EDITORIALS

Screening for Cervical Cancer: Prospects for the Future

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The Papanicolaou (Pap) cervical smear is one of the most successful cancer prevention screening techniques available today. As with any screening test, the cost effectiveness depends on several factors, including 1) the population screened, 2) the frequency of screening, 3) the diagnostic accuracy of the test, and 4) the costs and efficacy of follow-up and treatment. Let us briefly consider each of these elements in relation to the current state of cervical cancer screening and then contemplate the prospects for the future.

Population Screened

Although no prospective studies have been conducted to evaluate the efficacy of the Pap smear, numerous studies have documented significant reductions in the incidence and death rates from cancer of the cervix subsequent to the establishment of mass screening programs. In the United States, the death rate from cervical cancer has declined by over 70% during the last 40 years. Currently, the majority of invasive cervical cancers occur in women who have not undergone routine screening (2).

Increasing the percentage of women who receive regular Pap smears is probably the single most critical element in further reducing the estimated 4400 deaths per year due to cervical cancer in this country (3). Data from the 1987 National Health Interview Survey (4) indicate that Hispanic women and older women in particular are less likely to be adequately screened. Overcoming cultural barriers to screening will require intensive, targeted patient education. Women aged 65 years and over, who account for one fourth of new invasive cervical cancers, visit physicians on numerous occasions; these visits could be utilized as opportunities for screening.

Frequency of Screening

While there is unanimity regarding the value of screening, there is less consensus as to what screening interval is most appropriate. From a public health perspective, screening annually as opposed to every 2-3 years has only slightly increased effectiveness, but at two to three times the cost (5). Medicare coverage of Pap smears is restricted to every 3 years unless certain criteria for high risk of cancer are met. Cost-conscious British, Danish, and Australian health care systems also opt for screening every 3 years. However, the concept of annual screening for premenopausal women is well entrenched in the United States. Proponents argue that yearly evaluations are necessary to compensate for the inherent false-negative rate of Pap smears. The official National Cancer Institute position represents a hybrid approach: NCI recommends three consecutive annual Pap smears, which, if normal, may be followed by less frequent screening (interval not specified).

Diagnostic Accuracy

Cervical Pap smear cytology has an estimated 20%-40% false negative rate attributed to a combination of inadequate specimen collection, problems inherent in sampling small or inaccessible lesions, and errors in the microscopic reading of the cytology specimen. The false negative rate is defined as the number of false negatives divided by the number of false negatives plus the number of true positives.) Newer instruments for obtaining cervical samples (e.g., cervical brushes) provide a greater yield of endocervical material and may reduce sampling error, compared with the previously used cotton swab (6).

Technological efforts to improve cytologic screening and detection of abnormalities have centered on (a) the application of monolayer techniques for specimen preparation in lieu of direct smears (7) and (b) use of computers with image analysis and neural network capability to automate slide screening (8). Both approaches, either independently or perhaps in tandem, hold promise for increasing the sensitivity of cytologic diagnosis in the future.

Costs and Efficacy of Follow-up and Treatment

The costs of follow-up of abnormal cytology results depend on what degree of abnormality triggers action, as well as the extent of further evaluation and/or treatment. To develop rational screening guidelines, it is essential to determine the appropriate threshold for follow-up investigation and to evaluate the marginal benefit of treatment. The decisions of what degree of cytologic abnormality triggers colposcopic evaluation and what level of risk warrants therapeutic intervention are guided by medical, ethical, political, and economic considerations.

In this issue of the Journal, Bergstrom and colleagues analyze the rates of in situ (preinvasive) carcinomas detected and treated and the subsequent reduction in incidence of invasive cancers. The purpose of the study was to determine the marginal effects of detecting and treating in situ lesions in the Swedish population (9). These investigators conclude that the diagnosis of carcinoma in situ does not discriminate

*See "Notes" section following "References."
between lesions with a reasonable probability of progression to invasive disease and lesions that are unlikely to develop invasive potential. Many will take exception to this conclusion, particularly because the authors fail to define "reasonable probability" of progression to carcinoma.

Treatment issues have come into sharper focus over the past few years due to greater understanding of the role of human papillomavirus (HPV) in cervical carcinogenesis and the resulting changes in the terminology of cervical cytology reports, known as The Bethesda System (TBS) (70). In the United States, there is general consensus that all high-grade intraepithelial lesions as defined by TBS, including moderate and severe dysplasia as well as carcinoma in situ, should be treated. Rather, in this country, the debate centers on management of low-grade lesions, which encompass cellular changes of HPV, mild dysplasia, and cervical intraepithelial neoplasia grade 1. Low-grade lesions not only have much less propensity to progress to invasive cancer than high-grade abnormalities, but also affect a far greater number of women. The cost of treating the estimated 1 million women per year with low-grade lesions, which have a low estimated lifetime risk of becoming cancer, runs into the billions of dollars (71). Some clinicians advocate extending colposcopic evaluation to an even larger cohort of perhaps an additional 2-3 million women per year with "atypical squamous cells," a cytologic diagnosis indicating cellular changes that are insufficient to be diagnostic of an intraepithelial lesion. Approximately 20%-40% of these patients do have an intraepithelial lesion at colposcopy, but most of these are low grade.

Advocates of conservative management emphasize that many low-grade lesions will regress with time and that, with follow-up by repeat Pap smears, the estimated 15% of low-grade lesions that progress to high grade lesions can be detected and treated effectively. Opponents of a watch-and-wait strategy point out that women diagnosed by Pap smear as having a low-grade lesion may actually harbor a cytologically undetected high-grade lesion and that follow-up by repeat smears is associated with a significant false-negative rate. An additional consideration, separate from the question of the potential for carcinogenesis, is the issue of whether low-grade lesions should be treated to reduce the risk of spread of a sexually transmitted disease. Richart and Wright (72) discuss these controversies in a recent review of the management of low-grade lesions.

Definitive resolution of this debate must await ancillary triage techniques that can successfully identify cytologically undetected high-grade lesions and can prospectively stratify low-grade lesions by their biologic potential to progress. Such an approach would allow women with low-risk lesions to have conservative follow-up without treatment. At present, studies suggest that cervicography, which produces high-resolution photographic images of the cervix, and DNA testing for cancer-associated types of HPV are the best candidates for further investigation and clinical trials of potential ancillary diagnostic techniques (73).

As pathologists have pursued the morphologic detection of minimal lesions in an effort to reduce the false-negative rate of cervical screening, clinicians have felt compelled to treat any abnormalities detected, at an increasingly high cost per cervical cancer prevented. We must remind ourselves that the goal of cervical cancer screening should not necessarily be eradication of all intraepithelial lesions. Instead, the focus should be prevention of cervical carcinoma by treating lesions with the potential to become invasive.

We have reached the limits of routine light microscopy to predict biologic behavior. Identifying individual lesions with aggressive biologic potential will depend on our ability to apply emerging technologies to supplement pathologic diagnosis. This targeted approach has the potential to provide more cost-effective cervical cancer screening in the future.

References


Notes

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