“Recommendation Summary U S. Prevention Statement Task Force for HPV” (USPSTF)

Population	Recommendation	Grade (What's This?)
Women ages 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women ages 21 to 29 years. Th recommends either screening every 3 years with cervical cytology alone or every 5 years with high-risk human papillomavirus (hrHPV) testing alone in women ages 30 to 65 years. See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women age 30 years or older.	A
Women older than age 65 years	The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations section for a discussion of adequate prior screening and risk factors that support screening after age 65 years.	D
Women younger than age 21 years	The USPSTF recommends against screening for cervical cancer in women younger than age 21 years	D
Women who have had a hysterectomy	The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D

What the Grades Mean and Suggestions for Practice

The USPSTF updated its definition of and suggestions for practice for the grade C recommendation.

This new definition applies to USPSTF recommendations voted on after July 2012. Describing the strength of a recommendation is an important part of communicating its importance to clinicians and other users.

Although most of the grade definitions have evolved since the USPSTF first began, none has changed more noticeably than the definition of a C recommendation, which has undergone three major revisions since 1998.

Despite these revisions, the essence of the C recommendation has remained consistent: at the population level, the balance of benefits and harms is very close, and the magnitude of net benefit is small. Given this small net benefit, the USPSTF has either not made a recommendation "for or against routinely" providing the service (1998), recommended "against routinely" providing the service (2007), or recommended "selectively" providing the service (2012).

Grade C recommendations are particularly sensitive to patient values and circumstances. Determining whether or not the service should be offered or provided to an individual patient will typically require an informed conversation between the clinician and patient

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: - The number, size, or quality of individual studies. Inconsistency of findings across individual studies. - Limited generalizability of findings to routine primary care practice. - Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: - The limited number or size of studies. Important flaws in study design or methods. Inconsistency of findings across individual studies. - Gaps in the chain of evidence. Findings not generalizable to routine primary care practice. - Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

*The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

Importance

Cervical cancer deaths in the United States have decreased dramatically since the implementation of widespread cervical cancer screening, and continue to decline, from 2.8 deaths per 100,000 women in 2000 to 2.3 deaths per 100,000 women in 2014.1 Most cases of cervical cancer occur in

women who have not been adequately screened.2 Strategies that aim to ensure that all women are appropriately screened and receive adequate followup are most likely to be successful in further reducing cervical cancer incidence and mortality in the United States.

Detection

The USPSTF found convincing evidence that screening with cervical cytology or testing for high-risk HPV types ("hrHPV testing") can detect high-grade precancerous cervical lesions and cervical cancer.

Benefits of Early Detection and Treatment

The USPSTF found convincing evidence that screening women ages 21 to 65 years substantially reduces cervical cancer incidence and mortality. In women ages 21 to 29 years, screening every 3 years with cytology alone substantially reduces cervical cancer incidence and mortality. In women ages 30 to 65 years, screening every 3 years with cytology alone or every 5 years with hrHPV testing alone substantially reduces cervical cancer incidence and mortality.

The USPSTF found adequate evidence that screening women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer provides little benefit.

The USPSTF found adequate evidence that screening women younger than age 21 years does not reduce cervical cancer incidence and mortality compared with beginning screening at age 21 years.

The USPSTF found convincing evidence that screening women who have had a hysterectomy with removal of the cervix for indications other than a high-grade precancerous lesion or cervical cancer provides no benefit.

Harms of Screening

Screening with cervical cytology or hrHPV testing can lead to harms, including more frequent followup testing and invasive diagnostic procedures (e.g., colposcopy and cervical biopsy), as well as unnecessary treatment in women with false-positive results. Evidence from randomized, controlled trials (RCTs) and observational studies indicate that harms from diagnostic procedures include vaginal bleeding, pain, infection, and failure to diagnose (due to inadequate sampling). Abnormal screening test results are also associated with psychological harms. In particular, women who received positive hrHPV results reported greater distress and lower satisfaction with past and current sexual partners than women who received abnormal cytology results.

Harms of Treatment

The harms of treatment include risks from the treatment procedure and the potential downstream consequences of treatment. Evidence from observational studies indicates that certain treatments

for precancerous lesions (e.g., cold-knife conization and loop excision) are associated with subsequent adverse pregnancy outcomes, such as preterm delivery and related complications.2 The USPSTF found convincing evidence that many precancerous cervical lesions will regress, and that other lesions are indolent and slow-growing and will not become clinically important over a woman's lifetime; identification and treatment of these lesions constitute overdiagnosis. Estimating the precise magnitude of overdiagnosis associated with any screening or treatment strategy is difficult, but it is of concern because it confers no benefit and leads to unnecessary surveillance, diagnostic tests, and treatments, with associated harms.

