# 9. Screening for Cervical Cancer

***RECOMMENDATION***

Routine screening for cervical cancer with Papanicolaou (Pap) testing is recommended for all women who are or have been sexually active and who have a cervix. Pap smears should begin with the onset of sexual activity and should be repeated at least every 3 years (see *Clinical Intervention*). There is insufficient evidence to recommend for or against an upper age limit for Pap testing, but recommendations can be made on other grounds to discontinue regular testing after age 65 in women who have had regular previous screenings in which the smears have been consistently normal. There is insufficient evidence to recommend for or against routine screening with cervicography or colposcopy, or for screening for human papilloma virus infection, although recommendations against such screening can be made on other grounds (see *Clinical Intervention*).

## Burden of Suffering

Approximately 16,000 new cases of cervical cancer are diagnosed each year, and about 4,800 women die from this disease annually.[1] The lifetime risk of dying from cervical cancer in the U.S. is 0.3%.[1a] Although the 5-year survival rate is about 90% for persons with localized cervical cancer, it is considerably lower (about 14%) for persons with advanced (Stage IV) disease. The incidence of invasive cervical cancer has decreased significantly over the last 40 years, due in large part to organized early detection programs. Although all sexually active women are at risk for cervical cancer, the disease is more common among women of low socioeconomic status, those with a history of multiple sex partners or early onset of sexual intercourse, and smokers. The incidence of invasive cervical cancer among young white women has increased recently in the United States. Infection with human immunodeficiency virus (HIV) and certain types of human papilloma virus (HPV) also increases the risk of cervical cancer.[2]

## Accuracy of Screening Tests

The principal screening test for cervical cancer is the Pap smear. Although the Pap smear can sometimes detect endometrial, vaginal, and other cancers,[3,4] its use as a screening test is intended for the early detection of cer-

vical dysplasia and cancer. Other proposed cervical screening tests include cervicography, colposcopy, and testing for HPV infection. The role of pelvic examination, which usually accompanies the collection of the cervical specimen, is discussed in Chapter 14 in relation to ovarian cancer screening.

Precise data on the sensitivity and specificity of the Pap smear in detecting cancer and dysplasia are lacking due to methodologic problems. Depending on study design, false-negative rates of 1–80% have been reported; a range of 20–45% has been quoted most frequently, primarily in studies comparing normal test results with subsequent smears.[5–11] Studies using cone biopsy results as the reference standard have reported false-negative rates as low as 10%.[12] Although reliable data are lacking, specificity is probably greater than 90%[13] and may be as high as 99%.[6,11] The detection of precursor cervical intraepithelial neoplasia (CIN) by Pap smears may have poor specificity for cervical carcinoma, however, because a substantial proportion of CIN-1 lesions do not progress to invasive disease or may regress spontaneously. The test-retest reliability of Pap smears is influenced to some extent by variations in the expertise and procedures of different cytopathology laboratories.

A large proportion of diagnostic errors may be attributable to laboratory error. In one study of over 300 laboratories given slides with known cytologic diagnoses, false-negative diagnoses were made in 7.5% of smears with moderate dysplasia or frank malignancy, and false-positive diagnoses were made in 8.9% of smears with no more than benign atypia.[14] A survey of 73 laboratories in one state revealed a false-negative rate of 4.4% and a false-positive rate of 2.7%.[15] These data were reported in 1990, before the introduction of federal legislation designed to improve the accuracy of cytopathologic laboratory interpretation.[16] With the adoption of the Bethesda system for classification of cervical diagnoses,[17] a large proportion of benign smears are interpreted as “atypical,” a finding that poses little premalignant potential but that often generates intensive follow-up testing.

Another cause of false-negative Pap smears is poor specimen collection technique. A 1991 survey of 600 laboratories found that 1–5% of specimens received were either unsatisfactory or suboptimal, generally because endocervical cells were absent from the smear.[18] Another study found that poor sampling technique accounted for 64% of false-negative results.[19] The Pap smear has traditionally been obtained with a spatula, to sample the ectocervix, and a cotton swab, to obtain endocervical cells. A 1990 survey found that about half of physicians used a spatula and cotton swab to collect Pap smears.[20] In recent years, new devices have been introduced to improve sampling of the squamocolumnar junction. Controlled studies have shown that using an endocervical brush in combination with a spatula is more

likely to collect endocervical cells than using a spatula or cotton swab.[21–30] There is conflicting evidence, however, that the endocervical brush increases the detection rate for abnormal smears or affects clinical outcomes.[31–33] There is also conflicting evidence regarding the importance of collecting endocervical cells. Although some large series have reported that CIN is detected over 2 times more frequently when endocervical cells are present,[34,35] other series[36,37] have shown no association between the presence of endocervical cells and the detection rate for dysplasia. The brush is more expensive than the cotton swab, but studies suggest that this cost is easily recovered by the reduced need for repeat testing.[38] Other methods for improving the sensitivity of cervical cancer screening, such as acetic acid washes to improve the visibility of lesions, remain investigational.[39,40]

