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American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer

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ABSTRACT An update to the American Cancer Society (ACS) guideline regarding screening for the early detection of cervical neoplasia and cancer, based on recommendations from a formal review and recent workshop, is presented. The new screening recommendations address when to begin screening, when screening may be discontinued, whether to screen women who have had a hysterectomy, appropriate screening intervals, and new screening technologies, including liquid-based cytology and HPV DNA testing. (*CA Cancer J Clin* 2002;52:342-362.)

INTRODUCTION

Cervical cancer mortality in the United States has decreased over the last five decades by over 70 percent in large part attributable to the introduction of the Papanicolaou (Pap) test. Cervical cancer, once the number one cancer killer of women, now ranks 13th in cancer deaths for women in the United States.¹ As cervical cytology screening has become more prevalent, preinvasive lesions of the cervix are detected far more frequently than invasive cancers. In 2002, an estimated 13,000 cases of invasive cervical cancer will be diagnosed, and an estimated 4,100 women will die from this disease. Women with preinvasive lesions have a five-year survival rate of nearly 100 percent. When cervical cancers are detected at an early stage, the five-year survival rate is approximately 92 percent.¹

Between 93 and 100 percent of squamous cell carcinomas of the cervix contain DNA from high-risk types of human papillomavirus (HPV), which are transmitted during sexual activity.^{2,3} Studies of the natural history of cervical cancer have shown that infection with high-risk HPV types may lead to low-grade or high-grade intraepithelial lesions. High-grade lesions may progress to cervical carcinoma if not

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treated.^{4,5} Most HPV* infections, however, are transient, resulting either in no symptoms or cellular changes or producing low-grade intraepithelial lesions.^{6,7,8} The purpose of screening, in addition to detecting cervical cancers at an early stage, is to detect and remove high-grade lesions and thus prevent potential progression to cervical carcinoma.

The very success of the Pap test in cervical cancer screening has fostered an unrealistic expectation that the test is perfect. It is not. Pap test sensitivity for high-grade cervical intraepithelial neoplasia (CIN) is in the range of 70 to 80 percent.⁹ Factors that limit test sensitivity include: small size of a lesion, inaccessible location of the lesion, the lesion not being sampled, the presence of only a few abnormal cells on the slide, small size of the abnormal cells, or the presence of inflammation and/or blood obscuring cell visualization. False-negative results occur even in optimized screening programs and cannot be entirely eliminated.

Approximately half of the cervical cancers diagnosed in the United States are in women who have never been screened, and an additional 10 percent of cancers occur in women who have not been screened within the past five years.¹⁰ While the new American Cancer Society screening guideline includes a review of new cervical cancer screening tests, perhaps the largest gain in reducing cervical cancer incidence and mortality could be attained by increasing screening rates (regardless of the test used) among women who are currently unscreened or screened only infrequently. However, new technologies may offer advantages over what is already a successful screening test, when utilized.

Guideline Development

The ACS guideline for the early detection of cervical cancer was last reviewed in 1987. At that time it was recommended that all women

who are or have been sexually active, or have reached the age of 18, have an annual Pap test and pelvic examination; after a woman has had three or more consecutive, technically satisfactory, normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician.¹¹ This recommendation was accepted as policy in identical or similar wording by the National Cancer Institute, the American College of Obstetricians and Gynecologists, the American Medical Association, the American Academy of Family Physicians, the American Medical Women's Association, and the American Nurses Association.

In 2001 to 2002, the ACS convened an expert panel to review the existing guideline in the context of evidence that has accumulated since the last revision. The panel was divided into working groups to review the evidence and develop recommendations regarding (1) when to start screening; (2) when to discontinue screening; (3) screening of women who have had a hysterectomy; (4) screening intervals; and (5) screening tests.

During the current guideline review, published articles related to cervical cancer screening, including new screening tests, were identified using MEDLINE (National Library of Medicine), bibliographies of identified articles, personal files of panel members, and unpublished manuscripts. Expert panel members reviewed articles using specified criteria (Appendix A) and discussed them during a series of conference calls. Each work group developed recommendations, rationale, and evidence summaries, and reviewed the summaries developed by the other work groups prior to an April 2002 workshop. When evidence was insufficient or lacking, the final recommendations incorporated the expert opinions of the panel members. Relevant unpublished manuscripts were distributed to workshop attendees prior to the meeting. During the conference calls and workshop,

*Unless otherwise specified, HPV refers to high-risk types only throughout this document.

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consensus was reached on the key issues within the guideline recommendations. Following the workshop, ACS Gynecologic Cancer Advisory Group members deliberated over the guideline modifications. Each work group member and workshop attendee reviewed the draft of this manuscript.

Several organizations reviewed this manuscript, provided comments, and indicated their support of the new recommendations. These organizations include the American College of Obstetricians and Gynecologists, the American Social Health Association, the American Society of Colposcopy and Cervical Pathology, the Association of Reproductive Health Professionals, the Gynecologic Cancer Foundation, the National Association of Nurse Practitioners in Women's Health, and the Society of Gynecologic Oncologists.

RECOMMENDATIONS, RATIONALE, AND EVIDENCE

When to Start Screening

Recommendation

Cervical cancer screening should begin approximately three years after the onset of vaginal intercourse. Screening should begin no later than 21 years of age. It is critical that adolescents who may not need a cervical cytology test

obtain appropriate preventive health care, including assessment of health risks, contraception, and prevention counseling, screening and treatment of sexually transmitted diseases. The need for cervical cancer screening should not be the basis for the onset of gynecologic care.

Rationale

The published and unpublished data on the incidence of cervical cancer and the natural history of HPV infection and of low- and high-grade cervical lesions suggest that there is little risk of missing an important cervical lesion until three to five years after initial exposure to HPV (Evidence section). Thus, cervical cytology screening in adolescents is unlikely to add appreciable benefits within the first three years following onset of vaginal intercourse. It is the intent of the ACS that offering screening “approximately” three years after the onset of sexual intercourse will avoid denial of health insurance coverage for teens and young women who undergo their first cytology test prior to the suggested three years. However, the concern is that screening before the three-year-period may result in an overdiagnosis of cervical lesions that will regress spontaneously, leading to inappropriate intervention, which may result in more harm than good. Because the risk of HPV transmission to the cervix is low for other types of sexual activity, the onset of vaginal sexual intercourse has been selected as the historical marker for initiating cervical cytology screening.

An upper age limit for when to initiate screening is needed for providers who don't ask patients about their sexual history and for adolescents who are unable or unwilling to disclose prior consensual and/or nonconsensual intercourse. Such an upper age limit ensures that young women, including victims of sexual abuse, are protected.

In cases where a history of sexual abuse has been established, there is a lack of evidence to support earlier cervical screening for victims of

prepubescent sexual abuse. Abuse victims who have had vaginal intercourse, especially post-puberty, may be at increased risk of HPV infection and cervical lesions and should be referred for screening once they are psychologically and physically ready (i.e., post-puberty) by a provider who has experience and sensitivity for working with abused adolescents.

Provider discretion and patient choice following counseling should be used to guide the initiation of cervical cytology screening in young women aged 21 and older who have never had vaginal sexual intercourse and for whom the absence of a history of sexual abuse is certain.

