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Screening for Cervical Cancer
New Tools and New Opportunities

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Cervical cancer is the fourth most common cancer in women worldwide and disproportionately affects women in low-resource countries lacking a public health infrastructure to support cancer screening.[1] The slow rate of progression from precursor lesions to invasive cancer provides opportunities for early detection and cure. Cervical cancer incidence in the United States has declined substantially over the past half century. In 2018, 13 240 new cases of cervical cancer and 4170 cervical cancer deaths are projected to occur.[2] What is unique about US mortality attributable to this neoplasm is that the vast majority of deaths will occur among poor women, women from communities of color, non–US-born women, and women living in rural and remote settings. In general, these populations have limited access to preventive medical care, including screening and timely follow-up, prompt diagnosis and treatment, and culturally tailored education and outreach.

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Access to preventive health care varies considerably across and within communities in the United States. Cervical (and breast) cancer screening rates declined overall during the recession of 2007-2009, with the greatest decline noted among white women and among women in the Midwest, South, and Western regions of the United States.[3] By 2012, several years into the economic recovery, 10% of US women aged 21 to 65 years (an estimated 8 million women) reported not being screened for cervical cancer in the past 5 years.[4] Between 2012 to 2016, there was a continued decline in the number of women receiving cervical cancer screening in the National Breast and Cervical Cancer Early Detection Program, the Centers for Disease Control and Prevention (CDC) program that provides funding for screening services for low-income, uninsured, and underinsured women in all 50 states, District of Columbia, 6 US territories, and 13 American Indian/Alaska Native tribes or tribal organizations.[5] Community engagement is critical to reduce disparities in cervical cancer prevention through initiatives tailored to the specific cultures and priorities of diverse populations.[6]

Since its introduction 75 years ago, exfoliative cytology (commonly known as the "Pap test") has been the mainstay of screening for cervical cancer. Over time, several innovations have improved the quality and yield of cytologic screening programs. Routine use of agreed-on nomenclature and classification systems and automated processing of thin-layer cytology samples have optimized the quality and consistency of this screening modality.

The description by zur Hausen of the role of human papillomavirus (HPV) infection in cervical cancer was quickly followed by clinical advances that capitalized on this knowledge to enhance cervical cancer screening. He found novel HPV-DNA in cervix cancer biopsies and thus discovered the new, tumorigenic HPV16 type in 1983.[7] High-risk HPV (hrHPV) molecular testing was first used in the triage of "borderline" or ASCUS (atypical squamous cells of undetermined significance) cytology results at screening.[8] The improved knowledge of cervical carcinogenesis and the causal role of persistent hrHPV infection in this process was used to inform screening and clinical management guidelines for precursor lesions. In recognition that most hrHPV infection among immune-competent individuals is cleared spontaneously without intervention, screening and clinical management recommendations became more conservative in general and for young women in particular.[9,10] As a tangible result of these and other advances, currently there are fewer women with positive screening results warranting an invasive diagnostic test

(colposcopy with biopsy) or excisional procedure (conization or loop electrosurgical excisional procedure). More recently, hrHPV testing has been incorporated into screening when used simultaneously with cytology (cotesting), with subsequent triage of positive hrHPV test results using type-specific testing for HPV types 16 and 18.[11]

More notable perhaps is that primary prevention became feasible with the introduction of prophylactic HPV immunization. The Centers for Disease Control and Prevention estimates that as many as 93% of cervical cancers are preventable through effective screening and HPV vaccination programs.[4] This goal became more attainable with the recent introduction of a 2-dose vaccination regimen for children. Still, in 2016, 10 years after approval of the first HPV vaccine in the United States, only 43% of adolescents (50% of girls and 38% of boys) were up to date with the HPV vaccination guidelines, compared with 88% for tetanus, diphtheria, and acellular pertussis vaccine.[12] Although continued uptake of HPV vaccination will have a favorable influence on the prevalence of cervical cancer and its precursors in the future, it also has the potential to make the screening process more complicated as precursor lesions become less frequent and smaller, making the proverbial haystack (ie, positive screening test results) larger and the needle (ie, cancer and its precursors) smaller. For now, high-quality screening remains an essential tool in prevention of cervical cancer.

In 2012 the US Preventive Services Task Force (USPSTF), using a rigorous evidence review process, again affirmed its long-standing recommendation of the value of cytology in cervical cancer screening: an "A" recommendation based on high certainty of benefit of screening with cytology alone every 3 years from ages 21 to 29 years.[10] What was novel was that for the first time the option of primary screening with cytology with concurrent hrHPV testing (cotesting) every 5 years became available for women aged 30 to 65 years who wished to lengthen their screening interval. The unprecedented degree of concordance across recommendations from a variety of professional organizations, each developed using very different processes, was truly remarkable. In this way the USPSTF,[10] the American College of Obstetricians and Gynecologists,[13] the joint American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology,[9] and to a lesser extent the Women's Preventive Services Task Force of the Institute of Medicine[14] all arrived at very similar recommendations. For the first time, women and the clinicians serving them heard a consistent message regarding cervical cancer screening.