The USPSTF found adequate evidence that the harms of screening for cervical cancer with cytology alone or hrHPV testing alone in women ages 30 to 65 years are moderate. Screening strategies that include hrHPV testing are slightly more sensitive than those that include cytology alone but also yield more false-positive results.

The USPSTF found adequate evidence that the harms of screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk are at least small.

The USPSTF found adequate evidence that the harms of screening for cervical cancer in women younger than age 21 years are moderate.

The USPSTF found adequate evidence that screening for cervical cancer in women who have had a hysterectomy and do not have a history of a high-grade precancerous lesion or cervical cancer is associated with harms.

USPSTF Assessment

The USPSTF concludes with high certainty that the benefits of screening every 3 years with cytology alone substantially outweigh the harms in women ages 21 to 29 years. The USPSTF concludes with high certainty that the benefits of screening every 3 years with cytology alone or every 5 years with hrHPV testing alone outweigh the harms in women ages 30 to 65 years.

The USPSTF concludes with moderate certainty that the benefits of screening do not outweigh the potential harms in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.

The USPSTF concludes with moderate certainty that the harms of screening outweigh the benefits in women younger than age 21 years.

The USPSTF concludes with high certainty that the harms of screening outweigh the benefits in women who have had a hysterectomy with removal of the cervix for indications other than a high-grade precancerous lesion or cervical cancer.

Patient Population Under Consideration

This recommendation statement applies to asymptomatic women, regardless of their sexual history. This recommendation statement does not apply to women who have been diagnosed with a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who have a compromised immune system (e.g., women living with HIV).

Assessment of Risk

It is well established that hrHPV infection is associated with nearly all cases of cervical cancer, and that women are exposed to hrHPV through sexual intercourse. Although a large proportion of HPV infections resolve spontaneously, the high likelihood of exposure to hrHPV means that women are at risk for precancerous lesions and cervical cancer.

Certain risk factors increase risk for cervical cancer, including HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer. Women with these risk factors are not included in this recommendation and should receive individualized followup. Women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion or cervical cancer are not at risk for cervical cancer and should not be screened. As part of the clinical evaluation, clinicians should confirm through review of surgical records or direct examination that the cervix was removed.

Screening Tests

The decline in cervical cancer cases in the United States over the past several decades is attributed to the effectiveness and widespread uptake of cervical cancer screening, first in the form of conventional cytology and later in the form of liquid-based cytology. Current evidence indicates that there are no clinically important differences between liquid-based and conventional cytology. A variety of platforms are used to detect hrHPV; most use either signal or nucleic acid amplification methods. Published trials of hrHPV testing used in situ hybridization, polymerase chain reaction, and hybrid capture technology to test for HPV strains associated with cervical cancer. hrHPV testing has been used for primary screening, cotesting with cytology, and followup testing of positive cytology results (“reflex hrHPV”).2

Both screening with cytology alone and hrHPV testing alone offer a reasonable balance between benefits and harms for women ages 30 to 65 years; women should discuss with their provider which testing strategy is best for them. Evidence from RCTs suggests that screening with cytology alone is slightly less sensitive for detecting CIN2 and CIN3 than screening with hrHPV testing alone, whereas screening with hrHPV testing alone detects more cases of CIN2 and CIN3 but results in more diagnostic colposcopies for each case detected. Decision analysis modeling suggests that screening every 5 years with hrHPV testing alone in women ages 30 to 65 years translates into a

slightly lower mortality rate (approximately 10 life-years gained per 1,000 women screened) than screening every 3 years with cytology alone but much higher rates of followup 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).3

Both clinical trial evidence and modeling suggest that cotesting increases the number of followup tests by as much as twofold and does not lead to increased detection of CIN3+ (CIN3 and all invasive cancers) or cervical cancer compared with screening with hrHPV testing alone. Therefore, the USPSTF did not include cotesting in this recommendation statement.

