conducted individual interviews with 35 upper secondary year male students in Mid Sweden, in the spring of 2017. The interviews were analyzed using thematic content analysis.

Results

The preliminary analyses show that the boys had low knowledge about HPV and the HPV vaccine, especially about the transmission of the virus. Still, most were in favor of HPV vaccination in order to promote equal health and to limit virus transmission. It was considered important to vaccinate if it could protect others against a severe cancer disease. They preferred HPV vaccination rather than to use other preventive measures, i.e. condom. The boys had not discussed the HPV vaccine with their parents or friends. They wished to be vaccinated at a convenient place, such as in school by the school nurse or in a primary care setting nearby. Several barriers were revealed; they perceived low risk for an HPV-related disease and believed that the virus mainly affected girls.

Conclusions

The included boys were in favor of HPV vaccination for the good of others. Young males and their parents need to be informed about the benefits of vaccinating boys against HPV before including them in the national school-based vaccination program.
Background and Aims

Despite reductions in vaccine-type human papillomavirus (HPV) prevalence attributed to increased HPV vaccine uptake, HPV continues to be a cause of cancer in the US. Our objectives were to evaluate predictors, patterns, and effectiveness of HPV vaccination in women eligible for catch-up vaccination.

Methods

We used baseline data from 375 women aged 21-29 enrolled from 2012-2014 into a randomized controlled trial evaluating a novel approach to cervical cancer screening. We assessed factors associated with self-reported vaccine uptake and assessed vaccination effectiveness against HPV type 16 and/or 18 (HPV 16/18) DNA positivity.

Results

Over half (60.8%) of participants reported receipt of >1 HPV vaccine dose and 4.3% tested positive for HPV 16/18. College-educated participants were more than four times as likely to be vaccinated compared to those reporting high school education or less (OR=4.2, 95% CI 1.5 - 11.3). Over half (56.5%) of HPV-vaccinated participants reported receipt of their first dose after age 18 and 68.4% after first vaginal intercourse. Women vaccinated after age 18 (OR=3.2, 95% CI 0.4 - 29.2) and after first vaginal intercourse (OR=1.9, 95% CI: 0.2 - 16.2) were at somewhat greater odds of HPV 16/18 infection compared to older women and those reporting intercourse before vaccination, respectively, although those associations did not reach statistical significance.

Conclusions

HPV vaccination is effective at preventing HPV 16/18 infection among women in the catch-up population, especially those vaccinated prior to age 18 and first vaginal intercourse. Women without a college education may benefit from targeted HPV vaccination efforts.
Background and Aims

Background: Certain populations are at much greater risk of HPV infection and of developing related diseases, including cancers, and may have less access to preventive services. The CONDESA Study is being implemented in Mexico City to offer a comprehensive preventive intervention against HPV, associated cancers and other sexually transmitted infections (STIs), to vulnerable groups.

Objective: The CONDESA Study will evaluate the effectiveness of a vaccination-screening-treatment strategy in four groups in Mexico City: men who have sex with men, transgender women, people living on the street and people being treated for sexual assault. Facilitators and barriers to HPV prevention care will be explored. Prevalence and incidence of other STIs will be assessed.

Methods

This mixed-methods study combines HPV vaccination with early detection and treatment of HPV infection and HPV-related diseases. Men and women (including transwomen) will perform self-collection of anal, vaginal, oral and urine samples (only in women) for HPV testing; other STIs will also be tested for and treated. Diagnostic confirmation of neoplastic lesions and genital warts will be performed, and treatment provided. Qualitative interviews in a subsample of the study population will explore experiences and perceptions of the vaccination-screening-treatment strategy and related barriers.
Results

The impact of these interventions on decreased levels of high-risk HPV infection and intraepithelial lesions in anal canal and cervix will be evaluated during 12-months follow-up.

Conclusions

This study will provide scientific evidence on the effectiveness of a vaccination-screening-treatment strategy to decrease the burden of HPV-related neoplasms in highly vulnerable populations.
Background and Aims

Human papillomavirus (HPV) vaccines have been shown to be effective for the prevention of cervical cancer. However, comprehensive efficacy research information for Asian populations was lacking. We conducted a meta-analysis to assess efficacy of prophylactic HPV vaccines against cervical cancer precursor events in Asian women.

Methods

Randomized controlled clinical trials of HPV vaccination were identified among women in Asian countries from three electronic databases (PubMed, EMBASE and Cochrane Library), and assessed by two independent reviewers. Data were analyzed by Cochrane Review Manager version 5.3. Effect sizes were summarized as Risk Ratios (RRs) and associated 95 percent confidence intervals. Efficacy data were synthesized using fixed-effect models, and evaluated for heterogeneity using I² statistic.

Results

9 articles were considered in the meta-analysis, which contained two quadrivalent-vaccine studies and seven bivalent-vaccine studies, there were no significant heterogeneity among the included studies. The fixed-effect Relative Risk (RR) and 95% confidence intervals were 0.04 (0.02–0.07)/0.03 (0.01–0.08) for CIN1+/CIN2+, respectively. And a positive influence from HPV vaccination with regard to HPV 16/ HPV 18 associated the incidence of CIN1+ we were observed, with a pooled RR of 0.07 (95% CI: 0.02–0.25)/0.10 (95% CI: 0.02–0.52), respectively. The result illustrated a significant decrease in the incidence of CIN1+ and CIN2+ due to vaccination.

Conclusions

Prophylactic HPV vaccines are highly efficacious in preventing cervical cancer among Asian females. The government should focus on promoting the development of the HPV vaccine business, incorporate it into public health business and enhance the popularization of public vaccine related knowledge.
AUSVAXSAFETY ACTIVE VACCINE SAFETY SURVEILLANCE: MONITORING THE SWITCH TO 9-VALENT HPV VACCINE IN AUSTRALIAN ADOLESCENTS

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²SmartVax, c/o Illawarra Medical Centre, Ballajura- WA, Australia

Background and Aims

Australia’s active vaccine safety surveillance system, AusVaxSafety, monitors the safety of vaccines on the National Immunisation Program (NIP) through SMS reports of adverse events occurring within approximately 3 days post-immunisation. In 2018, Gardasil9 (in a 2-dose schedule) replaced 4-valent HPV vaccine (Gardasil) on the NIP in a 3-dose schedule for males and females. We compared safety data on the population use of both vaccines.

Methods

De-identified data from 2017 (Gardasil) and 2018 (Gardasil9) were obtained for adolescents (11–14 years) vaccinated at participating sentinel schools/primary care providers. Data were collected using SmartVax, an automated computer-based reporting tool that surveys all vaccine recipients/caregivers on an opt-out basis. Rates of adverse events following immunisation (AEFI) were summarised and compared.

Results

Data from 9,986 adolescents who received Gardasil (2017) were compared with 9,877 Gardasil9 recipients (2018). There was a higher rate of any reported AEFI associated with Gardasil9 compared with Gardasil (9.8% versus 7.5%; p<0.001), irrespective of dose number. Rates of fever (1.6% versus 1.1%; p=0.03), headache (2.0% versus 1.5%; p=0.04) and injection site reaction (3.9% versus 2.2%; p<0.001) were higher for any dose of Gardasil9 compared with Gardasil. Medical attention rates were comparable: 0.6% for each vaccine.

Conclusions

AEFI rates following Gardasil and Gardasil9 vaccines, including medical attendance, were low. Slightly higher AEFI rates associated with Gardasil9 are consistent with clinical trial data. AusVaxSafety data provide reassurance of HPV vaccine safety, with respect to events occurring within the first few days post-vaccination, and contribute to the global HPV vaccine safety evidence base.
Background and Aims

The bivalent (2vHPV) and quadrivalent (4vHPV) HPV vaccines induce cross-reactive antibodies and cross-protection to some HPV types not included in these vaccines. No data is available regarding the immune response to HPV31/33/45/52/58 when a dose of nonavalent vaccine (9vHPV) is administered to subjects who previously received a dose of 2vHPV or 4vHPV compared to naïve (unvaccinated) subjects.

Methods

We analysed the results from two studies conducted by the same team in the same region. Subjects were 9-10-year-old at the time of first visit. In one study a dose of 9vHPV was administered 6 months post-single dose of 2vHPV (n=90) and to naïve subjects (n=179). In another study 9vHPV was administered to subjects 36-96 months (mean 65 months) post-single dose of 4vHPV (n=31). Blood was collected 1 month post-9vHPV. Anti-HPV IgG was assessed using multiplex ELISA (M9ELISA).

Results

All subjects were seropositive to the 9vHPV types with the exception of one naïve subject who seroconverted for all types except HPV45. In (I) naïve subjects, (II) subjects previously vaccinated with 2vHPV or (III) vaccinated with 4vHPV the GMTs were as follows: HPV31:23/126/194AU/ml; HPV33:34/58/109AU/ml; HPV45:29/170/106AU/ml; HPV52:28/53/73AU/ml and HPV58:72/79/120AU/ml. GMTs to all HPV types were higher (all p<0.05) in subjects who previously received 2vHPV or 4vHPV; except for HPV58 in the 2vHPV group. No difference in GMTs was observed between the 2vHPV and 4vHPV groups.

Conclusions

The enhanced antibody response to HPV31/33/45/52/58 induced by a dose of 2vHPV or 4vHPV vaccine suggests cross-reactive priming has occurred. This priming effect may persist for up to 8 years.
HUMAN PAPILLOMAVIRUS INFECTION AND VACCINATION: KNOWLEDGE AND ATTITUDES AMONG HEALTH CARE PROFESSIONALS AND LAYPERSONS IN SLOVENIA
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³Community Health Centre Gornja Radgona, School healthcare, Gornja Radgona, Slovenia

Background and Aims
Due to the relatively low acceptance rates of human papillomavirus (HPV) vaccine in Slovenia (47.6% among girls aged 11-12 years in 2016), we aimed to evaluate the knowledge and attitudes on HPV infection and vaccination among health care professionals and laypersons.

Methods
Five statements were designed to evaluate participants' opinions regarding the age at HPV vaccine administration and potential delay in vaccination, associations of HPV vaccination with riskier sexual behavior, HPV vaccine safety, importance of the Internet as a source of information, and significance of HPV vaccination in boys. Participants were asked to express either agreement or disagreement with each statement.

Results
A total of 605 surveys were completed by medical students (n=259), parents of six graders in 2016 (n=103) and 2017 (n=103), pediatricians and specialists in school medicine (n=21), gynecologists (n=34), and women attending the gynecology outpatient clinic (n=85). The highest level of knowledge and belief in HPV vaccine and its safety was observed among pediatricians and specialists in school medicine. Medical students tend to have a very positive attitude toward HPV vaccination, although they need additional education on HPV vaccine safety. Among health care professionals, gynaecologist showed the highest level of HPV vaccine hesitancy and their beliefs were somewhat similar to those of laypersons.

Conclusions
Whereas the overall attitude towards HPV vaccination is generally positive, additional educational workshops and meetings must be provided to both health care professionals and laypersons in order to achieve higher HPV vaccination coverage rates in Slovenia.
Background and Aims

The aim of the EU-TOPIA project is to increase health, by improving cervical cancer screening programmes in all European countries through the use of country-specific microsimulation models. In this study we describe how we proceeded in developing those models.

Methods

A stepwise process was designed and applied to develop a Slovenian-specific model. Briefly, we started using a well validated microsimulation model (Dutch MISCAN-Cervix) and adjusted all observable parameters, such as demographic characteristics and relative survival; we validated the model by comparing outcomes as cancer incidence, mortality and stage distribution with observed data from the first years of the Slovenia organized screening programme (2006-2015); we calibrated a selection of parameters most likely to be different between countries within a plausible range (background risk, test sensitivity and probability cancer detection without screening; and, finally, we validated the new model using published evidence data.

Results

Dutch MISCAN-Cervix (before calibration) underestimated cancer incidence and mortality in Slovenia and predicted more lower stage cancers. The calibration increased the onsets of disease while decreasing the sensitivity of cytology and the probability of cancer detection without screening, resulting in a satisfying fit with data observed in the first round of the Slovenian screening programme.
Conclusions

The stepwise adjustment of a complex microsimulation model is an efficient way of developing a country specific model. Using this method, more insight is gained in how parameters change and
differences in outcomes between the different models can be explained more easily. This method will be applied for developing two more regional models for Europe.
Background and Aims

Existing modelling frameworks provide guidelines for general models, but modelling HPV encompasses unique complexities and distinct issues necessitating an additional, specific framework of reporting standards.

Methods

HPV-FRAME is a quality-based framework of reporting standards for epidemiologic and economic models. HPV-FRAME was developed using an established process involving distinct activities including workshops at international scientific meetings, feedback from interested parties and public consultation.

Results

Reporting standards for models are grouped into seven domains reflecting distinct policy questions in HPV and cancer prevention regarding vaccination and screening. Domains are further categorised by relevance to a population or an evaluation, namely: HPV vaccination in pre-adolescent individuals (Domain 1); HPV vaccination in older individuals (Domain 2); targeted vaccination in men who have sex with men (Domain 3); considerations for individuals co-infected with HIV (Domain 4) and considerations for low- and middle-income countries (Domain 5).

Additional considerations for evaluations (applicable to various sub-populations) are: cervical screening or integrated cervical screening and HPV vaccination approaches (Domain 6) and alternative vaccine types (e.g. nonavalent) and reduced-dose schedules (Domain 7). Reporting standards in all relevant domains should be addressed when reporting model parameters and outputs.

Conclusions
HPV-FRAME provides an explicit framework of reporting quality for HPV models. This initiative will guide modellers to clarify, and enable target audiences to assess, a model’s strength and weaknesses in addressing specific policy questions and the contributions of the model’s findings towards guiding healthcare policy decision-making.
MOLECULAR EVOLUTIONARY HUMAN PAPILLOMAVIRUS VARIANT DISTRIBUTION IN CERVICAL DISEASE FROM PAPUA NEW GUINEA

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²Kirby Institute- UNSW, Public Health Interventions Research Group, Sidney NSW, Australia
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⁴Murdoch Children’s Research Institute, Molecular Microbiology, Victoria, Australia

Background and Aims

Papua New Guinea (PNG) has among the highest estimated burdens of cervical cancer globally. Previous research found high proportions of archaic hominid Denisovan genome among PNG people. We hypothesized that this population may harbor archaic human papillomavirus (HPV) genomes relevant to cervical neoplasia.

Methods

A sample of 100 HPV-positive cervical specimens from a point-of-care study (PMID:27076663) were selected from different provinces/regions in PNG. HPV type was evaluated by MY09/11 PCR and oligonucleotide hybridization. The URR region of viral genomes was amplified by type-specific nested-PCR followed by Sanger sequencing for variant classification. HPV variant-specific SNPs were identified by multiple sequence alignment.

Results

HPV was detected in 87/100 samples. HPV33 was the most common type identified (28.7%, 25/87) followed by HPV16 in 27.6% (24/87). HPV18, 35 and 58 were detected in 10.3%, 9.2% and 5.7%, respectively. Of the 26 high-grade/cancer cases, HPV16 was present in 46% (12/26), HPV33 in 35% (9/26), and HPV18 in 12% (3/26). HPV16 (n=23) A1 variant was identified in 82.6%, A3 in 8.7% and C in 8.7%. HPV33 (n=21) A1 variant was present in 28.6% and the remaining 71.4% were classified as A variant of unknown sub-lineage.

Conclusions

A high proportion of cervical high-grade/cancer lesions were associated with HPV33 in this population. The distribution of HPV16 variants is similar to other settings and suggests populating of PNG during pre-history by a group of modern humans that had acquired Neanderthal-derived HPV16 variants. The origin of HPV33 variants and its association to patterns of disease in this setting, remain to be investigated.
Background and Aims

Widespread ignorance particularly among CALD populations of HPV, HPV vaccines and cervical screening persists a decade after the ethnocentric introduction of HPV vaccines into public health programs. Whilst the strategic intent was well-intended, the 'protectionist' discourse policy suppressed important HPV information mitigated personal control, and ignored salient cultural norms.

Methods

(a) A literature review of CALD experiences of HPV vaccination education (2007-2016); (b) a comparison of results from two Australian cross-cultural studies on CALD parental (2006, 2017) expectations toward HPV education. Participants were purposively selected from a range of cultural backgrounds. Recruitment was through hospital clinics and cultural networks.

Results

Participant responses signify the divergence between 'protectionist' and culturally targeted discourses among the health sector where assumptions were made about health literacy and HPV vaccine promotion. Dissatisfaction was held with the incongruence between the 'one-size-fits all' and normative cultural needs. This approach limited public awareness in specific CALD populations about the risks of persistent HPV infection to males and females, misinterpretation of their vulnerability, disempowerment when consenting to adolescent HPV vaccination, and screening.

Conclusions

The introduction of the 9-valent HPV vaccine and HPV testing provides an opportunity to reconceptualise HPV message-framing and differentiated CALD education. Recognition of the underlying socio-cultural determinants is fundamental to overcoming the low rates of awareness, and ongoing stigmatisation of sexuality discourses. Empowering CALD populations in making informed decisions relating to HPV prevention requires a commitment among health agencies to the premise that a culturally intelligent approach requires a collective responsibility.
REFRAMING HPV PUBLIC EDUCATION STRATEGIES IN THE DYNAMIC LANDSCAPE OF HPV PREVENTION: OPPORTUNITIES FOR HPV VACCINES AND HPV TESTING IN CALD POPULATIONS.

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Background and Aims

Widespread public ignorance of HPV as a sexually transmitted infection (STI) persists a decade after the gendered introduction of HPV vaccines and three decades of cervical screening into public health programs. Generic approaches to public education have created limited awareness of important HPV factors for CALD populations.

Methods

A literature review of public education strategies globally toward HPV vaccines and cervical screening (2007-2018); (b) results from two Australian cross-cultural studies on parental (2006, 2017) attitudes toward HPV education. Participants were purposively selected through cultural networks.

Results

Participant responses signify the tension between assumed health literacy among health stakeholders which unwittingly impacts on actual knowledge levels of targeted recipients. There were disparities between cultural groups on what HPV information was understood and their psycho-social responses. Dissatisfaction was held with the promotion of HPV and HPV vaccines which was found to lack an integrated and culturally-targeted approach. This approach limited public awareness about the risks of persistent HPV infection to males and females, misinterpretation of their vulnerability, vaccine confidence, and compromised informed consent.

Conclusions

The introduction of the 9-valent HPV vaccine and HPV testing provides an opportunity to reconceptualise HPV message-framing and differentiated public education. Recognition of the publics’ ‘need to know’ is fundamental to empowerment and overcoming the low rates of awareness and uptake in some population groups. Reducing the increase in HPV morbidities requires a commitment among health agencies to the premise that a culturally targeted and integrated approach is integral to the development of public confidence in managing health and well-being.
OVERCOMING HPV VACCINATION HESITANCY AND IGNORANCE. EMPOWERING MIGRANTS FROM THE HORN OF AFRICA THROUGH A CULTURALLY TARGETED APPROACH TOWARD HPV VACCINATION UPTAKE AND SCREENING.

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1RMIT University, Management, Melbourne, Australia

Background and Aims

Vaccine hesitancy towards adolescent HPV vaccination programs prevails in many groups globally. For immigrants from the Horn of Africa the lack of culturally targeted HPV vaccination services and information presents challenges in them gaining equitable and informed access to adolescent vaccination. The disparate socio-cultural and sexuality norms of this diaspora have implications for HPV vaccination uptake and reduction of HPV morbidities. The complex factors that contribute to decision making are especially prevalent in this population where sexual health literacy is low or non-existent.

Methods

We report the findings from a CALD study undertaken with Horn of Africa-Australian communities in Melbourne that has implications for the related diaspora worldwide. A community-partnership approach with multicultural agencies and a bi-lingual translator through focus group discussion explored the socio-cultural health, ecological and historical determinants contributing to HPV vaccine hesitancy and uptake.

Results

Parents had neither knowledge nor perceptions of HPV and HPV vaccines and risk factors. Factors contributing to adolescent vaccine hesitancy included disparate sexuality norms and stigma emanating from permissive discourses. Redevelopment of public HPV information resources that incorporate health culture, social inclusion, and cultural continuity in a common first language enabled community-partnership engagement and empowerment.

Conclusions

The increased knowledge of HPV factors among adult participants and the development of a community educator’s ‘TOOLKIT’ led to intentions of changes in their health behaviours. If migrants are to experience long-term well-being through their integration into Australian health and social systems, HPV prevention approaches to reduce the current cultural vacuum and insecurities will need to be re-framed.
Background and Aims

The overall success of the Australian adolescent HPV vaccine program (NHVP) is due to well organised implementation policies and processes resulting in high coverage. Less successful has been critical socio-cultural dynamics that reveal important lessons for the introduction of the 9-valent HPV vaccine.

Methods

A socio-ecological review of the NHVP (quadrivalent HPV-1 vaccine) and recommendations for policy and practice with the introduction of the 9-valent HPV vaccine into the vaccine schedule. It examined successes (National and State coverage data (males + females)); surveillance (NHVP Register data and targeting vaccination in vulnerable populations); and society (health promotion: school-based vaccination program materials & resources by state/territory; culturally and linguistically diverse (CALD) community needs).

Results

The HPV quadrivalent vaccine coverage data reveals disparate uptake rates. In some States of Australia eight years after introduction of the 3-dose regime there were up to forty percent of the eligible population not receiving the second dose. Conversely, Aboriginal populations with culturally targeted resources have high uptake. The surveillance and registering of vaccine uptake is world class with school-based vaccination program materials and resources both nationalised and customised. However, intracultural diversity is not sufficiently accounted for. The information needs of CALD populations are not being adequately resourced and for whom awareness and knowledge factors remain low.

Conclusions

The introduction of the 9-valent HPV vaccine presents an opportunity to revise the current approaches to CALD information and decision-making needs. A socio-cultural-impact analysis supported by a Community Based Participatory Marketing model is recommended to empower these population groups and optimise vaccine uptake.
HPV vaccine-related awareness and knowledge among caregivers of HPV vaccine-eligible adolescents from diverse backgrounds

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Background and Aims

To assess factors associated with HPV vaccine-related awareness and knowledge among caregivers of adolescents from five ethnic community groups in Utah, United States.

Methods

For this community-based participatory research study, we surveyed N=228 caregivers of teens aged 11-17 years from African American, African refugee, American Indian/Alaskan Native, Hispanic/Latino, and Native Hawaiian/Pacific Islander community groups in Utah about their HPV vaccine awareness and knowledge.

Results

Participants exhibited high awareness of cervical cancer (71.1%), moderate awareness of HPV (54.0%), and low awareness of the HPV vaccine (46.5%). HPV vaccine-related knowledge was mostly worse, with fewer than half the participants reporting knowing that HPV can cause cervical cancer (47.0%), that most people are infected with HPV at some point in their lives (29.0%), that HPV is asymptomatic in females (36.4%) and males (37.3%), that the HPV vaccine is recommended for adolescent females (41.7%) and males (36.4%), and that the HPV vaccine requires more than one dose (27.2%). HPV vaccine-related awareness and knowledge were significantly associated with race/ethnicity, educational attainment, income, occupation, birthplace, parents’ birthplace, English usage, health insurance coverage, type of health insurance, and child having a primary care provider (all p<0.05). HPV vaccine related-knowledge and awareness were also related to HPV vaccination (both p<0.05).

Conclusions

Our findings indicate a need to develop educational interventions in collaboration with diverse communities in Utah, United States. We underscore the importance of promoting knowledge about the existence of the HPV vaccine, as well as deeper HPV vaccine-related issues (e.g., HPV risks, treatment, and recommendations).
Background and Aims

HPV is a ubiquitous virus that causes many cancers: cervical, oropharyngeal, anal, penile, vaginal and vulvar cancers. 75% of HPV infections occur between the ages of 15-25 years. About 10% persist and can cause diseases and cancers.

Cervical cancer is almost completely preventable today. Existing tools such as the HPV vaccines are up to 90-97% preventive. In addition, simple screening tests and effective early treatment for precancerous conditions are also available.

However, lack of awareness is a major barrier. Since the HPV vaccines are recommended between 9-26 years in both sexes, our organization, Global Initiative Against HPV and Cervical Cancer empowered the next generation to join the fight against HPV.

Methods

A youth-focused educational power point presentation that was culturally and linguistically appropriate was developed for middle and high school students. Students used various forms of art such as dance, video, painting and poetry to spread awareness.

The presentation fit in a classroom period. A script for the presenter, a reference sheet, slides to highlight how HPV can affect both sexes, risk factors and prevention, with emphasis on the HPV vaccine were developed. This was followed by a game, and a short inspirational and aspirational film.

Results

Students in various countries are now using this presentation. They are continually developing creative ideas through the arts and social media to spread awareness.

Conclusions

Empowering the younger generation to play a pro-active role to interweave science with the universal language of games and arts can have greater impact to raise HPV awareness in diverse settings.
Background and Aims

Latinas comprise almost 10% of the United States population, and have one of the highest incidence and mortality rates of cervical cancer. Human papillomavirus (HPV) vaccination can prevent most HPV infections that cause over 90% of cervical cancer. Nevertheless, previous research shows Latina mothers still have low and inadequate knowledge of HPV, and Latina adolescents have low rates of HPV vaccine initiation and completion. Therefore, the aims of the present qualitative study were to identify and explore influences on HPV knowledge, and HPV vaccination acceptability and uptake among Latina immigrant mothers.

Methods

Semi-structured interviews were conducted in Spanish with Latina immigrant mothers of adolescents’ girls, ages 12-18 years (n = 22). All interviews were audio recorded, transcribed verbatim and thematically analyzed. Themes were identified and organized by individual and structural-level influences.

Results

Sociocultural factors (faith/religion, cultural taboos about discussing sexually transmitted infections, mistrust, etc.) emerged as important influences on mothers' knowledge, attitudes and acceptability HPV vaccination. Mothers expressed concerns about the HPV vaccine being an "untested" and a "newer" vaccine. Mothers reported that they would like more information on HPV and HPV vaccination that is culturally and linguistically appropriate. Structural-level factors (e.g., access to healthcare, need for multiple visits to complete vaccine series) emerged as barriers to HPV vaccine initiation and completion.

Conclusions

Health promotion interventions targeting Latino families should take into account sociocultural and structural-level influences on HPV and HPV vaccine knowledge, attitudes, acceptability and uptake, and address families' concerns about vaccine safety and efficacy in a cultural and linguistic appropriate manner.
Considerations regarding an age-expanded nonavalent HPV vaccine schedule for men who have sex with men (MSM) in the U.S.

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\textsuperscript{2}National Cancer Institute, Division of Cancer Control and Population Sciences, Washington- DC, USA

Background and Aims

Evaluate the acceptability of HPV vaccination among men who have sex with men (MSM) in the US between the ages of 27 and 45 and identify salient beliefs that may influence vaccine decision-making.

Methods

A measure of behavioral expectation (BE) (“How likely are you to get the HPV vaccine if the CDC recommendation was changed to include men older than 26?”) was evaluated on an ethnoracially diverse sample (N=318) of MSM (aged 27 to 45) along with a series of perceived outcome expectancies. Participants were recruited on a social networking mobile phone application in 2015. All variables were measured on 5-point interval scales.

Results

BE was moderate (M=3.83). Approximately 66.7% indicated that they would likely initiate vaccination in the event of a change in the current recommendations. Physical and psychological benefits of HPV vaccination were widely endorsed (e.g., 68.2% believe vaccination would prevent anal cancer), whereas barriers/harms of vaccination were endorsed less frequently (e.g., 25.5% were concerned about side effects). Only 15.4% were concerned that the vaccine would not be effective. The main driver of BE was perceived physical benefits ($R^2=0.34$). Psychological benefits were independently associated with BE, but did not improve the explanatory model. Barriers were not independently associated with BE.
<table>
<thead>
<tr>
<th>Table 1. Sample Characteristics (N=318)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Age, Mean (SD)</td>
</tr>
<tr>
<td>Ethnicity Identity*</td>
</tr>
<tr>
<td>White/Caucasian</td>
</tr>
<tr>
<td>African American</td>
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<tr>
<td>Latino/Hispanic</td>
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<tr>
<td>Asian</td>
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<tr>
<td>Native American</td>
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<td>Pacific Islander</td>
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<tr>
<td>Other</td>
</tr>
<tr>
<td>Education</td>
</tr>
<tr>
<td>High school or less</td>
</tr>
<tr>
<td>Some College</td>
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<tr>
<td>College Degree</td>
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<tr>
<td>Sexual Identity</td>
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<tr>
<td>Gay</td>
</tr>
<tr>
<td>Bisexual</td>
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<tr>
<td>Number of male sex partners</td>
</tr>
<tr>
<td>0 to 10</td>
</tr>
<tr>
<td>11 to 20</td>
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<tr>
<td>21 or more</td>
</tr>
<tr>
<td>HIV Status</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Never tested</td>
</tr>
<tr>
<td>Previous diagnosis of anogenital warts</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Unsure</td>
</tr>
<tr>
<td>Previously aware of HPV vaccine</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
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<tr>
<td>Unsure</td>
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</tbody>
</table>

Note. No sample characteristics were associated with HPV vaccine acceptability (p >0.10)

* Participants could select more than one response
Table 2. Bivariate correlation coefficients between outcome expectancies and HPV vaccine acceptability among men who have sex with men 27 to 45 years of age (N=318)

<table>
<thead>
<tr>
<th></th>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
<th>Column 4</th>
<th>Column 5</th>
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<th>Column 7</th>
<th>Column 8</th>
<th>Column 9</th>
<th>Column 10</th>
<th>Column 11</th>
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<tbody>
<tr>
<td><strong>Physical Benefits</strong></td>
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<tr>
<td>(Cronbach alpha = 0.87)</td>
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<tr>
<td>1. It would make me healthier</td>
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<td></td>
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<tr>
<td>2. It would prevent me from getting genital and anal warts</td>
<td>0.58*</td>
<td></td>
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<tr>
<td>3. It would prevent me from getting anal cancer</td>
<td>0.59*</td>
<td>0.84*</td>
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<tr>
<td><strong>Psychological Benefits</strong></td>
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<td>(Cronbach alpha = 0.87)</td>
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<tr>
<td>4. Feel protected from HPV</td>
<td>0.48*</td>
<td>0.52*</td>
<td>0.52*</td>
<td></td>
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<tr>
<td>5. Feel like there is one less thing to worry about</td>
<td>0.45*</td>
<td>0.57*</td>
<td>0.56*</td>
<td>0.79*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6. Be less likely to spread HPV to your future sex partner(s)</td>
<td>0.43*</td>
<td>0.57*</td>
<td>0.57*</td>
<td>0.65*</td>
<td>0.67*</td>
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<tr>
<td><strong>Perceived Barriers</strong></td>
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<td>(Cronbach alpha = 0.72)</td>
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<tr>
<td>7. I will contract HPV from the vaccine itself</td>
<td>0.08</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.03</td>
<td>-0.06</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>8. I would not be completely protected from future HPV infection</td>
<td>0.10</td>
<td>0.08</td>
<td>0.05</td>
<td>0.04</td>
<td>0.00</td>
<td>0.11</td>
<td>0.42*</td>
<td></td>
<td></td>
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<tr>
<td>9. The vaccine may not work for me</td>
<td>-0.08</td>
<td>-0.15*</td>
<td>-0.19</td>
<td>-0.15*</td>
<td>-0.17*</td>
<td>-0.11</td>
<td>0.38*</td>
<td>0.50*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. I would have side effects from the HPV vaccine</td>
<td>-0.08</td>
<td>-0.08</td>
<td>-0.11</td>
<td>-0.12*</td>
<td>-0.13*</td>
<td>-0.03</td>
<td>0.34*</td>
<td>0.27*</td>
<td>0.49*</td>
<td></td>
<td></td>
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<tr>
<td><strong>Behavioral Expectation</strong></td>
<td></td>
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<td></td>
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<tr>
<td>(Likelihood of getting HPV vaccine if the CDC recommendation was changed to include men older than 26)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>11. Likelihood of getting HPV vaccine</td>
<td>0.46*</td>
<td>0.52*</td>
<td>0.49*</td>
<td>0.43*</td>
<td>0.46*</td>
<td>0.47*</td>
<td>-0.12*</td>
<td>0.02</td>
<td>-0.06</td>
<td>-0.12*</td>
<td></td>
</tr>
</tbody>
</table>

Mean:
- 3.54
- 3.94
- 3.81
- 4.10
- 4.06
- 4.15
- 2.54
- 2.87
- 2.59
- 2.87
- 3.83

Standard Deviation:
- 1.09
- 1.07
- 1.09
- 0.96
- 1.04
- 1.03
- 1.23
- 1.15
- 1.05
- 1.05
- 1.20

Percent Likely/Vary Likely:
- 51.9
- 73.0
- 68.2
- 77.7
- 77.4
- 81.8
- 15.7
- 27.0
- 15.4
- 25.5
- 66.7

Note: *p < 0.05; Correlation coefficients are Spearman’s rho
Table 3. Explanatory models of HPV vaccine behavioral expectations among men who have sex with men 27 to 45 years of age (N=318)

<table>
<thead>
<tr>
<th>Perceived Benefits</th>
<th>Model 1 (Physical Benefits)</th>
<th>Model 2 (Physical + Psychological Benefits)</th>
<th>Model 3 (Benefits + Barriers)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>β</td>
</tr>
<tr>
<td>Physical</td>
<td>0.69*</td>
<td>0.06</td>
<td>0.55</td>
</tr>
<tr>
<td>Psychological</td>
<td>0.34*</td>
<td>0.08</td>
<td>0.26</td>
</tr>
<tr>
<td>Perceived Barriers</td>
<td>-0.09</td>
<td>0.07</td>
<td>-0.06</td>
</tr>
<tr>
<td>(F)</td>
<td>137.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted (R^2)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Delta R^2) (p-value)</td>
<td>0.04</td>
<td>(0.16)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Note.** *p < 0.05*
The implementation of an expanded age recommendations for HPV vaccination in the U.S. is unlikely to be hindered by a lack of acceptability and perceived efficacy of HPV vaccination among MSM in the expanded age range. Prevention of anogenital warts and anal cancer should be promoted as benefits of vaccination.
PUBLIC HEALTH

USE OF THERMO-COAGULATION (TC) WITHIN A ‘SCREEN AND TREAT’ CERVICAL CANCER SCREENING PROGRAMME IN MALAWI - OUTCOMES AND PERSPECTIVES AT ONE YEAR


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2University of Edinburgh, Usher Institute, Edinburgh, United Kingdom
3Nkhoma CCAP Hospital, Nkhoma Hospital, Nkhoma, Malawi
4Gold Coast Private Hospital, Obstetrics and Gynaecology, Queensland, Australia

Background and Aims

TC is increasingly being adopted as an alternative to cryotherapy for low-grade lesions within cervical screening services using VIA in resource-constrained settings. As most systematic review evidence comes from high-income settings, it is critical to strengthen the evidence base in LMICs. The Aim is to evaluate acceptability and effectiveness of TC treatment within a ‘screen and treat’ programme in Malawi.

Methods

Nkhoma Hospital has implemented a ‘screen and treat’ approach using VIA and TC treatment. VIA+ women receive same day treatment and are requested to return for review at 3-6 months and one year. Semi-structured qualitative face-to-face interviews were carried out in English with 19 providers, exploring their experience with TC. A patient experience questionnaire using validated facial pain scales was completed by women post-treatment.

Results

Between October 2013-July 2017, >1,650 women received TC treatment. Of 446 who had returned for 1-year review, 20 (4.48%) were VIA+, representing treatment failure rate of <5%, comparable to international literature. HR-HPV prevalence and VIA positivity were >2x higher in HIV+ women. In contrast to previous experience with unavailable cryotherapy resulting in loss to treatment, staff reported professional satisfaction associated with offering treatment consistently. Almost 90% (70/78) women who completed pain scales questionnaires after TC reported none or minimal discomfort.

Conclusions

VIA screening will remain central to cervical cancer control in many LMICs until the promise of HPV vaccination is fully realised. Same day treatment by TC is an effective and well accepted treatment modality.
MAILING HOME-BASED HPV SELF-SAMPLING KITS AS A STRATEGY TO INCREASE CERVICAL CANCER SCREENING EFFECTIVENESS IN UNDERSCREENED WOMEN: RESULTS FROM A U.S.-BASED PRAGMATIC RANDOMIZED TRIAL

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²University of Texas Southwestern Medical Center, Clinical Sciences, Dallas, USA
³Kaiser Permanente Washington, Health Research Institute, Seattle, USA
⁴University of California Davis, Public Health Sciences, Sacramento, USA
⁵Kaiser Permanente Washington, Kaiser Permanente Washington, Seattle, USA

Background and Aims

Of 12,000 cervical cancers diagnosed annually in the U.S., >50% are in underscreened women. We designed a pragmatic trial evaluating whether a programmatic strategy of mailed HPV kits increased detection and treatment of cervical pre-cancers and screening adherence. This is the first HPV self-sampling trial to evaluate impact on treated pre-cancer cases as a primary outcome.

Methods

From 2014-2016, we randomized 19,851 women aged 30-64 years who were overdue for Pap screening into a pragmatic trial within Kaiser Permanente Washington and followed women for up to 18 months. The control arm (n=9,891) included usual care (annual patient reminders, ad hoc clinic outreach); the intervention arm (n=9,960) included usual care plus a mailed HPV kit. Kaiser Permanente’s lab communicated kit results to primary care providers who were responsible for follow-up. Primary outcomes were pre-cancer (CIN2+) detection and treatment. A secondary outcome was screening uptake (kit return and reflex in-clinic screen if indicated, or no kit return but in-clinic screen).

We conducted intention-to-treat log-binomial regression to estimate relative risks (RR) and 95% confidence intervals (CI).

Results

Two additional CIN2+ cases were detected (10 versus 8; RR=1.24, 95% CI: 0.49-3.14) and 3 additional cases treated (10 versus 7; RR=1.42, 95% CI: 0.54-3.73) in the intervention versus control arm. Screening uptake was higher in the intervention arm (2,618 [26.3%] versus 1,719 [17.4%]; RR=1.51, 95% CI: 1.43-1.60).

Conclusions

Mailing HPV kits to overdue women increased screening uptake compared to usual care alone, with no significant difference in detection or treatment of CIN2+. Developing and evaluating strategies to engage the hardest-to-reach women in cervical cancer screening should remain a high priority.
Rapid Communication

Public Health

Yes, it is possible to implement HPV self-collection, testing, and treatment programs in a low-resource setting – Kweneng District, Botswana

R. Dialwa1
1Jhpiego, Monitoring- Evaluation & Research, Gaborone, Botswana

Background and Aims

Botswana has the third highest HIV prevalence globally at 21.9% among adults aged 15–49 (UNAIDS, 2016), and cervical cancer is the leading cause of cancer and cancer-related deaths. The Government of Botswana offers cytology and visual inspection with acetic acid as public cervical cancer screening services. Screening coverage is low, at 33% in 2017. HPV self-collection is anticipated to improve coverage.

Methods

A mixed methods prospective cohort study of women aged 30–49 years, from 4 clinics (and community campaigns), and 1 district hospital, with no recent or previous cervical cancer screening participated in HPV self-collection screen-and-treat. The Cepheid GeneXpert® platform was used to test samples for high-risk HPV; all HPV positive clients were offered treatment. Data was entered electronically using the CommCare® mobile data collection platform for client follow-up and tracking results.

Results

Study completed recruitment of 1022 (100%) women with 1019 (99.7%) test validity rate. Nearly one-third (33.7% or 343) tested HPV positive of whom 230 (67%) were HIV positive. Nearly all 1016 (99.7%) received their results; 93.3% received results within 7 days and 32.2% on same day of screening. The 3 who haven’t received their results are not reachable by phone. 313 (91.3%) of the HPV positive were assessed for treatment and 305 (97.4%) were treated. Facility management support its scale-up, “I am for integrating it”.

Conclusions

Clinic and community based HPV self-collection is feasible if integrated into existing health structures. Electronic data system optimized client follow-up. Decentralizing testing sites may support faster results' notification and access to assessment and treatment.
INTEGRATING RAPID HPV TESTING IN AN EXISTING SEE-AND-TREAT CERVICAL SCREENING PROGRAMME IN TANZANIA (AISHA), OPERATIONAL ASPECTS

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Background and Aims

To evaluate the impact of introduction of rapid HPV testing to the existing see-and-treat cervical screening programme using visual inspection with acetic acid (VIA) and cryotherapy in Tanzania.

Methods

Women age 30–50 were screened with VIA and HPV-testing (careHPV®) in 6 screening clinics from Dar es Salaam (D) and Kilimanjaro (K) region. VIA-positive women eligible for cryotherapy were immediately treated at the clinic or referred if cryotherapy was not available on-site (1 health-center D). VIA-negative/HPV-positive women were recalled for a second VIA2 examination and treated with cryotherapy if positive.

Results

Firstly, due to HPV-testing contamination in 1 laboratory, results from the K regional-hospital were excluded (58.8% HPV-positive). A total of 1,246 women with valid VIA and HPV results were 6.2% and 24.1% test-positive, respectively. Among 92 VIA-positive women, 90.1% received treatment. Failure to treatment adherence was mostly due to the need for treatment referral (16.1% failure in health-centre D) or to deferral of treatment to a later day (13% in district-hospital K). Among the 275 VIA-neg/HPV-pos women, 25% of women failed to adhere to the HPV results visit including VIA2, in 4/5 cases due to unreachable phone contacts. Of the 206 available VIA2 results, 56.3% were positive and 98.3% were treated.

Conclusions

HPV-testing was not always adequate and the nurses’ management workload increased 4-fold using HPV-testing, compared to VIA screening. Failure to treatment or HPV results visit attendance was mainly due to the need for referral or an additional clinic visit, suggesting the benefits of same-day screen-and-treat algorithms, including for HPV testing.
PUBLIC HEALTH

EVALUATION OF THE POCKET COLPOSCOPE FOR THE DIAGNOSIS OF CERVICAL INTRAEPITHELIAL LESIONS IN A MULTI COUNTRY INVESTIGATION

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Background and Aims

We have developed a Pocket Colposcope to make cervical cancer screening widely available to women in low and middle-income countries (LMICs). The Pocket has the form factor of a tampon with comparable resolution and field of view to a state-of-the-art colposcope. It is > 10X less expensive than a clinical colposcope and weighs less than 0.5 lbs.

Methods

The Pocket has been deployed in multi-country clinical investigations on > 750 patients in hospitals and clinics in the U.S., Tanzania, Kenya, Zambia and Peru. Images were collected with the use of up to three contrast mediators depending on the clinical setting. The contrast mediators were acetic acid, Lugol's iodine and vascular contrast achieved using green illumination. Results were compared to pathology. The results demonstrated that the image quality of the Pocket colposcope is comparable to that of a state-of-the-art colposcope.

Results

Blinded images read by expert colposcopists showed high concordance (80-90%) between the Pocket and a high-end colposcope for detection of cervical pre-invasive lesions. When compared specifically to pathology, images captured with the Pocket and a high-end colposcope agreed 69% for acetic acid images (n=434), 72% for acetic acid and green light images (n=156), and 83% for acetic acid and Lugol's iodine images (n=512). The concordance increased to 90% when all three, contrast mediators were used for image interpretation (n=89).

Conclusions

In conclusion, the Pocket can improve upon standard visual inspection methods by providing image capture, increased magnification and improved performance owing to its ability to capture multiple sources of contrast with one device.
Background and Aims

WHO recommends considering HPV testing also in developing countries, but less than 1% of the Ethiopian women have access to cervical cancer screening. A shift from a clinic-based screening to community-wide self-sampling could protect overburdened clinics and optimize access.

Methods

In cooperation with the Ethiopian Health Extension Program we conducted a home-based genital HPV self-sampling campaign in a rural community in Dabat district, northwestern Ethiopia. We screened a complete community by visiting every household door-to-door offering HPV screening using the Evalyn Brush®. Samples were analyzed in the central HPV reference laboratory (Addis Ababa Univ.). Data was collected digitally on an application for tablet computers. Ten Data Collectors were trained in cervical cancer screening education, promotion of the use of the Evalyn Brush® and usage of the app on the tablet. The campaign was preceded by consultation with political and health stakeholder and raising awareness during communal assembly and church meetings.

Results

723 of 741 households participated in the study with a total of 738 age-eligible women between 25-65 years. 521 (79.4%) of 656 screening-eligible women provided a sample. Reasons for ineligibility included pregnancy, absence of an intact uterus and cervical cancer history. The sample quality was adequate in 78%. A high-risk HPV infection was found in 17%.
Conclusions

A home-based genital HPV self-sampling campaign combined with a tablet computer application for data management is a promising strategy for cervical cancer screening in rural Ethiopia. Steps to ensure high sample quality are essential.
DOSE EFFECT OF QUADRIVALENT HPV VACCINE IN YOUNG PREGNANT WOMEN 6-7 YEARS POST VACCINATION IN FIJI: A PROSPECTIVE COHORT STUDY


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Background and Aims

In 2008/9 Fiji received a donation of quadrivalent human papillomavirus (4vHPV) vaccine. Approximately 30,000 girls aged 9 – 12 years were targeted for vaccination. Not all girls received the full three dose schedule. We determined the 4vHPV dose effects of genotype 16/18 HPV infection rates 6-7 years post vaccination.

Methods

From October 2015, a prospective cohort study is being undertaken in young pregnant women (≤22y) in Suva, Fiji. Participants had a vaginal swab (FLOQSwab, Copan Italy) taken. Following HPV L1 gene DNA detection by PGMY-primer PCR and DNA ELISA, all HPV positive samples were genotyped using LINEAR ARRAY® HPV Genotyping Assay (ROCHE DIAGNOSTICS) with modification for the detection of up to 37 genotypes.

Results

So far, we have recruited 769 of 820 women: 0 dose n=370; 1 dose n= 107; 2 doses n=100; 3 doses n=190. Interim results on the first 714 samples are shown. There was a significant difference between the 0 and 3 dose (p-value <0.001) groups and borderline significant difference between the 0 and 1 dose groups (p-value = 0.057) in HPV 16/18 detection rates.

<table>
<thead>
<tr>
<th>HPV 16 / 18, n (%)</th>
<th>0 dose n = 370</th>
<th>1 dose n = 70</th>
<th>2 dose n = 77</th>
<th>3 dose n =187</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>53 (14.3)</td>
<td>4 (5.7)</td>
<td>0</td>
<td>3 (1.6)</td>
</tr>
</tbody>
</table>

Conclusions
The interim results provide supportive evidence of 4vHPV effectiveness using a two or three dose schedule and suggestive evidence that a single dose may reduce infection rates by ~60%. Recruitment is ongoing.
IPVC8-0442
RAPID COMMUNICATION

PUBLIC HEALTH

LINEAR SIZE OF CIN2 AND CIN3 DETECTED BY CYTOLOGY AND BY 12-MONTH PERSISTENT HPV INFECTION
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Background and Aims

HPV based primary screening detects CIN2/3 earlier than cytology. In the ALTS trial on management of women with ASC-US cytology, the CIN3 lesions found postenrollment after HPV testing involved the fewest tissue fragments but no significant difference was observed when comparing arms at enrolment or during all phases combined.

Methods

In Turin, Italy, from March 2010, women were invited to cytology- or HPV-based screening on random basis. The latter group, if HPV+, had reflex cytology and, with findings ≥ASC-US, referral to colposcopy in two centers. Otherwise, new 12-month HPV testing, with colposcopy if positivity persisted, was recommended. From before 2010 the longest linear size of treated lesions was routinely reported. We compared it by arm in the surgical pieces with CIN2/3 diagnosis obtained in reference centers.

Results

Linear length was significantly greater (p=0.0127 by Wilcoxon’s test) in the cytology (229 women; mean 6.65 mm ; SD 3.11) than in the HPV group (250 women; mean 6.19; SD 3.25). The linear size in the cytology group was not significantly different (p=0.39) from that in the 167 HPV+ women with baseline cytology ≥ASC-US (mean 6.63; SD 3.39) while the difference with the 83 HPV+ women with cytology <ASC-US at baseline (mean 5.31; SD 2.76 ) was highly significant (p<0.0001).

Conclusions

Primary HPV-based screening detects CIN2/3 when smaller than those detected by cytology. This is, however, limited to the cases detected by referring to colposcopy cytologically normal women with persistent 12-mont HPV positivity. Plausibly cytology’s sensitivity increases with lesions’ size.
PUBLIC HEALTH

KINETICS AND PROGNOSTIC VALUE OF HPV16 E6 ANTIBODY RESPONSE IN HIV-POSITIVE PERSONS AT HIGH ANAL CANCER RISK: THE SWISS HIV COHORT STUDY

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Background and Aims

HPV16E6 antibodies are markers of HPV neoplastic processes and may have early prognostic value for anal cancer among high-risk persons infected with HIV (PHIV), particularly MSM.

Methods

A case:control study of 91 anal cancers (including 57 MSM) and 257 controls [3:1 matched by age, year at enrolment, follow-up time, and risk group/gender (MSM, other male, female)] was nested in the Swiss HIV Cohort Study (1989-2017). Serum samples at enrolment and, for cases, every year up to cancer diagnosis, were tested for HPV16E6 antibodies using multiplex HPV serology developed at DKFZ.

Results

HPV16E6-seropositivity was 22.0% (20/91) in samples closest to anal cancer diagnosis, versus 0.8% (2/257) in controls (OR=34.9 [8.0-153]). HPV16E6-seropositivity was 23.8% (20/84) in samples within 1 year of cancer diagnosis, 20.3% (15/74) 1-2yrs, 16.7% (13/78) 2-4yrs, 4.4% (3/69) 5-9yrs, and 7.0% (3/43) 10yrs+ prior. Of 25 anal cancers HPV16E6-seropositive at any time during follow-up, the majority (n=18, 72%) remained HPVE6-seropositive in all samples following HPVE6-seroconversion. For 7 (18%) cases, at least one subsequent sample was below HPV16E6-seropositivity cut-off. HPV16E6-seropositivity close in time to cancer was not significantly related to age, current or nadir CD4+ cell count, nor risk group/gender. Further analyses will estimate anal cancer incidence according to HPVE6-serology results, including for sub-populations of PHIV (e.g. age group and risk group/gender).

Conclusions

HPV16E6-seropositivity is a specific, albeit insensitive, marker that can appear many years prior to anal cancer diagnosis, suggesting possible utility for prioritizing highest-risk groups for early detection and treatment of anal (pre)cancer.
Clinical validation of Liferiver Harmonia HPV assay using the VALGENT-4 framework

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Background and Aims

To evaluate clinical performance of the Liferiver Harmonia HPV assay (Harmonia) using the international validation of HPV Genotyping Tests (VALGENT-4) framework.

Methods

The VALGENT-4 panel consisted 1,297 samples from women aged 30-59 years who participated in the Danish cervical cancer screening program (998 consecutive samples from routine screening enriched with 299 cytological abnormal samples). Harmonia identifies separately HPV16 and HPV18 and 12 other hrHPV types in aggregate. Disease was defined as histologically confirmed CIN2+ (n = 119 [denominator for sensitivity]), whereas two consecutive negative cytology was accepted as proxy for non-disease (n = 898 [denominator for specificity]). Performance relative to GP5+/6+-PCR-LMNX (standard comparator test) was assessed by a non-inferiority test. Intra/inter-laboratory reproducibility of Harmonia was performed in a subset of 500 randomly selected samples. Full clinical performance of Harmonia was analysed as per the criteria defined by Meijer et al. in 2009.

Results

The relative sensitivity and specificity of Harmonia vs GP5+/6+-PCR-LMNX was 1.06 (95% CI, 1.02-1.11; pₜₙᵢₙ < 0.001) and 0.97 (95% CI, 0.85-0.90; pₜₙᵢₙ = 1.000), respectively. Application of an optimised a-posteriori cut-off for HPV16, HPV18 and 12 other hrHPV types led to the relative values of 1.04 (95% CI, 0.99-1.08; pₜₙᵢₙ < 0.001) and 1.01 (95% CI, 0.99-1.03; pₜₙᵢₙ = 0.002), respectively. The assay showed good intra/inter-laboratory reproducibility (reproducibility ≥ 95%).

Conclusions

At the predefined cut-off, Harmonia HPV was statistically more sensitive but less specific than the GP5+/6+-PCR-LMNX for the detection of CIN2+. However, when applied the optimised cut-offs, Harmonia fulfilled international criteria for its use in cervical cancer screening.
PUBLIC HEALTH

HOW EFFECTIVE IS CERVICAL SCREENING AT PREVENTING CERVICAL CANCER INCIDENCE? A POPULATION-BASED NESTED CASE-CONTROL STUDY IN THE UNITED STATES (US)

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Background and Aims

Most evaluations of cervical screening in the US have focused on women receiving healthcare within individual or integrated health systems. We evaluated the effectiveness of screening on a state-wide level across all healthcare delivery settings in New Mexico (NM).

Methods

A case-control study for all women diagnosed with cervical cancer in NM, 2006-2015, and cancer-registry matched controls, with screening registry data 2006-2015. We evaluated the effect of attending screening 5-40 months prior to diagnosis (ignoring screens <5 months as potentially symptomatic, and allowing a 4-month referral window) on the odds of cervical cancer, and the period of reduced risk following a negative screening test (including screens <5months prior to diagnosis).

Results

433 women aged 20-64y with ≥40 months screening history were diagnosed with cancer and included in the primary analysis; 62% (270/433) had not been screened in the past 3 years. Screening 5-40 months prior to diagnosis had no effect on stage 1 cancer, but lowered the risk of advanced (stage 2+) cancer (odds ratio (OR)=0.27,95%CI:0.19-0.38) compared to women not screened in that period. Women remained at lower risk of advanced cancer for 3 years following a negative screen (OR=0.19,95%CI:0.08-0.45), and stage 1 cancer for 2 years. Similar benefits were seen for squamous and adenocarcinoma. Women remained at reduced risk of advanced cancer through 5 years following a negative screen vs those not screened (OR for 3.5-5yrs=0.36,95%CI:0.17-0.77), though the reduction was attenuated compared to 3 years.

Conclusions

Triennial screening is sufficient to prevent the majority of advanced cervical cancers in women aged 20-64y.
HARNESSING THE ENDORSEMENT OF NCI-DESIGNATED CANCER CENTERS TO IMPROVE UPTAKE OF HPV VACCINATION IN THE US

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Background and Aims

In the US, 69 National Cancer Institute (NCI)-designated Cancer Centers receive peer-reviewed support from the NCI to make cancer-related scientific discoveries that challenge existing paradigms, improve clinical care, or advance public health practices, thereby reducing the burden of cancer on individuals and at the population level. These Centers are expected to be a scientifically-credible and impactful resource in their self-defined geographic catchment areas. In 2014, 18 Centers were awarded supplements to examine the status of human papillomavirus (HPV) vaccination.

Methods

At the second annual meeting of awardees in 2016, we proposed to amplify the impact of NCI Centers’ individual efforts by drafting and releasing a single joint statement endorsing “HPV vaccination as cancer prevention” in alignment with the Centers for Disease Control and Prevention’s statement. The process was repeated in subsequent years highlighting major new milestones regarding the HPV vaccine: 1) 2017 – administration schedule revision from three to two doses for children <15 years of age; and 2) 2018 – American Cancer Society’s and IPVS’ statements on “cervical cancer elimination” as an aspirational, yet achievable, goal.

Results

This presentation will discuss establishment of the planning committee; the methods used to craft the joint statements and obtain endorsements from all Center Directors; press/media coordination; and the results of this process in terms of the statements, media coverage and HPV vaccination rates.

Conclusions

The process used in the US cancer community can serve as a model for other countries seeking impactful, collaborative actions to improve HPV vaccination.
IPVC8-0264
RAPID COMMUNICATION

PUBLIC HEALTH

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME AFTER HUMAN PAPILLOMAVIRUS VACCINATION
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Background and Aims

In the United States, the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD) are two primary post-licensure safety monitoring systems. To address concerns of postural orthostatic tachycardia syndrome (POTS) following HPV vaccination, we conducted a review of POTS reports to VAERS and have initiated an epidemiologic study of POTS in VSD.

Methods

POTS reports identified in VAERS following any type of HPV vaccination from 2006-2015 were reviewed and established POTS diagnostic criteria were applied. We calculated reporting rates based on HPV vaccine doses distributed and conducted empirical Bayesian data mining to screen for disproportional reporting of POTS following HPV vaccination. In VSD, we will identify presumptive POTS cases among 9-30 year olds using internal diagnosis codes for the period 2011-2017. Medical record review will be conducted and HPV exposure will be determined.

Results

Among 40,735 VAERS reports, 29 POTS reports fully met the diagnostic criteria. 27 (93.1%) were females and mean age was 14 years (range 12-32). Median time from vaccination to start of symptoms was 43 days (range 0-407). Twenty (68.9%) reports documented a history of pre-existing medical conditions such as chronic fatigue, asthma, and chronic headache. Approximately one POTS case is reported for every 6.5 million HPV vaccine doses distributed in the United States. No empirical Bayesian data mining signals for POTS and HPV vaccination were detected.

