Screening for Cervical Cancer: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2003 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for cervical cancer.

Methods: The USPSTF reviewed new evidence on the comparative test performance of liquid-based cytology and the benefits and harms of human papillomavirus (HPV) testing as a stand-alone test or in combination with cytology. In addition to the systematic evidence review, the USPSTF commissioned a decision analysis to help clarify the age at which to begin and end screening, the optimal interval for screening, and the relative benefits and harms of different strategies for screening (such as cytology and co-testing).

Recommendations: This recommendation statement applies to women who have a cervix, regardless of sexual history. This recommendation statement does not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).

The USPSTF recommends screening for cervical cancer in women aged 21 to 65 years with cytology (Papanicolaou smear) every 3 years or, for women aged 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 years. See the Clinical Considerations for discussion of cytology method, HPV testing, and screening interval (A recommendation).

The USPSTF recommends against screening for cervical cancer in women younger than age 21 years (D recommendation).

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 for discussion of adequacy of prior screening and risk factors (D recommendation).

The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (cervical intraepithelial neoplasia grade 2 or 3) or cervical cancer (D recommendation).

The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years (D recommendation).

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* For a list of the members of the USPSTF, see the **Appendix** (available at www.annals.org).

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The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific clinical preventive services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service, and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

See also:

Print

Editorial comment. 896
Summary for Patients. I-44

Web-Only

Appendix
CME quiz (preview on page I-23)
Conversion of graphics into slides

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendations and Evidence

This recommendation statement applies to women who have a cervix, regardless of sexual history. This recommendation statement does not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).

The USPSTF recommends screening for cervical cancer in women aged 21 to 65 years with cytology (Papanicolaou [Pap] smear) every 3 years or, for women aged 30 to 65 years who want to lengthen the screening interval,

screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years. See the Clinical Considerations for discussion of cytology method, HPV testing, and screening interval (A recommendation).

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The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer (D recommendation).

The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years (D recommendation).

See the **Figure** for a summary of the recommendations and suggestions for clinical practice.

Table 1 describes the USPSTF grades, and **Table 2** describes the USPSTF classification of levels of certainty about net benefit.

Rationale

Importance

The age-adjusted annual incidence rate of cervical cancer is 6.6 cases per 100 000 women, according to data from 2008 (1–3). An estimated 12 200 new cases of cervical cancer and 4210 deaths occurred in the United States in 2010 (1). Cervical cancer deaths in the United States have decreased dramatically since the implementation of widespread cervical cancer screening. Most cases of cervical cancer occur in women who have not been appropriately screened (2, 3). Strategies that aim to ensure that all women are screened at the appropriate interval and receive adequate follow-up are most likely to be successful in further reducing cervical cancer incidence and mortality in the United States.

Detection

Screening with cervical cytology or testing for multiple oncogenic HPV types (a test for the presence of >2 high-risk or carcinogenic HPV types, hereafter called *HPV testing*) can lead to detection of high-grade precancerous cervical lesions and cervical cancer.

Benefits of Detection and Early Intervention and Treatment

Women Aged 21 to 65 Years

There is convincing evidence that screening women aged 21 to 65 years with cytology every 3 years substantially reduces cervical cancer incidence and mortality. Among women aged 30 to 65 years, there is adequate evidence that screening with a combination of cytology and HPV testing (co-testing) every 5 years provides benefits similar to those seen with cytology screening alone every 3 years.

Among women younger than age 30 years, there is adequate evidence that screening with HPV testing (alone or in combination with cytology) confers little to no benefit.

Women Younger Than Age 21 Years

There is adequate evidence that screening women younger than age 21 years (regardless of sexual history) does not reduce cervical cancer incidence and mortality compared with beginning screening at age 21 years (4).

Women Older Than Age 65 Years

There is adequate evidence that screening women older than age 65 years who have had adequate prior screening and are not otherwise at high risk provides little to no benefits.

Women After Hysterectomy

There is convincing evidence that continued screening after hysterectomy with removal of the cervix for indications other than a high-grade precancerous lesion or cervical cancer provides no benefits.

Harms of Detection and Early Intervention and Treatment

Screening with cervical cytology or HPV testing can lead to harms, and the harms of screening can take many forms. Abnormal test results can lead to more frequent testing and invasive diagnostic procedures, such as colposcopy and cervical biopsy. Evidence from randomized, controlled trials and observational studies indicates that harms from these diagnostic procedures include vaginal bleeding, pain, infection, and failure to diagnose (due to inadequate sampling). Abnormal screening test results are also associated with mild psychological harms; short-term increases in anxiety, distress, and concern about health have been reported with cytology and HPV testing.

