## II. Cervical cancer and the Papanicolaou (Pap) Smear

A. History of the Pap Smear
   1. ***Screening test*** for cervical cancer named for George Papanicolaou
   2. Estimated 50 million performed annually in United States
   3. Test has reduced cervical cancer deaths by 79%
   4. Almost ¼ of those who develop cervical cancer fail to get regular Pap
   5. Progressive development of both classification and technique (Bundrick & Wright articles)

B. Epidemiology of cervical cancer (ACOG Practice Bulletin)
   1. Essentially a ***sexually transmitted disease***
      a. Overwhelmingly related to high-risk types of Human Papilloma Virus (HPV)
      b. Herpes Simplex Virus (HSV) originally implicated
      c. Increased risk with human immunodeficiency virus (HIV)
   2. Natural history of HPV infection and cervical cancer
      a. Peak incidence of infection - < 25 years of age – most do not progress
      b. Peak incidence of carcinoma in situ – 35-45 years of age
      c. Peak of invasive carcinoma – 45-55 years of age
      d. Infection with high-risk oncogenic HPV types may alter natural history
      e. Glandular lesions are a major exception to usual history
   3. Those at high risk (Bundrick article)
      a. Early unprotected sex with multiple partners
      b. Smokers have a 2-4 fold increased risk – independent of sexual history
   4. Payor rationale for coverage and patient education needs (Smith article)

C. Management of cervical cytological abnormalities (Bruner, Bundrick, Khan, McFadden & Wright articles)
   1. Importance of HPV typing
      a. Requires liquid-based cytological screening
      b. Reported as high-risk or low risk
   2. The Bethesda System used for reporting cervical cytology
      a. Atypical Squamous Cells of Undetermined Significance (ASC-US) and Low-grade Squamous Intraepithelial Lesion (LSIL) or High-grade SIL (LSIL or HSIL)
      b. Referral algorithms
   3. Importance of history
      a. Age
      b. Sexual history
      c. Previous Pap smear abnormalities

D. Technique (Carcio, Chapter 7)
   1. Traditional or liquid based cytology?
   2. Age and hormone based changes in location of Squamous-Columnar junction (endocervical cells)
   3. Obtained during speculum examination

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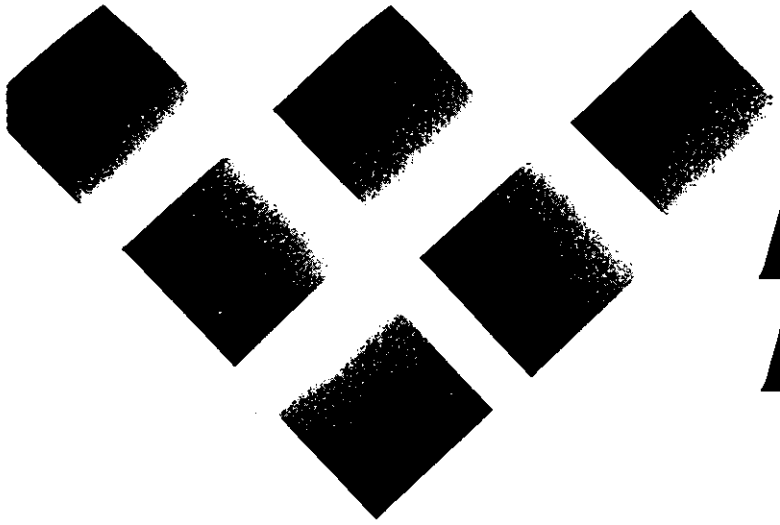

ACOG PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN–GYNECOLOGISTS

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This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Alan G. Waxman, MD, MPH. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.


# Cervical Cytology Screening

*Although cervical cancer was the leading cause of cancer death in American women as recently as the 1930s, both the incidence and mortality from cervical cancer have decreased by almost one half since the early 1970s, largely as a result of widespread screening with the Pap test (1–3). However, the annual incidence rate has remained at approximately 8 cases per 100,000 women over the past few years (4). New technology for performing cervical cytology is evolving rapidly, as are recommendations for classifying and interpreting the results. The purpose of this document is to provide a review of the best available evidence on screening for cervical cancer. Specific equipment and techniques for performing cervical cytology and interpretation of the results are discussed elsewhere.*

## Background

### Value of Cervical Cytology

Although the incidence and mortality from cervical cancer have decreased substantially in the past several decades among women in the United States, cervical cancer remains the third most common gynecologic malignancy (2, 5). In countries where cytologic screening is not widely available, cervical cancer remains common. Worldwide, it is the second most common cancer among women, the third most common cause of cancer-related death, and the most common cause of mortality from gynecologic malignancy (3, 6, 7). When cervical cytology screening programs have been introduced into communities, however, marked reductions in cervical cancer incidence have followed (7–9).