Conclusions

POTS is rarely reported following HPV vaccination. To our knowledge, the VSD study will be the first large population-based study to evaluate the relationship between POTS and HPV vaccination.
Background and Aims

Published case series have suggested a potential association between human papillomavirus (HPV) vaccination and primary ovarian insufficiency (POI). We describe POI incidence and estimate POI risk following HPV, tetanus-diphtheria-acellular pertussis (Tdap), inactivated influenza (IIV), and meningococcal conjugate (MenACWY) vaccination.

Methods

We searched Kaiser Permanente Northwest electronic health records for outpatient diagnoses suggestive of POI in females 11-34 years old between 2006 and 2014. We reviewed and adjudicated the medical record to confirm diagnoses and estimate symptom onset dates. We excluded POI cases with known causes and calculated the incidence of idiopathic POI. We estimated POI risk by calculating hazard ratios (HRs) and 95% confidence intervals (CIs).

Results

From a cohort of 199,078 females (58,871 vaccinated against HPV), we identified 120 with diagnoses suggestive of POI. After adjudication, and exclusion of 26 POI cases with known causes, we confirmed 46 idiopathic POI cases. POI incidence was low in 11-14 year olds (0.87 per 1,000,000 person-months) and increased with age. One confirmed case received HPV vaccine 23 months prior to the first clinical evaluation for delayed menarche. The adjusted hazard ratio was 0.30 (95% CI: 0.07-1.36) after HPV, 0.88 (95% CI: 0.37-2.10) after Tdap, 1.42 (95% CI: 0.59-3.41) after IIV, and 0.94 (95% CI: 0.27-3.23) after MenACWY vaccination.

Conclusions

We did not find a statistically significant elevated risk of POI after HPV, Tdap, IIV, or MenACWY vaccination in this population-based retrospective cohort study. These findings should lessen concern about POI risk following adolescent vaccination.
Background and Aims

Background: Cervical cancer is a leading cause of cancer-related deaths in Botswana with a mortality rate of 23.1% (WHO, 2014). In 2012, MOHW introduced Visual Inspection with Acetic acid (VIA), a method which can improve linkage to treatment for VIA positive clients. In both Pap and VIA programs, increasing screening coverage and access to screening to treatment remains a significant challenge. It is anticipated that HPV self-testing could improve coverage and treatment rates by referring only those who test HPV positive for determination of treatment type.

Methods

Methods: A prospective cohort study was conducted among women aged 30-49 years from five health facilities in Kweneng East district, Botswana over six-months. Vaginal self-collected samples for HPV were transported to a central laboratory using Cepheid GeneXpert® and clients were longitudinally tracked using tablets in Dimagi’s CommCare to ensure result notification and appropriate treatment. All clients who tested positive were offered treatment (cryotherapy or LEEP) after VIA triage.

Results

Results: Of the 1022 samples tested, 99.7% women had conclusive results. 99.7% were notified of their results, within 7 days. 91% (312/343) had positive HPV results and returned to the clinic and 85% received VAT within 3 weeks of initial testing. 97.4% (304/312) of those who returned for VAT completed treatment with 88% treated with cryotherapy and 8.2% receiving LEEP.

Conclusions

Conclusions: HPV self-collection could be a primary screening option for cervical cancer prevention programs with active client notification and follow-up to improve the completion rates for screening and treatment for women with abnormal results.
IPVC8-0707
RAPID COMMUNICATION

PUBLIC HEALTH

ACCURACY OF VISUAL INSPECTION WITH ACETIC ACID FOR CERVICAL CANCER SCREENING: A POOLED ANALYSIS OF 15 POPULATION-BASED STUDIES IN CHINA

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Background and Aims

Visual inspection with acetic acid (VIA) is recommended by International Agency for Research on Cancer as a complementary cervical cancer screening method in low-resource settings. This study aimed to assess the accuracy of visual inspection with acetic acid (VIA) for cervical cancer screening in China.

Methods

We did a pooled analysis of 15 population-based cervical cancer screening studies done in mainland China from 1999 to 2008 with concurrent HPV DNA testing (Hybrid Capture 2 assay), liquid-based cytology and VIA. All women positive for any test were referred for colposcopy and biopsy. The accuracy of VIA for detecting cervical intraepithelial neoplasia (CIN) grade 2 or worse (CIN2+) or CIN grade 3 or worse (CIN3+) were analyzed, stratified by age groups.

Results

A total of 28,446 women were included in the analysis. The pooled sensitivity and specificity of VIA were 50.3% and 89.8% for CIN2+, and 57.3% and 89.3% for CIN3+. The sensitivity showed a downtrend with the increase of age (from 66.7% at 15-29 years to 29.7% at 50-59 years for CIN2+; from 77.8% at 15-29 years to 45.0% at 50-59 years for CIN3+; all \( P_{\text{trend}} < 0.01 \)), while the specificity rose (all \( P_{\text{trend}} < 0.001 \)). Moreover, the positive rate of VIA declined from 15.5% at 15-29 years to 6.4% at 50-59 years (\( \chi^2 = 115.982, P_{\text{trend}} < 0.001 \)). And the risk of CIN2+ or CIN3+ ascended with the number of abnormal quadrants observed by VIA (all \( P_{\text{trend}} < 0.001 \)).

Conclusions

VIA is not suitable for elder women due to lower sensitivity. Sustained training and practice are required to improve the performance of VIA.
OVERCOMING BARRIERS TO ADOLESCENT VACCINATION: PERSPECTIVES FROM CHAMPION VACCINE PROVIDERS IN NORTH CAROLINA, USA

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Background and Aims

We summarized strategies used in North Carolina (N.C.) clinics to achieve high adolescent coverage of tetanus-diphtheria-acellular pertussis (Tdap), meningococcal conjugate (MenACWY), and human papillomavirus (HPV) vaccination.

Methods

Convenience sampling was used to recruit 20 clinics with adolescent vaccination rates higher than the state average ("Champions"). One vaccine provider or staff member per clinic completed a semi-structured survey on clinic characteristics and strategies for improving adolescent vaccination coverage.

Results

Most clinics had standing orders to administer vaccines to adolescents (Tdap, MenACWY: 75%; HPV: 70%). The most commonly reported barriers for all adolescent vaccinations were parental opposition due to lack of information or negative media coverage, and logistical barriers to presenting for vaccination. Specifically, for HPV vaccination, providers cited concerns related to sexual behavior and pain; lack of a school requirement; and low perceived benefit in boys. Most clinics (80%) had implemented a successful change to improve adolescent vaccination coverage, including consistently offering vaccination, database tracking of vaccination status (i.e. N.C. Immunization Registry and patient health records), providing reminders for vaccination appointments, educating providers on vaccination recommendations, and expanding vaccination hours. Most clinics liaised with the N.C. Immunization Branch to improve vaccination coverage (60%). Adolescent vaccination champions strongly recommended vaccination to parents (55%) and educated parents on vaccination recommendations (36%). Unique strategies to improve HPV vaccination included co-administration with Tdap and with MenACWY, and providing reminders to complete the vaccination series.

Conclusions
Clinics in N.C. and across the U.S. can implement complementary accessible and low-resource strategies to overcome adolescent vaccination barriers.
IPVC8-0587
RAPID COMMUNICATION

PUBLIC HEALTH

UNDERSTANDING PARENT’S STAGE OF DECISION-MAKING: A PRECAUTION ADOPTION PROCESS MODEL
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Background and Aims

Despite being an effective cancer prevention strategy, HPV vaccination in Canada remains suboptimal. This study is the first to concurrently evaluate HPV vaccine knowledge, attitudes, and the decision-making stage of Canadian parents for their school-aged daughters and sons.

Methods

Data were collected through an online survey from a nationally representative sample of Canadian parents of 9-16 year old children from August to September 2016. Measures included socio-demographics, validated scales to assess HPV vaccine knowledge and attitudes, and parents’ HPV vaccination adoption stage using the Precaution Adoption Process Model (PAPM; six stages: unaware, unengaged, undecided, decided not, decided to, or vaccinated).

Results

3,779 parents’ survey responses were analyzed (1,826 parents of sons and 1,953 parents of daughters). There was a significant association between child’s gender and PAPM stage of decision-making (p<.001), with parents of boys more likely to report being in earlier PAPM stages. In multinomial logistic regression analyses parents of daughters, parents of older children, and parents with a health care provider recommendation had decreased odds of being in any earlier PAPM stage as compared to the last PAPM stage (i.e. vaccinated). Parents who were in the ‘decided not to vaccinate’ stage had significantly greater odds of reporting perceived vaccine harms, lack of confidence, risks, and vaccine conspiracy beliefs as compared to those who had vaccinated their child.

Conclusions

Future research could use these findings to investigate theoretically informed interventions to specifically target subsets of the population with particular attention towards addressing knowledge gaps, perceived barriers, and concerns of parents.
LEVERAGING SIMULATION MODELS TO EXPLORE THE NATURAL HISTORY OF CERVICAL CARCINOGENESIS: A CISNET COMPARATIVE MODELING ANALYSIS

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Background and Aims

The natural history of HPV-induced cervical cancer is largely unobservable, yet the age of HPV acquisition and duration of preclinical disease (dwell time) impacts the effectiveness of alternative vaccination and screening policies. We explored differences in implicit model assumptions about HPV natural history using four independent models from the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium.

Methods

We used four CISNET-cervix natural history models (Policy1-Cervix, MISCAN-Cervix, Harvard, and University of Minnesota (UMN)) to project outcomes for a hypothetical cohort of individuals. The independently-developed models were calibrated to observed US epidemiological data, but varied in their underlying structure and assumptions about the carcinogenic process. For women with a cervical cancer diagnosis in the absence of screening or vaccination, we calculated the age of acquisition of the causal HPV infection, and dwell times associated with preclinical phases of cancer development.

Results

There were important similarities and differences between natural history models including the age of acquiring vaccine-preventable HPV infections, duration of screen-detectable precancers, and how these varied between HPV genotypes. For example, the median total dwell time from HPV acquisition to cancer detection was shortest for MISCAN-Cervix (17 years), followed by UMN (23 years), Harvard (26 years), Policy1-Cervix (27 years).

Conclusions

Our findings may have important implications for prevention policies, including vaccination programs and screening interval. As the complexity of models increases, understanding the impact of differences between model structures can elucidate important drivers of cervical cancer policy and provide guidance for areas of future research.
Background and Aims

The WHO recommends a 2-dose HPV vaccination schedule for girls ages 9–14 years, yet several studies have demonstrated similar protection with one dose. Our objective was to project the long-term health and economic impacts of routine one-dose HPV vaccination compared to 1) no vaccination and 2) two-dose HPV vaccination in Uganda.

Methods

We used a three-tiered hybrid modeling approach that captured HPV transmission, cervical carcinogenesis, and population demographics to project long-term health and economic outcomes associated with one-dose HPV vaccination (assuming 80% efficacy against HPV-16/18 infections under three waning scenarios) and two-dose HPV vaccination (assuming 100% efficacy over the lifetime) in Uganda. Costs included the vaccine program (dosage and delivery) costs over a 10-year period and cervical cancer costs over the lifetimes of the current population of Ugandan women. Incremental cost-effectiveness ratios (i.e., cost per disability-adjusted life years (DALY) averted) were calculated and compared against the Ugandan per-capita gross domestic product.

Results

Routine one-dose HPV vaccination of 9-year-old girls was cost-saving compared to no vaccination when accounting for the cost-offsets from future cancers averted. Under base case assumptions, one-dose vaccination averted ~19% fewer cases than two-dose vaccination but required only half the upfront economic investment. Vaccination with two doses had an attractive cost-effectiveness profile except if one-dose vaccination enabled higher coverage (90% vs. 70%) and did not wane.

Conclusions

One-dose HPV vaccination resulted in cost-savings compared to no vaccination and could be cost-effective compared to two-dose vaccination if protection is longstanding and higher coverage with differential outreach programs could be achieved.
HPV35 A2 SUBLINEAGE CONFERS INCREASED RISKS OF CERVICAL PRECANCER/CANCER IN AFRICAN-AMERICAN WOMEN USING 1,047 HPV35 GENOMES

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Background and Aims

HPV35 is estimated to cause 2% of invasive cervical cancers (ICC) worldwide, but is particularly prevalent in Sub-Saharan Africa where it may account for 4-10% of ICC. To assess if cervical precancer/cancer risks differ by HPV35 sublineages and are modified by a women's race/ethnicity, we whole-genome sequenced 1,047 HPV35-positive specimens from two large studies: the U.S. NCI-KPNC PaP study and the international collection of specimens by IARC.

Methods

We assessed HPV35 sublineage associations with worst histologic outcome, including 179 CIN2, 95 CIN3/cancer, and 334 controls (≤CIN1 or cleared-infection), and self-reported race/ethnicity, using NCI-KPNC PaP specimens. The worldwide distribution of sublineages was evaluated in 439 IARC cervical specimens, of which 21% were ICC and 50% were from Africa. Phylogenetic analyses classified sublineages. Logistic regression models estimated relative risks of CIN2+.

Results

Risks of CIN2+ associated with HPV35 sublineages, as well as with finer phylogenetic subgroups and individual SNPs, were modified by a women's race/ethnicity. In PaP, HPV35 A2 sublineage was riskier for African-American women compared with all other races (OR=3.63, 95%CI=1.20-11.02); in particular, African-American women had a 10-fold increased CIN3+ risk if infected with A2 compared to White women (OR=10.00, 95%CI=1.03-97.48). In IARC data, the prevalence of HPV35 lineages significantly differed in ICC by region (p=1.96x10⁻⁴); A2 was the most prevalent in Sub-Saharan Africa (52%).

Conclusions

HPV35 sublineages vary in risks of precancer/cancer and risk was modified by a women's race/ethnicity. This suggests that specific HPV35 sublineages are of greater importance in African ancestry women in the U.S., as well as in Sub-Saharan Africa.
MODEL ESTIMATED COST-EFFECTIVENESS OF INTEGRATING CERVICAL CANCER SCREENING AND TREATMENT WITH LEEP VERSUS CRYOTHERAPY INTO HIV CARE CLINICS IN KENYA
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Background and Aims
HIV-infected women have 2-fold higher cervical cancer (CC) risk. Integrating screening into HIV clinics may reduce CC. Lesions are often treated with cryotherapy in resource-limited settings but recent evidence suggests LEEP may be more effective in HIV-positive women. We sought to evaluate the cost-effectiveness of screening and treatment strategies for HIV-positive women in ART care.

Methods
Using effectiveness and cost data from Kenya, we parameterized a mathematical model of HPV pathogenesis in HIV-infected women. We evaluated cytology, visual inspection with acetic acid (VIA), and HPV DNA testing combined with cryotherapy and LEEP treatment. We varied number of visits required for precancer treatment.

Results
Assuming screening four times per lifetime (every five years, age 25-40), HPV DNA testing with LEEP treatment was the most effective strategy that was also cost-effective, reducing CC burden by 39% with an incremental cost-effectiveness ratio (ICER) of $1,342/year of life saved (YLS). VIA was projected to reduce CC incidence by 25% when combined with cryotherapy and 28% with LEEP; both strategies were cost-effective, with ICERs of $205 and $1,116/YLS, respectively. All cytology strategies were more costly and less effective than other strategies. If cryotherapy occurred in the same visit as screening results while LEEP required a follow-up visit, no LEEP strategies were cost-effective; HPV with cryotherapy was the most cost-effective strategy (ICER: $1,217/YLS).

Conclusions
Integrating CC screening with VIA or HPV DNA testing and treatment with LEEP into ART clinics provides moderate health benefits over cryotherapy and is cost-effective if cryotherapy and LEEP require the same number of visits.
<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cancer incidence reduction, %$^b$</th>
<th>Cancer mortality reduction, %$^c$</th>
<th>ICER ($ per year of life saved)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td>--</td>
<td>--</td>
<td>Dominated</td>
</tr>
<tr>
<td>Pap (HSIL+), cryo</td>
<td>10.8 (7.5-14.3)</td>
<td>13.8 (10.1-17.3)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Pap (HSIL+), LEEP</td>
<td>12.8 (9.1-16.8)</td>
<td>15.8 (11.7-19.8)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Pap (ASCUS+), cryo</td>
<td>17.1 (12.2-21.2)</td>
<td>20.5 (15.1-24)</td>
<td>Dominated</td>
</tr>
<tr>
<td>Pap (ASCUS+), LEEP</td>
<td>19.9 (14.4-24.1)</td>
<td>23.1 (17.3-27.1)</td>
<td>Dominated</td>
</tr>
<tr>
<td>VIA, cryo</td>
<td>25.2 (21.6-29.6)</td>
<td>28.1 (24.3-31.8)</td>
<td>205 (55-319)</td>
</tr>
<tr>
<td>VIA, LEEP</td>
<td>28.8 (25.0-33.5)</td>
<td>31.5 (27.5-35.6)</td>
<td>1,116 (554-1,731)</td>
</tr>
<tr>
<td>HPV, cryo</td>
<td>35.2 (31.4-40.5)</td>
<td>37.8 (34.2-42.6)</td>
<td>Dominated</td>
</tr>
<tr>
<td>HPV, LEEP</td>
<td>39.2 (35.2-44.8)</td>
<td>41.6 (37.5-46.7)</td>
<td>1,342 (729-2,009)</td>
</tr>
</tbody>
</table>

$^a$Assuming precancer treatment requires a follow-up clinic visit after screening results. ASCUS+: atypical squamous cells of undetermined significance or worse; HSIL+: high grade squamous intraepithelial lesion or worse; Pap: cytology screening; cryo: cryotherapy; ICER: incremental cost-effectiveness ratio

$^b$Values represent the average model output across the 50 best-fitting parameter sets from the calibrated model; values in parentheses indicate the minimum and maximum values across the 50 parameter sets. Strategies are listed in order of increasing cost.

$^c$Cancer reduction for each strategy reflects the percentage reduction in the absolute lifetime risk of cervical cancer incidence or mortality compared with no screening.
CANCER PREVENTION AND CONTROL AS PART OF UNIVERSAL HEALTHCARE COVERAGE: IMPLICATIONS FOR CERVICAL CANCER FOR THE WORLD HEALTH ORGANIZATION 2017 COUNTRY CAPACITY SURVEY

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Background and Aims

To assess the global status of package service availability (best buys and cost effective services), population coverage and policy cohesion.

Methods

Responses from the 2017 WHO Country Capacity Survey were used. This survey addresses cancer control plans, registries, primary prevention, screening, treatment and palliative care. All analyses were conducted in STATA 13 and provided in terms of WHO region and World Bank income strata.

Results

HPV vaccination exists in 53% of countries but only 24% of countries have at least 50% population coverage. Cervical screening is offered in 76% of countries but coverage is only 10-50% of the population in 30% of countries. Only 21% of countries were able to provide the NCD best buy package. No low or low middle income country provided this package of services. The most common missing service was radiation. In 58% of countries there were guidelines and surgery/radiation/chemotherapy. In 13% of countries that offered cervical cancer screening there was no treatment available and in 40%, there was no palliative care. Only 40% of countries had both cervical cancer screening and HPV vaccination coverage of more than 70%. In 25% of countries screening coverage was low but vaccination rates covered 10-50% of the population (a clear policy choice of one strategy over another).

Conclusions

Where resources are limited, implementation of cervical cancer care involves a step wise approach of having treatment and palliative care prior to implementing screening. Optimizing coverage and screening the appropriate women will provide return on investment.
Background and Aims

Genital wart (GW) incidence is high among men and continues to occur in older men. The percentage and rate at which subsequent GW events occur is understudied, leading to underestimation of the benefit of HPV vaccination to prevent GW caused by HPV 6/11. The purpose of this study was to describe the rate at which subsequent GWs occur, the associated HPV types, and time to a subsequent GW event among unvaccinated men.

Methods

The study was nested within the HIM Study, a multi-national prospective HPV natural history study of men ages 18-70 years in USA, Mexico, Brazil, examined every 6 months clinically for a median follow-up of 50.4 months (up to 129.2 months). Subsequent GW events were defined as GWs detected after >16 weeks of the prior event.

Results

44.3% of men experienced >1 GW following the initial episode and 6.5% experienced >4 subsequent events. Men with >2 subsequent events were at highest risk of continued GW experiences, with as high as 10 post-initial GW events. The incidence rate of each subsequent GW increased with increasing events (incidence of a first subsequent event was 13.1 vs 36.6/1,000 person-months for the 4th event). Age was not associated with the proportion diagnosed with subsequent GWs or the incidence rate. The proportion of GWs HPV 6 and/or 11 positive remained constant across events (~63-69% positive for >1 9-valent HPV vaccine types).

Conclusions

These data highlight the high burden of GW among men across the lifespan and the need for vaccination to prevent multiple GW episodes.
HPV PREVALENCE AMONG MALES AND FEMALES IN A NATIONALLY REPRESENTATIVE SURVEY, UNITED STATES

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Background and Aims

Evaluation of population-based HPV prevalence can provide important information on HPV epidemiology. We previously reported any HPV and high risk (HR) HPV prevalence, by sex and age group, in the United States. In this analysis, we extend investigations to include evaluation of quadrivalent vaccine (4vHPV) types.

Methods

We evaluated HPV prevalence overall and by sex and age group, using data from U.S. National Health and Nutrition Examination Survey, 2013-2014. Self-collected penile and cervicovaginal swabs were tested by PCR for 37 HPV types. Prevalence of any HPV, any 14 HR, and 4vHPV types were estimated for 1757 males and 1985 females. We compared males to females, calculated prevalence ratios (PR) and 95% confidence intervals (CI).

Results

Prevalence of any HPV among males and females was 45.2% and 39.9% (PR=1.13, 95% CI 1.04-1.24); HR-HPV, 25.1% and 20.4% (PR=1.23, 95% CI 1.09-1.39); 4vHPV, 8.5% and 5.5% (PR=1.54, 95% CI 1.09-2.16). Sex differences varied by age group; any and HR HPV were lower among males than females in 18-24 year-olds, but similar or higher at older ages (Table). Findings for 4vHPV were similar although differences by sex were significant only in the oldest age group.
Conclusions

Overall prevalence of any HPV, HR-HPV and 4vHPV were higher in males than females. Variation in prevalence by age group might be due to sex differences in the natural history of HPV infection and/or sexual behavior. Data on HPV prevalence across age groups can further inform vaccination policy and vaccine impact monitoring.
Background and Aims

In the context of HPV-based cervical cancer screening, the most suitable follow-up strategy for HPV-positive and cytology-negative women is still debated. Long-term type-specific HPV clearance may be an appropriate follow-up strategy but limited data are available. For 14 high-risk (hr) HPV types, we estimated type-specific five-year clearance and progression probabilities.

Methods

We included 829 hrHPV-positive and cytology-negative women at baseline (POBASCAM cohort). We discretized time at the target screening visit times: one-year (first round repeat test, time <4 years) and five-year (second round, time ≥4 and <9 years). With a tree-approach analysis, we calculated type-specific proportions for: i) clearance, ii) persistence and no CIN2, iii) CIN2, and iv) progression to ≥CIN3. In addition, we investigated the clearance hazard over continuous time with a parametric Weibull model for interval censored data.

Results

Five-year pooled type-specific estimates were: 74.1% for clearance; 11.2% for persistence and no CIN2; 5.0% for CIN2; 9.7% for progression to ≥CIN3. The HPV types that showed the lowest clearance were HPV16 (58.0%), HPV31 (70.6%), HPV18 (74.2%), and HPV52 (77.3%). HPV56, HPV66, and HPV68 showed clearance proportions >90% and no progression to ≥CIN3. The probability of clearance decreased at rate 0.27 per year the first two years and on average at 0.57 per year thereafter.

Conclusions

After five years, the majority of women cleared the infection and most women without clearance showed clinical progression. The small remaining group of women without clearance and progression had a decreased risk of clearance. Therefore, five-year type-specific persistence is a reason for immediate referral to colposcopy.
HPV E4 EXPRESSION AND DNA HYPERMETHYLATION OF CADM1, MAL, AND MIR124-2 GENES IN CERVICAL CANCER AND PRECURSOR LESIONS

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Background and Aims

In this study we evaluate the expression of the Human Papillomavirus (HPV) E4 protein (marker for the onset of a productive infection) and hypermethylation of host cell genes (marker for an advanced, transforming infection) in cervical intraepithelial neoplasia (CIN) and cancer.

Methods

One-hundred-fifteen cervical lesions were categorized as no dysplasia, CIN1, CIN2, CIN3 or cancer by classical histomorphological grading, and by an immunoscore grading system (cumulative value 0-6) based on Ki-67 (score 0-3) and p16⁰ink⁴a (score 0-3) expression. Lesions were immunostained for E4 protein and analyzed for hypermethylation of CADM1, MAL, or miR124-2 genes.

Results

Hypermethylation increased with severity of the lesion as defined by both classical histomorphological grading and immunoscore criteria, and was always present in carcinomas (22/22). Extensive E4 expression decreased with increasing CIN grade and immunoscore, being most frequent in classically graded CIN1 or in lesions with immunoscore 1-3, and absent in carcinomas. High-grade lesions (CIN2/3 or immunoscore 4-6) showed less E4 expression, which was inversely related to an increasing hypermethylation. Extensive E4 expression, as observed in a small proportion of high-grade lesions (6/49 and 8/43 respectively), was mostly associated with a negative methylation marker status (5/6 and 7/8 respectively).

Conclusions

Our results illustrate the gradual transition of productive CIN (reflected by extensive E4 expression) to advanced transforming CIN (reflected by extensive hypermethylation) and cancer. Expression patterns of E4 and hypermethylation status of host cell genes may be used to identify cervical lesions at risk for cervical cancer, providing a better guidance for clinicians on treatment decisions.
CLINICAL

PERSISTENCE OF HPV SAME-GENOTYPE AFTER TREATMENT OF HIGH-GRADE CIN: TEST OF CURE CLINICAL UTILITY

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Background and Aims

Two systematic reviews of HPV testing after treatment of ≥CIN2 were published in 2012. Two narrative reviews of HPV testing after treatment of ≥CIN2 were published in 2016. Guideline originators have not yet included an analysis of the body of science published recently about the clinical value of extended HPV genotyping in follow-up of women who were treated for high-grade CIN.

Methods

For this systematic review, PubMed was searched from 2001 through 2018 for relevant studies, and supplemented by hand-searching. Eligible studies included studies of women and retrospective studies of residual specimens from women who had been pretested and underwent treatment for high-grade CIN and were retested using HPV genotyping tests and had histopathology results. The reference standard was ≥CIN3. The timeframe for follow-up was ≥6-months.

Results

A PRISMA flow diagram is presented. Ten original research articles, with 2888 women, met inclusion and exclusion criteria. Persistence of the same HPV genotype confers a higher risk of ≥CIN3 than a new infection, by two orders of magnitude. Within persistence, there is a greater than tenfold risk stratification from highest with HPV 16 to lowest with HPV 56/59/66.

Conclusions

Reporting HPV genotype results provides critical discrimination and stratification of ≥CIN3 risks at test-of-cure. HPV genotyping could be utilized as follow-up to distinguish type-specific persistence versus clearance, to support risk-based clinical decisions, and reduce unnecessary retreatment. Guideline panels must decide whether to separate reporting by individual genotypes or to group genotypes with similar risks into risk tiers.
Co-expression of HPV E6, E7 mRNA and PD-L1 in cervical cytology samples

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Background and Aims

HPV infection in most women is transient and clears over time. For others, the virus is persistent and can lead to pre-cancerous lesions and subsequently cervical cancer. The relatively high regression rate of cervical intraepithelial lesions (CIN) has similarly been attributed to engagement of the immune response directed against neoplastic cells. Recent advances in immuno-oncology have shown the dramatic effects of PD-1/PD-L1 inhibitors in epithelial tumors including squamous cell carcinoma and adenocarcinoma, the major cancer subtypes in the female genital tract. Here, we present a novel assay that combines RNA in situ hybridization for HPV E6, E7 mRNA, cell cycle analysis, and PD-L1 cell surface staining on epithelial cells in liquid-based cervical cytology specimens.

Methods

Forty-six residual cervical cytology specimens were obtained for this study: 25 HPV DNA-, 12 LSIL HPV DNA+, and 9 HSIL HPV DNA+. Samples underwent in-situ hybridization with E6,E7 mRNA probes and a cell cycle dye. Anti-PD-L1 antibody was added following in-situ hybridization. Samples were collected on a Beckman Coulter CytoFLEX. Samples were deemed positive or negative for E6,E7 and Post G1 expression by a dual cut-off of 3.15%. PD-L1 expression was determined based on a cut-off of 2%.

Results

<table>
<thead>
<tr>
<th>HPV DNA</th>
<th>Positive % E6,E7 and Post G1</th>
<th>Positive % PD-L1</th>
<th>% Dual E6,E7 and PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>24% (6 of 25)</td>
<td>24% (6 of 25)</td>
<td>83% (5 of 6)</td>
</tr>
<tr>
<td>LSIL</td>
<td>50% (6 of 12)</td>
<td>25% (3 of 12)</td>
<td>50% (3 of 6)</td>
</tr>
<tr>
<td>HSIL</td>
<td>33% (3 of 9)</td>
<td>11% (1 of 9)</td>
<td>33% (1 of 3)</td>
</tr>
</tbody>
</table>

Conclusions

In this study we show dual E6,E7 and PD-L1 expression on the same sample. HPV and PD-L1 expression on cell by cell basis is not currently available in a single test by any other method. It appears PD-L1 expression decreases in high grade lesions indicative of immune surveillance which could support therapeutic options.
Background and Aims

Cervical cancer screening is transitioning from cytology to HPV testing. A negative HPV test provides great reassurance against precancer and cancer, but triage tests are needed to decide which HPV-positive women require colposcopy. We evaluated the clinical performance of liquid-based cytology (LBC), p16/Ki-67 dual stain (DS), and HPV16/18 genotyping for triage of HPV-positive women.

Methods

We included 3,331 HPV-positive women aged 25-65 undergoing co-testing at Kaiser Permanente Northern California (KPNC). Computer-assisted LBC, DS (CINtec PLUS), and HPV16/18 genotyping (cobas) were conducted at KPNC. We calculated clinical performance for detection of CIN3 or greater (CIN3+) within 24 months. We compared absolute risk for triage tests to clinical thresholds for immediate colposcopy and 1-year retesting.

Results

DS-positivity was significantly lower than LBC-positivity (ASC-US+) (50.3% vs. 60.4%, respectively; p<0.001). The specificity of DS for detection of CIN3+ was significantly higher than LBC (52.6% vs 41.4%, p<0.001), while sensitivity was nominally higher. DS-positivity indicated a higher risk than ASC-US+, while DS-negative women had a risk below the 1-year repeat threshold. Combined DS and HPV16/18 had lower positivity, higher specificity, and equal sensitivity compared to LBC with HPV16/18. The lowest risk was observed in DS-negative, HPV16/18-negative women. All strategies based on DS required substantially fewer colposcopies for detection of CIN3+ compared to LBC.

Conclusions

We demonstrate that DS can replace cytology with higher accuracy, greater immediate precancer detection, and substantially reduced colposcopy referral. Retesting intervals in DS-negative, HPV16/18-negative women can be safely extended to three years, reducing unnecessary colposcopies and treatment.
Rapid Communication

Clinical

Comparison of 2-dose and 3-dose regimens of 9-valent HPV vaccine: results from a 3-year randomized immunogenicity trial

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Background and Aims

We report 3-year persistence of HPV-antibody responses to the 9-valent HPV (9vHPV) vaccine among girls/boys receiving 2-dose regimens versus girls and young women receiving 3 doses.

Methods

In this international, randomized immunogenicity trial (NCT01984697), girls (age 9-14 years) received 2 doses of 9vHPV vaccine (Months 0.6 [n=301] or 0.12 [n=151]) or 3 doses (Months 0.2,6 [n=301]); boys (age 9-14 years) received 2 doses (Months 0,6 [n=301] or 0,12 [n=150]); and women (age 16-26 years) received 3 doses (Months 0,2,6 [n=314]). Anti-HPV geometric mean titers (GMTs) and seropositivity rates were assessed by competitive Luminex immunoassay through Month 36.

Results

Anti-HPV GMTs were highest 1 month after completing the 2-dose or 3-dose series, decreased sharply during the subsequent 6 to 12 months, then decreased more slowly through Month 36. At Months 24 and 36, GMTs in girls and boys given 2-dose regimens were generally similar to or greater than those in women given 3 doses. Month 36 seropositivity rates were ≥83.6% and 81.4% in girls and boys, respectively, vaccinated at Months 0.6; 87.9% among girls/boys vaccinated at Months 0.12; and 91.2% and 77.8% in girls and women, respectively, who received 3 doses.

Conclusions

HPV antibody responses persisted through 3 years in girls and boys who received 2 doses of 9vHPV vaccine, with GMTs similar to or greater than those observed in young women receiving 3 doses. Antibody responses generated by 2 doses in girls and boys may be sufficient to induce high-level protective efficacy through 36 months post-vaccination onset.
CLINICAL

PRECLINICAL STUDIES OF AN ORAL TABLET VACCINE TO TREAT HPV INFECTION AND HPV DERIVED TUMORS

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Background and Aims

Vaxart has developed an oral tablet vaccine platform which elicits strong systemic and mucosal immune responses. Several human clinical studies have been completed using this platform including vaccines to prevent influenza, RSV, and norovirus. In order to explore the ability of the platform to create therapeutic T cell responses, an HPV vaccine was made and tested in animals.

Methods

A vaccine was constructed that expressed the HPV-16 E6/E7 antigens (Ad-HPV). TC-1 cells (an HPV-16 transformed cell-line) were injected subcutaneously into C57Bl/6 mice, and allowed to grow for several days before mice were immunized with vaccine or controls. A checkpoint inhibitor (anti-PD-1) was used along with the vaccine in one group. A recombinant rAd vector identical to Ad-HPV, but doesn’t express the HPV antigens was used as an additional control. Survival and tumor size were measured for 65 days.

Results

The results showed use of Ad-HPV was able to stop tumor growth, create CD8 tumor infiltrating T cells, and eliminate the tumor. This occurred with or without the checkpoint inhibitor. The checkpoint inhibitor alone was not able to stop tumor progression, and all these animals perished. Other control animals without Ad-HPV also did not survive. The use of the checkpoint inhibitor with the Ad-HPV vaccine trended slightly better for survival (10/10 versus 9/10 survived), but this was not significant.

Conclusions

The ability to eliminate tumors in the TC-1 model was a promising first step. Preparations are being made to test the vaccine in human subjects next year.
CLINICAL

DEMETHYLATING TREATMENT INDUCES CELLULAR SENESCENCE IN HPV-TRANSFORMED CELL LINES

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Background and Aims

While the molecular biology of HPV-induced (pre-)cancer is well understood to date, still no targeted treatment exists for this disease. Hypermethylation of the HPV E2 binding sites (E2BS) within the viral upstream regulatory region of the HPV genome distorts the regulatory function of the E2 protein, promoting uncontrolled overexpression of the HPV E6/E7 oncogenes. Furthermore, aberrant methylation and associated silencing of tumor suppressor genes have been demonstrated in HPV-transformed cells. We hypothesized that treatment of HPV-transformed cells with demethylating agents could represent a novel, targeted treatment strategy for HPV-induced (pre-)cancer by reversing aberrant methylation of the viral and host genome and blocking associated transformation events.

Methods

A panel of seven HPV-transformed cell lines from the uterine cervix and the head and neck was subjected to treatment with the demethylating agent decitabine and analyzed for HPV oncogene expression and induction of cell death and senescence by various markers.

Results

A dose- and time-dependent down-regulation of HPV E6/E7 oncogene expression was demonstrated in the treated HPV-transformed cell lines. This finding was associated with significantly reduced proliferation. While a significant number of cells underwent apoptosis, a considerable proportion of cells were driven into cellular senescence. The induction of senescence, a phenomenon suppressed by HPV oncogene activity, was found to be dose- and time-dependent and evidenced by increased senescence-associated beta-galactosidase activity and markers of the senescence-associated secretory phenotype (SASP).

Conclusions

Demethylating treatment represents a promising treatment strategy for HPV-induced (pre-)cancer by blocking HPV oncogene expression and inducing apoptosis and cellular senescence.
TOPICAL ABI-1968, AN ACYCLIC NUCLEOSIDE PHOSPHONATE PRODRUG FOR TREATMENT OF HPV-ASSOCIATED ANAL AND CERVICAL HSILS

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Background and Aims

ABI-1968 (Octadecycloxyethyl benzyl 9-[(2-phosphonomethoxy)ethyl]guanine) is an acyclic nucleoside phosphonate prodrug of PMEG-pp under development for topical treatment of anal and cervical HSIL caused by hr HPV infection. ABI-1968 has potent activity against diverse lr and hr HPV genotypes, inhibiting HPV DNA synthesis in a luciferase reporter gene assay (EC₅₀ = 0.04 – 0.18 mM; CC₅₀ >10mM). It is also reported to be antiviral for productive HPV infection in 3D organotypic epithelial cultures causing DNA damage associated with induction of apoptosis in suprabasal strata. ABI-1968 is shown to induce DNA damage, S-phase arrest and induction of apoptotic markers in HPV-transformed cells. The ABI-1968 prodrug is designed to facilitate efficient transmembrane uptake into cells and controlled activation to PMEG-pp.

Methods

We have used data from cellular uptake and metabolism studies of ABI-1968 or cidofovir to model the integrated activation constants and intracellular elimination half-lives.

Results

The modeling reveals ABI-1968 is activated 8-fold more slowly and has an extended elimination half-life compared to cidofovir. These properties should result in slower accumulation of the active drug species following topical treatment, potentially minimizing local toxicities and permitting less frequent yet effective dosing regimens. ABI-1968 has been studied in 40 healthy volunteers and is now in two Ph1b studies (aHSIL and cHSIL). To date, ABI-1968 cream (0.01-1.0%) is well tolerated while preliminary improvements in histopathology and aHSIL appearance by HRA have been noted. No systemic exposure has been detected (assay LOQ = 0.2 ng/mL).

Conclusions

Topical ABI-1968 is a potential new therapy for HPV-associated anal and cervical HSILs.
TOWARDS QUALITY AND ORDER IN HUMAN PAPILLOMAVIRUS RESEARCH

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Background and Aims

The International Human Papillomavirus (HPV) Reference Center supports quality and order in HPV research and diagnostics. Notably, the center assigns HPV type numbers to novel HPV types, maintains a reference clone repository, and issues international proficiency panels for HPV genotyping.

The established HPV types, currently up to HPV225, belong to 5 different genera: alpha (65 types), beta (54 types), gamma (98 types), mu (3 types) and nu (1 type). Since 2014, 23 novel types have been established, 82.6% of which belong to the gamma genus.

Methods

Reference clones have been provided to 44 different research laboratories and the global proficiency program for HPV genotyping has seen an increasing participation (currently 146 laboratories). 141 datasets were submitted in the 2017 proficiency study.

Results

Complete proficiency has increased over time (from 26% to 66% of datasets). In 2017 21 datasets, 15% were not proficient (more than one false positive result) compared to the study 2008 when 37% (30 out of 80 datasets) were not proficient.

Conclusions

In summary, an increasing complexity of the HPVs requires international efforts to support a recognized quality and order among HPV types.
IPVC8-0740
RAPID COMMUNICATION

CLINICAL

TYPE-SPECIFIC HIGH-RISK HUMAN PAPILLOMAVIRUS VIRAL LOAD AS A Viable TRIAGE INDICATOR FOR HUMAN PAPILLOMAVIRUS-POSITIVE WOMEN: A NESTED CASE-CONTROL STUDY

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Background and Aims

To assess the associations between type-specific high-risk human papillomavirus (HR-HPV) viral loads and cervical lesions, and the triage effectiveness of type-specific HR-HPV viral load measurement for HR-HPV-positive women.

Methods

A total of 19,446 women with HPV detected by Cervista® HR-HPV assay were enrolled, and type-specific HPV viral load of 1,396 HR-HPV-positive women was absolutely quantified by BioPerfectus Multiplex Real-Time PCR assay. Pearson’s correlation coefficient was applied to determine the association between viral load and cervical lesion severity. The optimal cutoff levels of individual HR-HPV viral loads used to predict cervical intraepithelial neoplasia grade 2 or higher grades (CIN2+) . A logistic regression model was used to analyze the relationship between covariates and the probability of CIN2+.

Results

The viral loads of HPV-16, -31, -33, -52, -58, and total HR-HPV were positively correlated with the cervical lesion severity, the viral loads were significantly higher with CIN2+ than without CIN2+, but not for HPV-18, -45, -56, -59, and other types. The optimal cutoff levels of the log10-transformed viral loads for HPV-16, -31, -33, -52, -58, and total HR-HPV were 4.26, 4.46, 4.48, 4.36, 4.26, and 3.17 copies per 10,000 cells, respectively. Using multivariate analysis, HPV-16 viral load ≥ 4.26, HPV-31 viral load ≥ 4.46, HPV-33 viral load ≥ 4.48, HPV-52 viral load ≥ 4.36, HPV-58 viral load ≥ 4.26, and total HR-HPV viral load ≥ 3.17 were independent predictors for the incidence of CIN2+ in HR-HPV infections.

Conclusions

The viral load assay provides viable triage for HR-HPV infections, when using appropriate cutoff levels.
IPVC8-0631
RAPID COMMUNICATION

CLINICAL

ORAL AND SYSTEMIC HPV ANTIBODY KINETICS POST-VACCINATION AMONG HIV-NEGATIVE AND HIV-POSITIVE MEN

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⁶University of California, Department of Medicine, San Francisco, USA

Background and Aims

Duration and functional aspects of the oral and systemic antibody responses following HPV vaccination in HIV- and HIV+ men are not well characterized. Here, the oral and systemic HPV-specific antibody levels were evaluated over an 18-month period among HIV- and HIV+ vaccinated mid-adult men.

Methods

Sera and oral gargles from 147 HIV- men (Mid-Adult Male [MAM] Trial) and 75 HIV+- men (AMC052 Trial), ages 22-61, who received 3-doses of quadrivalent HPV vaccine (Day1, Month2 and 6) were tested for anti-HPV-16 and HPV-18 antibodies at Day1, Month7, and Month18 (1 and 12 months post-dose 3, respectively) and avidity (Day1, and Month7) using L1VLP-based ELISA. Antibody levels in oral gargles were normalized for total IgG levels.

Results

All individuals seroconverted, regardless of HIV-status, following 3-doses of vaccine for HPV-16 and HPV-18. Serum HPV-16 and HPV-18 antibody geometric mean levels were >2-fold lower in HIV+-men at Month7 (HPV-16: 808.5 versus 2119.8EU/mL, and HPV-18: 285.8 versus 611.6EU/mL, p<0.001) but not significantly different at Month18 (HPV-16: 281.8 versus 359.7EU/mL, p=0.145, and HPV-18: 120.2 versus 93.4EU/mL, p=0.372) compared to HIV-men. Post-vaccination, only HPV-16 antibody levels in oral gargles at Month7 were significantly different between HIV- and HIV-men (127.7 versus 177.1EU/mg of IgG, p=0.008). Serum HPV-16 and HPV-18 avidity was slightly lower among HIV+ compared to HIV-men at Month7 (HPV-16: 1.95M versus 2.12M, p=0.027; HPV-18: 1.50M versus 1.72M, p<0.001).

Conclusions

HIV+-men developed comparable plateau antibody levels following HPV vaccination, although lower peak antibody levels than HIV-men. The vaccine induced affinity maturation in both HIV+ and HIV-men.
PERSISTENT HIGH-RISK (HR) HPV INFECTION AND VAGINAL MICROBIOTA

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3Università di Firenze, Dipartimento di Medicina Sperimentale e Clinica, Florence, Italy
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5ISPRO Oncological network-prevention and research institute, S.C. Screening Prevenzione Secondaria, Florence, Italy
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Background and Aims

Persistent infection with high-risk (HR) human papilloma virus (HPV) is a necessary condition for cervical cancer (CC) development. We characterized the vaginal microbiota from seventy cervico-vaginal HPV–HR samples collected in ISPRO to identify metagenomic markers predictive of HR-HPV persistence.

Methods

Follow-up results after one year were used to divide the group of HR-HPV+ donors in (i) Clearance: HR-HPV+, patients with no evidence of HR-HPV DNA after one year; (ii) Persistence: patients that maintained the expression of HR-HPV-DNA. Pyrosequencing of V3-V5 region of 16S-rDNA gene was performed on bacterial genomic DNA and was used to characterize microbiota and to define community state types (CSTs). Enriched taxa were identified by Linear discriminant analysis effect size (LEfSe).

Results

Metataxonomic analysis showed differential microbiota profiles between HPV- and HPV+; an increased biodiversity was revealed in the group of persistence compared to the group of clearance and to the control group. A CST IV subgroup, frequently associated with bacterial vaginosis (BV), was present in 43% of women in the group of persistence and in only 7% of patients in the group of Clearance. Samples from patients developing persistent HPV infection showed significant enrichment in Atopobium, as well as a high frequency of Gardnerella strains producing sialidase.

Conclusions

The observed differential cervico-vaginal microbiota profiles in women with HPV infection suggest important insight on the role of bacterial vaginal microbiota in HPV infection. We propose the CST IV (BV) subgroup as a risk factor for the persistence of HPV infection and Atopobium as microbial markers of viral persistence.
CLINICAL IMMUNOGENICITY AND SAFETY OF AN E.COLI-PRODUCED BIVALENT HUMAN PAPILLOMAVIRUS (TYPE 16 AND 18) VACCINE IN GIRLS AGED 9 TO 17 YEARS: A RANDOMIZED CLINICAL TRIAL

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2Jiangsu Provincial Center for Disease Control and Prevention, Vaccine Clinical Evaluation Institute, Nanjing, China
3Innovax Biotech Company- Ltd., Innovax Biotech Company- Ltd., Xiamen, China

Background and Aims

To compare the immunogenicity and safety of an E. coli-produced bivalent human papillomavirus (type 16 and 18, HPV-16/18) vaccine in girls aged 9-17 years to women aged 18-26 years.

Methods

Girls (9-14 years) were randomized 1:1 to receive an E. coli-produced HPV-16/18 vaccine according to a standard 3-dose schedule (0/1/6 month, n=304) or a 2-dose schedule (0/6 month, n=301). Girls aged 15-17 years (n=149) and young women aged 18-26 years (n=225) were assigned to receive the standard 0/1/6 month schedule. HPV 16 and HPV18 IgG antibodies were measured at 0, 6 and 7 month to assess the vaccine immunogenicity.

Results

All participants achieved seroconversion for HPV 16 and 18 IgG antibodies. For girls aged 9-14 years (0/6 month schedule) to women (0/1/6 month schedule), the geometric mean concentration (GMC) ratios at month 7 were non-inferior: 1.42(95%CI: 1.25, 1.62) for HPV16 and 1.17(95%CI: 1.02, 1.33) for HPV18. For girls aged 9-17 years (0/1/6 month schedule) to women (0/1/6 month schedule), the GMC ratios at month 7 were also non-inferior: 1.76 (95%CI: 1.56, 1.99) for HPV16 and 1.93(95%CI: 1.69, 2.21) for HPV18. The vaccine was well tolerated in girls aged 9-17 years. No serious adverse events were identified related to vaccination.

Conclusions

The immunogenicity induced by the E.coli-produced HPV-16/18 vaccine in girls aged 9-14 years who received 2 doses regimen or in girls aged 9-17 years who received 3 doses regimen were high and non-inferior as compared to 18-26 women (3 doses schedule). The vaccine is safe in girls aged 9-17 years.
IPVC8-0301
RAPID COMMUNICATION

CLINICAL

A PERFORMANCE EVALUATION OF THE OPTOELECTRONIC CERVICAL SCREENING DEVICE IN COMPARISON TO LIQUID BASED CYTOLOGY AND HPV DNA TESTING FOR THE DETECTION OF CERVICAL NEOPLASIA.

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Background and Aims

Evaluation of the Optoelectronic screening device in the detection of CIN2+ in comparison to LBC and HPV DNA testing.

Methods

A total of 506 women were screened from a referred population from 3 Colposcopy Clinics in Australia. An optoelectronic device (TruScreen) examination was performed followed by HPV DNA, LBC, Colposcopy and biopsy when necessary.

Results

Normal results were found in 286 patients (56.5%); HPV changes in 80 patients (15.8%); CIN 1 in 23 patients (4.5%); CIN2+ in 82 patients (16.2%). The sensitivity for CIN 2+ by TruScreen, LBC, and HPV DNA was 73%, 80% and 88%, respectively. Specificity was 71%, 95% and 77%, respectively, and the NPV was 93%, 96% and 97%, respectively. From McNemar’s tests of the different screening tests, there was no significant difference in sensitivity between TruScreen and LBC (p-value 0.23). Amongst patients without previous treatment, as an approximation of a primary screening population, there was a marginally significant difference in sensitivity between the TruScreen and HPV DNA tests (p-value of 0.0525), and no significant difference in specificity between TruScreen and HPV DNA test (p= 1.0).
### Measures of Performance for Cervical Screening Measures

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TruScreen</td>
<td>73%</td>
<td>71%</td>
<td>93%</td>
<td>35%</td>
</tr>
<tr>
<td>LBC</td>
<td>80%</td>
<td>96%</td>
<td>96%</td>
<td>78%</td>
</tr>
<tr>
<td>HPV DNA</td>
<td>87%</td>
<td>22%</td>
<td>97%</td>
<td>43%</td>
</tr>
</tbody>
</table>

### Measures of Performance in a Population Without Previous Treatment

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TruScreen</td>
<td>72%</td>
<td>72%</td>
<td>86%</td>
<td>52%</td>
</tr>
<tr>
<td>LBC</td>
<td>81%</td>
<td>93%</td>
<td>93%</td>
<td>82%</td>
</tr>
<tr>
<td>HPV DNA</td>
<td>88%</td>
<td>69%</td>
<td>93%</td>
<td>53%</td>
</tr>
</tbody>
</table>

### Measures of Performance in a Population With Previous Treatment

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>TruScreen</td>
<td>80%</td>
<td>70%</td>
<td>99%</td>
<td>11%</td>
</tr>
<tr>
<td>LBC</td>
<td>70%</td>
<td>97%</td>
<td>99%</td>
<td>54%</td>
</tr>
<tr>
<td>HPV DNA</td>
<td>90%</td>
<td>18%</td>
<td>99%</td>
<td>19%</td>
</tr>
</tbody>
</table>
The optoelectronic device (TruScreen) demonstrated comparable sensitivity to high quality cytology conducted in a hospital clinical setting, and sensitivity and specificity approaching HPV DNA in an approximate primary screening setting. TruScreen has the advantage of producing an immediate result, low training and does not need laboratory equipment. This device, utilising optical and electrical technology, can potentially become an important tool in the prevention of cervical cancer, particularly in developing countries and resource-limited settings.
IPVC8-0277
RAPID COMMUNICATION

CLINICAL

ANAL INTRAEPITHELIAL NEOPLASIA, ANAL HUMAN PAPILLOMAVIRUS INFECTION AND ANAL WARTS AMONG RENAL TRANSPLANT RECIPIENTS IN DENMARK
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Background and Aims

To investigate the prevalence of high-grade anal intraepithelial neoplasia (AIN2/3), anal human papillomavirus (HPV) infection and anal warts in renal transplant recipients (RTRs) compared with immunocompetent controls.

Methods

250 RTRs and 250 immunocompetent controls (125 men and women in each group) were enrolled at the Department of Dermatology, Bispebjerg Hospital, Denmark, and at five Danish Departments of Nephrology. Anal cytology samples for cytologic diagnosis and HPV testing were obtained using Rover®Anex®Brush and SurePath liquid-based cytology medium. HPV testing was performed using Genomica CLART HPV2. Participants were examined with high resolution anoscopy preceded by application of 3% acetic acid. Areas suspicious for AIN or warts were biopsied. Prevalences were compared using Pearson’s chi-square test.

Results

The anal high-risk (hr)HPV prevalence was higher in RTRs (21%, 95%CI: 16%–27%) than controls (12%, 95%CI: 8%–16%) (p=0.004). Abnormal anal cytology (≥ASC-US) tended to be more common in RTRs (42%, 95%CI: 36%–49%) than controls (34%, 95%CI: 28%–41%), although not statistically significant (p=0.08). The prevalence of histologically confirmed AIN2/3 was higher in RTRs (11%, 95%CI: 8%–16%) than controls (2%, 95%CI: 1%–5%) (p<0.0001), with the highest AIN2/3 prevalence in female RTRs (16%, 95%CI: 10%–23%). Perianal warts (including sub-clinical lesions) were more common in RTRs than controls (15% versus 8%, p=0.03), whereas the prevalence of intra-anal warts was similar in RTRs and controls (8% versus 7%, p=0.77).

Conclusions

Anal hrHPV, AIN2/3 and perianal warts were more frequent in RTRs than immunocompetent controls. Analyses adjusted for age, number of sexual partners and sexual orientation will be presented.
CHARACTERIZATION OF HPV-6 TRANSCRIPTIONAL ACTIVITY

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Background and Aims

Genital warts are etiologically associated with HPV-6, one of the low-risk types most frequently detected. It was recently shown that variants of the HPV-6 B1 sub-lineage are associated with an increased risk of developing genital warts in males when compared to B3 sub-lineage variants. It was also reported that a B1 sub-lineage variant was ten times more transcriptionally active than a B3 sub-lineage variant. To date, very little has been described concerning the regulation of HPV-6 transcription. Therefore, our aim was to characterize in a comprehensive way the transcriptional activity of the HPV-6 E6 (P90) early promoter of molecular variants belonging to B1 and B3 sub-lineages.

Methods

Transcription Factor-Genome-wide full length cDNA transfection ready clone sets (GFC)-Transfection Array technology (Origene, Maryland, EUA) was used to analyze transcriptional activity of both variants.

Results

78 TFs were found to activate or repress the LCR in at least one of the variants tested. Among these, 10 TFs presented potential binding sites within the LCR of both sub-lineages variants, according to in silico JASPAR analysis, and were selected for further analysis. Luciferase assays revealed that E2F1, SP1, SOX7 and FOXA1 affected the transcription of both variants in a dose-dependent manner. On the other hand, ELF5, HOXA13, KLF5, SNAI and LHX2 TFs affected solely the transcription of one of the variants tested. ChIP assays are underway to analyze in vivo binding of selected TFs to the HPV-6 LCR.

Conclusions

These results are relevant to evaluate the significance HPV variability.

Financial support: CAPES - Cota Institucional/Demanda Social
HUMAN PAPILLOMAVIRUS 16 E6 MODULATES THE EXPRESSION OF MIRNA-496 IN OROPHARYNGEAL CANCER

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³University of Lisboa, Biosystems & Integrative Sciences Institute, Lisbon, Portugal

Background and Aims

Human papillomavirus (HPV), notably type 16, is a risk factor for up to 75% of oropharyngeal squamous cell carcinomas (SCC). It has been demonstrated that small non-coding RNAs known as microRNAs play a vital role in the cellular transformation process. The aim of this study was to determine the impact HPV16 on the expression of miRNAs in Oropharyngeal SCC.

Methods

In this study, we used an LNA array to further investigate the impact of HPV16 on the expression of microRNAs in oropharyngeal (tonsillar) cancer. The E6 oncogene and its spliced variants were overexpressed in head and neck cancer cell lines and specific miRNAs were validated using qPCR. A network representing putative interactions between specific miRNAs, HPV E6 and E7 proteins was built from publicly available datasets, using predicted miR targets and candidate regulatory transcription factors.

Results

Several miRNAs were shown to be significantly different in their expression levels between HPV16 positive and HPV16 negative oropharyngeal cancers, with miR-496 showing a four-fold decrease. Over-expression of the high risk E6 oncoprotein down-regulated miR-496, impacting upon the posttranscriptional control of the transcription factor E2F2. These HPV specific miRNAs were integrated with the HPV16 interactome to identify possible mechanistic pathways. This network analysis revealed a possible mechanism for the regulation of these miRNAs by HPV16.

Conclusions

In summary, our study has provided new insights into the novel molecular interactions between HPV16, miRNAs and their target genes, in oropharyngeal cancers.
CHARACTERISATION OF CIRCULATORY CD4+ T-CELLS RESPONDING TO HPV16 ANTIGEN FOR ASSESSMENT OF T-CELL SIGNIFICANCE IN THE DEVELOPMENT AND REGRESSION OF PREMALIGNANT HPV DISEASE

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Background and Aims

High-grade squamous intraepithelial-lesions (HSIL) of the anus, driven by human-papillomavirus (HPV) infection are cancer-precursors. Relatively high rates of regression, or (“clearance”) of HSIL are likely driven by immune responses. We previously identified a preliminary trend toward immune correlates with regression using immunological techniques. HPV-specific T-cell responses are difficult to detect, limiting prognostic potential. We characterise circulating HPV16-specific CD4+T-cells using flow-cytometry and single-cell molecular-biology methodology. Our objectives are to use immunoassays as a robust tool for detection of HPV-disease and to achieve this using biobanked cryopreserved peripheral-blood mononuclear cells (PBMC).

Methods

Cryopreserved PBMC analysed for this study were from a biobank repository of gay and bisexual-men in the Study-of-Prevention-of-Anal-Cancer (SPANC) based in Sydney, Australia. Detection of HPV16-specific CD4+T-cells responding to antigen was through cell-surface staining of CD25 (IL-2R) and CD134 (OX40) receptors on cryopreserved PBMC (compared to whole blood), after 44 hours stimulation with controls or HPV16 E6-and E7-peptide pools using flow cytometry (“OX40-immunoassay”). OX40+CD4+T-cells were single-cell sorted and measured for expression of transcription factors (scTF) Tbet, GATA3, RORgt, BCL6, and FOXP3, delineating which CD4+T-cell subsets respond to HPV-antigen.

