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Eurogin 2016 Roadmap: how HPV knowledge is changing screening practice

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Mini Review

Human papillomaviruses (HPVs) are the necessary cause of most cervical cancers, a large proportion of other anogenital cancers, and a subset of oropharyngeal cancers. The knowledge about HPV has led to development of novel HPV-based prevention strategies with important impact on clinical and public health practice. Two complementary reviews have been prepared following the 2015 Eurogin Conference to evaluate how knowledge about HPV is changing practice in HPV infection and disease control through vaccination and screening. This review focuses on screening for cervical and anal cancers in increasingly vaccinated populations. The introduction of HPV vaccines a decade ago has led to reductions in HPV infections and early cancer precursors in countries with wide vaccination coverage. Despite the high efficacy of HPV vaccines, cervical cancer screening will remain important for many decades. Many healthcare systems are considering switching to primary HPV screening, which has higher sensitivity for cervical precancers and allows extending screening intervals. We describe different approaches to implementing HPV-based screening efforts in different healthcare systems with a focus in high-income countries. While the population prevalence for other anogenital cancers is too low for population-based screening, anal cancer incidence is very high in HIV-infected men who have sex with men, warranting consideration of early detection approaches. We summarize the current evidence on HPV-based prevention of anal cancers and highlight important evidence gaps.

Introduction

A multidisciplinary group of international experts held a panel discussion at the 2015 Eurogin conference, summarizing the state of the art and future directions related to the burden and prevention of HPV-related diseases. This panel discussion, and the science presented at the conference are the basis of the latest Eurogin Roadmaps. While the last two Roadmaps[1,2] focused on comparative epidemiology and natural history of HPV-related cancers by site and by gender, the current Roadmap summarizes the status of prevention and management of HPV-related disease, updating the 2011 Roadmap.[3] Due to the extensive scope, the Roadmap was divided into two reports, one focusing on vaccination (2015 Roadmap),[4] and this document focusing on screening and management of HPV-related diseases (2016 Roadmap).

Carcinogenic HPVs are associated with anogenital cancers, most importantly of the cervix, as well as oropharyngeal cancers. Recognizing HPV as necessary cause for most cervical cancers has led to development of new primary and secondary prevention tools,[5] including highly efficacious HPV vaccines[4] and HPV assays as well as other biomarkers for screening and management.[6–8] The abundance of available assays has led to considerable confusion about the best approaches to screening among providers. In addition, screening programs will have to be modified when increasingly large proportions of women are vaccinated. While the efficacy of screening for cervical cancer is uncontested and current efforts focus on optimization of the programs and adjustment to accommodate the effects of HPV vaccination,

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there is no consensus about screening for other HPV-related cancers like anal cancer. Here, we summarize the state of the art in the field of screening of anogenital cancers and highlight future directions and necessary areas of research, with a particular focus on the integration of vaccination and screening. While the Roadmap primarily addresses screening in high resource settings, we also highlight important differences to cervical cancer prevention in low and middle income countries (LMIC).

Cervical Cancer Screening Strategies

Every screening strategy needs to weigh potential benefits and harms of the intervention. The benefit of cervical cancer screening is prevention of cervical cancer by finding and treating cervical precancers. However, it is currently not possible to distinguish true cervical precancers from morphologically similar lesions that would not progress to cancer in a woman's lifetime.[9] Many CIN2s regress spontaneously,[10] and only a subset of CIN3s will progress to cancer.[11] Thus, current screening programs accept a lot of extra-expenses and overtreatment to achieve high effectiveness. Harms associated with excisional treatment may include obstetric complications.[12,13]

Cytology-based screening remains the most widely used approach. Primary HPV screening recently received regulatory approval in the US and was recommended for introduction in the Netherlands and Italy and endorsed by the European Guidelines.[14–16] Several countries have decided to, or are considering switching to primary HPV screening and are conducting pilot studies or are implementing these new programs (Table 1). The algorithms adopted or proposed in different settings differ with respect to screening modality, starting age, screening interval, exit age and triage strategy for HPV positive women (Table 1). Importantly, many approaches described in this Roadmap need to be adapted to low-resource settings that suffer from the highest burden of HPV-associated cancers. While primary HPV screening has been successfully conducted in these places, follow up, triage, and adequate management of HPV positive women are notoriously difficult in low-resource settings, but a key requirement for a successful screening program (Table 2).

