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Review

The impact of human papillomavirus vaccination on cervical cancer prevention efforts

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ABSTRACT

Objectives. To review concepts, information, obstacles, and approaches to cervical cancer screening and prevention as vaccination against human papillomavirus (HPV) types 16 and 18 is adopted.

Methods. Expert forum, conducted September 12–13, 2008, hosted by the Society of Gynecologic Oncologists, including 56 experts in cervical cancer and titled *Future Strategies of Cervical Cancer Prevention: What Do We Need to Do Now to Prepare?*

Results. The current approach to cervical cancer screening in the U.S. is limited by its opportunistic nature. If given to women before exposure, a vaccine against HPV 16,18 can decrease cervical cancer risk by up to 70%. The impact on abnormal cytology and cervical intraepithelial neoplasia (CIN) will be less but still substantial. As the prevalence of high-grade CIN falls, fewer women with positive screening tests will have truly preinvasive disease. To minimize harm from false positive tests in women who are at low risk for cancer because of early vaccination, later initiation of and longer intervals between screenings are ideal. However, the vaccine is less effective when administered after first intercourse, and delivering and documenting HPV vaccination to girls at optimal ages may prove difficult.

Conclusions. Until population-based data on the performance of cytology, HPV testing, and alternate screening or triage interventions become available, modifying current screening guidelines is premature. Current recommendations to initiate screening as late as age 21 and to screen less often than annually are appropriate for young women known to have been vaccinated before first intercourse.

Contents

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Introduction

The introduction of a vaccine against human papillomavirus (HPV) types 16 and 18 promises to be a significant advance in efforts to minimize the impact of cervical cancer on women globally. When given to previously uninfected women, these vaccines appear to prevent most HPV 16,18 related precancerous lesions of the lower genital tract and by implication the cancers that otherwise might develop [1,2].

However, public health measures instituted over the past several decades have already made substantial inroads against cervical cancer. Once a leading killer of women, in 2009 cervical cancer is expected to occur in 11,070 women and to result in 3870 deaths [3]. This is largely attributable to widespread adoption of Pap screening [4,5], with established guidelines for management of abnormal results [6]. By preventing type-specific HPV infection, HPV vaccination decreases the subsequent incidence of cervical cancer precursors. HPV vaccination is expected to have a significant impact on screening and treatment guidelines in the future, but current guidelines are unchanged [7]. On September 12–13, 2008, the Society of Gynecologic Oncologists convened a forum including 56 cervical cancer experts from clinical medical, epidemiology, regulatory, and public health fields to discuss issues related to cervical cancer prevention arising as HPV vaccination is implemented more widely. The forum, titled "Future Strategies of Cervical Cancer Prevention: What Do We Need to Do Now to Prepare?" consisted of five sessions that addressed specific public policy, clinical, and cost-effectiveness issues. This paper highlights concepts, information, obstacles, and approaches discussed during sessions of the forum that focused on how the dissemination of HPV vaccination may affect screening recommendations.

Limits to current screening

Current guidelines recommend initiating Pap testing three years after first intercourse and no later than age 21 years, continuing every one to two years until age 30, and then screening at one- to three-year intervals until age 65–70 or indefinitely [4,5]. Despite recommendations to the contrary, most U.S. practitioners continue to screen at annual intervals [8]. Models suggest that annual screening of women with extensive prior screening is not cost-effective [9]. The risk of cancer in young women is quite low, and assessment of changes in cervical cancer rates where comprehensive screening has been initiated suggests that screening has little impact on rare early-onset cancers, especially those presenting before age 25 [10]. Screening after hysterectomy for benign indications also is not cost-effective, though still commonly done [11,12]. Overscreening can result in patient harms, including missed work, travel and child care costs, anxiety, stigmatization, and obstetric and surgical complications from treatment of lesions that would not have progressed to cancer [13,14].

While some women are overscreened, the absence of an organized screening program in the United States results in a substantial proportion of women falling outside the prevention system. Underscreened women account for some 50% of cervical cancers diagnosed in the U.S. [15]. Regrettably, with cost a barrier to care, increasing the intensiveness of screening among women in regular care to compensate for this not only has minimal impact, but the resulting cost increases also may raise barriers to access, decreasing the screening of at-risk women.

In addition, medicolegal concerns likely promote excessive screening, both by increasing the frequency of screening and by driving the development of more sensitive but less specific screening tests, as missed lesions on Pap specimens ranks third among the common causes of medical negligence claims against U.S. pathologists [16]. Most findings identified by cervical screening, including carcinogenic HPV infections, atypical and low grade cytology results, and grade 1 cervical intraepithelial neoplasia (CIN) are in fact not premalignant but rather clinical manifestations of transient HPV infections. A minority of these abnormalities may progress to cancer, and distinguishing these requires longitudinal observation. When patients or clinicians find observation burdensome, needless treatment may result.