Young women who are infected with HIV and/or are immunocompromised should follow the US Public Health System Guidelines, i.e., obtain a Pap test twice in the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter.¹²

Evidence

Cervical cancer in women less than 19 years of age is rare. Mount, et al.¹³ provided the highest reported prevalence (3.77 percent) of squamous intraepithelial lesions (SIL) among 10,296 cytology smears from patients aged 10 to 19 years, 18 percent of SILs were high grade, and no cases of invasive cancer were detected. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program reported that the incidence rate of invasive cervical cancer was 0/100,000/year for ages 10 to 14 years; 0/100,000/year for ages 15 to 19 years and 1.7/100,000/year for ages 20 to 24 years from 1995 to 1999.¹⁴ Based on the SEER data, the potential implied cost of missing high-grade SIL (HSIL) in 15- to 19-year-olds (by not screening or treating these lesions) is at most 1.7 cases of cervical cancer per 100,000/year (the incidence rate for 20- to 24-year-olds). It is not known, however, how many cervical cancer cases among the 20- to 24-year group were found in women who were immunosuppressed and/or HIV positive, how

many of the women were screened, or at what stage the cancers were diagnosed.

The goal of cervical screening in the United States is to identify and remove significant precancerous lesions in addition to preventing mortality from invasive cancer. HSIL is considered a significant precancerous lesion, whereas low-grade SIL (LSIL) is considered a much more benign lesion since most of these lesions regress. Data on regression and the natural history of LSIL and HPV infection in young women aged 13 to 22 have shown that most HPV infections are transient, with 70% regression rates of high-risk HPV types within three years and over 90% regression for low-risk types.⁷ HPV regression rates of over 90 percent within two years have been reported in college populations.⁸ Regression of LSIL is more common in adolescents than in adults. Fifty to eighty percent of LSIL in adult women will regress,^{15,16,17} whereas 90 percent of LSIL in adolescents and young women (aged 13 to 21) will regress.¹⁸ In one study, when HPV type was known, 81 percent of LSIL in young women with a high-risk HPV DNA type regressed, whereas six percent progressed.¹⁸ This discrepancy may reflect a more benign natural history for HPV infection in adolescents or reflect an increased accuracy of cytological diagnosis at entry, since LSIL greatly outnumbers HSIL in adolescents, reducing

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the misclassification rate compared to adult women. The high regression rate of LSIL parallels the high regression rates reported for HPV DNA detection, supporting the benign nature of most LSIL in adolescents and young women.

There are limited data on the progression rate of LSIL in adolescents. Moscicki, et al.¹⁸ found that only three percent of adolescents with LSIL progressed to HSIL within three years. On the other hand, five percent of adolescents who developed an HPV infection in an earlier study developed a HSIL, half of whom did not have a preceding detectable LSIL.⁷ Based on the prevalence of HSIL on cytology smears and the number of patients with HSIL (CIN2/3) found on histology who had only LSIL on cytology, approximately 1.7 percent of adolescents are estimated to harbor an HSIL. However, the risk of progression of these high-grade lesions among adolescents remains unknown. Nasiell, et al.¹⁹ observed that the time of progression for women with CIN2 to a carcinoma in situ or cancer over age 51 was 70 to 80 months, 41 to 42 months for women aged 26 to 50 years, and 54 to 60 months for women under 25 years of age. The relevance of these findings to young women today is unclear given that sexual behavior, contraceptive use, and smoking habits have all changed from the time when this and other cohort studies were performed in the 1960s to 1980s. The 54- to 60-month estimated progression for women under 25 years of age is the only available data. The difference from 41 months (for women aged 26 to 50) could be the result of study design rather than biology. Therefore the more conservative period of 41 months was used as the basis for recommending that screening begin approximately three years from potential exposure to HPV.

In support of this recommendation, mathematical modeling²⁰ suggests that the most cost-effective strategy (excluding HPV DNA testing) is to start screening three years after age

of onset of vaginal intercourse, with an age cap at 25 (this modeling used the assumption that cytology would be performed every three years following three annual, consecutive, technically satisfactory normal/negative cytology results). This strategy was modified to reflect the opinion of an expert panel of clinicians, which held that an age cap of 25 might result in a proportion of women not being screened until their late 20s in the absence of initiation based on an accurate sexual history. Consequently some high-grade lesions could progress. Furthermore, the SEER data indicate that invasive cervical cancer does occur in women under 25 years of age. The revised policy analysis showed that a sexual activity-based strategy with an age cap of 21 was also cost-effective, and particularly more cost-effective than universal age-based screening at age 18. The expert panel suggested that an age cap of 21 would represent a more practical and realistic age than 25 for compliance and access to patients, and would be more acceptable than postponing screening until age 25 in the United States. Of note, a sexual activity-based screening initiation criterion rather than an age-based criterion was superior even when screening was conducted every two years or every year.

When to Discontinue Screening

Recommendation

Women who are age 70 and older with an intact cervix and who have had three or more documented, consecutive, technically satisfactory normal/negative cervical cytology tests, and no abnormal/positive cytology tests within the 10-year period prior to age 70 may elect to cease cervical cancer screening. Screening is recommended for women who have not been previously screened, women for whom information about previous screening is unavailable, and for whom past screening is unlikely. Women who have a history of

cervical cancer, in utero exposure to diethylstilbestrol (DES), and/or who are immunocompromised (including HIV+) should continue cervical cancer screening for as long as they are in reasonably good health and do not have a life-limiting chronic condition. Until more data are available, women aged 70 and older who have tested positive for HPV DNA should continue screening at the discretion of their health care provider. Women over the age of 70 should discuss their need for cervical cancer screening with their health care provider based on their individual circumstances (including the potential benefits, harms, and limitations of screening) and make informed decisions about whether to continue screening. Women with severe comorbid or life-threatening illnesses may forego cervical cancer screening.

Rationale

There is general consensus that the incidence of cervical cancer in older women is almost entirely confined to the unscreened and underscreened. Screening in the unscreened population can reduce morbidity and mortality from cervical cancer.

Evidence suggests there is very low risk of cervical cancer for women aged 50 and older in countries with organized screening programs. Data do not exist to support screening over age 65 to 70 in women who have been regularly screened. Since screening the unscreened has been shown to affect mortality rates, there is rationale to screen the elderly unscreened population.

In the United States, cervical cancer is rare among older screened women. Furthermore, it may be difficult to get satisfactory samples from older women due to conditions such as atrophy and cervical stenosis. There is evidence that screening is associated with potential harms, including anxiety and discomfort during cytology sampling of some older women, and the invasive procedures, anxiety,

and higher health care costs due to false-positive cytology results.

The choice of exact age at which to cease screening is arbitrary. The choice of age 70 is based on the opinions of the expert panel members in an effort to balance the benefits and harms of screening older women. While some organizations have chosen the age of 65 (which is also arbitrary) in their guidelines, the ACS set the age at 70 based on mathematical modeling²¹ (Jeanne Mandelblatt, MD, MPH, unpublished data.) and demographic trends that may increase the likelihood of older women having new sexual partners and thus new exposures to HPV. Older women who choose to discontinue screening should continue to obtain appropriate preventive health care.

Evidence

Several studies have shown a low efficiency of cytological screening in women over the age of 50; the vast majority of cervical cancers in older women occurred in those who were not previously screened or who did not have three consecutive normal cytology results.^{22,23,24,25,26,27,28}

Few studies provide data on women aged 65 and older. Sigurdsson²⁴ reported decreasing rates of high-grade intraepithelial lesions in women aged 60 to 69 with increasing number of prior normal cytology tests. Sawaya, et al.²⁸ observed low rates of LSIL and HSIL in women aged 65 and over with at least one previous normal cytology result within the last three years.

