Optimizing secondary prevention of cervical cancer: Recent advances and future challenges

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Abstract
Although human papillomavirus (HPV) vaccines offer enormous promise for the ultimate control and possible elimination of cervical cancer, barriers to uptake and coverage of the vaccine both in high- and low/middle-income settings mean that advances in secondary prevention continue to be essential to prevent unnecessary deaths and suffering from cervical cancer for decades to come. While cytology (the Pap smear) has reduced cervical cancer incidence and prevalence in jurisdictions where it has been systematically implemented in population-based programs—mainly in high-income settings—limitations inherent to this method, and to program delivery, leave many women still vulnerable to cervical cancer. Recent evidence has confirmed that screening based on HPV testing prevents more invasive cervical cancer and pre-cancerous lesions, and offers innovative options such as self-collection of specimens to improve screening uptake broadly. In this paper, we review key advances, future opportunities, and ongoing challenges for secondary prevention of cervical cancer using HPV-based testing.

KEYWORDS
Cervical cancer; Eradication; HPV; Screening; Self-collection

1 | BACKGROUND

With the approval of the 9-valent human papillomavirus (HPV) vaccine, we move a step closer to the elimination of cervical cancer.1 However, elimination will only be possible with high rates of vaccine uptake for young girls across the globe, in all regions and countries. To date, addressing barriers to HPV vaccine uptake, such as acceptability, cost, and program infrastructure, remain a significant challenge for most countries, particularly in low- and middle-income countries (LMICs). A recent review of HPV vaccination found that globally, only 32.1% of girls aged 10-20 years in high-income settings and approximately 0.3% in low- and middle-income settings—where cervical cancer rates remain highest—have had an HPV vaccination series.2 An additional challenge is that the vaccine prevents viral infection at relatively young ages, and this infection results in cancers that occur decades later.3 Thus, any woman who did not receive the vaccine prior to infection with oncogenic HPV types may be at risk for developing cervical cancer, and she requires access to effective secondary prevention—i.e. screening, with treatment when needed. Without efforts to improve both the quality of, and access to, screening, it is estimated that the number of women developing cervical cancer annually worldwide will rise to more than 700 000 by 2030.4 Therefore, improving secondary prevention of cervical cancer should remain a key priority for women’s health globally for decades to come. Efforts need to focus on better access to, and improvements in, molecular platforms for detection of the HPV virus. In this paper, we describe recent advances in optimizing the effectiveness and access to secondary prevention for cervical...
cancer and outline the challenges and future priorities for researchers, policy specialists, and program leaders globally.

2 | SECONDARY PREVENTION OF CERVICAL CANCER

Cervical cancer is one of the few cancers with effective tools for both primary prevention, with the HPV vaccine, and secondary prevention, using screening tests to facilitate early detection and treatment of precancerous lesions.1 By detecting precancerous lesions through screening and then effectively treating them with ablative or excisional methods, development of invasive cervical cancer can be prevented. The cornerstone of screening programs in high-resource settings has been cervical cytology (Pap smears), ever since its introduction in the 1940s.2 Cytology-based programs have resulted in a significant reduction in cervical cancer in areas where they have been widely and properly implemented, but there are considerable limitations with this test.5 In well-designed studies, although the specificity of cytology for cervical intraepithelial neoplasia (CIN) 2+ is over 95%, the sensitivity of a single Pap is around 53%—far from optimal for a cancer screening test.6 In addition, a multi-center screening study in India concluded that the sensitivity of cytology varied widely between various sites.7 As a result of the low sensitivity, women need to undergo repeat cytology on a regular basis to ensure precancerous lesions are detected. In addition, to function reliably, cytology programs require substantial infrastructure, highly-qualified human resources, and a well-defined quality control system, which have proved to be costly and difficult to implement for most LMICs. This has resulted in the global disparity seen for cervical cancer rates, with LMICs experiencing over 80% of the global deaths from cervical cancer.8

With the understanding that persistent infections with high-risk HPV types are necessary for development of cervical cancer,9 and with knowledge of the limitations of cytology as a screening test, new opportunities have appeared for using molecular tests for the viruses themselves. These technological advances have permitted lengthening of screening intervals and initiation of screening at a later age, compared with the practice for cytology.