Results

Detection of HPV-specific T-cell response using PBMC was correlated with whole-blood (R=0.59, p=0.009) and observed at 3.2-fold increased sensitivity. T-cells surface-stained as CD39+(representing FOXP3+ CD4+ T-cells) were significantly increased in the E6-specific T-cell population versus controls, and confirmed using scTF data as FOXP3-transcripts were overrepresented in this population.

Conclusions

Our optimised methodology is able to robustly detect HPV-specific CD4+T-cells from biobanked-specimens direct ex-vivo. Further testing is needed to accurately determine assay cut-off and variation.
ALTERED INNATE IMMUNITY IN PATIENTS WITH RECURRENT RESPIRATORY PAPILLOMATOSIS

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Background and Aims

Recurrent respiratory papillomatosis patients (RRP) show both polarized (Th2/Treg) adaptive immunity in papillomas and blood and compromised innate functions, which likely prevent HPV6/11 clearance/control. COX2/PGE2 is also overexpressed. To better understand why HPV-specific adaptive immunity is skewed in RRP, and why Langerhans cells (LCs) in papilloma fail to activate, we studied LCs from RRP patients and controls.

Methods

Negatively selected (> 90% purity) PBMC-monocytes from 17 RRP patients and 11 controls were sorted into classical/intermediate/non-classical monocytes by CD14/CD16 expression, and differentiated into iLCs (CD1a+/CD207+/E-cadherin+) with GMCSF/IL-4/IL-10/TGFβ1. CD1a+ iLCs were analyzed for CD1a/E-cadherin/CD207 expression by flow cytometry, and activated by IL-36γ, PGE2, PGE2 + IL36γ, or LPS. LCs from papilloma and other tissues were analyzed for comparison. Chemokine/cytokine mRNA repertoires were identified after poly (I:C), or TNFα stimulation, ± added PGE2.

Results

RRP patients had fewer PBMC-monocytes (p=0.0049), the 3 monocyte sub-population ratios were significantly different in RRP vs. controls (p<0.0001), and controls produced more iLCs than RRP patients (p=0.047). Classical monocytes generated most of the iLCs; some were generated from intermediate/non-classical monocytes. Serum PGE2 was in RRP (p=0.004). PGE2, at concentrations found in papilloma tissues, reduced control monocyteiLC differentiation (p=0.021), had no effect on RRP iLC generation or CD83 expression. CCL-1 expression was constitutively in RRP iLCs (p<0.042). Added PGE2 reduced CCL-1 and CCL1/CCL20 expression in control iLCs to RRP levels (p<0.0016).

Conclusions

Monocyte and iLC innate immunity is altered in RRP, in part due to PGE2 which is elevated in both RRP serum and papilloma tissues.
EXPRESSION OF CODON MODIFIED HUMAN PAPILLOMAVIRUS 16 E7 GENE CONFIRMS
ACTIVATION OF PI3K/AKT/SRC SIGNALLING IN PRIMARY HUMAN KERATINOCYTES
ASSOCIATING WITH CERVICAL CARCINOGENESIS IN VIVO


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Background and Aims

We aimed 1) to characterize expression of HPV16 E7 gene (Wt-E7) and two codon modified E7 genes (HB1-E7 and HB2-E7) in different cell types (CHO cell, primary mouse and human keratinocytes); 2) to determine whether HPV16 E7 protein regulated expression/activation of PI3K/AKT/Src genes in human keratinocytes and 3) to investigate whether expression of AKT and Src regulated by HPV16 E7 in vitro was associated with their expressions in HPV16-positive cervical cancer specimens.

Methods

Northern blot and qRT-PCR were used to determine RNA transcription of wt and HB E7 genes. Immunoblotting and IF were used to examine expression of E7, p53, pRb, PI3k-p85α, AKT and Src proteins. ZHPV16E7384 affibody and HPV16 E7 polyclonal antibody, together with the antibodies against AKT, p-AKT, Src and p-Src, were used to carry out immunohischemistry staining for the targeted proteins in sixty-six cervical cancer biopsies and eight normal specimens.

Results

Codon modified HPV 16 E7 gene significantly increased expression of E7 protein in three cell types HPV16 E7 promoted expression of p-PI3k-p85α, p-AKT(Ser473) and p-c-Src(Tyr527) in human keratinocytes. IHC revealed that ZHPV16E7384 affibody and HPV16 E7 antibody had intense and specific staining for E7 in cancer specimens. E7 protein was highly expressed at both high cervical squamous intraepithelial lesion and invasive cervical cancer, correlating with high levels of p-AKT(Ser473) and p-c-Src(Tyr527). Co-immunoprecipitation assay confirmed that E7 strongly interacted with both p-AKT(Ser473) and p-Src(Tyr527).

Conclusions
We provide strong evidence that expression of HPV 16 E7 gene activated PI3K/AKT/Src signals in keratinocytes \textit{in vitro} associating tightly with cervical carcinogenesis \textit{in vivo}.
PROTAMINE SULFATE IS A POTENT INHIBITOR OF HUMAN PAPILLOMAVIRUS INFECTIONS VIA TARGETING VIRION ATTACHMENT TO HEPARAN SULFONATED PROTEOGLYCANS

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Background and Aims

The positive charge of HPV capsids facilitates binding to negatively-charged heparan sulfate (HS) chains of HS proteoglycans (HSPG) in the extracellular matrix (ECM) and on the plasma membrane of human keratinocytes. The polysaccharide carrageenan resembles HS and has greater affinity for HPV particles than does HS. Thus, carrageenan blocks cellular attachment of HPVs, and exerts a post-attachment inhibitory effect on HPV infectivity. Polycationic molecules bind to HS chains and have microbicidal activity against many viruses. We investigated the efficacy and mechanisms of action of protamine sulfate (PrS), a highly cationic (pI ≈ 11-13) antimicrobial peptide approved by the FDA, in preventing HPV infections.

Methods

HaCaT human keratinocytes were infected with HPV pseudovirions (PsVs) or tissue-derived virions. PsV infections were determined by luciferase quantification. Virion infections were assessed using RT-qPCR to quantify spliced HPV E1^E4 mRNAs.

Results

PrS is a potent inhibitor of HPV infection (IC₅₀ for PsV ~100nM). PrS prevents PsV binding to the cell and ECM. PrS added after PsV binding did not cause virion release, but remained strongly inhibitory to infection, even when added hours after infection.

Conclusions

Protamine sulfate is a potent inhibitor of HPV infections in vitro. PrS remained highly active at a low pH, boding well for clinical utility and testing in the vaginal tract. We are assessing the utility of PrS in preventing HPV PsV infection using the murine vaginal challenge model and the MmuPV1 infection model. We are also investigating whether PrS can prevent cell infection by HIV1, HSV1 and 2, adenoviruses, and Chlamydia trachomatis.
T-CELL AND B-CELL IMMUNITY IN GIRLS AFTER A SINGLE DOSE OF BIVALENT HPV VACCINATION COMPARED TO TWO- AND THREE DOSES UP TO 6.5 YEARS POST- VACCINATION

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Background and Aims

In ongoing follow up studies post-vaccination one-dose of the bivalent HPV16/18 vaccine results in the seroconversion of girls and young women. The seroconversion is associated with a low prevalence of HPV-16/-18 infections suggesting that the induced protection after one-dose of vaccine may be long lived. Since memory T- and B-cell responses are important in the long term immunogenicity, we evaluated these responses in individuals vaccinated with the different dosing schedules.

Methods

Blood was collected cross-sectionally up to 6.5 years post-vaccination and PBMC’s were isolated from young girls vaccinated at 12 years of age according to a one-, two- or three-dose schedule. Numbers of T-cells producing IFN-γ were determined by ELISPOT-assay after stimulation of PBMCs with virus-like particles for HPV-16, HPV-18, HPV-31 and HPV-45 for 4 days. Memory B-cell responses were determined by HPV-type-specific ELISPOT assays after polyclonal stimulation of purified (CD19+) B-
cells for 5 days.

Results

Even after 6.5 years post-vaccination of one dose of Cervarix® HPV-type-specific IFN-γ producing T-cells were detectable. However, these numbers are lower compared to those in two- and three-dose vaccinated individuals. Memory B-cell responses to HPV-type 16, 18, 31 and 45 are detectable post-vaccination; evaluation of potential differences in B-cell immunity between doses and follow-up time is ongoing.
Conclusions

The one-dose Cervarix® vaccination schedule in 12 years old girls induces long-term T-cell memory immune responses.
Background and Aims

We have initiated cGMP production of monovalent HPV16-RG1VLP vaccine for first-in-human studies. HPV16-RG1VLP is a chimeric papillomavirus VLP that displays 360 copies of the highly conserved epitope RG1 (amino acid 17-36 of minor capsid protein HPV16 L2) in the D-E loop of HPV16L1 VLP. RG1 generates broadly neutralizing antibodies against numerous HPV genotypes. Here, we benchmarked engineered-run cGMP grade HPV16-RG1VLP adjuvanted with alhydrogel® against Gardasil-9®, a licensed HPV vaccine in two well-established papillomavirus infection and disease animal models respectively.

Methods

Using cottontail rabbit papillomavirus disease model and murine passive-serum transfer mice models, in vivo protection 2 weeks post vaccination was assessed against eight high risk oncogenic HPVs following three intra-muscular administration of 80 ug of HPV16-RG1, or human doses of Gardasil-9®. In addition, in vivo protection from infection by HPV16, 18, and 58 murine vaginal challenges was evaluated in HPV16-RG1 vaccinated BALB/c mice using one-tenth human doses.

Results

All studies demonstrated that vaccination with monovalent HPV16-RG1VLP resulted in cross-neutralizing RG-1 antibodies that were able to provide equivalent protection as per Gardasil-9 against both HPV pseudovirus infections and actual disease development as seen in the CRPV/rabbit model.

Conclusions

HPV16 RG1-VLPs is a vaccine candidate that is able to provide comparable protection against high risk oncogenic HPV types that are included in the currently licensed HPV vaccines. As a monovalent VLP, HPV16 RG1VLP holds promise as a broad-spectrum preventative vaccine that could potentially provide broader protection at lower production costs. Future studies will focus on durability of protection.
IPVC8-0124
RAPID COMMUNICATION

BASIC SCIENCE - GENE EXPRESSION AND IMMUNOLOGY

EPITHELIAL BOOST ENHANCES ANTIGEN EXPRESSION BY VACCINIA VIRUS FOR THE GENERATION OF POTENT CD8+ T CELL-MEDIATED ANTITUMOR IMMUNITY FOLLOWING DNA PRIMING VACCINATION

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Background and Aims

Human papillomavirus (HPV) is the primary etiologic factor of cervical cancer and subsets of anogenital and oropharyngeal cancers. HPV viral oncoproteins E6 and E7 are consistently expressed in HPV-infected cells; therefore, they are promising targets for therapeutic vaccination. Both pNGVL4a Sig/E7(detox)/HSP70 DNA and TA-HPV recombinant vaccinia viral vector-based vaccines elicited HPV-specific CD8+ T cell responses in HPV16/E7-expressing tumor models, and have been used as a prime-boost regimen to enhance HPV-specific immune responses in humans. However, the optimal route of administration for TA-HPV remains unclear.

Methods

We examined the immunogenicity of priming with intramuscular pNGVL4a-Sig/E7(detox)/HSP70 DNA vaccination followed by TA-HPV boost through different routes of administration in a preclinical model.

Results

We observed that priming with a pNGVL4a-Sig/E7(detox)/HSP70 DNA vaccine followed by a single TA-HPV immunization boost through skin scarification generated the strongest antigen-specific CD8+ T cell response in C57BL/6 mice. Furthermore, boosting with TA-HPV skin scarification can simultaneously enhance immune responses against multiple antigens primed by DNA vaccination. Finally, intramuscular pNGVL4a-Sig/E7(detox)/HSP70 DNA vaccine prime followed by TA-HPV skin scarification boost on the tail resulted in potent therapeutic antitumor effects against cervicovaginal TC-1 tumors. These data translate to tumor control and prolonged survival of treated mice.

Conclusions

Our results provide rationale for future clinical testing of intramuscular pNGVL4a-Sig/E7(detox)/HSP70 DNA vaccine prime, TA-HPV vaccine skin scarification boost immunization regimen for the control of HPV-associated diseases.
BACKGROUND AND AIDS

Mucosal immunization is suggested to be crucial for controlling tumors in the mucosal region; however, therapeutic DNA vaccination with electroporation in various mucosal sites has yet to become clinically adaptable. Since tumor-draining lymph nodes (tdLNs) have been suggested as immune-educated sites that can be utilized to mount a potent antitumor immune response, we examined whether intramuscular DNA vaccination with electroporation at sites that target the mucosal tdLNs could elicit mucosal immune response to restrict tumor growth.

METHODS

The efficacy and mechanism of intramuscular administration of a therapeutic DNA vaccine with electroporation at different sites was examined by lymphocyte analysis, tumor growth, mouse survival, as well as integrin expression, in mice bearing orthotopic HPV16 E6/E7+ syngeneic TC-1 tumors in various mucosal areas.

RESULTS

While provoking comparable systemic CD8+ T cell responses, intramuscular hind leg vaccination generated stronger responses in cervicovaginal-draining LNs to control cervicovaginal tumors, whereas intramuscular front leg vaccination generated stronger responses in oral-draining LNs to control buccal tumors. Surgical removal of tdLNs abolished the antitumor effects of therapeutic vaccination. Mucosal-tdLN-targeted intramuscular vaccination induced the expression of mucosal-homing integrins LPAM-1 and CD49a by tumor-specific CD8+ T cells in the tdLNs. Inhibition of these integrins abolished the therapeutic effects of vaccination and the infiltration of tumor-specific CD8+ T cells into mucosal tumors.

CONCLUSIONS

Our findings demonstrate that tdLN-targeted intramuscular immunization can effectively control mucosal tumors, which represents a readily adaptable strategy for treating mucosal cancers in humans.
Blocking of Transporter Associated with Antigen Processing-2 by Human Papillomavirus E6 via Induction of Lymphotoxin in Oral Squamous Cell Carcinoma

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Background and Aims

Effect of human papillomavirus (HPV) on impairment of tumor cell killing by cytotoxic T-cells has reported. This study aimed to investigate the effect of HPV oncoproteins on lymphotoxin (LTβ) and its receptor (LTβR) in HPV-associated oral squamous cell carcinoma (OSCC).

Methods

OSCC tissues were detected for HPV DNA and the expression of LTβ and transporter associated with antigen processing-2 (TAP2) using PCR and qRT-PCR respectively. TAP2 expression was confirmed in OSCC cell lines with/without HPV16. To analyze the effect of HPV oncoproteins, the immortalized HTK1 cells expressing HPV16E6, E7, E6/E7, p53, LTβ, TAP2 and MHC class I as well as LTβ and LTβR-knockdown cells were established. The expression of MHC class I and LTβ were evaluated by immunohistochemistry (IHC).

Results

HPV-positive cases were 34.7% (8/23). The level of LTβ expression was significantly higher in HPV-positive than HPV-negative cases, whereas TAP2 expression was decreased in HPV-positive cases that was similarly found in OSCC cell lines with/without HPV16. The upregulation of LTβ and downregulation of TAP2 were detected in HPV16E6-expressing cell line compared to control, whereas they weren’t different in MHC class I expression. Knockdown of LTβ and LTβR in E6-expressing HTK1 cells showed upregulation of TAP2. Interestingly, weak IHC staining in OSCC tissues of MHC class I was found in HPV and LTβ-positive cells whereas strong staining was found in HPV-negative with LTβ-positive cells.

Conclusions

Our study suggested an effect of HPV16E6 on TAP2 downregulation via LTβ upregulation resulting in an impairment of MHC class I transportation in HPV-associated OSCC.
CELLULAR IMMUNE RESPONSES SIX YEARS FOLLOWING REDUCED-DOSE QUADRIVALENT HPV VACCINE IN ADOLESCENT FIJIAN GIRLS
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Background and Aims
Cellular immune response is important for robust antibody production, and remains unclear following HPV vaccination and also in the context of reduced-dose HPV vaccine schedules. We examined cellular immune responses following reduced doses of Gardasil® vaccine (4vHPV) in girls after 6 years, and their responses to a subsequent dose of Cervarix® vaccine (2vHPV).

Methods
A subset of girls (n=59) who previously received 0, 1, 2 or 3 doses of 4vHPV 6 years earlier were randomly selected from a cohort of 200 Fijian girls (aged 15-19 years old). Blood was collected before and 28 days after a dose of 2vHPV. The HPV16- and HPV18-specific response was determined by INFγ-ELISPOT and by measurement of cytokines (INFγ, IL-2, TNFα, IL-5 and IL-10) in PBMC supernatants using a multiplex bead-array assay.

Results
Six years after 4vHPV vaccination, HPV18-specific responses were significantly lower in the 1-(1D) or 2-dose (2D) recipients compared with 3-dose recipients (2D: INFγ-ELISPOT, p=0.008; cytokines, INFγ: p=0.002; IL-2: p=0.022; TNFα: p=0.016, IL-10: p=0.018, 1D: IL-2: p=0.031; IL-10: p=0.014). These differences were no longer significant post-2vHPV. No significant differences in HPV16 responses (except IL-2, p<0.05) were observed between the 2- or 1-dose recipients and 3-dose recipients at either timepoint.

Conclusions
These data suggest that cellular immunity against HPV18 following reduced-dose schedules may not persist as long as following 3-doses, although the clinical significance of this is unknown. Further studies on the long-term impact of reduced dose HPV vaccine schedules are needed, particularly in high disease burden settings.
Background and Aims

Interferon (IFN) –alphas and –beta have antiviral activities by inducing IFN-stimulated genes (ISG), are present at very low levels in non-infected cells and can be induced by pattern recognition receptor (PRR) signalling. In contrast, IFN-kappa is expressed constitutively in uninfected normal human keratinocytes (NHK) and can only be weakly induced by PRR stimulation. HR-HPV inhibit IFN-kappa transcription and IFN-kappa limits HPV31 transcription.

Methods

Cell culture, transfection, EMSA, qPCR

Results

Using the ENCODE database, we identified a distal region in the IFNK locus that displays, only in NHK, high levels of H3K27ac, a marker for active enhancers. Deletion analyses of IFN-kappa promoter constructs identify three separate domains in this region to be essential for promoter activity. Point mutations indicate members of the AP2-, HOX-, SMAD- and AP1-families as regulators of promoter activity. EMSA experiments confirm specific binding of nuclear proteins to the AP2, SMAD and AP1 binding sites. Activities of SMAD and AP1 members can be regulated by signal transduction cascades. Consistent with the SMAD BS being important, activation of the TGF-beta signal transduction cascade induces, whereas its inhibition reduces, IFN-kappa and ISG expression in NHK. Surprisingly, inhibition of ERK kinases induces IFN-kappa and ISGs. Importantly, IFN-kappa and ISG expression can also be induced in keratinocytes maintaining episomal HPV16 genomes by TGF-beta and ERK inhibitors and this coincides with a reduced viral transcription.

Conclusions

IFN-kappa expression is activated by TGF-beta and inhibited by ERK kinases in NHK and reactivation of IFN-kappa expression in HPV16-positive cells by such treatments inhibits viral transcription.
CD40 IS DOWNREGULATED BY HPV E6 ONCOPROTEIN VIA THE AT-HOOK TRANSCRIPTION FACTOR AKNA

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Background and Aims

During viral infection, an effective immune response is critical for the HPV clearance involving the activation of pro-inflammatory cytokines. The viral proteins promote an anti-inflammatory state in order to promote viral persistence contributing to the carcinogenic process.

HPV induces an anti-inflammatory state due to a down-regulation of the CD40 surface protein as one of the immune evasion mechanisms. CD40 is regulated by the AT-hook transcriptional factor AKNA which have been linked to cervical cancer development. The loss of this factor is strongly exhibits a deregulated inflammatory phenotype. However, there is no evidence regarding the effects of the HPV oncoproteins on AKNA. The aim of this work was to demonstrate the ability of the HPV E6 oncoprotein to modulate the CD40 levels by affecting AKNA.

Methods

HeLa cells were transfected with AKNA plasmids. Cell extracts were analyzed by SDS-PAGE. Immunofluorescence analysis, pull down assays, immunoprecipitation assays and flow cytometry were performed.

Results

We demonstrate that the HPV E6 oncoproteins decrease the levels of CD40 by binding to and inducing the degradation of the transcriptional factor AKNA involving the proteasome system. We also demonstrate a minimal expression of this factor and its co-stimulatory molecules in the HPV positive cell lines HeLa and SiHa in comparison with the HPV negative cell lines. Additionally, the ablation of E6 in HeLa cells restores the expression of AKNA and CD40.

Conclusions

These results indicate that a de-regulation of the transcriptional factor AKNA by HPV might contribute to avoid immune surveillance during the carcinogenic process induced by this virus.
Human Papillomavirus (HPV) is a known cause of 98% of cervical cancers, 50% of Head & Neck cancers and 25% of other ano-genital cancers. Elevated oxidative stress is a notable characteristic feature of HPV infected cancer. To counteract the oxidative stress, cells upregulate transcription factor NRF2, which transcribes nearly all the cellular antioxidants including GSH biosynthesis and phase II detoxification enzymes. Elevated Nrf2 is a mediator of radio and chemo resistance whereas down-regulation of Nrf2 is shown to sensitize cancer cells to treatment. When compared to HPV−ve, HPV+ve cancer patients show better responses to therapy, however the mechanisms are unclear. We hypothesize that HPV infection down-regulates Nrf2 signalling by depleting cellular antioxidants and sensitizing to therapy.

Methods

We evaluated Nrf2 signaling in HPV+ve (SiHa & HeLa) and HPV−ve (C33A) cervical cancer cell lines by assessing i) expression of Nrf2 and selected Nrf2 regulated antioxidants genes by qPCR ii) Nqo1 enzyme activity iii) GSH levels and iv) Cytotoxicity effect of Cisplatin treatment.

Results

qPCR data revealed marked decrease in expression of NRF2, NQO1, GCLC and GCLM genes in HPV+ve cells as compared to HPV−ve cells. In agreement with NQO1 gene expression, NQO1 enzyme activity was markedly depleted in HPV+ve as compared to HPV−ve cells. Similarly, we observed marked reduction in levels of GSH in HPV+ve cell as compared to HPV−ve cells. Dose dependent treatment showed that HPV+ve cells were more sensitive than HPV−ve cells to cisplatin treatment.
mRNA expression levels of NRF2, NRF2 target genes (NQO1, GCLC, GCLM, HO-1) and KEAP-1 in C33A (HPV -ve), SiHa (HPV 16 +ve) and HeLa (HPV 18 +ve). (N=3; data- Mean ±SEM )
Conclusions

This study suggests that HPV infection inhibits Nrf2 regulated antioxidant defences and enhance sensitivity to therapy in HPV associated cancers. Our on-going studies are focused on delineating underlying mechanism how HPV modulates Nrf2 signaling.
IPVC8-0192
RAPID COMMUNICATION

PUBLIC HEALTH

THE EFFECT OF HPV DNA VIRAL LOAD AND ABNORMAL CYTOLOGY AT BASELINE ON PROGNOSIS OF BIOPSY-CONFIRMED CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 1: A PROSPECTIVE STUDY

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Background and Aims

Nowadays, there are not many prospective studies on biopsy-confirmed CIN1 women. We explore the impact of abnormal cytology on CIN1 at different follow-up time points and evaluate the risk of progression to CIN2+ at different HPV DNA viral load, in order to explore follow-up intervals and strategies for CIN1 women.

Methods

Biopsy confirmed CIN 1 women were followed up in cervical screening program established during 1999 to 2008 in Shanxi province, China. In each follow-up visit, the participants were inspected using VIA, LBC and HR-HPV DNA testing. The risk of progression associated with ASCUS+ was assessed stratified by baseline and follow-up cytology results. Furthermore, the risk of CIN2+ incidence was also evaluated according to HPV DNA viral load at baseline.

Results

A total of 228, 218, 255 and 102 CIN1 women participated in the 1-year, 2-year, 6-year and 11-year follow-up examination, respectively. The cumulative incidence rate (CIR) for CIN2+ among women with ASCUS+ at baseline was 5.50%(6/109), 11.56%(17/147), 15.53%(25/161) and 26.39%(19/72) in the follow-up visits above, separately. The CIR for CIN2+ was respectively 10.7%(6/56), 16.7%(5/30), 19.7%(12/61), 50.0%(14/28) among women with ASCUS+ both at baseline and follow-up visit. No CIN2+ case was found in women with normal cytology results both at baseline and follow-up visit. Moreover, the incidence rate of CIN2+ was related to the HPV DNA viral load at baseline and increased with the viral load in the 6-year (RR\textsubscript{RLU/CO\textsubscript{>100}}: 11.976, 95%CI: 1.615-88.833; \(P_{\text{trend}}<0.01\)) and 11-year (\(P_{\text{trend}}<0.01\)) follow-up visits.
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<th>cytology results at baseline</th>
<th>Follow-up No.</th>
<th>Regression to normal No. (%)</th>
<th>Persistence as CIN1 No. (%)</th>
<th>Progression to CIN2+ No. (%)</th>
<th>RR of progression to CIN2+ (95% CI)</th>
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<tbody>
<tr>
<td><strong>1st year follow up</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Normal</td>
<td>61</td>
<td>51(83.61)</td>
<td>9(14.75)</td>
<td>1(1.64)</td>
<td>3.36</td>
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<tr>
<td>ASCUS+</td>
<td>109</td>
<td>73(66.97)</td>
<td>30(27.52)</td>
<td>6(5.50)</td>
<td>(0.41-27.25)</td>
</tr>
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<td><strong>2nd year follow up</strong></td>
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<tr>
<td>Normal</td>
<td>64</td>
<td>57(89.06)</td>
<td>9(9.38)</td>
<td>1(1.56)</td>
<td>7.40</td>
</tr>
<tr>
<td>ASCUS+</td>
<td>147</td>
<td>106(73.47)</td>
<td>22(14.97)</td>
<td>17(11.56)</td>
<td>(1.01-54.43)</td>
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<tr>
<td>Normal</td>
<td>84</td>
<td>72(85.71)</td>
<td>7(8.33)</td>
<td>5(5.96)</td>
<td>2.61</td>
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<tr>
<td>ASCUS+</td>
<td>161</td>
<td>118(73.29)</td>
<td>18(11.18)</td>
<td>25(15.53)</td>
<td>(1.04-6.57)</td>
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<td><strong>11th year follow up</strong></td>
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<tr>
<td>Normal</td>
<td>29</td>
<td>29(100)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>ASCUS+</td>
<td>72</td>
<td>51(70.83)</td>
<td>2(2.78)</td>
<td>19(26.39)</td>
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</table>

Note: ASCUS+: atypical squamous cell of undetermined significance or higher; CIN1: cervical intraepithelial neoplasia grade 1; CIN2+: cervical intraepithelial neoplasia grade 2 or worse; 95% CI: 95% confidence interval; 
\[1, 1\], 0, 0 participants weren't respectively included in the final analysis because they had no cytological results or unsatisfactory cytological results; 
The trend test of cumulative incidence rates for CIN2+: \( \chi^2 = 15.997 \), \( P_{\text{inc}} < 0.01 \);
Table 2: The risk of disease progression to CIN2+ for different HPV DNA viral load at baseline in different follow-up point time.

<table>
<thead>
<tr>
<th>HPV DNA viral load at baseline (RLU/CO)</th>
<th>Follow up No.</th>
<th>Progression to CIN2+ No.</th>
<th>&lt;CIN2 No.</th>
<th>Progression to CIN2+ RR (95% CI)</th>
<th>$\chi^2$ (P value)</th>
<th>Trend test ($\chi^2$)</th>
<th>$P_{\text{trend}}$</th>
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<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>57</td>
<td>1</td>
<td>56</td>
<td></td>
<td></td>
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<tr>
<td>1-100</td>
<td>60</td>
<td>1</td>
<td>59</td>
<td>0.95 (0.061-14.831)</td>
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<tr>
<td>&gt;100</td>
<td>66</td>
<td>5</td>
<td>61</td>
<td>4.318 (0.520-35.888)</td>
<td>0.139</td>
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<td>0.066</td>
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</tr>
<tr>
<td>&lt;1</td>
<td>54</td>
<td>2</td>
<td>52</td>
<td></td>
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<tr>
<td>1-100</td>
<td>69</td>
<td>5</td>
<td>64</td>
<td>1.957 (0.395-9.697)</td>
<td>4.251</td>
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<td>4.122</td>
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<tr>
<td>&gt;100</td>
<td>81</td>
<td>11</td>
<td>70</td>
<td>3.667 (0.846-15.396)</td>
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<td>0.042</td>
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<td><strong>6th year follow up</strong></td>
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<td>1-100</td>
<td>89</td>
<td>15</td>
<td>74</td>
<td>11.968 (1.619-88.426)</td>
<td>11.068</td>
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<td>7.959</td>
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<tr>
<td>&gt;100</td>
<td>83</td>
<td>14</td>
<td>69</td>
<td>11.976 (1.615-88.833)</td>
<td>0.004</td>
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<td>0.005</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>43</td>
<td>0</td>
<td>43</td>
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<td></td>
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</tr>
<tr>
<td>1-100</td>
<td>19</td>
<td>5</td>
<td>14</td>
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<td>19.865</td>
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<td>19.027</td>
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<tr>
<td>&gt;100</td>
<td>36</td>
<td>14</td>
<td>22</td>
<td></td>
<td>0.000</td>
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<td>0.000</td>
</tr>
</tbody>
</table>

Note: HPV: human papillomavirus; RLU/CO: relative light units/cutoff; CIN2+: cervical intraepithelial neoplasia grade 2 or worse
<table>
<thead>
<tr>
<th>Cytological results at baseline and follow up time</th>
<th>Follow up No.</th>
<th>Regression to normal No. (%)</th>
<th>Persistence as CIN1 No. (%)</th>
<th>Progression to CIN2+ No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st year follow up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both &lt; ASCUS</td>
<td>44</td>
<td>44 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Once ASCUS+</td>
<td>66</td>
<td>64 (97.0)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Twice ASCUS+</td>
<td>56</td>
<td>41 (73.2)</td>
<td>9 (16.1)</td>
<td>6 (10.7)</td>
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<tr>
<td><strong>2nd year follow up</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both &lt; ASCUS</td>
<td>32</td>
<td>31 (96.9)</td>
<td>1 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Once ASCUS+</td>
<td>53</td>
<td>45 (84.9)</td>
<td>5 (9.4)</td>
<td>3 (5.7)</td>
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<tr>
<td>Twice ASCUS+</td>
<td>30</td>
<td>19 (63.3)</td>
<td>6 (20.0)</td>
<td>5 (16.7)</td>
</tr>
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<td><strong>6th year follow up</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Both &lt; ASCUS</td>
<td>55</td>
<td>53 (96.4)</td>
<td>2 (3.6)</td>
<td>0</td>
</tr>
<tr>
<td>Once ASCUS+</td>
<td>105</td>
<td>92 (87.6)</td>
<td>5 (4.8)</td>
<td>8 (7.6)</td>
</tr>
<tr>
<td>Twice ASCUS+</td>
<td>61</td>
<td>39 (63.9)</td>
<td>10 (16.4)</td>
<td>12 (19.7)</td>
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<tr>
<td><strong>11th year follow up</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Both &lt; ASCUS</td>
<td>21</td>
<td>21 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Once ASCUS+</td>
<td>48</td>
<td>46 (95.8)</td>
<td>1 (2.1)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Twice ASCUS+</td>
<td>28</td>
<td>13 (46.4)</td>
<td>1 (3.6)</td>
<td>14 (50.0)</td>
</tr>
</tbody>
</table>

Note: ASCUS+: atypical squamous cell of undetermined significance or higher; CIN1: cervical intraepithelial neoplasia grade 1; a The trend test of cumulative incidence rates for CIN2+ among women with ASCUS+ both at baseline and follow up time: \( \chi^2 = 12.784 \), P trend < 0.01
Considering that the progression of CIN1 is associated with HPV DNA viral load and cytology results at baseline, different follow-up intervals and strategies for CIN1 women should be taken based on the HPV DNA viral load and cytology results.
Background and Aims

Māori (Indigenous) women experience unacceptably high rates of cervical cancer. Current cervical screening is invasive, and screening rates are significantly lower for Māori. The research objectives were to: explore Māori women's reactions to HPV self-testing/sampling (henceforth 'self-testing'); survey Māori women about their HPV self-testing attitudes and potential behaviours; and canvas key informants about HPV self-testing.

Methods

A multi-disciplinary team, including elders and community based researchers (CBRs), conducted the Kaupapa Māori (by Māori, for Māori) research. CBRs ran hui (focus groups/interviews) with 106 eligible Māori women (aged >25 years, no screen in >4 years) in four regions, and arranged peer surveying (397 eligible surveys returned). The views of 16 key informants (KIs), including GPs and nurses, were canvassed.

Results

Most survey participants were enrolled with a primary health care organisation (87%) and attended regularly (72% at least once in 12 months). However, they did not screen, with a desire for bodily autonomy, including embarrassment and shyness, the most frequently given reason. Three in four survey participants said they were likely/very likely to do an HPV self-test, and 88% of women said they were likely/very likely to seek follow-up if required. Women and KIs agreed the delivery of test results should be tailored and that follow-up should be supported.

Conclusions

When Māori women are engaged in the health system but do not screen, this is a system failure. With well introduced HPV self-testing, many currently never/under-screened Māori women would be screened and followed up if necessary.
EXPERIENCES AND ATTITUDES TOWARDS HPV AND HPV VACCINATION AMONG GB2M IN ONTARIO, CANADA: RESULTS FROM THE #ICRUISE STUDY

A. Yeung¹, R. Grewal¹, T. Bekele², M.A. Kesler², D.J. Brennan², A.N. Burchell¹

¹St-Michael's Hospital, Centre for Urban Health Solutions- Li Ka Shing Knowledge Institute, Toronto, Canada
²University of Toronto, Factor-Inwentash Faculty of Social Work, Toronto, Canada

Background and Aims

Gay, bisexual, two-spirit and other men who have sex with men (GB2M) are at higher risk for HPV-related diseases, particularly anal cancer. In September 2016, the province of Ontario, Canada, introduced a program to provide free HPV vaccine to young GB2M (≤26 years).

Methods

#iCruise is an Ontario-wide study of GB2M seeking sexual health information online. GB2M were recruited through websites and mobile socio-sexual apps from July 2017-January 2018. Items included awareness of HPV vaccination using Likert scales in different scenarios. We compared younger men (≤26) to older men (>26) using Pearson’s chi-square tests to assess their experience and attitudes.

Results

975 participants aged 14-89 years, with 34.7% aged ≤26, completed the baseline questionnaire. Most had heard of HPV (94.0%) and the HPV vaccine (79.2%). A higher proportion of younger versus older men reported discussing the vaccine with a health professional (41.5% vs 30.2%, p=0.005) and received 1+ doses (25.5% vs 14.3%, p<0.001). GB2M across all ages (but significantly more so among younger GB2M) were less likely to get vaccinated if they had to pay or disclose same-sex activity (Table 1). Young GB2M were more likely to have been vaccinated if a doctor/nurse was aware of their sexual orientation and had discussed vaccination with them (Table 2).
Conclusions

GB2M showed a willingness to get vaccinated, particularly if free. Younger GB2M were more likely to have received the vaccine, reflecting availability. However, 75% of young GB2M had not been vaccinated, suggesting a need for increased vaccine awareness and ensuring accessibility in non-stigmatizing and welcoming healthcare environments.
IPVC8-0169
RAPID COMMUNICATION

PUBLIC HEALTH

TENDER-BASED PRICING OF HPV VACCINES IN EUROPE: A SYSTEMATIC REVIEW
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¹VU University Medical Center, Epidemiology and Biostatistics, Amsterdam, The Netherlands
²National Institute for Public Health and Environment, Modelling Infectious Diseases, Bilthoven, The Netherlands

Background and Aims

Vaccine price is one of the most influential parameters in economic evaluations of HPV vaccination. Vaccine tendering is a cost containment method widely used across Europe, but information on factors affecting tender-based HPV vaccine prices is scarce. We aimed to collect historical information on tender-based HPV vaccine pricing in Europe.

Methods

Procurement notices and awards, published from January 2007 until January 2018, were systematically retrieved from the online platform for public procurement in Europe. Information was collected from national or regional tenders organised for preadolescent HPV vaccination programmes. Sensitivity of the vaccine price to contract characteristics was studied by mixed-effects modelling.

Results

Prices of the HPV vaccines were collected from 178 procurements announced in 15 European countries. The average price per dose for the first generation HPV vaccines decreased from €101.8 (95% CI: 91.3-114) in 2007 to €28.4 (22.6-33.5) in 2017, whereas the average dose price of the 9-valent vaccine in 2016-2017 was €49.1 (38.0-66.8). Unit prices were respectively €6.2 (3.2-9.2) and €29.1 (22.5 to 35.6) higher for the 4-valent and the 9-valent vaccines as compared to the 2-valent vaccine. Contract volume, level of vaccine procurement (country/region), GDP per capita and number of offers received had a significant effect on the award price.

Conclusions

The two- to four-fold decrease in tender-based vaccine prices compared to market introductory prices confirms the potential of tendering as an efficient cost-containment strategy and opens the way for expansion of immunization programmes to other target groups.
SENDING HPV VACCINE BACK TO SCHOOL IN THE UNITED STATES: AN EVALUATION OF RHODE ISLAND’S SCHOOL ENTRY REQUIREMENTS

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²University of North Texas Health Sciences Center School of Public Health, Health Behavior & Health Systems, Fort Worth, USA
³University of North Texas Health Sciences Center School of Public Health, Biostatistics & Epidemiology, Fort Worth, USA
⁴University of South Florida College of Public Health, Community and Family Health, Tampa, USA

Background and Aims

In the U.S., state-based school entry requirements represent the primary policy tool for achieving high immunization rates. However, Rhode Island (RI) is the only state to institute a true school-entry requirement for HPV vaccination, implemented in 2015. We assessed changes in HPV vaccine initiation for adolescent girls and boys in RI compared to all other states.

Methods

We estimated the gender specific effects of RI's school-entry HPV vaccination policy on parent-reported HPV vaccination initiation using difference-in-differences analysis with the National Immunization Survey-Teen household surveys from 2010 through 2016. Each year of the survey included over 30,000 respondents in the U.S. and 490 to 723 respondents from RI. To be conservative, our primary coding of the policy indicator for RI’s HPV requirement included only 2016 surveys.

Results

Compared to boys in other states, boys in RI increased their HPV vaccination rate by 13% (β=0.13, 95% CI:0.07, 0.19) after enactment of the requirement (see Figure 1). No difference was seen in the probability of HPV vaccination among girls in RI compared to girls in the multi-state control (β=-0.01, 95% CI:-0.08, 0.06). This may have been due to a ceiling effect, in that the vaccine initiation rate for RI girls was already at 87.9% in 2015.
Conclusions

Our findings suggest that enactment of RI’s school entry requirement led to an increase in vaccine initiation among adolescent boys. These results support the pursuit of school-entry requirements for HPV vaccination in other states as a way to achieve higher HPV vaccination rates.
PUBLIC HEALTH

IMPACT OF COMPREHENSIVE SCHOOL-BASED VACCINATION CLINICS ON INCREASING HPV VACCINATION UPTAKE

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¹University of Texas Health Science Center at Houston UTHealth, School of Public Health- Health Promotion and Behavioral Sciences, Houston, USA
²University of Texas Health Science Center at Houston UTHealth, School of Public Health- Center for Health Promotion and Prevention Research, Houston, USA
³University of Texas Health Science Center at Houston UTHealth, Cizik School of Nursing- Center for Nursing Research, Houston, USA
⁴Baylor College of Medicine, Pediatrics - Academic General, Houston, USA
⁵Baylor College of Medicine, Pediatrics - Infectious Disease, Houston, USA

Background and Aims

Using schools as the setting for immunization has been a successful approach for increasing HPV vaccination in many countries. Providing parents with vaccination opportunities that avoid time off from work, combined with education on the importance of HPV vaccine, can increase the likelihood of uptake. School-based vaccination programs can be cost effective but are underutilized in the US. All for Them provides an opportunity to test a comprehensive school-based vaccination strategy when coupled with a parent health education campaign to increase HPV vaccine uptake among early adolescents. The purpose of this study is to test the impact of All for Them among parents of middle-school youth in medically under-served areas.

Methods

Pre-consented school-based vaccination clinics, using a bundling approach of offering five recommended adolescent vaccines, including HPV, were implemented in 26 urban public middle schools (with 2 clinics to be conducted in May 2018).

Results

Consent packets were distributed to all enrolled students (n=21,892), 4% (n=948) of which were returned. Of those, 88% (n=837) were eligible to receive any adolescent vaccine [71% (n=595) of which were eligible to receive the HPV vaccine]. Among students who participated on the clinic days and were eligible for HPV vaccine, 96% (n=571) received the vaccine. Among students who received HPV vaccine, 73% (n=417) initiated and 27% (n=154) completed the series.

Conclusions

While participation rates present a challenge for pre-consented mobile vaccine clinics, data from this project suggest that bundling HPV vaccine with other recommended adolescent vaccines is an effective approach to increase uptake in school settings.
Background and Aims

As new technology such as HPV genotyping and HPV vaccination change screening practice, the principle of equal management of equal risk will be used to develop future guidelines. Patient level data on current screening results, past screening history, vaccination status, and demographic/behavioral factors will be combined. Clinical action (treatment, colposcopy, early return, routine screening) will be dictated by dividing the continuous risk score into a few risk groups decided at a consensus conference.

Methods

Based on 1.5 million women undergoing routine screening at Kaiser Permanente Northern California (KPNC), we estimated the cumulative risk of CIN2+, CIN3+, and Cancer from enrollment to 5 years after enrollment. We included HPV status, cytology, HPV type, past screening history, vaccination status, age, race/ethnicity, income, body mass index, smoking, and hormonal contraceptive use.

Results

The most important risk factors were HPV status, cytology, HPV genotype (HPV16), age, and screening history. Having one prior negative cotest reduced risk of subsequent HPV-positive cotests by one-half; having three reduced risk by three-quarters. Women vaccinated before age 18 had much lower risks for any given HPV-cytology result. Given these strong risk factors, other factors had only minor impact on risk.

Conclusions

The next set of ASCCP-sponsored management guidelines will yield simple recommendations, based on a risk matrix that condenses hundreds of possible combinations of HPV, cytology, HPV genotype, vaccination status, age, and past screening history into a few risk bands. Additional data from other sources will be needed to ensure portability of risk to different settings.
WIDE-FIELD RADIOFREQUENCY ABLATION (RFA) OF ANAL HIGH-GRADE DYSPLASIA (HSIL) DECREASES RECURRENCE OVER TARGETED ABLATION

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¹Ichan School of Medicine at Mount Sinai, Surgery, New York, USA
²Laser Surgery Care, Surgery, New York, USA

Background and Aims

Recurrence post HSIL ablation is high primarily from development of metachronous HSIL. Trials of hemi-circumferential and circumferential RFA of anal HSIL demonstrated reduced HSIL in treated areas at one year. We now examine long-term treatment durability and safety.

Methods

A retrospective analysis of long-term treatment results in participants returning for follow-up HRA after hemi-circumferential and circumferential RFA trials. Participants had to have an HRA >1 year post completion of initial RFA trials. A non-HSIL biopsy or no lesion on HRA without biopsy was considered no recurrence.

Results

Twenty-two participants underwent hemi-circumferential and 10 underwent circumferential RFA and 15 (68%) and 9 (90%), respectively returned for follow-up. Eighteen (75%) were white, 1 was female and 8 (33%) were HIV+ (all treated circumferentially). Median age was 52.5 (range 32-74) years with duration of follow-up post RFA a median 3.2 (range 1-4.5) years. During post-study follow-up median number of HRA’s was 1 (range 1-4). No participants developed HSIL within the RFA treatment zone after completion of the initial trial. One participant treated with hemi-circumferential RFA developed metachronous HSIL in the non-ablated area at 3.8 years. Another developed recurrence at 12 months, was retreated with targeted cautery ablation, and post-trial remains disease free for 2.5 years. At last follow-up 14/23 (61%) individuals tested were high-risk HPV negative (6 HIV+). No long-term treatment related adverse events were identified.

Conclusions

When compared to targeted ablation, wide-field RFA appears to reduce HSIL recurrence. No long-term adverse events related to treatment were identified. Further study is warranted.
INCIDENCE AND CLEARANCE OF ANAL HIGH-RISK HPV INFECTION AND THEIR DETERMINANTS AMONG HIV-NEGATIVE MEN WHO HAVE SEX WITH MEN OVER A FIVE-YEAR PERIOD

M. Schim van der Loeff1, E. Marra1, S. Kovalev1, S. Bruisten1, W. Vermeulen1, A. Boyd1
1GGD Amsterdam, Dpt. of Infectious Diseases, Amsterdam, The Netherlands

Background and Aims

The natural history of anal high risk human papillomavirus (hrHPV) infections is not fully clear; data on clearance of incident hrHPV infections are notably scarce. We aimed to assess the incidence and clearance of anal hrHPV infections and determinants thereof among HIV-negative men who have sex with men (MSM) over a five-year period.

Methods

From 2010 to 2015, HIV-negative MSM were followed every 6 months. Anal self-swabs were collected every 6 months and HPV genotyped using the SPF10-PCR DEIA/LiPA25 system v1. Incidence rate (IR) and clearance rate (CR) of incident anal hrHPV infection were assessed by hrHPV-type (types 16,18,31,33,45,52,58). Determinants of transitions between uninfected and infected states were assessed by hrHPV-type using a time-homogenous multi-state Markov model.

Results

713 HIV-negative MSM, with median age of 37 years (IQR 31-43), were included (with a median number of study visits of 6, IQR 2-7). IR of anal infection was a median of 5.2 per 100 person-years (range: 2.2-7.9) across types, with HPV16 being the highest. CR of incident anal hrHPV infection was a median of 53.7 per 100 person-years (range: 33.4-65.3) across types, with HPV16 being the lowest. The cumulative proportion with persistent infection at 3 years after incident anal HPV16 infection was 0.25 (95%CI: 0.14-0.37). Having had over 100 lifetime sex partners was significantly associated with incident anal hrHPV infection in multivariable analyses.

Conclusions

The high incidence and low clearance rates of anal HPV16 infection, compared to other hrHPV-types, is consistent with HPV16 being implicated in the large majority of anal cancer cases.
Background and Aims

HIV-positive men who have sex with men (MSM) have an increased risk for human papillomavirus (HPV)-induced lesions including anogenital carcinomas, its precursor lesions, and benign anogenital warts (AGW). So far, little is known about the HPV-type spectrum of AGWs of HIV-positive MSM. This study was initiated to evaluate the lesional HPV-type spectrum of AGWs in HIV-positive MSM and immunocompetent controls, using established histopathological/immunohistochemical criteria.

Methods

Histopathological analysis, immunohistochemical staining for p16\textsuperscript{INK4a} and Ki67, and HPV-typing were performed in AGWs (without areas of dysplasia) of 83 HIV-positive MSM and 52 HIV-negative control-patients.

Results

96.4% of AGWs of immunocompetent controls carried exclusively low-risk (LR)-HPVs, with HPV6 and HPV11-monoinfection in the majority (91.6%) of cases. In contrast, only 80.8% of AGWs of HIV-positive MSM carried LR-HPVs (75.0% LR-HPV-monoinfection). The proportion of HPV6/HPV11 in AGWs of HIV-positive MSM was substantially lower compared with control-patients (61.5 vs. 91.6%). Moreover, multiple HPV-infections (17.3 vs. 8.4%) and combined LR- and high-risk (HR)-HPV-infections (11.5% vs. 3.6%) were more frequent in AGWs of HIV-positive MSM as compared with controls. 85.5% of AGWs of immunocompetent controls, but only 53.8% of AGWs of HIV-positive MSM were completely covered by the 9-valent HPV-vaccine. The proportion of partially covered (11.5 vs.6.0%) and not covered HPV-types (28.8 vs. 8.4%) was significantly higher in HIV-positive MSM as compared to controls.

Conclusions

In contrast to immunocompetent patients, AGWs of HIV-positive MSM frequently contain other HPV-types than HPV6/HPV11. A substantial proportion of AGWs in HIV-positive MSM are not covered by the currently available HPV-vaccines.
Rapid Communication

Clinical

Estimating the Benefits and Harms of P16 Utilization on Cervical Biopsy Interpretation in Routine Clinical Practice

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Background and Aims

Studies supporting p16 immunohistochemical staining of biopsies for diagnosis of cervical intraepithelial neoplasia have relied on convenience samples. Larger evaluations are needed to estimate the potential impact of p16 use on excisional treatment in general populations.

Methods

A stratified random sample of 4100 cervical biopsies diagnosed in 2006-2009 was created through a population-based cervical screening registry based in the United States. Each of a study panel (SP) of 41 pathologists diagnosed 100 biopsies based on Hematoxylin and Eosin (H&E) staining alone and specified if a p16 stain would be requested. Subsequently, a new diagnosis was rendered based on a reread of an H&E slide in combination with a p16 slide. The SP, original community, and an expert panel (EP) of pathologist’s diagnoses were compared.

Results

After reweighting to the population, the SP requested p16 staining for 29% of biopsies versus 19% anticipated by recommending committees. p16 was requested in 19% of negative and low-grade biopsies combined. Restricting to cases where p16 was requested by the SP led to a 2·0% (1·6, 2·4) reduction in CIN2 or more severe (CIN2+) diagnoses versus the SP’s original CIN2+ diagnoses. Agreement between the SP and EP improved when p16 was requested (kappa 0·67 vs. 0·71; p=0·03). If the SP’s H&E plus p16 diagnoses were used for all cases, there would have been a 14·6% (13·6, 15·6) increase in CIN2+.

Conclusions

p16 may increase agreement between pathologists but broad use could increase the number of CIN2+ diagnoses and result in the referral of more women to excisional treatment.
LOWER GENITAL TRACT DYSPLASIA IN WOMEN WITH SOLID ORGAN TRANSPLANTS
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Background and Aims

Women with solid organ transplants are at increased risk of lower genital tract dysplasias. We sought to evaluate the incidence of disease in a large population and determine clinicopathologic factors associated.

Methods

We identified women who underwent transplantation at a large urban tertiary care center between 2000 and 2015. Demographic and clinicopathologic factors were extracted from medical records and incidence of lower genital tract disease was determined. Univariate analyses were performed to examine associations with dysplasia.

Results

Of 429 women post transplant, 47 (10.96%) developed lower genital tract dysplasia. Thirty-eight (8.86%) developed cervical intraepithelial neoplasia (CIN); 14 (3.26%) with CIN2+ and 1 (0.23%) with cervical carcinoma. Nineteen (4.43%) developed other lower genital dysplasias (vulvar, vaginal, or anal); 12 (2.80%) with high grade dysplasia and 5 (1.17%) with carcinoma (3 anal, 1 vaginal, and 1 vaginal). Only 21 women (4.9%) had documented yearly Pap smears for five years after transplant. Of those with CIN2+, 7 (50%) cleared the dysplasia with treatment, while 7 (50%) had persistent disease. Factors associated with development of lower genital tract dysplasia were black race (p=0.0015), history of pre-transplant dysplasia (p=0.0307), liver or kidney transplant (p=0.0193, 0.0259), and hydroxychloroquine immunosuppression (p=0.0022).

Conclusions

Lower genital tract dysplasias occur in approximately 5-10% of women with transplants; half are high grade or cancer, of which half are persistent. Black race is associated with dysplasia, however, other social determinants of health may play a significant role. While yearly cervical cancer screening is recommended, complete lower genital examination should also be performed.
Background and Aims

Cervical cancer development requires persistent infection with oncogenic HPVs, together with the accumulation of somatic mutations into the host genome. Recent studies have reported concomitant genetic changes in the HPV genome; however, their relevance to cervical carcinogenesis is poorly understood. Here we explored within-host genetic diversity of HPV by performing deep sequencing analyses of viral whole-genome sequences in clinical specimens.

Methods

The whole genomes of HPV16/52/58 were amplified by type-specific PCR from total cellular DNA of cervical exfoliated cells collected from patients with cervical intraepithelial neoplasia and invasive cervical cancer, and were deep-sequenced. Nucleotide positions showing changes with > 0.5% frequencies compared to the consensus viral sequence were determined for individual samples.

Results

A total of 1,052 positions of nucleotide variations were detected in HPV genomes from 151 samples (CIN1, n = 56; CIN2/3, n = 68; ICC, n = 27). Overall, C-to-T and C-to-A substitutions were the dominant changes observed across all histological grades. Analysis of the trinucleotide context for substituted bases revealed that TpCpN, a preferred target sequence for cellular APOBEC cytosine deaminases, was a primary site for C-to-T substitutions in the HPV genome. Although much less prevalent, C-to-G substitutions were similarly observed in the TpCpN context, which also supports APOBEC editing. Interestingly, among six nucleotide variations detected in the long control region, two APOBEC signature mutations observed in CIN1 samples resulted in upregulation of the viral early promoter responsible for E6/E7 expression in reporter assays.

Conclusions

The results suggest a potential role for APOBEC-mediated mutagenesis in cervical carcinogenesis.
Background and Aims

Phosphoinositide 3-kinase (PI3K) signaling pathway is crucial for cancer development. MicroRNAs (miRNAs) involved in PI3K signaling pathway play important roles in the processes of cancers through regulating their target genes. To evaluate the association of polymorphisms in miRNAs involved in PI3K signaling pathway with cervical intraepithelial neoplasia (CIN) and cervical cancer.

Methods

Eight SNPs in miRNA genes (rs543412 in miR-100, rs767649 in miR-155, rs999885 in miR-106b, rs1143770 in miR-Let7a2, rs2296616 in miR-107, rs4636297 in miR-126, rs8111742 in miR-125a and rs11614913 in miR-196a2) were selected to be genotyped in 358 CIN-patients, 547 cervical cancer patients and 573 healthy individuals using Taqman assay.

Results

The frequency of rs4636297 C allele was significantly higher in control group than in CIN and cervical cancer groups (P=0.019, OR=0.750; and P=0.030, OR=0.788; respectively). The C allele of rs11614913 occurred higher in control group than in CIN and cervical cancer groups (P=0.029, OR=0.812; and P=0.014, OR=0.788; respectively). The inheritance model analysis showed genotype TT of rs4626297 was associated with high risk of CIN under the recessive model (P=0.003, OR=3.02). In comparison of cervical cancer and control groups, TC-TT genotypes were associated with higher risk of cervical cancer (P=0.02, OR=1.34). The CC genotype of rs11614913 was associated with lower risk of CIN under recessive model (P=0.003, OR=3.02). In the comparison between cervical cancer and control groups, 2CC+CT genotype of rs11614913 was associated with lower risk of cervical cancer (P=0.013, OR=0.81) under log-additive model.

Conclusions

Our results indicate the C allele of rs4636297 in miR-126 and rs11614913 in miR-196a2 might be protective factors for CIN and cervical cancer in the Chinese Han population.
Background and Aims

Detection of highly divergent or yet unknown viruses from metagenomics sequencing datasets is a major bioinformatics challenge. When human samples are sequenced, a large proportion of assembled contigs are classified as “unknown”, as conventional methods find no similarity to known sequences. We wished to explore whether machine learning algorithms using Relative Synonymous Codon Usage frequency (RSCU) could improve the detection of viral sequences in metagenomic sequencing data.

Methods

We trained Random Forest and Artificial Neural Network using metagenomic sequences taxonomically classified into virus and non-virus classes.

Results

The algorithms achieved accuracies well beyond chance level, with area under ROC curve 0.79. Two codons (TCG and CGC) were found to have a particularly strong discriminative capacity.

Conclusions

RSCU-based machine learning techniques applied to metagenomic sequencing data can help identify a large number of putative viral sequences and provide an addition to conventional methods for taxonomic classification.
Basic Science - Genomics of HPV Lesions

HLA Class I (A, B, and C) Loci Were Associated with Cervical Cancer in a Chinese Han Population

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Background and Aims

Human leukocyte antigen plays a key role in the clearance of the Human papillomavirus (HPV) and HPV related cervical cancer. To investigate the association of HLA class I (A, B, and C) loci with cervical cancer in a Han population from the Yunnan province, Southwest of China.

Methods

A total of 435 patients with cervical cancer and 463 healthy individuals were collected to genotype HLA-I (A, B, C) loci using the next generation sequencing technology.

Results

Our results showed the allele frequencies of HLA-A*33:03, HLA-A*11:03, HLA-B*15:01, HLA-B*27:05, HLA-B*39:01, HLA-B*52:01, HLA-B*55:02, HLA-B*58:01, HLA-C*03:02, HLA-C*04:03 and HLA-C*12:03 showed significant difference between cervical cancer group and healthy group (P<0.001, P=0.001, P=0.026, P=0.039, P=0.030, P=0.006, P=0.007, P=0.035 and P=0.043, respectively). In the haplotype analysis, HLA-A*33:03-B*58:01 and HLA-B*58:01-C*03:02 showed significant difference between cervical cancer group and healthy group (P=0.024 and P=0.026, respectively).