Screening After Hysterectomy

Recommendation

Screening with vaginal cytology tests following total hysterectomy (with removal of the cervix) for benign gynecologic disease is not indicated. Efforts should be made to confirm and/or document via physical exam

and review of the pathology report (when available) that the hysterectomy was performed for benign reasons (the presence of CIN2/3 is not considered benign) and that the cervix was completely removed. Women who have had a subtotal hysterectomy should continue cervical cancer screening as per current guidelines. Women with a history of CIN2/3 or for whom it is not possible to document the absence of CIN2/3 prior to/or as the indication for the hysterectomy should be screened until three documented, consecutive, technically satisfactory normal/negative cervical cytology tests and no abnormal/positive cytology tests within a 10-year period are achieved. Women with a history of in utero DES exposure and/or with a history of cervical carcinoma should continue screening after hysterectomy for as long as they are in reasonably good health and do not have a life-limiting chronic condition.

Rationale

Use of cytology tests in women who have had their cervix removed for benign reasons screens the vaginal cuff. Vaginal cancer is an uncommon gynecologic malignancy with an incidence rate of 1 to 2/100,000/year.¹ Abnormal vaginal cytologic smears are uncommon and rarely of clinical importance. However, women with a history of in utero DES exposure are at increased risk for vaginal as well as cervical cancer. Women who have had a hysterectomy for cervical intraepithelial lesions may be at increased risk of vaginal cancer, but the data are limited. Women who have had a subtotal hysterectomy retain their cervix and should continue cervical screening. Women who discontinue screening should continue to obtain appropriate preventive health care.

For women in whom CIN2/3 was the indication for the hysterectomy, follow-up cytology is recommended every four to six months. Three documented, consecutive, technically satisfactory normal/negative vaginal cytology tests and no abnormal/positive cytology tests should be achieved

within an 18- to 24-month period following hysterectomy before discontinuing cytology screening. Women with a history of CIN2/3 prior to/but not as the indication for hysterectomy should be screened until three documented, consecutive, technically satisfactory normal/negative vaginal cytology tests and no abnormal/positive cytology tests (within a 10-year period) are achieved.

Evidence

A retrospective cohort study of vaginal cuff cytologic smears (VCS) in 5,862 women who had undergone a hysterectomy for benign disease found abnormal VCS among 79 women (1.1 percent of all smears). The mean length of time from hysterectomy to abnormal cytology result was 19 years. The positive predictive value for detection of vaginal cancer was 0 (95 percent CI 0 to 33 percent).²⁹ A 10-year retrospective study among 697 women after hysterectomy for benign disease found that 663 VCS were needed to detect one case of vaginal dysplasia.³⁰ A retrospective study of 220 women selected at random from 2,066 women who had a previous hysterectomy for benign conditions and followed for an average of 89 months identified seven patients (three percent) who had intraepithelial cytologic abnormalities, but no vaginal cancers. Four of these patients underwent successful excision or laser treatment of the lesions, and dysplastic lesions in the remaining three patients regressed without any treatment. No benefit in patient outcomes was observed.³¹ A cross-sectional study of 5,330 screening cytology tests in women who had had a hysterectomy found one case of dysplasia and no cancers.³²

Videlefsky, et al.³¹ reported two cases of severe dysplasia among 44 women (4.5 percent) after hysterectomies for HSIL. The difference in risk compared with women without a history of abnormal cytology prior to hysterectomy (3.6 percent) was not statistically significant. In a study of 193

women with CIN at hysterectomy, the incidence of abnormal vaginal cuff cytologic smears at least two years after hysterectomy was 0.7 per 1,000, and at 20 years 96.5 percent of the women continued to have normal smears.³³

Screening Interval

Recommendation

After initiation of screening, cervical screening should be performed annually with conventional cervical cytology smears OR every two years using liquid-based cytology; at or after age 30, women who have had three consecutive, technically satisfactory normal/negative cytology results may be screened every two to three years (unless they have a history of in utero DES exposure, are HIV+, or are immunocompromised by organ transplantation, chemotherapy, or chronic corticosteroid treatment).

Rationale (for Conventional Cervical Cytology)

The difference in absolute risk of an important lesion progressing to invasive disease is small when comparing one-, two-, and three-year screening intervals with conventional cervical cytology. While most data in this area come from countries with organized screening programs, data from the United States are similar. The difference in relative risk of an important lesion progressing to invasive disease between two- or three-year screening intervals compared with a one-year interval is significant; however, it is important to note that the probability of disease is quite small even among women screened every three years. The number of high-grade lesions that might progress during a screening interval longer than three years is considered to be unacceptably high in the United States. While more frequent screening increases sensitivity, it also increases patient harm and costs. Sensitivity, patient harm, and cost were all factors in determining the ACS guideline.

Screening interval recommendations apply to women who have been screened previously and received a technically satisfactory normal/negative result. Specimen adequacy and quality indicators should be considered when determining the timing of repeat screening for both conventional Pap smears and liquid Pap tests. If endocervical cells/transformation zone elements are absent or if there are partially obscuring factors, an annual repeat may be considered, and selected women may benefit from an earlier repeat test.^{34,35} Women who have had a recent abnormal cytology result would be classified as *under surveillance* rather than undergoing screening. A history of consecutive normal/negative cytology results has been associated with decreased risk of HSIL and cervical carcinoma.

Preliminary data suggest the most appropriate screening interval is age-dependent and younger women may benefit more from a shorter screening interval (Jack Cuzick, PhD, unpublished data.) e.g., one-year intervals rather than two- to three-year intervals for women under the age of 30. Women who are immunocompromised should follow the CDC guideline on screening HIV-infected women.¹² Women who have been exposed to DES in utero have an increased risk of cervical and vaginal cancers and should be screened annually. Other risk factors, such as early age of onset of sexual activity or multiple sexual partners, should not be used as a rationale for more frequent screening.³⁶ There are insufficient data to support recommendations for or against a more frequent screening interval (i.e., annual screening even after age 30) for women who smoke cigarettes, although one small study suggests that there would not be a benefit.³⁷

There is some concern that screening less than annually with conventional cytology will miss a proportion of endocervical adenocarcinomas. There is little data on the efficacy of cervical cytology as a screening and detection tool for nonsquamous cell

carcinomas. Use of the endocervical brush as well as new technologies including liquid-based cytology tests may increase the sensitivity to detect this type of cervical cancer.

Evidence for Screening With Conventional Cytology

The rigorous criteria established for the ACS guideline review process (Appendix A) resulted in exclusion of many studies. In most cases, excluded studies did not address whether the subjects had any prior history of cytology tests. Most of the case-series studies did not include information about prior screening nor did they have controls. Some measured incident cancer cases three to six years after the last screening test; however, the guideline review panel agreed that the risk of screening less frequently than three-year intervals was unacceptable, and therefore the panel was interested only in cases identified within three years. The number of such cases is very small even over a long period of time. Negative or normal results as presented across the studies were not consistent, standardized, or defined.