3 | HPV TESTING AS THE PRIMARY SCREENING METHOD

Data from large clinical trials and other studies have established that screening women for HPV leads to decreased rates of cervical cancer. In their comprehensive pooled analysis of four studies that had two rounds of screening and included HPV testing as part of the intervention, Ronco et al.10 showed an increased detection of CIN 3+ (the immediate precursor to squamous cell carcinoma of the cervix) in the first round of screening, followed by a reduction in CIN 3+ and, most importantly, invasive cervical cancer, after extended follow-up. As cytology is known to have limitations in detecting glandular lesions, HPV-based screening programs will also improve detection of adenocarcinoma.

While co-testing with both cytology and HPV tests is an option for screening programs, studies have confirmed that there is limited benefit from adding cytology to HPV screening. Long-term studies from Kaiser Permanente that included over 1 million women found that HPV testing has a very high negative predictive value for precancerous lesions.11 Women with negative HPV tests were very unlikely to develop precancerous lesions in the next 5 years. The 5-year risk of CIN 3 or cancer following a negative HPV test was 0.14%, whereas for women with a negative cytology it was 0.31%.11 The screening benefit of co-testing is largely driven by HPV testing and not cytology.

Based on data showing improved detection and reduced invasive cancers with HPV screening, leading health agencies and expert groups—including the WHO, the American Society for Clinical Oncology (ASCO), the American Society for Colposcopy and Cervical Pathology, and others—have recommended HPV testing as the primary screening method for cervical cancer screening programs in jurisdictions with sufficient resources.12-15 Depending on resources and existing capacity, jurisdictions can also opt for continuing with cytology or using visual inspection with acetic acid (VIA). But all should be examining opportunities to advance to HPV testing, given the vastly improved sensitivity and quality assurance, the opportunity to automate testing, and, ultimately, the prospect of reducing the overall number of lifetime screenings for women.13

4 | IMPLEMENTING HPV TESTING IN LOW-RESOURCE SETTINGS

While there is now consensus that the primary screening method for cervical cancer should be HPV testing where possible, numerous questions remain regarding the implementation and optimization of these programs. In LMICs, while HPV testing offers the opportunity for very accurate once-in-a-lifetime screening, there are significant infrastructure requirements to implement molecular-based testing effectively. Regions need to examine how to best facilitate access to this very effective tool for cancer prevention.

As noted above, HPV testing has a very high negative predictive value, which means that screening intervals can safely be extended for women who are HPV negative. In fact, there are unintended consequences if screening is done too frequently, as incident HPV infections that are likely to clear within a 3–4-year time period may be detected and lead to unnecessary and potentially harmful treatment.16 As such, it is essential that programs ensure that screening with HPV testing is not done too frequently. The 2014 guidelines from WHO recommend HPV screening every 5 years,12 and the 2016 ASCO guidelines recommend 2–3 screenings in the lifetime using HPV testing if resources are limited.13

5 | SELF-COLLECTION OF SAMPLES

As with HPV vaccination, high coverage with screening is required in the population at risk to reduce the incidence and mortality rates for cervical cancer. Unfortunately, in many jurisdictions, even with
longstanding screening programs, coverage rates remain very low (10%–20% in the poorest wealth deciles), resulting in socioeconomic, geographical, cultural, and educational disparities evident in screening rates and in follow-up for evaluation and treatment. A critical advantage of HPV testing over cytology is the capability for using self-collected vaginal samples, which represents an opportunity to offer solutions to these coverage disparities. For many women, in both high- and lower-income settings, attending clinical appointments can be challenging owing to childcare, work schedules, and transportation requirements. In addition, for many women, undergoing a pelvic examination is personally difficult owing to cultural barriers such as exposing private genital areas to an unknown evaluator, pain experienced in previous evaluations, or past history of abuse.

Self-collection has already proved to have substantial acceptability for women across a variety of jurisdictions and has demonstrated impressive diagnostic accuracy compared with clinician-collected specimens.

