Invited Commentary

Screening Options for Preventing Cervical Cancer

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Human papillomavirus (HPV) is responsible for approximately 570 000 cases of cervical cancer worldwide every year.[1] Most of these cases of cancer could be prevented, either through early vaccination against high-risk HPV, or by successful screening and management of precursors of cervical cancer. Although childhood vaccination against HPV would be ideal, most women have not received the HPV vaccination and screening for precancerous lesions is generally effective, as long as abnormal results are effectively managed. Despite years of screening, it is still estimated that 13 000 cases of cervical cancer will occur in the United States annually.[2]

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Two studies appear in this issue of *JAMA Internal Medicine* that will inform continuing efforts to improve the effectiveness of cervical cancer screening.[3,4] In the first study, Sawaya and colleagues[3] report a cost-effectiveness analysis of a variety of screening strategies, in which the preferences of a diverse set of patients from 2 clinics are incorporated. They find that 2 strategies are the most cost-effective options. The first option is Papanicolaou testing every 3 years in women at average risk of cervical cancer (not immune suppressed and not vaccinated) with repeat testing in 1 year for a first test result of atypical cells of uncertain significance, and referral to undergo colposcopy of all other women with abnormalities on cytologic test results. The second option is cytologic testing every 3 years for women age 21 to 30 years, followed by an HPV test every 5 years (if all results are normal). Neither cotesting (Papanicolaou and HPV testing together for primary screening) nor primary HPV testing for women younger than 30 years was found to be cost-effective.

In the second study, Wentzensen and colleagues[4] focus on primary HPV testing among women age 30 years or older and evaluate the effectiveness of combining p16 and Ki-67 staining with cytologic samples (known as *dual stain*) for triage of women with positive results of testing for high-risk HPV and partial genotyping to further evaluation. They found that after results of a primary HPV test are found to be abnormal, it was more informative to triage patients using a cytologic test combined with p16 and Ki-67 staining than to triage using cytologic testing alone. Although the US Preventive Services Task Force recently endorsed primary HPV screening for women age 30 years or older who are at average risk for cervical cancer, at present there are no consensus guidelines for how to manage abnormal results.[5] The dual stain method offers a promising approach to the next step in determining which women need further evaluation and management.

Cervical cancer screening is based on an understanding of the natural history of the disease, the availability of sensitive and specific screening tests, and effective approaches to detect and manage precancerous lesions before they become cancer, while minimizing harm to the patient or excessive cost to the health care system. Historically, cervical cancer screening with annual Papanicolaou testing (ie, cytologic testing), with evaluation and treatment of all abnormalities, was successful because of the simplicity of the approach, the frequency with which it was repeated, and the aggressive approach to management of abnormalities.

Recently, more has been learned about the association of HPV infection with the development of cervical precancerous lesions and cancer, including that most infections will resolve spontaneously over several years without consequence to the patient. Some infections, however, persist, and it is these infections that may lead to cancer. The costs both to patients and society of overevaluation and management of transient infections are considerable, as demonstrated in the study by Sawaya et al.[3] Vaccinating all children and adolescents against high-risk HPV infection might prevent many of these challenges, but it will take years to realize the full beneficial effects of vaccination. At the same time, the options for screening have expanded to include primary HPV testing and cotesting with a Papanicolaou and HPV test. These advances, although encouraging, have inevitably made it more difficult for clinicians to know which patients to screen, with what test, how often, and how to manage abnormal results.

How can cervical cancer screening be simplified and managed? Both clinicians and patients have historically felt comfortable with annual Papanicolaou testing. However, multiple evidence-based recommendations, based on large studies conducted in the last 15 years, show that for women at average risk of cervical cancer, a 3-year interval with Papanicolaou testing alone is safe and minimizes overtreatment, while keeping cancer risk low.[6] Despite these findings, many women still receive annual testing. An easy change would be to perform Papanicolaou testing only once every 3 years, and refer all women with abnormal results for colposcopy. As Sawaya et al report,[3] this remains a cost-effective approach for women with a history of normal Papanicolaou test results. If cytologic testing is available and acceptable to clinicians and patients, the use of this approach could continue, with consideration of changes in the next several years.

Primary HPV testing alone is also an option for screening. As a result of findings from the 2015 ATHENA (Addressing the Need for Advanced HPV Diagnostics) study,[7] which studied primary HPV testing using the cobas test with well-defined study algorithms, its use is rapidly expanding. As of March 2019, only 2 primary HPV tests (cobas and BD Onclarity) were approved by the US Food and Drug Administration for primary screening, although more may become available soon. The American Society of Colposcopy and Cervical Pathology and 26 other national societies are currently convening to review data provided by the National Institutes of Health and to develop

evidence-based management guidelines for how to manage abnormal HPV screening results. At present, 2015 guidance, based on expert opinion, recommends using HPV16/18 genotyping and reflex cytologic testing after an initial abnormal HPV test result to determine the next steps.[8]

Cotesting (Papanicolaou and HPV testing together) is the easiest change to make. Both clinicians and patients generally find it acceptable and most laboratories offer this option. But the costs and harms of this approach over time may be great because of the use of 2 tests rather than 1, and the greater potential for abnormal results that trigger colposcopies and other additional testing. Nonetheless, this approach may offer clinicians and some patients reassurance as they transition from cytologic testing to primary HPV testing. Furthermore, as more young women receive the HPV vaccination, the number of colposcopies and the risks of overtreatment may decrease.

The biggest challenge for cervical cancer screening, however, is likely not which test to use, but determining which women are at low enough risk of cervical cancer to undergo screening at less frequent intervals. Recent data show that a woman's prior screening results are very important to interpreting and managing her current screening result.[9] Even one prior abnormal Papanicolaou or HPV test result, in particular a history of high-grade dysplasia or HPV16/18, greatly increase the risk that the patient will develop high-grade dysplasia or cancer during the next few years. To accurately understand risk, clinicians will need greater infrastructure to access prior test results along with decision support systems to generate management recommendations.

Primary HPV screening among women older than 30 years will likely become the standard of care, but challenges remain. These challenges include clinician and patient education and acceptance; access to primary HPV tests; the development of simple, easily implementable, and evidence-based management advice; and systems-based approaches to help clinicians implement optimal care. In a 2016 study, Tosteson et al[10] showed that in a range of primary care practices, only 46% of abnormal cervical cancer screening test results were appropriately triaged for evaluation. The effectiveness of all cervical cancer screening is directly linked to timely evaluation of patients with abnormal results. It would be desirable if all children were to receive the HPV vaccination before the onset of sexual activity, ideally by age 9 to 12 years. Ultimately, once all children have received the HPV vaccination, the incidence of both cervical cancer and precancerous abnormalities should markedly diminish. Ultimately, we may hope to prevent all cervical cancer.

ARTICLE INFORMATION

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