Conclusions

Our result indicated that HLA-A*33:03 (OR=0.542, 95% CI: 0.383-0.767), HLA-B*15:01 (OR=0.548, 95%CI: 0.320-0.937), HLA-B*27:05 (OR=0.324, 95%CI:0.105-0.999), HLA-B*39:01 (OR=0.292, 95%CI: 0.108-0.789), HLA-B*58:01 (OR=0.549, 95%CI:0.356-0.847) and HLA-C*03:02 (OR=0.557, 95%CI:0.363-0.855) may be protective factors in the cervical cancer. However, the HLA-A*11:03 (OR=14.032, 95%CI:1.832-107.492), HLA-B*52:01 (OR=1.648, 95%CI: 1.021-2.658), HLA-B*55:02 (OR=1.687, 95%CI: 1.048-2.716), HLA-C*04:03 (OR=1.774, 95%CI:1.035-3.040) and HLA-C*12:01 (OR=1.992, 95%CI:1.008-3.938) may be the risk factor for cervical cancer in the current population. The HLA haplotypes HLA-A*33:03-B*58:01 (OR=0.499, 95% CI: 0.308-0.808) and HLA-B*58:01-C*03:02 (OR=0.503, 95%CI: 0.322-0.785) might be associated with lower risk of cervical cancer.
INHIBITION OF HPV-18 DNA AMPLIFICATION BY NVN1000, A NOVEL NITRIC OXIDE RELEASING COMPOUND, IN RAFT CULTURES OF PRIMARY HUMAN KERATINOCYTES.

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Background and Aims

Robust HPV-18 DNA amplification occurs in differentiated strata in organotypic epithelial raft cultures of primary human keratinocytes (PHK). NVN1000, a polymeric macromolecule developed by NOVAN Inc, releases NO in an aqueous environment. We evaluated whether NVN1000 has anti-viral effects in HPV-18 infected PHK raft cultures.

Methods

Raft cultures of PHKs containing replication-competent HPV-18 genomic plasmid or HPV-16 E6 and E7 expressing construct were prepared. Infected and control cultures were exposed topically to aqueous solutions of NVN1000 daily for one hour on 6 consecutive days. Biochemical and in situ analyses were performed to assess host DNA replication, viral DNA amplification, viral and host protein expression and DNA damage.

Results

Very low or negligible levels of HPV-18 DNA amplification and the L1 capsid protein synthesis were detected upon exposure to 2 mg/ml NVN1000. The reduction of E7-induced suprabasal BrdU incorporation and appearance of p53-positive nuclei demonstrated compromised HPV-18 E7 and E6 activities relative to vehicle-exposed cultures. Immunoblots confirmed reduced E6 and E7 proteins and elevated p53. E7-induced PCNA and cyclin B1 were also diminished. Further analyses showed significantly higher DNA damage and apoptosis in infected relative to uninfected cultures. NVN1000 also inhibited HPV-16 E6 and E7 functions in PHK raft cultures expressing these oncogenes, causing DNA damage and apoptosis.

Conclusions

NVN1000 is expected to inhibit DNA amplification of HPV-18, HPV-16 and other genotypes, all of which depend on E6 and E7 functions. This agent is a promising therapeutic candidate for further evaluation against pre-neoplastic HPV infections.
Background and Aims

The World Health Organization (WHO) recommends a 2-dose HPV vaccine schedule for girls aged 9-14. As randomised controlled trials assessing the immunogenicity and efficacy of a 1-dose schedule are ongoing, we interviewed immunisation programme managers and advisors in low and middle-income countries (LMIC) about motivators, barriers and information needs for a hypothetical, future reduction in the HPV vaccine schedule.

Methods

We conducted semi-structured interviews with LMIC immunisation programme managers and national immunisation technical advisory group members (key informants; KIs) in 2017, recruited for their knowledge/experience in national HPV vaccine policy and provision. Data were analysed thematically.

Results

We conducted 30 interviews with KIs from 18 countries in Africa, Asia, Latin America and Eastern Europe. Perceived advantages of a 1-dose schedule included reduced logistical resources needed for vaccine delivery, reduced programme costs, reduced cold chain requirements, and easier integration into routine immunization services. Perceived barriers to dose reduction included community acceptance given recent 3- to 2-dose reductions, health-worker acceptance, resources needed to re-mobilize communities and re-train health-workers, potential misrepresentation of schedule changes by anti-vaccine groups or media, and decreased opportunity for service integration, e.g. sexual and reproductive health services. Most interviewees supported a reduced schedule. Half of interviewees suggested a WHO position paper or recommendation would be necessary prior to policy change.

Conclusions

We found wide-ranging support among LMIC immunisation managers and advisors for a 1-dose vaccine schedule if (i) research demonstrated immunological and clinical evidence of efficacy, and (ii) WHO provided a formal recommendation.
A PILOT OF HPV SELF-SAMPLING OF ABORIGINAL WOMEN FROM RURAL COMMUNITIES IN WESTERN NSW: EVALUATING A NURSE LED COMMUNITY ENGAGEMENT MODEL

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²Marathon Health, Primary Health Care, Dubbo, Australia
³Dubbo Medical & Allied Health Group, General Practice, Dubbo, Australia

Background and Aims

Aboriginal & Torres Strait Islander women in Australia are significantly under-screened with respect to cervical cancer screening due to complex cultural and socio-economic factors. The discovery of Human Papilloma Virus (HPV) as the primary causative agent in most cervical cancers has opened the door to HPV testing as an alternative to the traditional Pap test for detecting prospective cervical cancer. HPV testing allows for self-sampling which may overcome some of the barriers to Pap testing, including being less-obtrusive, and this may make it a more acceptable screening practice for Aboriginal & Torres Strait Islander women. This study seeks to assess the feasibility and acceptability of HPV self-sampling as a cervical screening approach for Aboriginal & Torres Strait Islander women using a nurse-led community engagement approach.

Methods

Marathon Health Primary Healthcare Nurses are working alongside Local Aboriginal Land Council Community Engagement Workers in eight rural towns in Western New South Wales to engage with local women and invite them to participate in HPV self-sampling.

Results

Data collection will be completed by the end of June 2018. Current data are showing high engagement with the service model and high acceptability rates. Of the 108 women who have participated in self-sampling, 24% have never had a Pap test and 70% have not had one in the previous 4 years. Twenty women have tested positive for HPV, five to the high risk 16/18 type.

Conclusions

This early data suggests that this service model can successfully engage never screened and under-screened women in cervical cancer screening.
PUBLIC HEALTH

WORLDWIDE FEMALE AND MALE HPV VACCINATION COVERAGE UP TO 2018

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Background and Aims

Objective: To present an updated estimate up to 2018 of HPV vaccine coverage in public programs worldwide for women and men. We will present projections on the expected number of averted cases in vaccinated cohorts for cervical cancer and, for the first time, other HPV-related cancers in both sexes.

Methods

A systematic review of PubMed, Scopus, LILACS, and official websites to identify HPV immunisation programmes worldwide and retrieve program characteristics and age-specific HPV vaccination coverage rates. Using previously published methodology, coverage rates are converted and standardized into birth-cohort-specific rates, with an imputation algorithm for missing data, and applied to global population estimates and HPV-related cancer projections by country and income level.

Results

By March 2018, 85 countries reported data on publicly-funded HPV immunisation programmes; 21 of which offer gender-neutral vaccination. Almost all countries vaccinate with a 2-dose schedule under 15-years-olds. There is a wide variation in vaccine coverage across countries ranging from 2% to 98%, and an increasing number of vaccinated cohorts. The expected global impact presents marked disparities by geographical region and income level, determined by large differences in vaccine introduction and coverage across countries.

Conclusions

HPV vaccination is in steady progress in developed countries with a sizeable expected impact in cancer burden.
PUBLIC HEALTH

PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV)-VACCINE TYPES BY RACE/ETHNICITY IN WOMEN WITH HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN2+)

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Background and Aims

To evaluate racial/ethnic differences in prevalence of oncogenic HPV types targeted by quadrivalent vaccine (4vHPV, 16/18) and nonavalent vaccine (9vHPV, 16/18/31/33/45/52/58) in CIN2+ after 4vHPV introduction.

Methods

HPV typing data for 1612 CIN2+ cases from population-based surveillance in Alameda County, California, United States were analyzed. We calculated 4vHPV type prevalence by race/ethnicity in 2008-2011 and 2012-2014. We evaluated 9vHPV types by race/ethnicity for 2008-2014, since 9vHPV was introduced in 2015. We used Poisson regression to calculate prevalence ratios (PR) and 95% confidence intervals (CI) comparing prevalence by race/ethnicity, adjusted for CIN grade.

Results

Among CIN2+ cases from 2008-2011, Asians, Blacks, and Hispanics had significantly lower prevalence of HPV 16/18 compared with Whites (PR: 0.71, 0.82, and 0.79, respectively). In 2012-2014, Asians had significantly higher prevalence compared with Whites due to significant increases in 16/18 among Asians (16.2%, p=0.01) and significant declines among Whites (-12.0%, p=0.003). HPV 16/18 prevalence also declined among Blacks (-10.0%, NS) and Hispanics (-3.7%, NS). Prevalence of 9vHPV types did not differ significantly by race/ethnicity.
Conclusions

Decreasing HPV 16/18 prevalence in CIN2+ in White, Black, and Hispanic women may suggest benefit from 4vHPV vaccination in these groups. Further study is needed on HPV 16/18 increases in Asians to determine if this resulted from differences in vaccination coverage, increasing Asian immigration to the region, or other factors. The lack of racial/ethnic differences in 9vHPV types is reassuring and suggests that 9vHPV vaccine should have equitable impact on CIN2+ rates, regardless of race/ethnicity, if similar vaccination coverage by race/ethnicity is achieved.

Table 1: Prevalence of Oncogenic HPV types targeted by Quadrivalent HPV Vaccine in CIN 2/3/AIS Lesions: Adjusted Prevalence Ratios by Race/Ethnicity, 2008-2011 and 2012-2014

<table>
<thead>
<tr>
<th></th>
<th>Prevalence Ratio* (95% CI)</th>
<th>p</th>
<th>Prevalence Ratio* (95% CI)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n=838)</td>
<td></td>
<td>(n=774)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>41.8 (59/141)</td>
<td>0.71 (0.57, 0.88)</td>
<td>0.001</td>
<td>58.0 (80/138)</td>
</tr>
<tr>
<td>Black</td>
<td>47.2 (84/178)</td>
<td>0.82 (0.68, 0.97)</td>
<td>0.024</td>
<td>37.2 (45/121)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>46.8 (103/220)</td>
<td>0.79 (0.57, 0.93)</td>
<td>0.005</td>
<td>43.1 (81/188)</td>
</tr>
<tr>
<td>White</td>
<td>58.2 (174/299)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for CIN grade.

Table 2: Prevalence of Oncogenic HPV types targeted by Nonavalent HPV Vaccine in CIN 2/3/AIS Lesions: Adjusted Prevalence Ratios by Race/Ethnicity, 2008-2014

<table>
<thead>
<tr>
<th></th>
<th>Prevalence Ratio* (95% CI)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(n=1612)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>81.4 (227/279)</td>
<td>1.03 (0.96, 1.10)</td>
</tr>
<tr>
<td>Black</td>
<td>74.2 (222/299)</td>
<td>0.94 (0.87, 1.01)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>77.0 (314/408)</td>
<td>0.97 (0.91, 1.04)</td>
</tr>
<tr>
<td>White</td>
<td>79.2 (496/626)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Adjusted for CIN grade.
BARRIERS TO SUCCESSFUL TREATMENT ACQUISITION FOR CRYOTHERAPY AMONG HPV POSITIVE WOMEN IN WESTERN KENYA

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Background and Aims

While highly preventable, cervical cancer remains a leading form of cancer in women globally, with disproportionate impacts in Sub-Saharan Africa. Human papillomavirus (HPV) testing is a cost-effective screening strategy with the potential to increase screening uptake; however, the two-visits required often lead to substantial lost to follow-up (LTFU) for treatment.

Methods

We carried out a mixed-methods study to understand factors related to LTFU following an HPV-based cervical cancer screening campaign in rural Western Kenya. We randomly selected HPV positive women from the parent study to complete quantitative surveys, where we aimed to reach equal numbers of treated and LTFU women. A subset of women was selected for in-depth interviews (IDIs).

Results

Sixty-one treated and 39 LTFU women completed the survey, and 10 women from each group completed IDIs. Cost of transportation and distance to the hospital were barriers among all women, who often depended on their partners to facilitate this. Among treated women 67% (n=41) reported that their peers knew their HPV test result, compared to 38% (n=15) among LTFU women. Stigma and lack of partner and peer support emerged as consistent themes among LTFU women. Women proposed peer encouragement, including men in educational sessions, bringing facilities closer and providing transportation as facilitators to treatment seeking.

Conclusions

The greatest difference between the two groups was the frequent lack of partner and social support among LTFU women. Future interventions should explore stigma reduction, male involvement, peer support and alternative transportation options as potential facilitators to treatment seeking.
Background and Aims

To mitigate the high morbidity/mortality of cervical cancer in LMICs, screening of un-vaccinated women remains essential. We compared the performance of visual inspection with acetic acid (VIA), the most cost-effective approach, with genital HPV testing, a tool with considerable public health potential, in detecting a transforming cervical HPV infection defined as p16INK4a/Ki-67 dual stain cytology positivity.

Methods

Women were recruited as part of a VIA-based cervical cancer screening program in two rural health centres of Ethiopia. Consenting women had a VIA examination preceded by collection of a cervical smear and an HPV sample. Methanol-stored samples were tested using Hybrid capture 2 test (Qiagen®). Cervical smears were stained using the CINtecPLUS® protocol.

Results

In 415 of a total of 763 women aged 18-64 years all three investigations could be analysed. The HPV test was true positive (TP) in 6 of 7 p16/Ki-67 positive cases and false positive (FP) in 40 of 408 p16/Ki-67 negative cases giving a sensitivity of 85.7% (95%CI 42.1% to 99.6%) and a specificity of 90.2% (95%CI 86.9% to 92.9%). The VIA was TP in 1 of 7 and FP in 116 of 292 respectively giving a sensitivity of 14.3% (95%CI 0.4% to 57.9%) and a specificity of 71.6% (95%CI 66.9% to 75.9%). The HPV positivity rate of VIA positive cases was 7.4%.

Conclusions

The performance of HPV-based cervical cancer screening is far superior to VIA screening in detecting p16INK4a/Ki-67 positive transforming infections. HPV testing should be considered as primary screening test also in LMICs.
DIFFERENT EFFECT OF AGE ON THE RISK OF CIN2/3 AND OF CANCER AFTER NEGATIVE CYTOLOGY AND HPV TEST

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Background and Aims

The risk of CIN2/3 and of invasive cervical cancer (ICC) after a negative HPV test is known to be lower than after negative cytology. However, the effect of age is not well studied.

Methods

We used data of the NTCC, POBASCAM, ARTISTIC and Swedscreen RCTs. We computed the incidence of CIN2/3 and of ICC after a negative entry cytology in the control arm and a negative entry HPV test in the experimental arm in women aged <50 and ≥50 years (overall 161220 women with normal baseline testing, including 736 CIN2/3 and 54 ICC).

Results

The age-adjusted relative incidence in the experimental vs. conventional arm was 0.63 (95% CI 0.54-0.73) for CIN2/3 and 0.36 (0.20-0.66) for ICC. The arm-adjusted relative incidence in women aged ≥50 vs. <50 years was 0.22 (0.16-0.30) for CIN2/3 and 1.93 (1.09-3.43) for ICC. The arm-age interaction was not significant (p=0.14 for CIN2/3 and 0.21 for ICC). The 3.5-year risk of CIN2/3 per 10,000 women aged < and ≥50 years was 18.7 and 5.5 respectively after a negative entry cytology and 14.5 and 3.0 respectively after a negative HPV test. The corresponding ICC risks were 1.2 and 2.5 after a negative cytology and 0.3 and 1.0 after a negative HPV test.

Conclusions

The effect of HPV was similar in both age groups. However, at variance with CIN2/3, the risk of ICC increased at age ≥50 in both arms. It must be kept in mind that HPV-screened women were at their first screen with HPV.
PUBLIC HEALTH

PREVALENCE OF GENITAL QUADRIVALENT VACCINE AND NON-VACCINE HPV TYPES AMONG AUSTRALIAN WOMEN AGED 18–24 YEARS, A DECADE AFTER PROGRAM IMPLEMENTATION

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2Murdoch Children’s Research Institute, Infection and Immunity, Melbourne, Australia
3University of Melbourne, School of Population and Global Health, Melbourne, Australia
4University of Melbourne, Obstetrics and Gynaecology, Melbourne, Australia
5National HPV Vaccination Program Register, Victorian Cytology Service, Melbourne, Australia
6Family Planning, New South Wales, Sydney, Australia
7The University of Sydney, Discipline of Obstetrics- Gynaecology and Neonatology, Sydney, Australia
8Family Planning, Victoria, Melbourne, Australia
9University of New South Wales, The Kirby Institute for infection and immunity in society, Sydney, Australia
10Alfred Health, Melbourne Sexual Health Centre, Melbourne, Australia
11Monash University, Central Clinical School, Melbourne, Australia

Background and Aims

All Australian women aged <25 years have been eligible to receive free quadrivalent HPV vaccine in the national school-based vaccination program. We examined HPV prevalence among vaccinated and unvaccinated women aged 18–24 years, 9–10 years after program implementation.

Methods

Sexually active women were recruited at health services across Australia in 2015–2016, as part of an ongoing surveillance program. Participants provided a self-collected vaginal swab for HPV genotyping (Roche Linear Array), completed a questionnaire, and gave consent to validate vaccine doses with the National HPV Vaccination Program Register. Adjusted prevalence ratios (aPRs) were estimated comparing HPV prevalence between vaccinated (≥1 vaccine dose) and unvaccinated women.

Results

Of the 640 women included in the study, 67.2% received ≥1 vaccine dose as recorded in the National Register. Vaccinated women were more likely to be recruited from Family Planning/General Practice clinics (p=0.05), be Australian born (p<0.001), and be older at first vaginal sex (p=0.03) compared with unvaccinated women (Table 1). Prevalence of HPV16/18 was significantly lower among vaccinated compared with unvaccinated women (0.2% [95% CI: 0–1.3] versus 4.8% [95% CI: 2.3–8.6] respectively; aPR=0.05 [95% CI: 0.01–0.42]; p=0.005). By contrast, prevalence of HPV6/11, and other HR- and LR-HPV types did not differ significantly between the groups (Figure 1 and Table 2).

Conclusions

A decade into the program, overall prevalence of quadrivalent vaccine-targeted HPV types was very low among young sexually active women. However, prevalence of HPV types 16 and 18 was
significantly higher among unvaccinated compared with vaccinated women, despite strong herd effects of the vaccine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Unvaccinated n=210 (32.8%)</th>
<th>Vaccinated (≥1 dose) n=430 (67.2%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Mean (SD)</td>
<td>21.6 (1.7)</td>
<td>21.6 (1.7)</td>
<td>21.6 (1.7)</td>
</tr>
<tr>
<td>18–21 years</td>
<td>303 (47.3)</td>
<td>98 (46.7)</td>
<td>205 (47.7)</td>
<td>0.81</td>
</tr>
<tr>
<td>22–24 years</td>
<td>337 (52.7)</td>
<td>112 (53.3)</td>
<td>225 (52.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Source of recruitment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family Planning/General Practice</td>
<td>581 (90.8)</td>
<td>184 (87.6)</td>
<td>397 (92.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Sexual Health/AMS</td>
<td>59 (9.2)</td>
<td>26 (12.4)</td>
<td>33 (7.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Country of birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>548 (86.9)</td>
<td>163 (78.7)</td>
<td>385 (90.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>83 (13.2)</td>
<td>44 (21.3)</td>
<td>39 (9.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Secondary</td>
<td>316 (49.4)</td>
<td>105 (50.0)</td>
<td>211 (49.1)</td>
<td>0.83</td>
</tr>
<tr>
<td>Tertiary</td>
<td>324 (50.6)</td>
<td>105 (50.0)</td>
<td>219 (50.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Area of residence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cities</td>
<td>597 (93.4)</td>
<td>198 (94.7)</td>
<td>399 (92.8)</td>
<td>0.35</td>
</tr>
<tr>
<td>Other areas</td>
<td>42 (6.6)</td>
<td>11 (5.3)</td>
<td>31 (7.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Socio-economic status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>More disadvantaged</td>
<td>155 (24.4)</td>
<td>49 (23.6)</td>
<td>106 (24.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Less disadvantaged</td>
<td>481 (75.6)</td>
<td>159 (76.4)</td>
<td>322 (75.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>489 (78.5)</td>
<td>150 (73.9)</td>
<td>339 (80.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>134 (21.5)</td>
<td>50 (26.1)</td>
<td>81 (19.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at first vaginal sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤16 years old</td>
<td>150 (24.3)</td>
<td>60 (29.7)</td>
<td>90 (21.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;16 years old</td>
<td>467 (75.7)</td>
<td>140 (70.3)</td>
<td>325 (78.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Lifetime number of sexual partners</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>227 (37.4)</td>
<td>72 (36.2)</td>
<td>155 (38.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>5–10</td>
<td>218 (35.9)</td>
<td>75 (37.7)</td>
<td>143 (33.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>162 (26.7)</td>
<td>52 (26.1)</td>
<td>110 (27.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Partners in the previous 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>241 (39.1)</td>
<td>77 (38.5)</td>
<td>164 (39.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>≥2</td>
<td>375 (60.9)</td>
<td>123 (61.5)</td>
<td>252 (60.6)</td>
<td></td>
</tr>
</tbody>
</table>

Numbers do not always total 640 because of missing data; p-values presented are score test of homogeneity between unvaccinated and vaccinated groups; AMS: Aboriginal Medical Services; SD: Standard deviation.
Figure. 1 Prevalence and 95% confidence intervals (CI) of genital quadrivalent vaccine and non-vaccine HPV types among 640 Australian women aged 18-24, overall and by vaccination status.

Table 2. Crude and adjusted prevalence ratios (PR) for genital quadrivalent vaccine and non-vaccine HPV types among 640 Australian women aged 18-24, by vaccination status.

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>PR (95% CI); p-value</th>
<th>Adjusted PR(^1); (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HPV 16/18</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated (n=210)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>≥ 1 dose vaccinated (n=430)</td>
<td>0.05 (0.01–0.38); 0.004</td>
<td>0.05 (0.01–0.42); 0.005</td>
</tr>
<tr>
<td><strong>HPV 6/11</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated (n=210)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>≥ 1 dose vaccinated (n=430)</td>
<td>0.16 (0.02–1.56); 0.12</td>
<td>0.18 (0.02–1.76); 0.14</td>
</tr>
<tr>
<td><strong>HR-HPV not 16/18</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated (n=210)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>≥ 1 dose vaccinated (n=430)</td>
<td>0.98 (0.75–1.27); 0.86</td>
<td>1.02 (0.78–1.34); 0.882</td>
</tr>
<tr>
<td><strong>Any-HPV not 6/11/16/18</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated (n=210)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>≥ 1 dose vaccinated (n=430)</td>
<td>1.04 (0.87–1.25); 0.64</td>
<td>1.08 (0.90–1.31); 0.390</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for age group, source of recruitment, country of birth, smoking status and age at first vaginal sex; p-values presented are score test of homogeneity between the groups.
Background and Aims

Cervical screening programmes worldwide are converting from primary cytology to primary HR-HPV testing. While there are conclusive data from controlled trials demonstrating greater sensitivity of HR-HPV testing in the detection of cervical intraepithelial neoplasia (CIN), large data on its implementation under routine conditions are scarce. This large pilot was established in 2013 by Public Health England, to demonstrate ‘real life’ practicability of screening with primary HR-HPV, and the safety of screening interval extension.

Methods

Six large English NHS screening laboratories partially converted to primary HR-HPV testing. Women aged 25-64 were screened following routine invitations. HR-HPV positive women were referred to colposcopy if reflex liquid based cytology (LBC) was abnormal. If normal, women were recalled at 12 months, and if HPV persisted, again at 24 months. Women were routinely recalled after three years for a second screening round. Outcomes were compared using odds ratios (OR).

Results
By 31st December 2014, 578,547 women had been screened; 183,970 by HR-HPV and 394,577 by LBC. Including early recall, colposcopy referral was 7%, and 4% following primary LBC with HR-HPV triage. HR-HPV detected substantially more CIN3+; OR 1.44 (95%CI: 1.36-1.51) and cancer; OR 1.27 (95%CI: 0.99-1.63). 80% attended early recall and 95% attended referrals for colposcopy. One quarter of CIN2+ was detected following early recall. At the second round HPV negative women at baseline had substantially less CIN3+; OR 0.14 (95%CI: 0.09-0.23).

Conclusions

This uniquely large experience indicates the feasibility of primary HPV screening and safe interval extension in a large routine national programme.
ORGANISED PRIMARY HPV SCREENING OF WOMEN AGED 30 - 64 IN SWEDEN: RANDOMIZED HEALTHCARE POLICY

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²Karolinska University Hospital, Karolinska University Laboratory, Stockholm, Sweden
³Regional Cancer Center, Cancer Screening Unit, Stockholm, Sweden

Background and Aims

To evaluate the effectiveness of primary HPV screening for women aged 30-64 when introduced into a real-life organised, population-based cervical screening program.

Methods

Primary HPV screening for women age 30 and upwards was implemented in the organized screening program in Stockholm 2014, randomising all resident women to either invitation to primary HPV screening with cytology triage or to cytology screening. HPV+/Cyt- women in the screening ages are referred to the next round of organised screening and will be referred if HPV++/Cyt-. For HPV+/Cyt- women aged 64 (who otherwise would be acquitted from the programme) will continue to be screened.

The primary evaluation is the sensitivity for CIN2+ detection and cost-effectiveness of the new policy in relation to previous policy.

Results

395275 women were enrolled. Attendance was similar in the 2 arms (HPV/cytology 56.7%/54.1%). The population HPV prevalence was 8.8%. As women with persisting HPV have not yet been referred to colposcopy an at least equal yield of CIN2+ (similar sensitivity of primary screening (safety)) is expected. Evaluation up to 2016-06-30 found 1042 cases of CIN2+ out of 2455 biopsies in the HPV arm and in the cytology arm 803 women with CIN2+ out of 1699 biopsies.

Conclusions

The primary HPV screening was safe, with an increased yield of CIN2+ already at baseline, resulted in a slightly higher attendance rate and reduced screening costs. An increased number of biopsies was seen, the PPV for CIN2+ in a woman with HPV-positivity and abnormal reflex cytology (ASCUS+) was very high (42.4%). This was considered acceptable.
IPVC8-0676
SCIENTIFIC STREAM

SCIENTIFIC STREAM 1: IMPLEMENTATION EXPERIENCE FOR HPV SCREENING IN HIGH INCOME COUNTRIES

FIRST RESULTS OF HIGH-RISK HPV SCREENING IN THE CERVICAL CANCER SCREENING PROGRAMME IN THE NETHERLANDS: PARTICIPATION, REFERRAL AND DETECTION


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3 National Institute for Public Health and the Environment, Centre for Population Screening, Bilthoven, The Netherlands
4 Erasmus MC, Department of Pathology, Rotterdam, The Netherlands
5 University Medical Center Groningen, Department of Medical Microbiology- Division of Clinical Virology, Groningen, The Netherlands
6 University Medical Center Groningen, Department of Pathology, Groningen, The Netherlands
7 RadboudUMC, Department of Medical Microbiology and Pathology, Nijmegen, The Netherlands
8 University Medical Center Utrecht, Department of Medical Microbiology, Utrecht, The Netherlands
9 Jeroen Bosch Hospital, Pathology-DNA, ’s-Hertogenbosch, The Netherlands
10 VU University Medical Center, Department of Pathology, Amsterdam, The Netherlands
11 DDL Diagnostic Laboratory, Leiden Cytology and Pathology Laboratory, Rijswijk, The Netherlands
12 Symbiant, Pathology Expert Centre, Pathology Expert Centre, The Netherlands

Background and Aims

In January 2017, the Dutch cervical cancer screening programme was changed from a cytomorphological screening to primary high-risk HPV DNA (hrHPV) screening for women between ages 30 and 60. This is the first time in the world, that primary hrHPV screening is nation-wide implemented in the actual population. Women can request a self-sampling set or have a cervical smear taken by their GP. Cytology testing is performed on hrHPV positive samples only. Women with cytological abnormalities (i.e. ASCUS+) are referred for colposcopy and women without cytological abnormalities have repeat cytology testing after six months. Monitoring of the renewed screening programme is aimed at participation, hrHPV prevalence and the associated referral- and CIN rates.

Methods

Screening history data was obtained from the national registry of histo- and cytopathology (PALGA), based on 350,147 primary tests performed in women who were invited in 2017 for the renewed screening programme.

Results

Overall, the hrHPV positive rate was 8.9%, ranging from 21.8% (age 30) to 4.5% (age 60). Cytology was assessed in 98.8% of all hrHPV positives, leading to 30.9% referrals. The CIN2+ detection from colposcopy was 51.3%. 5.4% of the participating women opted for the self-sampling device. At a later stage, we will calculate the total referral and CIN detection rates, including those from follow-up examinations, based on full follow-up data.
Conclusions

Primary high-risk HPV DNA screening in the Netherlands leads to the detection of a large proportion of CIN2+ lesions, as a result of a substantial number of referrals for colposcopy.
SAFE IMPLEMENTATION OF PRIMARY HRHPV-SCREENING IN NORWAY: THREE YEARS LATER

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1Cancer Registry of Norway, Norwegian Cervical Cancer Screening Programme, Oslo, Norway
2Cancer Registry of Norway, Research Department, Oslo, Norway

Background and Aims

A shift of primary cervical screening from cytology every 3 years to high-risk human papilloma virus (hrHPV) detection every 5 years can introduce major changes in laboratory routine and diagnosis. To ensure a safe shift while improving diagnostic accuracy, the Norwegian Health authorities implemented this change in a randomized manner.

Methods

Between February 2015 and December 2017, 185,114 women, aged 34 to 69 years, who returned for their routine cervical cancer screening were assigned hrHPV-testing (cobas®HPV Test (Roche Diagnostics)) or cytology, based on even/odd day of birth. Cervical intraepithelial neoplasia grade 3/cervical cancer (CIN3+) were detected among 58,971 women completing positive screening test followup by 2017.

Results

Screening attendance by age was similar in both HPV-screening and cytology-screening groups. After the first screening call, attendance was 53.6% vs 52.3%, respectively. After the second reminder, attendance was 31.8% vs 32.4%, respectively. The proportion of screening test positives was 5.4% in cytology-screening and 6.5% in HPV-screening, and declined with increasing age. HPV16/18 were detected in 28% of hrHPV-positives. Compared to cytology-screening, we observed 40% more biopsies and 50% more CIN3+ in the HPV-screening group. After three months in the randomized implementation, we identified over-diagnosis of abnormal cytology triage in the HPV-screening group in one region. This prompted a quick correction of the over-diagnosis by emphasizing the standardized cytology criteria in the HPV screening group.

Conclusions

Randomized implementation of a shift in cervical cancer screening methodology allows an evidence-based monitoring of its performance in real-world setting, ensuring the high performance of the program during the transition period.
Background and Aims

In a large, population-based implementation study, we compared the clinical performance of human papillomavirus (HPV)-based versus cytology-based cervical cancer screening in Denmark.

Methods

Since May 2017, a pilot implementation of HPV-based cervical cancer screening has been ongoing for women aged 30–59 years in the Region of Southern Denmark. Based on geographical area of residence, women screened in the uptake area of Vejle Hospital are allocated to either HPV-based screening (with HPV16/18 genotyping and cytology triage) or cytology-based screening (with HPV triage for ASC-US/LSIL) (Figure 1). Here, we compare the proportion of unsatisfactory tests and referral rates during the first 10 months of implementation.
## Results

Until March 2018, 8,851 women were screened by HPV testing and 13,359 by cytology. The age distribution (median [interquartile range]) was similar in the HPV (44 years [37–49]) and cytology (43 years [37–49]) groups. The proportion of unsatisfactory tests was lower in the HPV (0.03%, 95% CI: 0.01%–0.09%) than cytology (0.53%, 95% CI: 0.42–0.67) group. The proportion referred to colposcopy was higher in the HPV (4.0%, 95% CI: 3.6%–4.4%) than cytology (2.2%, 95% CI: 2.0%–2.5%) group. The proportion referred to repeat testing at 12 months was also higher in the HPV (5.0%, 95% CI: 4.5%–5.4%) than cytology (0.2%, 95% CI: 0.1%–0.3%) group.
Conclusions

Results for CIN2+ detection will be presented at the conference. HPV-based screening resulted in fewer unsatisfactory tests, but in this initial screening round, more women were referred to colposcopy and repeat testing than with cytology-based screening.
Background and Aims

Human papillomavirus (HPV) genotype influences the development of invasive cervical cancer (ICC), however, there is uncertainty regarding the association of HPV genotype with survival among ICC patients.

Methods

Follow-up data were collected from 693 previously selected and HPV-typed ICC cases that were part of the CDC Cancer Registry Surveillance System. Cases were diagnosed between 1994 and 2005. The Kaplan-Meier method was used to estimate five-year all-cause survival. A multivariate Cox proportional hazards model was used to estimate the effect of HPV genotype on survival after adjusting for demographic, tumor, and treatment characteristics.

Results

Five-year all-cause survival rates varied by HPV status (HPV 16: 66.9%, HPV 18: 65.7%, HPV 31/33/45/52/58: 70.8%, other oncogenic HPV genotypes: 79.0%, non-oncogenic HPV: 69.3%, HPV-negative: 54.0%). Following multivariate adjustment, no significant survival differences were found for ICC patients with HPV 16-positive tumors compared to women with tumors positive for HPV 18, other oncogenic HPV types, or HPV-negative tumors. Women with detectable HPV 31/33/33/45/52/58 had a statistically significant 40% reduced hazard of death at five years (95% CI: 0.38-0.95), and women who tested positive for non-oncogenic HPV genotypes had a significant 57% reduced hazard of death at five years (95% CI: 0.19-0.96) compared to women with HPV 16 tumors. Few significant differences in HPV-positivity, tumor characteristics, treatment, or survival were found by race/ethnicity.

Conclusions

HPV genotype significantly influenced five-year survival rates among women with ICC, however, screening and HPV vaccination remain the most important factors to improve patient prognosis and prevent future cases.
AUTOMATED VISUAL EVALUATION FOR CERVICAL CANCER SCREENING AND MANAGEMENT: PROMISE AND LIMITATIONS

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¹National Cancer Institute NCI, Division of Cancer Epidemiology and Genetics DCEG, Rockville, USA
²Intellectual Ventures, Intellectual Ventures Lab, Seattle, USA
³National Institutes of Health, National Library of Medicine, Rockville, USA
⁴Information Management Services Inc, Information Management, Calverton, USA
⁵Albert Einstein College of Medicine, Department of Obstetrics & Gynecology and Women’s Health, Bronx, USA

Background and Aims

Automated visual evaluation (AVE) of cervical images shows great promise for cervical cancer screening, and potential utility for triage of HPV-positive women. To evaluate the possible performance of AVE as a colposcopy adjunct, we used data from the ASCUS-LSIL Triage Study (ALTS).

Methods

We applied deep learning to archived cervical images from 9,450 women from the population-based cohort in Guanacaste, Costa Rica, and 5,000 women attending colposcopy for minor cytologic abnormalities in ALTS. Three AVE algorithms were trained and validated on cervigrams to recognize histologically-confirmed high-grade lesions. The three training/validation populations were: general screening, triage of HPV-positive women, and colposcopy clinic for triage of ASCUS-LSIL. AVE generated a severity score between 0 and 1 to predict CIN2+. We evaluated the AVE algorithm using receiver operating characteristic (ROC) curves and the area under the curve (AUC) statistic.

Results

In screening settings, AVE distinguished CIN2+ accurately, identifying ~90% of prevalent cases with referral of ~10% of screened women. The AUC in the entire screening set was 0.95, higher than cervicography or cytology (Figure 1). The AUC was 0.88 for triage of HPV-positive women. AVE results for women at colposcopy clinic showed similar trends as severity by cytology, HPV, or cervigram (Table 1). However, the accuracy to predict CIN2+ in this population was reduced with an AUC of 0.69 (Figure 1).
Figure 1. Performance of Automated Visual Evaluation (AVE) algorithms in screening population, triage of HPV-positive women, and colposcopy clinic.
Conclusions

AVE could identify CIN2+ accurately in screening populations and for triage of HPV-positive women but its performance was questionable for risk discrimination in colposcopy settings, where controls look less normal.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>&lt;CIN2&gt;</th>
<th>CIN2+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Freq</td>
<td>Median AVE severity score</td>
</tr>
<tr>
<td>Cytology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2608</td>
<td>0.25</td>
</tr>
<tr>
<td>Reactive changes</td>
<td>1994</td>
<td>0.26</td>
</tr>
<tr>
<td>ASCUS</td>
<td>2041</td>
<td>0.27</td>
</tr>
<tr>
<td>LSIL</td>
<td>1741</td>
<td>0.31</td>
</tr>
<tr>
<td>HSIL+</td>
<td>235</td>
<td>0.30</td>
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</tr>
<tr>
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<td>0.25</td>
</tr>
<tr>
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<td>0.29</td>
</tr>
<tr>
<td>HPV16+</td>
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<td>0.31</td>
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<tr>
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<tr>
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<td>0.32</td>
</tr>
<tr>
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<td>0.38</td>
</tr>
<tr>
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<td>0.50</td>
</tr>
<tr>
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Background and Aims

Retrospective data suggests high rates of spontaneous regression of CIN2 in young women. In this large prospective multicentre study, we aim to describe rates of CIN2 regression and predictors of regression in young women undergoing observational management.

Methods

N=614 women with newly-diagnosed biopsy-proven CIN2 were prospectively recruited to the multicentre PRINcess (CIN2 observational management in women <25 years) trial between 2010 – 2016. The women undertook observational management (i.e., repeat colposcopy, cytology, and cervical biopsy every six months for up to 2 years).

Results

At this date, 30 (5%) women continue to be observed, 37 (6%) are lost to follow up, and 25 (4%) have withdrawn from the study or elected treatment. Of the remaining n=522 women, none have been diagnosed with microinvasion or invasion. 25% (n=133) have been diagnosed with CIN3, 0.4% (n=2) were found to have AIS, 5% (n=28) had persistent CIN2 at 24 months. In contrast 59% (n=310) had persistent regression (i.e., two consecutive colposcopy follow-ups showing CIN grade 1 or less), and an additional 9% (n=49) had unconfirmed regression (i.e., a single regression observed at their last observation). Provisional regression analysis indicates that HPV16 or 18 positivity and larger lesion size were associated with a reduced incidence of regression.
Conclusions

Observational management of CIN2 in women under 25 years is feasible and the majority of women will show spontaneous regression of their lesion within 24 months. This prospective study assists the individual counselling of young women undergoing management of CIN2.
Background and Aims

HPV FOCAL was conducted through an established cervical cancer screening program in Canada, and compared high-risk HPV DNA testing (LBC triage for HPV positives) to LBC (HPV triage for ASCUS) for the detection of CIN2+ and CIN3+ over 48 months. Presented are the complete 48 months exit CIN2+ detection rates for women who were baseline HPV or LBC negative.

Methods

Over 18,000 women aged 25-65 were randomized into the Control (CTRL) (LBC testing) and Intervention (IA) (HPV testing) arms. IA: baseline HPV; if HPV neg, exit at 48 months with HPV/LBC co-testing. CTRL: baseline LBC; if LBC negative, re-screened at 24 months with LBC and exit at 48 months with co-testing (in CTRL arm, 48 month disease detection also includes disease found at 24 months).

Results

At baseline, 8769 women in IA were HPV negative and 9074 women in CTRL were LBC negative. For all age groups, at 48 months significantly more CIN2+ was detected in the CTRL vs. IA (10/1000 [95%CI: 8,12] vs. 4/1000 [95% CI: 3,5], respectively, p<0.01). CIN3+ detection was also significantly higher in the CTRL vs. IA (5/1000 [95%CI: 4,7] vs. 1/1000 [95% CI: 1,2] respectively, p<0.01).

Conclusions

At FOCAL exit, more CIN2+ was detected in baseline cytology negative than HPV negative women, confirming the safety of the 48 month interval for HPV negative women. HPV positivity at 48 months was more predictive of CIN2+ than cytology. Since most women who undergo cervical screening have negative results, FOCAL trial results will inform HPV-based program planning.
Background and Aims

There is limited information on cervical cancer screening in transgender men in low and middle-income countries (LMIC). It has been reported that the use of the Pap smear in this underserved population provides a greater number of unsatisfactory Pap smear results than in non-transgender persons. The purpose of this pilot study is to assess the feasibility of cervical cancer screening among members of this group using a self-sampling HPV test.

Methods

Participants were transgender men of the Organización Generación Hombres Trans El Salvador (Trans Men Generation Organization of El Salvador) between the ages of 19 and 55. After providing informed consent, 24 participants were administered a questionnaire pertaining to sociodemographic information, lifestyle and sexual behaviors, and knowledge about cervical cancer prevention. Screening was performed with a vaginal self-sample careHPV test. Participants who had a positive HPV result were offered a colposcopy evaluation.

Results

Almost all participants (23 out of 24) agreed to conduct vaginal self-sampling with a careHPV brush. Of these, 3 out of 23 (13%) tested positive and the rest were negative. Colposcopies and biopsies were accepted by all 3. One was diagnosed with CIN3, while 2 were diagnosed with CIN1.

Conclusions

The use of HPV self-sampling tests in transgender men is a viable method that can significantly improve the participation and acceptance of cervical cancer screening in a LMIC setting. HPV testing may reduce the number of unsatisfactory results generated when using Pap smears as a screening method.
NUCLEAR AGO2 PARTICIPATES MICORRNA REGULATION OF HPV16 L1 RNA SPLICING BY INTERACTING WITH RNA CIS-ELEMENTS

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Background and Aims

MicroRNAs (miRNAs) bind to complementary sequences on target mRNAs for translational repression and gene silencing. Our recent report indicates that nuclear or cytoplasmic AGO2 distribution varies from cell types and tissues, with human AGO2 in cervical and skin tissues and in primary keratinocytes being primarily nuclear, but in all examined cancer cell lines and in laryngeal tissues being primarily cytoplasmic (Sharma NR, Zheng ZM, et al. J. Biol. Chem. 291:2302-2309, 2016).

Methods

To investigate the role of miRNAs in native immunity against HPV infection, we conducted a genome-wide search for miRNA binding sites (BS) in four HPV types and found several dozens of potential miRNA BS in each HPV genome.

Results

HPV-16 L1 and E6 dramatically increase its expression in Dicer⁻/⁻ knockout cells over the Dicer wild-type cells. 15 miRNA BS were found in the coding regions of HPV-16 L1. A miR-10a BS in an exonic splicing suppressor of the HPV-16 L1 was identified for its response to nuclear miR-10a detectable by Northern blot. This suppressive effect by miR-10a on L1 splicing and expression was greatly reduced in highly differentiated keratinocytes where miR-10a expression is dramatically decreased and HPV-16 infection further suppresses miR-10a expression. Disruption of the miR-10a BS promotes L1 RNA splicing and L1 protein expression by preventing L1 RNA association with SRSF1 and AGO2, a major component of RISC in keratinocytes.

Conclusions

This study provides the first evidence of miRNA involvement in regulation of RNA splicing by direct interaction with RNA cis-elements.
SCIENTIFIC STREAM

SCIENTIFIC STREAM 3: REGULATION OF GENE EXPRESSION

INCREASED EXPRESSION OF E2F1 AND P73 THROUGH TOPBP1 IS NECESSARY FOR HPV GENOME AMPLIFICATION

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Background and Aims

High-risk human papillomaviruses (HPVs) require activation of the ataxia telangiectasia and Rad3-related (ATR) DNA damage repair pathways for HPV genome amplification. For this pathway, HPV utilizes STAT-5 to act through the topoisomerase IIβ-binding protein 1 (TopBP1), which is a scaffold protein that binds ATR and helps to recruit it to sites of DNA damage. TopBP1 also acts as a transcriptional regulator and this activity is controlled by AKT phosphorylation. In this study, we investigated whether this transcriptional activity of TopBP1 is important for HPV genome amplification.

Methods

We induced cell differentiation in high calcium media for 48-96 hours. The cells were extracted for RNAs and DNAs, and assayed by Southern blot analysis or RT-PCR. The protein expression was examined by western blot analysis.

Results

We confirmed that TopBP1 levels are increased in cervical intraepithelial neoplasias as well as cervical carcinomas. Suppression of TopBP1 by shRNAs impairs activation of the ATR pathway but does not affect the total ATR and CHK1. In contrast, knockdown greatly reduces the expression of other DNA damage factors such as RAD51, RAD50, and Mre11. Interestingly, TopBP1 knockdown also decreases the levels of E2F1, a TopBP1 binding partner, and p73. Inhibition of TopBP1 phosphorylation by the AKT inhibitor MK2206 suppresses the expression of E2F1 and p73 without interfering with ATR signaling. The levels of p73 are increased in HPV-positive cells and knockdown impairs HPV genome amplification.

Conclusions

p73 is an important regulator of the HPV life cycle that is controlled by the transcriptional properties of the multifunctional TopBP1 protein.
THE MYB-RELATED PROTEIN MYPOP IS A NOVEL INTRINSIC HOST RESTRICTION FACTOR OF ONCOGENIC HUMAN PAPILLOMAVIRUSES

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Background and Aims

The skin represents a physical and chemical barrier against invading pathogens that is additionally supported by restriction factors providing cellular intrinsic immunity. These factors detect viruses to block their replication cycle. Here, we uncover the Myb-related transcriptional repressor MYPOP as a novel restriction factor against high-risk HPV types.

Methods

We performed pseudovirus (PsV) infection assays, luciferase-based promoter analyses, chromatin immunoprecipitations, measurements of viral transcription, and colony formation assays.

Results

In this study, we identified the so far unknown human Myb-related transcription factor, MYPOP, as a novel restriction factor for oncogenic HPV types 16 and 18 as it potently silences the LCR activity of both HPV types. It is highly expressed in the epithelium and chromatin immunoprecipitation experiments showed binding of MYPOP to the HPV LCR. Furthermore, MYPOP mediates reduction of HPV16 E6*I and E1^E4 early gene transcripts. Cellular MYPOP-depletion relieves the restriction of HPV16 infection. Interestingly, total MYPOP amounts are strongly reduced in diverse HPV-transformed cell lines suggesting MYPOP-downregulation as precondition for oncogene expression, which is required for proliferation. Accordingly, overexpression of MYPOP resulted in a substantial decrease in the number of HPV16- or HPV18-immortalized SiHa and HeLa cells in colony formation assays.

Conclusions

Our results show that MYPOP binds to the LCR of oncogenic HPV types, represses early gene expression, and is able to block virus-induced proliferation of HPV-transformed tumor cells. These data provide strong indication that MYPOP is a novel protein of first line cellular defense against HPV infection and might act as tumor suppressor.
HPV16/18-REGULATED FAM83A EXERTS TUMOR SUPPRESSIVE ROLE IN CERVICAL CANCER

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Background and Aims

Dysregulation of gene expression networks is common in carcinogenesis. Here, we identify FAM83A as a novel key downstream target of oncogenic HPV16/18, demonstrate its functional role, and uncover the transcriptome profile of FAM83A in cervical cancer cells.

Methods

Cervical tissues and HFK/HVK-derived raft culture tissues with or without HPV16/18 infection were used for validation of FAM83A by TaqMan real-time PCR. Cell proliferation, apoptosis, cell migration and invasion were done for functional validation. RNA-seq approach was applied to investigate the main altered pathways regulated by FAM83A in cervical cancer cells.

Results

We found FAM83A was firstly down-regulated in normal cervix with HPV16/18 infection, and then increasingly expressed along with cervical lesion progression from CIN to cancer with HPV16/18 infection, when compared to the normal tissues without HPV16/18 infection. We further confirmed that the dysregulated expression of FAM83A was a result from infection of HPV16 or HPV18 in organotypic cultures. However, we found knockdown of FAM83A increased cervical cancer cell proliferation, decreased apoptosis, promoted cell migration and invasion. We further identified 192 genes including 175 up-regulated and 17 down-regulated that were changed in the context of FAM83A knockdown. Both KEGG pathway analysis and qRT-PCR validation showed ECM-receptor interaction, focal adhesion, PI3K-Akt signaling and TNF signaling were the main activated pathways.

Conclusions

Our study identify FAM83A as a novel target of HPV16/18 and also a tumor suppressor in cervical cancer cells, which enables us to develop potential biomarkers and intervention strategies for better diagnosis and treatment of patients with cervical cancer.
Background and Aims

Determining the single causative HPV genotype of each high-grade cervical lesion and/or cancer is an important measure of vaccine effectiveness in preventing vaccine-type-specific disease. Laser capture microdissection (LCM) and genotyping of lesions is considered the gold standard, however it is resource-intensive and many large studies use easier-to-collect samples and mathematical algorithms to attribute genotype where multiple genotypes are detected. To date, these algorithms have not been assessed against LCM genotyping.

Methods

Cervical biopsy specimens (n=531) containing cervical intraepithelial neoplasia grade 3 (CIN3) lesions were genotyped as whole tissue sections (WTS) (RHA kit HPV SPF10-LiPA25, v1.0 and SPF+ strips). Laser capture microdissection (LCM), and proportional, hierarchical, single type only and maximum (any type) attribution methods were used to resolve mixed genotype detections. LCM was also used to re-test any samples that were negative for high-risk-HPV genotypes.

Results

Of 531 specimens, 14 were excluded from analysis (13 invalid DNA results, 1 could not be resolved to a single genotype using LCM), leaving 517. Of these, mixed-genotype detection occurred in 71 (13.7%) of WTS. The results of the 5 attribution methods are shown in Figure 1 for nonavalent vaccine genotypes. There were no statistically significant differences between proportions of each genotype by attribution method, although proportional attribution provided the lowest genotype-
Conclusions

In CIN3 biopsy specimens including mixed-genotype detections, attribution algorithms to resolve mixed infections to a single causative genotype gave comparable results to the reference method laser capture microdissection.
LONG TERM IMMUNOGENICITY OF TWO VERSUS THREE DOSES OF THE QUADRIVALENT HPV VACCINE: A PHASE III POSTLICENSURE RANDOMIZED TRIAL

Background and Aims

Since 2014, several countries have implemented a two-dose schedule (2D) for HPV vaccination of adolescents based on immuno-bridging studies. This study compared immunogenicity of 2D versus 3-dose (3D) schedules of quadrivalent HPV-vaccine (Q-HPV) up to ten years after the first dose.

Methods

Girls between 9-13 years old (n=520) were randomized (2007-2008) to either receive 2D or 3D of Q-HPV, and these were compared to a control group of 16-26 year old women (n=310) receiving 3D. Blood samples were collected at several time points time and all subjects had samples available at 24 (24M) and 120 months (120M) post first dose. Seropositivity rates and Geometric mean titers (GMT) for anti-HPV6, 11, 16 and 18 (cLIA mMU/mL) were compared.

Results

A total of 114 participants completed the 10 year study visit. Seropositivity for HPV16 and HPV18 at 120M were for 2D-girls: 100%, 87%; 3D-girls: 100%, 92%; 3D-women 97%, 65%. At 24M, GMTs for HPV16 were 1561 (95%CI 1118-2180) for 2D girls (n=38), 1472 (1063-2038) for 3D girls (n=39) and 1028 (739-1430) for 3D women (n=37). For HPV18, values were respectively 188 (125-281), 315 (202-488) and 103 (64-167). At 120M the respective GMTs were 737 (530-1024), 589 (420-808) and 477(320-712) for HPV 16 and 81 (52-125), 107 (70-164) and 41 (24-70) for HPV 18.

Conclusions

At 120M after first dose, seropositivity and GMTs for HPV16 and 18 in girls receiving a 2D Q-HPV remained higher than the 3D Q-HPV in the comparator adult women group and comparable with the GMTs in the 3D Q-HPV girls' group.
Background and Aims

As of 2016, all Australian-born females aged <36 and males aged <19 have been offered free quadrivalent human papillomavirus (HPV) vaccine from the national school-based or catch-up vaccination program. We describe the trends in genital wart diagnoses among Australian-born heterosexuals attending sexual health clinics throughout Australia.

Methods

A serial cross-sectional analysis of new genital wart diagnoses among Australian-born females and heterosexual males attending a national surveillance network of 36 clinics between 2004 and 2016 (i.e. 3 years before and 10 years into the vaccination programme).

Results

We included 224,329 new patients (112,018 males and 112,311 females) in the analysis. There was a 74% reduction in genital wart diagnoses in females (7.6% to 2.0%; \( p_{\text{trend}}<0.001 \); Figure 1) and 65% in males (13.5% to 4.7%; \( p_{\text{trend}}<0.001 \); Figure 2). The proportion of genital wart diagnoses decreased remarkably in young heterosexuals aged 15-20 years, a 92% reduction in females (from 9.0% to 0.7%) and 90% in males (from 6.3% to 0.6%). Proportions of genital wart diagnoses remained stable and prevalent among both males and females aged ≥36 years.
Figure 1. Annual proportion of Australian-born females newly diagnosed with genital warts from 2004 to 2016, stratified by age group.

Female vaccination programme

Proportion of Australian-born females with genital warts (%)

Year


Age group

15-20
21-25
26-30
31-35
36+
All
Conclusions

With the high HPV vaccination coverage in females, there was a substantial decline in diagnoses of genital warts among Australian-born females aged 15-20 years which has remained <1% for the last 4 years. A more modest reduction was also observed among young heterosexual males due to herd protection and the introduction of male vaccination in 2013. Genital warts among individuals aged ≥36 years remained common as they were not eligible for the vaccination programme.
SCIENTIFIC STREAM 4: VACCINATION EVALUATION

EFFECTIVENESS OF 1, 2, OR 3 HUMAN PAPILLOMAVIRUS (HPV) VACCINE DOSES AGAINST HPV16/18-POSITIVE HIGH-GRADE CERVICAL LESIONS

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Background and Aims

We estimated HPV vaccine effectiveness (VE) against vaccine-type cervical lesions by number of doses among women eligible for vaccination with a 3-dose schedule.

Methods

We analyzed data on cervical intraepithelial neoplasia grades 2-3 and adenocarcinoma in situ (CIN2+) collected from population-based surveillance in five U.S. sites, 2008-2014. Archived diagnostic specimens from cases age-eligible for vaccination were tested for 37 HPV types. Exposure was classified by number of vaccine doses received ≥24 months before screening that led to diagnosis. We compared vaccination history between HPV16/18-positive and negative CIN2+ using logistic regression, adjusting for site, insurance, and race, overall and by birth cohort (1979-1986, 1987-1995). VE was estimated as 1-adjusted odds ratio (aOR).

Results

Among 3310 CIN2+ cases (1569 HPV16/18-positive), 326 received 3 vaccine doses whereas 108 received 2 doses and 138 received 1 dose. Among vaccinated women, more doses were associated with later diagnosis year, white race, and private insurance. The aORs for vaccination with 1, 2, and 3 doses were 0.54 (95% CI 0.37-0.77; VE=46%), 0.45 (95% CI 0.30-0.68; VE=55%), and 0.26 (95% CI 0.20-0.34; VE=74%) (Table). VE for women born 1987-1994 (57%, 64%, 83% for 1, 2, 3 doses, initiated median 19 years) was higher (p<0.05) than for women born 1979-1986 (32%, 44%, 59%,...
Significant effectiveness against vaccine-type lesions was evident for 1, 2, and 3 doses. VE point estimates were highest with 3 doses after controlling for known differences among vaccinees, although residual confounding might exist. VE was higher in younger than in older cohorts.
Background and Aims

HPV vaccination programs have been introduced in large parts of the world, but monitoring of effectiveness is not routinely performed. Many countries introduced vaccination programs without establishing the baseline of HPV prevalences. We developed and validated methods to estimate protective effectiveness (PE) of vaccination from the post-vaccination data alone using references, which are invariant under HPV vaccination.

Methods

Type-specific HPV prevalence data for 15–39 year-old women were collected from the pre- and post-vaccination era in a region in southern Sweden. In a region in middle Sweden, where no baseline data had been collected, only post-vaccination data was collected. The age-specific baseline prevalence of vaccine HPV types were reconstructed as Beta distributions from post-vaccination data by applying the reference odds ratios between the target HPV type and non-vaccine-type HPV (nvHPV) prevalences. Older non-vaccinated age cohorts and the southern Sweden region were used as the references. The PE estimates among 18–21 year-old women were validated by comparing the PE estimates that were based on the reconstructed baseline prevalences against the PE estimates based on the actual baseline prevalences.