While the format and definitions employed in measuring relative risk of invasive cervical cancer for one-, two-, and three-year screening intervals were often inconsistent, most studies suggest that compared to annual screening, the relative risks with a two-year or a three-year screening interval are in the range of one to two and two to three, respectively, above annual screening.^{38,39,40,41,42,43} Risk increases with longer screening intervals of 4 to 10 years.^{38,39,40,41,42,44}

Because most studies do not provide data on the number of women screened, measurements of absolute risk are even more limited. Sawaya, et al.²⁸ provided data from a prospective cohort study of 128,805 women in the United States and determined the age-adjusted incidence rate of HSIL, carcinoma-in situ, or invasive carcinoma within three years of normal cytology results to be 25 per 10,000 for

women screened at 9 to 12 months, 29 per 10,000 for women screened at 13 to 24 months, and 33 per 10,000 for women screened at 25 to 36 months following a normal cytology result. The differences in incidence were not statistically significant.²⁸ A case control study reported that a two-year or three-year interval led to doubling the relative risk of being diagnosed with invasive cancer, but only a slight increase in absolute risk.⁴³ This finding was based on 482 cases observed over 13 years in a health maintenance organization with an enrollment of about one million women each year. Fifty-three of the cases occurred within three years of three or more negative/normal Pap smears. In this population, the absolute risk of invasive squamous cell cancer within the three years following three or more normal Pap smears was estimated at less than 5 per 100,000 women per year.

Several studies have shown that a history of normal/negative results has a protective effect on cervical cancer incidence.^{39,40,45,46} One case control study in Italy found a decrease in the risk of invasive cervical cancer of 90 percent among women with three or more normal/negative cytology smears compared to women with no previous cytology test.⁴⁵ A cohort study in Denmark found that women with two- to four-previous normal/negative cytology results had a negligible risk of developing cancer within two years, and a slower increase in risk compared to women with only one previous negative result.⁴⁰ Sawaya, et al.⁴⁶ estimated the absolute risks of cervical cancer (within 18 months of the last negative smear) following one, two, and three or more consecutive negative cytology smears as 3.09, 2.56, and 1.43 per 100,000 women, respectively, based on 2.4 million long-term members of a prepaid health plan. Further, it is important to note that there is an irreducible risk of cervical cancer in the United States. If all women in the United States were screened

annually, it is estimated that there would be 1.5 cases of cervical cancer per 100,000 women having a negative cytology result within 0 to 18 months and at least three prior consecutive normal/negative results.⁴⁷

Patient harm is very difficult to measure, and studying patient harm resulting from screening for a rare outcome such as cervical cancer poses particular challenges. Sawaya, et al.²⁷ reported that in approximately 2,561 postmenopausal screened women, 110 required diagnostic work ups for incident abnormalities (one or two years after a negative smear) involving 231 total interventions, and one woman was found to have a mild to moderate intraepithelial lesion.

The recommended screening interval for older women is rarely addressed in the available published literature. One exception is the Heart and Estrogen/Progestin Replacement Study (HERS) study,²⁷ which included women up to age 80. This study concluded that cervical cytology screening of previously-screened postmenopausal women at a rate more often than every two years had a positive predictive value of 0 to 2.7 percent (PPV varied depending on whether women without available biopsy results were included or excluded) and therefore supports not screening postmenopausal women within two years of normal cytologic results.

NEW TECHNOLOGIES

Recently, interest has been focused on new technologies that enhance the accuracy of cervical cancer screening. The expert review panel considered several cervical screening technologies with sufficient published clinical data and with potential application within the United States. The panel excluded technologies that are currently under development or that may have utility only in low-cost screening settings, i.e., aided visualization, cervicography,

computer-assisted screening devices, optical probe devices, self-collected vaginal samples for HPV DNA testing, and spectroscopy/electronic detection devices.

When evaluating and comparing the utility of the technologies, several points must be emphasized. Data on sensitivity are generally derived from research settings with optimized testing conditions; the same results may not be achievable in actual practice. Certain research designs by their nature may also over- or underestimate test sensitivity.

Test sensitivity must be distinguished from program sensitivity. Test sensitivity is the probability that a single test performed at a specified point in time will detect the presence of underlying disease. Program sensitivity is the probability that tests repeated at specified intervals will detect underlying disease over a period of time. Repeat screening at regular intervals therefore compensates somewhat for the limitations of the sensitivity of the technique.

For any test, sensitivity for detection of disease can be improved by lowering the test threshold for a "positive" result but only with concomitant loss in specificity, resulting in more false-positive results. When screening a population for a very low-prevalence disease, even a small percentage change in specificity affects a large number of women because the vast majority of women screened do not have disease. For example, if disease prevalence is 10 percent and test specificity is 95 percent, then a five percent decrement of specificity for 50 million screening tests represents an increase of 2.25 million women (from 2.25 million to 4.5 million) who will receive a "false-positive" result.

Prevailing management paradigms, medico-legal issues, economic factors, and societal expectations are all factors in determining the balance between sensitivity and specificity for a screening program. Risk perception, understanding, and acceptability all vary among individual patients, care providers, and

policy makers.^{48,49,50,51} Criteria for the ACS review and evaluation of new technology articles are summarized in Appendix B.

Liquid-based Pap Technology

Recommendation

As an alternative to conventional cervical cytology smears, cervical screening may be performed every two years using liquid-based cytology; at or after age 30, women who have had three consecutive, technically satisfactory normal/negative cytology results may be screened every two to three years (unless they have a history of in utero DES exposure, are HIV+, or are immunocompromised).

Rationale

Currently, two liquid-based Pap (LBP) technologies have been approved by the FDA as being at least equivalent to the conventional Pap smear in their ability to detect cervical precancerous lesions and cancers. Most studies have shown improved sensitivity for LBP compared to conventional smears. LBP specificity has been difficult to calculate but generally is thought to be comparable or moderately decreased compared to conventional cytology when performed less frequently. Although the ACS and others have recommended since before 1980 that conventional cytology can be safely performed up to every three years for most women, in the United States, annual screening is expected by most women and health care providers. A longer interval for LBP, i.e., every two to three years, compared to annual conventional Pap testing compensates for the decrease in specificity. Conversely, screening with LBP at the same interval as conventional cytology will likely lead to significant increases in the detection of atypical squamous cells - uncertain significance (ASC-US) and low-grade abnormalities, with subsequent increases in referral of women to colposcopy

unnecessarily, risking the potential for overtreatment and increased health care costs.

Several problems with conventional cytology smears are addressed by liquid-based methods. With LBP, the sampling device is directly placed into a liquid fixative instead of being spread onto a glass slide providing immediate fixation, thereby decreasing air-drying artifact and thus improving specimen adequacy. Additionally, LBP are felt to improve cellular sampling, distribute the cells more evenly over the slide and reduce cell overlapping, and decrease obscuring background factors (such as blood and inflammatory cells) often seen in conventional cytology (factors that may also affect test accuracy). Another advantage of LBP is the availability of residual material, which potentially may be used for ancillary testing (e.g., for oncogenic HPV DNA).

There are currently no data to support a particular screening interval for LBP. This recommendation was based on modeling by two independent researchers^{52,53} (Evan Myers, MD, MPH, unpublished data.) as well as expert opinion based on the existing data described below.

Evidence

Compared with conventional cytology, LBP provides at least equivalent percentages of satisfactory specimens.^{54,55,56} The key criteria for evaluating the available published literature were the sample size of the study, the type of population utilized (with a screening population similar in risk to the US population preferred), comparable medical practices to those of the United States, comparable patient demographics for historical cohort studies, an acceptable method of addressing inter/intra-observer variability, a way to address false-negative outcomes, and histology outcomes in a significant portion of the patients screened (Appendix B).