Analyses from diagnostic laboratory databases have suggested that HPV testing may miss some cervical cancers detected by cytology.[17,18] However, biases inherent to these retrospective analyses have been pointed out.[19] Large randomized trials have demonstrated that HPV testing is more effective at detecting precancer in the first round of screening compared to cervical cytology; this has been shown to lead to long term protection against CIN3+.[2] In a pooled analysis of four randomized trials conducted in Europe, HPV testing provided greater protection against invasive cervical cancer compared to cytology; the 3-year cancer risk after a negative HPV test was about 70% lower than after negative cytology.[21] HPV-cytology cotesting for primary screening has been recommended in the US, but is not considered elsewhere.[22] The European RCTs as well as a large observational study from Kaiser Permanente demonstrated that the additional benefit of adding cytology to HPV testing is low at the cost of performing cytology in the entire population,[23] substantially reducing cost-effectiveness compared to primary HPV screening.

Role of Self-Collection in HPV-Based Screening

In contrast to cytology, HPV testing can be performed on self-collected specimens. A meta-analysis showed comparable accuracy between self- and clinician-collected samples when established PCR-based hrHPV assays were used.[24,25] Self-sampling can increase population coverage by reaching women who are reluctant to participate in a screening program that requires a gynecological examination. The response doubles when women not attending screening receive a self-sampling kit compared to an invitation for a physician collection.[26] However, response rates varied substantially between studies, indicating that the findings are not universally portable. Therefore, pilot studies to assess feasibility, costs, logistics and population compliance before general roll-out are important.[27,28] In the new HPV-based screening program starting 2017 in the Netherlands, self-sampling will be offered to women not responding to the screening invitation.[29] Self-collection has been included as an option for underscreened women in the new primary HPV screening program in Australia; however efforts are being made to communicate to women that although a single self-collected sample is better than no screening, it may not be as effective as regular screening.[30] Self-sampling has also been proposed as a strategy to improve screening coverage in LMIC where it may allow up-scaling of screening despite the scarcity of health staff and screening facilities.[31]

Triage of Screen-Positive Women

HPV-based screening strategies (both HPV-cytology co-testing and HPV-alone) require additional triage of screen-positive women. In co-testing, repeat testing or triage is recommended for the group of HPV-positive women with normal cytology.[22] In HPV-alone screening, all screen-positive women require triage. It is most efficient to perform a triage test from the primary screening specimen (reflex triage), rather than inviting women back for sample collection. Many candidates for triage assays are being evaluated, but few have been approved or recommended so far.

Cytology

All currently suggested primary HPV screening programs use reflex cytology for triage. Due to the increased risk of precancer in HPV-positive women, and the elimination of a large group of borderline results with very low risk of cancer (e.g., HPV-negative ASC-US), cytology is expected to perform better in triage compared to primary screening. Recent studies have reported increased sensitivity of cytology for detection of precancer when it is evaluated with knowledge of HPV status, with a potential loss in specificity.[32–34] In the Dutch guidelines, cytology is recommended for triage of all HPV-positive women, while in the US, cytology has been

Table 1. Examples for different approaches of transitioning to HPV-based cervical cancer screening in high-income countries