There are a number of different protocols for triage of abnormal results from screening with either cytology or hrHPV testing. Both clinical trial evidence and modeling suggest that different triage protocols have generally similar detection rates for CIN2 and CIN3, but going directly to diagnostic colposcopy without additional triage leads to a much larger number of colposcopies compared with other triage protocols. Maintaining comparability of the benefits and harms of screening with cytology alone or hrHPV testing alone requires that patients, clinicians, and health care organizations adhere to currently recommended protocols for repeat testing, diagnostic colposcopy, and treatment.4, 5

Timing of Screening

Women Younger Than Age 21 Years

Cervical cancer is extremely rare before age 21 years. The USPSTF found little evidence to determine whether and how sexual history affects the age at which to begin screening. Exposure of cervical cells to hrHPV during vaginal intercourse may lead to cervical carcinogenesis, but the process has multiple steps, involves regression, and is generally not rapid. Because of the slow progression of disease and the high likelihood of regression in this age group, evidence suggests that screening earlier than age 21 years, regardless of sexual history, would lead to more harm than benefit. Treatment of CIN2 or CIN3 in women younger than age 21 years may increase risk for adverse pregnancy outcomes.6 This recommendation does not apply to women living with HIV or who otherwise have a compromised immune system.

Women Older Than Age 65 Years

The USPSTF recommends against routine screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. Joint guidelines from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology (ACS/ASCCP/ASCP) define adequate prior screening as three consecutive negative cytology results or two consecutive negative cotesting results within 10 years before stopping screening, with the most recent test occurring within 5 years.4 The guidelines further state that routine screening should continue for at least 20 years after spontaneous regression or appropriate management of a high-grade precancerous lesion, even if this extends screening past age 65 years. Once screening has stopped,

it should not resume in women older than age 65 years, even if they report having a new sexual partner.

Women Older Than Age 65 Years Who Have Not Been Adequately Screened

Screening may be clinically indicated in older women with an inadequate or unknown screening history. Recent data suggest that one-quarter of women ages 45 to 64 years have not been screened for cervical cancer in the preceding 3 years.7 In particular, women with limited access to care, women from racial/ethnic minority groups, and women from countries where screening is not available may be less likely to meet criteria for adequate prior screening. Certain considerations may also support screening in women older than age 65 years who are otherwise at high risk (i.e., women with a history of high-grade precancerous lesions or cervical cancer, in utero exposure to diethylstilbestrol, or a compromised immune system).

Screening Interval

Screening more frequently than every 3 years with cytology alone confers little additional benefit, with large increases in harms, including additional procedures and assessment and treatment of transient lesions. Treatment of lesions that would otherwise resolve on their own is harmful because it can lead to procedures with unwanted adverse effects, including the potential for cervical incompetence and preterm labor during pregnancy. Limited trial evidence and modeling studies suggest that a 5-year screening interval offers the best balance of benefits and harms. Screening more frequently than every 5 years with hrHPV testing alone does not substantially improve benefit but significantly increases the number of screening tests and colposcopies.

Treatment

Screening aims to identify high-grade precancerous cervical lesions to prevent progression to cervical cancer. High-grade cervical lesions may be treated with excisional and ablative therapies. Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemotherapy. Treatment of precancerous lesions is less invasive than treatment of cancer.

Race/Ethnicity, Geography, and Cervical Cancer

Although deaths from cervical cancer have decreased dramatically since the implementation of screening, incidence and mortality remain relatively high among certain populations. The reasons for higher incidence and mortality vary considerably among different populations.

The overall mortality rate from cervical cancer in African American women is 10.1 deaths per 100,000 women, which is more than twice that among white women (when adjusted for hysterectomy rate), although the gap has narrowed over time. Mortality is highest among the oldest African American women. Several studies have found that African American women are screened for cervical cancer at similar or higher rates than white women and that inadequate followup after screening and unequal treatment may be important contributing factors. The

higher mortality rate in African American women may also be due, in part, to the higher than average rate of adenocarcinoma, which carries a worse prognosis than the most common type of cervical cancer (squamous cell carcinoma).8-10

American Indian/Alaska Native women also have higher rates of cervical cancer mortality (3.2 deaths per 100,000 women [unadjusted for hysterectomy rate]) than the U.S. average. Factors driving this higher rate may include lower screening rates (16.5% of American Indian/Alaska Native women in the 2012 Behavioral Risk Factor Surveillance System reported not receiving a Papanicolaou [Pap] test in the past 5 years)11 and inadequate treatment.2 Hispanic women have a significantly higher incidence rate and slightly higher mortality rate (2.6 deaths per 100,000 women [unadjusted for hysterectomy rate]), with especially high rates occurring along the Texas-Mexico border. Although white women overall have the lowest mortality rate from cervical cancer, white women living in geographically isolated and medically underserved areas (particularly Appalachia) have much higher mortality rates than the U.S. average.11, 12 In contrast, Asian women overall have lower mortality rates than the U.S. average but lower screening rates, especially among women who have recently immigrated to the United States and may have language or cultural barriers to screening.11, 12