All of the available studies have important flaws, and the results are all presented in

different ways. Taken as a whole, the available evidence supports the conclusion that LBP is an acceptable option for cervical screening, that LBP is somewhat more sensitive but less specific for high-grade lesions, and that it may increase the number of ASC-US referrals and possibly the proportion of samples lacking an endocervical component. Of the studies reviewed^{54,55,56,57,58,59,60} all but one⁶⁰ showed increased sensitivity. Three studies showed a significant increase in the ASC-US detection rate,^{57,58,59} while others showed similar or slightly decreased rates.^{54,55,56,60} In the studies that provided data on specificity, the specificity was significantly decreased in two,^{57,58} was similar in two,^{56,60} and was uncertain in one.⁵⁹ One study found improved sample adequacy⁵⁶ while three found an increased rate of samples lacking an endocervical component.^{54,55,60} Importantly, in the one study that found no significant differences in sensitivity between LBP and conventional cytology, sampling for conventional testing was greatly enhanced by use of a specialized collection device, removal of mucus and cellular debris from the cervical surface prior to sampling, and colposcopically-guided sampling to verify harvesting of cells from the endocervical canal and full circumference of the cervical surface.⁶⁰

Although there have been questions regarding the detection of glandular lesions by LBP, recent studies^{62,63,64} have shown an improvement in sensitivity and specificity for biopsy-proven adenocarcinoma. Ashfaq, et al.⁶² demonstrated similar rates of glandular abnormalities on LBP as conventional cytology; however, the positive predictive value for LBP was higher and there were fewer false-negative LPB reports preceding biopsy-confirmed adenocarcinomas and adenocarcinoma in situ (AIS). Bai, et al.⁶³ reported a 50 percent lower rate for glandular atypia on LBP, but the positive predictive value for AIS was five-fold higher. Thus it is felt that LBP are capable of more precisely predicting AIS/adenocarcinoma. This is particularly important given the recent literature indicating

an overall rise in the rate of invasive cervical adenocarcinoma.

The preponderance of the data considered in this review of LBP utilized the first of the two FDA-approved techniques (ThinPrep). The studies and abstracts of the other LBP method (SurePath, previously Autocyte) suggest equivalent performance, but the few studies limit opportunities for comparison.

HPV DNA Testing With Cytology for the Screening of Cervical Cancer and Its Precursor Lesions

Preliminary Recommendation

HPV DNA testing with cytology for primary cervical cancer screening has not been approved by the FDA. Based on the available data, both published and unpublished, the ACS guideline review panel found this technology to be promising. Should the FDA approve HPV DNA testing for this purpose, it would be reasonable to consider that for women aged 30 and over, as an alternative to cervical cytology testing alone, cervical screening may be performed every three years using conventional or liquid-based cytology combined with a test for DNA from high-risk HPV types. Frequency of combined cytology and HPV DNA testing should NOT be more often than every three years. Counseling and education related to HPV infection is a critical need. Consensus guidelines for the management of women with a technically satisfactory normal/negative cytology result and a HPV DNA test result that is positive for high-risk HPV types would need to be developed.

Rationale

Since the mid-1990s there has been substantial interest in the use of HPV DNA testing as a cervical cancer screening tool based on the premise that standardized molecular testing of exfoliated cervical cells for the causative agent of cervical cancer could have

acceptable diagnostic performance while being more reproducible and more easily adapted for clinical practice than conventional cytology.

There have been several studies assessing the relative utility of both a cytology test and HPV DNA testing compared to the cytology test alone as a primary cervical cancer screening tool. Most studies have used the Hybrid Capture® (HC) system, the only HPV DNA test currently approved by the FDA. The currently marketed system is Hybrid Capture II® (HC2). It detects the presence of 13 types of HPV that have been associated with cervical cancer. Most of the studies reviewed by our panel indicate that women with a concurrent normal cytology test and a negative HC2 result have substantially decreased risk of high-grade lesions on colposcopy relative to those for whom the only screening information is a normal conventional cytology result. On the other hand, a positive HC2 result is not an absolute indicator that high-grade lesions exist or will develop; the prognostic value of a positive test result, especially in the absence of a cytologic abnormality, has not been fully validated in prospective studies.

HPV DNA testing has greater sensitivity than cytology for detecting clinically relevant lesions. Restricting screening to women aged 30 and older reduces the number of women to be referred to colposcopy due to transient HPV infection. The high negative predictive value resulting from concomitant screening with cytology and HPV DNA testing could safely permit increasing screening intervals, thus lowering costs. While definitive evidence of efficacy is still needed from long-term follow-up studies with CIN2/3 as an outcome and from randomized controlled trials, the opinion of the majority of expert panel members was that the available evidence supports consideration of the use of HPV DNA testing as an adjunct to cervical cytology with a screening interval no more frequently than every three years. More frequent screening would not significantly improve sensitivity, but would likely result in over-

evaluation and potential overtreatment of many women for transient HPV infections.⁵³

Only testing for high-risk HPV types would be of value. Testing for low-risk HPV types is not useful, and may have a negative psychological impact on the patient.

HPV DNA testing for the triage of patients with a cytology result of ASC-US was considered outside the scope of this screening guideline review. Consensus recommendations for the management of women with abnormal cytology tests were developed through a process sponsored by the American Society for Colposcopy and Cervical Pathology, and published in April 2002.⁶⁵

Evidence

Only studies using the HC2 test were taken into account for the purpose of this guideline review.^{59,66,67,68,69,70,71,72,73} All of them assessed the diagnostic performance for existing lesions using cross-sectional or short-term follow-up investigations of European,^{59,66,67} African,^{69,72,73} Asian,⁶⁸ Latin American,⁷¹ and North American (Canada)⁷⁰ populations. Lesion definition varied across studies and included either CIN of all grades or CIN2/3 or worse lesions, diagnosed by histology on specimens obtained by colposcopy-guided biopsy. In some studies, the colposcopic result was used if no biopsy was taken. None of these studies were based on long-term follow-up for more relevant endpoints, such as incidence of/or mortality from invasive cervical cancer. No results from randomized controlled trials have yet been published; all studies were based on concomitant testing. The review panel took into account the statistical issues that make it necessary to use different criteria to judge sensitivity and specificity when two tests are used together.

HPV DNA testing at the manufacturer's recommended threshold of positivity of one pg/ml (equivalent to 5,000 viral copies) has been shown to have greater sensitivity than cytology (on average, 25 percent higher in

absolute terms) but lower specificity (on average, 10 percent lower in absolute terms) for detecting high-grade lesions.^{59,66,67,68,69,70,71,72,73} Screening of women aged 30 or older or 35 or older tended to improve the specificity of HPV DNA testing considerably because viral infections in this age group are less common and are less likely to be of a transient nature than those in younger women. An important finding of most studies was the realization that the combination of cytology and HPV DNA testing attained very high negative predictive values (approaching 100 percent). Although none of these studies has been on an American population, it is reassuring that ongoing analyses from the NIH-funded Portland cohort corroborate the enhanced value of HPV DNA testing in screening for high-grade cervical lesions as compared with cytology.⁷⁴

ADDITIONAL RECOMMENDATIONS

The expert panel made several additional recommendations: (1) The ACS and others should educate women, particularly teens and young women, that a pelvic exam does not equate with a cytology (Pap) test, and that women who may not need a cytology test still need regular health care visits, including gynecologic care and STD screening and prevention. (2) The current guideline review did not address the potential usefulness of pelvic and/or rectal examinations. Pelvic exams are not effective in detecting cervical cancer, however both pelvic and rectal exams may facilitate identification of other types of cancer and of other gynecologic conditions. Women should discuss the need for these exams with their provider. (3) Referrals of women with low-grade lesions for colposcopy may be less necessary for adolescents given the self-limited nature of many LSILs in this age group. Detection and treatment of HSIL should be the goal of adolescent screening and referral. (4) Health insurance payers should not exclude adolescents or women of any age from

coverage for cervical health on the basis of false-positive cytology results and/or mild abnormalities on cervical cytology. (5) Health insurance coverage for new cervical screening technologies is not uniform. Providers should confirm coverage before ordering tests such as LBP and HPV DNA testing, including use for triage of patients with ASC-US.