Harms of Treatment of Screening-Detected Disease

The harms of treatment include risks from the treatment procedure itself and the potential downstream consequences of treatment. Summary evidence from observational studies indicates that some treatments for precancerous lesions (such as cold-knife conization and loop excision) are associated with adverse pregnancy outcomes, such as preterm delivery, that can lead to low birthweight in infants and perinatal death (2). Evidence is convincing that many precancerous cervical lesions will re-

Figure. **Screening for cervical cancer: clinical summary of U.S. Preventive Services Task Force recommendation.**

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

SCREENING FOR CERVICAL CANCER

CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Women Aged 21 to 65 Years	Women Aged 30 to 65 Years	Women Younger Than Age 21 Years	Women Older Than Age 65 Years Who Have Had Adequate Prior Screening and Are Not High Risk	Women After Hysterectomy With Removal of the Cervix With No History of High-Grade Precancer or Cervical Cancer	Women Younger Than Age 30 Years
Recommendation	Screen with cytology (Pap smear) every 3 years Grade: A	Screen with cytology every 3 years or co-testing (cytology/human papillomavirus testing [HPV]) every 5 years Grade: A	Do not screen Grade: D	Do not screen Grade: D	Do not screen Grade: D	Do not screen with HPV testing (alone or with cytology) Grade: D

Risk Assessment	HPV infection is associated with nearly all cases of cervical cancer. Other factors that increase a woman's risk for cervical cancer include HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer.					
Screening Tests and Interval	Screening women aged 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms. Screening with cytology more often than every 3 years confers little additional benefit, with large increases in harms. HPV testing combined with cytology (co-testing) every 5 years in women aged 30 to 65 years offers a comparable balance of benefits and harms, and is therefore a reasonable alternative for women in this age group who would prefer to extend the screening interval.					
Timing of Screening	Screening women younger than age 21 years, regardless of sexual history, leads to more harms than benefits. Clinicians and patients should base the decision to end screening on whether the patient meets the criteria for adequate prior testing and appropriate follow-up, per established guidelines.					
Interventions	Screening aims to identify high-grade precancerous cervical lesions to prevent development of cervical cancer and early-stage asymptomatic invasive cervical cancer. High-grade lesions may be treated with ablative and excisional therapies, including cryotherapy, laser ablation, loop excision, and cold-knife conization. Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemoradiation.					
Balance of Benefits and Harms	The benefits of screening with cytology every 3 years substantially outweigh the harms.	The benefits of screening with co-testing (cytology/HPV testing) every 5 years outweigh the harms.	The harms of screening earlier than age 21 years outweigh the benefits.	The benefits of screening after age 65 years do not outweigh the potential harms.	The harms of screening after hysterectomy outweigh the benefits.	The potential harms of screening with HPV testing (alone or with cytology) outweigh the potential benefits.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for breast cancer and ovarian cancer, as well as genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility. These recommendations are available at www.uspreventiveservicestaskforce.org.					

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

Pap = Papanicolaou.

gress and that other lesions are so indolent and slow-growing that they will not become clinically important over a woman's lifetime; identification and treatment of these lesions constitute overdiagnosis. It is difficult to estimate the precise magnitude of overdiagnosis associated with any screening or treatment strategy, but it is of concern because it confers no benefit and leads to unnecessary surveillance, diagnostic tests, and treatments with the associated harms.

Women Aged 21 to 65 Years

There is adequate evidence that the harms of screening for cervical cancer with cytology alone or in combination with HPV testing in women aged 30 to 65 years are moderate. Positive screening results are more common with strategies that include HPV testing than with strategies that use cytology alone. Therefore, the likelihood of prolonged surveillance and overtreatment may increase with strategies that incorporate HPV testing. Cervical

Table 1. **What the USPSTF Grades Mean and Suggestions for Practice**

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	*Note: The following statement is undergoing revision.* Clinicians may provide this service to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.	Offer or provide this service only if other considerations support the offering or providing the service in an individual patient.
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.

treatments may increase the risk for adverse pregnancy outcomes (for example, cervical insufficiency and preterm delivery) in women who have not yet completed childbearing.

Women Younger Than Age 30 Years

There is adequate evidence that the harms of HPV testing (alone or in combination with cytology) in women younger than age 30 years are moderate.

Women Younger Than Age 21 Years

There is adequate evidence that the harms of screening in women younger than age 21 years are moderate.

Women Older Than Age 65 Years

There is adequate evidence that the harms of screening in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk are at least small.

Women After Hysterectomy

There is adequate evidence that screening after hysterectomy among women who do not have a history of a high-grade precancerous lesion or cervical cancer is associated with harms.

USPSTF Assessment

The USPSTF concludes that for women aged 21 to 65 years, there is high certainty that the benefits of screening with cytology every 3 years substantially outweigh the harms. For women aged 30 to 65 years, there is high certainty that the benefits of screening with a combination of cytology and HPV testing (co-testing) every 5 years outweigh the harms.

For women younger than age 21 years, regardless of sexual history, there is moderate certainty that the harms of screening outweigh the benefits.

For women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer, there is moderate certainty that the benefits of screening do not outweigh the potential harms.

For women who have had a hysterectomy with removal of the cervix for indications other than a high-grade

Table 2. **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; and 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 that are not generalizable to routine primary care practice; and a 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.

precancerous lesion or cancer, there is high certainty that the harms of screening outweigh the benefits.

For women younger than age 30 years, there is moderate certainty that the potential harms of screening with HPV testing (alone or in combination with cytology) outweigh the potential benefits.

