

Screening for Cervical Cancer: Recommendations and Rationale

U.S. Preventive Services Task Force

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This statement summarizes the current U.S. Preventive Services Task Force (USPSTF) recommendations on screening for cervical cancer and the supporting scientific evidence, and updates the 1996 recommendations contained in the *Guide to Clinical Preventive Services, Second Edition*.¹ Explanations of the ratings and of the strength of overall evidence are given in Appendix A and in Appendix B, respectively. The complete information on which this statement is based, including evidence tables and references, is available in the Systematic Evidence Review "Screening for Cervical Cancer,"² available through the USPSTF Web site (<http://www.preventiveservices.ahrq.gov>) and through the National Guideline Clearinghouse™

(<http://www.guideline.gov>). The summary of the evidence and the recommendation statement are also available in print through the AHRQ Publications Clearinghouse (call 1-800-358-9295 or E-mail ahrqpubs@ahrq.gov).

*Member of the USPSTF at the time this recommendation was finalized.

SUMMARY OF RECOMMENDATIONS

- The USPSTF strongly recommends screening for cervical cancer in women who have been sexually active and have a cervix. **A recommendation.**

The USPSTF found good evidence from multiple observational studies that screening with cervical cytology (Pap smears) reduces incidence of and mortality from cervical cancer. Direct evidence to determine the optimal starting and stopping age and interval for screening is limited. Indirect evidence suggests most of the benefit can be obtained by beginning screening within 3 years of onset of sexual activity or age 21 (whichever comes first) and screening at least every 3 years (see Clinical Considerations). The USPSTF concludes that the benefits of screening substantially outweigh potential harms.

- The USPSTF recommends against routinely screening women older than age 65 for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer (*see Clinical Considerations*). **D recommendation.**

The USPSTF found limited evidence to determine the benefits of continued screening in women older than 65. The yield of screening is low in previously screened women older than 65 due to the declining incidence of high-grade cervical lesions after middle age. There is fair evidence

that screening women older than 65 is associated with an increased risk for potential harms, including false-positive results and invasive procedures. The USPSTF concludes that the potential harms of screening are likely to exceed benefits among older women who have had normal results previously and who are not otherwise at high risk for cervical cancer.

- The USPSTF recommends against routine Pap smear screening in women who have had a total hysterectomy for benign disease. **D recommendation.**

The USPSTF found fair evidence that the yield of cytologic screening is very low in women after hysterectomy and poor evidence that screening to detect vaginal cancer improves health outcomes. The USPSTF concludes that potential harms of continued screening after hysterectomy are likely to exceed benefits.

- The USPSTF concludes that the evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer. **I recommendation.**

The USPSTF found poor evidence to determine whether new technologies, such as liquid-based cytology, computerized rescreening, and algorithm based screening, are more effective than conventional Pap smear screening in reducing incidence of or mortality from invasive cervical cancer. Evidence to determine both sensitivity and specificity of new screening technologies is limited. As a result, the USPSTF concludes that it cannot determine whether the potential benefits of new screening devices relative to conventional Pap tests are sufficient to justify a possible increase in potential harms or costs.

- The USPSTF concludes that the evidence is insufficient to recommend for or against the routine use of *human papillomavirus* (HPV) testing as a primary screening test for cervical cancer. **I recommendation.**

The USPSTF found poor evidence to determine the benefits and potential harms of HPV screening as an adjunct or alternative to regular Pap smear screening. Trials are underway that should soon clarify the role of HPV testing in cervical cancer screening.

CLINICAL CONSIDERATIONS

- The goal of cytologic screening is to sample the transformation zone, the area where physiologic transformation from columnar endocervical epithelium to squamous (ectocervical) epithelium takes place and where dysplasia and cancer arise. A meta-analysis of randomized trials supports the combined use of an extended tip spatula to sample the ectocervix and a cytobrush to sample the endocervix.³
- The optimal age to begin screening is unknown. Data on natural history of HPV infection and the incidence of high-grade lesions and cervical cancer suggest that screening can safely be delayed until 3 years after onset of sexual activity or until age 21, whichever comes first.⁴ Although there is little value in screening women who have never been sexually active, many U.S. organizations recommend routine screening by age 18 or 21 for all women, based on the generally high prevalence of sexual activity by that age in the U.S. and concerns that clinicians may not always obtain accurate sexual histories.

