Current approaches to cervical-cancer screening

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors’ clinical recommendations.

CURRENT APPROACHES TO CERVICAL-CANCER SCREENING

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A 72-year-old woman has had an annual Papanicolaou (Pap) smear with normal findings (Fig. 1) for the past 30 years. She finds it difficult to undergo pelvic examinations because she has severe arthritis in her hips and vaginal atrophy. She has not been sexually active since the death of her husband 10 years earlier, and she wants to know whether she can stop being screened for cervical neoplasia.

THE CLINICAL PROBLEM

Although screening for cervical cancer with the Pap smear is one of the most effective preventive interventions that clinicians can provide in their offices, concern about the accuracy of the traditional Pap smear, controversy about the frequency of screening, and the advent of new techniques raise questions about how best to approach screening today. This review considers strategies for optimal cervical-cancer screening, highlights areas of uncertainty, summarizes current guidelines, and provides screening recommendations for the practicing clinician.

STRATEGIES AND EVIDENCE

Dramatic reductions in the incidence of squamous-cell cancers of the cervix have accompanied the widespread use of Pap tests in the United States. All U.S. women who have a cervix and who are or who have been sexually active — a group that numbers approximately 87 million — are encouraged to participate in screening programs.

Cervical cancer is thought to be the long-delayed consequence of sexually transmitted human papillomavirus (HPV) infection. In a small minority of women exposed to HPV, the infection progresses to asymptomatic high-grade preinvasive dysplastic lesions and, ultimately, to invasive cancer. An estimated 40 percent of untreated high-grade lesions will progress to invasive cancer over an average of 10 years. Periodic screening offers many opportunities to discover and treat preinvasive lesions (Fig. 2). Consequently, even though HPV infection is common, with screening a U.S. woman’s lifetime risk of cervical cancer is estimated to be only 0.8 percent.

Further reductions in the approximately 12,800 cases of cervical cancer that are diagnosed each year in the United States may be achieved by a variety of means. Given that about half of the U.S. women in whom cervical cancer develops have never been screened, efforts aimed at encouraging women to be screened hold the most promise for reducing the incidence of and mortality from cervical cancer. Although it is difficult to increase the rate of Pap testing, particularly among women who seldom visit clinicians, practitioners can help by offering screening to women who are being seen for other reasons. For example, in one study of a large prepaid health plan with few barriers to access, most of the women with invasive cervical cancer had not had a Pap smear in the three years before their diagnosis, even though...
75 percent had been seen in primary care outpatient clinics during that period.\(^5\)

Another strategy to reduce the incidence of cancer is to minimize errors related to the sampling technique itself and the interpretation of the findings. These errors account for approximately one fourth of all cases of invasive cervical cancer.\(^6\)–\(^8\) Clinicians can decrease the likelihood of sampling error — the failure to obtain and transfer dysplastic cells to the slide — by choosing a method of cell collection that will obtain adequate samples from the endocervical canal.\(^9\) In a systematic review of studies that focused on histologically confirmed high-grade cervical dysplasia,\(^10\) the use of a spatula in combination with an endocervical brush appeared to increase the rate of detection of disease without increasing the rate of false positive findings.

**AREAS OF UNCERTAINTY**

Although it is widely accepted that screening for cervical neoplasia saves lives, there is no consensus about when screening should start, how long it should continue, the frequency of screening, or the optimal screening technique. The information needed to make informed decisions is, in many respects, incomplete.

**When to Begin Screening**

Screening is unlikely to be beneficial before a woman becomes sexually active and thus at risk for exposure to HPV. Concern about the potential inaccuracy of a woman’s reported sexual history, however, has prompted recommendations that screening begin at the age of 18 years, regardless of the woman’s reported sexual activity. Determining the optimal age to begin screening is important for several reasons. Acute HPV infection is common soon after the initiation of sexual activity, and most infections clear within 24 months.\(^11\),\(^12\) These infections can cause cytologic abnormalities, the majority of which are not associated with high-grade cervical dysplasia. These abnormal findings lead to further diagnostic evaluations.

Treatment of dysplastic lesions with cryotherapy, the loop electrosurgical excision procedure (known as LEEP), laser ablation, and cone biopsy is common, though data are lacking from large-scale studies on the effect that these interventions may have on future fertility and pregnancy outcomes. Moreover, false positive results can cause patients needless anxiety and concern.\(^13\) The transient nature of most HPV infections, the long preinvasive phase of dysplasia,\(^3\) and the potential harm that can result from overdiagnosis and overtreatment argue against introducing screening too soon after the initiation of sexual activity. Research is needed to quantify the reduction in the risk of cancer, as well as the harm, that might result from early initiation of screening.