In this issue of *JAMA*, the USPSTF updates its 2012 recommendations with 1 important addition. The A recommendation for women aged 30 to 65 years now includes primary hrHPV testing (without cotesting) every 5 years as an option along with the previous recommendation of hrHPV and cytology cotesting every 5 years or continuation of cervical cytology (recommended for women aged 21 to 29 years) every 3 years.[15] An earlier draft of the recommendations posted for public comment in September 2017 had removed the cotesting strategy from the recommendation.[16] For women aged 30 to 65 years, the draft statement recommended either cytology alone every 3 years or hrHPV testing alone every 5 years, in light of findings from the accompanying evidence review and modeling studies that cotesting did not improve either the efficiency or effectiveness of testing.[17,18] The public comments raised questions about the strength of evidence supporting the inferiority of cotesting compared with primary hrHPV testing. Concerns about the need for a transition to a molecular-based hrHPV-only strategy for practitioners and patients were also highlighted. In the final recommendations, cotesting was added back to the A recommendation for women aged 30 to 65 years.

The USPSTF has shown a high degree of responsiveness to the concerns of clinicians and patients about cotesting. The modeling results were nearly identical for hrHPV testing alone and for cotesting. Compared with no screening (8.34 deaths per 1000 women), switching to primary hrHPV testing or cotesting every 5 years starting at age 30 years was predicted to reduce the number of cervical cancer deaths to 0.29 (primary hrHPV testing) or 0.30 (cotesting) per 1000 women, compared with 0.76 deaths per 1000 women continuing with cytology every 3 years.[18] The table in the new USPSTF recommendation also acknowledges an important trade-off.[15] Cotesting is slightly better than primary hrHPV testing at detecting precancerous lesions but is associated with increased tests and diagnostic procedures that may not benefit the patient and that have real costs to the health system.

In suggesting primary screening with testing for hrHPV, the USPSTF recommendation follows US Food and Drug Administration (FDA) approval of a request by an HPV test manufacturer that the additional indication of primary cervical cancer screening be added to its labeling in 2014. The FDA decision prompted the development of interim consensus clinical guidance by 7 professional organizations: the Society of Gynecologic Oncology, American Society for Colposcopy and Cervical Pathology, American Cancer Society, American Society for Clinical Pathology, American Society of Cytopathology, College of American Pathologists, and American College of Obstetricians and Gynecologists.[11]

The current USPSTF recommendation statement preserves the greatest range of choices for practitioners and patients; in that sense, both will benefit. How the new guidelines will affect patient and clinician adherence, screening program participation, and ultimately cervical cancer mortality remains to be determined. What is clear is that new strategies will be needed to assist health care consumers in making informed choices from a broader range of options. New risk communication tools and messaging strategies will be needed to promote adherence and to increase acceptance of the lengthened intervals. By establishing the legitimacy of primary hrHPV screening, the new guidelines create a space for innovation including the development of self-sampling approaches at home or in community settings, further development of molecular markers to enhance screening and improve diagnostic performance, and individualized risk stratification for the purpose of precisely tailoring therapeutic and surveillance recommendations.

In light of continued gaps in access to cervical cancer screening and prevention programs, where are the updated

screening guidelines likely to make a difference? The new recommendations mark the continued evolution of cervical cancer screening in the United States. These recommendations continue the trend of decreasing participant burden by lengthening screening intervals, making the "annual Pap" a historical artifact. With the new recommendations come new demands on patients, especially those receiving sporadic and fragmented care from a variety of safety net clinicians and health care settings in which medical records may continue to be unintegrated. For the public health planner, the more inclusive screening menu provides a greater range of options creating more opportunities to tailor approaches to target populations. Public health systems in general will more explicitly face trade-offs between less expensive techniques (cytology every 3 years) involving more clinician visits and more expensive approaches with substantially fewer patient touch points. This will be done in settings in which the range of recommended screening options will be a covered benefit and in safety net settings that must make explicit decisions about whom and how to screen.

Clinicians have all the tools necessary to make cervical cancer mortality a memory. When delivered as recommended to children, prophylactic HPV vaccination is highly effective in preventing hrHPV infection associated with cervical cancer. New HPV molecular screening approaches allow clinically meaningful early detection of cancer precursors and future risk stratification. Effective and acceptable outpatient procedures for cervical cancer precursor lesions are widely available. Even women with advanced disease may receive effective surgical, radiation oncology, and chemotherapeutic approaches that provide a meaningful mortality advantage. Yet this promise will not be realized unless these tools also can be made available to the populations that bear the greatest disease burden from cervical cancer: poor women, women from communities of color, and other women with compromised access to timely and effective care.

ARTICLE INFORMATION

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