Results

In Southern Sweden the PEs against vaccine-type HPV were 52.2% (95% CI: 44.9–58.5) using the reconstructed baseline and 49.6% (43.2–55.5) using the actual baseline In the middle Sweden region where baseline data was missing, the PE was estimated at 40.5% (31.6–48.5).

Conclusions

Protective effectiveness of HPV vaccination can be estimated from post-vaccination data alone via reconstructing the baseline using non-vaccine HPV type data.
ONE DOSE OF HUMAN PAPILLOMAVIRUS VACCINE IS AS EFFECTIVE AS THREE FOR PREVENTION OF HIGH-GRADE CERVICAL LESIONS: NATIONAL COHORT STUDY

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⁸VCS Foundation, VCS Pathology, Carlton, Australia

Background and Aims

Prophylactic human papillomavirus (HPV) vaccines are highly effective at preventing pre-cancerous cervical lesions when given in a three-dose schedule. Some post-hoc trial data suggest that one dose prevents HPV infection. If one dose could prevent pre-cancerous cervical lesions, then global cervical cancer prevention would be greatly facilitated. We assessed the effectiveness of quadrivalent HPV vaccine by number of doses against cervical intraepithelial neoplasia (CIN) 2 or 3/adenocarcinoma-in-situ (AIS) in Australia up to seven years post vaccination.

Methods

We created a linked dataset containing HPV vaccination history, cervical screening results, vital status and de-identified demographic details for all Australian women aged 15 or under when eligible for vaccine who had a screening test between April 2007 (when vaccination commenced) and 31 December 2014. We used Cox proportional hazard regression, adjusted a priori for age, socioeconomic status, and area of residence, to estimate hazard ratios of histologically confirmed CIN2/CIN3/AIS.

Results

We included 250,648 women: 48,845 (19.5%) unvaccinated, 174,995 (69.8%) had received three doses, 18,190 (7.3%) two doses and 8,618 (3.4%) one dose. The adjusted hazard ratio was significantly lower and not significantly different between dose groups compared to unvaccinated women (1 dose 0.63 (95%CI 0.51-0.79), 2 doses 0.60 (0.51-0.71) and 3 doses 0.60 (0.55-0.66).)

Conclusions

Despite differences in underlying characteristics of partially vaccinated women, we found that one dose was as effective as three at preventing high-grade disease. This finding supports decision
makers to include one dose vaccination as a viable strategy when working towards the global elimination of cervical cancer.
CLEARANCE OF ANAL HSIL IS INVERSELY RELATED TO PERSISTENT HIGH-RISK HPV –
THREE-YEAR FOLLOW UP RESULTS FROM THE STUDY OF PREVENTION OF ANAL CANCER
(SPANC)
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Background and Aims

Persistent HSIL is the presumed precursor to anal cancer and gay and bisexual men (GBM) are at considerably increased risk. We investigate risk factors associated with clearance of anal HSIL in GBM.

Methods

SPANC participants underwent anal cytological and histological assessments and HPV genotyping at baseline, 6 months and three annual visits. Composite HSIL was defined as detection of cytological and/or histological HSIL, and clearance as a positive baseline finding followed by a negative finding. Only those who attended all 4 annual visits were included in this analysis.

Results

617 men were recruited. By April 2018, 377 (61.1%) had attended all annual visits. Among them, 147 (39.0%, 95% CI 34.0-44.1) had baseline composite HSIL (median age 50, 40.1% HIV-positive). Of these, 85 cleared their composite HSIL during study follow-up. The overall clearance rate was 26/100 person-years (95% CI 21.0-32.2). There was no association between HSIL clearance and HIV status, cigarette smoking, recent sexual behaviour, lesion size and prevalent HPV18 infection. Factors associated with significantly lower clearance rates included: increasing age (p=0.034), higher numbers of lifetime male partners (p=0.008), higher lesion grade (HR 0.50, 95% CI 0.32-0.79, p=0.003), baseline HPV16 (HR=0.50, 95%CI 0.6-0.36, p<0.001), persistent HPV16 (HR 0.21, 95% CI 0.09-0.45) and persistent non-HPV16 HR-HPV infection (HR 0.38, 95% CI 0.18-0.81).

Conclusions

Clearance of anal HSIL was common in sexually active GBM. Persistence of HSIL was strongly associated with persistent HR-HPV infection. Among GBM with HSIL, repeat HR-HPV testing may identify a subgroup who are unlikely to clear their disease.
Efficacy of IRC Ablation of Anal HSIL Following Observation in HIV-Infected Participants: AIDS MALIGNANCY TRIAL 076

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Background and Aims

Anal HSIL ablation may reduce the incidence of invasive cancer, but few data exist on treatment efficacy in patients with delayed treatment after observation.

Methods

A multisite clinical trial of HIV-positive participants (≥27 years old) with 1-3 biopsy-proven anal HSIL randomized to IRC ablation (IRC) or active monitoring (AM). After 12 months AM participants with persistent disease could be treated and followed for an additional 12 months. Initial IRC arm participants could remain on-study 12 additional months. Participants were followed every three months undergoing high-resolution anoscopy with biopsy and treatment of recurrent HSIL.

Results

Of 60 participants initially randomized to AM, 35 returned for IRC at 12m with 30 (86%) evaluable at 24m; 25 participants (83%) achieved complete clearance (CC). Of 51 lesions treated, 41 (80%) did not recur. 80% were HSIL free (of treated/new lesions) at 24m. The cumulative HSIL-free probability in AM participants who crossed over to treatment was 87.5 ± 5.9% at 6m and 63.5 ± 9.6 at 12m post treatment. Results did not significantly differ from the initial IRC arm. Sixteen AM participants without HSIL at 12m continued for year 2 and 4/11 (36%) recurred by 24m. Of 35 IRC participants who returned at 24 months, 63% maintained CC and the HSIL-free probability was 42.1 ± 7.1% at 24 months.

Conclusions

In those with limited disease, delaying ablation to allow for HSIL regression before treating remaining disease does not appear to reduce response.

Funding: National Cancer Institute
LONG-TERM OUTCOME OF TREATMENT OF ANAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HSIL) IN PATIENTS WITH FIVE YEARS FOLLOW UP

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Background and Aims

Office-based or surgical ablation of HSIL may prevent anal cancer; however, limited data exist on long-term outcome regarding HSIL or cancer. It is not established that treating HSIL reduces the incidence of cancer, but long-term remission of HSIL may be a good clinical indicator necessary for cancer prevention.

Methods

Between 2006 and 2008, 369 new patients were diagnosed with HSIL. Follow-up data were extracted in 285/369 patients with HSIL (follow-up not determined in 84). 133 (46.7%) were followed for more than 5 years. As a preliminary analysis, every third patient was analyzed for outcome defined as no HSIL for at least 2 years (HSIL-free) (n=50).

Results

Forty-six patients were men (39 HIV-positive) and 4 were women (1 HIV-positive) ranging in age from 26 to 67 years (mean 45.7 years) and followed from 5.1 to 11.4 years (mean 8.8 years). Patients had between 1-10 (mean 2.58, median 2) ablations to become HSIL-free. Three patients never became HSIL-free; 1 with inadequate follow up and treatment developed cancer at 5.1 years. There was no recurrence of HSIL in 31 patients (62%) followed for 3.2 to 10.1 years (mean 7.0 years). HSIL recurred in 16 patients (32%) at 2.1 to 6.2 years (mean 3.8 years) and only four had another recurrence after becoming HSIL-free.

Conclusions

In patients with more than five years follow-up, 94% became HSIL-free with treatment. Although HSIL recurred in 16 patients, most became HSIL-free. Only 1 patient developed cancer as a result of inadequate treatment. Becoming HSIL-free after ablation may effectively prevent anal cancer.
Background and Aims

The incidence of cancer of the vulva tripled during the last 20 years in Germany. At least a part of these cancers could be prevented by early detection of precursors.

Methods

WOLPHSCREEN, a local pilot project started 2006 with Pap and HC2 co-testing every five years for 30+ years old women. HPV+ cases with abnormal Pap or persistency were transferred to colposcopy. Colposcopy included evaluation of vagina, vulva an anus.

Results

26,624 women were recruited between 2006 and 2016. 1,457 cases were transferred to colposcopy and overall we detected 284 cases of CIN3+, 14 VIN3+, 5 VaIN3+ and 3 AIN3+. Only 8 out of 22 non-cervical lesions were associated with CIN2+, the remaining cases were detected in women with cervical HPV persistency only.

Conclusions

HPV screening programs may offer an opportunity to detect precursors of cancers of vagina, vulva and anus.
HOST CELL DNA METHYLATION MARKERS FOR THE DETECTION OF HIGH-GRADE ANAL INTRAEPITHELIAL NEOPLASIA AND ANAL CANCER

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Background and Aims

High-grade anal intraepithelial neoplasia (AIN2/3; HGAIN) is highly prevalent in HIV+ men who have sex with men (MSM), but only a minority will eventually progress to cancer. Currently the cancer risk cannot be established, and therefore all HGAIN are treated, resulting in overtreatment. Host cell DNA methylation analysis is a promising tool to detect cervical cancer and high-grade cervical intraepithelial neoplasia with a high cancer risk. We assessed the potential of methylation markers for detecting HGAIN and anal cancer.

Methods

Tissue samples of HIV+ men with anal cancer (n=26), AIN3 (n=24), AIN2 (n=42), AIN1 (n=22) and controls (n=34) were analysed for DNA methylation of nine genes using quantitative methylation-specific-PCR. Univariable and LASSO logistic regression, followed by leave-one-out-cross-validation (LOOCV) were used to determine the performance for the detection of AIN3 and cancer.

Results

Methylation of all genes increased significantly with increasing severity of disease (p<2x10^-6). HGAIN revealed a heterogeneous methylation pattern, with a subset resembling cancer. Four genes (ASCL1, SST, ZIC1 and ZNF582) showed very good performance for AIN3 and anal cancer detection (AUC>0.85). The most potent marker, ZNF582 (AUC=0.89), detected all cancers and 54% of AIN3 at 93% specificity. Slightly better performance (AUC=0.90) was obtained using a marker panel including five markers.

Conclusions

DNA methylation is significantly associated with anal carcinogenesis. A methylation marker panel, including ZNF582, had good performance for the detection of cancer and HGAIN with a cancer-like methylation pattern. Validation studies are warranted to verify their potential for the screening and management of HIV+ MSM at risk for anal cancer.
HPV16 INCREASES THE NUMBER OF MIGRATORY CANCER STEM CELLS AND MODULATES THEIR MICRORNA EXPRESSION PROFILE IN OROPHARYNGEAL CANCER

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Background and Aims

HPV16 is a major risk for development of oropharyngeal squamous-cell-carcinoma (OPSCC). Although HPV+ OPSCC metastasize faster than HPV- tumors, they have a better prognosis. The molecular and cellular alterations underlying this pathobiology of HPV+ OPSCC remain elusive. In this study we examined whether expression of HPV16-E6E7 targets the number of migratory and stationary cancer-stem-cells (CSC). Furthermore, we wanted to elucidate if aberrantly expressed miRNAs in migratory CSC may be responsible for progression of OPSCCs and whether they may serve as potential novel biomarkers for increased potential of metastasis.

Methods

Retroviral transduction; FACS analysis, qRT-PCR, miRNA microarray; in situ hybridization

Results

HPV16-E6E7 expression leads to an increase in the number of stationary (CD44⁺/EpCAM⁺) stem cells in primary keratinocyte cultures. Most importantly, expression of E6E7 in the cell line H357 increased the migratory (CD44⁺/EpCAM⁻) CSC pool. This increase in migratory CSCs could also be confirmed in HPV- OPSCC. Differentially expressed miRNAs from HPV16-E6E7 positive CD44⁺/EpCAM⁻ CSCs were validated by RT-qPCR and in situ hybridization on HPV16+ OPSCCs. These experiments led to the identification of miR-3194-5p, which is upregulated in primary HPV16+ OPSCC and matched metastasis. MiR-1281 was also found to be highly expressed in HPV+ and HPV- metastasis. As inhibition of this miRNA led to a markedly reduction of CD44⁺/EpCAM⁻ cells it may prove to be a promising drug target.

Conclusions

Our findings highlight the capability of HPV16 to modify the phenotype of infected stem cells and that miR-1281 and miR3194-5p may represent promising targets to block metastatic spread of OPSCC.
HPV8 E6 EXPANDS THE P63-POSITIVE EPIDERMAL STEM CELL COMPARTMENT VIA A NOVEL P300/C/EBPα/L/MIR-203 PATHWAY

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Background and Aims

Cutaneous genus beta-HPV types infect skin keratinocytes. Their potential role in skin carcinogenesis, particularly in immunosuppressed patients, has become a major field of interest. Patients suffering from the rare genetic disorder Epidermodysplasia verruciformis (EV) are highly susceptible to persistent genus beta-HPV infection and have an increased risk to develop non-melanoma skin cancer at sun-exposed sites. Thus, EV serves as a valuable model disease for studying genus beta-HPV biology.

Methods

We used skin biopsies from EV patients, organotypic 3D-cultures and retrovirally infected primary human keratinocytes to study the impact of HPV8 on epidermal stemness and the underlying signalling pathway.

Results

Here, we demonstrate that in human HPV8-infected EV skin lesions, the ‘stemness-repressing’ microRNA-203 is strongly down-regulated. In contrast, cells expressing the miR-203-regulated ‘stemness-maintaining’ factor p63, are highly amplified. Notably, we identified the transcription factor C/EBPα, a well-known suppressor of UV-induced skin carcinogenesis, as a p300-dependent target of the HPV8-encoded E6 oncoprotein and as a critical inducer of miR-203 gene expression.

Conclusions

Our data provide evidence for a novel p300/C/EBPα/miR-203-dependent pathway, which links HPV8 infection to the expansion of p63-positive stem cells in the epidermis of EV-patients. This may contribute to the beta-HPV-induced disturbance of epidermal homeostasis and pave the way for skin carcinogenesis.
SCIENTIFIC STREAM 6: TRANSFORMATION AND CARCINOGENESIS

ROLE OF EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) PATHWAY IN THE REGULATION OF HYPOXIA AND TUMOUR MICROENVIRONMENT IN HPV POSITIVE OROPHARYNGEAL CANCERS

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Background and Aims

The incidence of HPV-related OPC has increased at an epidemic rate. In general HPV positive cancer have a better prognosis, however, the molecular mechanisms linked to the favorable outcome of this HNSCC subtype remains unknown.

Epidermal growth factor receptor (EGFR) plays a central role in HNSCC, linked to survival and progression of cancer cells thus representing a promising molecular target for this disease. EGFR overexpression is detected in 80-90% of HPV negative HNSCC and correlates with worse disease outcome. The importance of EGFR pathway in HPV negative cancers remains unclear. Importantly, EGFR expression is lower in HPV positive HNSCC subtype.

Methods

We have assessed the expression of EGFR receptor tyrosine kinase (RTK) family members in a panel of HPV positive and negative HNSCC samples and have performed functional analysis to identify the role of these RTKs in the development and treatment outcome of HPV positive HNSCC.

Results

We demonstrated a distinct activation and subcellular distribution of EGFR and its signaling pathways (STAT-3, ERK, PI3K and AKT) between the two HNSCC subtypes. Additionally, we found that whilst EGFR on its own is an important signaling pathway in HPV negative HNSCC, in the HPV positive tumours the consequence of EGFR activation depends on the presence of other family members mainly HER-3 as well as expression of c-Met oncogene.

Conclusions

We demonstrated specific signaling pathways involved in the pathogenesis of HPV positive head and neck cancers and obtained insight into their roles in modulation of tumour hypoxia, tumour immune microenvironment and therapeutic response.
ROLE OF CERVICAL RESERVE CELLS IN UNDERSTANDING THE VULNERABILITY OF THE CERVIX TO HPV-DRIVEN NEOPLASIA AND CANCER

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Background and Aims

Why High-Risk Human Papilloma Viruses (HR-HPV) drive neoplasia at the cervical transformation zone (TZ) has been long speculated. TZ has a unique regulation and suspected to be a stem cell niche, it also harbours reserve cell (RC) that are thought to have dual fate ability depending on local microenvironment, in a process of metaplasia. Infection of RC leads to abortive infection resulting in cervical carcinoma. Challenge in examining this is the lack of relevant models, we explore the use of murine cervical epithelium and organoid system to study this hypothesis.

Methods

Cervical cells were isolated from mouse and human hysterectomies. Isolated cells were embedded in Matrigel using the organoid culture method. Combinations of growth factors and inhibitors were tested to identify conditions that sustain their growth. Established cervical organoids were characterized using RNA seq, immunohistochemistry.

Results

Using our markers, we found that there are fundamental similarities between murine and human cervical epithelium. In both cases, K17+/p63 RC were apparent under the stratified and columnar epithelium of the cervix, both at TZ, and in areas of metaplasia (1). In addition, we have been able to generate a long-term cervical organoid culture system. The established organoids have similar cellular organisation to the columnar and stratified epithelium of the cervix (2).

Conclusions

We have established long term organoid cultures of mouse and human cervical organoids which recapitulate features of cervical epithelium in vivo. This will provide a model to study the physiology and homeostasis of the cervical epithelium, and to be used as an infection model.
NFX1-123 EXPRESSION IS INCREASED DURING DIFFERENTIATION AND IS REQUIRED FOR TARGETED DIFFERENTIATION PATHWAY ACTIVATION WHILE MAINTAINING GROWTH IN 16E6-EXPRESSING KERATINOYTES

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Background and Aims

High-risk (HR) HPV E6 is one of two viral oncogenes that dysregulates key cancer pathways. HR HPV type 16 E6 (16E6) and the endogenous protein NFX1-123 partner in keratinocytes to increase telomerase activity and Notch1. This partnership also increases differentiation markers while appearing to protect cells from growth arrest. We wanted to determine if NFX1-123 expression itself changed during differentiation and how 16E6 and NFX1-123 collaborate to regulate differentiation and continued growth.

Methods

16E6 keratinocytes with overexpressed NFX1-123, knocked down NFX1-123, or endogenous NFX1-123 levels were grown in: monolayer with differentiating or non-differentiating media; methylcellulose suspension; three-dimensional rafts; or colony formation assays. Monolayer cultures, suspension cultures, and colony formation assays were collected for RNA and protein, with additional imaging under bright field for colony formation assays. Rafts were processed for immunostaining.

Results

When grown under differentiating conditions, 16E6 keratinocytes increased NFX1-123 RNA and protein amounts over time. This was also seen in 16E6 keratinocytes with overexpressed NFX1-123, as NFX1-123 rose even further during differentiation. Supporting this, greater NFX1-123 was seen in the upper, more differentiated layers of rafts. Specific activation of differentiation pathways demonstrated that NFX1-123 augmented JNK and Notch1 signaling, and knock down studies showed NFX1-123 was required to activate differentiation pathways. In colony formation assays, greater NFX1-123 led to increased cellular differentiation while maintaining continued growth, leading to formation of multilayered tracks of cells with blister-like structures.

Conclusions

Greater NFX1-123 may support differentiation pathways and cellular growth and immortalization, both of which are important to HPV and cancer development.
METHYLATION IN HPV16 E2 BINDING SITES 3/4 IS INDEPENDENT OF GLOBAL HOST GENOME METHYLATION AND RELATED TO SURVIVAL IN A COHORT OF OPSCC PATIENTS

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Background and Aims

The HPV16 upstream regulatory region (URR) undergoes shifts in methylation during HPV-induced carcinogenesis. Four binding sites for E2 (E2BS), a key regulatory protein of HPV E6/E7 oncogene expression, are located there. E2BS 3/4 methylation can promote the overexpression of both oncogenes.

We have shown previously that shifts in E2BS methylation occur during metastasis formation in oropharyngeal squamous cell carcinomas (OPSCC). We hypothesized that these happen in a specific manner independent from global methylation status, indicative of a distinct functional role of E2BS methylation in HPV-driven OPSCC.

Methods

Formalin-fixed, paraffin-embedded tissue from 67 HPV16 DNA+ and p16INK4a+ tumors (42 OPSCC primaries, 25 matched lymph-node metastases) was obtained from a German OPSCC cohort. Bisulfite-converted DNA was analyzed for methylation in 4 CpGs in E2BS3/4 and 3 CpGs in the LINE1 retrotransposon by pyrosequencing. Cut-offs for low/high methylation were established using cluster analysis and Kaplan-Meier-curves and log-rank-tests were used to examine overall and progression-free survival (OS,PFS).

Results

Lower methylation levels were observed in all E2BS CpGs in lymph node metastases versus OPSCC primaries, reaching statistical significance for CpG 43 in E2BS3 (p=.02). There was no significant difference in LINE1 methylation between primaries and associated metastases. High E2BS methylation (> 52%) was associated with reduced OS and PFS.

Conclusions

Shifts in E2BS methylation in OPSCC occur in specific patterns that are not associated with global host genome methylation as assessed in LINE1 retrotransposons in HPV-driven primary tumors and associated metastases, suggesting that distinct HPV16 URR methylation patterns play a functional role during OPSCC progression.
Background and Aims

In addition to providing nearly complete protection against its target types, the AS04-HPV-16/18 vaccine provides some degree of cross-protection against others, including 6/11/31/33/45. Lower levels of protection may exist for additional types, explaining the high reported efficacy of the AS04-HPV-16/18 vaccine (>90%) against cervical intraepithelial neoplasia grade 3 or greater (CIN3+).

Methods

To better quantify the effects of the AS04-HPV-16/18 vaccine against cervical HPV infections and cytological/histological disease outcomes, we pooled data from the Costa Rica Vaccine Trial (NCT00128661) and PATRICIA trial (NCT00122681) – two large-scale, double-blind randomized controlled trials of the AS04-HPV-16/18 vaccine. Primary analyses focused on disease-free women without detectable HPV infection at baseline.

Results

12,550 women were included in our main post-hoc analyses (HPV arm=6,271; control arm=6,279). Incidence of oncogenic/non-oncogenic infections, excluding known/accepted protected types (focusing on types 34/35/39/40/42/43/44/51/52/53/54/56/58/59/66/68/70/73/74), was significantly lower in the HPV arm than control arm (efficacy=9.9%, 95% Confidence Interval [CI] 1.7%-17.4%). Significant efficacy (p<0.05) was observed for individual oncogenic types 16, 18, 31, 33, 45, and 52 and non-oncogenic types 6, 11, 53, and 74. Efficacy against cervical abnormalities ranged from 27.7% (95% CI 21.7%-33.3%) to 58.7% (95% CI 34.1%-74.7%) for cytologic outcomes (low-grade squamous intraepithelial neoplasia or greater and high-grade squamous intraepithelial lesion or greater, respectively) and 66.0% (95% CI 54.4%-74.9%) to 87.8% (95% CI 71.1%-95.7%) for histologic outcomes (CIN2+ and CIN3+, respectively).

Conclusions
Modest additional cross-protection beyond established protected types appears to exist; however, it does not fully explain the high efficacy against CIN3+.

**Funding**
National Cancer Institute & GlaxoSmithKline Biologicals SA
BIVALENT HPV VACCINE LEADS TO REDUCED (VACCINE TYPE) INCIDENT AND PERSISTENT HPV INFECTIONS AND LOWER VIRAL LOAD IN YOUNG DUTCH FEMALES

Background and Aims

Bivalent HPV vaccination is efficacious against HPV16 and 18 infections and cross-protection against some other HPV types has been demonstrated. Here, we assessed (cross-) protective effects of the bivalent HPV vaccine on incidence, persistence and viral load (VL) of fifteen HPV types.

Methods

Samples were obtained annually from an observational cohort study monitoring HPV vaccine effects. Type-specific VL assays were developed for HPV6, 11, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 and used in addition to existing HPV16 and 18 assays. Differences in rates of incident and persistent infections as well as differences in viral load were assessed based on vaccination status.

Results

Significant protection against persistent HPV16 and 18 infections was observed. VL was significantly lower in vaccinated individuals who had HPV16 or 18 infections despite vaccination. Cross-protective vaccine effects were observed against HPV31, 33, 35 and 45. In general, VL is lower in infections occurring in vaccinated than in non-vaccinated individuals, irrespective of HPV type.

Conclusions

Beyond strong effectiveness against HPV16 and 18 infections, bivalent vaccination leads to reduced HPV16 and 18 VL in breakthrough infections. This effect is also visible for various non-vaccine HPV types and could indicate long-term protective effects.
Background and Aims

Men who have sex with men (MSM) are at high risk for human papillomavirus (HPV) infection and HPV-related diseases. Since 2011, vaccination has been recommended for U.S. MSM through age 26 years. We evaluated oral and anal prevalence of HPV vaccine types among young MSM by vaccination history.

Methods

The Vaccine Impact in Men (VIM) study enrolled MSM and transgender women aged 18–26 years in Seattle, Chicago, and Los Angeles, during 2017. Participants self-reported demographic characteristics, sexual behaviors, and vaccination status, and submitted self-collected anal swab and oral rinse specimens. Type-specific DNA testing was conducted for 37 HPV types by L1-consensus PCR assay. We compared 4vHPV-type prevalence (any HPV6/11/16/18) among vaccinated and unvaccinated participants, and determined prevalence ratio adjusting for age, race/ethnicity, and HIV status (aPR).

Results

Among 693 participants, 71 (10.2%) disclosed being HIV-positive. By self-report, 276 (39.8%) had received any HPV vaccine [140 (50.7%) with 3 doses], 274 (39.5%) were unvaccinated, and 143 (20.6%) were unsure. Median lifetime number of sex partners was 25 among vaccinated and 20 among unvaccinated participants; median age at vaccination (20 years) was older than at first sex (17 years). 4vHPV-type prevalence was 27.0% (187/693) in anal specimens, 2.3% (16/693) in oral specimens, and 27.6% (191/693) in either. Prevalence in either specimen was 21.7% (60/276) in vaccinated compared with 34.7% (95/274) in unvaccinated participants (aPR:0.64, 95% confidence interval:0.49-0.83).
Conclusions

Findings suggest effectiveness of HPV vaccine among MSM. Ongoing monitoring will allow refinements in vaccine effectiveness estimates in this high-risk population.
CURRENT REASONS FOR LACK OF HPV VACCINE INITIATION IN THE UNITED STATES: SHIFTING THE FOCUS FROM GENDER AND SEXUALITY TO NECESSITY AND SAFETY

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Background and Aims

HPV vaccination rates in the United States remain below the Healthy People 2020 goal and behind those of other developed nations. We sought to evaluate trends in reasons for lack of HPV vaccine initiation in the US from 2010-2016 using data from the National Immunization Survey-Teen (NIS-Teen).

Methods

Survey-weighted log binomial regression was used to estimate trends in parent-reported reasons for lack of HPV initiation over time for boys and girls aged 13-17, and to compare these reasons between adolescent boys and girls in 2016.

Results

In girls, safety was the most common reason in both 2010 (23%) and 2016 (22%). Lack of necessity (21% vs. 20%), knowledge (14% vs. 13%), and recommendation (9% vs. 10%) also remained stable, whereas concern regarding child’s lack of sexual activity decreased from 19% to 10% (p<0.01). In boys, lack of necessity (24% vs. 22%), recommendation (22% vs. 17%), and knowledge (16% vs. 14%), and child’s lack of sexual activity (16% vs. 9%) and gender (13% vs. 2%), decreased from 2010-2016 (p<0.05). Safety concerns increased significantly (5% vs 14%) (p<0.01). In 2016, parents of girls were significantly more likely to report concerns about safety compared to boys (22% vs 14%, p<0.001), whereas parents of boys were more likely to report lack of recommendation as a concern (17% vs 10% for girls, p<0.001).

Conclusions

The HPV vaccine messages should reflect the current trends and focus on persistent concerns about knowledge, safety, and necessity, rather than sexuality and gender, in order to be responsive to current parental concerns.
Background and Aims

Quadrivalent HPV vaccine was included in the Norwegian childhood immunisation programme in September 2009 to girls in 7th grade. At present, 88% of all eligible girls have received at least one dose, and 86% all three vaccine doses. In the national HPV-surveillance programme, HPV-testing in urine is used to monitor the impact of HPV vaccination on HPV prevalence and type distribution in pre-screening age. Two HPV prevalence base-line studies have previously been performed in non-vaccinated cohorts at age 17. Here, we include also the first vaccinated cohort (born 1997) and present final results of the impact of HPV-vaccination on HPV-prevalence and genotype distribution in 17-year old girls.

Methods

First void urine samples from 17,749 17-year old girls were analysed for 37 HPV genotypes using a modified GP5+/6+ PCR protocol and Luminex suspension array technology. Individual vaccination records were retrieved from the Norwegian immunisation register, and HPV-prevalence in vaccinated and unvaccinated girls were compared.

Results

A significant reduction in overall HPV prevalence in vaccinated as compared to unvaccinated 17-year old girls was seen. The vaccine effectiveness (VE) against vaccine types was 90% (95% CI 86%–92%). Significant VE was observed also for several non-vaccine types. The prevalence of vaccine types and some non-vaccine types was significantly reduced also among unvaccinated 1997-girls.

Conclusions

In this largely HPV naïve population, we observed a substantial direct and cross-protective effect in vaccinated girls. Moreover, a substantial direct and cross-protective herd effect was seen in unvaccinated girls.
Background and Aims

Mathematical model predictions are an integral part of the evidence-base used to inform HPV vaccination policy. Although pre-vaccine era data are often used to calibrate models, predictions are rarely compared to post-vaccine era data. The objective of this study is to examine whether the HPV-ADVISE model reproduces observed HPV vaccination population-level effectiveness in the United States, to gain insights into HPV epidemiology in the post-vaccine licensure period.

Methods

We used HPV-ADVISE, an individual-based dynamic model of HPV infection/diseases. We compared our model predictions to the observed changes in HPV-6/11/16/18 prevalence (NHANES 2003-2014) and anogenital warts (AGW) diagnoses (MarketScan health-care claims). Outcomes were stratified by age, number of sexual partners, and geographic region. We used the observed HPV vaccination coverage in the U.S. stratified by year, age, gender, region, and number of sexual partners. For AGW, we observed increasing trends in diagnoses in young women in the pre-vaccine licensure period, and older women/men (>30 years-old) in the pre- and post-vaccine licensure periods, whereas HPV prevalence stayed relatively stable in both periods. We thus produced simulations with and without adjustment for trends in AGW diagnoses.

Results
Conclusions

The model reproduces changes in gender- and age-specific HPV-6/11/16/18 prevalence (overall and by number of sexual partners) and adjusted AGW diagnoses (overall and by region) over time. Using AGW diagnoses without adjusting for underlying increasing trends may underestimate vaccination impact. Our results provide evidence of the external validity of HPV-ADVISE predictions. Furthermore,
the analysis illustrates how models can be a tool to help interpret post-vaccine licensure surveillance data.
THE 6-YEAR LONGITUDINAL NEGATIVE PREDICTIVE VALUE OF THE APTIMA RNA HPV TEST IS NON-INFERIOR TO THE DNA-BASED HC2 IN A ROUTINE SCREENING POPULATION IN GERMANY

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Background and Aims

To date there are no data available on the 5-6-year longitudinal clinical performance of the RNA-based Aptima HPV test (AHPV) from screening populations.

Methods

Women (N=10,040) aged 30–65 years were screened at office-based gynaecologists. All specimens were collected and tested centrally by LBC, AHPV and HC2. Women were referred to colposcopy if they had an abnormal cytology result and/or were tested positive on either HPV assay. All values were calculated based on review histology. For follow-up, 482 women with a positive test result and no treatment were followed up for 5 years with annual testing by LBC, AHPV and HC2. In addition, after a median of 6 years after baseline, cervical samples were randomly collected from 3166 women who tested triple negative at baseline and were re-tested.

Results

Cross-sectional results of 9336 women have recently been published and show comparable sensitivities, while the positive predictive value (PPV) and specificity for CIN3+ was significantly higher for the AHPV test compared to HC2.

Using a logistic-exponential model we calculated a 6-year PPV of HC2 and AHPV of 24.4% vs 26.8%, respectively. Using CIN3+ as endpoint the negative predictive value was 99.1%, 99.8% and 99.6% and the six year cumulative risk for CIN3+ was 1.15%, 0.21% and 0.4% for Cytology, HC2 or AHPV, respectively.

Conclusions

In conclusion, our data demonstrate a 6-year longitudinal non-inferior performance of the RNA-based AHPV test in comparison to the gold-standard DNA-based HC2 test.
Background and Aims

Anal HPV-infection and dysplasia are very frequent in HIV-positive men who have sex with men (HIV+MSM), and progression of low-grade (LSIL) to high-grade lesions (HSIL) occurs faster than in HIV-negative persons. We compared the diagnostic accuracy of high-risk (HR)-HPV-E6/E7-mRNA and HR-HPV-DNA-testing for the detection of anal dysplasia in HIV+MSM.

Methods

2923 intraanal swabs from 841 HIV+MSM participating in a screening program were collected between 05/2010 and 01/2018. In 675 baseline samples HR-HPV-DNA- detection (22 types) as well as E6/7-mRNA-detection of 14 HR-HPV-types (APTIMA® HPV assay, Hologic) were performed. So far, follow-up samples with cytology/histology and HPV-DNA genotyping results taken within 36 months after the first visit are available from 399 patients.

Results

659 swabs had valid results in both test-formats (238 normal, 84 ASCUS, 226 LSIL, 111 HSIL by cytology/histology). For the detection of LSIL+HSIL sensitivity, specificity, negative and positive predictive value were 88.7%, 23.0%, 66.1%, 54.7% for HR-HPV-DNA-testing and 78.6%, 44.4%, 66.5%, 54.9% for E6/E7-mRNA-testing. For the detection of HSIL, the values were 95.5%, 19.5%, 95.5%, 19.4% for HR-HPV-DNA-testing and 91.0%, 37.4%, 95.3%, 22.7% for E6/E7-mRNA-testing, respectively. 46 of 206 (22.3%) patients with an E6/E7-mRNA-positive swab and a cytology ≤LSIL at baseline developed HSIL within 36 months compared to 7 of 116 (6.0%) baseline E6/E7-negative HIV+MSM.

Conclusions

HPV oncogene mRNA detection has an (almost 2-fold) increased specificity and a slightly decreased sensitivity for the detection of anal dysplasia in HIV+MSM compared to HR-HPV-DNA-testing. A positive E6/E7-mRNA result at baseline could be predictive for future HSIL.
Background and Aims

High-risk HPV (hrHPV) testing on self-sampled material was introduced as part of the renewed Dutch cervical cancer screening programme in January 2017. We compared results of self-sampling with clinician-collected samples taken as part of the screening programme.

Methods

Using data from the Dutch national pathology database (PALGA), all primary screening tests were selected from all women aged 29 to 63 years. We compared hrHPV positivity rates, rates of positive cytology and CIN 2+ detection rates between self-sampling and clinician-collected samples. HrHPV testing was performed using the Roche Cobas4800 HPV tests. Chi-squared tests were performed to compare differences between proportions.

Results

A total of 21,851 self-sampling and 367,305 clinician-collected samples were analysed. The hrHPV positivity rate for self-sampling was 7.5%, compared with 9.3% for clinician-collected samples (p < 0.05). HrHPV positivity rates were lower in the self-sampling group across all age groups when compared to clinician-collected samples. However, the rate of low- and high-grade cytology abnormalities in the follow-up cervical smears of hrHPV positive self-sampling (35.9%) was higher.
than in hrHPV positive clinician-collected samples (31.0%) \( (p < 0.05) \). Of those women who were directly referred and had follow-up histology, CIN 2+ was diagnosed following self-sampling (61.5%) more often than following clinician-collected sampling (51.4%) \( (p < 0.05) \).

**Conclusions**

Early results indicate that self-sampling seems to have a higher positive predictive value for CIN 2+ lesions than clinician-collected samples. This may be due to either test characteristics or differences in background risk. Further investigation of the determinants of these differences is currently underway.
Background and Aims

HPV testing on self-collected samples is a potential primary screening method, but non-inferiority as compared to HPV testing on clinician-collected samples remains to be assessed in the regular screening population. The IMPROVE-study is a randomised non-inferiority trial that aims to evaluate the clinical accuracy of HPV testing on self-collected samples within an organized screening setting.

Methods

187,473 women (age 29-61) were invited to participate in the study as part of their regular screening invitation. Women providing informed consent were randomised (1:1) to self-collection or clinician-collection and tested for HPV using the clinically validated GP5+/6+-PCR-EIA. HPV-positive women were retested using the other collection method and triaged by cytology and repeat cytology in accordance with Dutch screening guidelines. Primary endpoints were CIN2+ and CIN3+.

Results

7,643 women were enrolled in the self-collection and 6,282 in the clinician-collection group. HPV prevalence was similar in self- and clinician-collected samples (7.4% vs. 7.2%; relative risk: 1.04; 95% CI: 0.92-1.17). The CIN2+ sensitivity and specificity did not differ between self-collected and clinician-collected HPV testing (relative sensitivity: 0.96; 95% CI: 0.90-1.03; relative specificity: 1.00; 95% CI: 0.99-1.01). For CIN3+, relative sensitivity was 0.99 (95% CI: 0.91-1.08) and relative specificity was 1.00 (95% CI: 0.99-1.01).

Conclusions
HPV testing using a clinically validated assay on self-collected samples has similar accuracy as HPV testing on clinician-collected samples. This supports the use of HPV self-sampling as a primary screening method in routine screening.
Background and Aims

To respond to requests from different national screening programs to keep up-to-date evidence regarding performance of HPV testing on self-samples. To extend previous meta-analyses on: 1) accuracy of HPV testing on self- vs clinician-taken samples to detect CIN2+; 2) efficacy of offering self-sampling kits vs control interventions to reach under-screened women.

Methods

Methods described in Arbyn, Lancet2017 and Verdoodt EJC2015 were applied to update prior published systematic reviews including new references published up to 15 April 2018.

Results

56 accuracy studies and 25 randomized participation trials were included.

Signal-amplification based hrHPV tests were less accurate on self-samples (relative sensitivity and specificity for CIN2+ significantly <1). However, clinically validated PCR-based assays were as sensitive (ratio=0.99, CI 0.97-1.02) and slightly less specific (ratio=0.98, CI 0.97-0.99) on self-samples. Subgroup analyses did not reveal significant effects related to the self-sample device or storage media.

On average, 19% (range 6-34%) of under-screened women who received a self-sample kit at home returned it to the laboratory, whereas 11% (range 2-26%) of women in control arm had a specimen taken by a clinician, yielding a pooled participation ratio of 1.87 (CI 1.43-2.44). Opt-in self-sample strategies were less effective than mail-to-all strategies.

Conclusions

Under the condition of using validated PCR-based assays, hrHPV testing on self-samples is as accurate as on clinician-taken samples. Offering self-sampling kits generally is more effective in reaching under-screened women than sending invitations. However, response rates are highly variable among settings and therefore pilots should be set up before regional/national roll-out of self-sampling strategies.
3D SQUAMOUS EPITHELIAL TISSUE CULTURE SYSTEM FOR ANTI-HPV DRUG DISCOVERY AND VALIDATION

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Aims. Management of HPV lesions requires better therapeutic options than presently available. We developed a three-dimensional epithelial tissue culture system from primary human keratinocytes harboring HPV-18 replicons, fully recapitulating a robust infectious program. Investigations of virus-host cell interactions identified critical regulatory pathways on which HPV DNA amplification depends, revealing potential host targets for anti-viral therapies. Our strategy is to repurpose existing pharmacologic agents to inhibit viral DNA amplification, interrupt HPV transmission, or preferentially eradicate HPV-infected cells.

Methods. Inhibitors are delivered to raft cultures topically or through the medium for up to two weeks. Durability of responses is evaluated by post-treatment chase. We then probe for HPV DNA amplification, cellular DNA replication, viral protein and targeted host proteins, tissue morphology and differentiation, as well as indicators of DNA damage or apoptosis. To model various stages of neoplasias, 3D raft cultures are established from HPV-immortalized or -transformed epithelial cells. Moreover, 3D cultures can be grown directly from patient lesions, and tissues can be transferred reciprocally between patient-derived xenografts in SCID mice and the raft culture system.

Results. Squamous epithelia tolerate pharmaceutical agents previously abandoned because of toxicity upon systemic delivery, supporting the potential for new drug indications against epitheliotropic viruses.

Conclusions. The authenticity of this experimental model of HPV infections and diseases should greatly reduce preclinical research time and expense. As proof of principle, several molecularly distinct inhibitor candidates we have found to be safe and effective have advanced to clinical trials to treat benign HPV lesions.

Assays:

H&E staining for histology: epithelial thickness and normal vs. dysplastic cell structure are informative.

Differentiation markers: eg. various cytokeratins, involucrin, filaggrin, loricrin

Bromouracil or (EdU) incorporation into replicating host cell DNA

Feulgen staining of host DNA in situ to determine ploidy as a function of tissue anatomy
qPCR for HPV DNA copy number

Fluorescence in situ hybridization for HPV DNA abundance and tissue localization

RNA in situ hybridization using mRNA exon-specific probes to identify splicing isoforms

Reverse transcription PCR of mRNAs to ID and sequence mRNAs from both the virus and host cell. This can be targeted using specific PCR primers or global, followed by various versions of RNA-Seq.

Protein assays can be performed in situ if the antibody reagents work in fixed tissues or via western blots of tissue extracts for semi-quantification

HPV late gene expression: L1 major capsid protein; Immature, somewhat amorphous and dispersed intra-nuclear virions or mature, para-crystalline virion arrays by electron microscopy

S-phase: PCNA, Ki-67, and other replication proteins; pRB (retinoblastoma susceptibility protein and pRB family memberp130

G2-phase: cytoplasmic cyclin B

Proteins regulating cell cycle (p21, p27)

DNA Damage Response (DDR): p53, E6AP (a ubiquitin E3 ligase), γ-H2AX, Chk1, Chk2, ATM, ATR

Apoptosis: cleaved caspase-3; PARP, Bcl2, Bim, Bid ; condensed nuclei by morphology, severe thinning of epithelium

Autophagy: LC3

Stress response proteins such as nitric oxide synthetases,

Antibodies to serine or tyrosine nitrosylation or phosphorylation of potential target proteins
Papillomavirus transmission studies have typically used cell-free virus prepared in organotypic raft culture, or recombinant pseudo-virus isolated from monolayer 293TT cells. During natural in vivo infection however, virions are shed from the epithelial surface in squames that contain high levels of E1^E4, a viral protein that assembles into amyloid fibres.

Methods

The roles of E1^E4 in virus transmission and survival are now being analysed using mouse papillomavirus (MmuPV) as an in vivo model, in conjunction with ex vivo infection of human foreskin/cervical tissue by HPV16/18 using WT and E4KO viral genomes.

Results

These cytoplasmic E4 fibres associate with newly-assembled virus particles following nuclear degeneration, in order to increase virus stability and to modulate extracellular virus survival. The E4 proteins also facilitate the shedding of virus-infected squames by disrupting the desmosomal structures that connect differentiating keratinocytes. Depending on the papillomavirus type, up to 10 million virus particles can be transmitted by contact with the surface layers of productively infected tissue, with an approximate one log drop in infectivity if transmission is mediated indirectly on fomites. Electron microscopy shows that MmuPV is E4 fibre-associated, and is stable following desiccation, with minimal loss of titre on fomites over 6 months. The preservation of virus infectivity by E4 was noticed for all three papillomaviruses.

Conclusions

E4 modifies epithelial cell structure to facilitate virus release, and preserves virus integrity outside the cell. In addition, we speculate that the E4 fibre/virus aggregates may contribute to papillomaviruses adherence to the surface of the skin prior to infection.
BACKGROUND AND AIMS

Treatment of diseases caused by human papillomaviruses, such as genital warts and recurrent respiratory papillomatosis, is difficult; complete clearance without regression is not guaranteed. The earliest stages of the virus life cycle from the initially infected cell to appearance of a lesion are poorly characterised. This project aims to clarify early stages of lesion formation in vivo to better understand infection and how papillomaviruses interact with their microenvironment.

METHODS

Using GFP-expressing pseudovirions and markers to detect wound sites and infected cells, a mouse model of papillomavirus infection was used to follow lesion formation from the first infected cell to a macroscopic lesion.

RESULTS

Lesions first became visible at seven days, and decreasing the virus titre extended this period up to three months. Markers of inflammation and extracellular matrix proteins were used to distinguish stages of wound healing, and no viral gene expression was visible until five days after wounding. Studies utilising in situ hybridisation (RNAscope®) showed that during the earliest stages of viral gene expression detectable, density of cells in the basal layer was increased above that of surrounding uninfected epithelium, and initiation of papillomatosis relieved this increased density.

CONCLUSIONS

Virus titre correlates to speed of lesion formation and it is therefore plausible that lesions can form from multiple foci of infected cells as opposed to one single stem-like basal cell. Viral gene expression is controlled in the microenvironment of a healing wound, and lesion formation only begins afterward. Viral gene expression modulates basal cell density and cell proliferation as a lesion forms.
INTACT HPV16 CAPSIDS MEDIATE NUCLEAR ENTRY DURING INFECTION

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Background and Aims

Fundamental aspects of intracellular papillomavirus virion transport and disassembly during infection remain poorly understood.

Methods

Confocal microscopy, employing new and underutilized L1 monoclonal antibodies, and electron microscopy were used to evaluate vesicular trafficking of HPV16 L1/L2 pseudovirions and L1 VLPs.

Results

Infectious HPV16 L1/L2 pseudovirions were found to remain largely intact during vesicular transport to the nucleus. By electron microscopy, capsids with a diameter of 50 nm were clearly visible within small vesicles, most often containing one or two juxta-membrane particles, attached to mitotic chromosomes and, to a lesser extent, within interphase nuclei. Based on the high number of particles visualized on mitotic chromosomes compared to within the nucleus, it is likely that the vesicles are disrupted and capsids disassociated relatively soon after nuclear delivery. Robust nuclear anti-L1 staining imaged by confocal microscopy, through late G1 and S phase, might reflect the detection of pentamers following disassembly. Nuclear entry of assembled L1 is dependent upon the presence of the minor capsid protein, L2, but independent of encapsidated DNA. We also demonstrate that L1 nuclear localization and mitotic chromosome association can occur in vivo in the murine cervicovaginal challenge model of HPV16 infection.

Conclusions

These findings fundamentally challenge the prevailing concepts of PV uncoating and disassembly. They document that a structurally intact viral capsid can enter the nucleus within a transport vesicle, establishing a novel mechanism by which a virus avoids triggering cytoplasmic nucleic acid sensing components of innate immunity to gain access to the nuclear cellular machinery.
AIMS: Histone acetyl transferases (HAT) and deacetylases (HDAC) mediate chromatin remodeling and the activity of many non-histone proteins to regulate transcription. In addition, S-phase progression depends on HDACs to deacetylate histones in newly replicated chromatin. High-risk HPV-18 DNA amplification depends on HPV E7-induced S-phase reentry in differentiated cells in raft cultures developed from primary human keratinocytes (PHKs). We propose that suprabasal cellular DNA replication and viral DNA amplification would be adversely affected by HDAC inhibitors.

Methods: We examined effects of pan-HDAC inhibitors, Vorinostat, Belinostat and Panobinostat, in raft cultures of HPV18-infected PHKs and of HPV16-positive cervical cancer CaSki cells. These inhibitors are FDA-approved against lymphomas and multiple myelomas.

Results: HPV-18 infection elevated several HDACs. Vorinostat (suberoyl-anilide-hydroximic-acid, SAHA) prevented host DNA replication and viral DNA amplification at 5 µM and abrogated progeny virus production. When compared to vehicle-treated, infected raft cultures, Vorinostat reduced E6 protein, inhibited activities of E6 and E7 proteins, induced DNA damage, elevated the pro-apoptotic protein Bim and induced apoptosis. Vorinostat induced very few apoptotic nuclei in uninfected raft cultures. Pan-HDAC inhibitors Belinostat and Panobinostat also reduced viral DNA amplification and induced cytotoxicity in HPV18 raft cultures. Importantly, Vorinostat was highly toxic to raft cultures of CaSki cells.

Support: Pilot research grant from the UAB Comprehensive Cancer Center to NSB and an Anderson Family Endowed Chair to LTC.
SCIENTIFIC STREAM 10: TRIAGE AND EVALUATION

ASSESSING THE ROLE OF HPV GENOTYPING AS TRIAGE FOR PRIMARY HPV-BASED CERVICAL CANCER SCREENING AMONG 10,762 HPV-INFECTED WOMEN

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Background and Aims

HPV testing is very sensitive but infections with the dozen high-risk types are common; secondary tests are needed to identify which infections predict high risk of cervical precancer/cancer requiring treatment. HPV typing might be useful.

Methods

We typed a stratified random sample of 10,762 residual test specimens from HPV-infected women aged 30-65 in the NCI-Kaiser Permanente Northern California cohort study. Using Logistic-Cox modeling, we estimated absolute risks over 8.5 years for the 3 typing strategies (hc2, cobas, and Onclarity) of progression to precancer versus HPV clearance.

Results

By year 3, most infected women had cleared or progressed (Figures 1 and 2). By the end of follow-up, virtually no infections were persistent without progression. Risk of progression substantially differed by type, with HPV16 conveying qualitatively highest risk (2.6% at 1 year and 5.5% at 3 years) (Table 1). The 12-type HPV group could be further stratified into intermediate and low risk groups (e.g., 1-5% and <1% at 3 years). Infections in women with high grade cytology or younger age had higher risk of progression. Absent progression, viral clearance did not vary substantially by type.
Figure 1. Type-specific* absolute risk of clearance of HPV infection over 8.5 years of follow-up.

* HPV types were grouped to resemble the major FDA-approved HPV DNA tests in the US (hc2, cobas, and Onclarity). HR12 includes HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Clearance rates did not vary substantially by type group.
Figure 2. Type-specific* absolute risk of progression (CIN2/CIN3/AIS) of HPV infection over 8.5 years of follow-up.

* HPV types were grouped to resemble the major FDA-approved HPV DNA tests (hc2, cobas, and Onclarity). HR12 includes HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Progression rates varied substantially by type group, with HPV16 yielding qualitatively higher risk.
Table 1. Type-specific* absolute risk of progression (CIN2/CIN3/AIS), clearance, and persistence of HPV infection at 1-year follow-up.

<table>
<thead>
<tr>
<th>HPV type/channel</th>
<th>Progression</th>
<th>Clearance</th>
<th>Persistence</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16</td>
<td>2.6%</td>
<td>44.7%</td>
<td>52.7%</td>
</tr>
<tr>
<td>HPV 18</td>
<td>1.1%</td>
<td>50.1%</td>
<td>48.7%</td>
</tr>
<tr>
<td>HPV HR12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 33/58</td>
<td>0.7%</td>
<td>48.2%</td>
<td>51.1%</td>
</tr>
<tr>
<td></td>
<td>1.3%</td>
<td>49.8%</td>
<td>48.9%</td>
</tr>
<tr>
<td>HPV 33</td>
<td>2.5%</td>
<td>56.6%</td>
<td>40.9%</td>
</tr>
<tr>
<td>HPV 58</td>
<td>1.5%</td>
<td>45.8%</td>
<td>52.8%</td>
</tr>
<tr>
<td>HPV 31</td>
<td>1.4%</td>
<td>46.7%</td>
<td>51.9%</td>
</tr>
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<td>HPV 52</td>
<td>1.1%</td>
<td>43.7%</td>
<td>55.2%</td>
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<td>HPV 66</td>
<td>0.5%</td>
<td>61.2%</td>
<td>38.3%</td>
</tr>
<tr>
<td>HPV 45</td>
<td>0.5%</td>
<td>51.3%</td>
<td>48.2%</td>
</tr>
<tr>
<td>HPV 39/68/35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 68</td>
<td>0.5%</td>
<td>55.3%</td>
<td>44.2%</td>
</tr>
<tr>
<td>HPV 35</td>
<td>0.9%</td>
<td>52.1%</td>
<td>47.1%</td>
</tr>
<tr>
<td>HPV 39</td>
<td>0.8%</td>
<td>56.1%</td>
<td>43.0%</td>
</tr>
<tr>
<td>HPV 59/56/66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV 51</td>
<td>0.3%</td>
<td>56.6%</td>
<td>43.1%</td>
</tr>
<tr>
<td>HPV 59</td>
<td>0.4%</td>
<td>62.3%</td>
<td>37.7%</td>
</tr>
<tr>
<td>HPV 56</td>
<td>0.4%</td>
<td>57.7%</td>
<td>41.9%</td>
</tr>
</tbody>
</table>

* HPV types were grouped to resemble the major FDA-approved HPV DNA tests in the US (hc2, cobas, and Oncology). Persistence meant neither progression nor clearance. Even at 1-year, considering absolute risks, the possible clinical value of typing is shown to be in distinguishing risk of progression to precancer.

Conclusions

In a large clinical follow-up of HPV-infected women, we demonstrated that HPV genotyping stratified subsequent risk of precancer within 3 years of follow-up. Distinguishing HPV16 was especially important and further HPV typing might be clinically useful. The value of dividing the 12 “other” types into 2+ risk-groups is worth considering in detailed decision analyses.
EIGHT-TYPE HUMAN PAPILLOMAVIRUS E6/E7 ONCOPROTEIN DETECTION AS A NOVEL AND PROMISING TRIAGE STRATEGY FOR MANAGING HPV-POSITIVE WOMEN
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Background and Aims
The management of HPV-positive women becomes particularly crucial in cervical cancer screening. Here we assessed whether detection of E6 or E7 oncoproteins targeting eight most prevalent HPV types could serve as a promising triage option.

Methods
Women (N=1,415) aged 50-60 from Shanxi, China underwent screening with HPV testing and liquid-based cytology (LBC), with any positive results referring to colposcopy and biopsy if necessary. Women with HPV-positive results received further tests using DNA-based genotyping, E6 or E7 oncoprotein detection targeting HPV16/18 (for short: E6(16/18) Test) or HPV16/18/31/33/35/45/52/58 (for short: E6/E7(8 types) Test) respectively.

Results
Among HPV-positive women, E6/E7(8 types) oncoproteins had lower positivity (18.05%) compared with DNA-based genotyping for same 8 types (57.40%) and LBC with ASC-US threshold (48.01%); HPV16 was the genotype showing the highest frequency (8.66%) for oncoprotein detection followed by HPV52 (3.61%), 58 (2.17%), 33 (2.17%), 18 (1.08%), 45 (0.72%), 31 (0.36%), and 35 (0.36%). For detection of cervical intraepithelial neoplasia grade 3 or higher (CIN3+), E6/E7 (8 types) Test had similar sensitivity (100.00%) and superior specificity (85.02%) as well as positive predictive value (PPV, 20.00%) compared to both LBC and DNA-based genotyping (8 types); For detection of CIN2+, E6/E7(8 types) Test was less sensitive (65.63%) but still more specific (88.16%) and risk predictive with PPV of 42.00%. Notably, E6/E7(8 types) Test remarkably decreased the number of colposcopies needed to detect one CIN2+ and CIN3+ (2.38 and 5.00).
Figure 1. Type-specific positivity of HPV DNA and E6/E7 oncoprotein among HPV positive women.
**Figure 2.** Positivity of different tests by different cervical lesions among HPV positive women. Abbreviations: LBC: liquid-based cytology; HC2: hybrid capture 2; VIA: visual inspection with acetic acid; CIN: cervical intraepithelial neoplasia; E6(16/18): E6 oncoprotein testing for HPV types 16 and 18; E6/E7 (8 types): E6 or E7 oncoprotein testing for HPV types 16,18,31,33,35,45,52 and 58.
### Table 1 Screening performance of different triage tests for CIN2+ and CIN3+ diagnoses among HPV positive women

<table>
<thead>
<tr>
<th>Triage tests</th>
<th>Sensitivity% (95%CI)</th>
<th>Specificity% (95%CI)</th>
<th>PPV% (95%CI)</th>
<th>NPV% (95%CI)</th>
<th>Colposcopy referral rate (%)</th>
<th>NNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN2+(N=32)</td>
<td>65.63 (48.31-79.59)</td>
<td>88.16 (83.52-91.63)</td>
<td>42.00 (29.37-55.77)</td>
<td>95.15 (91.53-97.27)</td>
<td>18.05</td>
<td>2.38</td>
</tr>
<tr>
<td>E6/E7(8 types)</td>
<td>90.63 (75.78-96.76)</td>
<td>46.94 (40.79-53.19)</td>
<td>18.24 (13.01-24.97)</td>
<td>97.46 (92.79-99.13)</td>
<td>57.40</td>
<td>5.48</td>
</tr>
<tr>
<td>Geno(8 types)</td>
<td>50.00 (33.63-66.37)</td>
<td>93.88 (90.15-96.25)</td>
<td>51.61 (34.84-68.03)</td>
<td>93.50 (89.70-95.96)</td>
<td>11.19</td>
<td>1.93</td>
</tr>
<tr>
<td>E6(16/18)</td>
<td>53.13 (36.45-69.13)</td>
<td>84.08 (78.98-88.13)</td>
<td>30.36 (19.90-43.34)</td>
<td>93.21 (89.10-95.84)</td>
<td>20.22</td>
<td>3.30</td>
</tr>
<tr>
<td>Geno(16/18)</td>
<td>87.50 (71.93-95.03)</td>
<td>57.14 (50.88-63.18)</td>
<td>21.05 (14.99-28.74)</td>
<td>97.22 (93.08-98.91)</td>
<td>48.01</td>
<td>4.75</td>
</tr>
<tr>
<td>LBC (ASC-US+)</td>
<td>100.00 (72.25-100.00)</td>
<td>85.02 (80.24-88.80)</td>
<td>20.00 (11.24-33.04)</td>
<td>100.00 (98.34-100.00)</td>
<td>18.05</td>
<td>5.00</td>
</tr>
<tr>
<td>CIN3+(N=10)</td>
<td>100.00 (72.25-100.00)</td>
<td>44.19 (38.36-50.19)</td>
<td>6.30 (3.45-11.19)</td>
<td>100.00 (96.85-100.00)</td>
<td>57.40</td>
<td>15.90</td>
</tr>
<tr>
<td>E6/E7(8 types)</td>
<td>80.00 (49.02-94.33)</td>
<td>91.39 (87.41-94.19)</td>
<td>25.81 (13.70-43.25)</td>
<td>99.19 (97.08-99.78)</td>
<td>11.19</td>
<td>3.88</td>
</tr>
<tr>
<td>Geno(8 types)</td>
<td>80.00 (49.02-94.33)</td>
<td>82.02 (76.97-86.16)</td>
<td>14.29 (7.42-25.74) &amp; 99.10 (96.76-99.75)</td>
<td>20.22</td>
<td>7.00</td>
<td></td>
</tr>
<tr>
<td>E6(16/18)</td>
<td>100.00 (72.25-100.00)</td>
<td>53.93 (47.94-59.81)</td>
<td>7.52 (4.14-13.29)</td>
<td>100.00 (97.40-100.00)</td>
<td>48.01</td>
<td>13.30</td>
</tr>
</tbody>
</table>

Abbreviations: HPV=human papillomavirus; CIN = cervical intraepithelial neoplasia; CIN2+= cervical intraepithelial neoplasia grade 2 or worse; CIN3+= cervical intraepithelial neoplasia grade 3 or worse; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; NNR = number needed to refer to colposcopy to find one case of CIN2+ or CIN3+; LBC = liquid-based cytology; E6(16/18): E6 oncoprotein testing for HPV types 16 and 18; E6/E7(8 types): E6 or E7 oncoprotein testing for HPV types 16,18,31,33,35,45,52 and 58; Geno(16/18): DNA-based genotyping for HPV types 16 and 18; Geno(8 types): DNA-based genotyping for HPV types 16,18,31,33,35,45,52 and 58.