- Discontinuation of cervical cancer screening in older women is appropriate, provided women have had adequate recent screening with normal Pap results. The optimal age to discontinue screening is not clear, but risk of cervical cancer and yield of screening decline steadily through middle age. The USPSTF found evidence that yield of screening was low in previously screened women after age 65. New American Cancer Society (ACS) recommendations suggest stopping cervical cancer screening at age 70. Screening is recommended in older women who have not been previously screened, when information about previous screening is unavailable, or when screening is unlikely to have occurred in the past (eg, among women from countries without screening programs). Evidence is limited to define "adequate recent screening." The ACS guidelines recommend that older women who have had three or more documented, consecutive, technically satisfactory normal/negative cervical cytology tests, and who have had no abnormal/positive cytology tests within the last 10 years, can safely stop screening.⁴
- The USPSTF found no direct evidence that annual screening achieves better outcomes than screening every 3 years. Modeling studies suggest little added benefit of more frequent screening for most women. The majority of cervical cancers in the U.S. occur in women who have never been screened or who have not been screened within the past 5 years; additional cases occur in women who do not receive appropriate follow-up after an abnormal Pap smear.^{5,6} Because sensitivity of a single Pap test for high-grade lesions may only be 60% to 80%, however, most organizations in the U.S. recommend that annual Pap smears be performed until a specified number (usually 2 or 3) are cytologically normal before lengthening the screening interval.² The ACS guidelines suggest waiting until age 30 before lengthening the screening interval⁴; the American College of Obstetricians and

Gynecologists (ACOG) identifies additional risk factors that might justify annual screening, including a history of cervical neoplasia, infection with HPV or other STDs, or high-risk sexual behavior,⁷ but data are limited to determine the benefits of these strategies.⁷

- Discontinuation of cytological screening after total hysterectomy for benign disease (eg, no evidence of cervical neoplasia or cancer) is appropriate given the low yield of screening and the potential harms from false-positive results in this population.^{8,9} Clinicians should confirm that a total hysterectomy was performed (through surgical records or inspecting for absence of a cervix); screening may be appropriate when the indications for hysterectomy are uncertain. ACS and ACOG recommend continuing cytologic screening after hysterectomy for women with a history of invasive cervical cancer or DES exposure due to increased risk for vaginal neoplasms, but data on the yield of such screening are sparse.
- A majority of cases of invasive cervical cancer occur in women who are not adequately screened.^{5,6} Clinicians, hospitals, and health plans should develop systems to identify and screen the subgroup of women who have had no screening or who have had inadequate past screening.
- Newer Food and Drug Administration (FDA)-approved technologies, such as the liquid-based cytology (e.g., ThinPrep®), may have improved sensitivity over conventional Pap smear screening, but at a considerably higher cost and possibly with lower specificity. Even if sensitivity is improved, modeling studies suggest these methods are not likely to be cost-effective unless used with screening intervals of 3 years or longer. Liquid-based cytology permits testing of specimens for HPV, which may be useful in guiding management of women whose Pap smear reveals atypical squamous cells. HPV DNA testing for primary cervical

cancer screening has not been approved by the FDA and its role in screening remains uncertain.

SCIENTIFIC EVIDENCE

Epidemiology and Clinical Consequences

Approximately 13,000 new cases of cervical cancer and 4,100 cervical cancer-related deaths were projected to occur in 2002 in the United States. Rates in the U.S. have decreased from 14.2 new cases per 100,000 women in 1973 to 7.8 cases per 100,000 women in 1994. Despite falling incidence, cervical cancer remains the tenth leading cause of cancer death.¹⁰ The *Healthy People 2010* target for cervical cancer is a reduction in mortality to 2.0 deaths per 100,000 women. Since 1998, the rate remains near 3.0 deaths per 100,000 women.¹¹

Squamous cell carcinoma of the cervix and its cytologic precursors occur among women who are sexually active. Risk factors relating to sexual behavior associated with an increased risk of cervical cancer include early onset of intercourse and a greater number of lifetime sexual partners. Cigarette smoking is the only nonsexual behavior consistently and strongly correlated with cervical dysplasia and cancer, independently increasing risk two- to four-fold.¹²⁻¹⁴

Infection with high-risk strains of human papilloma virus (HPV), generally acquired sexually, is the most important risk factor for cervical cancer. Using modern HPV detection methods, 95% to 100% of squamous cell cervical cancer and 75% to 95% of high-grade CIN lesions have detectable HPV DNA.¹⁵⁻¹⁷ HPV is a necessary but insufficient precursor of squamous cell carcinoma of the cervix. Host factors such as age, nutritional status, immune function, smoking, and possibly silent genetic polymorphisms modulate incorporation of viral DNA into host cervical cells. In the U.S., peak incidence and prevalence of HPV infection occur

among women younger than 25 but most infections in younger women are transient. Infections with HPV in older women are much less prevalent but carry a higher risk of progressing to cervical neoplasia. Although the prevalence of HPV infection is higher among immunocompromised hosts such as HIV-infected women, the speed of progression to cervical cancer is not increased. Natural history studies confirm that, in the vast majority of cases, the course of infection and cervical abnormalities that progress do so in an orderly fashion from less severe to more severe lesions.