Increasing evidence suggests that testing for carcinogenic HPV infection may be a useful replacement or adjunct for conventional cytologic screening in cervical cancer prevention programs [17]. However, barriers to adoption of HPV screening are multiple. Appropriate follow-up for a positive stand-alone test, an approach that is currently investigational, is unclear and may include interval repeat HPV testing, reflex cytology, colposcopy, or other interventions. HPV testing requires patient education. Some consider HPV exclusively as a sexually transmitted disease whose diagnosis results in stigmatization, anxiety, and anger [18]. Others overestimate the cancer risk underlying the diagnosis of a carcinogenic HPV infection, driving overtreatment. Also, extending screening intervals using HPV testing may pose a financial disincentive to some clinicians.

Cytology is limited by human error, fatigue, and subjectivity, by sampling errors, and by lesion biology [19]. Specimen collection requires technical skill in obtaining samples to ensure assessment of the full transformation zone. As a triage test, colposcopy appears to miss a quarter of CIN3 lesions identified during two years of observation of women with ASCUS cytology [20]. Clinician interpretations of colposcopic findings are limited; reproducibility of colposcopic diagnosis is problematic even among experts, and lesion detection and eradication require training to develop skills in performing colposcopy and treatment. Problems maintaining proficiency in cytologic and colposcopic interpretation will likely increase as vaccination results in a decline in the prevalence of serious abnormalities. Some patients fail to understand that these processes are imperfect, that a single negative test does not mean no cancer risk, and that even with annual lifetime screening some cancers will be missed. These unrealistically high expectations of screening increase medicolegal hazard and drive overscreening [19].

Impact of eliminating HPV 16/18

Given the decade-long lag between HPV infection and the development of cancer, even universal HPV vaccination will have minimal impact on cervical cancer rates for decades after vaccine introduction [21]. This means that current phase III trials will be unable to demonstrate efficacy against cancer as an endpoint, and ongoing population-based studies will require decades as well. However, impact on cancer precursors has been demonstrated in vaccine trials and may be apparent in the general population within a few years [1,2]. Recent surveys indicate that some 25% of women 13–17 years of age have been vaccinated against HPV 16,18 [22], and consideration of the impact vaccination should have on screening and cancer prevention will become increasingly important as these young women age.

The impact of HPV vaccination on colposcopy usage will be modest unless screening is done less frequently [23]. Eliminating HPV 16,18-associated lesions should decrease the risk of cervical cancer by up to 70%, but screening must continue or cancers caused by carcinogenic HPV types other than 16,18 will occur. Understanding the impact of vaccination on colposcopy triage and treatment requires an appreciation of epidemiologic and statistical perspectives. HPV types other than 16 or 18 are more common in cancer precursors than in cancer [24], reflecting the lower risk for progression to cancer associated with these types. However, estimating the proportion of cervical disease attributable to HPV 16,18 is complicated by the common occurrence of multiple HPV genotype infections. In screening populations, 30–54% of HPV-positive women harbor multiple HPV genotype infections [25–28], as do over 50% of HPV-positive women in referral populations [29–31]. In all these studies, HPV16 was the most common genotype found, but co-infections with other carcinogenic genotypes were frequent. While analyzing HPV genotypes from

biopsies can increase the proportion of single genotypes and facilitate causative attribution, it is not trivial to determine lesion-specific genotypes [32,33] and the available data are limited [24].

Despite ambiguities arising from multiple-type HPV infections, vaccination before HPV exposure will reduce the prevalence of precursor disease in the female population but at a rate lower than 70%. Extrapolations from data from the longitudinally observed Guanacaste cohort suggest that removing HPV 16,18 from the population would result in a 17% overall reduction in Pap abnormalities, with reductions of 8% in ASCUS, 23% in LSIL, 45% in HSIL, and 72% in invasive cancer [34]. Thus, the greatest impact of vaccination on cytologic diagnosis will be a reduction in HSIL, while impact on atypical and low grade cytology will be less. Since these borderline cytologic changes make up the majority of colposcopy referrals, vaccination's impact on colposcopy resource utilization is likely to be attenuated compared to the impact on true cancer precursors and cancer.