Country	Proposed screening approach[1]	Type	Implementation status
Australia	HPV screening age 25–70 at 5-year intervals (discharge at age 70–74 for HPV-negative women) Triage of HPV-positives: partial genotyping for HPV16/18 and direct referral to colposcopy. Other oncogenic types triaged with LBC–LBC high grade cytology referred to colposcopy, all others to 12-month follow-up repeat HPV testing	Organized	Evaluation completed in 2014; clinical management guidelines and laboratory quality processes and standards developed in 2016, Implementation in 2017
Belgium	Currently cytology every 3 years (25–64 years), HPV triage of ASC-US HPV-based screening proposed.	Organized in Flemish region, not in rest of country	Negotiations to introduce HPV screening will start in 2016
Canada	Cytology-based screening age 25–69 years[2]	Opportunistic in most provinces	Awaiting results from ongoing trials before making formal recommendations: Evaluation of HPV screening age 25 and older; triage of HPV-positives with cytology
England	HPV screening proposed; triage of HPV-positives with cytology	Organized	Demonstration projects at six sentinel sites
Finland	Cytology-based screening age 30–60 (25–65 in some municipalities)[2]	Organized	Randomized studies of HPV *vs*. cytology ongoing
France	Cytology every 3 years (25–64 years), HPV triage of ASC-US	Opportunistic, organized screening recommended	HPV screening pilot projects ongoing
Germany	HPV screening every 3–5 years proposed; triage of HPV positives with cytology, genotyping or p16/Ki-76	Currently opportunistic, organized screening proposed	Pilot projects in development
Italy	HPV screening age 30 or 35 (according region) −65 at 5-year intervals; from 25 to 30–34 Pap test every 3 years; triage of HPV positives with cytology	Organized	In 2014, 13% of target population was invited to HPV screening. Transition is mandatory for all regions from 2016 to 2018
The Netherlands	HPV screening every 5 years age 30–60, HPV-negative women age 40 and 50 are re-invited after 10 years; triage of HPV-positives with cytology	Organized	Implementation in 2017
New Zealand	HPV screening age 25–70 at 5-year intervals (discharge at age 70–74 for HPV-negative women) Triage of HPV-positives: partial genotyping for HPV16/18 and direct referral to colposcopy. Other oncogenic types triaged with LBC–LBC high grade cytology referred to colposcopy, all others to 12-month follow-up repeat HPV testing	Organized	Evaluation completed in 2016; Clinical management guidelines development underway; Implementation expected in 2018
Norway	Randomized implementation study cytology *vs*. HPV in 4/19 counties	Organized	Nationwide HPV primary screening, expected 2019
Scotland, Wales, Northern Ireland	Cytology-based screening age 25–64 years[2]	Organized	In the short time, HPV-based triage of minor cytology is planned
Sweden	Under age 30 cytology every 3 years, age 30–49 HPV screening every 3 years, age 41 co-testing, age 50–64 HPV screening every 7 years Triage of HPV-positives with cytology	Organized	Implementation ongoing, expected to be nationwide in 2017

Table 1. Examples for different approaches of transitioning to HPV-based cervical cancer screening in high-income countries (Continued)

Country	Proposed screening approach[1]	Type	Implementation status
USA	Cytology alone every 3 years, age 21–65 Co-testing every 5 years, age 30–65 (with cytology screening age 21–30) HPV alone every 3 years, age 25–65 (with cytology screening age 21–25) Triage with HPV16/18 or cytology	Opportunistic	FDA approval; Recommended by guidelines (interim guidance for primary HPV screening)
European guidelines	Recommendation to implement HPV-based screening starting at 30–35 years at >=5-year interval up to 60–69 years	Organized	
WHO guidelines	HPV screening age 30 and older, every 3–5 years Cytology acceptable if HPV not available and cytology of good quality Visual inspection after application of acetic acid as alternative in low resource settings		

[1]Proposed HPV screening approaches that are either approved, undergoing implementation studies, or are currently discussed. If no HPV-based screening approach has been proposed, the current cytology-based screening is described.
[2]No HPV-based screening approach has been currently proposed.

approved for triage of HPV-positive, HPV16/18-negative women (Table 1).[14,15] Management options for HPV-positive, cytology-negative include repeat HPV/cytology testing or release to regular screening intervals.

HPV genotyping

Among the 13–14 carcinogenic HPV types, the risk of precancer and cancer varies widely, suggesting potential of HPV genotyping for risk stratification. However, HPV genotyping alone cannot differentiate between a transient infection and a prevalent precancer or cancer. Worldwide, HPV16 has by far the highest risk of cancer, while the relative importance of some less carcinogenic types may vary across populations.[35,36] Since complete individual genotyping is not clinically useful, there is an ongoing debate about which types should be included in HPV genotyping assays. Across studies, there is consensus that the highest risk group includes HPV16 and the lowest risk group HPV39, 56, 59, 66 and 68.[37–39] Due to its high risk of cancer and particularly strong association with adenocarcinomas, HPV18 is typically included in genotyping assays, even if the risk of precancer is lower compared to HPV16. Additional inclusion of genotypes increases the sensitivity at the cost of lower specificity and increasing referral to colposcopy.