There are important potential adverse effects associated with inaccurate interpretation of Pap smears. False-negative results are significant because CIN or more invasive lesions may escape detection and progress to more advanced disease during the period between tests. The potential adverse effects of false-positive results include patient anxiety regarding the risk of cervical cancer,[41,42] as well as the unnecessary inconvenience, discomfort, and expense of follow-up diagnostic procedures. Studies have shown that the distribution of patient education materials that explain the meaning of abnormal results is associated with a reduction in patient anxiety and stress and a better patient understanding of test results.[43–45]

Other tests, such as cervicography and colposcopy, have been proposed to help improve the sensitivity of screening,[46] but their accuracy and technical requirements are suboptimal. Cervicography, in which a photograph of the cervix is examined for atypical lesions, has a sensitivity that is comparable to the Pap smear (approximately 60%) but a much lower specificity (approximately 50%); the reported positive predictive value in most studies is only 1–26%, and about 10–15% of cervigrams are unsatisfactory.[47–51] Colposcopy, in which the cervix is examined under magnification with acetic acid washing and suspicious lesions are biopsied, is widely performed on women with abnormal Pap smears but has poor sensitivity (34–43%), specificity (68%), and positive predictive value (4–13%) when used as a screening test for cervical neoplasia in asymptomatic women.[52–54] Other disadvantages of colposcopy screening include its cost, the limited availability of the equipment, the time and skills required to perform the procedure, and patient discomfort. Using a 10-point score for assessing pain, one study reported that women who underwent colposcopy gave the procedure a range of scores from 3 to 4.6.[55]

Another proposed screening strategy is testing for HPV infection, a known risk factor for cervical cancer. Of the more than 70 types of HPV that have been identified, several oncogenic forms (e.g., types 16 and 18) have a strong epidemiologic association with cervical cancer. However, the

natural history of how HPV infection progresses to cancer is poorly understood.[56] One study of women infected with either HPV type 16 or 18 found that 67% of the lesions remained unchanged or regressed after a mean of 5 years, 29% progressed to a more advanced stage of dysplasia, and 3% recurred.[57] The high prevalence of HPV infection in young women also limits its predictive value. In one study, nearly half of female college students had evidence of HPV when tested by polymerase chain reaction technology.[58] The reported positive predictive value of this HPV test for CIN-2 or CIN-3 lesions and carcinoma is less than 10%.[59] HPV typing to identify women with oncogenic strains may improve the future accuracy of the test and its role in directing follow-up, but its current suitability for routine screening in asymptomatic women is limited by its poor predictive value, uncertain natural history, and, due to the absence of an effective treatment, the lack of evidence that screening affects clinical outcomes.[60]

### Effectiveness of Early Detection

Early detection of cervical neoplasia provides an opportunity to prevent or delay progression to invasive cancer by performing clinical interventions such as colposcopy, conization, cryocautery, laser vaporization, loop electrosurgical excision, and, when necessary, hysterectomy.[61] There is evidence that early detection through routine Pap testing and treatment of precursor CIN can lower mortality from cervical cancer. Correlational studies in the United States, Canada, and several European countries comparing cervical cancer data over time have shown dramatic reductions in the incidence of invasive disease and a 20–60% reduction in cervical cancer mortality rates following the implementation of cervical screening programs.[62–70] Case-control studies have shown a strong negative association between screening and invasive disease, also suggesting that screening is protective.[71–75] These observational studies do not constitute direct evidence that screening was responsible for the findings,[76] and randomized controlled trials to provide such evidence have not been performed. Nonetheless, the large body of supportive evidence accumulated to date has prompted the adoption of routine cervical cancer screening in many countries and makes performance of a controlled trial of Pap smears unlikely for ethical reasons.

Observational data suggest that the effectiveness of cervical cancer screening increases when Pap testing is performed more frequently.[72] Aggressive dysplastic and premalignant lesions are less likely to escape detection when the interval between smears is short. There are, however, diminishing returns as frequency is increased.[71,77] Although studies have shown that reducing the interval between Pap smears from 10 years to 5

years is likely to achieve a significant reduction in the risk of invasive cervical cancer, case-control studies and mathematical modeling have demonstrated that increasing to a 2–3-year interval offers only slight added benefit.[71,78–80] There is little evidence that women who receive annual screening are at significantly lower risk for invasive cervical cancer than are women who are tested every 3–5 years. These findings were confirmed in a major study of eight cervical cancer screening programs in Europe and Canada involving over 1.8 million women.[81] According to this report, the cumulative incidence of invasive cervical cancer was reduced 64.1% when the interval between Pap tests was 10 years, 83.6% at 5 years, 90.8% at 3 years, 92.5% at 2 years, and 93.5% at 1 year. These estimates were for women aged 35–64 who had at least one screening before age 35, and they are based on the assumption of 100% compliance.

