Published in final edited form as:

JAMA Intern Med. 2018 October 01; 178(10): 1293–1295. doi:10.1001/jamainternmed.2018.4282.

Cervical Cancer Screening—Moving From the Value of Evidence to the Evidence of Value

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Widespread implementation of cytology-based screening programs has resulted in marked declines in cervical cancer incidence and mortality in the United States. Nonetheless, an estimated 13 240 women will be diagnosed with cervical cancer in 2018, and 4170 will die from the disease.¹ It is likely that a sizable proportion of these women will not have been appropriately screened.²

In its 2018 cervical cancer screening recommendation statement,³ supported by a modeling study⁴ and systematic review,⁵ the US Preventive Services Task Force (USPSTF) continues to recommend screening with cytology alone every 3 years for women aged 21 to 65 years (A recommendation). For the first time, it also recommends screening with a stand-alone test for high-risk types of human papillomavirus (hrHPV) in women aged 30 to 65 years (A recommendation). And in contrast to its position in an earlier draft of the recommendation statement,⁶ the Task Force in the final version continues to recommend cytology plus hrHPV testing (cotesting) every 5 years for women aged 30 to 65 years (A recommendation). Cotesting, however, is designated as an “alternative” strategy to the “preferred” strategies of cytology or hrHPV testing alone. Uncertainty about the overall effect of HPV vaccination on the incidence of cervical cancer and precancerous conditions led the Task Force to recommend no change in the approach to screening for vaccinated women.

In 2016, the US Food and Drug Administration approved an hrHPV test (the cobas analyzer series, Roche) for primary cervical cancer screening in women 25 years and older. Subsequently, the Society for Gynecologic Oncology (SGO) issued provisional recommendations for the test’s use.⁷ Specifically, the SGO endorsed screening beginning at age 25 years and, if the test result was negative, recommended that re-screening occur no sooner than every 3 years. Also in 2016, the American Congress of Obstetricians and Gynecologists (ACOG) stated that hrHPV testing alone was an appropriate alternative to cytology-based screening if performed in accordance with the SGO guidelines.⁸

The new USPSTF recommendations³ differ from the SGO recommendation in 2 important ways. First, the Task Force recommends beginning hrHPV testing at age 30 years, not age 25 years. Second, it recommends that testing be performed every 5 years, and not more

frequently. Although from 2012 to the present, the ACOG,⁹ American Cancer Society (ACS),¹⁰ and USPSTF¹¹ have all agreed on the general approach to screening, it remains to be seen whether ACOG and the ACS will now adopt the latest Task Force approach.

New screening paradigms raise old unanswered questions. What is the optimal management of women with hrHPV-positive testing?¹² The USPSTF suggests that sending all such women directly for colposcopy would lead to a much greater number of colposcopies than would triage.³ It does not, however, recommend a particular triage strategy, nor does it discuss any in detail. Instead, the Task Force cites the importance of adhering to protocols published by the ACS¹⁰ and the SGO.⁷

Current SGO guidelines recommend triage using HPV genotyping for women with hrHPV-positive testing; those testing positive for HPV types 16 or 18 (considered the highest risk among the high-risk types for cervical cancer) are referred for colposcopy.⁷ Those testing negative are further triaged with cytology; those with abnormal cytology findings are referred for colposcopy. Most women with hrHPV-positive testing, however, will not be referred to colposcopy and will be advised to follow up in 12 months, although the precise surveillance strategy is not specified.

Another option for managing hrHPV-positive testing identified through primary screening is to perform cytology and then colposcopy in those with any cytological abnormality. In a Canadian randomized trial reported in July 2018,¹³ this strategy was compared with primary cytology testing with hrHPV testing for women with cytology findings of atypical squamous cells of undetermined significance (ASC-US). The authors concluded that primary HPV testing detects cervical neoplasia earlier and more accurately than cytology. The trial was not designed to elucidate optimal ways to manage women with hrHPV testing. Of note, the option of triaging women with positive hrHPV testing with cytology is not included in current guidelines.