Even though there is no test yet approved for use with self-collected vaginal samples, data about the sensitivity and acceptability of self-collection among women who have prompted several countries to move ahead with that strategy. In a meta-analysis, self-collection has been found to significantly increase participation in cervical cancer screening in women who did not routinely attend screening programs previously. Self-collection offers an opportunity to engage women, as it can be offered in a variety of settings, including at home, community centers, places of gathering, and clinical sites. Self-collection also means that practitioners do not need to conduct the first part of screening—collection of the specimen—and allows programs to focus scarce resources on follow-up of women who are HPV positive. In addition, with a paradigm shift to integration of broader reproductive health issues, self-collection for HPV testing can be coupled with testing for sexually transmitted infections, such as Chlamydia trachomatis and Neisseria gonorrhoea, further expanding access to important reproductive health interventions for women.

Several jurisdictions are examining how to implement self-collection to improve screening uptake. As the Netherlands transitions to HPV-based primary screening, they plan to offer self-sampling devices to women who do not respond to invitations for screening. Several countries in Latin America are implementing HPV testing in their national screening programs. Argentina was the first country to implement HPV-DNA testing within the population-based screening system in several provinces. In that country’s initial experience, the uptake of screening increased from 20% with Pap smear to 86% when it was done with HPV-DNA testing using vaginal samples self-collected by women. The same authors also demonstrated that the detection rate of CIN 2+ almost doubled from 0.6% to 1.06%. More recently, four Central American countries (El Salvador, Guatemala, Honduras, and Nicaragua) have begun introduction of careHPV (Qiagen, Gaithersburg, MD, USA) testing in their national programs; Guatemala and Nicaragua are using the self-sampling strategy that allowed them to reach hard-to-reach populations in pilot studies; nearly half of women screened with the self-collection strategy were never screened in the past. Experience in Uganda with community-based self-collection has also confirmed substantial acceptability, with uptake rates of greater than 95% compared with attendance of 48.4% for screening by VIA.

6 | PERFORMANCE OF HPV TESTING

While HPV testing offers vastly superior sensitivity than cytology for detection of precancerous lesions, its lower specificity means that there could be an increased number of unnecessary diagnostic or treatment procedures. Additional tests can triage HPV positive results to improve specificity by delineating which HPV-positive women require follow-up. Triage testing could include cytology, VIA, tests for specific HPV genotypes, mRNA tests, assays for DNA methylation, and tests for other biomarkers. Further research, including using stored specimens and economic modeling, is urgently needed to provide programs with guidance on the impact of different triage methodologies on specificity, detection rates, and overall program impact and costs. The International Agency for Research on Cancer (IARC) is implementing an evaluation of triage options for women with positive HPV test results; the multicountry evaluation is being developed in several countries in Central and South America. Recently, the US Food and Drug Administration has approved the cobas HPV test (Roche, Basel, Switzerland) as a primary cervical cancer screening test; this test detects DNA from 14 high-risk HPV types. The development of new simpler, accurate, and cost-effective kits for HPV DNA—such as the careHPV test (portable, short interpretation time of 2.5 hours, low cost and accurate)—could make HPV DNA testing a promising screening strategy for LMICs.

7 | QUALITY ASSURANCE

Comprehensive quality assurance programs, particularly in low-resource settings, are a crucial consideration for the implementation of HPV-based cervical cancer screening. Such programs should mirror best practices for other laboratory programs and encompass aspects such as training, laboratory processing, and overall program implementation. All relevant tiers of healthcare personnel should receive appropriate training, including how to collect and report specimens, transport and store specimens, conduct laboratory testing, and deliver results. Once trained, healthcare personnel should undergo regular proficiency assessment to ensure they are performing their work in accordance with test requirements and national guidelines.

Test instruments, reagents, laboratory supplies, and specimens need to perform properly in the test environment, which is a particularly important consideration for low-resource settings. Screening programs should ensure that the laboratory environment meets the manufacturer requirements for their specific test (e.g., consistent supply of electricity, lab temperature, and humidity requirements). Programs need to develop tools to ensure adherence to storage and handling instructions and to procure the correct supplies. Quality assurance of overall program implementation should consider the entire test continuum and monitor key steps and processes to ensure
high-quality testing and accuracy of results delivered to patients. Standard operating procedures, checklists, and other tools will assist program managers in identifying and monitoring these areas of importance.

8 | TREATMENT AFTER SCREENING

Screening programs offer benefits to individuals only if safe, accurate, and accessible follow-up and treatment are available. Indeed, without a pathway that leads from screening to treatment, neither programs nor the participants will gain any benefit, and the screening will only create anxiety and distress for women. Women who are positive on screening must be referred to receive effective and reliable clinical management. Women suspected of having invasive cancer should have access to appropriate follow-up with colposcopy and, where needed, cancer centers staffed with trained surgeons and physicians to conduct appropriate gynecological surgeries and chemotherapeutic and radiation interventions to treat cancers.