In addition to race/ethnicity and geography, insurance coverage plays an important role in access to cervical cancer screening: 23.1% of women without health insurance and 25.5% of women with no regular health provider reported not receiving a Pap test in the past 5 years, compared with 11.4% of the general population. Data analysis from the Behavioral Risk Factor Surveillance System demonstrates that insurance status interacts with other demographic factors, such as race/ethnicity and age, to increase disparities.11 Disability and identification as lesbian or transgender are also associated with barriers to screening and lower screening rates.13-15

Progress in reducing cervical cancer incidence and mortality has been uneven. The most important factors contributing to higher rates include financial, geographic, and language/cultural barriers to screening; barriers to followup; unequal treatment; and difference in cancer types, all of which vary across subpopulations. Therefore, clinicians should be aware of the factors affecting their patient population and take steps to address them. Research and more effective policies to ensure equitable access to screening, appropriate followup, and treatment are also needed.

Additional Approaches to Prevention

Traditionally, many patients and clinicians have used the cervical cancer screening visit as an opportunity to discuss other health problems and preventive measures. Patients, clinicians, and health systems should seek effective ways to facilitate the receipt of other recommended preventive services at intervals that are beneficial to the patient. Clinicians and health systems should also ensure that patients are able to seek care for additional health concerns as they present.

The Centers for Disease Control and Prevention's Advisory Council on Immunization Practice recommends routine HPV vaccination. A two-dose schedule is recommended for girls and boys

who initiate the vaccination series at ages 9 to 14 years. Three doses are recommended for those who initiate the vaccination series at ages 15 to 26 years and for those who have a compromised immune system.16 The overall effect of HPV vaccination on high-grade precancerous cervical lesions and cervical cancer is not yet known. Current trials have not yet provided data on long-term efficacy; therefore, the possibility that vaccination might reduce the need for screening with cytology or hrHPV testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened as recommended until further evidence accrues.

Useful Resources

The 2012 ACS/ASCCP/ASCP guidelines4 and 2015 interim guidance from ASCCP and the Society of Gynecologic Oncology (SGO)5 provide algorithms for followup of abnormal screening results.

The Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America have issued recommendations on screening for and management of cervical cancer in patients living with HIV.17

The National Cancer Institute provides strategies for reducing cervical cancer mortality in the report “Excess Cervical Cancer Mortality: A Marker for Low Access to Health Care in Poor Communities.”12

Implementation

Participation in regular screening has a far greater effect on cervical cancer morbidity and mortality than which of the two recommended screening methods is chosen. Implementation should therefore focus on ensuring that women receive adequate screening, regardless of which method is used.

While low screening rates contribute to high mortality rates in certain underserved populations, screening alone is not sufficient to reduce cervical cancer morbidity and mortality and related disparities. Loss to followup and disparities in treatment are also contributing factors. Therefore, having systems in place to ensure followup of abnormal results, appropriate treatment of any pathology, and support to retain patients throughout the entirety of cancer treatment are important.

Research Needs and Gaps

Regular screening for cervical cancer, either with cervical cytology alone or hrHPV testing alone, is highly effective for preventing cervical cancer. To further reduce the incidence and mortality of cervical cancer, it is necessary to find effective strategies to reach inadequately screened and unscreened women and to address followup and treatment issues.

As previously discussed, the mortality rate from cervical cancer is significantly higher in certain populations. Research is needed to evaluate whether different screening strategies could play a

part in reducing mortality rates, as well as ways to improve followup for current screening strategies and to ensure equitable access to treatment across populations. In addition, research is needed to determine whether screening after age 65 years has a different balance of benefits and harms in different subpopulations.

Unlike cytology, samples for hrHPV testing have the potential to be collected by the patient and mailed to health programs for analysis, meaning self-collection may be one strategy for increasing screening rates among populations where they are currently low. Rigorous comparative studies are needed to verify this hypothesis and to identify effective strategies for implementation.

Another important area for future research is the effect of HPV vaccination, as an increasing number of women and men of screening age are being vaccinated. Decreases in hrHPV type prevalence due to vaccination could reduce the positive predictive value of hrHPV testing, which, along with potential reductions in cancer incidence, may increase the number of false-positive results, and therefore the balance of benefits and harms. In either case, screening strategies may need to be adjusted.