Many European countries with low rates of cervical cancer do not screen adolescents and young, sexual-
ly active women. For example, the National Health Service of the United Kingdom recommends that screening begin at the age of 21 years, and the Finnish Cancer Organization recommends beginning screening at the age of 30 years.

When to End Screening

Although most cases of cervical cancer and deaths from cervical cancer occur in women older than 50 years of age, most of these women have not been screened adequately. The very low incidence of new cases of cervical disease among older women who have no evidence of recent disease and who have been screened regularly and properly argues against continued screening in this population. Furthermore, with advancing age or the presence of serious coexisting conditions, the potential benefits of screening are offset by the likelihood that a woman will die of another cause or will suffer needlessly as a consequence of a false positive result. Older women who have undergone a total hysterectomy for diseases other than cervical neoplasia are not at risk for cervical cancer and should not be screened. Practitioners should be aware, however, that some women may have undergone a supracervical hysterectomy in which the cervix is retained.

Frequency of Screening

Repeated screening after a normal result can detect abnormalities missed on earlier tests, as well as abnormalities that have developed since the first test. The frequency of screening should therefore depend on the sensitivity of the screening test and the rate of progression of preinvasive disease. An individual woman’s risk factors should have little effect on the frequency of screening unless these factors are associated with low test sensitivity (as may be the case if a woman has had only one prior test with normal results, which may have missed disease) or an accelerated rate of progression of preinvasive disease (as may be the case in an immunocompromised woman).

Although the absolute risk of the development of invasive squamous-cell cancer as a consequence of a false negative test is small (occurring in fewer than 5 women per 100,000 per year), annual screening has been common practice in the United States for many years. There is little evidence to suggest, however, that outcomes are substantially better with annual screening than with biennial or triennial screening. Although a single conventional Pap test may have a relatively low sensitivity, the cumulative sensitivity of several tests performed within a relatively short time should be high. No cytologic test, however, is likely to detect cervical neoplasia in the unknown but small percentage of women with disease in whom abnormal cells are not exfoliated.

High-grade dysplasia or rapidly progressive cervical disease is unlikely to be overlooked or to develop within three years after a normal examination in immunocompetent women who have had multiple normal smears. Further research is needed to determine the optimal number of normal results after which the interval between tests can safely be lengthened. Because the preinvasive stage of disease may be briefer in women who are immunocompromised, women who are receiving immunosuppressive therapy or those who are infected with the human immunodeficiency virus (HIV) are thought to be poor candidates for less frequent screening. In the case of women with HIV infection, a pattern of annual testing after two tests performed six months apart have had normal results has been shown to be cost effective.

Newer Methods of Screening

Litigation and media coverage have led to broad public awareness of the imperfect sensitivity of Pap smears. Several new techniques are being promoted that increase sensitivity by reducing errors in sampling and interpretation. Clinicians should be aware that all such techniques may also decrease specificity: more abnormalities may be discovered at the cost of an increase in the number of healthy women who are unnecessarily alarmed by a false report of an abnormality and who subsequently undergo needless diagnostic procedures and interventions.

Among the most commonly used innovations in cervical-cancer screening is liquid-based cytologic collection and analysis. The literature on this technique, which has been approved by the Food and Drug Administration for primary screening, is voluminous, and three systematic reviews have been published recently. Two found evidence of improved sensitivity and one found evidence of decreased specificity. All three concluded that too few studies of sufficient methodologic rigor have been performed to indicate the true accuracy of liquid-based cytologic analysis, with the chief concern being inadequate data on specificity.

Reevaluation of conventional smears initially interpreted as negative, either on the basis of a manual review or with the assistance of a computerized technique, can also improve the sensitivity of testing by decreasing errors in the interpretation of results. Liquid-based preparations and computerized rescreening increase both the sensitivity and the costs of screening for cervical cancer. The cost effectiveness of these methods depends on the manner in which they are used. They are most likely to be cost effective if they are used as an adjunct to a program in which screening is done every three years; the cost per year of life saved is very high if they are used to improve the sensitivity of annual screening.