Clinical Considerations

Patient Population Under Consideration

This recommendation statement applies to all women who have a cervix, regardless of sexual history. This recommendation statement does not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).

Screening Tests

The effectiveness of cervical cancer screening observed in the United States over the past several decades is attributed to the use of conventional cytology. Current evidence indicates that there are no clinically important differences between liquid-based cytology and conventional cytology. The USPSTF realizes that the choice of cytology method may not be under the direct control of the clinician and considers cytology screening in appropriate age groups at appropriate intervals to be of substantial net benefit, regardless of method. Human papillomavirus testing with Digene Hybrid Capture 2 (HC2) (Qiagen, Germantown, Maryland) is commonly used in the United States, and both HC2 and polymerase chain reaction–based methods have been evaluated in effectiveness trials. Although alternative HPV detection methods are emerging, the clinical comparability and implications of these methods are not completely understood.

Screening Interval

Screening women aged 21 to 65 years every 3 years with cytology provides a reasonable balance between benefits and harms. Among women aged 30 to 65 years, HPV testing combined with cytology (co-testing) every 5 years offers a comparable balance of benefits and harms and is therefore a reasonable alternative for women in this age group who would prefer to extend the screening interval. Screening with cytology more often than every 3 years 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 side effects, including the potential for cervical incompetence and preterm labor. Similarly, HPV testing with cytology should not be done more often than every 5 years to maintain a reasonable balance of benefits and harms similar to that seen with cytology alone every 3 years. Maintaining the comparability of the benefits and harms of co-testing and cytology alone demands that patients, clinicians, and health care organizations adhere to currently recommended screening intervals, protocols for repeated testing, cytologic thresholds for further diagnostic testing (that is, colposcopy) and treatments, and extended surveillance as recommended by current American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology (ACS/ASCCP/ASCP) guidelines.

Women who choose co-testing to increase their screening interval (and potentially decrease testing) should be aware that positive screening results are more likely with HPV-based strategies than with cytology alone and that some women may require prolonged surveillance with additional frequent testing if they have persistently positive HPV results. Because HPV test results may be positive among women who would otherwise be advised to end screening at age 65 years on the basis of previously normal cytology results alone, the likelihood of continued testing may increase with HPV testing. The percentage of U.S. women undergoing co-testing who will have a normal cytology test result and a positive HPV test result (and who will therefore require additional testing) ranges from 11% among women aged 30 to 34 years to 2.6% among women aged 60 to 65 years (5, 6).

Timing of Screening

Women Younger Than Age 21 Years

Cervical cancer is rare before age 21 years. The USPSTF found little evidence to determine whether and how sexual history should affect the age at which to begin screening. Although exposure of cervical cells to sexually transmitted HPV during vaginal intercourse may lead to cervical carcinogenesis, the process has multiple steps, involves regression, and is generally not rapid. There is evidence that screening earlier than age 21 years, regardless of sexual history, would lead to more harm than benefit (4). The harms are greater in this younger age group because abnormal test results are likely to be transient and to resolve on their own; in addition, treatment may have an adverse effect on childbearing.

Women Older Than Age 65 Years

Clinicians and patients should base the decision to end screening on whether the patient meets the criteria for adequate prior testing and appropriate follow-up per established guidelines. The ACS/ASCCP/ASCP guidelines define adequate prior screening as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years before cessation of screening, with the most recent test occurring within 5 years. They 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 (7). The ACS further states that screening should not resume after cessation in

women older than age 65 years, even if a woman reports having a new sexual partner.

Women Older Than Age 65 Years Who Have Never Been Screened

Screening may be clinically indicated in older women for whom the adequacy of prior screening cannot be accurately accessed or documented. Women with limited access to care, minority women, and women from countries where screening is not available may be less likely to meet the criteria for adequate prior screening. The USPSTF realizes that certain considerations may support screening in women older than age 65 years who are otherwise considered high risk (such as women with a high-grade precancerous lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised).

Assessment of Risk

It is well-established that HPV infection is associated with nearly all cases of cervical cancer. Other risk factors include HIV infection, a compromised immune system, in utero exposure to diethylstilbestrol, and previous treatment of a high-grade precancerous lesion or cervical cancer.

Women who have had a hysterectomy with removal of the cervix and who 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. Women who had their cervix removed during surgery for ovarian or endometrial cancer are not at high risk for cervical cancer and would not benefit from screening. Clinicians should confirm through review of surgical records or direct examination that the cervix was removed.

Treatment

Screening aims to identify high-grade precancerous cervical lesions to prevent development of cervical cancer and early-stage asymptomatic invasive cervical cancer. High-grade lesions may be treated with ablative and excisional therapies, including cryotherapy, laser ablation, loop excision, and cold-knife conization. Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemoradiation. The treatment of precancerous rather than early-stage cancerous lesions is unique to cervical cancer and is the foundation of the success of cervical cancer screening. Treatment of precancerous lesions is less invasive than treatment of cancer and results in fewer adverse effects.

