3. CERVICAL CANCER SCREENING

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This chapter is based primarily on the U.S. Preventive Services Task Forces (USPSTF) review of screening for cervical cancer (USPSTF, 1996) and the 1992 National Cancer Institute Workshop on management of abnormal cervical cytology (Kurman, 1994). In addition, we performed a MEDLINE search of English language literature between 1990 and 1996 using the search terms cervix dysplasia, cervix neoplasms, and vaginal smears. This document addresses the questions of which populations should be screened for cervical cancer and at what interval, as well as management of women with abnormal screening tests. This review does not address treatment of confirmed cervical cancer.

IMPORTANCE

There are approximately 16,000 new cases of cervical cancer diagnosed each year in the United States, and about 4,800 deaths annually from the disease (Wingo, 1995). The lifetime probability of dying from cervical cancer in the US is 0.3 percent (Ries, 1994). Five year survival for women with advanced (Stage IV) disease is about 14 percent, whereas it is about 90 percent for women with localized cancer (USPSTF, 1996). Cervical cancer is a good candidate for a screening program because it has a long preinvasive stage during which the disease can be detected and cured.

SCREENING

The Papanicolaou (Pap) smear is the primary method of screening for cervical cancer. Pap smears can detect early dysplastic cell changes which are precursors to invasive disease. Women in whom such abnormalities are detected can then have further diagnostic testing and treatment with

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1 This chapter is a revision of one written for an earlier project on quality of care for women and children (Q1). The expert panel for the current project was asked to review all of the indicators, but only rated new or revised indicators.
interventions such as colposcopy, biopsy, and cervical conization, which can prevent further progression of the disease.

Evidence of the effectiveness of screening programs comes from observational studies showing decreases in cervical cancer mortality following the introduction of population screening programs. Such decreases have been observed in the United States and Canada, as well as in several European countries (USPSTF, 1996). For example, data from Iceland demonstrated a rising cervical cancer mortality rate during the early 1960s. Screening was introduced in 1964, and by 1970 the annual mortality rate began to decline. By 1974, it had fallen significantly, decreasing from 23 per 100,000 in 1965-1969 to about 15 per 100,000 in 1970-74 (Johannesson et al., 1978). Further evidence comes from Canada, where the reduction in cervical cancer mortality has been noted to correlate with the proportion of the population screened with Pap tests (Eddy, 1990). In addition to this evidence, several case control studies have noted a marked decrease in risk of developing cervical cancer in women screened with pap smears when compared to unscreened women. Such studies indicate that screening for cervical cancer with Pap smears is highly effective, decreasing the occurrence of invasive cancer by 60 to 90 percent (Eddy, 1990).

The effectiveness of cervical cancer screening appears to increase with decreasing screening intervals. This evidence also comes from case control studies, which demonstrated decreased relative risks of invasive disease in women with shorter screening intervals (Eddy, 1990). However, there is also evidence that annual screening may produce only a minimally lower risk of invasive disease than screening every two to three years (USPSTF, 1996; Eddy, 1990). According to one study of eight cervical cancer screening programs in Europe and Canada, the incidence of cervical cancer can be reduced by 64 percent with a screening interval of ten years, by 84 percent with a five year interval, and by 91 percent, 93 percent and 94 percent with intervals of three, two and one years, respectively (IARC Working Group, 1986).

Several important risk factors have been identified for cervical cancer (Eddy, 1990). These include:

1. Race/ethnicity, with African Americans and Hispanics having a two-fold increased risk;
2. Early age at first sexual intercourse;
3. Multiple sexual partners;
4. Smoking;
5. Human immunodeficiency virus (HIV) infection; and
6. Human papillomavirus (HPV) infection.

There has been debate in the literature about whether or not women with such risk factors should be screened more frequently than the general population of women. Published recommendations leave room for physician discretion in screening such women. Consensus has been reached by the American Cancer Society, the National Cancer Institute, the American College of Obstetricians and Gynecologists (ACOG), the American Medical Association, the American Nurses Association, the American Academy of Family Physicians and the American Medical Women's Association (American Cancer Society, 1993; ACOG, 1995) on a guideline that recommends annual Pap smears for all women who are or have been sexually active, or who are at least 18 years of age. After three normal annual smears, and if recommended by the physician, less frequent testing is permitted. No upper age limit for cessation of testing is specified in this recommendation (Indicators 1, 2, 3 and 4).