Burden of Disease

Cervical cancer incidence and mortality have decreased significantly since the 1960s due to widespread screening. In 2017, it is estimated that 12,820 new cases and 4,210 deaths will occur, making it the 18th most common cause of cancer death in the United States.18 Although incidence and mortality rates continue to decline among African American women, they remain much higher than rates among non-Hispanic white women. At the same time, progress in reducing the number of new cases appears to have stalled among white women and younger women.19 Most cases of cervical cancer and related deaths occur in women who have not been adequately screened or treated.2 In 2013, 81.7% of women ages 21 to 44 years and 79.2% of women ages 45 to 64 years reported receiving a Pap test in the past 3 years, as recommended.7 While this is a much higher coverage rate than that of many other cancer screening programs, it still leaves approximately 8 million women at risk, and falls short of the Healthy People 2020 goal of screening 93% of women ages 21 to 65 years.20 Further, the burden of cervical cancer incidence and mortality falls disproportionately on racial/ethnic and sexual/gender minority groups, persons with disabilities, and low-income and geographically-defined populations.

Scope of Review

The USPSTF commissioned a review of the evidence on screening for cervical cancer to update its 2012 recommendation.21 The review focused on outcomes from trials and cohort studies in high-resource countries comparing screening with hrHPV testing alone, cytology alone, and cotesting. The review did not examine data on test accuracy or the effectiveness of cytology for screening for cervical cancer, as this was established in the previous evidence review. Similarly, the review did not systematically examine data for women younger than age 21 years or for women who have

had a hysterectomy except to confirm that the evidence has not changed since the previous review.

In addition to the systematic evidence review, the USPSTF commissioned a decision analysis model to evaluate the age at which to begin and end screening, the optimal interval for screening, the effectiveness of different screening strategies, and how these factors affect the relative benefits and harms of different screening strategies. The USPSTF approach to the use of model-based analysis as a complement to systematic evidence reviews is described in detail elsewhere.22

Accuracy of Screening Tests

Evidence from good- and fair-quality observational studies indicates that hrHPV testing and cotesting have a higher sensitivity but lower specificity (i.e., more false-positive results) than cytology for the detection of CIN2 and CIN3.2 False-positive rates are higher among women younger than age 30 years compared with older women because of the higher incidence of transient HPV infection in younger women, even though cervical cancer incidence is lower in this age group.

Estimates of sensitivity and specificity of any screening strategy are heavily influenced by the followup of abnormal results, and followup protocols in cervical cancer screening trials varied widely. In general, trials used cytology for followup of positive hrHPV test results and hrHPV testing (with or without HPV typing) for followup of positive cytology results (atypical squamous cells of undetermined significance), but the timing of repeat testing varied and the thresholds for diagnostic colposcopy greatly differed.2

Benefits and Harms of Early Detection and Treatment

The reduction of mortality and morbidity associated with the introduction of cytology-based screening is consistent across populations. Correlational studies of cervical cancer trends in North American and European countries demonstrate dramatic reductions in incidence of invasive cervical cancer and a 20% to 60% reduction in cervical cancer mortality since the onset of widespread screening.23 A more recent cluster RCT conducted in India found a nearly 50% reduction in cervical cancer mortality after a single round of hrHPV testing compared with a nonscreening control group after 8 years of followup.24 The evidence review did not address whether screening for cervical cancer is effective but rather which screening strategies are most effective, when to start screening, and when to stop screening.

Women Younger Than Age 21 Years

The USPSTF considered the following types of evidence to determine when screening for cervical cancer should begin: cervical cancer incidence, prevalence, and mortality in young women; the natural history of precancerous lesions and HPV infection; and the effects of screening in populations of young women. Cervical cancer is rare in women younger than age 20 years; according to U.S. Surveillance, Epidemiology, and End Results data, 0.1% of all incident cancer

cases occur in this age group.18 Precancerous lesions are also uncommon. Estimated prevalence of CIN3 in women younger than age 20 years is 0.2%, with a concurrent false-positive cytology rate of about 3.1%.25 In addition, the decision analysis model commissioned for the 2012 USPSTF recommendation showed no net benefit to starting screening before age 21 years.26 The USPSTF did not look at evidence for women younger than age 21 years living with HIV or who are otherwise at higher risk of cervical cancer, as they are outside the scope of this recommendation.