Accuracy and Reliability of Screening Tests

Cervical cancer screening tests potentially appropriate for primary care settings include cervical cytology, conventional and new technologies, and tests for HPV infection.

Screening Using Cytologic Methods

The USPSTF did not re-examine test characteristics of conventional cervical cytology smears. A previous review estimated that the sensitivity of a single Pap test was 60% to 80% for high-grade lesions, and even lower for low-grade lesions.¹⁸ The USPSTF review focused on new evidence about thin layer cytology (ThinPrep[®], AutoCyte PREP[®]), computerized rescreening (PapNet[®]), and algorithm-based screening (AutoPap[®]), all recent technical extensions of conventional cytology methods. The USPSTF found few studies testing the new technologies against an adequate reference standard (colposcopy or histology) and few that included validation of normal screening test results.^{2,18} As a result, sensitivity, specificity, and predictive values of the new technologies cannot be directly assessed or compared with the test characteristics of conventional cytology in the same population. Furthermore, no prospective

studies have compared the new technologies to conventional Pap screening using the most important health outcomes (eg, invasive cervical cancer) or costs and cost-effectiveness. The only model identified finds that new technologies are more costly than conventional cytology and that new technologies will fall within the traditional range considered to be cost-effective (\$50,000 per life-year) only if used in screening intervals of 3 years or longer.¹⁸ In the absence of studies with cervical cancer outcomes, the USPSTF concluded that the available data on the accuracy of new technologies were insufficient to determine whether they are more effective than conventional cervical cytology for preventing invasive cervical cancer.

The literature provides fairly reliable estimates of the number of women who need to be screened to detect serious lesions. Among previously screened women with a history of normal Pap tests, fewer than 1 woman in 1,000 screened (in some scenarios as few as 1 woman in 10,000) will have a high-grade cytologic abnormality. As an example, if the sensitivity of cytology is 60% and the specificity is 98% for detection of high-grade abnormalities, then 34 women will be evaluated for high-grade squamous intraepithelial lesions for each true high-grade cervical lesion identified; moreover, 2 high-grade lesions will have been missed by cytology for every 3 cases identified. The ratio of true positives to false positives is much higher if low-grade cytologic changes are considered, but many of these will regress without treatment.¹⁸

Screening Using Tests for HPV

Six studies prior to 2002 examined the role of HPV as a primary screening test, 5 of which used a study population at high risk for cervical dysplasia. Only one study of 2,988 women having routine cervical cancer screening at 40 general practitioner practices in the U.K.

approximates screening use in routine primary care practice in the U.S.¹⁹ In conditions of low prevalence of high-grade squamous intraepithelial lesions (HSIL) typical of primary care practice, the USPSTF estimated sensitivity of testing for HPV using Hybrid Capture II for HSIL at 82%; specificity, 78%; positive predictive value, 18%; and negative predictive value, 99%. The estimated sensitivity of testing for HPV using Hybrid Capture II for LSIL was 66%; specificity, 91%; positive predictive value, 26%; and negative predictive value, 98%. Similar results were reported in a recent study in Planned Parenthood clinics: both Hybrid Capture II and PCR testing were more sensitive than liquid-based cytology (88% to 91% vs 61%) but were less specific (73% to 79% vs 82%).²⁰

The benefits of HPV testing as an alternative or adjunct to primary Pap screening have not yet been tested in prospective studies. Adding HPV testing to conventional screening is unlikely to be worthwhile, but HPV testing may have a role in primary screening if it can reliably distinguish between women who would benefit from more intensive Pap testing (more frequent, different technologies, or extended over longer periods) and women for whom screening can be less intensive or even discontinued. There are at least 8 studies evaluating HPV testing in large populations underway or recently completed but not yet in the published literature. At the same time, there are few data on the potential harms of HPV testing, which may include anxiety or stigmatization among infected women and affects on relationships with sexual partners.

Special considerations in older women and in women who have had a hysterectomy

Multiple studies published since 1995 provide sufficiently detailed information about results of screening by age to examine the evidence about screening among older women.² The incidence and prevalence of cervical intraepithelial neoplasia peak in the mid-reproductive years

and begin to decline in approximately the fourth decade of life, a general pattern also apparent among previously unscreened women. Cervical cancer in older women is not more aggressive or rapidly progressive than it is in younger women. Finally, the rates of high-grade squamous intraepithelial lesions diagnosed by cytology are low among older women who have been screened. These and other data suggest that the risks of high-grade cervical lesions and cancer fall with age; that a history of prior normal Pap tests further reduces risk; and that if screening recommendations are not modified with age, older women are disproportionately likely to be evaluated for false-positive findings. In one study of more than 2,561 postmenopausal women (average age 67 years) who had normal baseline smears and were generally at low risk for cervical cancer, annual screening done over 4 years produced 110 abnormal results requiring diagnostic evaluations, which generated 231 additional interventions (ranging from repeat Pap smears to colposcopy and biopsies); one case of “mild to moderate dysplasia” was diagnosed.²¹ The difficult trade-off between over-screening and missing rare but potentially preventable cases of cervical cancer is a challenge for policy.