The USPSTF (1996) makes similar recommendations about the onset of testing and adds that Pap tests should be performed at least every three years. The interval for each patient should be recommended by the physician based on risk factors (e.g., early onset of sexual intercourse, history of multiple sexual partners, low socioeconomic status). Women who have never been sexually active or who have had a total hysterectomy for benign indications with previously normal screening do not need regular Pap smears because they are not at risk for cervical cancer.

Some groups have proposed that women over the age of 65 who have had regular and normal screening prior to age 65 may not require further Pap screening because the incidence of disease is low in women this age with previously normal smears (Miller, 1991). The USPSTF states there is insufficient evidence to recommend an appropriate upper age limit for screening, but suggests that 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. They also state that women who have not had regular screening before the age of 65 should continue to receive smears every three years. (USPSTF, 1996). The ACOG
does not support cessation of screening at any age, regardless of prior screening history (ACOG, 1995). It appears that the age at which screening for cervical cancer can safely be stopped, if any, is not clearly known.

Management Of Women With Abnormal Pap Smears

Although there is generally less consensus about appropriate treatment and follow-up of abnormal pap smears than there is about their effectiveness as a screening technique, reductions in cervical cancer mortality are dependent on follow-up and treatment of women who have positive screening exams. The classification of abnormal smears is variable, with different systems for reporting abnormalities (Table 3.1).

Table 3.1
Cytopathology Reporting Systems for Pap Smears

<table>
<thead>
<tr>
<th>Class System</th>
<th>World Health Organization System</th>
<th>Cervical Intraepithelial Neoplasia System</th>
<th>The Bethesda System</th>
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</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal</td>
<td>Normal</td>
<td>Within normal limits</td>
</tr>
<tr>
<td>II</td>
<td>Inflammation</td>
<td>Other</td>
<td>Reactive and reparative</td>
</tr>
<tr>
<td>III</td>
<td>Dysplasia:</td>
<td>CIN-1</td>
<td>Squamous intraepithelial lesions:</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>CIN-2</td>
<td>Low grade</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td></td>
<td>High grade</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Carcinoma in situ</td>
<td>CIN-3</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Invasive squamous cell carcinoma</td>
<td>Invasive squamous cell carcinoma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>

Source: Miller et al., 1992

The Bethesda system was introduced to replace the previous Pap classifications and to facilitate precise communication between cytopathologists and clinicians. There is not universal agreement that it is superior to the CIN designations (Kurman et al., 1991). The Bethesda system contains a new classification, atypical squamous or glandular cells of undetermined significance or ASCUS (AGCUS). This category can be used by pathologists to signify the presence of atypical cells which are not clearly
dysplastic but are of undetermined significance. The National Cancer Institute recommendations for follow-up of Pap smear abnormalities use the Bethesda Classification, and we have used the Bethesda Classification in recommending follow-up of mildly abnormal Pap smears. Recommendations for follow-up of abnormal smears have been summarized by the report of a Canadian National workshop on screening for cancer of the cervix (Miller, 1991), and a National Cancer Institute Workshop on management of abnormal cervical cytology (Kurman, 1994). First, they stress that screening recommendations (as summarized above) apply only to women with normal screening exams, and that women with abnormal smears should be screened and treated differently (Indicator 4). The National Cancer Institute Workshop recommends that women with low grade squamous intraepithelial lesions (LGSIL), which includes changes consistent with HPV infection without dysplasia, or atypical squamous cells of undetermined significance (ASCUS), should be rescreened at intervals of 6 to 12 months and referred for colposcopy if the abnormality persists at 24 months past the original smear (Indicators 6 and 7). The Canadian Consensus does not use the Bethesda system, but agrees with this management for atypia, mild dysplasia, CIN I, or HPV using the older designations. This management is based on the finding that many of these lesions will regress spontaneously without intervention (Montz et al., 1992); however, some have argued that the inconvenience, distress, and possibly the cost of this strategy are excessive, and that all women with abnormal smears should be referred immediately for colposcopic evaluation (Soutter, 1992; Wright, 1995). ACOG suggests that women with these low grade lesions may either be followed at six-month intervals or referred for colposcopy. All groups recommend colposcopic evaluation eventually for all women with persistent lesions (ACOG, 1993; Miller, 1991; Kurman, 1994) (Indicator 7).