As outlined above, genotyping and cytological triage approaches can be combined: The approved primary screening approach in the US, and the proposed approach in Australia, is to directly refer HPV 16/18 positive women to colposcopy but triage other oncogenic HPV types via cytology.

p16

p16 is uniformly upregulated in transforming HPV infections and has been evaluated as a biomarker for cervical precancer. In histology, p16 staining can be used to differentiate precancers from look-alikes and has been recommended for use in cervical histology.[40] A cytological assay has been developed for screening and triage, combining detection of p16 and Ki-67 (dual stain). The assay has been evaluated both for primary screening and for triage of HPV-positives.[41,42] Data from a large Italian screening trial and from the US suggests that HPV-positive women who are p16- or dual stain positive should be referred to colposcopy, while follow-up can be extended in p16-negative women.[34,43]

Other markers

Increased methylation of several genes has been observed in women with precancer and cancer.[44,45] The most widely evaluated methylation markers for triage of HPV-positive women include CADM1, MAL, miR-124–2 and EPB41L3, with performance comparable to cytology. Advantages of methylation testing include the objectivity of the assay and the compatibility to self-collected specimens as demonstrated in a randomized trial in the Netherlands.[46] Recently, studies have shown that HPV genomes are increasingly methylated at the transition from HPV infection to precancer.[47–49] Other markers, including

Table 2. Characteristics of cervical cancer screening in high and low-to-middle income countries

Modality	High-income countries	Low-to-middle-income countries
Cytology	Primary screening, triage	Hard to implement and sustain
HPV test	Primary screening, many options	Few robust low cost options
Self-collection	Focus on non-compliant women	Targeting all women due to limited staff and facilities
Molecular triage	Very useful, many options	Very important, but few robust low cost options
Recruitment and recall of women	Individual invitation, screening registries	Community mobilization
Colposcopy and biopsy	Triage, diagnosis	Hard to implement and sustain
Treatment	Multiple excisional and ablational options	Cryotherapy, cold-coagulation, excisional treatment options limited and hard to implement on large scale

detection of chromosomal abnormalities, viral oncogene mRNA, or viral proteins have been developed, but a rigorous evaluation in a HPV triage setting remains lacking.[8] A robust low-cost assay for detection of viral E6 oncoproteins has been developed for LMIC and is currently being evaluated.[50]

Colposcopy-Biopsy and Post-Treatment Surveillance

All screening programs in high-resource settings rely on colposcopy as the central diagnostic procedure and to guide treatment. It is widely accepted that colposcopic evaluation lacks reproducibility and there is controversy about how many and where cervical biopsies should be taken. Single biopsy protocols may miss up to a third of prevalent precancers, which has led some to propose routinely taking random four-quadrant biopsies.[51] However, data from the ATHENA trial demonstrates that overly aggressive biopsy protocols may lead to overdiagnosis of lesions that are not associated with cancer risk.[52] Data from the UK and the US support that in women with low grade cytologic abnormalities and a completely normal colposcopic impression, the risk of precancer is very low.[53,54] Taking multiple lesion-directed biopsies can improve detection of precancer compared to a single-biopsy protocol.[54] Recently, the IFCPC revised the colposcopy nomenclature to improve accuracy of colposcopic evaluation and to link diagnostic and therapeutic categories.[55] With introduction of HPV-based screening programs, new challenges may arise, since cervical lesions are detected earlier and the mix of disease seen at colposcopy is expected to be different.

Recent management guidelines and systematic reviews support the utility of hrHPV testing in post-treatment active management[20,56] since the risk of recurrence following a negative hrHPV test is low.[57] Recent US management guidelines allow for a path to "routine screening" post-LEEP following repeated negative hrHPV tests.[20,56]

How to Move Forward: Risk-Based Screening and Management

There are now many different options available for cervical cancer screening and triage that allow predicting individual risk of precancer with very high precision. However, the abundance of choices is challenging for providers and women, since screening and management recommendations may become increasingly complicated.