Other Approaches to Prevention

Many individuals and clinicians have used the annual Pap smear screening visit as an opportunity to discuss other health problems and preventive measures. Individuals, clinicians, and health systems should seek effective ways to facilitate the receipt of recommended preventive services at intervals that are beneficial to the patient. Efforts should also be made to ensure that individuals are able to seek care for additional health concerns as they present.

The overall effect of HPV vaccination on high-grade precancerous cervical lesions and cervical cancer is not yet known. Current trials do not provide data on long-term efficacy (8); therefore, the possibility that vaccination might reduce the need for screening with cytology alone or in combination with HPV testing is not established. Given these uncertainties, women who have been vaccinated should continue to be screened.

Other Considerations

Research Needs and Gaps

There are notable limitations to the current evidence. There is limited direct evidence on the harms of various screening strategies that incorporate HPV testing. Additional data from ongoing trials on cervical cancer outcomes and the resulting number of false-positive test results, colposcopies, and biopsies should help to clarify some of the current uncertainties related to strategies that include HPV testing. Moreover, these data should help to better assess the comparative effectiveness and harms of various screening strategies using cytology and HPV testing alone, in combination, or sequentially.

An important clinical limitation of the current evidence is the lack of long-term cumulative data from screening trials on cervical cancer. Much of the data to date are limited to detection of CIN grade 3. Although CIN3 may be considered an acceptable surrogate for cancer, additional data are needed to determine benefits, harms, and net benefit. Future screening trials should plan for and report round-specific data as well as cumulative results from multiple screening rounds to obtain useful cumulative data on CIN3, cervical cancer by stage and type, and program requirements (such as colposcopy, biopsy, treatments, or harms of treatment). More complete outcomes data will help to better assess the relative benefits of different screening strategies, particularly in comparing various approaches involving cytology and HPV testing.

There is limited evidence on the benefits and harms of HPV testing alone as a screening strategy. An emerging chain of evidence suggests that HPV testing followed by cytology in women with positive HPV test results may also be a reasonable screening strategy. Ongoing studies, such as the HPV FOCAL (HPV Testing for Cervical Cancer Screening) trial, which compares HPV with cytology triage to cytology with HPV triage of test results interpreted as atypical squamous cells of undetermined significance, should provide relevant direct evidence on HPV testing that applies to current U.S. practice.

Finally, more research is needed to determine whether and how individual risk factors may be used to tailor screening, thereby preventing overdiagnosis and overutilization of resources in women at low risk for cervical cancer, as well as underdiagnosis in those at high risk. Deter-

mining risk factors that move lower-risk women (such as older women with normal cytology findings or negative HPV test results) into higher risk categories (such as older women with positive HPV and negative cytology results or exposure to new partners) will also be important.

Discussion

Burden of Disease

Cervical cancer incidence and mortality have declined in the United States since the introduction of cervical cancer screening in the 1950s and 1960s. The current annual incidence rate is 6.6 cases per 100 000 women, and the age-adjusted mortality rate is 2.4 deaths per 100 000 (for 2003 to 2007) (1). However, cervical cancer still remains a substantial public health issue. Incidence rates (2004 to 2008) vary by age and race or ethnicity; Hispanic (11.1 per 100 000) and black (10.0 per 100 000) women experience the highest rates, whereas non-Hispanic white (7.4 per 100 000), American Indian and Alaska Native (7.8 per 100 000), and Asian and Pacific Islander (7.3 per 100 000) women have lower rates (1). Cervical cancer most commonly occurs in women aged 35 to 55 years. In contrast to cervical cancer, abnormal cytology test results and precancerous lesions are fairly common. According to Centers for Disease Control and Prevention data from low-income, uninsured, and underserved women, approximately 3.0% of cytology test results are abnormal (9).

Scope of Review

To update the 2003 recommendation, the USPSTF commissioned a targeted systematic review of the evidence on screening strategies incorporating HPV testing that may apply to current screening practices in the United States. The USPSTF reviewed new evidence regarding the comparative test performance of liquid-based cytology and the benefits and harms of HPV testing as a standalone test or in combination with cytology.

In addition to the systematic evidence review, the USPSTF commissioned a decision analysis to help clarify the age at which to begin and end screening, the optimal interval for screening, and the relative benefits and harms of different strategies for screening (such as cytology and co-testing). The USPSTF uses modeling as a complement to evidence reported in the systematic review, to provide information about alternate screening or treatment strategies in the absence of direct evidence, or when the complexities required to conduct randomized, controlled trials to address knowledge gaps would preclude the ability to obtain direct evidence. The USPSTF does not use modeling to make recommendations for or against screening or treatment.

The USPSTF did not review evidence on automated screening technologies because they are less relevant to primary care clinicians, and it did not review evidence on HPV vaccination because data to determine long-term vaccine efficacy or how vaccination will affect screening are limited.

Accuracy of Screening Tests

Liquid-Based Cytology Compared With Conventional Cytology

Evidence suggests that there are no clinically meaningful differences in accuracy between liquid-based cytology and conventional cytology. One large, good-quality randomized trial (10) and one large, fair-quality randomized trial (11) of more than 130 000 women compared the 2 screening methods and found no difference in detection of CIN2+ or CIN3+ at any cytologic threshold of positivity.