The accuracy of screening tests is not expected to change dramatically as the prevalence of premalignant lesions declines in the vaccinated population, although maintaining proficiency among cytotechnologists as HSIL rates fall from the current 0.5% will be difficult. As the prevalence of true cancer precursors decreases while test accuracy remains constant, a very high negative predictive value will result, with a concomitant fall in positive predictive value (PPV) [34,35]. Lower PPV means that most abnormal tests will be falsely positive–that is, will not lead to a diagnosis of CIN2+–either because lesions are misidentified as neoplastic or because they represent infection with HPV types with a lower risk of progression to cancer than HPV 16,18. A lower PPV also means that much subsequent treatment in a vaccinated population will be overtreatment. For example, many cases of CIN2 are transient, and the proportion of transient lesions would be expected to rise as the absolute risk of progression to cancer falls with the elimination of HPV 16,18. Although this may lead to a greater emphasis on observation for lesions less than CIN3, there may be an increase in risk for those lesser lesions that nevertheless represent preinvasive disease. Revised guidelines will need to balance the risk of overtreatment of many women with the risk of missing true preinvasive disease in a relatively smaller number. This may increase risk for those with true preinvasive disease.

Implications for screening

Since HPV vaccination prevents infection by targeted HPV types but is not therapeutic, its cancer prevention benefit is greatest for girls vaccinated before first intercourse. A rational shift in screening strategies after widespread vaccination would be to initiate screening later and less often in these women. The more immediate impact may result from later initiation of screening. Since cervical cancer is rare before age 25 and since cytology is minimally effective in identifying preventable cancers destined to arise in women before age 25 [10], later initiation of screening should result in few missed cancers. Since most abnormalities on Pap or HPV tests are attributable to transient HPV lesions with minimal oncogenic potential, later initiation of screening also would decrease false positive tests, those associated with HPV disease destined to resolve without therapy. Fewer false positive tests would in turn mean less use of needless triage and follow-up tests, lower costs, and fewer cancer prevention treatments that carry potential for harm, especially preterm delivery with subsequent pregnancies.

Extending intervals between screening tests also would allow for regression of transient lesions. These lesions are truly abnormal (i.e., there are atypical or dysplastic cells on cytology or HPV is detected in DNA assay), but they are falsely positive from a cancer prevention perspective because they have minimal malignant potential. Models suggest that in unvaccinated women screening every 3–5 years is optimally cost-effective [9]. Most CIN3 lesions and cancers found within 10 years of a negative Pap in mature women occurred in women who were HPV 16 and/or HPV 18 positive [36]. Prolonging screening intervals for vaccinated women should be safe, especially because the lower prevalence of lesions resulting from vaccination increases the negative predictive value of a normal test.

Obstacles to a separate screening recommendation for vaccinated women

One barrier to developing a separate guideline for women vaccinated against HPV is the difficulty in defining the specific population. Although vaccine recommendations target routine immunization for girls 11–12 years of age [37], catch-up vaccination of women through age 26 is acceptable: although benefits decline as risk for exposure to included HPV types rise, the risk of infection with all vaccine types is low, and some benefit may accrue. However, studies have suggested that vaccine efficacy falls with age, increasing numbers of lifetime sexual partners, and abnormal cytology. In intent-to-treat arms of clinical trials, efficacy fell from >90% in per-protocol women to about 30% in women with risk factors [1]. In a recent cost-effectiveness study, extending recommendations for attenuated screening to those vaccinated after first intercourse actually increased in cervical cancer risk in the latter group over current guidelines [38]. Efficacy also may fall when vaccination series is incomplete, and attenuating screening for women who failed to receive all three vaccinations may increase risk. Women may not recall vaccination accurately: unvaccinated women may recall vaccination for other diseases, resulting in increased cancer risk if attenuated screening is applied, while adolescents may not recall vaccination years later. Development of a comprehensive vaccine registry for adolescents and adults might allow clinicians to verify vaccination status, but current vaccination registration registries are inadequate or nonexistent for nonpediatric populations. In part because some HPV vaccines are being given by clinical specialists such as gynecologists who do not traditionally deliver childhood or adolescent vaccines and so have not adopted the practice of registering vaccination, even states with web-based vaccine registries may have incomplete information. Medical specialists should engage with existing vaccine registration programs, and agencies should collaborate to facilitate compilation of lifetime vaccine data in states where lifetime registries not already exist.

Measuring vaccine uptake

While initial uptake of the vaccine has been rapid compared to other recommended but not mandated vaccines early in their post-approval periods, compliance with the full three dose series with the appropriate time intervals between doses has been relatively poor, even in the early adopters who are generally more educated and more knowledgeable about the vaccine and infection than the general population [39]. Studies of vaccine efficacy after two vs. three injections are ongoing and may provide insight into differences in efficacy between fully and incompletely compliant vaccine recipients. Population-based studies sponsored by the CDC and other registries co-sponsored by universities or healthcare entities are ongoing and will provide data to support altering screening recommendations in the vaccine era.