There is agreement about follow-up of women with more dysplastic lesions on Pap smear. Women with Pap smears read as moderate dysplasia, severe dysplasia, carcinoma in-situ, CIN II or greater, high grade squamous intraepithelial lesions, squamous cell carcinoma or adenocarcinoma should be referred for colposcopic evaluation (Indicator 5). The prevention of cervical cancer is dependent on the diagnostic evaluation and treatment given to women with these abnormalities.
REFERENCES


**RECOMMENDED QUALITY INDICATORS FOR CERVICAL CANCER SCREENING**

The following criteria apply to women age 18 and over. These indicators were not rated by this panel; they were endorsed by a prior panel.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Quality of Evidence</th>
<th>Literature</th>
<th>Benefits</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The medical record should contain the date and result of the last Pap smear.</td>
<td>II-2</td>
<td>USPSTF, 1996; ACOG, 1995; ACOG, 1993</td>
<td>Prevent cervical cancer morbidity and mortality. Prevent cervical cancer.</td>
<td>The appropriate timing of the next Pap smear is determined by the time elapsed since the last smear, and the result of the last smear.</td>
</tr>
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<td>2. Women who have not had a Pap smear within the last 3 years should have one performed (unless never sexually active with men or have had a hysterectomy for benign indications).</td>
<td>II-2</td>
<td>USPSTF, 1996; ACOG, 1995; ACOG, 1993</td>
<td>Prevent cervical cancer morbidity and mortality. Prevent cervical cancer.</td>
<td>The maximum interval for women with intact uteri is every three years. The incidence of cervical cancer is increased when screening intervals exceed 3 years.</td>
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<tr>
<td>3. Women who have not had 3 consecutive normal smears and who have not had a Pap smear within the last year should have one performed.</td>
<td>III</td>
<td>ACOG, 1995; ACS, 1993</td>
<td>Prevent cervical cancer morbidity and mortality. Prevent cervical cancer.</td>
<td>A normal Pap smear is defined as one without atypia, dysplasia, CIS or invasive carcinoma. If there is no documentation of the actual pathology/cytology reports (e.g., because previous Pap smears were done at another facility) but there is documentation in the history that all previous Paps were normal, then the appropriate screening interval may be regarded as three years.</td>
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<td>4. Women with a history of cervical dysplasia or carcinoma-in-situ who have not had a Pap smear within the last year should have one performed.</td>
<td>III</td>
<td>Miller et al., 1991; ACOG, 1993</td>
<td>Prevent cervical cancer morbidity and mortality. Prevent cervical cancer.</td>
<td>These women are at increased risk for cervical disease, and should not be returned to the usual screening intervals.</td>
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<td>5. Women with a severely abnormal Pap smear should have colposcopy performed within 3 months of the Pap smear date.</td>
<td>III</td>
<td>Miller et al., 1991; Kurman, 1994</td>
<td>Prevent cervical cancer morbidity and mortality.</td>
<td>Appropriate follow-up for abnormal findings is key in preventing progression to cervical cancer. The 3 month time period is arbitrary.</td>
</tr>
<tr>
<td>Indicator</td>
<td>Quality of Evidence</td>
<td>Literature</td>
<td>Benefits</td>
<td>Comments</td>
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<td>6. If a woman has a Pap smear that shows a low grade lesion (ASCUS or LGSIL), then one of the following should occur within 6 months of the initial Pap: 1) repeat Pap smear; or 2) colposcopy.</td>
<td>III</td>
<td>Kurman, 1994</td>
<td>Prevent cervical cancer morbidity and mortality.</td>
<td>Patients with these intermediate findings should be monitored closely. In many cases, abnormal findings resolve spontaneously, so follow-up with Pap smears or immediate colposcopy are both appropriate.</td>
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<td>7. Women with a Pap smear that shows ASCUS or LGSIL, and who have had the abnormality documented on at least 2 Pap smears in a 2 year period should have colposcopy performed.</td>
<td>III</td>
<td>Kurman, 1994; ACOG, 1993</td>
<td>Prevent cervical cancer morbidity and mortality.</td>
<td>Patients with intermediate findings should be monitored closely since some portion of these may represent preinvasive disease, or progress to a high-grade SIL. If findings persist, colposcopy should be performed. This may be difficult to operationalize for women who have not been enrolled in the same plan for two years or more.</td>
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</tbody>
</table>

Definitions and Examples

1 Morbidity of cervical cancer includes postsurgical and chemotherapeutic complications, infertility, incontinence, and pain from metastases.

2 Severely abnormal Pap smear: moderate dysplasia, severe dysplasia, carcinoma in situ, CIS, CIN II, CIN III, high grade SIL, squamous cell carcinoma, or adenocarcinoma.

Quality of Evidence Codes

I  RCT
II-1  Nonrandomized controlled trials
II-2  Cohort or case analysis
II-3  Multiple time series
III  Opinions or descriptive studies