### Recommendations of Other Groups

A consensus recommendation that all women who are or have been sexually active, or who have reached age 18, should have annual Pap smears has been adopted by the American Cancer Society, National Cancer Institute, American College of Obstetricians and Gynecologists (ACOG), American Medical Association, American Academy of Family Physicians (AAFP), and others.[82] The recommendation permits Pap testing less frequently after three or more annual smears have been normal, at the discretion of the physician. Guidelines for determining frequency based on risk factors have been issued by ACOG.[83] The consensus did not recommend an age to discontinue Pap testing. The AAFP recommends that screening can be discontinued at age 65 if there is documented evidence of previously negative smears, but its recommendations are currently under review.[84] The American College of Physicians (ACP) recommends Pap smears every 3 years for women aged 20–65, and every 2 years for women at high risk.[85] The ACP also recommends screening women aged 66–75 every 3 years if not screened in the 10 years before age 66. The Canadian Task Force on the Periodic Health Examination recommends screening for cervical cancer with annual Pap smears in women following initiation of sexual activity or age 18, and after two normal smears, screening every 3 years to age 69.[86] The Canadian Task Force recommends considering more frequent screening for women at increased risk. In their guidelines for adolescent preventive services (GAPS), the American Medical Association recommends annual screening with a Pap test for female adolescents who are sexually active or age 18 or older.[87] Bright Futures also recommends annual Pap testing for sexually active adolescent females.[88] Similar recommendations have been endorsed by the American Academy of Pediatrics.[89]

Discussion

It has been estimated that screening women aged 20–64 every 3 years with Pap testing reduces cumulative incidence of invasive cervical cancer by 91%, requires about 15 tests per woman, and yields 96 cases for every 100,000 Pap smears. Annual screening reduces incidence by 93%, but requires 45 tests and yields only 33 cases for every 100,000 tests.[81] Empirical data also support the effectiveness of a 3-year interval. A study of 25,000 Dutch women found that screening a stable population every 3 years reduced the incidence of squamous cell carcinoma of the cervix from 0.38 per 1000 to zero within 12 years.[67] There are, in addition, important economic considerations to performing Pap tests every 2–3 years, since annual testing could double or triple the total number of smears taken on over 92 million American women at risk,[90] yet provide only limited added benefit in lowering mortality.[81]

Annual testing, however, has been common. In the mid-1980s, a survey of recently trained gynecologists found that 97% recommend a Pap test at least once a year.[91] The preference of many clinicians for performing annual Pap smears is based on concerns that less frequent testing may result in more harm than good, but reliable scientific data to support these opinions are lacking. Specifically, advocates of annual testing have expressed concerns that data demonstrating little added value to annual testing are based on retrospective studies and mathematical models that are subject to biases and invalid assumptions; that an interval longer than 1 year may permit aggressive, rapidly growing cancers to escape early detection; that the public may obtain Pap smears at a lower frequency than that publicized in recommendations; that a longer interval might affect compliance among high-risk women, a group with poor coverage even with an annual testing policy; that repeated testing may offset the false-negative rate of the Pap smear; that the test is inexpensive and safe; and that a large proportion of women believe it is important to have an annual Pap test and, while visiting the clinician, may receive other preventive interventions. Definitive evidence to support these concerns is lacking.

Women who have never engaged in sexual intercourse are not at risk for cervical cancer and therefore do not require screening.[92–94] In addition, screening of women who have only recently become sexually active (e.g., adolescents) is likely to have low yield. The incidence of invasive cancer in women under age 25 is only about 1–3 per 100,000, a rate that is much lower than that of older age groups.[11] One study found that most women with CIN who had become sexually active at age 18 were not diagnosed with severe dysplasia or carcinoma in situ until age 30.[93]

Although invasive cervical cancer is uncommon at young ages, authorities have recommended since the early 1980s that screening should begin

with the onset of sexual activity.[82,92,94] This policy is based in part on the concern that a proportion of young women with CIN may have an aggressive cell type that can progress rapidly and go undetected if screening is delayed to a later age. There is some evidence that adenocarcinomas are accounting for a growing proportion of new cervical cancer cases in young women,[95,96] but the exact incidence and natural history of aggressive disease in young women remain uncertain. The Pap smear is also a poor screening test for adenocarcinoma, compared with squamous cell carcinoma. Another reason given for early screening is the concern that the incidence of cervical dysplasia occurring in young women appears to be on the rise, coincident with the increasing sexual activity of adolescents. On these grounds, testing should begin by age 18, since many American teenagers are sexually active by this age. Screening in the absence of a history of sexual intercourse may be justified if the credibility of the sexual history is in question.