HPV Testing Compared With Cytology

Evidence from good- and fair-quality observational studies indicates that HPV testing generally has a higher sensitivity but lower specificity (that is, more false-positive test results) than does cytology in the detection of CIN2+ and CIN3+ (12–18). False-positive rates are higher among women younger than age 30 to 35 years than women in older age groups because of the higher prevalence of HPV, but the incidence of cervical cancer is lower in the former age group.

Effectiveness of Early Detection or Treatment

Introduction of screening to populations naive to screening reduces cervical cancer rates by 60% to 90% within 3 years of implementation (19). The reduction of mortality and morbidity associated with the introduction of cytology-based screening is consistent and equally dramatic across populations. Correlational studies of cervical cancer trends in countries in North America and Europe 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.

No published studies have evaluated, in an ideal way, the age at which to begin screening, the age at which to end screening, and how often to screen. The USPSTF considered the following types of evidence to determine when screening for cervical cancer should begin: incidence, prevalence, and mortality of cervical cancer in young women; the natural history of precancerous lesions and HPV infection; and the effects of screening in populations of young women. Cervical cancer in women younger than age 20 years is rare; according to U.S. Surveillance, Epidemiology, and End Results (SEER) data, 0.1% of all incident cancer cases occur in women younger than age 20 years. Older data from SEER (1) report declining rates of cervical cancer in the years 1973 to 1999; in some years, no cases occurred in women younger than age 20 years (2, 3, 18). Deaths due to cervical cancer in women younger than age 20 years are also rare; fewer than 16 such deaths occurred in the United States from 1992 through 2008 (1). Precancerous lesions are also uncommon. Prevalence of CIN3 among women younger than age 20 years is estimated at 0.2% (20, 21), with a concurrent rate of false-positive cytology results of about 3.1% (21). Because of the lack of

direct evidence, the USPSTF considered results of decision analyses using the best available data to estimate and understand the benefits and harms of screening at different starting ages and intervals; colposcopy was used as a proxy measure for harms. Results of the analyses show that screening every 3 years with cytology starting at age 21 years confers a similar number of life-years as does annual screening (69 247 vs. 69 213 per 1000 women), yet prompts fewer than half of the number of colposcopies and fewer false-positive test results. Varying the age at which to start screening shows no benefit to starting earlier than age 21 years; screening with cytology every 3 years starting at 15 years of age, 18 years of age, and 21 years of age finds cervical cancer death rates of 1.54, 1.54, and 1.55 per 1000 women, respectively (4). The results of these analyses suggest that screening beginning at age 21 years with an interval of 3 years provides the most acceptable balance of benefits and harms.

When deliberating on the age at which to end screening, the USPSTF considered the incidence of cervical cancer in older women and whether there is a difference in the pattern of cervical cancer incidence in screened versus unscreened women. The incidence and prevalence of CIN peak in the midreproductive years and begin to decline in approximately the fourth decade of life, a general pattern also apparent among some previously unscreened women. Cervical cancer in older women is not more aggressive or rapidly progressive than that in younger women. Finally, the rate of high-grade squamous intraepithelial lesions diagnosed by cytology is low among older women who have been previously screened. Modeling studies of the age at which to end screening indicate no substantial benefit beyond age 65 years in women who have been previously screened. Specifically, varying the age at which to end screening from 65 years to 95 years by 5-year intervals provides a very small (<1 life-year) improvement in life-years after age 65 years but increases potential harms due to false-positive results and the increase in the number of colposcopies and cervical biopsies (4).

Although screening women older than age 65 years who have an adequate screening history is not recommended, modeling studies suggest that screening women who have never been screened would reduce mortality by 74% (3, 22). Strategies that include screening previously unscreened women every 2 to 5 years and ending at age 70 to 75 years represent reasonable tradeoffs between benefits and harms (4). Current guidelines define adequate screening as 3 consecutive negative cytology results or 2 consecutive negative HPV results within 10 years before cessation of screening, with the most recent test performed within 5 years (7). Women with a clearly inadequate screening history are those who have never been screened or have not been recently screened before age 65 years. About half of all invasive cervical cancer cases are diagnosed in women who have never been screened or have not been screened in the last 5 years (and another 10% occurs in women who did not have appropriate follow-up for an abnormal Pap smear) (23). Data from a statewide cervical cancer screening program reveal that 29% of invasive cervical cancer cases occurred in women who had never undergone cervical cytology screening (23). Data varied by age; 25% of women aged 18 to 29 years with cancer reported no previous Pap tests, and 42% of those aged 65 years or older with cancer had never been screened (24). Efforts to further reduce the burden of cervical cancer mortality can be best achieved by focusing on women who have not been adequately screened.