Cervical cytology screening is, in many respects, the ideal screening test (8). Cervical cancer has a defined premalignant phase of many years, which allows repeated tests to significantly reduce the impact of individual false-negative test results. Cervical cytology is inexpensive and is readily accepted

among American women. In 1998, 79% of women aged 18 years and older had cervical cytology screening in the preceding 3 years (10). Treatment is effective in reducing the chance of progression to invasive disease.

Despite effective screening measures and treatment, it is estimated that 50% of the women who receive cervical cancer diagnoses each year have never had cervical cytology screening. Another 10% had not been screened within the 5 years before diagnosis (11). Thus, one approach to reducing the incidence and mortality of cervical cancer would be to increase screening rates among women who currently are not screened or undergo screening infrequently (5).

## Addressing Errors in Cervical Cytology

In some cases, cervical cancer is undetected despite a recent screening test because of errors in sampling, interpretation, or follow-up. Sampling errors occur when dysplastic cells on the cervix are not transferred to the slide; errors of interpretation are attributed to lack of recognition of abnormal cells in the laboratory. These two sources of false-negative test results are associated with 30% of the new cases of cervical cancer each year (12, 13).

The problem of errors in interpretation is compounded by inconsistency among cytologists. When results of monolayer cytology specimens were reviewed by quality control pathologists, only negative and low-grade squamous intraepithelial lesion (LSIL) readings had greater than 50% consistency (14). Most revised results were downgraded to lesser diagnoses. Of those reported as atypical squamous cells of undetermined significance (ASCUS), 39% were downgraded to negative on further review. Of those originally interpreted as high-grade squamous intraepithelial lesions (HSIL), 50% were reinterpreted as LSIL, ASCUS, or negative.

The 1998 Clinical Laboratory Improvement Amendments (CLIA), passed in response to claims of poor or absent quality control practices in U.S. cytology laboratories, limited the number of cervical cytology tests a technician could read each day to a maximum of 100. In addition, CLIA mandated that each laboratory rescreen at least 10% of the cervical cytology tests that have negative results (15).

## Techniques of Cervical Cytology

Sampling involves collecting exfoliated cells from the ectocervix and endocervical canal and transferring them to a glass microscope slide or into a liquid transport medium for review. Patient preparation and proper provider technique can help optimize the collection of cells:

- Cells should be collected before the bimanual examination.
- Care should be taken to avoid contaminating the sample with lubricant.
- If testing for sexually transmitted diseases is indicated, cell collection for cervical cytology should be undertaken first.
- Ideally, the entire portio of the cervix should be visible when the sample is obtained.
- Routine swabbing of the discharge from the cervix may result in cytologic samples of scant cellularity (16).
- In an effort to reduce air-drying artifact, the specimen should be transferred and fixed as quickly as possible.

When performing cervical cytology by standard preparation, a single slide, combining both the endocervical and ectocervical samples, or two separate slides can be used. The most important consideration is rapid fixation. If liquid-based preparations are used, rapid immersion in liquid media is equally important.

## New Screening and Interpretation Devices

Many methods to refine and improve cervical cytology have been proposed (17). In the 1980s, new devices were developed for enhancing the collection of exfoliated cells from the cervix. These included nylon brushes for sampling the endocervix and "broom" sampling devices, which simultaneously sample both the ectocervix and endocervix. These devices have been shown to increase the amount of cells captured from the transformation zone and to increase the amount of dysplastic cells collected when compared with cotton-tipped applicators and wooden Ayre's spatulas (18, 19). In 1996, the U.S. Food and Drug Administration (FDA) approved the first of two currently available liquid-based thin-layer cytology preparations for cervical screening. In addition, automated, computer-based technologies have been marketed that use digitally scanned images to facilitate primary screening and the CLIA-mandated rescreening of cervical cytology tests that have negative results.

## Cytologic Reporting

The nomenclature for reporting cervical cytology results has undergone several changes since the publication of the original Papanicolaou system. The Bethesda System of reporting is the most widely used system in the United States (20). First proposed in 1988, it was revised in 1991 and again in 2001 (21–23). The most important changes in the 2001 revised terminology are listed as follows (23):

- Specimen adequacy—Slides are to be reported as "satisfactory" or "unsatisfactory" for interpretation.

"Satisfactory, but limited by ..." is no longer reported as a separate category under the heading "specimen adequacy." The presence or absence of an endocervical or transformation zone component is described in the narrative portion of the laboratory report, as are other quality indicators, such as partly obscuring inflammation or blood. If a slide is categorized as unsatisfactory, the reason should be specified. If abnormalities are found on an otherwise unsatisfactory slide, it will, by definition, be considered satisfactory for interpretation.