**Conclusions**

E6/E7 oncoprotein detection showed a good “trade-off” between sensitivity and specificity with more efficient colposcopy referrals, which is of great importance to maximize the benefits of HPV-based screening program, especially applicable for the areas with high HPV prevalence and low-resources.
Background and Aims

A single hrHPV test has limited specificity and can lead to unnecessary overtreatment and distress. VIA is an easy-to-perform test suitable for limited-resource settings and triage of hrHPV positives with VIA has been recommended by WHO. We aim to evaluate the performance of VIA for the triage of HPV positive women in cervical cancer screening settings of Latin America.

Methods

This is a nested analysis within the Multicentric Study of Cervical Cancer Screening and Triage with Human Papillomavirus Testing, the ESTAMPA study (NCT01881659). Briefly, 30-64 years old women from well-defined catchment areas of 12 centres located in nine Latin American countries are referred to colposcopy if HPV positive or abnormal cytology. VIA is being blindly done before the colposcopy. The main outcome was cervical intra-epithelial neoplasia grade 2 or worse (CIN2+) locally reported on biopsy. We estimated sensitivity and specificity for CIN2+ of VIA among hrHPV positive women.

Results

Between May, 2013 and March, 2018, 26,544 women have been recruited and 3,700 (14%) have tested hrHPV positive. Of these, 2,162 have had VIA (47% with a positive result) in Colombia, Honduras and Paraguay. The sensitivity for CIN2+ was 87% (95%CI 82.4-90.6), and the specificity 59% (95%CI 56.6-61.0).

Conclusions

VIA seems to retain acceptable sensitivity and to detect most of the cervical lesions with an improvement in specificity and reduction in the number of women treated in screen-and-treat contexts. We will conduct further analysis stratifying on age, study site and other relevant variables.
Background and Aims

Data to inform evidence-based policy of human papillomavirus (HPV) vaccination delivery strategies in low- and middle-income countries (LMICs) are limited. In this paper, we examine campaign delivery strategies according to key parameters, including coverage, interval, target age range, and delivery costs, to project the health benefits and costs compared to routine delivery strategies of female HPV vaccination.

Methods

We used a hybrid modeling approach that captured HPV transmission, cervical carcinogenesis, and population demographics to project health and economic outcomes associated with campaign HPV vaccination compared with routine vaccination. Both strategies assumed 1-dose 80% efficacy against HPV-16/18 infections with waning after 15 years and 2-dose 100% efficacy over the lifetime. Costs included vaccination and operational costs over a 10-year period and cervical cancer costs over the lifetimes of the current female population in 56 LMICs. Health outcomes included number of cervical cancer cases and disability-adjusted life years.

Results

Compared with routine HPV vaccination of 9-year-old girls with 70% coverage and a 1-year catch-up program to age 14, campaign vaccination yielded greater health benefits for intervals of 3, 4, or 5 years, coverage levels of 40% or 60%, and target age groups of 9-to-14, 9-to-18, or 9-to-30 years. Campaign HPV vaccination also resulted in greater long-term cost offsets from future averted cervical cancer cases compared to a routine program.

Conclusions

Assuming a coverage level of 40% or 60%, campaign one-dose HPV vaccination can be cost-effective compared to a routine one-dose vaccination program if campaigns occur frequently and target a wide age range.
HPV-positive tonsillar and base of tongue cancer (TSCC/BOTSCC) has good (80%) 3-year survival with radiotherapy alone. Intensified treatment comes with side effects without improving prognosis. New biomarkers are needed for stratifying patients to de-escalated treatment and new treatment targets are needed for poor-prognosis patients. Since recent studies have identified various microRNAs (miR) as de-regulated in HNSCC, our aim was to study miR-155, -185 and -193b as biomarkers in TSCC/BOTSCC.

Methods

168 patients (110 HPV+ ) diagnosed between 2000-2013 were examined for miR-155, -185 and -193b expression using RT-PCR. Associations between miR expression, clinical and biological characteristics were analysed using univariate testing, while Cox regression was used to model 3-year progression-free survival.

Results

Tumours showed decreased miR-155 and increased miR-193b expression compared to normal tonsils. miR-155 was associated with HPV-positivity, low T-stage, high CD8+ TIL counts and improved survival, while miR-185 was associated with HPV-negativity and decreased survival. miR-193b increased with higher T-stage, male gender and lower CD8+ TIL counts, but was not related to survival. miR-185 was the only miR independently associated with survival upon Cox regression. Combining miR-155 and miR-185 to predict non-survivors in HPV+ patients yielded 71% sensitivity and 67% specificity, with 90% negative predictive value.

Conclusions

The positive impact of miR-155 on survival was mainly due to CD8 infiltration, while miR-185 independently associated with decreased survival. These markers alone managed to predict patient prognosis reasonably well. Addition of miR-155 and -185 to previously validated prognostic biomarkers could improve patient stratification, and further studies of these miRs as treatment targets are indicated.
LONG TERM IMMUNOGENICITY AND EFFECTIVENESS OF THE 9-VALENT HPV (9VHPV) VACCINE IN PREADOLESCENTS AND ADOLESCENTS

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2Nutricional anexo Huáscar, Research, Lima, Peru
3Centro de Investigación Clínica, Research, Medellin, Colombia
4Pharmangkutklao Hospital, Research, Bangkok, Thailand
5Centro Medico Imbanaco, Research, Calli, Mexico
6Phillipine General Hospital, Research, Manila, Philippines
7EBA Cantelles, Research, Catalonia, Spain
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Background and Aims

The pivotal Phase III immunogenicity study of the 9vHPV-vaccine in girls and boys (age 9-15 years) was extended to provide long-term immunogenicity and effectiveness through 10-years post-dose 3. We describe the first interim analysis at month 72.

Methods

Overall, 1272 subjects (971-females, 301-males) who received 3 doses of 9vHPV-vaccine at day 1 and months 2 and 6 were enrolled in the study extension. Serum was collected at month 66 to assess antibody responses. Starting at age 16-years, genital swabs were collected every 6 months and tested by PCR to detect HPV DNA. Pap tests were collected annually in female subjects starting at age 21-years. External genital and cervical biopsies were performed as indicated in the protocol. Tissue samples were adjudicated by a pathology panel and tested by PCR to detect HPV DNA.

Results

Geometric mean titers peaked around month 7 and gradually decreased through month 66. Seropositivity rates remained >90% through month 66 for each of the 9vHPV-vaccine types. No cases of HPV 6/11/16/18/31/33/45/52/58-related disease (cervical/vulvar/vaginal lesions and genital warts in females, external genital lesions and genital warts in males) were observed in the per-protocol population (maximum follow-up: 6.4-years [median 5.9-years] post-dose 3). Incidence rates of HPV6/11/16/18/31/33/45/52/58-related 6-month persistent infection in females and males were low (20.3 and 24.3 per 10,000 person-years, respectively) and within ranges expected in vaccinated cohorts (based on results from efficacy trials of 4-valent and 9-valent HPV-vaccines).

Conclusions
This analysis demonstrates sustained immunogenicity through 5-years post-vaccination and durable effectiveness through 6-years post-vaccination in girls and boys aged 9-15 years.
Background and Aims

Affordable safe and efficacious HPV vaccines are in urgent need in resource limited areas. A randomized, double-blind, placebo-controlled Phase 3 clinical trial was conducted to evaluate the safety and efficacy of an Escherichia coli-expressed recombinant bivalent (HPV-16/18) vaccine against HPV infection (PI) and high-grade cervical lesions associated with HPV-16/18.

Methods

During 11/2012-05/2013, 7372 women aged 18-45 years old were enrolled from 5 sites in China and intramuscularly received 3 doses of HPV-16/18 bivalent vaccine (3689 women) or the control vaccine (recombinant hepatitis E vaccine, Hecolin®, 3683 women) at month 0-1-6. Two co-primary endpoints were HPV 16 and/or 18 associated 6-month PI and CIN2+. The primary analysis was carried out in a per-protocol set (PPS) cohort that included women who had no violation of the protocol and had no evidence of HPV-16/18 infection through 1 month post the third dose (month 7).

Results

Participants were followed-up for an average of 4 years after they received the first dose. Vaccine efficacy against 6-month PI was 97.8%(87.1-99.9) in the PPS cohort and 97.9(88.0-99.9) in the modified intention-to-treat cohort (mITT, baseline HPV-16 or HPV-18 negative and received at least one dose). Vaccine efficacy against CIN2+ was 100.0%(55.6-100.0) in PPS cohort and 100.0%(55.4-100.0) in the mITT cohort. In PPS cohorts of both 18-26 age group and 27-45 age group, the vaccine is similar efficacious against the two end points.

Conclusions

The candidate HPV bivalent vaccine is safe and efficacious in preventing HPV-16/18 related 6-month PI and CIN2+ in both age group of 18-26 and 27-45 year.
A single dose of the bivalent HPV vaccine provides a decade of protection against HPV infection: non-randomized results from the Costa Rica HPV vaccine trial

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7 Independent contractor, Formerly PEG, San Jose, Costa Rica

Background and Aims

Similar HPV16/18 vaccine efficacy (VE) and stable HPV16/18 antibody levels were demonstrated 7 years post-vaccination in a non-randomized analysis of women who received 1, 2, or 3 doses of the bivalent HPV16/18 vaccine in CVT.

Methods

A decade after HPV vaccination, prevalent HPV infection was compared between HPV16/18 vaccinated women who received one (N=112), two (N=62), or three (N=956) doses and unvaccinated women (N=1107). Cervical HPV infections were measured at two study visits, approximately 9- and 11-years after initial HPV vaccination, using the NCI NGS-based assay, TypeSeqer, and compared across groups to compute VE and 95% confidence intervals (CI). Analyses were restricted to women who contributed cervical samples at both timepoints. HPV16/18 specific antibody testing by ELISA is ongoing.

Results

Compared to the unvaccinated group (Table), VE against prevalent HPV16/18 infection at either 9- or 11-years was 81% (95%CI: 70 to 89%) among three-dose women, 84% (95%CI: 20 to 99%) among two-dose women, and 82% (95%CI: 41 to 97%) among single-dose women (p values for differences in VE by dose group =1.0). Similar VE against HPV31/33/45 was observed independent of dose group: VE ranged from 61 to 77% (p values for difference in VE by dose group >0.3). In the same groups, prevalence of genital HPV types unrelated to HPV vaccination was high and not statistically different among vaccinated and unvaccinated groups.

Table. HPV prevalence at years 9 or 11.
## Conclusions

A decade after bivalent HPV vaccination, VE against HPV16/18 and HPV31/33/45 infection remained similarly high independent of the number of vaccine doses received.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>3 Doses</th>
<th>2 Doses (1/2)</th>
<th>1 Dose</th>
<th>0 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td># with outcome/ # of women</td>
<td>%; 95%CI</td>
<td>%; 95%CI</td>
<td>%; 95%CI</td>
<td>%; 95%CI</td>
</tr>
<tr>
<td>16/128</td>
<td>18/155</td>
<td>63.4%</td>
<td>69.9% to 83.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>21/134</td>
<td>43/196</td>
<td>60.5%</td>
<td>44.5% to 72.3%</td>
<td>0.001</td>
</tr>
<tr>
<td>other endo</td>
<td>24/192</td>
<td>2.3%; 95%CI</td>
<td>-22.5% to 28.3%</td>
<td>0.72</td>
</tr>
<tr>
<td>non-endo</td>
<td>5/196</td>
<td>2.5%; 95%CI</td>
<td>9.7% to 13.4%</td>
<td>0.94</td>
</tr>
</tbody>
</table>
LONG-TERM EFFECTIVENESS AND IMMUNOGENICITY OF QUADRIVALENT HPV VACCINE IN YOUNG MEN: 10-YEAR END-OF STUDY ANALYSIS

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Background and Aims

We report the 10-year, end-of-study analysis of a long-term follow up (LTFU) study that assessed the effectiveness and immunogenicity of the quadrivalent human papillomavirus (qHPV) vaccine in men.

Methods

In the 3-year base study (NCT00090285), young men (16-26 years old) were randomized 1:1 to receive 3 doses qHPV vaccine or placebo; results from participants who received 3 vaccine doses and participated in the LTFU are reported. Participants were assessed annually in the 7-year LTFU for HPV6/11-related genital warts and HPV6/11/16/18-related external genital lesions (EGL), and a subpopulation was assessed for HPV6/11/16/18-related anal intraepithelial neoplasia (AIN) or anal cancer. Persistence of anti-HPV6/11/16/18 antibodies was evaluated from serum samples collected 48-72 months (first LTFU visit) and 10 years post-Dose 1.

Results

A total of 917 participants were followed for effectiveness for up to 11.5 years (median: 9.5 years) post-Dose 3. There were no new cases of HPV6/11-related genital warts, HPV6/11/16/18-related EGL, or HPV6/11/16/18-related high-grade AIN during the LTFU in the per-protocol population. One low-grade AIN (AIN1) with positive PCR results for HPV6 and HPV58 was reported. Seropositivity rates based on competitive Luminex immunoassay were >97% at Month 7; remained high over time for HPV6/11/16; and decreased for HPV18 (40.2% at Month 120). Seropositivity rates at Month 120 assessed by IgG Luminex immunoassay (a more sensitive assay) were>90% for all 4 HPV types.

Conclusions

The qHPV vaccine provides durable protection from vaccine-type–related anogenital disease and elicits persistent HPV antibody responses through 10 years post-vaccination onset in 16-26–year-old men.
Background and Aims

Most cervical cancers are caused by vaccine-preventable infections with human papillomaviruses (HPV). HPV prophylactic vaccines Gardasil™ and Cervarix™ both contain the major oncogenic HPV types 16 and 18, have been widely used for >10 years and are reported to induce high antibody levels and long-lasting protection. A head-to-head comparison of the antibody responses induced by the two vaccines has been performed only up to 5 years.

Methods

About 3,500 Finnish females, who participated in phase III licensure trials of the Gardasil™ and Cervarix™ vaccines, consented to follow-up. Linkage with the Finnish Maternity Cohort found that they had donated >2,500 serum samples up to 12 years later. The most recently donated serum samples of 337 Gardasil™ and 730 Cervarix™ vaccine recipients were retrieved and HPV serum antibody levels were determined using HPV pseudovirions and reported in international units.

Results

Post-vaccination HPV16 and HPV18 antibody levels remained stable and above natural infection-related antibody level for up to 12 years for most vaccine recipients. The median antibody levels were higher among Cervarix™ vaccine recipients in all time-windows from 7 to 12 years post vaccination (p <0.0001).

Conclusions

The long-term stability of vaccine-induced antibody levels is in accordance with the high long-term protection reported previously. The observed significant differences in the antibody levels induced by the two vaccines imply that continued follow-up to identify possible breakthrough cases and estimation of the minimal protective vaccine-induced levels of serum antibodies is a research priority.
SCIENTIFIC STREAM 12: HPV AND THE MICROBIOME

PREVALENT HIGH-RISK HPV AND MULTIPLE HPV INFECTIONS ARE ASSOCIATED WITH CORYNEBACTERIUM-DEFICIENT PENILE MICROBIOTAS AMONG BLACK SOUTH AFRICAN MEN

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Background and Aims

Recent studies have revealed that bacterial communities on the penis may impact the risk of sexually transmitted infections, such as HIV, in men and their sexual partners. The role of the penile microbiota in HPV infection in men is unknown. We therefore investigated the association of HPV infection with penile microbiotas in a South African cohort.

Methods

Penile samples from 238 Black men aged 21-67 years were collected by swabbing of the penile shaft, foreskin (if uncircumcised), and glans. Bacterial communities were profiled by Illumina sequencing of the V3-V4 hypervariable regions of the bacterial 16S rRNA gene. HPV was detected by the Roche Linear Array HPV Genotyping assay.

Results

One hundred and thirty men (54.6%) were HPV-positive. The penile microbiotas clustered into six community state types (CSTs, designated 1-6). A majority of the men (53.4%) had Corynebacterium-dominated microbiotas (CST-1). The remaining CSTs had reduced abundances of Corynebacterium and were colonized with several cervicovaginal bacteria. Men with Corynebacterium-deficient microbiotas were more likely to have high-risk (HR)-HPV (odds ratio (OR): 1.8 [95% CI 1.1-3.0], p=0.004) and multiple HPV infections (OR: 1.7 [95% CI 1.0-2.9], p=0.047) relative to men in CST-1. Prevalent HPV infection was strongly associated with greater abundances of Campylobacter, Sneathia, Dialister, Porphyromonas, and Prevotella (LDA>3.0, p<0.05). Men with HR-HPV infection had greater abundances of Campylobacter, Peptoniphilus, Dialister, and Prevotella than uninfected men (LDA>3.0, p<0.05).

Conclusions
Approximately 50% of the South African men have *Corynebacterium*-deficient microbiotas that are associated with HR-HPV and multiple HPV infections. The bacteria associated with HPV infections need further investigation.
THE INVERSE RELATION BETWEEN EXPRESSION OF PAN-HPV E4 AND METHYLATION MARKERS FAM19A4/miR124-2 IN THE IDENTIFICATION OF PRODUCTIVE AND TRANSFORMING CERVICAL INTRAEPITHELIAL NEOPLASIA

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Background and Aims

To identify productive and transforming cervical intraepithelial neoplasia using HPV E4 and p16 immunohistochemistry; to determine the methylation positivity as detected on cervical smear, of E4/p16-identified transforming lesions.

Methods

Women whose inclusion smear was tested for FAM19A4/miR124-2 hypermethylation and who had a worst lesion of CIN1-3 detected on biopsy were selected from a prospective follow-up study (EVAH study). Biopsies were cut and stained for H/E, E4 and p16Ink4a. Lesions of which the diagnosis on the original section differed from the diagnosis on the new section were excluded; 188 remained. Women with initial E4 positive and E4 negative lesions were compared for methylation status in the inclusion smear and grade of p16 stain of the initial worst lesion.

Results

179 biopsies were included: 58 CIN1, 78 CIN2 and 43 CIN3. 44.8% of CIN1, 19.2% of CIN2 and 4.7% of CIN3 lesions were E4 positive. A cervical smear positive for FAM19A4/miR124-2 was found in 22.4% of women with CIN1, 43.6% CIN2 and 72.1% CIN3. We found a significantly higher proportion of E4 positivity of the worst lesion present in women with a methylation- smear (30.7% E4+) compared to a methylation+ smear (15.4% E4+) (p=0.017, r=-0.178). 69.8% of E4+ lesions showed p16 in ≥2/3 of the epithelium.

Conclusions

E4 positive lesions are lesions in the productive phase of the HPV lifecycle and most likely relatively recent infections as indicated by the negative correlation (r=-0.178, p=0.017) with methylation status. Extensive diffuse p16 expression did not indicate a non-productive, fully transformed lesion.
THE VAGINAL MICROBIOME AS A PREDICTOR OF HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION IN WOMEN OF REPRODUCTIVE AGE

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Background and Aims

The association between the vaginal microbiome and human papillomavirus (HPV) remains unclear, partly due to heterogeneity of the microbiota. We evaluated the association between the vaginal microbiome and high-risk (HR) HPV

Methods

We enrolled 546 women aged 18-51 years in a cross-sectional study in five Brazilian regions. We genotyped cervicovaginal samples for HPV using Roche’s Linear Array test. For vaginal microbiome analysis, we sequenced V3-V4 of 16S rRNA gene (Illumina). We used stepwise (forward, p<0.15) logistic regression to construct two linear scores to predict HR-HPV: one based exclusively on the presence of individual bacterial species (microbiome-based [MB] score) and the other exclusively on participants' behavioral, sociodemographic, and clinical (BSC) characteristics. The MB score combined coefficients of 30 (out of 116) species retained in the model. The BSC score retained seven (age, marital status, new sex partner, hormonal contraceptive use, body mass index and smoking) out of 25 candidate variables. We constructed receiver operating characteristic (ROC) curves for the scores as HR-HPV correlates and compared the areas under the curve (AUC) and 95% confidence intervals (CI) to infer the difference in predictive performance

Results

The HR-HPV prevalence was 15.8% (n=86) and 143 (26.2%) participants had Lactobacillus-depleted microbiomes. The AUCs were 0.8022 (CI: 0.7517-0.8527) for the MB score and 0.7027 (CI: 0.6419-0.7636) for the BSC score (P=0.0163 for the difference between AUCs)

Conclusions

Our findings suggest that the composition of the vaginal microbiome is strongly correlated with HR-HPV positivity, warranting further validation of its clinical utility via longitudinal studies
Background and Aims

We aimed to study the association of bacterial microbiota of breast milk with that of newborn’s mouth. The influence of HPV infection to microbiota was investigated in breast milk and in the infant mouth.

Methods

Altogether 31 mother-infant pairs with known HPV status were selected from the Finnish Family HPV Study cohort. Twenty infants were born vaginally and eleven by cesarean section.

Microbiota composition and diversity in breast milk and infant mouth was characterized by 16S rRNA gene sequencing (V1-V3 region, Illumina protocol, Illumina, San Diego, CA, USA).

Results

HPV genotype distribution of the mother-child samples is presented in Table 1. In all, eight genera were shared in the breast milk and infant’s oral microbiota: Streptococcus, Staphylococcus, Unclassified Gemellaceae, Rothia, Veillonella, Haemophilus, Propionibacterium and Corynebacterium (Fig 1). No individual pair-level similarities between mother-infant pairs were detected.

HPV infection did not influence the microbiota richness or diversity in infant oral or in breast milk samples. However, the oral microbiota of HPV positive infants clustered distinctly from HPV negative infants (redundancy analysis, p=0.036). Higher abundance of Propionibacterium (p=0.095) genus was detected in HPV positive infant oral samples whereas Veillonella dispar (p=0.048) was characteristic of HPV negative samples. No significant differences according to the delivery mode were detected. The impact of HPV infection on breast milk microbiota was not assessed due to only three HPV positive milk samples.

Conclusions

HPV infection is associated with distinct oral bacterial microbiota composition in infants. The direction of causality remains unclear.
Background and Aims

To investigate the association of oral microbiota and HPV in the development of head and neck squamous cell carcinoma (HNSCC).

Methods

Prospectively collected tumor tissues and their adjacent normal tissues from 44 HNSCC patients were analyzed with 16S rRNA gene profiling for bacteria community. The presence of HPV DNA in tissues was detected using a L1-target Next-Gen sequencing assay.

Results

We found 6/44 (13.6%) of tumor tissues and 1/44 (2.3%) of normal tissues were positive for high-risk HPV DNA (OR 6.79, p=0.1099). HPV16 was the most predominant type, presenting in 5 tumor and 1 normal tissue infection. The overall oral bacterial community contained Fusobacterium (mean abundance of 9.6%) and Prevotella (9.2%), with Streptococcus, Haemophilus and Leptotrichia constituting 5.9%, 5.6% and 5.3%, respectively. The bacteria community diversity was significantly depressed in tumor tissues compared to the adjacent normal tissues (p<0.004). A linear discriminant analysis for effect size (LEfSe) determined 18 "core" bacterial taxa (>1% mean abundance) were tissue-type discriminative. Particularly, Fusobacterium was significantly predominant in tumor tissues (12.9% vs 6.3%, p<0.001). In contrast, Streptococcus and another 10 genera were more common in normal tissues. There was no association between the abundance of Fusobacterium and HPV infection in HNSCC tumor tissues; however, the non-smokers had relatively higher abundance of Fusobacterium than the smokers did (7.1% vs 4.2%, p=0.0245).

Conclusions

There is a reduced diversity of oral microbiota and increased abundance of Fusobacterium in HNSCC tumor tissues. These findings implicate oral microbes in the pathogenesis of HNSCC.
Background and Aims

Despite increased global availability of HPV vaccination, uptake remains suboptimal in many countries due in part to indecision or lack of vaccine confidence referred to “vaccine hesitancy”. The objective was to identify and examine recent evidence on effectiveness of interventions designed to address or reverse “vaccine hesitancy” by increasing confidence in and acceptability of HPV vaccination.

Methods

PubMed/Medline and EMBASE databases were systematically searched to retrieve full publications (published since 2013) reporting interventions to address HPV vaccine hesitancy. Original studies evaluating interventions designed to improve confidence/acceptability of HPV vaccination, reporting on HPV vaccine uptake, vaccine refusal/delay, attitudes, and/or vaccination intention were included. Information extracted included study type, country, targeted population, type of intervention, and results for relevant outcomes.

Results

Among 53 eligible publications (45 from the United States), 38 reported on studies designed to evaluate the impact of dialogue/communication strategies, and 15 assessed multimodal approaches combining dialogue/communication with reminder-recall (12), incentives (2), or both (1). These interventions targeted parents, adolescents/young adults eligible for vaccination, and healthcare providers in 30, 29, and 10 studies, respectively. More than 90% of the 31 studies that investigated the impact of interventions on vaccination attitudes and/or intent reported a statistically significant beneficial effect on these outcomes. Increases in vaccine initiation and/or completion were reported by 50% of 14 studies evaluating dialogue/communication and by 83% of 12 studies evaluating multimodal approaches.

Conclusions

A majority of studies report studied interventions improve vaccination intention and attitudes. Multimodal approaches were more often successful than dialogue/communication in increasing vaccine initiation/completion.
UNTANGLING HPV VACCINE HESITANCY: CHARACTERISTICS OF “FLEXIBLE” AND “RIGID” HESITANT PARENTS

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Background and Aims

HPV vaccine uptake in school-based vaccination programs in Canada is suboptimal. The WHO SAGE Working Group conceptualizes vaccine hesitancy as a continuous refusal process, rather than a dichotomous behaviour (yes/no), and defines it as a “delay in acceptance or refusal of vaccination despite availability of vaccination services”. This study is the first to provide a more fine-tuned understanding of hesitancy using a stage-based perspective of HPV vaccine attitudes and beliefs in parents of boys and girls.

Methods

Using an online survey, we collected data from a nationally representative sample of parents at Time 1 (September/2016) and Time 2 (July/2017).

Results

Parents reported they were in either unaware, unengaged, undecided, decided not, decided to, or already vaccinated stages. Most decided not parents ("rigid" hesitant) at Time 1 (~70%) remained decided not at Time 2 and <10% changed to decided to or vaccinated. In contrast, more parents who were unengaged or undecided at Time 1 ("flexible" hesitant) changed to decided to or vaccinated at Time 2 (30% parents of boys; 42% parents of girls).
Those who changed (Time 1 to Time 2) reported more significant favorable attitudes (e.g., benefits) when compared to those who did not change stage.
At Time 2, influence from significant others and healthcare providers (OR's ≥ 2.95), and perceiving more harms (OR's ≤ 0.61), were significantly associated with decided to or vaccinated stages in
parents who transitioned from “flexible” hesitant at Time 1.

Multivariate logistic regression analysis for boys and girls unengaged/undecided at Time 1 who changed to unengaged/undecided/not at Time 2 (reference) or changed to decided to vaccinated at Time 2

<table>
<thead>
<tr>
<th></th>
<th>Boys (n = 305)</th>
<th>Girls (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knowledge, attitudes and beliefs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General knowledge</td>
<td>0.96 (0.95; 1.00)</td>
<td>1.29 (1.03; 1.58)</td>
</tr>
<tr>
<td>Vaccine knowledge</td>
<td>1.01 (0.84; 1.21)</td>
<td>1.68 (0.79; 3.58)</td>
</tr>
<tr>
<td>Susceptibility</td>
<td>1.40 (0.93; 2.15)</td>
<td>1.82 (0.91; 3.69)</td>
</tr>
<tr>
<td>Severity</td>
<td>0.65 (0.42; 1.05)</td>
<td>1.25 (0.67; 2.35)</td>
</tr>
<tr>
<td>Benefits</td>
<td>1.15 (0.53; 2.56)</td>
<td>1.03 (0.39; 2.79)</td>
</tr>
<tr>
<td>Affordability</td>
<td>0.88 (0.65; 1.18)</td>
<td>0.73 (0.45; 1.15)</td>
</tr>
<tr>
<td>Accessibility</td>
<td>1.12 (0.76; 1.65)</td>
<td>1.42 (0.79; 2.53)</td>
</tr>
<tr>
<td>Harms</td>
<td>0.61 (0.38; 0.98)</td>
<td>0.43 (0.25; 0.74)</td>
</tr>
<tr>
<td>Influence</td>
<td>3.18 (1.96; 5.12)</td>
<td>2.65 (1.45; 4.88)</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>1.27 (0.85; 1.90)</td>
<td>1.63 (0.85; 3.13)</td>
</tr>
<tr>
<td>Conspiracy beliefs</td>
<td>1.38 (0.72; 2.61)</td>
<td>1.50 (0.82; 2.76)</td>
</tr>
<tr>
<td>Resistant-confidence</td>
<td>0.84 (0.38; 1.78)</td>
<td>1.78 (0.60; 5.32)</td>
</tr>
<tr>
<td>Resistant-risk</td>
<td>1.34 (0.79; 2.26)</td>
<td>0.62 (0.23; 1.56)</td>
</tr>
</tbody>
</table>

| **Sociodemographics**                |                |                 |
| Parents' education                  | 1.01 (0.83; 1.23) | 0.89 (0.72; 1.10) |
| Education (Elementary/high school)  | (reference)     | (reference)     |
| Unemployment                        | 1.46 (0.53; 4.22) | 1.49 (0.41; 5.40) |
| Number of children/child            | (reference)     | (reference)     |
| Two children                         | 1.53 (0.25; 1.00) | 0.56 (0.31; 0.98) |
| Three or more children              | 1.29 (0.53; 3.19) | 2.53 (0.64; 9.99) |
| Parent/gender (male)                | (reference)     | (reference)     |
| Female                               | 1.32 (0.85; 2.07) | 0.42 (0.13; 1.32) |
| Income (<$50K)                      | (reference)     | (reference)     |
| <$50K                                | 1.42 (0.80; 2.51) | 0.25 (0.06; 0.86) |
| Income (Other)                      | (reference)     | (reference)     |
| White                                | 0.40 (0.17; 0.92) | 0.47 (0.12; 1.77) |
| Child's age                          | 0.95 (0.52; 1.71) | 1.62 (0.81; 3.28) |

Note: AOR: adjusted odds ratio; reference category. For knowledge, attitudes and beliefs, parents and child's age. AOR = protection against increased bold and yellow = significant AOR.

Conclusions

“Flexible” and “rigid” hesitant parents will likely require different intervention strategies to improve acceptability and HPV vaccine uptake.
LIVES LOST DUE TO VACCINE HESITANCY IN JAPAN: A MISSED OPPORTUNITY AND THE POTENTIAL GAIN IF COVERAGE IS RESTORED
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²Hokkaido University Graduate School of Medicine, Department of Women’s Health Medicine, Sapporo, Japan

Background and Aims

Over 80% coverage for HPV vaccination was initially achieved in Japan; however, proactive recommendations for vaccination have been suspended since 2013, and coverage is now <1% per year. We evaluated lives lost due to the vaccine hesitancy crisis in Japan to date, and the potential impact of scaling-up HPV vaccination coverage to 80% by the year 2019 (quick recovery) versus no recovery before 2024.

Methods

We used a calibrated dynamic model of screening and vaccination (’Policy1-Cervix’) to evaluate the impact of the HPV vaccination crisis in Japan to date, accounting for national age-specific coverage rates from 2010 onwards. We also evaluated the impact of a quick recovery, assuming 80% vaccination coverage is achieved in 12-year-olds from 2019 onwards, versus no recovery before 2024. We report outcomes in cohorts age 12 between the years 2010-2018 when evaluating the impact of vaccine hesitancy, and cohorts age 12 between the years 2019-2024 when evaluating the impact of recovery.

Results

If vaccine coverage rates had not declined in Japan, 37,300 cancer cases and 8,500 deaths could have been averted. If 80% coverage is restored by 2019, compared to no recovery before 2024, 27,500 cancer cases and 6,200 deaths could be averted. Therefore, every year of low coverage results in approximately 5,500 cases and 1,200 deaths.

Conclusions

Vaccination hesitancy to date will result in 8,500 preventable cervical cancer deaths. Over 6,000 deaths could be averted in Japan if uptake were restored by 2019 compared to no recovery before 2024.
Background and Aims

The 9-valent HPV vaccine (9vHPV) was licensed in the United States in 2014 and recommended for vaccination in 2015. We describe the safety monitoring findings for 9vHPV from the two major post-marketing surveillance systems in the United States: the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

Methods

In VAERS, we searched for U.S. reports of adverse events (AE) following 9vHPV between December 2014 and December 2017. We conducted descriptive analyses, estimated AE reporting rates, and performed clinical review of pre-specified conditions. In VSD, we conducted weekly near-real time monitoring of 11 pre-specified health conditions (Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, anaphylaxis, stroke, venous thromboembolism, appendicitis, pancreatitis, seizures, syncope, allergic reaction, injection site reactions) among 9-26 years olds between October 2015 and October 2017, and performed sequential analyses to detect associations.

Results

From December 2014 and December 2017, approximately 29 million 9vHPV doses were distributed in the United States. VAERS received 7,244 reports following 9vHPV; 31% in females, 22% in males, 47% sex missing/unknown. 97% of reports were non-serious; dizziness (8%) and syncope (7%) were most commonly reported. Approximately 900,000 9vHPV doses were administered in the VSD; statistically significant findings (i.e. signals) were detected for syncope and local reactions, both expected AEs, as well as for allergic reaction, pancreatitis, and appendicitis, which were not confirmed after further evaluation.

Conclusions

The 9vHPV safety profile to date is consistent with data from pre-licensure trials and comparable with findings of post-licensure surveillance and epidemiologic studies for 4vHPV.
The role of communication in public health: the HPV experience in India

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¹Indian Council of Medical Research, National Institute of Cancer Prevention and Research, Noida, India
²Global Health Strategies, Advocacy and Communications, New Delhi, India

Background and Aims

Communication is critical for informing, influencing and motivating individuals, communities and policymakers about important public health issues – ranging from disease prevention and epidemic response to health promotion and health policy. Studies have shown that well-designed, evidence-based communication interventions can positively influence health behaviours and outcomes, particularly in supportive environments. This is especially true for the HPV vaccine, for which the World Health Organization recommends countries invest in a comprehensive communication strategy.

Methods

Using India as a case study, we will discuss how communication efforts, or lack thereof, have played a role in shaping the environment around HPV vaccine introduction. Despite India having the highest burden of cervical cancer globally, and HPV vaccines being licensed for use in India since 2008, coverage remains low. This is partly because the HPV vaccine is not included in the government’s Universal Immunization Programme (UIP), and also due to limited awareness among political, technical and community stakeholders on the value and efficacy of the vaccine.

Results

After several communication efforts made over the years, there have been some positive steps taken toward HPV vaccine introduction, including pilot programmes in states like Punjab and Delhi. In 2017, India’s National Technical Advisory Group on Immunization recommended introduction of the HPV vaccine into the UIP.

Conclusions

Communication around HPV vaccine introduction is essential to build awareness, address myths and misconceptions, and reduce stigma and hesitancy. Going forward, the successful uptake and acceptance of the HPV vaccine will require concerted communication efforts from the policy level down to the community level.
IPVC8-0259
STRUCTURED SCIENTIFIC SESSION

STRUCTURED SCIENTIFIC SESSION 2: HPV DIAGNOSTICS AND BIOMARKERS/VALGENT

ORAL RINSE PROTEOME: A SOURCE OF POTENTIAL SECRETORY BIOMARKERS IN HPV RELATED ORAL SQUAMOUS CELL CARCINOMA
Z. rubab1, S. Baig1
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Background and Aims
HPV related oral squamous cell carcinoma (OSCC) constitute an epidemiological, molecular and clinical distinctive subset of oral cancer. Proteomic studies may help in identification of prospective biomarkers for HPV associated OSCC. The study was designed to identify prospective tumor biomarker in oral rinse of HPV related OSCC.

Methods
A case control study was designed with 100 OSCC patients and 200 controls. After RT PCR, a random subset of 75 subjects were selected: 25 each of HPV +ive OSCC, HPV –ive OSCC and non-tobacco chewers. The peptides were separated by nanoflow liquid chromatograph system coupled online to LTQ-Orbitrap Velose mass spectrometer using a nanoelectrospray ion source (Thermo Scientific, Schwerte, Germany). Enrichment and protein–protein interaction (PPI) network analysis of the identified proteins was performed using FunRich.

Results
A total of 1995 proteins from HPV +ive OSCC (995), HPV –ive OSCC (816) and control samples (184) respectively were identified. Pairwise comparison revealed 37% of HPV +ive OSCC proteins were also present in HPV –ive OSCC samples whereas HPV-ive and HPV +ive OSCC share 18.6% and 17.1% of control proteins respectively. The 7-10 differentially expressed proteins were observed which were associated with 10 fold enriched pathways related to viral mRNA translation. The common proteins related to this pathway were ribosomal and glycosylated proteins.
Conclusions

**Conclusion:** The extensive ribosomal protein variations and their interaction in viral mRNA translation pathway may be the potential biomarker for HPV related OSCC,
Interacting genes (Direct Neighbours) outside dataset: BIOMARKERS
Interacting genes (Direct Neighbours) from dataset: BIOMARKERSt
Genes from Viral mRNA Translation but not present in dataset: BIOMARKERS
RPLP1 (Focused Gene)
COMPARISON OF THE HYBRIBIO’S 21 HPV GENOARRAY DIAGNOSTIC TEST AND HYBRID CAPTURE 2 IN THE VALGENT-3 FRAMEWORK

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2Unit of Cancer Epidemiology, Belgian Cancer Centre- Sciensano, Brussels, Belgium

Background and Aims


Methods

The VALGENT framework is designed for comprehensive comparison and clinical evaluation of HPV tests with limited to extended genotyping capacity. 21 HPV GenoArray targets and allows separate readings for 21 HPV genotypes; however, for the purpose of this study, it was considered positive if one or more of the 13 hrHPV types targeted by hc2 was detected. The VALGENT-3 panel constitutes 1,300 samples that were collected from women aged 25-64 years who participated in the national cancer screening program in Slovenia, in addition to 300 cytologically abnormal samples (100 HSIL, 100 LSIL, 100 ASC-US).

Results

The 21 HPV GenoArray had a relative sensitivity of 0.99 (95% CI, 0.95–1.04; P_{McN}=0.7055 and P_{n.inf}=0.0014) for CIN2+ and 0.99 (95% CI, 0.93–1.04; P_{McN}=0.6547 and P_{n.inf}=0.0123) for CIN3+. The relative specificity of the 21 HPV GenoArray for ≤CIN1 was 0.99 (95% CI, 0.98–1.01; P_{McN}=0.3113 and P_{n.inf}=0.0752) when assessed on women with two consecutive negative cytology results.

Conclusions

21 HPV GenoArray has demonstrated similar clinical sensitivity and specificity compared to the hc2. Although the 21 HPV GenoArray was not intended for the use in primary HPV-based cervical cancer screening, it could be considered for analysis of discordant genotyping results.
FIVE-YEAR RISK OF CERVICAL PRECANCER FOLLOWING P16/KI-67 DUAL STAIN TRIAGE OF HPV-POSITIVE WOMEN

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¹National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, USA
²Albert Einstein College of Medicine, Epidemiology & Population Health, Bronx, USA
³Kaiser Permanente, TPMG Regional Laboratory, Berkeley, USA
⁴Global Coalition Against Cervical Cancer, n/a, Arlington, USA

Background and Aims

Human papillomavirus (HPV)-based screening requires triage to avoid unnecessary colposcopy referral while maintaining high sensitivity for cervical precancer. Triage with p16/Ki-67 dual stain (DS) has shown high sensitivity and specificity for detection of cervical precancers; however, longitudinal studies are needed to determine how long a negative DS indicates a low risk of precancer. We evaluated the longitudinal performance of p16/Ki-67 DS triage for detection of cervical precancer over 5 years of follow-up.

Methods

1,549 HPV-positive women undergoing screening with HPV/cytology (SurePath) co-testing were enrolled in 2012. Histological endpoints were ascertained from the clinical database through 2017. We estimated 5-year cumulative risks of cervical intraepithelial neoplasia grades 2 or worse (CIN2+) or grades 3 or worse (CIN3+) by baseline p16/Ki-67 DS and cytology at yearly intervals using Logistic Weibull models. Risks were compared to benchmarks for colposcopy referral and a one-year return interval.

Results

p16/Ki-67 DS-positivity predicted significantly higher cumulative 5-year risks of CIN2+ compared to abnormal cytology (p<0.05). p16/Ki-67 DS-negative women had significantly lower 5-year risks of CIN2+ compared to women with normal cytology (p<0.05). Similar results were observed for CIN3+. In p16/Ki-67 DS-negative women, the risks of both CIN2+ and CIN3+ remained below the colposcopy referral threshold for all 5 years, and crossed the one-year return threshold at 3 years.

Conclusions

Triage with p16/Ki-67 dual stain provides better long-term risk stratification compared with cytology over 5 years. The low risk of cervical precancer in women testing p16/Ki-67 DS-negative permits safe extension of follow-up intervals for 3 years.
AUTOMATED EVALUATION OF DUAL-STAIN CYTOLOGY SLIDES BASED ON DEEP LEARNING (CYTOREADER): CLINICAL EVALUATION IN A LARGE SCREENING PROGRAM

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2Steinbeis Center, Medical Systems Biology, Heidelberg, Germany
3Global Coalition Against Cervical Cancer, Global Coalition Against Cervical Cancer, Arlington, USA
4Kaiser Permanente Northern California, Regional Laboratory, Berkeley, USA
5Albert Einstein College of Medicine, Epidemiology, Bronx, USA

Background and Aims

p16/Ki-67 dual stain cytology (DS) is evaluated for triage of HPV-positive women in cervical cancer screening. We developed a cloud-based digital cytology system comprising whole-slide imaging and automated image analysis of DS slides. We evaluated the clinical performance of CYTOREADER in a large cervical cancer screening program.

Methods

The CINtec Plus assay (Roche) was used to stain 5,045 Surepath slides from HPV-positive women at Kaiser Permanente Northern California. Slides were scanned on a Hamamatsu Nanozoomer. Over 9,000 DS-positive and 11,000 DS-negative cells from a training set of 238 slides were used to develop deep learning classifiers for DS detection. ROC analyses were performed to evaluate optimal cutoffs of DS-positive cells at different likelihoods (range 0-1) of DS-positivity. We evaluated CYTOREADER in comparison to manual DS evaluation in a validation set from 4,807 HPV-positive women. Additionally, we developed an assisted manual evaluation of DS slides ranking DS-positive cells by severity.

Results

At a likelihood of 0.35 and a threshold of 2 positive cells, CYTOREADER achieved equal sensitivity compared to manual reading (88% vs. 90%, p>0.05) with increased specificity (59% vs. 53%, p<0.001). The AUC for detection of CIN3+ was 0.83. At a higher threshold, CYTOREADER equaled the sensitivity and specificity of HSIL cytology.

Conclusions

CYTOREADER surpasses performance of manual evaluation. Both assisted and fully automated DS evaluation allow for faster, more accurate and more reproducible evaluation of DS cytology.
A promising human gene methylation triage classifier for self-sampling HPV positive women

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Background and Aims

Methylation of specific human genes is a promising biomarker for cervical cancer and precancer. We aimed to explore a gene methylation panel to triage self-sampling HPV-positive women.

Methods

A total of 7,128 women aged 30–65 years in China were recruited in 2017. All the participants performed self-sampling and clinician-sampling specimen. Only self-sampling specimen was tested by PCR-based hrHPV genotyping. Women with HPV positivity would be referred to colposcopy and biopsy if necessary. While clinician-sampling specimen was used for cytology and targeted human genes (ASTN1/DLX1/ITGA4/RXFP3/SOX17/ZNF671) methylation assay among self-sampling hrHPV positive women. We compared the clinical performance of human gene methylation panel with cytology as well as HPV 16/18 genotyping.

Results

1,246 hrHPV positive women were included in the final analysis. 1,187, 37 and 22 women were diagnosed with ≤CIN1, CIN2 and CIN3, respectively. At the predefined cutoff, the panel positive rate of human gene methylation was related to the histology severity (17.4% for ≤CIN1, 73.0% for CIN2, 100% for CIN3, p<0.05) and the colposcopy referral rate was reduced to only 20.5%. The PPV for CIN2+ of the panel, cytology (≥ASCUS) and HPV16/18 genotyping was 19.2%, 10.3% and 19.3% with corresponding AUC of 0.828, 0.768 and 0.829, respectively. Besides, the panel showed similar sensitivity (83.1% vs 94.9%, p>0.05) for CIN2+ and higher specificity (82.6% vs 58.7%, p<0.05) than cytology and comparable sensitivity and specificity to HPV16/18 genotyping (83.1% vs 83.1%, 82.6% vs 82.7%, p>0.05).

Conclusions

Human gene methylation analysis was a valuable alternative to cytology and HPV16/18 genotyping for hrHPV triage.
DETECTR: HOW CRISPR-CAS12A MYSTERIES LED TO A HUMAN PAPILLOMAVIRUS DETECTION PLATFORM

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²University of California- San Francisco, Medicine, San Francisco, USA
³University of California- Berkeley, Chemistry, Berkeley, USA

Background and Aims

CRISPR-Cas12a proteins are RNA-guided enzymes that bind and cut DNA as components of bacterial adaptive immune systems. Here we show that RNA-guided DNA binding by Cas12a unleashes indiscriminate single-stranded DNA (ssDNA) degradation. By combining Cas12a ssDNase activation with isothermal amplification, we created a method termed "DNA Endonuclease Targeted CRISPR Trans Reporter (DETECTR)", which achieves attomolar sensitivity for DNA detection. DETECTR enables rapid and specific detection of human papillomavirus in patient samples, thereby providing a simple platform for CRISPR-based, molecular diagnostics.

Methods

Anal sample donors were recruited from the UCSF Anal Neoplasia Clinic, Research and Education Center (ANCRE). After informed consent was obtained, participants had an anal swab inserted into a Thinprep™ vial for anal cytology and HPV testing. DNA was extracted from cell suspension left over after monolayer cytology slides were made and was used for HPV DNA PCR or DETECTR experiments.

Results

We tested 25 human anal swabs previously analyzed by a MY-09/MY-11 PCR-based method for HPV DNA detection. Within one hour, DETECTR accurately identified HPV16 (25/25 agreement) and HPV18 (23/25 agreement) in patient samples containing a heterogeneous mixture of HPV types, with good correlation between the PCR-based intensity and DETECTR signal. These results demonstrate a new platform for CRISPR-based diagnostics, and suggest that DETECTR could detect any HPV DNA sequence with high sensitivity and specificity.
Conclusions

CRISPR-Cas12a proteins unleash non-specific, ssDNase activity upon guide RNA-dependent DNA binding, which can be harnessed for rapid and specific HPV genotype detection in patient samples.
Human papillomavirus (HPV) is a major carcinogen, with an estimated 4.6% of all cancers worldwide linked to the virus in 2008. Historically, HPV-associated cancers have primarily been considered a disease of women, particularly cervical cancer, which is caused by HPV in an estimated 99% of cases. However, the rising incidence of certain HPV-associated cancers is now a significant health concern in men, too. Most notably, recent data suggest HPV-associated oropharyngeal squamous cell carcinoma (OPSCC) incidence is growing far faster than previously predicted.

It is the aim of this talk to give an overview of genomic and epigenomic analyses which aim to better understand the phenotype of these HPV-associated cancers. Molecular alterations will be discussed and linked with interactions between the host genome and viral genome, in particular changes specific for the viral genome will be discussed.

Large-scale molecular research projects in the field of cancer, such as the 100,000 Genomes Project (100k project) in the UK and The Cancer Genome Atlas (TCGA) Project in the US will further advance our understanding of the molecular basis of HPV-associated cancers. Not only will some of these projects include trials in the field of HPV-associated oropharyngeal cancer, thus allowing to link molecular data to clinical outcomes, but also will they inform about the design of screening tools for e.g. persistent, oncogenic oropharyngeal HPV infection and early detection strategies for HPV-associated oropharyngeal cancer.
Background and Aims

Oropharyngeal squamous cell carcinoma (OPSCC) is increasingly being caused by infection with HPV. To study the role of HPV in this cancer we have been using different whole genome sequencing technologies which can reveal the physical status of HPV in each cancer and also genome-wide alterations that occur either due to HPV infection or to the progression of these cancers. Our aims were to compare two different whole genome sequencing strategies and to explore their utility as a clinical tool.

Methods

The two techniques utilized were mate-pair next generation sequencing (MP-Seq) and 30X whole genome sequencing (WGS) on the Beijing Genomics Institute sequencing platform. We then compared the data obtained from these two techniques for their ability to identify sites of HPV integration into the human genome as well other genomic alterations in these cancers.

Results

Using MP-Seq we found that HPV was integrated into the human genome in only 30% of HPV-positive OPSCCs. MP-Seq also detected between 10 and 90 other genomic alterations in each OPSCC. Utilizing 30X WGS (which only costs a total of $600) we could also detect HPV integrations, but could also identify single nucleotide polymorphisms and structural rearrangements in each cancer.

Conclusions

Both of these techniques provide valuable information about the physical status of HPV in each HPV-positive OPSCC. We find that the sites of integration in the human genome are non-random and could be clinically significant. We propose that WGS could be a powerful clinical tool for the management of OPSCC patients.
PROPOSING A NEW SCHEME FOR PAPILLOMAVIRUS CLASSIFICATION

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¹University of Arizona, ACBS, Tucson, USA

Background and Aims

Papillomavirus classification is currently based on nucleotide sequence identity. This nomenclature system was adopted by the papillomavirus community and has facilitated inter-disciplinary collaborations within the field. However, the rise of high-throughput sequencing and metagenomics has resulted in a dramatic increase in the absolute number of viral types, as well as the diversity of this viral family. While it is relatively straightforward to classify novel viruses that fall into existing genera/species, many of these novel viruses are the sole member of a novel species within a novel genus. Therefore, the fast-increasing viral diversity demonstrates a need for an update to the taxonomic classification within the family *Papillomaviridae*.

Methods

We propose to construct a phylogenetic tree based on three of the four ‘core’ viral proteins (E1, E2, and L1), leveraging the appropriate evolutionary models. Next an automated, depth-first algorithm determines the whole-tree distance distribution. Next, starting from a root node a subtree's reliability and distance distribution are calculated. This process is repeated until a subtree that meets the clustering conditions is identified, and the types belonging to that clade are grouped.

Results

The proposed taxonomy scheme classifies >400 papillomavirus types into 25 genera and 62 species, while minimizing disruptions to the accepted classification system. The approach described here appears to be fairly robust to the inclusion of highly diverse viral sequences. In addition, this classification scheme could be applied to many viral families.

Conclusions

We will discuss the strengths and weaknesses of the current classification system and propose steps towards improving the papillomavirus classification system.
Background and aims

We have previously shown that human monoclonal antibodies (hmAb) cloned from vaccinees recognize a diverse set of epitopes on the HPV16 virus surface. We sought to identify characteristics of these antibodies that correlate with epitope recognition.

Methods

Antibody gene segment usage among 57 unique neutralizing hmAb cloned from 4 subjects who had received the H4 Gardasil vaccine were examined to determine if specific sequences correlated with epitope specificity.

Results

Residues on the C-terminal portion of the FG loop were commonly required for neutralization. This epitope was required by all 9 antibodies utilizing the diversity gene segment D3-16*02 (all subjects contributed at least one hmAb), which was significantly more frequent than antibodies with other diversity gene segments. Among those 48 antibodies, 17 (35.4%) required the C-terminus of the FG loop for neutralization (Fishers exact p < 0.001).

In initial testing, we were not able to define the epitope for 19 (33.3%) antibodies. This pattern of reactivity was found in 6 of 7 (85.7%) hmAbs using the heavy chain variable gene (IGHV) segment 2-70 paired with the lambda light chain variable gene (IGLV) 1-40 segment (at least one from three of four subjects). Among hmAbs using other heavy chain variable gene segments, 13 of 50 (26%) had this neutralization pattern (p = 0.004).

Conclusions

We found that antibodies with the D3-16*02 gene segment required a specific epitope on the FG loop for neutralization, and antibodies using IGHV2-70 with IGLV1-40 shared a similar neutralization pattern but the epitope was not defined.
A METHYLOMIC CLASSIFIER FOR HPV-POSITIVE VULVAR LESIONS OVERLAPS WITH ANAL AND CERVICAL CANCER PROGRESSION SIGNATURES

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Background and Aims

Human papillomavirus (HPV) has been implicated in carcinogenesis and is associated with genome-wide epigenetic alterations. We have previously identified methylomic signatures associated with progression of anal (AC) and cervical (CC) cancers from normal mucosa. These signatures can also classify AIN3 and CIN3 as cancer-like or normal-like lesions. We sought to identify an independent methylomic progression classifier for HPV+ vulvar cancers (VC) with comparison to anal/cervical signatures.

Methods

DNA from 45 formalin-fixed paraffin-embedded specimens (15 VC, 17 VIN3, and 13 normal vulvar tissues (NV)) underwent HPV genotyping (SPF10-LiPA25) and genome-wide methylation profiling (Illumina EPIC array). Differentially methylated regions (DMR) were defined by false discovery rate of <0.01 and mean Δβ methylation score >0.3. Partial Least Squares (PLS) method was used to model DMRs between NV and VC.

Results

Forty-three of 45 specimens were HPV+. An 80-gene PLS signature was able to separate VC and NV but also distinguished VIN3 into normal- and cancer-like types (Figure 1). An included HPV-negative VC case was an outlier. Methyloic progression signatures for AC, CC and VC showed a total of 32 overlapping genes between at least 2 of 3 signatures with 7 genes in all (Figure 2). Cross-application of anal, cervical and vulvar signatures demonstrated interchangeability with identical separation of tissue types (Figure 3).
Figure 1. PLS model classification of vulvar tissue types
Conclusions

Distinct methylomic alterations can distinguish between HPV+ NV, VIN3 and VC. Interchangeability of vulvar, anal and cervical progression signatures suggest that HPV-driven oncogenesis is associated with similar methylation events. Our findings have implications for the development of shared early detection and prevention biomarkers.
MOLECULAR CHARACTERIZATION OF CERVICAL CANCERS HARBORING EPISOMAL AND INTEGRATED HPV16 GENOME BASED ON TRANSCRIPTOME PROFILING OF MRNAS AND MiRNAS

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Background and Aims

Heterogeneity in cervical cancers (CaCx), in terms of HPV16 physical status, prompted us to investigate the mRNA and miRNA signatures among the different categories of cervical samples.

Methods

We performed microarray-based mRNA expression profiling and quantitative real-time PCR based expression analysis of some prioritized miRNAs implicated in cancers among HPV negative normal, HPV16 positive normal and HPV16 integrated (pure) CaCx cases or episomal HPV16.