Although cervical cancer screening with cytology alone every 3 years is an effective strategy, HPV testing combined with cytology every 5 years is a reasonable alternative for women aged 30 to 65 years who want to potentially increase the testing interval. The USPSTF reviewed 4 fair-quality randomized, controlled trials conducted outside of the United States (NTCC [New Technology in Cervical Cancer], POBASCAM [Population Based Screening Study Amsterdam], Swedescreen, and ARTISTIC [A Randomised Trial of HPV Testing in Primary Cervical Screening]) that compared cytology alone with cytology plus HPV testing (HC2 or polymerase chain reaction) (25–30). Published data from the 4 trials show a similar number of detected cancer cases with either strategy, although differences in colposcopy referral and treatment thresholds and incomplete reporting of data from the second screening round make interpretation complex. In all 4 trials, there were slightly lower rates of CIN3+ detected in the second round of screening and fewer cancer cases in the co-testing group than in the cytology group. These differences were very small, and not all were statistically significant. In one of the largest trials with the longest follow-up (POBASCAM), more than 44 000 women in the Netherlands were randomly assigned to HPV testing with cytology or cytology alone, with repeated screening with co-testing at 5-year intervals. Cumulative data at 9 years of follow-up demonstrated a similar absolute number of cancer cases in each group (16 vs. 20 cases; $P = 0.67$) (30). Detection of CIN3+ was similar between the 2 groups. Further data on the comparability of these 2 strategies from a longitudinal cohort study by Katki and colleagues of 330 000 U.S. women were published in 2011 (31). Cumulative 5-year incidence of cervical cancer was lower in the HPV-negative and cytology-negative group than in the cytology-negative group (3.2 per 100 000 vs. 7.5 per 100 000). Detection of CIN3+ was higher in earlier screening rounds with co-testing than with cytology alone. Modeling studies support similar benefits of co-testing every 5 years and cytology every 3 years, demonstrating small differences in expected cancer cases (7.44 vs. 8.50 cases, respectively) and cancer deaths (1.35 vs. 1.55 deaths, respectively) (4).

Two large studies documenting the low risk for cytologic abnormalities after hysterectomy have been published. A cross-sectional study of more than 5000 cytology tests among women older than age 50 years documented

that identification of vaginal intraepithelial neoplasia and cancer was rare in this age group after hysterectomy (0.18 per 1000 women screened) (32). In a second study of nearly 10 000 Pap tests performed over 2 years in 6265 women who had a hysterectomy with removal of the cervix, screening yielded 104 abnormal Pap results but only 4 high-grade lesions: 3 cases of vaginal intraepithelial neoplasia and 1 case of squamous cell carcinoma of the vagina (rate of 0.42 high-grade lesion per 1000 Pap tests) (33). Whether detection of these vaginal lesions improved clinical outcomes is unknown.

Potential Harms of Screening or Treatment

Harms of screening with cytology include short-term psychological distress (anxiety, concern) related to positive results and the time and burden resulting from the evaluation of false-positive test results. Colposcopies and biopsies can occur in response to false-positive results and can be used as a proxy measure for potential downstream harms. Recent data suggest that there is a risk for adverse effects with these procedures. The results of a randomized trial comparing surveillance with immediate colposcopy among women with minimally abnormal cytology test results showed a substantially lower proportion of women in the surveillance group who reported pain (15% vs. 39%), bleeding (17% vs. 47%), or discharge (9% vs. 34%) (34).

Common treatments of high-grade precancerous lesions in the United States include cervical conization or loop electrosurgical excision, both of which can be associated with potential short- and long-term risks. Studies show that short-term risks include pain, bleeding, and discharge (2). One cohort study found that 67% of women who had loop excision reported pain, 87% reported bleeding, and 63% reported discharge (34). In addition to surgical risks inherent to excisional therapies for neoplastic lesions, treatment may increase risk for adverse outcomes of future pregnancies, including perinatal mortality, preterm delivery before 34 weeks' gestation, and low birthweight (35, 36). To date, the evidence for adverse pregnancy events after cold-knife conization or loop excision is incomplete and based largely on retrospective studies, with some inconsistencies in the categorization of the procedures performed (2).

Because the rate of positivity on HPV testing is generally higher than that for cytology, strategies that incorporate HPV testing will identify women who are HPV positive but have no evidence of a high-grade precancerous lesion; among women aged 30 years or older in primary screening settings, this proportion ranges from 4.8% to 17% (14, 16). From U.S. studies, the proportion of women undergoing co-testing who can expect to have a positive HPV test result and normal cytology findings varies by age, ranging from 11% among women aged 30 to 34 years to 2.6% among women aged 60 to 65 years (5, 6). Guidelines for management of these women have been published by ACS/ASCCP/ASCP (7). Achieving the benefits of HPV testing with cytology without increasing the risk for overtreatment will require clinicians to be responsive to currently recommended algorithms for clinical surveillance.