Recent guidelines efforts have adopted a risk-based approach to develop guidelines for screening, triage, management and treatment.[56] This approach focuses on the absolute risk of precancer in test-positive and test-negative women.[58,59] Importantly, different risk estimates are only relevant when they translate to different clinical management. There are about four different clinical action levels: At the lowest risk, women return to regular screening intervals. In an intermediate risk group additional testing or increased surveillance may be required. Next is the colposcopy referral threshold, and at the highest risk level (e.g., women with HSIL cytology) there is an option for immediate treatment.[56] A risk-based guidelines approach separates the thresholds for different clinical actions from evaluating risk levels for individual test results. While risk estimates for different assays can be generalized across populations, the risk thresholds may vary in different healthcare settings depending on previous screening practice. A similar strategy can be pursued for LMIC, albeit with different risk and action thresholds.

Screening of Vaccinated Populations

Over the last decade, HPV vaccination has been implemented in the majority of developed countries.[4] Routine vaccination is generally delivered to 11- to 12-year-old females but many countries also implemented catch-up vaccination up to 18–26 years.[4] In many countries, cohorts offered vaccination now have entered the target age for cervical screening.

In the era of HPV vaccination, the central challenge is that individual women in the population have a wide range of lifetime risks of invasive cervical cancer. The risk for any individual woman depends not only on screening history but also on whether she was offered vaccination, HPV type coverage, whether she completed the vaccination course, whether she was vaccinated in catch-up programs with a possibility of

prior exposure to HPV, or even if she was not vaccinated, whether vaccination in the population led to herd protection.

Two approaches to managing cervical screening in the context of vaccine-related variation in risk for individual women have been proposed. Individual-based screening approaches attempt to take vaccination factors into account in deciding how best to screen an individual woman. HPV genotyping data from two large screening trials (POBASCAM and NTCC) suggest that it may be possible to define different screening intervals for unvaccinated and vaccinated HPV-negative women. However, using vaccination status to modify screening strategies poses logistical challenges since comprehensive and accessible registries are required and need to be accessible at the cervical screening visit. An alternative screening strategy uses the same approach for both unvaccinated and vaccinated women, such that accurate knowledge about vaccination status for an individual is not required. Primary HPV screening, particularly if it involves HPV16/18 genotyping, allows implementing the same screening approach in unvaccinated and vaccinated women, at least for cohorts vaccinated with first generation vaccines. An HPV positive woman can be managed on that basis, without needing to have information on vaccination status - what counts is her HPV status. In the context of first generation vaccines, for HPV negative women, the interval can be tailored to the group at highest risk in the population, i.e. unvaccinated women. Even with such a conservative approach, the screening interval could be extended to 5 years or even longer and, if vaccine coverage is high, a woman will require fewer cervical screens in a lifetime than currently recommended.

Next generation nonavalent vaccines are likely to have a further impact on the optimal strategy for cervical screening; but their impact on screening programs will be delayed for decades, since they are being "rolled into" existing vaccination programs which primarily target 11- to 12-year-old adolescents. With high vaccine coverage in these cohorts it is likely that in the long term a woman will require very few cervical screens in a lifetime. Initial analyses suggest that the most cost-effective number of screening tests offered to cohorts who received nonavalent vaccines will be highly variable depending on vaccine uptake, but that in some countries only 1–2 lifetime screens will be required.[60]

In 2007, Australia was one of the first countries to implement a large scale publicly-funded HPV vaccination program. The rapid implementation and high coverage of the Australian Vaccination Program resulted in substantial relative reductions in HPV infections,[61] anogenital warts and high grade cervical abnormalities for women in their early twenties 3–5 years after its implementation. Similar effects have been observed in other countries.[62] This has prompted a major reconsideration of cervical screening in Australia and in 2014, the Australian Government announced its new recommendations for a transition to a primary HPV-based cervical screening program (Table 1). Moving from 26 Pap smear tests in a lifetime to 9 or 10 lifetime HPV tests is expected to not only save costs by better targeting women at the right age range and interval, but is also expected to further lower cervical cancer incidence and mortality.[30] Detailed clinical management guidelines, which specify the approach to managing HPV positive women have now been developed.