Results

mRNA expression profile differed characteristically between CaCx subtypes for enriched biological pathways. miRNA expression profiles also differed among CaCx cases compared to controls (upregulation – miR-21, miR-16, miR-205, miR-323; downregulation - miR-143, miR-196b, miR-203, miR-34a; progressive upregulation -miR-21 and progressive downregulation - miR-143, miR-34a, miR-196b and miR-203) in the order of HPV-negative controls >HPV16-positive non-malignant samples > HPV16-positive CaCx cases. miR-200a was upregulated in HPV16 positive cervical tissues irrespective of histopathological status. Expression of majority of the predicted target genes was negatively correlated with their corresponding miRNAs, irrespective of the CaCx subtypes. E7 mRNA expression correlated positively with miR-323 expression among episomal cases and miR-203, among integrated cases. miR-181c expression was downregulated only among the episomal CaCx cases and negatively correlated with proliferative target gene, CKS1B, which belongs to “Cell Cycle: G2/M DNA Damage Checkpoint Regulation” pathway.

Conclusions

Thus, CaCx cases harboring integrated and episomal HPV16 are molecularly distinct with strong translational relevance. In fact, availability of a small molecule inhibitor of CKS1B, suggests that drugging CKS1B could be a potential avenue of treating such CaCx cases harboring episomal HPV16 as opposed to those harboring purely integrated HPV16.
Background and Aims

Frequent call-backs, examinations and long waiting time of conventional screening practice contribute to the serious problem of lost to follow-up and lower screening coverage in LMICs. We aim to validate a new “screen-and-treat” strategy by combining self-sampling HPV testing and thermolcoagulation within a single visit to cut costs and streamline screening programs in low-resource settings in China.

Methods

9,526 qualified women aged 30–65 years from rural areas in China were recruited in 2017. All participants performed HPV self-sampling, tested by careHPV and point-of-care PCR HR-HPV DNA testing. HPV-positive women were invited for colposcopy. Punch biopsies were taken under abnormal colposcopy and thermolcoagulation treatment was performed if indicated within the same visit.

Results

For self-collected samples, PCR-based HPV testing showed higher sensitivity (96.7%) and moderately specificity (82.1%) for CIN2+ compared with careHPV testing (72.5%, 86.0%). Women positive for HPV16/18 were 13.2 times more likely to harbor CIN2+ than other HR-HPV types. 96.2% (2032/2112) of women with positive HR-HPV results received colposcopy, 11.0% (224/2032) had abnormal colposcopy and underwent biopsy, and 58.5% (131/224) matched CIN1+ pathological diagnosis. Among women with abnormal colposcopy, 96 women were eligible for thermolcoagulation, and 100.0% underwent thermolcoagulation immediately. Overtreatment rates are 31.9% and 33.3% for women positivity in careHPV and PCR-HPV tests. Triage by HPV16/18 genotyping showed the lowest overtreatment rate (15.2%).

Conclusions

PCR-based self-sampling HPV testing followed by colposcopy and thermolcoagulation within a single visit to hospital is feasible in low-resource areas in China. Immediate treatment for women with HPV16/18 positive might be a practical approach in the future.
DECENTRALISING COLPOSCOPY SERVICES TO PRIMARY CARE CLINICS RAISES ACCESS TO CERVICAL CANCER DIAGNOSIS IN INNER-CITY, JOHANNESBURG, SOUTH AFRICA

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Background and Aims

Objective: To assess whether decentralising colposcopy to a primary care facility in inner-city Johannesburg, South Africa raises access to colposcopy services.

Methods

Design: Before-after study comparing two years before and two years after decentralisation, using clinical records, and laboratory data on cervical cytology and histology.

Setting: Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) has provided colposcopy services for decades. The Hillbrow Community Health Centre (HCHC), located about 3km away, began colposcopy services in 2014.

Participants: Women, aged 18-65 years, who had a colposcopy for cervical cancer diagnostic purposes from 2012-2016 at CMJAH or HCHC.

Results

Results: Pre-decentralisation at CMJAH 910 women had colposcopy (2012-2014). Post-decentralisation (2014-2016), 721 had colposcopy at CMJAH and 399 at HCHC. The number who had a Pap smear at HCHC and then a colposcopy rose three-fold post-decentralisation (113 versus 350). Forty-three complicated colposcopy cases were referred from HCHC to CMJAH. Compared to CMJAH, the median months from Pap smear to colposcopy was 1 month shorter at HCHC post-decentralisation (4.7 versus 5.7 months, p<0.001). Across all three groups, 30.2-33.6% of women had CIN III lesions or carcinoma on colposcopy. The proportion of invalid specimens was similar at CMJAH and HCHC (1.8 to 2.8%). Of 401 women who had an abnormal Pap smear at HCHC post-decentralisation, 267 had colposcopy (66.6%).

Conclusions

Conclusion: Decentralisation decreased the time to diagnosis and reduced the case load for the tertiary hospital. Overall, more women accessed services. Decentralisation did not appear to affect quality of services and this model could be extended to similar settings in South Africa.
IPVC8-0285
STRUCTURED SCIENTIFIC SESSION

STRUCTURED SCIENTIFIC SESSION 4: SCREENING FOR HPV RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

IMPROVING CERVICAL CANCER SCREENING IN CENTRAL AMERICA: THE SCALE-UP PROJECT

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Background and Aims

Since 2014, the Scale-Up project has aimed to improve the quality of cervical cancer screening in Guatemala, Honduras, and Nicaragua by introducing HPV screening tests in predefined areas using self-sampling and providing technical assistance to ministries of health (MOHs). We present the Scale-Up results for 2017.

Methods

PATH engaged key stakeholders at various levels of MOHs to define target areas, algorithms, laboratory locations, and outreach strategies. MOHs offered cervical cancer screening free-of-charge to women aged 30 to 59/64/65 years (respectively) using careHPV® (donated by PATH). Active community-mobilization strategies were implemented. Self-sampling was offered at all target areas in Guatemala and Nicaragua and in a subset of the target areas in Honduras. HPV tests were processed locally. MOHs routinely compiled data on women screened, screening test used, use of self-sampling, age, time elapsed since last screening, and number of eligible women treated. Data was gathered by local partner organizations and jointly analyzed with PATH.

Results

Preliminary data show that in 2017, 126,198 women were screened using HPV tests, achieving an annual coverage in the target areas of 33.9% in Nicaragua, 6.2% in Guatemala, and 13.5% in Honduras. First-time screening was 46.7% in Nicaragua and 27.6% in Guatemala. HPV positivity ranged from 9.7% to 14.3%. Treatment of screen-positive women deemed eligible for treatment ranged from 26.6% to 80.8%.

Conclusions

MOHs have overcome multiple challenges to implement HPV testing, reaching many unscreened women using a self-sampling approach. Local leadership, political, systemic, and policy issues are key in screening-program performance.
Background and Aims

Human papillomavirus (HPV)-based cervical cancer screening strategies are improving screening coverage in low-resource settings, but effective and efficient results delivery remains a challenge. We evaluated cell phone-based approaches for notifying patient of their test results and follow-up plan compared to in-person notification.

Methods

As part of a cluster-randomized trial of HPV testing strategies in Migori County in western Kenya, women could opt to receive test results via text message, phone call, home visit or clinic visit. We examined preferences and predictors of notification method and associations with treatment uptake.

Results

Among the 4,944 women who underwent HPV testing, 1,595 (32%) received results via text message, 1,181 (24%) phone call, 1,563 (32%) clinic visit, and 605 (12%) home visit. Women opting for texts or calls were younger and had higher rates of prior cervical cancer screening, HIV testing, and modern contraceptive use (p<0.001 for all. Women who had a home visit had significantly higher rates of treatment acquisition (47%) than women who opted for text (37%), phone call (38%) or a clinic visit (23%; p<0.001). In a multivariable logistic model controlling for age, prior screening, HIV testing and contraceptive use, clinic visits remained significantly associated with a decreased odds of treatment (0.45, AOR 0.29-0.70) compared to text messaging. Among treated women, there was no significant difference in time to treatment by notification method.

Conclusions

Cell phone-based results-notification strategies were preferred by women with more health seeking behavior; however, HPV-positive women who received results via home visit were more likely to follow up for treatment.
PREVALENCE OF HIGH RISK HPV INFECTION AND E6/E7 ONCOPORTEINS AMONG RWANDAN HIV-INFECTED WOMEN SCREENED FOR CERVICAL CANCER

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Background and Aims

Rates of invasive cervical cancer (ICC) and ICC-related mortality are particularly high in SSA, which also has the highest rates of HIV infection in the world. Over 12 million HIV+ women in SSA are living longer because of ART, only to increase their likelihood of dying from ICC. We are conducting a cervical cancer screening study of ~5,000 HIV+ women, aged 30-54 years, living in Rwanda to compare different screening strategies.

Methods

During the screening visit, a nurse administers a questionnaire on demographics and ICC risk factors and a specimen is collected for HPV testing by GeneXpert, and then VIA and digital imaging are conducted. At colposcopy for screen-positive women, two additional specimens are taken for biomarker evaluations (E6/E7 oncoproteins) followed by rigorous colposcopic evaluation that includes 4-quadrant microbiopsies/biopsies and ECC for those women whose squamocolumnar junction is not entirely visible and/or their lesion extends into the endocervical canal.

Results

By April 2018, we had screened 5,025 women with 3,823 available HPV results. The prevalence of high risk (hrHPV) infection among our study population is 26.4%, with 6.1% HPV16+, 5% being HPV18/45+, and 15.3% other hrHPV+. We found a consistency of HPV DNA positivity compared with E6/E7 positivity with 93% and 90% for HPV16 and HPV18/45 respectively.

Conclusions

HrHPV prevalence in HIV+ women is lower than previous studies indicative of high coverage and compliance with HIV management with ART in Rwanda over time. As expected, E6/E7 positivity is in significant agreement with HPV DNA positivity although the former is more specific.
The incidence and burden of HPV-driven oropharyngeal cancer is expected to increase for decades, thus motivating discussions on possibilities for screening. This talk will addresses issues related to the validity and timeliness of screening for HPV-driven OPC, and raises important questions, highlights deficits in the existing literature, and proposes needed steps in the research agenda.
DETECTION OF IMMUNE CELL MARKERS AND METABOLIC PROFILES IN SALIVA FROM OROPHYRANGEAL CANCER PATIENTS
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Background and Aims
HPV is a predominant cause of oropharyngeal cancers (OPC) in the US. HPV-related OPC incidence is more common in, and rapidly increasing among males. However, immune profiles at the oral cavity in the context of OPC is still largely uncharacterized. To better understand the oral environment in OPC, immune-cell populations, and metabolic profiles were assessed in oral specimens from OPC patients and controls.

Methods
Fifty newly diagnosed OPC patients (35 with oral oncogenic HPV infection), and fifty age-matched controls (8 with oral oncogenic HPV infection) were recruited at the Moffitt Cancer Center. Flow cytometry was performed for innate and lymphocyte markers on CD45⁺ cells in saliva, and on those collected with Orcellex® brushes. Metabolic profiles of saliva supernatants were assessed using ultra-high performance liquid chromatography-tandem mass spectroscopy at Metabolon.

Results
Percentages of CD1a⁺, CD14⁺, CD3⁺, CD56⁺, and CD163⁺ cells within the CD45⁺ gate were reduced in saliva in cases compared to controls (Mann-Whitney test, p < 0.05). Lipid oxidation was elevated in OPC cases, possibly from reduced glycolysis. In addition, a significant increase in 3-hydroxybutyrylcarnitine, aconitate, and 2-methylcitrate was observed (Welch’s t-test, p <0.05), and a trend in reduction of glucose, pyruvate, lactate and glycate in cases.

Conclusions
Our findings suggest that immune cell populations are reduced in OPC cases, which may lead to immune suppression. Furthermore, the increase in lipid oxidation is suggestive of increased oxidative stress. Future studies are needed to confirm findings and delineate the role of these markers in cancer development.
PREVALENCE AND INCIDENCE OF ORAL HPV AMONG SEXUALLY-ACTIVE ADOLESCENT WOMEN RECEIVING THE HPV VACCINE

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Background and Aims

The natural history and epidemiology of oral HPV in vaccinated or unvaccinated sexually active inner-city adolescent women is unknown.

Methods

We conducted a longitudinal study involving repeated collection of oral rinse specimens from 1,259 sexually active girls attending a large adolescent health clinic in NYC between 2007 and 2017 that provides free healthcare and HPV vaccination. Specimens were collected every six months and tested for HPV-DNA using a MY09/MY11-PCR system. Demographic and behavioral data were obtained by risk-factor survey. We assessed differences in incidence and prevalence of over 40 HPV types between vaccinated and unvaccinated subjects using multivariate methods for repeated data.

Results

The median age at enrollment of participants was 18 years (range 13-21). All had practiced vaginal sex with a median age of first vaginal intercourse of 15 years. At enrollment, 21% had not received the quadrivalent HPV vaccine and 51% had received three doses. Participants were followed prospectively (median follow-up=2.15 years) and all eventually received the HPV vaccine. Vaccinated adolescents had a 71% lower oral HPV detection rate for vaccine types (HPV6/11/16/18; OR=0.29, 95%CI:0.09-0.88) compared to unvaccinated adolescents. Incidence of oral HPV vaccine types post-vaccination was 0.72 per 100 person-years (95%CI:0.5-1.1), though the majority of infections were transient with 88% of all incident oral HPV detected clearing within 12 months.

Conclusions

Oral HPV is common in sexually-active inner-city adolescent women. HPV vaccination is associated with a significant decrease in detection of oral HPV vaccine types.
3–12% of healthy adults carry oral HPV-DNA and most infections are transient. Higher prevalence rates have been reported for HIV-infected individuals and HIV-positive patients have an increased risk for oropharyngeal cancer.

Methods

Between 02/2006 and 03/2018, 4183 oral swabs from 925 HIV-positive MSM were collected (median follow-up 57 months). HPV-DNA detection and typing (broad-spectrum PCR/bead-based multiplex-hybridization), HPV-DNA-load determination (type-specific real-time PCRs), and E6/E7-oncogene-mRNA detection (transcription-mediated amplification) were performed.

Results

At baseline, 24.6% of the men carried oral HPV-DNA, and 28.1% (initially HPV-negative) patients acquired new infections within the study period. Within the study period, 45.9% (329/716) of the men who delivered >= 2 swabs were HPV-DNA-positive. 58 different HPV-types were detected. HR-HPV-types were found in 29.2% of patients, with HPV16 being the most frequent HR-type (11.9%). 49.8% (164/329) of ever HPV-positive and 50.7% (106/209) of HR-HPV-positive patients had type-specific HPV-persistence in consecutive samples. 39.6% of those with persistent HR-HPV infections carried HR-types not included in the nonavalent vaccine. 53.9% of the patients with persistent HR-HPV-infections were smokers and smokers had higher HR-HPV DNA-loads than non-smokers (p<0.01). HR-HPV-E6/E7-mRNA was detected in 21.9% of 160 analyzed HR-DNA-positive and in 31.7% of 60 HPV16-DNA-positive samples. 6% of the men had oral HPV-induced lesions, mostly condyloma. Nine patients had oral intraepithelial neoplasias.

Conclusions

(Persistent) HR-HPV infections are frequent in HIV-positive MSM. It might be reasonable to inspect the oral cavity of HIV-positive patients regularly and to reinforce non-smoking recommendations. Vaccines with an extended HPV-type spectrum could be important for this patient group.
TIMING OF HPV TYPE 16 E6 ANTIBODY SEROCONVERSION PRIOR TO OROPHARYNGEAL CANCER (OPC) DIAGNOSIS: ANALYSIS WITHIN 9 COHORTS

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**Background and Aims**

HPV16E6 antibodies are present in >90% of HPV16-driven OPC but nearly absent in controls. To further evaluate time from HPV16 E6 seroconversion to OPC diagnosis, we conducted nested case-control studies in nine cohort studies worldwide, with blood collected up to 40 years prior to diagnosis.

**Methods**

Pre-diagnostic blood samples were tested for HPV16E6 antibodies from OPC cases and matched controls from 9 cohorts with a total base population for sampling exceeding 1.3 million individuals from Europe, North America and Australia. Seroconversion was defined as a change from below to above the predefined assay cutoff for seropositivity (MFI>1000). Average time between blood collection and diagnosis was 11.6 years (IQR: 6-20); 18% of cases contributed serial samples.

**Results**

HPV16 E6 antibodies were present in 0.4% of 5923 controls and 27.5% of 703 cases. OPC cases diagnosed more recently were more frequently seropositive than those diagnosed earlier in calendar time. Increasing time from blood draw to cancer diagnosis decreased HPV16 E6 seropositivity from 38.8% in 214 cases with lag <10 years, 22.1% in 190 cases with lag between 10-20 years, 13.5% of 148 with lag between 20-30 years, and 0% of 24 cases with >30-year lag. Among 47 HPV16E6-seropositive OPSCC cases with >1 sample, 16 seroconverted up to 30 years prior to diagnosis and 31 were HPV16E6 seropositive in all samples.

**Conclusions**

This study shows the immune response to HPV16 infection can occur nearly 30 years in advance of clinical OPC diagnosis.
Therapeutic HPV16 vaccine requires combination treatments to be effective in HPV16-induced cancers

The HPV16 synthetic long peptide (SLP) vaccine elicits strong T-cell responses and was shown to be clinically effective in HPV16+ pre-cancers\(^1,2\) but not in advanced cervical cancer\(^3\). Our in-depth studies revealed different immunological hurdles, including cancer-induced suppressive myeloid cells and checkpoint expression, impairing vaccine efficacy\(^4-6\). Standard chemotherapy transiently normalized the myeloid cell population and provided a window-of-opportunity for SLP vaccines to stimulate strong T-cell immunity and as a result an improved clinical outcome in a multicentre phase 2 study\(^4\). Vaccine-induced T cells express high levels of checkpoint molecule PD-1 which may be counteracted by administration of anti-PD-1 antibodies. Treatment of incurable HPV16+ oropharyngeal cancer patients with nivolumab and the SLP vaccine resulted in approximately twice the overall response rate and overall survival of that reported in patients treated with nivolumab monotherapy\(^7\). In conclusion, therapeutic HPV16 SLP vaccination requires combination with other modalities to overcome the immune suppressive environment within cancer patients.

References

\(^1\)Kenter et al. New Engl. J. Med. 361: 1838, 2009


\(^5\)Welters et al. Clin Cancer Res 24: 634, 2018

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BACKGROUND ANDAIMS

The nonavalent vaccine protects against nine types of HPV (6/11/16/18/31/33/45/52/58), as opposed to four types with the quadrivalent vaccine (6/11/16/18) and two types with the bivalent vaccine (16/18). Following recommendations from national health authorities, several countries have implemented HPV gender neutral vaccination (GNV) programs. This study aims to identify and summarize all available evidence on the cost-effectiveness of national nonavalent HPV vaccination programs in a gender neutral population.

METHODS

MEDLINE, EMBASE, Cochrane CENTRAL, EconLit and NHS EED were systematically searched for cost-effectiveness analyses published in the last 10 years in English that met the pre-set eligibility criteria. The Drummond checklist was used to assess the quality of included studies.

RESULTS

Eight studies, based on four model types, were identified from five countries. The main study characteristics and results for nonavalent GNV versus quadrivalent GNV and/or girls’ quadrivalent vaccination are presented in Table 1. The incremental cost-effectiveness ratio (ICER) did not exceed the respective local willingness to pay thresholds in any of the studies reporting these comparisons (n=3). The ICERs were most sensitive to vaccine cost, discount rate and duration of protection parameters although these remained cost-effective. None of the studies included costs related to work productivity loss.
Conclusions

Across the five countries with published evidence, HPV GNV with a nonavalent vaccine was cost-effective, cost-saving or dominating compared with a gender neutral quadrivalent vaccination or girls’ quadrivalent vaccination. This study supports the continued implementation of HPV vaccination with the nonavalent vaccine on a gender neutral population.

Table 1 Study characteristics and main results

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Model type</th>
<th>Vaccine doses</th>
<th>Currency year</th>
<th>Time horizon</th>
<th>Discount rate</th>
<th>Herd immunity</th>
<th>ICER/QALY 9v CN vs 4v GN</th>
<th>ICER/QALY 9v CN vs 4v girls only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brissos 2016</td>
<td>United States</td>
<td>Individual based transmission dynamic model†</td>
<td>3</td>
<td>USS 2010</td>
<td>70 years</td>
<td>3%</td>
<td>Yes</td>
<td>Cost-saving</td>
<td>NR</td>
</tr>
<tr>
<td>Simms 2016</td>
<td>Australia</td>
<td>Individual based transmission dynamic model‡</td>
<td>2</td>
<td>AUS$ 2013</td>
<td>NR</td>
<td>5%</td>
<td>Yes</td>
<td>NR</td>
<td>Cost-effective, maximal additional cost per dose (9v over 4v): 22.74</td>
</tr>
<tr>
<td>Meinni 2017</td>
<td>Italy</td>
<td>Deterministic, dynamic, population based model‡</td>
<td>2</td>
<td>€ 2014</td>
<td>100 years</td>
<td>3%</td>
<td>NR</td>
<td>10,463</td>
<td>13,341</td>
</tr>
<tr>
<td>Largeron 2017</td>
<td>Germany</td>
<td>Deterministic, dynamic, population based model‡</td>
<td>2</td>
<td>€ 2014</td>
<td>100 years</td>
<td>3%</td>
<td>No</td>
<td>NR</td>
<td>22,987</td>
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<td>Laprise 2016</td>
<td>United States</td>
<td>Individual based transmission dynamic model</td>
<td>2 or 3</td>
<td>USS 2013</td>
<td>100 years</td>
<td>3%</td>
<td>NR</td>
<td>NR*</td>
<td>NR*</td>
</tr>
<tr>
<td>Bouzon 2016</td>
<td>United States</td>
<td>Deterministic, dynamic, population based model‡</td>
<td>3</td>
<td>USS 2015</td>
<td>100 years</td>
<td>3%</td>
<td>NR</td>
<td>16,441</td>
<td>NR</td>
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<td>Dubram 2016</td>
<td>Austria</td>
<td>Age structured compartmental model‡</td>
<td>2</td>
<td>€ 2014</td>
<td>2015 to 2050</td>
<td>3%</td>
<td>Yes</td>
<td>Dominates (vs. 2v/4v)</td>
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<td>Chason 2016</td>
<td>United States</td>
<td>Deterministic, dynamic, population based model‡</td>
<td>3</td>
<td>USS 2013</td>
<td>100 years</td>
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<td>Yes</td>
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2v: bivalent HPV vaccine; 4v: quadrivalent HPV vaccine; 9v: nonavalent HPV vaccine; GNV: gender-neutral vaccination; ICER: incremental cost-effectiveness ratio; NR: not reported; QALY: quality adjusted life-year
† Based on HPV-ADVISE, http://www.marc-brissos.net/HPVadvise-US.pdf
‡ Based on Elbashir E, Dubach E. Impact of vaccinating boys and men against HPV in the United States. Vaccine. 2010; 28(42):6598-6607
* Laprise 2016 compared a 2-dose nonavalent vaccination schedule with no vaccination, and a 3-dose nonavalent vaccination schedule with a 2-dose vaccination schedule. A 2-dose vaccination schedule was shown to be cost-saving compared to no vaccination. A 2-dose vaccination schedule that provides at least 20 years of protection is cost-effective compared to a 3-dose vaccination schedule. However, if a 2-dose vaccination schedule provides less than 20 years of protection or a 3-dose vaccination schedule provides more than 20 years of protection, the 3-dose vaccination schedule yields a substantial increase in QALYs gained.
STRUCTURED SCIENTIFIC SESSION 6: PAPILLOMAVIRUS VACCINES (I.E. NEW DEVELOPMENTS)

THERAPEUTIC/PREVENTIVE HPV VACCINES, AN OLD IDEA WITH SOMETHING NEW: DNA CHIMERIC VACCINES WITH PLANT-DERIVED SIGNAL SEQUENCES

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¹Regina Elena National Cancer Institute, HPV UNIT, Rome, Italy
²ENEA, Department of Sustainability, Rome, Italy

Background and Aims

In previous works, we developed strategies for the production of HPV antigens in plants. Exploiting the signal sequence (ss) of the Polygalacturonase-inhibiting protein (PGIPss) from Phaseolus vulgaris, we targeted the HPV16 E7 protein to the plant secretory compartment. The protein was expressed with a 5-fold change accumulation level compared with the unfused version of the antigen by transient plant expression. Recently, we showed that this PGIPss, fused to N-terminal portion of a HPV16 antigen, was able to modify the antigen compartmentalization / processing also in transfected mammalian cells (HEK-293), promoting its secretion in the culture medium. Thus, in a DNA vaccine formulation, the PGIPss fusion was able to enhance the humoral response to HPV antigens, providing a tool for a HPV DNA preventive vaccine.

Methods

To develop a preventive/therapeutic vaccine, a chimeric construct consisting of L2 (first 200 aa.)-E7 (E7GGG harmless version) of HPV16 was fused to PGIPss and cloned in pVax vector. This DNA vaccine was delivered by electroporation and immunological responses recorded in animal models.

Results

The chimeric PGIPss-L2-E7 construct induced a high titre of both anti-L2 and anti-E7 IgGs, that persisted for at least six months after immunization. Tumor challenge experiments were performed in two mouse models of HPV expressing tumors (TC-1-C57BL/6 and the orthotopic AT84E7luc-C3H). Preliminary results showed a dramatic reduction of tumor growth with the induction of specific antibody and cell-mediated immune responses.

Conclusions

Thus, our chimeric DNA vaccine is a promising tool for preventive-therapeutic vaccination, particularly useful in patients already infected by HPV and in low-income countries.
COMPARATIVE IMMUNOGENICITY OF ONE DOSE OF NONAVALENT AND ONE DOSE OF BIVALENT HPV VACCINE VERSUS TWO DOSES OF NONAVALENT VACCINE

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¹INSPO, Drbst, Quebec, Canada
²CDC, Chronic Viral Diseases Branch, Atlanta, USA

Background and Aims

The immunogenicity of a mixed vaccination schedule with one dose of nonavalent (9vHPV) and one dose of bivalent vaccine (2vHPV) versus two doses of 9vHPV vaccine was evaluated.

Methods

371 girls and boys aged 9-10 years were randomized (1:1) to receive one dose of 9vHPV and one dose of 2vHPV vaccine (in different order) or two doses of 9vHPV (0-6 months). Antibodies to HPV were tested by ELISA in blood samples collected one or six months post-first dose and one month post-second dose.

Results

Post-first dose of 9vHPV all subjects were seropositive to HPV types included in the vaccine; except 1 subject (0.4%) for anti-HPV45. GMTs varied from 4.6 to 75.1 AU(IU)/ml depending on HPV type. Post-first dose of 2vHPV all subjects were seropositive to HPV16 and 18 and 50.0-76.7% were seropositive to 7 types not included in 2vHPV. GMTs varied from 0.3 to 16.7 AU(IU)/ml. Post-second dose all subjects were seropositive to 9 HPV types, independent of vaccines used. Depending on study group and HPV type a 1.2-143-fold increase in GMTs was observed post-second dose. Anti-HPV16 and 18 GMTs were higher in subjects who received two different vaccines. GMTs for the other 7 HPV types were higher in subjects who received two doses of 9vHPV vaccine.

Conclusions

Virtually 100% seropositivity observed after a single dose of 9vHPV and the increase in GMTs to nine HPV types after 2vHPV vaccine given six months post-9vHPV dose suggest the two vaccines might be used in a mixed schedule.
DEVELOPMENT OF NANOVACCINES AGAINST HPV DERIVED CANCERS

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\textsuperscript{1}The University of Queensland, The University of Queensland Diamantina Institute, Brisbane, Australia
\textsuperscript{2}The University of Queensland, Australian Institute for Bioengineering and Nanotechnology, Brisbane, Australia

Background and Aims

Cervical and other anogenital cancers account for 5% of the global cancer burden, largely caused by persistent infection with high-risk human papillomavirus genotype 16 (HPV16). Currently available prophylactic HPV vaccines have the potential to prevent HPV infection but are not effective for treatment of existing HPV infections and associated cancers. Development of HPV-specific immunotherapy has proven challenging due to virus-mediated immuno-suppressive mechanisms. Our aim was to develop a novel potent nano-adjuvant for therapeutic HPV vaccines.

Methods

The potency of designed nano-adjuvant (50 nm in size) was developed and investigated its ability and potency in inducing anti-HPV immunity using established HPV16E7-expressing tumour and E7-expressing skin grafting models in mice.

Results

The developed nano-adjuvant is a pH regulating system and showed enhanced peptide delivery into the cytosolic major histocompatibility I (MHC-I) pathway and subsequent CD8+ cytotoxic T lymphocyte (CTL) responses. This adjuvant has also demonstrated increased generation of reactive oxygen species (ROS), thereby promoting maturation of antigen presenting cells (APCs). When combined with the peptide of the oncoprotein HPV16E7 nano-adjuvant significantly augmented CTL immune responses against E7-expressing solid tumours and skin grafts. It is hypothesised that the intracellular ROS-mediated inflammatory signalling pathway via NLRP3 inflammasome may account for the nano-adjuvant efficacy.

Conclusions

In conclusion, we have developed a novel and potent nano-adjuvant, which encapsulates HPV16E7 peptide for therapeutic HPV vaccines. This research will provide a novel strategy to develop potent therapeutic HPV vaccines. This approach has strong translational value, making significant improvement in the treatment of established HPV infection associated cancers.
Background and Aims

Persistent infection with high-risk human papillomavirus (HPV) is linked to the development of many mucosal-epithelial cancers, however the precise mechanism of infectious viral entry into host cells is not fully understood. Upon initial interaction with target epithelial cells, HPV establishes infection by traversing through a non-canonical endocytic pathway that is independent of clathrin and caveolin, but dependent on the annexin A2/S100A10 heterotetramer (A2t).

Methods

Here, we examine the specific contribution of monomeric annexin A2 vs. A2t in HPV endocytosis, and using HPV as a model, we further characterize the role that A2t plays in protein trafficking.

Results

Specifically, we show that cell surface A2t is not required for HPV attachment, and that in the absence of A2t virions are still internalized through a mechanism independent of clathrin. Without A2t, viral progression from early endosomes to multi-vesicular endosomes is significantly inhibited, capsid uncoating is dramatically reduced, lysosomal degradation of HPV is accelerated, and successful infection by multiple oncogenic HPV types is ablated.

Conclusions

These findings suggest that A2t is a central mediator of high-risk HPV intracellular trafficking post-entry and pre-viral uncoating.
In May 2018, the WHO Director-General made a global call for action towards the elimination of cervical cancer as a public health problem. Key questions that must be addressed to achieve elimination include: 1) **what will be the** cervical cancer elimination threshold, 2) what combination of screening and vaccination strategies can lead to elimination, and 3) when could elimination be reached, for different strategies and countries? Mathematical models are required to examine these questions. In order to help provide guidance to WHO, the Cervical cancer elimination modeling consortium was created, which includes 4 modeling groups. The aim of the work is to examine the key cervical cancer elimination questions, using multiple models to provide greater robustness in predictions and illustrate variability in findings. In the talk, we will present the main approach and findings of the Cervical cancer elimination comparative modeling consortium, which are being used to develop global **plans towards elimination of cervical cancer**.
TIMELINE TO GLOBAL ELIMINATION OF CERVICAL CANCER: PROJECTIONS OF THE IMPACT OF HPV VACCINATION AND CERVICAL SCREENING IN 181 COUNTRIES; 2020-2099
K. Simms¹, J. Steinberg¹, M. Caruana¹, M. Smith¹, J.B. Lew¹, I. Soerjomataram², P. Castle³, F. Bray², K. Canfell¹
¹Cancer Council NSW, Cancer Research Division, Sydney, Australia
²International Agency for Research on Cancer, Cancer Surveillance Section, Lyon, France
³Global Coalition against Cervical Cancer, Gc3, Arlington, USA

Background and Aims

Cervical screening and HPV vaccination programs have been implemented in most high-income countries; however, coverage is low in low-and-middle-income countries (LMIC). We aimed to (i) quantify the impact of increased global vaccination and screening coverage on cervical cancer cases over 2020-2069, and (ii) extend predictions out to 2099 to identify the earliest years by which cancer incidence could drop below the rare cancer threshold (6 per 100,000) and a potential ‘elimination’ threshold (4 per 100,000).

Methods

We performed a statistical analysis of trends combined with a dynamic multi-cohort model of HPV vaccination and cervical screening (‘Policy1-Cervix’) to evaluate the impact of potential future prevention scenarios.

Results

Without further intervention, global cervical cancer incidence is predicted to increase over the period 2020-2069 from 14 to 18 per 100,000, resulting in >45M cases over the period. High-coverage (80-100%) nonavalent vaccination could avert 7.1-8.1M cases over 2020-2069, but more than half would be averted after 2060. Adding twice-lifetime HPV screening would reduce cancer rates sooner and avert an additional 5.7-5.9M cases. Combined screening and vaccination strategies will result in cervical cancer becoming rare from 2040-2045,2050-2055,2060-2065 and 2080-2090 and ‘eliminated’ from 2050-2055,2060-2065,2070-2075 and 2095-2100 for very-high, high, medium and low HDI countries, respectively.

Conclusions

Over 45M women will be diagnosed with cervical cancer in the next 50 years if prevention programs cannot be scaled up in LMIC. Widespread high-coverage HPV vaccination and cervical screening could avert >13M cases in the next 50 years, and eliminate cervical cancer (rates<4 per 100,000) globally by the end of the century.
MODELLED EVALUATION OF THE POPULATION-LEVEL EFFECTIVENESS OF HPV-FASTER IN LOW-RESOURCE SETTINGS AND THE COST-EFFECTIVENESS SCREEN-AND-VACCINATE STRATEGIES IN HIGH-RESOURCE SETTINGS

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¹Cancer Council NSW, Cancer Research Division, Sydney, Australia
²The National HPV Vaccination Program Register, Melbourne, Victoria, Australia
³Victorian Cytology Service, Melbourne, Victoria, Australia
⁴Royal Women’s Hospital, Microbiology and Infectious Diseases, Melbourne, Australia
⁵ICO/IARC Information Centre on Papillomavirus and Cancer, Information Centre on HPV and cancer, Barcelona, Spain
⁶Catalan Institute of Oncology, Cancer Epidemiology Research Program, Barcelona, Spain
⁷Albert Einstein College of Medicine, Department of Epidemiology and Population Health, New York, USA

Background and Aims

High effectiveness (>80%) of HPV vaccination in DNA and sero-negative females aged 26-45 has inspired the concept HPV-FASTER, which aims to accelerate the impact of vaccination in low-middle-income-countries (LMIC) by expanding the recommended age-ranges for vaccination. Existing screening programs in high-income-countries (HIC) allows for ‘screen-and-vaccinate’ scenarios, where vaccination is offered to women who test HPV negative, thereby improving cost-effectiveness. We therefore evaluated the impact of HPV-FASTER for LMIC and screen-and-vaccinate for HIC, using Australia as an example HIC.

Methods

We used an extensively validated platform (‘Policy1-Cervix’) to evaluate the impact of the quadrivalent, bivalent or nonavalent vaccine in women aged 25-45.

Results

For LMIC, HPV vaccination at age 25,35 or 45 years reduced the lifetime risk of cervical cancer mortality by 29-42%, 17-26% and 11-16%, respectively and the number-needed-to-vaccinate to avert a death was 210-308,340-510 and 540-780 (range depends on whether quadrivalent/bivalent/nonavalent was used). Conversely, once-lifetime HPV-testing between ages 30-45 reduced cervical cancer mortality by 42-52%.

For HIC, compared to 5-yearly HPV screening, discharging HPV-negative women from screening after vaccination at ages 25-45 is less effective, regardless of the vaccine used; however, referring vaccinated women to extended 10-yearly screening has similar effectiveness, and was cost-effective provided the cost per-vaccinated-female was <40% the cost per-vaccinated-girl under the adolescent program.

Conclusions
In LMIC, once-lifetime HPV-testing between ages 30-45 is more effective than HPV vaccination for ages 25+. In HIC, vaccinating HPV-negative women, followed by extended interval screening, could be considered provided the vaccine is supplied at a cost-effective price, which is less than the price for 12-year-olds.
Background and Aims

In 2017 the Dutch cervical cancer screening programme has switched from cytology to the HPV-test as the primary screening test, using five instead of seven lifetime screens. The aim of this study was to quantify both costs and the effects of this programme change.

Methods

The microsimulation model MISCAN was used to calculate the number of screening tests, colposcopies, CIN/cancer diagnoses, cancer deaths, life years and QALYs gained and costs for the old and the new screening programme. Costs and effects were discounted annually by 4% and 1.5% respectively. Univariate sensitivity analyses were performed adjusting test characteristics of cytology, costs of screening tests, participation in HPV self-sampling and utility losses for false positive referrals.

Results

The new programme reduces the cervical cancer mortality from 217 to 184 per 100,000 women simulated (-15%) and the incidence from 577 to 503 (-13%) compared to the old programme combined with a cost reduction of 20%, mainly caused by the reduction in number of screening rounds. Although the new programme results in 214% more referrals to colposcopy of women without CIN2+ (from 938 to 2,943 per 100,000 women simulated), it is still more cost effective (€3,497/QALY) than the old programme (€5,741/QALY). The new programme remained more cost-effective in all sensitivity analyses.

Conclusions

Although the new programme increases the amount of unnecessary referrals substantially, causing negative consequences for individual women, it decreases the cervical cancer incidence and mortality and reduces costs on the population level, making it a more cost-effective programme compared with the cytology based programme.
Background and Aims

To inform discussions about clinical guidelines, optimal resource use, and the integration of women’s health interventions with HIV-related care in low-resource settings, we evaluated the cost-effectiveness of different Pap and HPV screening and management algorithms among HIV-infected women in South Africa.

Methods

We modified a mathematical model of HPV infection and cervical disease to reflect co-infection with HIV. The model was calibrated to epidemiologic data from HIV-infected women in South Africa. Clinical and economic data were drawn from in-country data sources. The model was used to project reductions in the lifetime risk of cervical cancer and incremental cost-effectiveness ratios (ICERs) of Pap and HPV DNA screening and management algorithms beginning at HIV diagnosis, at one-, two-, or three-year intervals. Strategies with an ICER below South Africa’s 2016 per capita GDP (US$5,270) were considered ‘cost-effective.’

Results
HPV testing followed by treatment (test-and-treat) at two-year intervals was the most effective strategy that was also cost-effective, reducing lifetime cancer risk by 56.6% (ICER: US$3,010 per year of life saved [YLS]). Other cost-effective strategies included Pap (referral threshold: HSIL+) at one-, two-, and three-year intervals, and HPV test-and-treat at three-year intervals. Pap (ASCUS+), HPV testing with 16/18 genotyping, and HPV test-and-treat with Pap or visual triage of HPV-positive women were less effective and more costly than alternatives (Figure).

Conclusions

Considering per capita GDP as the benchmark for cost-effectiveness, HPV test-and-treat is optimal in South Africa. Where resources are available, HIV-infected women may benefit from screening more frequently than the recommended 3-year interval.
ESTIMATING THE BENEFITS, HARMS AND COST-EFFECTIVENESS OF PRIMARY HPV SCREENING IN THE UNITED STATES: A COMPARATIVE MODELING STUDY

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²Cancer Council New South Wales, Cancer Research Division, Sydney, Australia
³Erasmus Medical Center, Department of Public Health, Rotterdam, The Netherlands
⁴University of Minnesota School of Public Health, Health Policy and Management, Minneapolis, USA
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⁶Massachusetts General Hospital, Institute for Technology Assessment, Boston, USA
⁷University of Minnesota School of Public Health, Epidemiology, Minneapolis, USA

Background and Aims

In order to inform screening guidelines in the United States, we evaluated the benefits, harms, and costs of primary HPV testing compared to current guidelines-based strategies through comparative modeling as part of the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium.

Methods

Four independent microsimulation models were calibrated to U.S. epidemiological data but varied in underlying structures and assumptions about the carcinogenic process. Screening strategies included cytology, HPV testing, and cotesting, varying age to switch from cytology (25, 27, 30 years) and interval (3, 5 years). Full adherence for all strategies was assumed. Outcomes included measures of benefits (cancer reduction, life-years), harms (colposcopies), costs, and cost-effectiveness.

Results

Primary HPV screening was estimated to have higher effectiveness in terms of cancer reduction and life-years than guidelines-based cytology testing when administered every 3 years (in all models) or every 5 years (in 3 of 4 models), irrespective of switch age. In contrast, colposcopy rates and costs were generally higher with 3-year HPV testing (all models), but lower with 5-year HPV testing (in 3 of 4 models). Cotesting strategies were associated with higher colposcopies and costs but similar effectiveness as primary HPV screening; as a result, strategies involving cotesting were not cost-effective. All models identified 5-year HPV testing as the most cost-effective strategy, but the preferred switch age varied across models.

Conclusions

In this comparative base-case analysis involving four independent models, 5-yearly primary HPV screening was found to potentially improve health, reduce harms, and be cost-effective compared to current guidelines-based screening.
EVALUATION OF IMMUNE AND HPV BIOMARKER CORRELATES IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER TREATED WITH ANTI-CTLA4 IMMUNE THERAPY FOLLOWING DEFINITIVE CHEMORADIATION (GOG9929)

Background and Aims

A Phase I nationwide clinical trial examined the safety and efficacy of adjuvant immune modulation therapy with the checkpoint inhibitor ipilimumab (anti-CTLA4) following chemoradiation therapy (CRT) for newly diagnosed locally advanced node-positive cervical cancer. To better understand the mechanism of action and identify novel potentially predictive biomarkers, immunological and viral correlates were assessed before, during, and after treatment.

Methods

HPV-specific T cells were evaluated in a subset of patients by IFNg ELISpot after HPV genotyping. Twenty patients who received CRT and ≥ 2 doses of ipilimumab were evaluable for translational endpoints.

Results

Circulating percentages of CD4+ T cells decreased following CRT while CD8+ T cells increased. Expression of the activation markers ICOS and PD1 increased on both T cell subsets following CRT, which were sustained or increased following ipilimumab treatment. Combined CRT/ipilimumab treatment resulted in a significant expansion of both central and effector memory T cell populations. Genotype-specific E6/E7-specific T cell responses increased post-CRT in 1/8 HPV16+ patients and in 2/3 HPV18+ patients, supporting the hypothesis of HPV antigen release during CRT as a priming event for the immune system. Treatment-induced changes in the immune profile of patients or HPV genotype were not significantly correlated to clinical outcomes (1-yr PFS or OS), likely due to the low number of events.

Conclusions

Our data indicate that adjuvant ipilimumab immunotherapy shows immune modulating activity in women with locally advanced cervical cancer and may be a promising therapeutic option for the
enhancement of anti-tumor immune cell function after primary chemoradiation for this high-risk population.
SEVERE HPV-ASSOCIATED-DISEASES IN PATIENTS WITH IDIOPATHIC CD4-LYMPHOPENIA: A CLINICAL MODEL TO ELUCIDATE HPV IMMUNE-PATHOGENESIS AND NOVEL IMMUNOLOGICAL THERAPIES.

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2NIH, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, USA
3Baylor College of Medicine and Texas Children's Hospital, Center for Human Immunobiology, Houston, USA
4NIH, National Cancer Institute, Bethesda, USA

Background and Aims

Idiopathic CD4-lymphopenia (ICL) is a heterogeneous clinical syndrome characterized by CD4-T-cell counts <300 cells/mL in absence of HIV-infection or any other known cause. Such cellular immunodeficiency can increase the risk of HPV-associated-diseases.

Methods

Prevalence and management of HPV-associated-diseases was evaluated in 89 ICL patients (ICLpts). The immunological evaluation included T-cell phenotyping by multicolor-flow-cytometry and NK-cytotoxicity by Cr51-release-assay.

Results

HPV-associated-diseases were found in 35% (29/84) of ICLpts: 66% (19/29) had mucosal involvement [genital condyloma, low- or high-grade-intraepithelial neoplasia or invasive SCC (iSCC)], while 34% (11/29) had recalcitrant cutaneous HPV-diseases [verruca plana/vulgaris, plantar warts and verrucaous carcinoma (VC)]. Concurrent cutaneous and mucosal involvement was found in 34% (10/29) of ICLpts with HPV-associated-diseases. Mucosal high-grade-intraepithelial-neoplasia and iSCC developed in 34% (10/29) of these patients. Compared to ICLpts without HPV-associated-diseases, ICLpts with HPV-associated-diseases were younger (median age: 35 vs 53 years, p<0.001), had lower CD4-T-cell counts (median: 55 vs 111 cells/mL, p<0.01) and reduced NK-cytotoxicity (median cell-lysis at Effector:Target ratio 50: 15% vs 4%, p=0.02). Interferon-α immunotherapy was used in three ICLpts with severe HPV-associated-disease and led to stable regression of VC in one of these patients. Allogeneic reduced-intensity conditioning bone marrow transplantation (RIC-BMT) was performed in three ICLpts with iSCC and recurrent in-situ-SCC.

Conclusions

Host defenses against HPV rely on adequate T-cell function and NK-cell cytotoxicity. As with other immunocompromised hosts, ICLpts can develop severe and recurrent HPV-associated-diseases. ICL represents a clinical model to characterize the immunological determinants of protection and develop immunotherapies for HPV-associated-diseases. RIC-BMT can be considered in CD4-lymphopenic patients with VC, iSCC or recurrent in-situ-SCC.
EFFICACY OF REBACIN COMBINATION WITH ALA-PDT ON THE TREATMENT OF HPV-INDUCED INTRAEPITHELIAL NEOPLASIA

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¹Peking Union Medical College Hospital, Department of Gynaecology, Beijing, China
²Hainan Province Key Laboratory of Protein Engineering, Protein Engineering, Haikou, China
³SR Life Sciences Institute, Viral molecular biology, Clarksburg, USA

Background and Aims

Objectives: Evaluation of REBACIN combination with 5-aminolevulinic acid-photodynamic therapy (ALA-PDT) in the treatment of genital tract lesion caused by hrHPV infection.

Methods

Methods: 383 patients (Age 20-60) with cervical and/or vaginal lesions caused by hrHPV infection were enrolled, which 323 were CIN patients, including 187 CIN1, 96 CIN2 and 40 CIN3, 48 were VIN patients, including 24 VIN1, 19 VIN2, and 5 VIN3, 12 were positive for both CIN and VIN. All were treated by REBACIN for three months, combining with six-time of ALA-PDT. Two weeks after the treatment, efficacy was evaluated by the analysis of TCT and HC-II HPV test. Patients with both normal TCT and negative HPV were considered as recovery from CIN/VIN, while only normal TCT but positive HPV as effective.

Results

Results: The recovery and effective rate were 71.6% and 86.6% for CIN1 patients, 55.2% and 74.0% for CIN2 patients, while 22.5% and 62.5% for CIN3 patients respectively. The recovery and effective rate were 45.8% and 83.3% for VIN1 patients, 21.0% and 63.1% for VIN2 patients, while 20.0% and 60.0% for VIN3 patients. The recovery and effective rate were 25.0% and 75.0% for patients with both CIN and VIN.

Conclusions

Conclusion: The treatment of REBACIN WITH ALA-PDT demonstrated a potent efficacy both in regression of CIN/VIN and in HPV infection clearance with no recurrence and significant adverse events in the absence of sexual activity after the treatment. These studies suggested that the REBACIN/ALA-PDT treatment could be as a substitute for the physical and surgical therapies such as freezing, laser or LEEP-knife.
Background and Aims

A randomized controlled trial on the safety, acceptability and efficacy of a new cordless, rechargeable, hand-held thermal ablation (TA) technique for the treatment of cervical pre-cancerous lesions is underway in Lusaka, Zambia.

Methods

VIA screen-positive women eligible for ablative treatment are randomized to receive TA, cryotherapy or LLETZ. Side-effects, pain and client satisfaction are scored and recorded. Samples for HPV DNA testing are collected at baseline and follow-up. Treatment efficacy is based on VIA and HPV status at
6 month follow up. The PPV of VIA was evaluated using the histology of LLETZ specimens.

Results

Hitherto, 454 (61%) of 750 targeted women have been randomized (154, 147 and 153 in TA, cryotherapy and LLETZ arms, respectively). The proportion reporting moderate to severe pain/cramps during treatment was lower in the TA than cryotherapy (5.2% vs 15.1%) or LLETZ (5.2% vs. 6.6%) arms. Over 96% reported least pain (scores 1-3) and 98% highly satisfied (scores 7-9) with and willing
to recommend the treatments. Treatment success rates assessed by repeat VIA at 6 months were 71%, 68% and 78% in the TA, cryotherapy and LLETZ arms, respectively. These rates were lower among all the treatment arms compared to that reported earlier, likely due to the high HIV positivity (56%) in the study population. HPV follow up, to date, is too limited to be used as a determinant of treatment efficacy.

Table 1: Treatment success rates at 6 months follow-up after treatment (disease clearance based on follow-up VIA results alone)

<table>
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</table>

VIA: visual inspection with acetic acid; LLETZ: Large loop excision of the transformation zone; HIV: human immunodeficiency virus; HPV: human papilloma virus; * Based on VIA results at 6 months follow-up
Table 2: Histology findings at baseline in the LLETZ arm

<table>
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<tr>
<th></th>
<th>Women treated n</th>
<th>Women with histology report n (%)</th>
<th>Normal n (%)</th>
<th>CIN 1 n (%)</th>
<th>CIN 2 n (%)</th>
<th>CIN 3 n (%)</th>
<th>CIN 2/3 n (%)</th>
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<tr>
<td>Overall</td>
<td>153</td>
<td>95 (62.1)</td>
<td>56 (38.0)</td>
<td>14 (14.7)</td>
<td>10 (10.5)</td>
<td>15 (15.8)</td>
<td>25 (16.4)</td>
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<td>Age (years)</td>
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<td>25-29</td>
<td>52</td>
<td>32 (61.5)</td>
<td>21 (56.2)</td>
<td>4 (13.9)</td>
<td>3 (9.4)</td>
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<td>30-39</td>
<td>63</td>
<td>38 (60.3)</td>
<td>20 (52.6)</td>
<td>4 (10.5)</td>
<td>6 (15.8)</td>
<td>8 (21.1)</td>
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<td>40+</td>
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<td>3 (12.0)</td>
<td>4 (16.0)</td>
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<td>Negative</td>
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<td>29 (74.4)</td>
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<td>Positive</td>
<td>79</td>
<td>51 (64.6)</td>
<td>23 (45.1)</td>
<td>5 (9.8)</td>
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<td>6 (23.1)</td>
<td>8 (30.8)</td>
<td>14 (53.8)</td>
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<td>25 (64.1)</td>
<td>11 (44.0)</td>
<td>5 (20.0)</td>
<td>4 (16.0)</td>
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<tr>
<td>Negative</td>
<td>64</td>
<td>42 (65.6)</td>
<td>24 (57.1)</td>
<td>11 (26.2)</td>
<td>3 (7.1)</td>
<td>4 (9.5)</td>
<td>7 (16.7)</td>
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<tr>
<td>Positive</td>
<td>85</td>
<td>50 (58.8)</td>
<td>30 (60.0)</td>
<td>3 (6.0)</td>
<td>7 (14.0)</td>
<td>10 (20.0)</td>
<td>17 (34.0)</td>
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</table>

LLETZ: Large loop excision of the transformation zone; CIN: cervical intraepithelial neoplasia; HIV: human immunodeficiency virus; HPV: human papilloma virus

Conclusions

This pilot phase demonstrates the new TA device is extremely safe and highly acceptable. TA efficacy will be further confirmed at trial end.
 HOW COULD THERAPEUTIC HPV VACCINES BE USED IN CLINICAL PRACTICE? PREDICTED IMPACT OF THERAPEUTIC VACCINATION IN A CLINICAL SETTING.

K. Simms1, M. Caruana1, M. Smith1, I. Frazer2, K. Canfell1
1Cancer Council NSW, Cancer Research Division, Sydney, Australia
2The University of Queensland, Faculty of Medicine, Brisbane, Australia

Background and Aims

A phase 2b trial found that 3 doses of a therapeutic vaccine (VGX-3100) can induce an additional 20-30% probability of regression of HPV16/18-related CIN2/3 within 36 weeks, compared to spontaneous rates, and that the infection was also cleared in most regressed cases. We aimed to determine the impact of offering women aged <35 years therapeutic HPV vaccination instead of precancer treatment, using Australia as an example setting that has implemented primary HPV testing with partial genotyping.

Methods

We used a validated model of HPV transmission, cervical cancer natural history and screening ('Policy1-Cervix') coupled with a model of obstetric outcomes to evaluate the impact of therapeutic vaccination. We modelled 5-yearly HPV screening with partial genotyping for women aged 25-74, and assumed women testing HPV16/18-positive were referred to colposcopy and - once cancer was ruled out - offered therapeutic vaccination with one-year follow-up if aged <35 years. We assumed the therapeutic vaccine induced an additional 20-30% chance of complete viral clearance compared to spontaneous rates for HPV16/18-associated HPV/CIN1/CIN2/CIN3.

Results

Therapeutic vaccination for all women aged <35 years who test HPV16/18-positive at a routine test would result in an additional 27-33 cervical cancer cases and 5-6 cervical deaths in the lifetime of a cohort of 100,000 women, but 1,600-1,900 fewer women would receive precancer treatment. Consequently, 135-148 preterm deliveries and 127-140 low birth weight events would be averted.

Conclusions

Offering therapeutic HPV vaccination to women under age 35 could avert a substantial number of precancer treatments and avert adverse obstetric outcomes, but cancer rates could increase as a consequence.
IPVC8-0251
STRUCTURED SCIENTIFIC SESSION

STRUCTURED SCIENTIFIC SESSION 9: BOOSTING THE IMMUNOLOGICAL RESPONSE

T-REGULATORY CELLS IN RESPIRATORY PAPILLOMAS EXPRESS TIGIT AND ARE FUNCTIONALLY ACTIVE DESPITE BEARING THE T-CELL "EXHAUSTION" MARKER PD-1.

J. DeVoti¹, F. Lam¹, A. abramson¹, B. Steinberg¹, V. Bonagura¹
¹Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, The Feinstein Institute for Medical Research, Manhasset- New York, USA

Background and Aims

Respiratory papillomas, caused by HPV6/11 infection, are not cleared by adaptive T-cell responses. Previously we demonstrated that papillomas are enriched with CD4+/CD25+/Helios-/Foxp3+ induced T-regulatory cells (iTregs) that express PD-1, but are functionally active by suppressing anti-CD3/CD28-induced, PBMC proliferation. We also reported that natural killer (NK) cells enriched in papillomas fail to lyse K562 cells. This suggests that the micromilieu in papillomas is strongly immunosuppressive. New Treg markers, recently described, identify a Treg subset that suppresses both innate and adaptive immunocytes. We have identified and characterized these iTregs in respiratory papillomas.

Methods

Biopsies of papillomas were manually minced and filtered to obtain single cells. CD4+/CD25+ lymphocytes were obtained by magnetic isolation (Miltenyi), stained for CD4, CD25, Foxp3, CCR8, Tigit, CD8 and PD1 and analyzed by flow cytometry. Total Treg mRNA was extracted and quantified by qPCR for expression of IL2RA, FCRL3, CD96, CD226, TGFB1, Helios, and IL-10. iTreg inhibitory function was measured by co-culture with innate or adaptive immunocytes.

Results

The CD4+/CD25+ Foxp3+ Tregs from papillomas also express PD1, Tigit, CCR8, IL2RA, FCRL3, CD96 and CD226. They do not express Helios, the thymus-derived, natural Treg (nTreg) marker. Therefore all or nearly all Tregs in papillomas are iTregs. CD8+ cells in the papillomas also expressed these markers. Both populations were able to suppress innate and adaptive immune function, demonstrating that they function as Tregs.

Conclusions

RP iTregs co-express Tigit and FCRL3, but not Helios (thymus-derived, nTreg marker). >98% of these iTregs are CD4+, CCR8+, Tigit+, and PD-1+ T-cells that function as suppressor Tregs.
DEFECTIVE DENDRITIC CELL ACTIVATION AND ANTIGEN PRESENTATION IN HUMAN PAPILLOMAVIRUS 16 E7 TRANSGENIC MICE.
A. Bashaw¹, I. Frazer¹, G. Leggatt¹, J. Chandra¹
¹Faculty of Medicine- Diamantina Institute- The University of Queensland- Brisbane- Queensland- Australia, Immunology, Brisbane, Australia

Background and Aims

Cervical cancer caused by human papillomavirus (HPV) is one of the leading causes of morbidity and mortality among women worldwide. The virus infects basal keratinocytes and persistent high-risk HPV infection together with an elevated level of E6 and E7 oncoproteins associates with malignancy. As a model of HPV-mediated precancers, we have utilized K14E7 transgenic mice which express HPV16 E7 oncoprotein in keratinocytes and as a result display epithelial hyperplasia and suppressed local immune responses.

Methods

We investigated the role of HPV16 E7-induced hyperplasia on dendritic cell activation and CD4 T cell priming using flow cytometry.