The lower specificity of HPV testing (that is, higher false-positive rate) raises important concerns about unnecessary diagnostic testing (that is, colposcopy) as well as identification and treatment of precancerous lesions (such as CIN2) that may regress. The POBASCAM trial reported a modestly higher cumulative detection of CIN2 with HPV testing and cytology versus cytology alone (168 vs. 127 cases) (26, 30). On the basis of these findings, 8 CIN2/CIN3 lesions would have to be treated to prevent 1 case of cervical cancer (37). Although most trials have not yet reported final cumulative colposcopy rates, data from ARTISTIC show a slightly higher proportion of colposcopy referrals in the co-testing group than with cytology alone (6% vs. 4.9%, respectively), and early results from an ongoing trial comparing screening with HPV testing versus cytology also suggests higher rates of colposcopy referrals resulting from the first round of screening with HPV (28, 29, 37). Modeling studies commissioned by the USPSTF, however, show a modest increase in colposcopy with cytology alone compared with HPV testing plus cytology and fewer overall positive test results over a lifetime of screening. Assuming screening with cytology every 3 years before age 30 years and then co-testing every 5 years in a hypothetical cohort of 1000 women, modestly fewer lifetime colposcopies could be expected with co-testing than with cytology (758 vs. 575, respectively), but more lifetime tests could be expected (approximately 5000 more lifetime tests per 1000 women with co-testing). Cumulative data from the POBASCAM trial as well as round-specific results from ongoing trials reviewed by the USPSTF should be interpreted cautiously because there are limitations in study design and diagnostic protocols (for example, cytologic thresholds for colposcopy referral and randomization schemes in subsequent rounds of screening) that could alter the balance of benefits and harms, particularly when these findings are translated to U.S. practice. Additional round-specific and cumulative data from ongoing trials may further inform the balance of potential benefits and harms of HPV testing combined with cytology versus cytology alone.

Other potential harms of HPV testing include psychological distress associated with a positive result and unnecessary evaluation of a false-positive result, as well as the time required by the patient for repeated sampling due to an inadequate or insufficient specimen. Although some women may value information about HPV status, the USPSTF found evidence of adverse short-term psychological harms associated with knowledge of HPV positivity. Four fair-quality observational studies conducted in countries with well-developed cervical cancer screening programs, including a subset of women in an Australian trial (38), examined the immediate and short-term effect of

HPV testing in more than 4000 women (2). Immediate anxiety and stress levels increased in women who tested positive for HPV compared with those who tested negative; these differences were resolved after 6 months of follow-up. Data on longer-term follow-up of women undergoing HPV testing are limited. No treatments are available to eliminate HPV. Although there is evidence of harms of strategies that incorporate HPV testing in women aged 30 to 65 years, the USPSTF concludes that there is adequate evidence that the longer screening interval for HPV testing with cytology reduces the magnitude of these harms by decreasing the opportunity for false-positive test results. Current evidence suggests that there are moderate harms of HPV testing among women younger than age 30 years. The high prevalence of HPV, higher likelihood of regression of precancerous lesions, and low incidence of cervical cancer in this age group potentiate the harms of unnecessary colposcopy and biopsy. The higher false-positive rate also increases the possibility of unnecessary treatment and the potential for adverse pregnancy outcomes.

Estimate of Magnitude of Net Benefit

The effectiveness of cervical cancer screening observed in the United States over the past several decades is attributed to the use of conventional cytology. Although there is little direct evidence from studies applicable to the U.S. population that provides an estimate of the magnitude of net benefit, observational evidence provides high certainty that the introduction of screening substantially reduces rates of cervical cancer. Recommendations regarding appropriate screening intervals seek to achieve these benefits with relatively few harms.

The harms of screening women younger than age 21 years outweigh the benefits given the high prevalence of HPV infection and associated transient cytologic abnormalities in young women; detection of these abnormalities may prompt invasive procedures and excisional treatments that have been associated with subsequent adverse pregnancy outcomes. Because of the low incidence of high-grade precancerous lesions and cervical cancer in adequately screened older women, screening for cervical cancer in women older than age 65 years is of little benefit. The harms of screening women older than age 65 years, including false-positive results and complications from follow-up and treatment of abnormalities, are judged by the USPSTF to be small. After balancing the potential benefits and harms, there is moderate certainty that screening women older than age 65 years has no benefit if they have been previously adequately screened. After hysterectomy for reasons other than a high-grade precancerous lesion or cervical cancer, screening the vagina for precancerous lesions is of little benefit and has the potential for harm due to positive test results, with subsequent invasive procedures and treatments.

Although none of the reported trials compared HPV testing with cytology-based screening as currently performed in the United States, the USPSTF was able to draw several relevant conclusions from these trials and others (26–29, 39–43), in addition to epidemiologic and natural history data (2, 18). In women younger than age 30 years, the USPSTF found evidence that the potential harms of HPV testing outweigh the potential benefits and concluded that there was no net benefit of HPV testing, alone or in combination with cytology, in this age group. This conclusion was based on the consistent and substantially higher HPV positivity rates in young women compared with older women and the potential to cause short-term adverse psychological effects and adverse pregnancy outcomes in this group of childbearing women. Detection of CIN2 is also increased with HPV testing. Many CIN2 lesions will regress, and overtreatment is a concern. In women aged 30 to 65 years, the USPSTF found that the evidence was adequate to conclude that the potential benefit of HPV testing in combination with cytology every 5 years is similar to the benefits achievable with cytology alone every 3 years.