The USPSTF recommendation that HPV testing not begin until age 30 years seems prudent.³ After a single round of screening, about 21% of women aged 25 to 29 years will have a positive hrHPV test result; few, however, will have a high-grade precancerous lesion or cancer.¹⁴ Even after genotyping triage, most women with hrHPV-positive testing will be placed in surveillance, either because of a negative test result for HPV types 16 or 18 and a concurrent normal cytology test result, or after a colposcopy that does not identify a clinically important cervical abnormality. With cytology screening, about 10% of women will have abnormal cytology findings; after using hrHPV testing to triage cytology results interpreted as ASC-US, the only women placed in surveillance will be those who have normal findings on colposcopy.¹⁴ Similar patterns are seen in women aged 30 years and older but are more pronounced in younger women. Minimizing the proportion of women placed in surveillance is important, given the well-known association of cervical cancer surveillance with adverse psychological effects.¹⁵

The rarity of death from cervical cancer in the United States and other developed nations makes it difficult to perform randomized trials to assess the comparative effectiveness of different screening approaches. Decision analytic modeling has become an indispensable

tool to better understand the trade-offs that can be expected from various primary screening strategies, as well as various triage strategies for abnormal testing results.

In its new recommendation statement,³ the Task Force enumerates some anticipated trade-offs based on results of a model it commissioned.⁴ It estimates that hrHPV testing alone and cotesting would avert approximately 1 additional cancer case per 1000 women screened compared with cytology alone, representing a “very small” improvement in life-years gained (64 193 vs 64 182 life-years). However, hrHPV testing alone and cotesting subject women to “more tests and procedures” than cytology alone. In the draft recommendation,⁶ these harms were described as “much higher rates of follow-up testing and colposcopy (39 colposcopies per each cancer case averted for cytology alone vs 640 additional colposcopies per additional cancer case averted for hrHPV testing alone).” These harms, however, are not quantified in the final recommendation statement.

The Task Force assesses the balance of benefits and harms with the added advantage of being able to look across a variety of health conditions for which it has made similar judgments. Two important perspectives, however, could be captured more fully: the economic implications of each strategy as viewed from a societal perspective and the preferences of women eligible for screening.

Traditional cost-effectiveness analyses measure health outcomes using quality-adjusted life-years (QALY).¹⁶ As a single metric that incorporates both benefits and harms, the QALY has the added benefit of incorporating a patient-derived weighting factor (a utility) into a decision analysis rather than relying on an expert panel to make such a judgment. Total costs per strategy and incremental cost-effectiveness ratios can then be estimated, thus pointing clinicians and patients toward high-value screening strategies, defined as those that maximize benefits and minimize harms and costs. In fact, the authors of the Canadian trial cited the need to understand the cost-effectiveness associated with the strategies they compared.¹³

The Task Force, however, does not consider costs and, in contrast to its 2016 breast cancer screening recommendation,¹⁷ does not consider QALYs in this new recommendation. Although the USPSTF sets the standard for evidence-based recommendations and acknowledges the critical value of high-quality evidence in making recommendations, it might reasonably be asked, where is the evidence of value in cervical cancer screening?

Value can be considered from various perspectives. From the perspective of individual women, the USPSTF states that those aged 30 to 65 years “should discuss with their health care professional which testing strategy is best for them.”³ If it is left to individuals to decide whether hrHPV testing or cotesting provides an appropriate balance of benefits and harms as compared with cytology, user-friendly educational tools will need to be developed to assure that women are making informed choices reflective of their preferences.

From the perspective of society, it has been proposed that cost-effectiveness analyses be an essential part of the guideline process.¹⁸ To assist in policy decisions that many professional societies will soon face, a study that I am leading is seeking to use cost-effectiveness

analyses to determine the range of reasonable options for cervical cancer screening. Such analyses may inform future screening recommendations.

Acknowledgments

Conflict of Interest Disclosures: Dr Sawaya reports that he is the principal investigator of a study funded by the National Cancer Institute (1R01CA169093) to use cost-effectiveness analyses to determine the range of reasonable options for cervical cancer screening. He was a member of the US Preventive Services Task Force from 2004 to 2008. No other conflicts are reported.

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