Results

DCs from the epidermis and skin draining lymph nodes of K14E7 mice displayed significantly reduced MHCII expression compared to C57BL/6 mice. Using FITC skin sensitization or intradermal protein/adjuvant immunisation we demonstrated that antigen exposed K14E7 DCs were incompetent to up-regulate MHCII and the co-stimulatory molecule CD86. Skin-resident K14E7 DCs showed significantly reduced capacities to take up antigens. After intradermal protein/adjuvant immunisation we observed no significant difference in the proliferation of adoptively transferred antigen-specific CD4+ T cells, but IFNγ-secretion by CD4 T cells in skin-draining lymph nodes of K14E7 mice was impaired compared to C57BL/6 controls.

Conclusions

In conclusion, DCs in K14E7 skin are defective in antigen uptake, activation, and CD4 T cell priming, highlighting the effect of HPV16 E7-expressing dysplastic skin in the prevention of DC activation and CD4 T cell responses. This finding widens our understanding on HPV-mediated immune modulation and its potential inhibiting impact on dendritic cell maturation and generation of T cell help.
HPV8 E2 SYNERGIZES WITH C/EBPβ TO INDUCE S100A8/A9 PROTEINS CREATING A PRO-TUMORIGENIC INFLAMMATORY MICROENVIRONMENT

M. Podgórska¹, M. Oldak¹, A. Marthaler¹, A. Fingerle¹, B. Walch-Rückheim¹, S. Lohse¹, C.S.L. Müller², T. Vogt¹, M. Ustav³, A. Wnorowski¹, M. Malejczyk⁴, S. Majewski⁴, S. Smola¹

¹Saarland University, Virology, Homburg, Germany
²Saarland University, Dermatology, Homburg, Germany
³University of Tartu, Institute of Technology, Tartumaa, Estonia
⁴Medical University of Warsaw, Dermatology and Venereology, Warsaw, Poland

Background and Aims

Persistent genus β-HPV infection is a major co-factor for non-melanoma skin cancer in patients suffering from epidermodysplasia verruciformis (EV). There is evidence that HPV8 actively suppresses epithelial immunosurveillance by interfering with the recruitment of Langerhans cells, which may favor viral persistence. Mechanisms how persistent HPV8 infection promotes the carcinogenic process are, however, less well understood.

Methods

We used skin biopsies from EV patients, organotypic 3D-cultures and retrovirally infected primary human keratinocytes to study the impact of HPV8 on the regulation of inflammatory responses.

Results

We demonstrate that skin lesions of EV-patients are massively infiltrated with CD15⁺ granulocytes and we observed a very strong expression of the pro-inflammatory S100A8 and S100A9 proteins in suprabasal layers of lesional epidermis. Notably, HPV8 oncoproteins E6 and E7 rather suppressed S100A8/A9 expression, while the viral transcription factor E2 strongly enhanced S100A8/A9 up-regulation in primary human keratinocytes. A tremendous up-regulation of both S100 proteins was observed, when minute amounts of the differentiation-associated transcription factor C/EBPβ were co-expressed together with HPV8 E2. This confirmed our previous observation that C/EBPβ interacts and functionally synergizes with the HPV8 E2 protein in differentiation-dependent gene expression. Potent synergistic up-regulation of S100A8/A9 was seen at transcriptional and protein levels. S100A8/A9 containing supernatants from keratinocytes co-expressing HPV8 E2 and C/EBPβ significantly induced chemotaxis of granulocytes in migration assays supporting the relevance of our finding.

Conclusions

In conclusion, our data suggest that the HPV8 E2 protein actively contributes to the recruitment of myeloid cells into EV-skin lesions, which may support chronic inflammation and progression to skin cancer.
ROLES OF FC DOMAIN AND EXUDATION IN L2 ANTIBODY-MEDIATED PROTECTION AGAINST HUMAN PAPILLOMAVIRUS

1Johns Hopkins University, Pathology, Baltimore, USA
2Taipei Medical University, College of Medical Science and Technology, Taipei, Taiwan R.O.C.
3National Institutes of Health, National Institute of Child Health and Human Development, Bethesda, USA

Background and Aims

Our aim was to address how systemically administered L2-specific antibodies prevent human papillomavirus (HPV) infection of the genital tract in a mouse challenge model.

Methods

We generated neutralizing monoclonal antibodies (MAbs) WW1, a rat IgG2a that binds L2 residues 17-36 (like mouse MAb RG1), and JWW3, a mouse IgG1 derivative of Mab24 specific to L2 residues 58-64.

Results

By Western blot, WW1 recognized L2 of 29/34 HPV genotypes tested, compared to only 13/34 for RG1, and 25/34 for JWW3. WW1 IgG and (Fab')2 bound HPV16 pseudovirions similarly, but whole IgG provided better protection against HPV vaginal challenge. Passive transfer of WW1 IgG was similarly protective in wild type and FcRn-deficient mice. Local microtrauma, which is required for genital infection and induced by either brushing or nonoxynol-9 treatment, released serum IgG in the genital tract, suggesting Fc-independent exudation. Depletion of neutrophils and macrophages reduced protection of mice upon passive transfer of whole WW1 or JWW3 IgGs. Similarly, IgG-mediated protection by L2 MAbs WW1, JWW3 and RG1 was reduced in Fc-receptor knockout compared to wild type mice. However, in vitro neutralization by WW1 IgG was similar in TRIM21 knockout and wild type cells indicating that the Fc does not contribute to antibody-dependent intracellular neutralization (ADIN).

Conclusions

The Fc domain of L2-specific neutralizing IgGs is not active for ADIN, but it opsonizes bound extracellular virions for phagocytes in protecting mice from intra-vaginal HPV challenge. Systemically administered neutralizing IgG can access the site of infection in an abrasion via exudation without need for FcRn-mediated transcytosis.
REGULATION OF EXPRESSION AND RELEASE OF INTERLEUKIN-36Γ (IL36Γ) IN NORMAL KERATINOCYTES AND RESPIRATORY PAPILLOMA CELLS

C. Papayannakos1, D. Zhu2, A. Rana2, L. Blanc3, J. Devoti4, A. Abramson5, B. Vincent4, B. Steinberg2

1Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Oncology, Manhasset- NY, USA
2The Feinstein Institute for Medical Research, Oncology, Manhasset- NY, USA
3The Feinstein Institute for Medical Research, Autoimmune- Musculoskeletal and Hematopoietic Diseases, Manhasset- NY, USA
4The Feinstein Institute for Medical Research, Immunology and Inflammation, Manhasset- NY, USA
5Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Otolaryngology and Communicative Disorders, New Hyde Park - NY, USA

Background and Aims

TLR stimulation induces expression and release of soluble IL36γ, a cytokine that promotes both inflammation and wound healing, in normal keratinocytes. IL36γ is constitutively expressed in HPV6/11-induced respiratory papillomas, but soluble secretion is suppressed. Our aim was to determine the regulation of IL36γ in normal and papilloma cells.

Methods

IL36γ expression and release were studied in normal human foreskin keratinocytes (HFKs) stimulated with poly(I:C) (TLR3-agonist), flagellin (TLR5-agonist), or solvent, ± select inhibitors, and analyzed at 24 and 48 hrs for expression by western blot. Conditioned medium was analyzed at 72 hrs by ELISA for soluble secretion, and by ultracentrifugation, density gradient centrifugation and western blot for small extracellular vesicles (EVs).

Results

The transcription factor Nrf2 mediates poly(I:C)-induced IL36γ expression in HFKs, while p38 (constitutively active in papilloma cells) mediates flagellin-induced expression. Inhibiting NF-κB, also constitutively active in papilloma cells, had no effect on IL36γ expression. EVs from both poly(I:C) treated and flagellin treated HFKs (density 1.09-1.11 g/mL), are positive for ALIX, TSG101, Hsc70, and Flotillin-1, but only EVs from poly(I:C)-treated cells contain IL36γ. IL36γ+ EVs track primarily with Hsc70 and the autophagosome marker LC3-II rather than TSG101. Papilloma cells contain much less LC3-II than normal larynx keratinocytes, and preliminary results suggest they release little IL36γ+ EVs.

Conclusions

IL36γ expression and release are differentially regulated depending on the TLR stimulus, and provide a novel example of the selective packaging of a cytokine as vesicular cargo. These results guide studies in progress into the impaired release of this constitutively-expressed cytokine from papilloma cells.
High-risk human papillomavirus (HPV) infection is involved in the development of anogenital cancers. To understand the immunological consequences of chronic HPV infection in pre-cancer and cancer, we used RNA-sequencing to examine transcriptomic changes that is associated with immune cell infiltration, regulatory cytokine expression and immunosuppression. This is performed using a transgenic mouse model expressing HPV E7 oncoprotein in keratinocytes, modelling skin epithelial pre-malignancy (K14E7). We observed similar enrichment of transcriptome profiles between human CIN3 lesions and K14E7 skin. To separate the effects found in an admixture of cells from a bulk sample, we performed single-cell RNA sequencing on immune cells derived from E7-expressing and normal control murine skin. We sequenced 12,413 antigen-presenting cells sorted from the skin of the K14E7 mice and wild-type controls. We found that 6748 cells (~54%) were expressing Langerhans cell (LC) related-genes such as Cd207 and Epcam. Upon closer inspection, there were only 1190 (~17%) LCs in the K14E7 group. Further, the K14E7 LCs displayed reduced expression of Cd207 and several genes encoding the major histocompatibility complex II (MHCII), an important APC maturation marker. Clustering analysis revealed 7 sub-clusters of LCs and the K14E7 LCs constituting 90% of one of the sub-clusters. Differential gene expression testing, gene network analysis and pseudo-time trajectory analysis suggests that the K14E7 LC subcluster are in a state of reduced maturity, potentially enacting immune suppressive function in the tissue environment. Loss of LC maturation as a result of keratinocyte hyperproliferation may be an important feature that is exploited by HPV to escape immune surveillance.
HPVs can cause tumors, but also life-long latent infections that can be reactivated to cause recurrent disease. In most individuals either HPV remains latent or cells with activated virus are quickly eliminated by the immune system. Patients with RRP have frequent regrowth of papillomas following surgical removal - requiring surgery every 3-4 weeks to maintain an airway in severe disease. Thus, we have asked whether people with RRP have a defect in HPV-specific immune responses. We previously reported that RRP patients have a biased adaptive immune response to HPV-specific antigens, and papilloma tissues are markedly enriched in functional Tregs that express a number of inhibitory molecules. Genetic profiling of these patients shows enriched prevalence of some HLA Class II alleles and absence of others, and they are also more likely to lack a subset of activating KIR alleles, which could impair NK function. Most recently, we have found that innate immune responses are also impaired in RRP, driven in part by the constitutive expression of PGE\textsubscript{2} in these airway of these patients.

We conclude that patients with active RRP fail to mount an effective immune response to activation of latent HPV 6/11. Therapies to overcome this defect could significantly improve or cure this disease.
Recent advances in immunotherapeutics are having a major impact on management and outcomes of several cancer types, also including virus-driven tumors. Despite the success of immune checkpoint inhibitors, a large number of patients treated with these innovative drugs do not benefit from therapy. Early research indicates that a therapeutic combination of cancer vaccines with checkpoint inhibitors may lead to synergistic effects and higher response rates than monotherapy. Nevertheless, cancer vaccines of high potency and antigen-specificity are not available yet due to the limited efficacy of current strategies to target antigen and adjuvants to cross-presenting dendritic cells (DCs), the critical antigen presenting cells required to generate therapeutically effective anti-tumor immune responses. To overcome these limitations, we have developed a versatile antigen delivery platform targeting cross-presenting DCs in vivo with the aim to improve antigen-specific immunotherapy of virus-driven and virus-unrelated tumors. By preparing of a solid-in-oil-in-water double emulsion through sequential reagent addition, we developed a tailored nanoemulsion (TNE), which was functionalized to target Clec9A (Clec9A-TNE), a DC-specific endocytic receptor expressed by cross-presenting CD103+ and CD8+ DCs and plasmacytoid (p)DCs in mice and BDCA3+/CD141+ DCs in humans. Clec9A-targeting TNEs are stable in physiological environments and after i.v. injection in mice, they are selectively taken up by CD8+ DCs and pDCs in spleen and tumor bed. TNEs traffic to both early endosomes and lysosomes, essential prerequisite for an efficient antigen processing and presentation through MHC class I and II pathways. Clec9A-targeting TNE encapsulating a reference antigen (ovalbumin) without adjuvant targeted and activated cross-presenting DCs and promoted antigen-specific CD4+ and CD8+ T-cell proliferation, cytotoxic T-cell activity and antibody responses in vivo.

To exploit the tumour “mutanome” with our TNE platform, we have developed a functional assay to rank immunogenicity of individual neo-epitopes using the murine B16-F10 melanoma as a model. Four weekly i.v. injections of Clec9A-targeting TNEs loaded with a functionally selected pool of neo-epitopes strongly inhibited the in vivo growth of the highly aggressive and poorly immunogenic B16F10 melanoma cells and induced strong epitope-specific IFN-g T-cell immunity.

The therapeutic efficacy of a Clec9A-targeting TNE-based vaccine was investigated in mice transplanted with the TC1 tumor cells, derived from primary lung epithelial cells co-transformed with the HPV-16 oncoproteins E6 and E7 and c-Ha-ras oncogenes. Weekly vaccination with Clec9A-targeting TNE loaded with recombinant E6 and E7 proteins markedly inhibited the growth of TC1 tumors, whereas standard s.c. vaccination with the same proteins in combination with CpG as
adjuvant had only limited effects. These therapeutic effects were associated with a marked increase in the number of antigen-specific T cells in the blood of mice treated with E6/E7 loaded Clec9A-targeting TNEs.

Versatile, personalized, antigen-specific cancer vaccines are a long-sought therapeutic strategy in cancer immunotherapy. Clec9A-targeting nanoemulsions represent such a platform to deliver recombinant viral or tumor antigen proteins or neo-epitope peptides specifically to cross-presenting DCs in vivo. This platform can fully exploit the immunogenicity of viral antigens and that of the neo-antigen repertoire of individual tumors, thereby improving the feasibility and efficacy of antigen-specific cancer immunotherapy.
Cervical cancer is an important public health problem in the LMICs. GLOBOCAN 2018 has shown declining trends but the incidence and mortality rates are still far in excess of what can be achieved by universal HPV vaccination and cervical screening. In India, Sri Lanka and Bhutan, efforts are on to implement a national screening program that is effective, feasible, acceptable, affordable and quality assured. Although human papillomavirus (HPV) testing is the method of choice, it is not yet affordable for widespread implementation in the national programs of these countries. In India, all three methods, namely, HPV testing, Pap smear and VIA (visual inspection with acetic acid) are available in private clinics, but in the national program, VIA has been selected being the affordable pragmatic method. It has currently been rolled out in 150 districts. In Bhutan too, VIA is being used. In Sri Lanka, cytology forms the basis of the screening program but quality assurance and coverage are a challenge. HPV testing is being tried out in pilot programs.

Improving participation in screening programs is a major challenge. Compliance of screen positive cases with colposcopy and biopsy and later for treatment of lesions is also a concern. Screen-and-treat programs with a single visit approach have therefore been proposed in the Indian program. Portable colposcopes have been developed to allow screening in the field. Experience with these devices will be presented. Health workers can be trained to use these devices to capture and transmit images for expert review. This can reduce both the dropout rate and risk of over-treatment.

The World Health Organization (WHO) has recently announced a call for elimination of cervical cancer. It is expected that by 2030, 70% of women between 35 and 45 years will have been screened once or twice by HPV testing and all positive cases would be appropriately managed. The availability of an affordable HPV test can dramatically change the paradigm with incorporation of techniques like self-sampling to improve coverage and compliance. Increased awareness about cervical cancer, its highly preventable nature and easy options of treatment of precancerous lesions will improve uptake and compliance and lead to this goal.

Acknowledgements: Deepa Gamage (Sri Lanka), Ugyen Tshomo (Bhutan)
Papua New Guinea (PNG) has among the highest estimated burdens of cervical cancer globally, but lacks national programs for cervical screening or human papillomavirus (HPV) vaccination. Following the disappointing performance of visual inspection of the cervix with acetic acid (VIA) for cervical screening in this setting, we evaluated a novel test-and-treat screening algorithm based on point-of-care (POC) HPV-DNA testing of self-collected vaginal specimens followed by same-day cervical ablation by cryotherapy or thermocoagulation. Self-collected specimens tested at POC on the GeneXpert platform (Xpert HPV; Cepheid, Sunnyvale, CA) had comparable performance to laboratory-based assays for the detection of HPV and underlying high-grade cervical disease. This approach represents a promising new screening strategy for under-served women in PNG and other high-burden, low-income countries worldwide.
Primary prevention of all HPV-induced cancers by vaccination must be globally the ultimate goal. It is achievable and this is the good news. But additional research, commitment, funding and time are required. While high and some middle income countries (HMIC) can cope with 2 or 3 dose schedules and even discuss the potential for boosters during reproductive years, low income countries need a single dose regime which offers 'life-time' protection.

Until then, secondary prevention by screening is required for the generation of women too old for vaccine, but at highest risk of developing cervical cancer. Again, the screening methods adopted by HMIC have little relevance for the poorest countries, yet the medical and scientific worlds have been slow to accept that alternative models, potentially with lesser efficacy, can be made to work and delivered in population-based programmes to reduce the current and immense challenge of cervical cancer.

This talk will cover selected primary and secondary prevention strategies to show how far along the road we have come.
IMPLEMENTATION OF TWO DOSE, NONAVALENT, GENDER NEUTRAL VACCINATION IN NEW ZEALAND

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Implementation of a two dose, nonavalent HPV, gender neutral vaccination in New Zealand

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**Background:** In September 2008 New Zealand introduced HPV4 (Gardasil) on the national schedule for adolescent women aged 12 years with a catch up programme for those up to 20 years of age.

On 1 January 2017 HPV was replaced with HPV9 (Gardasil9), with a two dose regime for under 15 years of age, and extended to males as well as females aged from 9 years to 26 years. Delivery is primarily through schools at year 8 with catch up in primary care.

**Results:** Coverage rates for young women at the age of 12 for the first three years of the programme was initially around 52% with lower rates for the catch up programme. Since 2012 coverage has steadily increased to 65 - 67% fully immunised for 12 year olds, with variability by district health board. There has been no formal evaluation of the effectiveness of the programme for young men, but to date the uptake is almost identical to women.

**Findings:** NZ provider feedback on the strengths and the challenges for the current programme will be presented.
Background

The 9-valent HPV vaccine (9vHPV) was licensed in the United States in 2014 and recommended for vaccination in 2015. We describe the safety monitoring findings for 9vHPV from the two major post-marketing surveillance systems in the United States: the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD).

Methods:

In VAERS, we searched for U.S. reports of adverse events (AE) following 9vHPV between December 2014 and December 2017. We conducted descriptive analyses, estimated AE reporting rates, and performed clinical review of pre-specified conditions. In VSD, we conducted weekly near-real time monitoring of 11 pre-specified health conditions (Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, anaphylaxis, stroke, venous thromboembolism, appendicitis, pancreatitis, seizures, syncope, allergic reaction, injection site reactions) among 9-26 years olds between October 2015 and October 2017, and performed sequential analyses to detect associations.

Results:

From December 2014 and December 2017, approximately 29 million 9vHPV doses were distributed in the United States. VAERS received 7,244 reports following 9vHPV; 31% in females, 22% in males, 47% sex missing/unknown. 97% of reports were non-serious; dizziness (8%) and syncope (7%) were most commonly reported. Approximately 900,000 9vHPV doses were administered in the VSD; statistically significant findings (i.e. signals) were detected for syncope and local reactions, both expected AEs, as well as for allergic reaction, pancreatitis, and appendicitis, which were not confirmed after further evaluation.

Conclusions:

The 9vHPV safety profile to date is consistent with data from pre-licensure trials and comparable with findings of post-licensure surveillance and epidemiologic studies for 4vHPV.
TARGETED MSM HPV VACCINATION PROGRAM IN THE UK: WHY, HOW AND LESSONS LEARNED

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The United Kingdom has a country-wide HPV vaccination programme that was introduced for 12-13 year old girls in 2008 (with a catch-up to 17-18 years) and will soon be extended to boys. In 2015, the Joint Committee on Vaccination and Immunization (JCVI) advised that a targeted HPV vaccination programme for MSM aged up to 45 who attend sexual health and HIV clinics should be undertaken. This followed an economic evaluation showing that vaccinating MSM against HPV would be cost-effective and could lead to substantial declines in HPV-related disease despite generally taking place long after sexual debut. The vaccine was introduced in Wales, Scotland and Northern Ireland in 2016, while in England a two-year pilot preceded national introduction in 2018. Overall, recorded first dose uptake was just below 50\% although this varied greatly across clinics, with some clinics achieving uptake of over 80\%. Only 3.4\% of MSM refusing an offer of vaccination, and anecdotal reports suggest that there may be issues with data recording at some clinics which led to an underestimate of overall vaccination uptake. The English pilot showed that the programme could be delivered opportunistically in an acceptable and equitable manner through sexual health and HIV clinics.
HPV vaccination rates vary considerably across high income countries (HIC). Some countries rapidly achieved and maintained high vaccination rates, whereas others have struggled to vaccinate their targeted populations. Still other countries achieved high rates, but then experienced temporary or extended setbacks in HPV vaccination. Furthermore, HPV vaccination programs vary greatly across HICs with respect to where the vaccine is administered, the target population, the target age, and vaccination policy. These areas of variability mean that different groups are missing out on HPV vaccination in different HICs. This presentation will focus on the U.S. and the U.K. as two examples of HIC countries that are quite different in terms of HPV vaccine coverage achieved and the characteristics of their respective approaches to HPV vaccination. These two countries also differ with respect to populations missing out on vaccination. In the U.S., white race, living in a rural area, and having a higher income are associated with lower vaccination rates. In the U.K., ethnic minorities and males (particularly young men who have sex with men) are missing out on the benefits of HPV vaccination.
Across the world, there are two trends hindering HPV vaccine uptake: (1) increase in vaccine hesitancy—delay in acceptance or refusal of vaccination despite availability of services; and 2) spread of misinformation about the HPV vaccine via social media. U.S. surveys reveal that 40% of parents delayed or refused 1+ vaccines in 2009; and more recently, 88% of healthcare providers reported parental requests to delay a vaccine. As a result, more parents are questioning guideline-based vaccination schedules, providers are uneasy during conversations with parents, and vaccination coverage is falling short of our goals for the HPV, influenza, and other vaccines. These trends make our job as public health practitioners harder. We cannot rely only on fact-based informational campaigns and educational materials. To more effectively reach and inform parents of vaccine-eligible children, we need to apply the latest science in decision-making such as nudge theory. This talk will illustrate how anti-vaccine movement and public health practitioners have been using nudge theory principles to reach parents and what challenges lie ahead.
Clearance of HPV and development of cervical neoplasia are under significant genetic control. Total heritability assessed in families has been assessed at 27%, and common variant heritability assessed in unrelated case-control studies at 36%. Monogenic diseases associated with HPV persistence (epidermodysplasia verruciformis and WHIM syndrome) also indicate that genetic factors can play a major role in clearance of HPV. A major role for protective and risk HLA-haplotypes has been demonstrated in candidate gene and GWAS studies. At amino-acid level it has been shown that these associations are determined by the amino-acid identify at positions 13 and 71 in pocket 4 of HLA-DRB1, and in HLA-B at position 156. No convincing association of any non-HLA variant with cervical neoplasia has been reported to date, although substantial non-HLA heritability has been shown from GWAS studies. Polygenic risk scores for cervical neoplasia can identify a subset of women at high disease risk, with those in the top 10% of genetic risk having a 7.1% risk of cervical neoplasia, and those in the top 5% of risk having a 21.6% risk of neoplasia. These risks are so high as to warrant consideration of combining polygenic risk scores with other risk stratification criteria to guide management of such women.
Most high-risk HPV infections are transient and resolve without causing clinically apparent lesions. Even when lesions develop, they frequently undergo spontaneous regression with clearance of the virus. Cervical cancers commonly develop years to decades after the initial infection. Hence, they arise as a consequence of a persistent high-risk HPV infection. Unlike some herpesviruses that establish latent, non-productive infections in post-mitotic cells in immune privileged locations, HPVs persistently infect cells within the mitotically active basal layer of squamous epithelia. Moreover, these persistent infections produce progeny virus in terminally differentiated keratinocytes. Hence, HPVs are exposed to a constant barrage of cellular defense mechanisms, many of which are held in check by viral countermeasures, which are the determinants of viral persistence. A detailed molecular understanding of the viral strategies that empower HPVs to persistently infect a cell and escape elimination by host defenses will be key to the development of antiviral therapeutic strategies.
HPV related HSIL of the vulva and the vagina can be effectively prevented by HPV vaccination. The ninevalent HPV vaccine prevents the majority of infections leading to vulvovaginal HSIL or invasive cancer. Careful examination of the vulva including the anus is mandatory, abnormal findings have to undergo biopsy. Treatment of choice is surgery since it provides a specimen for histopathological workup and the best possible diagnosis. Local destruction with LASER and topical treatment with Imiquimod is feasible but cancer has to be excluded by prior biopsies and patients have to be followed carefully. Therapeutic vaccines are promising but unfortunately not available. In patients treated for HPV related vulvovaginal disease prophylactic HPV vaccination reduces the risk for recurrent or other HPV related disease significantly.
Non HPV Vulval conditions: A/Prof Gayle Fischer

October 2

HPV commonly causes typical genital warts, which can at times be very challenging to treat. The same genotypes that cause cervical carcinoma are implicated in HPV-induced vulval cancer. Immunisation has already greatly reduced the incidence of genital warts in Australia.

Non-HPV vulval skin conditions can be confused with genital warts. Benign neoplastic lesions particularly seborrheic keratosis and normal variants such as vulval papillomatosis are common sources of confusion and lichenified skin conditions including dermatitis and lichen sclerosus can also simulate warts. Conditions which can be hypertrophic, such as vulval Crohn's disease, can also look like warts.

When non-HPV conditions are mistakenly diagnosed as genital warts a great deal of distress can occur. A diagnosis of genital warts in a child is a sign of possible sexual abuse, however many non-HPV conditions have been wrongly reported to be mistaken as signs of sexual abuse. It is of utmost importance not to make these sort of mistakes and if in doubt a biopsy will resolve any diagnostic doubt.
PROGRESS ON THE GUIDELINES FOR THERMAL ABLATION

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Progress on the guidelines for thermal ablation

WHO recommends the implementation of screen-and-treat algorithms where screen-positive women (HPV or VIA) are treated with ablative treatment of cancer precursors through destruction of the cervical transformation zone (TZ) including the lesion. Cryotherapy was endorsed by WHO since 2011 through systematic review of the evidence. Cryotherapy is based on freezing the TZ and requires a refrigerating gas, for which access can be challenging. New ablative treatments have become available, such as thermal ablation (TA), also called thermal or cold coagulation. TA is based on application of a probe heated at 100–120 Celcius for 20–40 sec. The devices are powered by electricity and battery-powered hand-held devices are also available. Portable cryotherapy powered by electricity is another development, both facilitating access to treatment. WHO is developing guidelines for the use of these novel ablative treatments for pre-cancerous lesions of the cervix.
Colposcopy is the most frequently performed office procedure in gynaecology and forms part of the highly successful cervical cancer screening program that exist here in Australia, and in other countries. Other components of the screening program, ie cytology and histology, have always been subject to strict quality assurance (QA) requirements. QA for colposcopy is required to ensure that all parts of a screening program are subject to minimum quality standards.

QA involves measurement of both the delivery of the service and its outcomes, data collection to monitor outcomes, feedback to improve training and education, and a commitment to continuing professional development.

The Renewed National Cervical Screening Program (NCSP) in Australia has imbedded colposcopy QA in the program. It is expected that all colposcopists (diagnostic & therapeutic), who provide services to the NCSP, will participate in a cervical management QA program. Quality standards have been developed by the NCSP to provide guidance for individual performance review.
This workshop will highlight how HPV vaccination programs have been successfully delivered at scale in LMICs from five global regions. Attendees will hear real world examples implementation experiences from Guyana, Moldova, Zimbabwe, Sri Lanka, and the Philippines. Program aspects related to securing sustainable financing, developing effective communication plans to prevent rumors, vaccinating a large multi-age cohort of girls, implementing school-based vaccination program, and overcoming supply, economic, and geographic barriers to vaccines will be reflected upon. A framing of these country-level experiences within the current status of global HPV vaccine uptake will be summarized.
Guyana piloted the HPV vaccine in 2012 to 2014 in the coast-land regions but didn't have countrywide roll out because of vaccine prices which were very high for the country. The country subsequently wasn't eligible for introduction grants after graduating to a Low Middle Income Country, however in 2016 GAVI offered to assist the government by paying for one cohort and assisting with negotiating a reduced price for the other cohorts. The country decided on vaccinating all girls 9 to 13 years old. The country's EPI has a budgetary line that receives allocations yearly so the fiscal space already existed which aided in ensuring sustainability through secure funding. To support this also a cost benefit analysis was conducted on the introduction of HPV which further supported the need for this intervention. Lessons learned in the introduction is that other supporting activities such as communications campaigns are very costly and must be factored in, also utilizing existing mechanisms for other vaccines such as distribution plans can reduce additional costs.
More effective treatments for late stage HPV associated cancers are required and immunotherapies offer new opportunities. While viral oncogenic activity is obligate for continued tumorigenicity, any natural immunity will have been severely compromised by a plethora of immune suppressive mechanisms particularly in the tumor microenvironment. Optimizing the immunogenicity of HPV oncogene vaccines will need to reduce the inhibitory immune factors, allowing recovery of functional cellular immunity and/or the capacity to elicit de novo anti-tumour responses. Strategies to reduce the negative influences of T regulatory cells, myeloid derived suppressor cells, tumor-associated macrophages, metabolic inhibitory factors and release from immune checkpoint inhibition are all being explored. Other immunotherapies being investigated include the use of adoptive cell transfer of expanded tumor infiltrating lymphocytes or chimeric -immune or -antibody receptor transduced autologous T cells. Optimizing immunotherapy will require careful deployment in the context of standard of care radiation and/or chemotherapy components where timing and dose need to be reevaluated to deliver potential immune synergism.
HPV infections are typically cleared within two years of infection, however some lesions persist and may progress to cervical cancer. Antigen presenting cells (APCs) initiate a protective adaptive immune response, but the importance of skin and lymph node APC populations in the response to HPV and how the virus regulates their function is not well understood. Here we describe the relationship between APC populations and T cell infiltrates in cervical high-risk HPV lesions in humans and we report the effects of exosomes from HPV E7-expressing cells on APC activation and function in a mouse model. From these studies we conclude that CD11c positive cells are associated with GATA3, T-bet, and granzyme B positive infiltrates in HPV lesions and that exosomes from E7-expressing cells are immune suppressive for dendritic cells in the mouse. These data support blocking suppression of APCs as a novel immunotherapeutic strategy for persistent HPV infection.
Persistent infection with mucosal high-risk HPV is causative for cancers of the anogenital region and oropharynx, and cutaneous HPVs have been implicated as cofactors in skin cancer development. HPV oncogene-driven evasion from immunosurveillance favors viral persistence. However, evidence is emerging that the mere presence of oncogenic HPV is not sufficient for malignant progression and that additional tumor-promoting steps are required. Our recent studies have demonstrated that HPV-transformed cells actively promote chronic stromal inflammation and conspire with cells in the local microenvironment to promote carcinogenesis. In my presentation, I will highlight the complex interplay between HPV-infected cells and the local immune microenvironment during oncogenic HPV infection, persistence and malignant progression, and discuss new prospects for immunotherapy of HPV-associated cancers.
Immune response upon high-risk HPV infections and therapeutic vaccination.

A minority of people infected with HPV has to cope with a persistent infection because their immune system is not able to clear the virus. This may result in development of cancer in case of high-risk HPV types. In the presentation some ways how HPV is able to evade the immune system will be discussed\(^1\)\(^-\)\(^4\). To overcome this immune evasion by the virus it is required to restore the HPV-specific immunity in patients suffering from HPV-induced premalignant lesions or cancer. One way to do this is by therapeutic vaccination. The obtained results with the HPV16 synthetic long peptide vaccine and the hurdles that were encountered and needed to be taken to get the vaccination clinically effective will be presented\(^5\)\(^-\)\(^7\).

References:

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Gay and bisexual men (GBM) are at increased risk of anal cancer. Persistent high-grade squamous intraepithelial lesions (HSIL) are the presumed precursor to anal cancer. Currently there are no national guidelines for HSIL management. Participants in the Study of the Prevention of Anal Cancer underwent anal HPV, cytological and histological assessments at 5 visits over 3 years. We developed an anal cancer risk algorithm to guide follow-up of participants after study completion. Based on their results, men were categorised as Low, Moderate, Elevated or Highest estimated anal cancer risk. 369 men attended all 5 visits. 105 (28.5%) participants were low, 59 (16.0%) moderate, 166 (45.0%) elevated and 39 (10.6%) were classified as highest risk of anal cancer. Repeated testing identified a small subset of GBM, likely to be at greatest risk of progression to anal cancer. These men may benefit most from closer monitoring and potential treatment of their HSIL.
Invasive Anal Squamous cell carcinoma is an uncommon malignancy that has been managed with curative definitive radiation therapy since the 1970’s. The aim of modern treatment is cure with preservation of the anal sphincter. Sequential Phase 2 and 3 clinical trials in Europe and the USA over the last 3 decades have attempted to optimise cancer outcomes by integrating radiation sensitising chemotherapy. Concurrent 5 FU and mitomycin-C remain standard of care, and there is no proven benefit to neoadjuvant and adjuvant chemotherapy. The greatest improvement in clinical care has come from technological advances in Radiation delivery together with the integration of modern imaging. This has enabled better targeting of the cancer and the simultaneous avoidance of normal tissues (genitalia, bladder, skin). This improvement in the therapeutic ratio has translated to improved patient outcomes and clinical trials underway are investigating a more personalised approach to management.
Despite much higher cervical cancer incidence and mortality for Aboriginal and Torres Strait Islander (Indigenous) women, the National Cervical Screening Program has had no capacity to report and did little to improve screening outcomes for Indigenous women since it began 25 years ago. Through the National Indigenous Cervical Screening Project (NICSP) we successfully reported screening participation for Indigenous women in Queensland, with semi-national statistics forthcoming. Importantly, we found that in Queensland, Indigenous women who screen tend to do so as frequently as non-Indigenous women, but the majority of Indigenous women never screen.

The NICSP has produced Indigenous research leaders who are expert in cervical cancer control and demonstrated the deficiencies of the national program for Indigenous women. Consultation with and the support of Indigenous health organisations and advisors during our data linkage and statistical analysis laid the foundation for rapid dissemination of our results. It also led to the enthusiastic collaboration of Indigenous primary care services in our current work investigating why most Indigenous women do not screen and how to enable them to do so. The improving capacity of, and collaborations between, Indigenous health organisations and researchers in cervical cancer control is now progressing towards developing and trialing an approach to cervical screening that will work for Indigenous women. With the upcoming national cervical screening register, the longer screening interval, and the option for self-collection of the new HPV test, there is now opportunity for the ‘renewed’ national program to get it right for Indigenous women; this will require a strong commitment to consultation, collaboration, capacity building and reciprocity.
In Australia, Aboriginal and Torres Strait Islander (hereafter, respectfully, Indigenous) women are 2.5 times more likely to be diagnosed, and 3.8 times more likely to die from cervical cancer, compared to non-Indigenous women. Cervical cancer is largely preventable through cervical screening; however, analysis in Queensland indicates that the majority (55%) of Indigenous women do not participate in screening. The Screening Matters study aims to describe Indigenous women’s beliefs and attitudes toward participation in cervical screening and their perceptions of Australia’s renewed screening program. We conducted semi-structured interviews with 56 Indigenous women aged 25 – 70 years, purposively sampled and recruited through Primary Health Care Centres (PHCCs) from across two jurisdictions. PHCCs identified Indigenous women who had or had not participated in cervical screening within the past 5 years; approximately equal numbers of each group of women participated in the study. Emerging themes from preliminary data from 13 women in one jurisdiction include: relationships with doctors; having choices and options; personal experiences; and lacking knowledge and information. Women generally held positive attitudes toward the availability of self-sampling in the renewed program; however, there were mixed feelings towards the instructions and process of completing the self-sampling test. This ongoing study will provide insights into Indigenous women’s views and attitudes about cervical screening, leading to new approaches to screening for these women, and in turn, informing the renewed program on how to improve screening participation for Indigenous women.
Cervical cancer incidence and mortality are substantially higher in Aboriginal and Torres Strait Islander women in Australia (Indigenous women) than in non-Indigenous women. The strongest driver of this disparity is likely to be differences in screening participation.

Australia transitioned to primary HPV screening in December 2017, and with this came the option for never- and under-screened women to access screening using a self-collected sample. Self-collection may help to reduce some of the barriers to screening experienced by Indigenous women in Australia, and early data from pilots suggest that it can be acceptable and successfully delivered; however current restrictions on access to self-collection (to never- and under-screened women) potentially also limit its effectiveness. Modelling will be used to explore the impact of different aspects of the self-collected pathway on its effectiveness, including age restrictions, the requirement to be at least 2 years overdue, and possible differences in test performance.
Human papillomaviruses and the DNA damage repair pathways

High-risk human papillomaviruses (HPV) activate the ataxia telangiectasia mutated-dependent (ATM) DNA damage response as well as the ataxia telangiectasia mutated-dependent DNA related (ATR) pathway in the absence of external DNA damaging agents for differentiation-dependent genome amplification. Through the use of comet assays and pulsed-gel electrophoresis our studies show that these pathways are activated in response to DNA breaks induced by the viral proteins E6 and E7 alone and independent of viral replication. The majority of these virally induced DNA breaks are present in cellular DNAs and only minimally in HPV episomes. This preferential repair occurs as a result of the preferential recruitment of homologous recombination repair enzymes, such as RAD51 and BRCA1, to viral genomes at the expense of cellular DNAs. Overall our studies demonstrate that human papillomaviruses induce breaks into cellular and viral DNAs and that the preferential repair of these lesions in viral episomes leads to genome amplification.
Objectives: Human papilloma virus (HPV) is the main culprit in cancers of the cervix, penis, anus, skin, eye and head and neck. Current treatments for HPV cancers have not altered survival outcomes for 30 years and there is a significant lack of targeted therapeutic agents in the management of advanced HPV-related HNSCC. Here we show that survival and maintenance of HPV-positive HNC cells relies on the continuous expression of the major HPV oncogene, E7, and that Aurora kinases are critical for survival of high-risk HPV-positive HNC cells.

Materials and Methods: To assess the role of HPV E7 on HNC cell survival, RNA interference (RNAi) of the E7 gene was initially performed. Using an Aurora kinase inhibitor, Alisertib, the role of Aurora kinases in the carcinogenesis of HPV E7 positive HNC tumour lines was then investigated. An in vivo HNC xenograft model was also utilised to assess loss of tumour volume in response to RNAi E7 gene silencing and Alisertib treatment.

Results: RNAi silencing of the HPV E7 gene inhibited the growth of HPV-positive HNC cells and in vivo tumour load. We show that HPV E7 oncogene expression confers sensitivity to Alisertib on HNC cells where Alisertib-mediated loss in in vitro cell viability and in vivo tumour load is dependent on E7 expression. Moreover, Aurora kinase inhibition induced degradation of MCL-1 in HPV E7-expressing HNC cells.

Conclusion: Overall, we show that Aurora kinases are a novel therapeutic target for HPV-positive HNCs. It might be feasible to combine Aurora kinase and MCL-1 inhibitors for future HNC therapies.
Immunocompromised women are at risk for HPV-associated cancers, specifically cervical as well as anal cancers. The best studies of immunocompromised women are those with HIV infection. Other groups include women with solid organ transplants, hematopoietic stem cell transplants and autoimmune diseases. All of these groups now have longer life expectancy. In the case of HIV, antiretroviral medication are responsible. Ironically, atrogenic immunosuppressive agents have increased life expectancy in the non-HIV infected groups. Currently, the immune health of treated HIV-infected women is likely more robust than that of women with iatrogenic immunosuppression. Rational for current cervical cancer recommendations include overall increased risk starting shortly after sexual debut and extending through-out life. The current recommendations include: a) start screening within one year of onset of sexual debut, b) annual screening with cytology until 3 consecutive normal screens then every 3 years with cytology alone or >30 years of age, co-testing (cytology plus HPV) and c) continue screening through-out lifetime (past 65 years). Recommendations for anal cancer screening vary depending on available skills and tools for detection and treatment. This workshop will cover recommendations for both CC and anal cancer screening.
Societies recognition of sexual abuse is a relatively recent phenomena. The global prevalence of sexual abuse is around 11.8%, with around 5-10% of girls and 1-5% of boys exposed to penetrative abuse. However shame and secrecy surrounding sexual abuse combined with lack of resources mean that prevalence estimates in many countries are unknown. Australia has the highest reported prevalence of sexual abuse for females (21.5%). Incidence is around 0.8/1000 children under 18 years, but this is grossly underreported, and compounded by variations in statutory definitions of abuse and mandatory reporting requirements between states. There are growing reports linking violence victimisation to risk of cervical cancer however longitudinal studies are sparse. Risk may be mediated through i) survivors fear of cervical screening ii) maladaptive coping resulting in psychological distress, substance abuse, risky sexual behaviours iii) physiological factors related to earlier acquisition of HPV. Furthermore abuse can sometimes force children to flee their homes and disengage with school, potentially compounding disparities in HPV vaccination. The CDC now recommend opportunistic HPV vaccination within forensic protocols. Sexual abuse is a societal issue associated with social dysfunction and disadvantage. Clinicians should understand their responsibilities in child protection. Earlier cervical screening may be considered in adulthood, as an individualised decision. However provision of compassionate respectful healthcare and implementation of social supports may be more critically important in order to improve compliance with long-term screening. We must be mindful amidst this rapidly changing landscape of cervical cancer prevention that sexual abuse survivors are not left behind.
INTRODUCTION

El Salvador has one of the highest cervical cancer incidence and mortality rates in Latin America. To improve cervical cancer screening in El Salvador, the Ministry of Health (MOH), in cooperation with Basic Health International, has included a screen and treat approach with primary HPV screening and cryotherapy for treatment of HPV positive women in the public sector health system.

BACKGROUND

The Ministry of Health of El Salvador (MOH) received a donation of careHPV® tests as part of a 3-phase demonstration project that screened over 28,000 women. This project provided the base for population-based screening for women aged 30-59 living in the Paracentral Region of El Salvador. This year the MOH was the first Low-middle income country to procure this test to scale the intervention as part of their cervical cancer program.

CONCLUSION

Implementation of a primary HPV screen and treat strategy is feasible in a limited resource setting.
HSV initially infects the keratinocytes and Langerhans cells (DCs) of oro-genital epidermis. In biopsies of initial genital herpes, infected emigrating LCs were observed to interact with different dermal dendritic cell subsets (dDCs) which in turn interact with CD4+ and/or CD8+ T cells. Topical application of HSV-1 to human inner foreskin explants, simulating *in vivo* infection, resulted in infection of LCs, but also a novel epidermal CD11c+ DC subset. *In vitro* these new eDCs took up HSV-1 by endocytosis, were productively infected and also developed apoptosis, like LCs, but there were some marked differences. Infected apoptosing LCs emigrated into the dermis where they were taken up by three subsets of dDCs, consistent with different roles in stimulating CD4 and CD8 T cells. We have defined the chemokines and receptors and also the apoptotic receptors which facilitate these LC-DC interactions. These studies may help define appropriate DC targets for future vaccine adjuvant.
HPV particles attach preferentially to HSPGs present in the extracellular matrix (ECM) or the basement membrane of an epithelium. The protein convertase, furin, cleaves the L2 minor capsid protein, facilitating membrane vesicle escape of the HPV capsid and/or L2-genome complex during infectious entry. However, there are conflicting accounts as to the role that furin plays in HPV movement from HSPGs to virus entry receptors.

One model suggests that furin catalyzes HPV capsid conformational changes that permit HSPG-independent infectious entry. As furin activates MMPs involved in HSPG processing, we tested the hypothesis that furin promotes association between HPVs and HSPGs to permit HPV infection of HSPG-deficient cells. Using conditioned medium from furin-overexpressing cells (FCM), we verified that FCM supports HPV infection of cells lacking HSPGs. However, infection was inhibited by heparinase or a drug that neutralizes HS. This finding is inconsistent with the model that L2 cleavage by furin promotes HSPG-independent infection, which should be irreversible and unaffected by HS digestion/inhibition. Our data are consistent with furin’s function as an activator of MMPs, which process HSPGs and ligands.

Conclusion: Furin functions to decorate HPV particles with HSPGs and potentially other bioactive molecules, thereby permitting HPVs to infect HSPG deficient cells.
Over the last two decades, many host-cell proteins have been described to be involved in the process of infectious entry of oncogenic human papillomaviruses (HPV). After initial binding a sequence of events on the cell surface precedes the formation of endocytic, virus-associated tetraspanin entry platforms. Tetraspanins are a family of four-span transmembrane proteins, known as plasma membrane “master organizers.”

We found that downstream of initial virus binding the proteinase ADAM17 activates a signaling pathway that, in turn, triggers the formation of a large virus associated entry platforms. It has been shown that these platforms are composed of tetraspanin CD151, additional tetraspanins, and associated partner proteins such as integrins, growth factor receptors, and the annexin A2 heterotetramer (A2t). Further recruitment of cytoplasmic factors such as the Obscurin-like protein 1 and actin results in a tetraspanin mediated endocytosis.

After virus internalization, tetraspanin CD63 together with its adaptor syntenin-1 and A2t might form a modified trafficking platform, which is required for early intracellular trafficking of the virus particle to multivesicular endosomes. This is a crucial step for capsid disassembly and further trafficking of the virus towards the host cell nucleus.

In conclusion, tetraspanin assemblies may organize cofactors for viral entry into distinct molecular platforms, which mediate specific endocytosis and trafficking processes.
We have recently described a new cell culture model that allows highly efficient infection of primary keratinocytes and completion of the viral life cycle without the need for immortalization and selection (PLoS Pathogens 14(3): e1006846, 2018. This system is amenable to extensive genetic screens of viral factors. Using E6 and E7 knockout viruses, we provided evidence that both oncogenes are dispensable for establishment of infection. However, E6 but not E7 is required for episomal genome maintenance in primary keratinocytes. A transcriptome analysis revealed that some 100 host genes are deregulated at the transcriptional level after infection with wtHPV16. In contrast to HPV16 immortalized cells, which have more than 5000 genes deregulated, interferon-regulated genes were not altered after wtHPV16 infection. The vast majority of deregulated genes after HPV16 infection are under the control of the E2F family of S phase transcription factors. Indeed, most alterations were not evident after infection with E7 knockout virus. We will further present the characterization of organotypic raft cultures obtained from wt and E7-TTL infected keratinocytes.
HPV vaccination was initiated in Canada in 2007. The incidence and prevalence of juvenile onset recurrent respiratory papillomatosis has been monitored at the national level since 2007. Population-level statistics indicate that the mean incidence of recurrent respiratory papillomatosis in children has decreased by approximately 65% compared to a 15 year period prior to 2007. This presentation will review the methodology employed by the Canadian Juvenile Onset RRP Working group, the observed trends in incidence and prevalence of RRP in children, and hypothetical mechanisms that may be responsible for the observed decrease in incidence. More importantly, it will demonstrate a clinically relevant unintended outcome of HPV vaccination.
Human papillomavirus (HPV) is the causative agent in a growing proportion of incident cases of head and neck squamous cell carcinoma (HNSCC). HPV infected cells express immunogenic, foreign viral antigens. However, in a subset of patients, the virus is able to evade the host immune system resulting in persistent infection and subsequent malignant transformation. We reported on the activation of the PD-1:PDL-1 pathway as an immune evasion mechanism utilized by HPV-associated HNSCCs and provided rationale for the treatment with anti-PD-1 blocking antibody in this patient population. Two phase III clinical trials have demonstrated clinical benefit of anti-PD-1 blockade in HNSCC patients, in particular HPV-associated HNSCC patients. We review the results of key clinical studies that support the application of immunotherapy as a feasible treatment option for HPV-associated cancer patients as well as discuss novel strategies which are actively being explored to enhance HPV-specific anti-tumor host immune responses.
Several countries have replaced or are considering replacing cytology-based screening by HPV testing or HPV-cytology co-testing for primary screening. The implementation of HPV-based screening often comes together with an extension of the screening interval to limit the number of colposcopy referrals, treatments, and costs. Most HPV-based programs recommend 3 to 5-yearly HPV screening, but intervals beyond 5 years have been included in the new HPV-based programs in Sweden and the Netherlands. In Sweden, the interval has been extended to 7 years for women 50 years and older and in the Netherlands, the interval has been extended to 10 years for women 40 years and older. Interval extensions in screening programs are usually supported by long-term precancer and cancer risks after a negative screening test. This type of longitudinal evidence depends on implicit assumptions about the duration to cancer that may become uncertain for intervals beyond 5 years. Further support for the use of screening intervals beyond 5 years can be obtained from model-based analyses that synthesize information about durations of precancerous disease states and the disease state-specific probability of a positive screening test.
Human papillomaviruses (HPVs) infect the cutaneous or mucosal epithelia and are classified phylogenetically as genera and species. Persistent infections by the mucosal high-risk (HR) HPV types from genus alpha are associated with cancer development of the genital and upper respiratory tracts. The products of two early genes, E6 and E7, are the major HR HPV oncoproteins, being essential in all steps of the carcinogenic process. Cutaneous beta HPV types are proposed, together with ultraviolet (UV) radiation, to promote skin squamous cell carcinoma. However, in contrast to the HR HPV types, beta HPV types appear to be required only at an early stage of carcinogenesis, facilitating the accumulation of UV-induced DNA mutations. Findings in in vitro and in vivo experimental models also suggest that beta HPV types and other carcinogens may synergize in the induction of additional malignancies. Data in supporting the association of beta HPV types with human carcinogenesis will be presented.
During the 1970’s the first genus beta HPVs (HPV5 and HPV8) were isolated from skin lesions of individuals affected by the genetic disease Epidermodysplasia verruciformis (EV). EV patients display a high susceptibility to beta HPV infections and are at high risk for developing keratinocyte cancer at sun-exposed body sites. Stimulated by compelling evidence for the carcinogenicity of beta HPV in the EV skin, highly sensitive PCRs were developed to identify beta HPV also apart from EV in cutaneous squamous cell carcinoma (SCC) of immunocompetent and immunosuppressed individuals. These findings were right away difficult to interpret because beta HPV infect the skin of all people as a commensal flora. PCR-based epidemiologic case-control studies failed to consistently associate specific types with SCC. IARC therefore considered beta HPV “not classifiable as to their carcinogenicity to humans” in 2009. However, later natural history studies showed that the individual HPV flora has to be differentiated into transiently detectable and persisting types and pointed to a type-specific susceptibility of different individuals. More recent epidemiologic studies addressed biologically relevant beta HPV infections by looking at the viral DNA load. These studies revealed increased odds ratios for beta HPV infection with skin cancer and provided strong evidence for this association. These findings are further supported by many experimental data providing biological plausibility for the carcinogenicity of beta HPV.
MmuPV1 provides, for the first time, the opportunity to study infection and pathogenesis of papillomaviruses in the context of laboratory mice. The defined MmuPV1 transcriptome consists of thirty-six RNA isoforms transcribed mainly from three early (P_{7503}, P_{360} and P_{859}) and two late (P_{7107} and P_{533}) promoters unidirectionally on one strand of the double stranded DNA genome. All of these transcripts are polyadenylated either at an early polyadenylation (pA) site (pA_{E3844}) or a late pA site (pA_{L7047}). MmuPV1 genome contains five splice donor and three acceptor sites and does not encode an E5. Although E1 and L2 are expressed from unspliced transcripts, the majority of viral early E6, E7, E2 and E8^E2 and late E1^E4, L1 and L2 transcripts are single or double spliced transcripts detectable in MmuPV1-infected tissues with viral DNA amplification. The delineated MmuPV1 genome structure and expression are close to that of HR cutaneous beta HPVs and some low-risk mucosotropic HPVs.
Population level HPV vaccination programmes have largely focussed on adolescent females (and more recently males); however there is evidence that where catch up vaccination to age 26 years has occurred, this has accelerated the impact of vaccination programmes on HPV infection and related disease. Vaccination of older women is an important clinical question as this age group is at higher risk of HPV related cancer than younger women and are unlikely to have been vaccinated in a population-based vaccination programme.

In this presentation, key data relevant to this age group will be summarised to provide an understanding of 1) the epidemiology and natural history of HPV infection and related disease in older women, 2) clinical efficacy of HPV vaccines in older women and women with previous HPV infection and related disease and 3) indications for vaccination of older women.
This interactive presentation will be a question and answer time. Registrants to IPV 2018 were asked to furnish clinical questions they deal with on a daily basis around HPV vaccination. The three speakers will provide answers to these questions based on best available evidence, as well as expert opinion. To give a flavour to the session, here are two questions:

**For females** “As an unvaccinated older woman in my early 50s, who is contemplating a new relationship, should I be vaccinated?” The response requires consideration of multiple factors including potential benefits and costs.

**For males** “Do I need to have Gardasil 9, having already had the quadrivalent Gardasil vaccine?” This is particularly relevant for HIV+ MSMs, in whom a higher proportion of anal cancers are non-HPV 16 related.
Clinical encounters, and the questions arising from them, are often with individuals seeking vaccination. However, many health professionals will encounter parental hesitancy or refusal of the HPV vaccine for their adolescent. This presentation will draw on behavioural and communication science to provide practical strategies for health professionals addressing vaccine hesitancy and refusal. It suggests a structured approach with tips that enhance the existing skills of professionals. The strategies aim to strike the balance between maintaining the therapeutic relationship and encouraging vaccination.
The anti-vaccination movement is as old as vaccination itself, but with the age of the internet, and social media in particular, their audience has grown. In Australia the most prominent anti-vaccination group was the Australian Vaccination-risks Network (AVN) who were formed in 1994 and grew to a position of power based on income of ~$300,000 a year and regular media appearances.

In 2009 an infant died of pertussis and the parents were harassed by anti-vaccinationists including the President of the AVN on a national television show, Sunday Night. Outrage at this behaviour led to the formation of a group on Facebook that became known as Stop the Australian (Anti) Vaccination Network (SAVN)

Since 2009, SAVN’s work combatting professional anti-vaccination organisations like the AVN has resulted in a reduction in their media profile through the education of media outlets on false balance. As a result the income of the AVN has dropped by ~90%. 

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In August 2008, it was decided to start HPV vaccination in Ireland in September 2009. However, the introduction of the vaccination program was postponed leading to a lot of media coverage stating that girls were left unprotected. A school-based vaccination program began in May 2010 using the quadrivalent HPV vaccine, aimed at 12-13-year-old girls. In the first four years, the program reached its vaccination coverage goal of 80%, and 97% of girls who started vaccination, completed their course. In 2015, due to anti-vaccine group actions vaccine uptake plummeted to 50%. The major concerns were about vaccine safety, and lack of information.

In response to the vaccine crisis, the HSE liaised with stakeholders: the Irish Cancer Society, the National Cancer Screening Service, the Department of Education, as well as schools, national Parents Councils, and politicians. Training of health professionals was organized, and an information campaign was run, aimed at parents, all with strong support from politicians, especially the Minister of Health. In July 2017 the HPV vaccination alliance was established, it is an umbrella body of over 35 organisations including women’s and children’s rights, cancer charities and wider civil society all committed to promoting HPV vaccine. This led to an increase in uptake of the first dose of HPV vaccine in the school year 2017/2018.
In October 2006, HPV vaccination (quadrivalent HPV vaccine) was licensed in Denmark. It was introduced into the childhood vaccination program, which is free of charge, in January 2009 covering 12-year old girls. There was also implemented a catch-up program for respectively girls 13-15 years (initiated Oct.-2008) and women up to age 27 years (initiated Aug.-2012). These vaccination programs were also free of charge.

The Danish HPV vaccination is delivered through a clinic-based program by general practitioners. Initially, a high vaccination coverage (80-90%) was achieved in most birth cohorts covered by the vaccination program, and together with e.g. Australia, Denmark was one of the first countries to demonstrate a real world impact and effectiveness of HPV vaccination in relation to the occurrence of both genital warts and high-grade cervical lesions (CIN2/3).

HPV vaccination was strongly recommended by the Danish National Board of Health, and by other organizations such as the Danish Cancer Society. In spite of this, there has subsequently been a substantial decline in HPV-vaccine coverage in Denmark. This decline followed reports of a number of women suffering from adverse events claimed to be related to vaccination.

A number of initiatives have been launched and these will be described and discussed.
HPV vaccine was introduced into the Japanese National Immunization Programme (NIP) in April 2013 and just two months later, on June 14th, 2013, proactive recommendations for the HPV vaccines were suspended due to the unconfirmed media reports of AEFI. Very quickly uptake dropped from >70% to <1%, and five years later, this suspension remains, despite no evidence to suggest the vaccine is responsible for the reported symptoms. The reasons why the Ministry of Health, Labour and Welfare has been unable to resume proactive recommendations for the HPV vaccine are complex and varied. They include: poor risk communication and risk management, a public health infrastructure that makes it difficult to convince the public that the vaccine is both effective and safe, and an anti-vaccine movement more organized than the government and supported by the media. Each of these factors will be discussed in detail in this presentation.