A few randomized screening trials are now underway to optimize screening programs in vaccinated populations. In the framework of a community randomized trial in Finland,[63] 22,500 women vaccinated against HPV16/18 at age 13–15 will be randomized into three arms to receive cytology at ages 22, 25 and 30 years, 25 and 30 years or at age of 30 only (EUdraCT 2014–002143-17); the study will provide important evidence about the safety of postponing age to start screening in vaccinated populations. In Australia, Compass (Clinicaltrials.gov NCT02328872), is recruiting 121,000 women in the period prior to transition of the national screening program for a sentinel experience of HPV-based screening. Women are randomized to either cytology or HPV-based screening and recruitment is being stratified by whether a woman was in a birth cohort offered vaccination or not. The trial will provide evidence of the effectiveness of primary HPV screening with partial genotyping *vs*. cytology, in both unvaccinated and vaccinated women.

Anal Cancer Screening

Incidence and natural history of anal cancer

The ultimate aim of cancer screening is to reduce cancer-specific mortality. To achieve this aim, the incidence of cancer in the screened population must be sufficiently high, a screening test needs to be sufficiently accurate and acceptable to patients and there must be an effective intervention that is well tolerated. Anal cancer is rare in the general population, but very common in men who have sex with men (MSM),[64] with highest incidence observed in HIV-positive MSM.[65–68] A rise in incidence has been widely observed in HIV MSM[69] with an incidence of anal cancer in HIV positive MSM similar to the incidence of cervical cancer before introduction of cytological screening.[70] Unlike AIDS-defining Kaposi sarcoma and lymphomas, the risk of anal cancer is less clearly related to CD4 cell count[71,72] and there has been no decline in incidence in the post-HAART era.[67] The typically late clinical presentation, morbidity of treatments for invasive disease and high relapse rates indicates that effective early detection and treatment of pre-invasive disease may be of considerable importance. Anal cancer has many parallels with cervical cancer in that human papillomavirus (HPV) infection is the causative factor in nearly all cases, and there is a spectrum of anal pre-cancerous changes. The prevalence of anal HPV infection in HIV-negative MSM is 50–60% across all age groups. In HIV positive MSM the prevalence of any anal HPV genotype is 93% based on a meta-analysis of 21 studies.[64] Anal cancer probably arises due to HPV infection of metaplastic reserve cells at the junction of the anal squamous and rectal columnar epithelia but also occurs elsewhere in the anal canal and perianal areas. Anal dysplasia is classified according to the Richart (AIN) or the

LAST (LSIL/HSIL) terminology.[40] Progression from high grade squamous intraepithelial lesion (HSIL) is thought to culminate in invasive anal cancer. It has been suggested that much LSIL is associated with low-risk HPV genotypes and that the risk of progression to malignancy is therefore low.[73] Compared to cervical cancer, a greater proportion of anal cancers is caused by HPV16/18.[3]

In HIV-negative MSM, the prevalence of LSIL and HSIL is 15% and 5% respectively[74] and HSIL prevalence reaches up to 43% in HIV-positive MSM.[75–77] The rate of progression from AIN3 to anal cancer is not well known, estimates vary widely. Some small prospective studies of subjects with HSIL who were under active surveillance and received surgical interventions or declined treatment showed progression to invasive cancer in up to 10% over 5 years.[78–80] However, these figures contrast with a meta-analysis that estimated average annual progression to be only 0.2%.[81] Similarly, a retrospective study of 2804 people living with HIV who had baseline HSIL anal cytology had an estimated 5-year risk of progression to anal cancer of 1.7%.[82]

Approaches to anal cancer screening and management

Since AIN2/3 is the likely precursor of anal cancer, and given the parallels in natural history with cervical cancer, screening programs based on anal cytology have been proposed for many years.[83] The diagnostic accuracy of anal cytology has not been systematically evaluated. Compared to high resolution anoscopy (HRA) the sensitivity of anal cytology ranges from 61% to 93% and the specificity from 32% to 67% in various populations.[84,85] Several biomarkers have been evaluated in MSM populations and have shown performance for detection of HSIL comparable to what has been observed for cervical lesions.[86]