Women Ages 21 to 65 Years

Screening With hrHPV Testing Alone vs. Conventional Cytology Alone

The USPSTF found seven trials of cervical cancer screening: three RCTs comparing screening with hrHPV testing alone vs. cytology alone and four RCTs comparing screening with cytology alone vs. cotesting (cytology plus hrHPV testing).2 No trials directly compared screening strategies using hrHPV testing alone vs. cotesting. Meta-analysis was not possible because the trials varied substantially in terms of cytology type (conventional vs. liquid-based), hrHPV test (polymerase chain reaction vs. hybrid capture), screening interval (2 to 5 years), followup protocols for abnormal results, and protocols for screening beyond the first screening round. No trial included more than two rounds of screening. Although the purpose of screening is to reduce cervical cancer mortality, the mortality rate is so low in countries that have organized cytology screening programs that it is impractical to directly measure the effects of different screening strategies on mortality through clinical trials. Therefore, trials measured the rate of CIN3+ detection, and some trials also reported the rate of invasive cervical cancer. The primary harms measured were the total number of followup tests, number of colposcopies, and false-positive rates. Although followup tests and colposcopies are essential to detection of cancer, they represent a burden and risk to patients and are a proxy measure for downstream harms; therefore, screening strategies that minimize the number of tests and colposcopies per each cancer case averted are desirable.

Three RCTs (N >275,000 women) compared screening with hrHPV testing alone vs. cytology alone: New Technologies for Cervical Cancer (NTCC) phase II trial (Italy),27-30 HPV for Cervical Cancer Screening (HPV FOCAL) trial (Canada),31 and FINNISH trial (Finland).32 The NTCC phase II and HPV FOCAL trials enrolled women ages 25 to 60 or 65 years and had two rounds of screening 2 to 4 years apart; however, the results for the second round of screening in HPV FOCAL have not yet been published. The FINNISH trial, which enrolled women ages 25 to 65 years, had a single round of screening and then followed participants for 5 years through a cancer registry. Overall, the three trials found that hrHPV testing alone led to a two- to threefold increase in the rate of CIN3+ detection compared with cytology alone in the first round of screening. The NTCC phase II trial found that hrHPV testing alone had a lower rate of CIN3+ detection compared with cytology alone in the second round of screening, but the cumulative rate was still double that of cytology alone (0.4% vs. 0.2%). The FINNISH trial also measured the rate of invasive cervical cancer detection at 5 years; screening with hrHPV testing alone had a detection rate of 0.03% and screening with cytology alone had a detection rate of 0.01%. The other two trials did not report the rate of invasive cervical cancer detection.

The potential harms of hrHPV testing result from the evaluation of positive test results. The three trials of hrHPV testing alone vs. cytology alone found an hrHPV positive rate of 7% to 8%, with higher rates in women younger than age 30 years. Colposcopy rates were two- to threefold higher for hrHPV testing alone than for cytology alone in two of three trials (NTCC and HPV FOCAL) and similar in the third (FINNISH). False-positive rates for CIN2+ were twice as high for hrHPV testing alone in one trial (NTCC phase II), similar in one trial (FINNISH), and not reported in the third trial (HPV FOCAL).

Cotesting

Four RCTs (N >130,000 women) compared screening with cytology alone vs. cotesting with cytology plus hrHPV testing: NTCC phase I trial (Italy)27, 29, 30, Swedescreen (Sweden),33, 34 A Randomised Trial in Screening to Improve Cytology (ARTISTIC) (United Kingdom),35-37 and Population-Based Screening Study Amsterdam (POBASCAM) (the Netherlands).38 The trials varied considerably in starting age (20 to 29 years), stopping age (38 to 64 years), and followup protocols, which likely contributed to the variation in outcomes. The NTCC phase I, ARTISTIC, and POBASCAM trials reported two rounds of screening at 3- to 5-year intervals, while Swedescreen reported one round of screening with registry followup at 3 years. As with hrHPV testing alone, most trials found that cotesting led to much higher detection rates of CIN3+ in the initial screening round, followed by lower rates in the second round. The cumulative relative ratio of detection of CIN3+ between the two strategies ranged from 0.91 to 1.13 after two rounds. Two trials (Swedescreen and POBASCAM) reported no difference between strategies at 13 to 14 years of followup.