How Does Evidence Fit With Biological Understanding?

The natural history of cervical cancer has been well-studied. Human papillomavirus infection of the cervix is generally transient, but when the infection is not cleared by an appropriate immune response and the HPV 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 efficiently screen for and identify precancerous lesions and treat them, thereby reducing the incidence of cervical cancer incidence and mortality.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 19 October, through 30 November 2011. Many comments pointed out a lack of clarity about the harms of false-positive results and the harms of screening with cytology more frequently than every 3 years or screening women younger than age 21 years. Several comments requested clarification on how information about sexual history may affect screening. Some comments highlighted the importance of reaching women who are not being screened at all. Many comments urged the USPSTF to reconsider its draft recommendation on HPV co-testing and review new evidence that had been published since its deliberation. In response to these comments, the USPSTF clarified throughout the statement the harms that would occur from screening too frequently and in women younger than age 21 years. The USPSTF also clarified that this recommendation statement applies to women regardless of sexual history. The USPSTF agrees that the greatest effect on cervical cancer incidence and mortality would result from

efforts to screen women who have not been adequately screened, and this is stated in the Rationale and elsewhere.

After the public comment period, the USPSTF considered new evidence that was published since its initial deliberation—specifically the update of the POBASCAM results and the study by Katki and colleagues (30, 31). With this new evidence, in addition to the previously considered evidence, the USPSTF decided to recommend HPV testing combined with cytology (co-testing) as a reasonable alternative for women aged 30 to 65 years who wish to extend the screening interval beyond 3 years.

Update of Previous USPSTF Recommendation

This recommendation updates the 2003 USPSTF recommendation (44) on screening for cervical cancer. It differs from the previous recommendation in that it recommends cytology screening every 3 years among women aged 21 to 65 years. In addition, this recommendation includes more guidance on the appropriate age ranges and frequency of screening, including a new recommendation that women younger than age 21 years not be screened because the evidence shows no net benefit. The previous recommendation suggested that most of the benefit of screening could be obtained by beginning screening within 3 years of onset of sexual activity or age 21 years (whichever comes first) and screening at least every 3 years. This recommendation reaffirms the previous recommendations against screening in adequately screened women older than age 65 years and in women who have had a total hysterectomy with removal of the cervix. The current recommendation includes new evidence on the comparative test performance of liquid-based versus conventional cytology that indicates no substantial difference in test performance (that is, relative detection or absolute sensitivity or specificity) for detection of CIN2+/CIN3+. It also includes more guidance on the appropriate use of HPV testing in cervical cancer screening, including a new recommendation that women younger than aged 30 years not be screened with HPV testing. The USPSTF found new evidence that addressed the gaps identified in the previous recommendation and allowed the USPSTF to recommend HPV testing combined with cytology as an acceptable screening strategy for women aged 30 to 65 years who prefer to lengthen their screening interval beyond 3 years.

Recommendations of Others

The ACS, ASCCP, and ASCP recently published screening guidelines that are very similar to the USPSTF's recommendations (7). The ACS/ASCCP/ASCP recommend that women aged 21 to 29 years be screened with cytology (cervical cytology testing or Pap testing) alone every 3 years. Women aged 30 to 65 years should be screened with cytology and HPV testing (co-testing) every 5 years or cytology alone every 3 years. The guidelines further state that no woman should be screened every year and that women aged 21 to 29 years should not be screened with HPV testing or combined cytology and HPV testing. The American Congress of Obstetricians and Gynecologists and the American Academy of Family Physicians have previously published screening guidelines (45, 46) and are evaluating new evidence, including these recommendations on screening for cervical cancer from the USPSTF.

From U.S. Preventive Services Task Force, Rockville, Maryland.

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

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Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force† at the time this recommendation was finalized are Virginia A. Moyer, MD, MPH, *Chair* (Baylor College of Medicine, Houston, Texas); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Adelita Gonzales Cantu, RN, PhD (University of Texas Health Science Center, San Antonio, Texas); David C. Grossman, MD, MPH (Group Health Cooperative, Seattle, Washington); Joy Melnikow, MD, MPH (University of California, Davis, Sacramento, California); Wanda K. Nicholson, MD, MPH, MBA (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Carolina Reyes, MD, MPH (Virginia Hospital Center, Arlington, Virginia); and Timothy J. Wilt, MD, MPH (University of Minnesota Department of Medicine and Minneapolis Veteran Affairs Medical Center, Minneapolis, Minnesota). Former USPSTF members who contributed to the development of this recommendation include George J. Isham, MD, MS (HealthPartners, Minneapolis, Minnesota); Rosanne M. Leipzig, MD, PhD (Mount Sinai School of Medicine, New York, New York); Bernadette Melnyk, PhD, RN (Ohio State University College of Nursing, Columbus, Ohio); George F. Sawaya, MD (University of California, San Francisco, San Francisco, California); and J. Sanford Schwartz, MD, MBA (University of Pennsylvania Medical School and the Wharton School, Philadelphia, Pennsylvania).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.