Two large series documenting the low risk of cytologic abnormality after hysterectomy have been published since the last USPSTF made its recommendations. A cross-sectional study of more than 5,000 Pap tests among women older than age 50 documented that identification of dysplasia and cancer was rare in this age group after hysterectomy (0.18/1,000 women screened).²² Women after hysterectomy were one tenth as likely as those with a cervix to have any Pap test diagnosis of abnormality. In a second study of nearly 10,000 Pap tests performed over 2 years in 6,265 women who had hysterectomies for benign disease, screening yielded 104 abnormal Pap tests 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 lesions per 1,000 Pap tests).²³ Whether detection of these vaginal lesions improved clinical outcomes is unknown.

Effectiveness of Early Detection

Detection of cervical cancer in its earliest stages is lifesaving, as survival of cancer of the cervix uteri depends heavily on stage at diagnosis. Although 92% of women will survive 5 years when the cancer is localized, only 13% will survive distant disease.²⁴ Introduction of screening programs to populations naïve to screening reduces cervical cancer rates by 60% to 90% within 3 years of implementation.^{25,26} This reduction of mortality and morbidity with introduction of the Pap test is consistent and dramatic across populations. Although no prospective trial of Pap screening has ever been conducted, 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.

No prospective studies have directly compared the outcomes of screening at different intervals in a given population. Data from 8 cervical cancer screening programs involving 1.8 million women compared the effects of different intervals among the programs: screening at intervals of 5, 3, 2 years or 1 year was estimated to reduce incidence of invasive disease by 84%, 91%, 93%, and 94%, respectively, among women aged 35-64, assuming perfect compliance. Data from a large screening program in the U.S. indicate that a longer interval (3 years vs 1 or 2 years) between Pap tests is not associated with a higher risk for developing high-grade lesions.²⁷

Potential Harms of Screening and Treatment

The USPSTF did not identify studies that specifically addressed harms of new technologies for cervical cancer screening. Better data on the performance characteristics (sensitivity, specificity, and predictive values) of the new screening technologies are needed to determine the risk for harm to an individual patient. Although the data are limited, on average these tools improve sensitivity and reduce specificity. This finding suggests that increased detection of low-grade lesions and false positives are the primary potential sources of harm; ie, harm may take the form of increased evaluations, including repeated Pap tests and biopsies; possible unnecessary treatment for low-grade lesions; and psychological distress for the women diagnosed with low grade lesions that may not have been clinically important. These harms are poorly documented for conventional Pap testing and have not yet been assessed for new technologies.

With regard to HPV testing, the USPSTF did not identify any studies that quantified harms. Potential harms commented upon in the literature include stigma, partner discord, adverse effects of labeling some women as being at high risk for cervical cancer, and the potential undermining of routine cytologic screening known to be effective.

RECOMMENDATIONS OF OTHERS

The new guidelines of the American Cancer Society (ACS) recommend initiating screening 3 years after onset of sexual activity but no later than age 21.⁴ ACS recommends annual screening with conventional Pap tests, or screening every 2 years if liquid-based cytology

is used, until age 30; thereafter the screening interval can be extended to 2-3 years based on past screening results and risk factors. Most other North American organizations have previously recommended beginning screening at onset of sexual activity or at age 18; these include the American Academy of Family Physicians (AAFP),²⁸ American College of Obstetricians and Gynecologists (ACOG) [7], American College of Preventive Medicine (ACPM),²⁹ American Medical Association (AMA),³⁰ the Canadian Task Force on Preventive Health Care (CTFPHC),³¹ and the American Academy of Pediatrics (AAP),³² among others. Some of them may update their guidelines in light of the new recommendations on starting age. These organizations recommend that initial screening be conducted annually, but most recommendations permit Pap testing less frequently after 3 or more normal annual smears, based on patient risk factors and the discretion of the patient and physician.

Guidelines of the ACS,⁴ AAFP,²⁸ ACPM,²⁹ and the CTFPHC³¹ recommend discontinuing screening, or offering the option for patients to discontinue screening, after age 65 or 70 provided there is documented evidence of adequate past screening; details of what constitutes “adequate” past screening vary. No current screening guidelines specifically recommend using HPV testing for screening, or recommend newer Pap test technologies in favor of conventional Pap tests.

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APPENDIX A

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS AND RATINGS

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

- A.** The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
- B.** The USPSTF recommends that clinicians routinely provide [this service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
- C.** The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
- D.** The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
- I.** The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

APPENDIX B

U.S. PREVENTIVE SERVICES TASK FORCE STRENGTH OF OVERALL EVIDENCE

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.