The four trials reported hrHPV positive rates of 7% to 22% for cotesting; again, rates were highest in women younger than age 30 to 35 years. Colposcopy rates were 1.3 times higher for cotesting than for cytology alone in one trial (ARTISTIC), threefold higher in another trial (NTCC phase I), and not reported in the other two trials (Swedescreen, POBASCAM). False-positive rates were two- to threefold higher for cotesting in three of four trials (Swedescreen did not report the false-positive rate for the intervention group).

The ARTISTIC trial also surveyed a subsample of patients (N=2,508) about the psychological effects of screening.39 It found no difference in distress or anxiety between women who had received cotesting and women who had received cytology alone. However, women who were notified of positive HPV results reported lower sexual satisfaction, regardless of their cytology results, and also greater psychological distress (although the difference was not statistically significant).35 A separate cross-sectional study used a survey to evaluate the psychological effects of hrHPV cotesting in women ages 20 to 64 years (N=428) and found that women who received a positive HPV result were more distressed and had more negative feelings about their sexual partners than women who received negative HPV results.40

Net Benefit of Screening Strategies

The decision model commissioned by the USPSTF reported benefits and harms consistent with the outcomes observed in the trials. Both hrHPV testing alone and cotesting would avert approximately 1 additional cancer case per 1,000 women screened vs. cytology alone (17.7 vs. 16.5 cases), representing a very small improvement in life-years gained (64,193 vs. 64,182 life-years).3 However, these two strategies would also subject women to more tests and procedures. Modeling estimates found that screening every 3 years with cytology alone requires 39 colposcopies per each cancer case averted; by comparison, screening every 5 years with hrHPV testing alone, starting at age 30 years, requires an additional 640 colposcopies per each additional cancer case averted, and cotesting results in an even higher number of colposcopies. Although no head-to-head trials compared screening with hrHPV testing alone vs. cotesting, modeling suggests that both hrHPV testing alone and cotesting offer similar benefit over cytology in terms of cancer cases averted, but cotesting requires more than 7,000 more lifetime tests than hrHPV testing alone, and when using cytology to triage positive HPV results, more than 100 more colposcopies per 1,000 women.

In summary, all three screening strategies offer substantial benefit in terms of reducing cancer incidence and mortality compared with no screening. Screening strategies using hrHPV testing alone or cotesting lead to slightly higher detection rates of CIN3+ compared with cytology alone but also more tests and procedures. Modeling found that cotesting does not offer any benefit in terms of cancer reduction or life-years gained over hrHPV testing alone but increases the number of tests and procedures per each cancer case averted. Therefore, the USPSTF concluded that there is convincing evidence that screening with either cytology alone or hrHPV testing alone provides substantial benefit and are preferable to cotesting.

Age at Which to Start Screening With hrHPV Testing

Given the high prevalence of transient HPV infection among adolescents and young adults, initial screening at age 21 years should be with cytology alone. The question of what age at which screening with hrHPV testing alone offers comparable benefit has not been directly studied. The three trials that compared screening with hrHPV testing alone vs. cytology alone found a consistently higher detection rate in younger women (age <30 or 35 years), raising concerns for overdiagnosis and overtreatment of transient infection. Modeling estimates of the effects of switching from screening with cytology alone to hrHPV testing alone at ages 25, 27, and 30 years found minimal differences in terms of life-years gained when switching screening strategies at age 30 vs. 25 years (64,193 vs. 64,195 life-years gained per 1,000 women screened, respectively). However, screening with hrHPV testing alone starting at age 25 years rather than age 30 years increased the number of colposcopies by nearly 400 colposcopies per 1,000 women screened. Therefore, switching from cytology alone to hrHPV testing alone at age 30 years appears to offer similar benefits in terms of cancer reduction as switching at younger ages but with fewer associated tests and procedures.

Screening Interval

Modeling analysis conducted for the 2012 USPSTF recommendation found that screening every 3 years with cytology alone starting at age 21 years confers a similar number of life-years gained as annual screening (69,247 vs. 69,213 life-years gained per 1,000 women screened, respectively), yet results in fewer than half the number of colposcopies and fewer false-positive results.26 No trials directly compared the effect of different screening intervals for hrHPV testing alone. However, modeling suggests similar gains in life-years with 3- and 5-year screening intervals but more tests and procedures with 3-year screening intervals (64,193.19 vs. 64,193.07 life-years gained per 1,000 women screened every 3 and 5 years, respectively).3