There is no established clinical management for HSIL, nor has the value of any therapy been unequivocally demonstrated. Infra-red coagulation of HSIL yields regression rates of 35–63% with follow up between 6 and 14 months.[87,88] Studies of imiquimod treatment have reported response rates up to 74%, but with limited follow-up time and high recurrence rates.[89,90] Trichloroacetic acid applied topically at HRA has been shown to cause regression of 71% of HSIL.[91] However, a common problem associated with topical treatments is the high rate of relapse. In one clinical trial, 58% to 71% of HSIL relapsed by 72 weeks depending on the treatment used.[92]

So far, anal cancer screening pilot studies have rarely evaluated appropriate endpoints, often included symptomatic as well as asymptomatic individuals and have not included a control group. Due to the limited evidence, few evidence-based guidelines currently address anal cancer screening.[93] Recently, a large randomized study has been initiated in the US to systematically evaluate whether treatment of anal HSIL reduces incidence of anal cancer (ANCHOR study).[94]

In a recently published pilot study of HRA screening, 368 asymptomatic HIV positive MSM were followed up to 13 years and patients with high grade AIN were treated with imiquimod, trichloroacetic acid or surgical excision. Despite repeated screening and interventions, 5 patients (1.4%) developed invasive anal cancer. Progression to cancer was associated with higher age and AIN3.[76] These findings suggest that HRA screening followed by treatment of high-grade AIN can reduce but not avoid the risk of anal cancer. All tumors in this population were early stage and could be successfully treated, suggesting that screening by HRA may reduce cancer mortality.

This model of downstaging has been explored in a number of studies of annual digital rectal examinations (DARE) among HIV positive MSM. Investigators found that that a DARE was highly acceptable to MSM.[95] A cost effectiveness analysis of this approach recently found that adding DARE to routine HIV care was cost effective for MSM with HIV.[93]

Summary

Screening programs are complex entities and establishing or changing programs requires considerable investment to ensure that appropriate evidence is available supporting population-level effectiveness and cost-effectiveness. The biggest task for cervical cancer prevention is to expedite an integrated approach of HPV vaccination and HPV-based screening. Important questions that need to be addressed include the optimal triage of HPV-positive women, optimal age of starting and ending screening, and optimal screening intervals. For most countries, a pragmatic unified approach for unvaccinated and vaccinated women seems most appropriate, managing women based on the risk in unvaccinated women. Importantly, many screening and management options described here and pursued in HIC are not feasible in LMIC and the strategies may differ substantially. The improved understanding of HPV-related carcinogenesis has led to development of many great tools for cancer prevention. But there clearly is no "on-size-fits-all" approach: The challenge now lies in the optimal implementation of these tools in very different settings.

Competing Interests

CKF has received honoraria and travel funding from CSL and MSD and owns shares in CLLS Biotherapies.

ME has advised, but does not receive an honorarium from any companies. In specific cases his employer has received payment for his consultation from Photocure, Papivax, Inovio, PDS Biotechnologies, Natera and Immunovaccine. If travel is required for meetings with any industry, the company pays ME's travel-related expenses. Also, his employers have received grant funding for research-related costs of clinical trials that ME has been the overall PI or local PI for the past 12 months from Baxalta, Pfizer, Inovio, Photocure, Fujiboro, Eli Lilly, PDS Biotechnologies and Becton-Dickinson.

JB has received speakers' fees from Qiagen and consultancy fees from Roche, DDS Diagnostic Laboratory, GlaxoSmithKline, and Merck/SPMSD, and all fees were collected by his employer.

KC is PI of an investigator-initiated trial of cytology and primary HPV screening in Australia ("Compass"), which is conducted and funded by the Victorian Cytology Service

(VCS), a government-funded health promotion charity. The VCS have received equipment and funding contribution for the Compass trial from Roche Molecular Systems and Ventana, Inc., USA. However, neither she nor her institution on her behalf (Cancer Council NSW) receives direct funding from industry for this trial or any other project.

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