Liquid-based cytologic collection and analysis and computerized rescreening are most likely more cost effective when they are used by laboratories where tests have relatively poor sensitivity. They are unlikely to
be cost effective when they are adopted by laborato-
ries that already interpret Pap smears with a high
degree of accuracy.\textsuperscript{26} Cost-effectiveness models to date
have assumed that the specificity of new techniques
is no different from that of older approaches; if li-
quid-based cytologic collection and analysis have a lower
specificity, for example, the cost effectiveness will
be adversely affected.\textsuperscript{27}

The advent of newer methods of HPV detection
has led to increasing interest in the role of testing for
this virus in screening. One of the most promising
uses of HPV testing is to determine which women
with low-grade cytologic abnormalities require col-
poscopic evaluation. Preliminary results of a random-
ized trial designed to clarify the roles of HPV testing,
repeated Pap testing, and colposcopy in the evalua-
tion of low-grade abnormalities indicate that HPV
testing can help identify which women with a single
smear that shows atypical squamous cells of undeter-
dined significance should undergo colposcopy,\textsuperscript{28}
but that it is not as helpful in women with smears that
show low-grade squamous intraepithelial lesions.\textsuperscript{29}
Less information is available for other uses of HPV
testing, and important questions remain about the
implications of a positive HPV test. There is little
evidence to support the use of any specific manage-
ment strategy for a woman with no detectable cer-
vical disease who is found to have a high-risk type of
HPV. At present, the role of HPV testing as an adjunc-
to or substitute for established and effective cy-
tologic screening programs has not been evaluated
adequately.\textsuperscript{30}

**GUIDELINES**

The American Cancer Society\textsuperscript{31} and the American
College of Obstetricians and Gynecologists\textsuperscript{32} recom-
ment that screening begin at the age of 18 years, re-
gardless of whether a woman is sexually active. The
American Academy of Family Physicians, the Canadian
Task Force on Preventive Health Care, the American
College of Preventive Medicine, and the U.S. Preven-
tive Services Task Force support the view that screen-
ing should be initiated when women become sexually
active.\textsuperscript{33} The latter two recommend beginning screen-
ing at the age of 18 years if a woman’s sexual history
is unknown or if the reported history is thought to
be unreliable.

Most groups do not specify an age at which screen-
ing may end, though the U.S. Preventive Services
Task Force recommends discontinuing screening in
women over the age of 65 years who have been
screened regularly and who have had consistently
normal results. The Canadian Task Force recom-
ends that such women should stop being screened at
the age of 69 years. The American College of Preventive
Medicine recommends that screening be stopped at
the age of 65 years in women who have undergone
regular screening and who have had no abnormal re-
sults within the previous nine years. All guidelines
state that the interval between tests may be extended
to as long as three years if two or three consecutive
tests have been normal. Some guidelines, however, in-
dicate that continued annual screening be considered
in women with certain risk factors, such as a first oc-
currence of sexual intercourse at an age of less than 18
years, multiple sexual partners or a consort with mul-
tiple sexual partners, smoking, or low socioeconomic
status.

**CONCLUSIONS AND RECOMMENDATIONS**

The Pap smear remains the archetype of a success-
ful preventive intervention. Some strategies used to
increase the sensitivity of screening — such as new-
er methods of collection and interpretation, as well
as more frequent testing — may, however, also in-
crease the false positive rate. Clinicians should con-
sider the costs and consequences of false positive tests
along with the benefits that result from heightened
sensitivity.

Women obtain health care information from diverse
sources, including the mainstream press and direct-
to-consumer marketing. They may perceive recom-
mandations for less frequent screening, the policy of
discontinuing screening after a certain age, and the
slow rate of adoption of new screening methods as
attempts to save money at their expense, even when
respected professional groups are the source of the
recommendations. Women who have actively partici-
pated in screening programs and who have had no
evidence of cervical disease should be informed that
their absolute risk of undiagnosed but clinically im-
portant cervical disease is very small and that any ad-
ditional benefits of frequent screening with conven-
tional smears and more sensitive techniques are likely
to be small. Evidence concerning technological ad-
vances in screening, such as liquid-based cytologic
collection and analysis and HPV testing, accrues rapidly
and will need to be continually updated and summa-
rized. In the future, combinations of techniques and
more focused screening strategies hold the promise of
making screening more effective, safer, and less costly.

In summary, practitioners should seek out and of-
fer screening to women at risk for cervical cancer who
have not been screened within at least the preceding
three years. Until better data become available, screen-
ing should begin after the initiation of sexual activity
or the age of 18 years if information about a woman’s
sexual history is unknown or is deemed unreliable.
Regularly screened women who are 65 years of age
or older and who have a documented history of con-
secutive normal Pap smears and no evidence of recent
cervical dysplasia gain little from continued screening,
especially if they are no longer sexually active. This
is the case for the woman described in the clinical
vignette. Women who have undergone a total hys-
terectomy for diseases other than cervical neoplasia
should no longer be screened. In the case of immuno-
cOMPETENT women who have had multiple consec-
tutive normal Pap smears, clinically important cervical
disease is unlikely to develop within a period of three
years and the interval between tests could probably be
safely extended to as long as three years. Clinicians
should remain up to date about the benefits and harms
associated with various screening strategies so that they
can provide women with accurate and complete infor-
mation to facilitate fully informed decision making.

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