Women Older Than Age 65 Years

None of the screening trials enrolled women older than age 65 years, so direct evidence on when to stop screening is not available. When deliberating on the age at which to stop screening, the USPSTF considered the incidence of cervical cancer in older women and whether the pattern of cervical cancer incidence differs in screened vs. unscreened women. The incidence and prevalence of CIN peak in the mid-reproductive years and begin to decline in approximately the fourth decade of life, a general pattern also apparent among certain previously unscreened women. Cervical cancer in older women is not more aggressive or rapidly progressive than it is in younger women. The rate of high-grade squamous intraepithelial lesions diagnosed by cytology is low in older women who have had adequate prior screening. The model commissioned by the USPSTF also supports the current practice of stopping screening at age 65 years in adequately screened women. The model projected that extending screening beyond age 65 years in women with an adequate screening history would not have significant benefit using any of the considered screening strategies. For example, using a strategy of screening every 3 years with cytology alone, starting at age 21 years, and then screening every 5 years with hrHPV testing alone, starting at age 30 years (and thus extending screening from age 65 to 75 years), would extend life by 1 year per 1,000 women screened but would subject women to more tests and procedures (approximately 1,500 tests and 100 additional colposcopies per 1,000 women screened).3

Although screening women older than age 65 years who have an adequate screening history is not recommended, data suggest that screening rates begin to drop before that age. As a result, approximately 13% of 65-year-old women have not been adequately screened, and this number increases if the patient has no regular health provider.11 A Kaiser Permanente registry study found that the majority of cases of invasive cervical cancer in women older than age 65 years occurred among those who had not met criteria for stopping screening.41 This suggests that the decision to stop screening at age 65 years should only be made after confirming that the patient has in fact received prior adequate screening. Current guidelines define adequate screening as three consecutive negative cytology results or two consecutive negative HPV results within 10 years before stopping screening, with the most recent test performed within 5 years.4

Women Who Have Had a Hysterectomy

Two large studies have documented the low risk for cytology abnormalities after hysterectomy. A cross-sectional study of more than 5,000 cytology tests among women older than age 50 years found that identification of vaginal intraepithelial neoplasia and cancer was rare in this age group after hysterectomy (0.18 cases per 1,000 women screened).42 In a second study of nearly 10,000 Pap tests performed over 2 years in 6,265 women who had a hysterectomy with removal of the cervix, screening yielded 104 abnormal Pap results and no cases of cervical cancer; in addition, 4 cases of high-grade vaginal lesions were detected, but it is unknown whether detection of these cases improved clinical outcomes.43

How Does Evidence Fit With Biological Understanding?

The natural history of cervical cancer has been well studied. HPV infection of the cervix is generally transient, but when the infection is not cleared by an appropriate immune response and the virus is of an oncogenic type, the infection can result in incorporation of HPV gene sequences into the host genome, which can lead to precancerous lesions. The long preclinical phase from infection to development of precancerous lesions and cervical cancer allows for the opportunity to effectively screen for, identify, and treat precancerous lesions, thereby reducing cervical cancer incidence and mortality.

Recommendation:

This recommendation replaces the 2012 USPSTF recommendation. The major change in the current recommendation is that screening with hrHPV testing alone is recommended as an alternative to cytology screening alone starting at age 30 years, and cotesting is no longer recommended. As in the 2012 recommendation, the USPSTF continues to recommend against screening in women younger than age 21 years, in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer, and in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion or cervical cancer.

Recommendation of others:

ACS/ASCCP/ASCP recommend that women ages 21 to 29 years be screened every 3 years with cytology alone (cervical cytology or Pap testing). Women ages 30 to 65 years should be screened every 5 years with cytology and HPV testing (cotesting) or every 3 years with cytology alone. Women at increased risk of cervical cancer (i.e., women with a compromised immune system or diethylstilbestrol exposure) may need to be screened more often. Women who have had CIN2 or worse should continue screening for 20 years after the last abnormal test result, even if it extends screening beyond age 65 years.4 ASCCP and SGO issued interim guidance in 2015 that recommended primary HPV screening starting at age 25 years as an alternative to cytology alone or cotesting.5 The American Academy of Family Physicians' guidelines are in agreement with the

ACS/ASCCP/ASCP guidelines.44 The American College of Obstetricians and Gynecologists stated in 2016 that cytology alone and cotesting are still specifically recommended in current guidelines from most major societies; however, primary HPV screening in women age 25 years or older can be considered as an alternative to current cytology-based screening if performed as per ASCCP and SGO interim guidance.45 The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents has issued guidance on screening for and management of HPV in patients living with HIV.17

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