9 | HEALTH INFORMATION SYSTEMS

In settings where women will have more than once-in-a-lifetime cervical cancer screening, effective health information systems are required to facilitate communication about previous screening results and call-back systems. With the extended screening intervals for women tested for HPV, mechanisms to ensure they maintain engagement with practitioners between screening visits and follow-up will ensure that screenings are not missed. Creative and innovative solutions that are based on new technologies, including use of mobile health (mHealth) platforms and tele-health could keep women engaged with screening and ensure timely and appropriate follow-up.

10 | COMMUNITY AND PROVIDER EDUCATION

Cervical cancer screening with cytology, as a long-established disease prevention activity, is well entrenched in many jurisdictions. The shift from cytology to HPV testing will be a significant change—from an oncologic screening paradigm to a communicable disease paradigm. Even when understood and supported, such a substantial change in a long-established program with a broad reach will have significant implications for both participants and practitioners. Studies of both groups have demonstrated hesitancy in adopting HPV testing for cervical cancer screening and continued misunderstandings about the reasons for the extended interval and later starting age for screening with HPV testing.31,32 Careful education about the rationale of the switch from cytology to HPV, the meaning of an HPV-positive result, implications of HPV acquisition and resolution, reasons for extended and delayed screening, and treatment requirements are essential to ensure there is not a reduction in screening acceptability using HPV testing.

11 | SCREENING PROTOCOLS IN SPECIFIC POPULATIONS

Although there is considerable room for improvement, jurisdictions globally are starting to implement population-level HPV vaccination programs for girls.5 With the reduction in cervical dysplasia seen after HPV vaccination, screening protocols will need to adjust and evolve to consider a woman’s screening history, age, and HPV vaccination history, among other factors. Rigorous development of these protocols is required to provide practitioners with optimal guidance.

Special populations, such as HIV-positive women, who are at greater risk for cervical cancer than the general population, will require unique screening protocols that take the clinical status of the patient into consideration. Specifically, HIV-positive women who are virally suppressed and treatment-adherent may have cervical cancer screening protocols that more reflect the general population. Women who have high viral loads and low immune function may require more frequent screening, and more rapid referral to treatment and follow-up.

Ultimately, to achieve our goal of cervical cancer elimination, we need to reach the point when HPV vaccination coverage is equitably high across all regions and all birth cohorts. Over time, more and more women in the age span appropriate for cervical cancer screening will have been vaccinated against HPV, so screening policies will have to be revisited when this ideal scenario is reached.33 The reduction in transmission of the vaccine-targeted HPV types in the population and the consequent rarity of cervical lesions caused by these types will lead to a change in the balance of benefits to harms from cervical cancer screening, even with the improved molecular technologies now coming of age.34 A future challenge to this end is defining the research agenda for deciding on the optimal technology and intensity of screening to make cervical cancer a very rare disease while minimizing the possible harms from screening for a very rare condition.

AUTHOR CONTRIBUTIONS

All authors participated in designing the original outline for the paper. GO wrote the first draft of the manuscript. All authors contributed to substantive revisions and editing of the final manuscript.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare. In terms of involvement with industry, GO has not received industry grants, funds, or honoraria. However, her co-investigators have received contract funding paid to their institution to compare the accuracy of different manufacturers’ HPV assays as adjunct studies to the main
HPV FOCAL trial. EF has served as occasional consultant to pharmaceutical (GSK, Merck) and biotechnology (Roche, Gen-Probe, BD, Qiagen, Ikonisys) companies involved with HPV vaccination, HPV diagnostics, and cervical cytology screening. WH serves as a consultant to InCellDx and Merck Vaccines. JJ was the co-owner and Deputy Manager of Onco Prev International, a Peruvian company, from 2012 through March 2017. Onco Prev offers cervical cancer screening services and in 2016 also began positioning for distribution of medical devices including colposcopes and the Liger thermo-coagulator. Onco Prev International did not commercialize any medical instrument during the time JJ was part of that company. The other authors report no involvement with industry.

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