When screening is initiated, it is frequently recommended that the first two to three smears be obtained 1 year apart as a means of detecting aggressive tumors at a young age. There is little evidence to suggest, however, that young women whose first two tests are separated by 2 or 3 years, rather than 1 year, have a greater mortality or person-years of life lost.[78] Recommendations to perform these first tests annually are based primarily on expert opinion.

Elderly women do not appear to benefit from Pap testing if repeated cervical smears have consistently been normal.[97,78] Modeling data suggest that continued testing of previously screened women reduces the risk of dying from cervical cancer by only 0.18% at age 65 and 0.06% at age 74.[80] Many older women have had incomplete screening, however. A reported 17% of women over age 65 and 32% of poor women in this age group have never received a Pap test.[98] In a study of elderly minority women with an average age of 75 years, the mean reported number of prior Pap smears received since age 65 was 1.7.[99] Further screening in this group of older women is important[78,100] and some studies suggest that it is cost-effective.[101] Women who have undergone a hysterectomy in which the cervix was removed do not benefit from Pap testing, unless it was performed because of cervical cancer. Post-hysterectomy screening has the potential to detect vaginal cancer, but the yield and predictive value are likely to be very low. Women who had hysterectomies performed in which the cervix was left behind probably still require screening.

The effectiveness of cervical cancer screening is more likely to be improved by extending testing to women who are not currently being screened and by improving the accuracy of Pap smears than by efforts to increase the frequency of testing. Studies suggest that those at greatest risk for cervical cancer are the very women least likely to have access to test-

ing.[102,103] Incomplete Pap testing is most common among blacks, the poor, uninsured persons, the elderly, and persons living in rural areas.[98,104–106] In addition, many women who are tested receive inaccurate results due to interpretative or reporting errors by cytopathology laboratories or specimen collection errors by clinicians. The failure of some physicians to provide adequate follow-up for abnormal Pap smears is another source of delay in the management of cervical dysplasia.[107] Finally, a large proportion of patients with abnormal smears (30% in studies of poor, elderly black women[108]) do not return for further evaluation. Various techniques may enhance physician and patient compliance with screening, follow-up of abnormal results, and patient compliance with rescreening.[109–112]

### *CLINICAL INTERVENTION*

Regular Pap tests are recommended for all women who are or have been sexually active and who have a cervix ("A" recommendation). Testing should begin at the age when the woman first engages in sexual intercourse. Adolescents whose sexual history is thought to be unreliable should be presumed to be sexually active at age 18. There is little evidence that annual screening achieves better outcomes than screening every 3 years. Pap tests should be performed at least every 3 years ("B" recommendation). The interval for each patient should be recommended by the physician based on risk factors (e.g., early onset of sexual intercourse, a history of multiple sex partners, low socioeconomic status). (Women infected with human immunodeficiency virus require more frequent screening according to established guidelines.[113]) There is insufficient evidence to recommend for or against an upper age limit for Pap testing, but recommendations can be made on other grounds to discontinue regular testing after age 65 in women who have had regular previous screening in which the smears have been consistently normal ("C" recommendation). Women who have undergone a hysterectomy in which the cervix was removed do not require Pap testing, unless the hysterectomy was performed because of cervical cancer or its precursors. Patients at increased risk because of unprotected sexual activity or multiple sex partners should receive appropriate counseling about sexual practices (see Chapter 62).

The use of an endocervical brush increases the likelihood of obtaining endocervical cells, but there is conflicting evidence that sampling these cells improves sensitivity in detecting cervical neoplasia. Physicians should submit specimens to laboratories that have adequate quality control measures to ensure optimal accuracy in the interpretation and reporting of results. Thorough follow-up of test results should also be ensured, including repeat testing and referral for colposcopy as indicated. Physicians should consider providing patients with a pamphlet or other written information

about the meaning of abnormal smears to help ensure follow-up and minimize anxiety over false-positive results.

There is insufficient evidence to recommend for or against routine cervicography or colposcopy screening for cervical cancer in asymptomatic women, nor is there evidence to support routine screening for HPV infection ("C" recommendation). Recommendations against such screening can be made on other grounds, including poor specificity and costs.

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