CONCLUSION

Compared to the previous ACS guideline published in 1988,¹¹ this guideline represents more comprehensive recommendations based on the body of accumulated evidence. Changes were made concerning what age to start screening and, to a lesser extent, the screening intervals. New recommendations were developed to address when screening may be discontinued, screening of women who have had a hysterectomy, and the use of new screening technologies. Changes to the screening recommendations are unlikely to have a significant impact on the relatively low incidence and mortality associated with cervical cancer in the United States. Yet the large number of women currently being screened each year (50 million) who receive an abnormal result (two million ASC-US and ASC-H, 1.25 million LSIL, 300,000 HSIL, in addition to 13,000 cancers) and undergo additional procedures represents a potential for a large impact in reducing patient discomfort, anxiety, and inconvenience as well as health care costs.

The guideline continues to emphasize the importance of flexibility for women and their providers in the context of informed decision-making. Individual patients will have different perceptions of risk and risk tolerance that may affect their choice of screening interval, screening test, and whether to discontinue screening after a certain age. Ideally these decisions should be based on discussions of the benefits, risks, and limitations of cervical cancer screening between women and their providers.

Screening interval remains a controversial issue in the United States. While the evidence supports the conclusion that conventional cytology can be safely performed at two- to three-year intervals, many women and

providers in the United States may be more comfortable with annual screening. A key factor is the limited sensitivity of the conventional Pap test. A significant proportion of false-negative conventional cytology results

APPENDIX A

Evidence Grading 1 = Strong evidence. 2 = Limited evidence. 3 = No evidence/exclude.

Study Type Code (from US Preventive Services Task Force)

Primary Reports of New Data Collection

- Class A:** Randomized, controlled trial.
- Class B:** Prospective cohort study; Case-control study nested within a prospective cohort study.
- Class C:** Non-randomized trial with concurrent or historical controls; Case-control study (except for the preceding); Retrospective cohort study; Study of sensitivity and specificity of a diagnostic test; Population-based descriptive study.
- Class D:** Cross-sectional study; Case series; Case reports.

Reports That Synthesize or Reflect Upon Collections of Primary Reports

- Class M:** Meta-analysis; Decision analysis; Cost-benefit analysis; Cost-effectiveness study.
- Class R:** Review article; Consensus statement; Consensus report.
- Class X:** Medical opinion.

Criteria for Evidence Grading

(1) Strong Evidence

- Evidence is useful to our task (reviewer's conclusion may be different from authors').
- Sample size is adequate to give statistical power.
- Unbiased or biases addressed.
- Endpoint defined as CIN2/3.

(2) Limited Evidence

- Conclusions/assumptions are not supported by data, but some useful data is provided.
- Sample size insufficient to give statistical power to observe a true effect.
- Flaws or biases that could negate conclusions.
- Study design weakens conclusions (reviewer should provide explanation).
- Review article with a new perspective.

(3) No Evidence/Exclude

- No relevant data (e.g., review article).
- Symptomatic women.
- Shortcomings negate conclusions.
- Articles not in English.

Key Data to Abstract for Each Article that Meets Inclusion Criteria

Country
Sample size
Sample description (age, risk, ethnicity, screening history)
Time period

Biases (selection, verification, observer)
Issue addressed
Endpoints
Length of follow up (e.g., average, individual, person-years)

Major flaws
Major strengths
Authors' conclusions
Reviewer's conclusions

are due to inadequate sampling; improvements in the ability to obtain an adequate sample would increase the sensitivity and effectiveness of conventional cytology. In addition, many experts believe that the use of new technologies such as liquid-based Pap tests and HPV DNA testing (in combination with cytology), when performed at a less frequent interval, offers several advantages over conventional cytology smears alone. These advantages may include increased sensitivity, lower long-term costs, and facilitation of the triage of ASC-US results. If used at the same interval though (e.g., annual LBP compared to annual conventional cytology), new technologies would significantly increase the number of women referred for colposcopy unnecessarily, greatly increasing health care costs and harms to patients, with little or no benefit.

It is important to reiterate that the biggest gain in reducing cervical cancer incidence and mortality would be achieved by increasing screening rates among women who have not been screened or who have not been screened regularly. Missed opportunities for screening abound, particularly among unscreened older women, women of low income and/or low education, and women who are uninsured or underinsured. Clinicians, hospitals, health plans, and public health officials should seek to identify and screen these women, and to ensure continued screening at regular intervals.

APPENDIX B

Criteria for Evaluating Studies of Cervical Screening Technologies

The purpose of these suggested criteria is not to exclude any study because it is missing any of the following criteria, nor to grade a particular study based on the criteria, but to give a sense of weight of the evidence for a given technology. At least one study should provide evidence that supports use of the technology, and meet the individual evidence

criteria. For example, if every study of Technology A suggests it is more sensitive than Technology B, and at least one study addresses at least one of these methodological issues, then Technology A would be considered more sensitive. Issues of study design come into play in trying to estimate how much more sensitive, but trying to come up with quantitative estimates was beyond the scope of this guideline review.

Reference Standard Specified

The minimum criteria for inclusion is that the reference standard is explicitly stated. Timing is an important issue to be considered (e.g., how soon after the cytology was the colposcopy done). Suggested acceptable reference standards included cone biopsy/hysterectomy specimen, colposcopy/biopsy, and (under defined circumstances) comparison of cytological results.

Test Results Directly Comparable: Should Be Applied to the Same Patient/Specimen or Be Randomly Assigned

Studies that do not involve direct comparison of the results of two or more tests in either the same patients, or in patients drawn from the same population and randomly assigned to a particular test, are less preferable than studies where either the new technology was randomly assigned or where it was applied to the same population of patients and/or slides.

Tests Performed in the Context of Screening, Not Follow-up of Abnormal Results

When an imperfect reference standard (colposcopy/histology) is used, test characteristics are dependent on the prevalence of the disease. Studies that report test performance in a general screening population are preferable. Any study should provide adequate characterization of the study population.

Study Reports Results of Detection of HSIL/CIN2/3

Because no study will be able to demonstrate reduction in the incidence of cervical cancer, the next best alternative is the ability to improve detection of high-grade precursors. In order to infer that a new technology will result in a decrease in cervical cancer, evidence about its ability to detect CIN2/3 must be provided.

Verification Bias Addressed

If the reference standard is applied only to positive screening tests, then the sensitivity will always be overestimated. Ideally, at least one study of a technology will have a design that avoids verification bias.