Registries would facilitate retrieval of accurate vaccination records across providers and healthcare delivery systems. While HPV genotyping is not generally available to U.S. clinicians, registries that link HPV vaccination data with cytology and HPV genotyping results would provide the most comprehensive picture to help determine future screening strategies in the HPV vaccine era. Creating these registries will require new public funding and will also require data inputs from a variety of sources, including existing registries, electronic and paper medical records, and billing claims data. The value of this data increases if the information on vaccine uptake as well as screening

and diagnosis can be linked to patient histories. However, creation of such comprehensive registries will not be easy in the face of privacy laws protecting health information. The requirement for additional public funding will impose an additional constraint.

Population-based HPV genotyping detects the earliest expected HPV vaccine impact and is 1) a more sensitive initial indicator of vaccine impact than either cytologic or histologic outcomes, 2) less observer-dependent and 3) amenable to standardization, automation and required large-scale evaluations. Although genotyping is not useful in individual cases, studies defining population-based HPV genotype prevalence at baseline and following HPV vaccine introduction also will be informative for evaluating changes in the positive predictive value of screening. Tracking HPV genotypes would be able to identify vaccine cross-protection or the replacement of HPV 16,18 by other types if this occurs in widely-vaccinated populations.

Considering the future

Development of a separate guideline for screening vaccinated women is not feasible at present because of the difficulties inherent in defining women to whom it might apply. Currently, vaccinated women should continue cervical cancer screening according to recommendations applied to the general population of unvaccinated women.

Even for women who are unvaccinated, strong scientific evidence supports biennial screening using liquid based technology for women in their twenties and biennial to triennial screening for women ages 30 and above [4]. Despite this, many U.S. clinicians have not adopted screening intervals beyond one year and are refractory to cost-effectiveness considerations [8,40,41]. Women's belief that recommendations to screen later and less frequently arise from cost considerations rather than balanced safety concerns may also inhibit uptake of newer screening recommendations [42]. Nevertheless, for reasons discussed above, vaccination should lead U.S. clinicians away from annual Pap testing. As the penetrance of HPV vaccination into the population rises and the prevalence of HPV 16,18 falls, applying current permissive recommendations for later and less frequent screening tests will become compelling, especially for women with documentation of early completion of full vaccination series. Whether those women are candidates to start screening at age 25 or later or are candidates for 5 year screening intervals remains an area for future research.

Later and less frequent screening will become acceptable public policy only if vaccination uptake is evenly distributed across social and economic strata or if clinicians can reliably identify adequately vaccinated women for less intensive screening. Identifying vaccinated women may require development of adult vaccine registries and broader clinician participation in existing registries, both of which are currently inadequate. If cultural differences result in the preferential adoption of vaccination by low risk women while rural, minority, and poor women at highest risk reject it, attenuating screening after reaching a threshold level of adoption in the population may paradoxically increase cervical cancer rates. Careful monitoring of vaccine acceptance by age cohorts according to ethnicity, socio-economic status, and geographic region will be important as policy planners continue to consider the implications of HPV vaccination on cervical cancer prevention strategies.

Conflict of interest statement

The forum was supported by grants from Merck, GlaxoSmithKline, Hologic, Roche, and Qiagen directly to the Society for Gynecologic Oncologists (SGO). The authors received no funding from these commercial interests but did receive honoraria and had expenses paid by SGO, except that Dr. Solomon and Dr. Wentzensen did not receive honoraria or paid expenses.

Dr. Massad and Dr. Wentzensen declare that they have no conflicts of interest.

Dr. Solomon is Medical Monitor for the Costa Rica HPV vaccine trial, which is fully supported by the National Cancer Institute, with the exception that GSK provided the vaccines for the study and paid for costs related to regulatory submission requirements.

Dr. Einstein receives no honorarium for advising, consultation or speaker participation from the following companies: Merck, GSK, Roche, Tigris, Nventa, PDS Biotechnology, Qiagen/Digene, and Hologic/Cytec. However, his employer, Montefiore Medical Center, receives monetary reimbursement for some of Dr. Einstein's industry-related time spent on these activities.

Dr. Myers has received research funding from Merck, and served as a consultant for Merck and GlaxoSmithKline.

Dr Wheeler has received funding through the University of New Mexico from GlaxoSmith Kline and Merck to conduct HPV vaccine research and from Roche Molecular Systems to conduct HPV genotyping research.

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