Chance Gains in Sensitivity Have Been Considered

Adding an adjunct screening test in parallel to Pap cytology will always yield an increased combined sensitivity that may not be greater than that contributed by an unrelated adjunct test in the same screening setting. Ideally, studies should consider sensitivity gains of combined testing only after taking into account this chance increase in sensitivity.⁷⁵

Observer Variability Addressed

Inter- and intraobserver variability may have significant impacts on the consistency of test sensitivity and specificity. All other things being equal, a more consistent test is preferable. Ideally, at least one study of a technology will address inter- and intraobserver variability in the interpretation of results.

Statistical/Sample Size Issues Addressed

Because most comparisons of cervical screening tests are based on categorical outcomes, statistical power is inherently

somewhat reduced compared to continuous outcomes. Sample size can also affect study interpretation in other ways. In addition, use of multivariate analytic techniques invariably results in some loss of power. Power calculations, preferably a priori, should be stated. Studies that present results that allow quantification of uncertainty (point estimates of sensitivity and specificity with 95% confidence limits) are in general preferable to studies that provide only the results of significance testing (chi-square comparison of two different sensitivities).

APPENDIX C

Collection of Cervical Cytology Samples

It is estimated that at least one third or more of false-negative cytology tests (negative results when a woman has a high-grade cervical lesion) are related to sampling issues—specifically that abnormal cells are not present on the cytologic slide examined in the laboratory.^{76,77,78,79} Sampling problems can occur if abnormal cells are not collected onto the sampling instrument or if collected cells are not transferred to the slide to be examined, but rather remain on the sampling instrument. Regardless of the collection device, only a relatively small percentage of cells are transferred to the slide to be submitted as compared to the total number of cells collected on the device.^{80,76,81}

Obtaining an Adequate Cervical Cytologic Sample

An adequate cervical cytologic specimen involves circumferential sampling of the ectocervix adjacent to the transformation zone, the endocervix, and the cervical transformation zone (T-zone). A vaginal cytologic sample is not necessary for cervical cytologic sampling, and is not recommended for cervical cytologic sampling. Vaginal samples

are recommended for the detection of vaginal carcinoma in women exposed to DES in utero.

Collection Instruments

Using a combination of the extended tip spatula and the endocervical brush provides sampling of the ectocervix, T-zone, and endocervix, and has the lowest false-negative rate when compared to less thorough sampling.^{82,83,84} Both samples are usually placed on a single slide, rather than using two slides.⁸⁵

The extended tip spatula is superior to the conventional Ayres spatula for sampling the ectocervix and the T-zone.⁸¹ The spatula has been traditionally made of wood; however, plastic spatulas perform equally well for conventional smears and perform better when used in liquid-based systems because the cells can be washed from the plastic more readily than from wood spatulas.

To collect the endocervical cytologic sample, it is necessary to insert the collection device within the endocervical canal and collect cells by gently scraping or brushing the endocervical mucosa. When using the endocervical brush, the brush should be inserted until it has moved into the endocervix and until the bristles most proximal to the handle are approximately even with the apparent external cervical os. The brush is then rotated 180 degrees (one-half turn) in the canal. Additional rotation does not improve sampling and may cause bleeding. In the non-pregnant patient, the use of an endocervical brush provides a cellular sample that is generally rich in endocervical and/or high T-zone cervical cells. This device is used after the spatula sampling of the ectocervix and T-zone. The endocervical brush can be used to prepare conventional cervical smears, as well as with liquid-based cervical cytology. The endocervical brush collects more diagnostic cellular material than the swab, as studied in patients who had undergone prior treatment to the T-zone, including cryotherapy, laser ablation, and conization.^{84,86,87} Although the endocervical

brush is not generally recommended by the manufacturer for use in pregnant women because of the potential risk of inadvertent perforation of the amniotic sac, there is considerable clinical experience with the use of the brush in pregnant women with no apparent complications.⁸⁸

Cervical broom instruments and other single sampling instruments are designed to simultaneously sample the ectocervix, T-zone, and endocervical areas, and are fairly comparable to the combination of extended tip spatula and endocervical brush. The cervical broom may be used for conventional cytology smear samples as well as for liquid-based systems, and may be used in pregnant women.

Use of a Small Swab for Endocervical Sampling

An endocervical swab is less sensitive than the endocervical brush and its use is discouraged for endocervical cytologic sampling.⁸¹ It may be considered for pregnant women when there is concern about using other endocervical sampling devices. It should be used in combination with an ectocervical and T-zone sampling instrument such as the extended tip spatula. The swab should be moistened with a small amount of saline prior to use in order to prevent cellular desiccation on contact with the swab, and to release cells from the swab more easily when making a smear. A swab is not recommended with liquid-based systems. For liquid-based systems, the cervical broom is recommended in the pregnant patient, rather than the spatula and swab collection method.

Patient Advice Prior to a Cytology Test

The patient can be advised that there are several actions she can take to optimize the cytology test (based on American Society of Cytopathology 2001 guidelines available at: <http://www.cytopathology.org/guidelines/cervical-cytologyiii.php>). These include:

1. Try to schedule the appointment when it

- is not during the menstrual period.
2. Do not douche 48 hours prior to the cytology test.
 3. Refrain from intercourse 48 hours prior to the test.
 4. Do not use tampons, birth control foams, jellies, or other vaginal creams or vaginal medications for 48 hours prior to the test.

Schedule the test to avoid menses if possible. Ideally, screening is best performed in the absence of heavy menstrual flow but should not be deferred in the event of abnormal bleeding (i.e., bleeding between periods, postcoital bleeding, postmenopausal bleeding) or if accessibility for return examination is difficult.

Collection of a Specimen With the Cervical Broom Device

There are a number of single-sampling devices that sample both the endocervix and the T-zone at the same time, with one collection scraping of the cervix. The cervical broom is the most commonly used among such devices. It can be used instead of the extended tip spatula and the endocervical brush, and can be used in pregnant women. The long central bristles of the broom are inserted into the endocervical os while the broom is pressed against the cervix so that the outer bristles bend. The broom is then rotated in one direction for five complete rotations. (Rotating in one direction, and then the other is not recommended because it can result in loss of cells.) The cervical broom can be used with conventional cervical cytology, as well as with liquid-based cervical cytology. For conventional cytology, the broom sample is smeared on a slide (labeled with the patient's name) by stroking the broom on the usable surface of the slide (excluding the frosted label) from the label margin toward the other end of the slide. The sample is then quickly fixed with a spray fixative or by immersing the slide in 95% ethanol. For liquid cytology, one

manufacturer recommends that the broom be rinsed as free of cells as possible in the preservative medium. Another manufacturer recommends snapping off the handle of the instrument and leaving the broom end of the instrument in the fixative solution to be sent to the laboratory.

Typical Procedure for Making the Cervical Cytologic Smear When Employing the Extended Tip Spatula and the Endocervical Brush Using a Single Slide Technique

Using a glass slide labeled with the patient's name (a slide with a frosted label space on one end is preferred, so the patient's name can be written on the slide with pencil) the endocervical brush with the cellular sample is rolled onto the surface of the glass slide. The brush sample can be rolled on the slide immediately adjacent to the frosted label area, usually using about a two cm portion of the slide. The extended tip spatula sample can then be smeared on the same slide, smearing the sample immediately adjacent to the endocervical sample and, using a circular motion, smearing the cellular sample onto the glass slide. The slide is then rapidly fixed with a spray fixative, or immersed in 95% ethanol. If a liquid-based Pap test is used, the brush and the extended tip spatula are carefully rinsed in a vial of preservative, and the container is labeled with the patient's name.

Submitting Samples Using Liquid-based Techniques

For liquid cytology, both the endocervical brush sample and the extended tip spatula cytologic sample are submitted in a single container with appropriate fixative solution and labeled with the patient's name. A plastic extended tip spatula is recommended for liquid-based techniques. One manufacturer recommends that the spatula and the

endocervical brush (or the cervical broom, if used) be rinsed as free of cells as possible in the fixative solution. Another manufacturer recommends the sampling devices be separated or cut from the handle and placed into the fixative

solution for transport to the laboratory. CA

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Errata

In the November/December 2002 issue, in the article “Cancer Statistics for African Americans” (Ghafoor A, Jemal A, Cokkinides V, et al. *CA Cancer J Clin* 2002;52;326-341), an error appeared in the data for Tables 2 and 3

(pages 330 and 331, respectively). Table 2 and Table 3 have been modified with the corrected data and are reproduced here. We apologize for these errors and any confusion they may have caused.

TABLE 2

African American to White Incidence Rate Ratios, US, 1995 to 1999*							
Males				Females			
Cancer Type†	African American	White	African American/White	Cancer Type†	African American	White	African American/White
	Rate	Rate	Ratio		Rate	Rate	Ratio
Myeloma	13.1	6.5	2.0	Myeloma	10.3	4.2	2.5
Stomach	19.3	10.7	1.8	Stomach	10.3	4.6	2.2
Esophagus	12.8	7.6	1.7	Esophagus	4.4	2.0	2.2
Larynx	12.2	7.1	1.7	Small Intestine	2.9	1.5	1.9
Prostate	266.8	163.2	1.6	Larynx	2.9	1.6	1.8
Liver and Intrahepatic Bile Duct	10.3	6.4	1.6	Uterine Cervix	13.6	8.1	1.7
Lung and Bronchus	125.6	84.4	1.5	Pancreas	15.2	9.5	1.6
Pancreas	18.2	12.3	1.5	Liver and Intrahepatic Bile Duct	4.0	2.5	1.6
Oral Cavity and Pharynx	21.8	16.5	1.3	Kidney and Renal Pelvis	9.8	7.8	1.3
Kidney and Renal Pelvis	18.4	15.6	1.2	Colon and Rectum	56.1	47.1	1.2
Colon and Rectum	69.0	65.0	1.1	Soft Tissue (including heart)	2.6	2.4	1.1
Non-Hodgkin's Lymphoma	19.9	24.5	0.8	Lung and Bronchus	54.4	53.3	1.0
Leukemia	12.6	16.7	0.8	Breast	123.7	140.9	0.9
Myeloid Leukemia	5.7	6.9	0.8	Urinary Bladder	7.7	10.2	0.8
Acute Myeloid Leukemia	3.4	4.5	0.8	Leukemia	7.6	9.8	0.8
Hodgkin's Lymphoma	2.7	3.4	0.8	Uterine Corpus	17.3	26.1	0.7
Lymphocytic Leukemia	5.3	7.4	0.7	Hodgkin's Lymphoma	2.0	2.8	0.7
Chronic Lymphocytic Leukemia	4.1	5.5	0.7	Ovary	12.0	18.1	0.7
Brain	4.6	8.3	0.6	Non-Hodgkin's Lymphoma	11.2	16.5	0.7
Urinary Bladder	19.3	39.8	0.5	Thyroid	5.6	10.0	0.6
All Cancers	695.3	560.1	1.2	All Cancers	412.9	433.5	1.0

*Rates are per 100,000 and age adjusted to the 2000 US standard population.

†Site selected if cases greater than 100.

Source: Surveillance, Epidemiology, and End Results program, Division of Cancer Control and Population Sciences, National Cancer Institute, 2002.

TABLE 3

African American to White Mortality Rate Ratios, US, 1995 to 1999*							
Males				Females			
Cancer Type†	African American	White	African American/White	Cancer Type†	African American	White	African American/White
	Rate	Rate	Ratio		Rate	Rate	Ratio
Larynx	5.8	2.4	2.4	Stomach	6.8	3.0	2.3
Prostate	72.8	31.2	2.3	Myeloma	6.8	3.0	2.3
Stomach	14.2	6.3	2.3	Uterine Cervix	6.2	2.8	2.2
Myeloma	9.2	4.5	2.0	Esophagus	3.5	1.7	2.1
Oral Cavity and Pharynx	8.3	4.2	2.0	Larynx	0.9	0.5	1.8
Esophagus	12.9	7.2	1.8	Uterine Corpus	3.2	2.0	1.6
Liver and				Soft Tissue			
Intrahepatic Bile Duct	9.2	5.9	1.6	(including heart)	1.9	1.3	1.5
Lung and Bronchus	109.1	79.7	1.4	Colon and Rectum	25.4	18.0	1.4
Pancreas	16.2	12.0	1.4	Pancreas	13.0	9.0	1.4
Small Intestine	0.5	0.7	1.4	Liver and			
Colon and Rectum	34.4	25.8	1.3	Intrahepatic Bile Duct	3.9	2.8	1.4
Kidney and				Breast	37.1	28.2	1.3
Renal Pelvis	6.2	6.2	1.0	Urinary Bladder	3.1	2.3	1.3
Leukemia	9.3	10.6	0.9	Lung and Bronchus	40.2	41.7	1.0
Hodgkin's Lymphoma	0.7	0.7	1.0	Kidney and Renal Pelvis	2.9	2.9	1.0
Lymphocytic Leukemia	3.0	3.3	0.9	Leukemia	5.6	6.1	0.9
Myeloid Leukemia	3.7	4.5	0.8	Myeloid Leukemia	2.5	2.8	0.9
Non-Hodgkin's Lymphoma	7.8	11.2	0.7	Ovary	7.6	9.3	0.8
Urinary Bladder	5.7	8.0	0.7	Non-Hodgkin's Lymphoma	4.7	7.5	0.6
Brain	3.2	6.0	0.5	Brain	2.3	4.1	0.6
Melanoma	0.5	4.4	0.1	Melanoma	0.5	2.1	0.2
All Cancers	359.2	253.0	1.4	All Cancers	203.5	169.8	1.2

*Rates are per 100,000 and age adjusted to the 2000 US standard population.

†Site selected if number of deaths is greater than 100.

Source: Underlying mortality data provided by the National Center for Health Statistics. Available at: <http://www.cdc.gov/nchs>.

In the November/December 2002 issue, in the article "American Cancer Society Guideline for the Early Detection of Cervical Neoplasia and Cancer" (Saslow D, Runowicz CD, Solomon D, et al. *CA Cancer J Clin* 2002;52:342-362), an error appeared in the author byline on page 342.

The byline should have read "Debbie Saslow, PhD; Carolyn D. Runowicz, MD (for the Work

Group on Interval, Older Women, and Hysterectomy); Diane Solomon, MD (for the Work Group on Technologies); Anna-Barbara Moscicki, MD (for the When to Start Screening Work Group); Robert A. Smith, PhD; Harmon J. Eyre, MD; Carmel Cohen, MD (for the Gynecologic Cancer Advisory Group)."

We apologize for this error and any confusion it may have caused.