- Negative for intraepithelial lesion or malignancy—This designation should be used for slides with no cytologic evidence of neoplasia. This category includes findings previously designated as "benign cellular changes." When specific organisms are identified (eg, *Trichomonas vaginalis, Candida* species, shift in flora suggestive of bacterial vaginosis, bacteria consistent with *Actinomyces* species, and cellular changes consistent with herpes simplex virus), they are reported and categorized as "negative for intraepithelial lesion or malignancy." Other nonneoplastic findings, including reactive cellular changes associated with inflammation, radiation, or an intrauterine device, as well as glandular cells posthysterectomy or atrophy, also may be included in this category. Endometrial cells found in a woman aged 40 years or older will be listed under this category, but the finding of endometrial cells will not be reported routinely if noted in a woman younger than 40 years.
- Atypical squamous cells—The epithelial abnormality ASCUS has been replaced by "atypical squamous cells" (ASC) with the subcategories "atypical squamous cells of undetermined significance" (ASC-US) and "atypical squamous cells cannot exclude HSIL" (ASC-H). The modifier of "favor reactive" was eliminated. The category ASC-H was introduced to include those cytologic changes suggestive of HSIL but lacking sufficient criteria for definitive interpretation. The literature suggests ASC-H should represent 5–15% of the total pool of ASC but would have a significantly higher predictive value for diagnosing cervical intraepithelial neoplasia (CIN) of grades 2 or 3 than ASC-US (24, 25).
- Atypical glandular cells—This term designates cells exhibiting atypia that are of glandular rather than squamous origin and replaces the term "atypical glandular cells of undetermined significance." The finding of atypical glandular cells on cytology is more likely to be associated with both squamous and glandular abnormalities than is ASC-US, and the workup required of atypical glandular cells is more aggressive (26, 27). The 2001 terminology subdivides atypical glandular cells by cell type, ie, atypical endocervical cells, atypical endometrial cells, or atypical glandular cells not otherwise specified. Although the subdivision of "favor neoplastic" is maintained in the 2001 reporting system, favor reactive is not. In addition, because sufficient cytologic criteria exist to designate endocervical adenocarcinoma and adenocarcinoma in situ, these two findings are reported when identified.
- Low-grade squamous intraepithelial lesions—As in the original terminology, the 2001 nomenclature combines cytologic findings of CIN 1 (mild dysplasia) and those consistent with human papillomavirus (HPV) infections into the category LSIL (22, 28, 29).
- High-grade squamous intraepithelial lesions—The 2001 nomenclature maintains the category of HSIL, which combines CIN 2 and CIN 3 (moderate dysplasia, severe dysplasia, and carcinoma in situ). Although the natural history of CIN 2 lies between CIN 1 and CIN 3, the virology of CIN 2 is more like CIN 3 than CIN 1 in its likelihood of representing aneuploidy and monoclonal proliferation with a single high-risk HPV type (29).
- The absence of endocervical cells or a transformation zone component on the cervical cytology sample may reflect that the transformation zone was not well sampled. This finding is common in pregnant women and in postmenopausal women in whom the transformation zone has receded onto the canal. Data conflict as to whether the lack of these cells is associated with an increase in squamous intraepithelial lesions. Women with this finding whose recent cervical cytology test results have been normal without intervening findings of ASC-US or worse may be monitored by repeat cervical cytology screening in 1 year. Others, including those with incompletely evaluated abnormal test results, incompletely visualized cervix, immunocompromised status, and poor prior screening, should have repeat cervical cytology screening within 6 months. Pregnant women lacking endocervical cells or transformation zone component should have repeat cervical cytology screening postpartum (30).

## Natural History of Cervical Neoplasia

Infection with HPV is a necessary factor in the development of cervical neoplasia; however, most HPV-infected women will not develop significant cervical abnormalities (7, 29, 31–33). The infection is easily transmitted during sexual intercourse. Most women, especially

younger women, have an effective immune response that clears the infection or reduces the viral load to undetectable levels in an average of 8–24 months (32, 34–36). Factors that determine which HPV infections will develop into squamous intraepithelial lesions have been poorly identified. Cigarette smoking may be a co-factor, and a compromised immune system appears to play a role in some women (7, 29, 32).

Despite decades of study, the natural history of cervical intraepithelial lesions is still not completely understood. The once widely held concept that low-grade lesions are necessary precursors to the high-grade lesions that, in turn, may progress to invasive cancer has been questioned as the sole pathogenesis (32, 33, 37). It has been observed, for example, that many women present with CIN 2 or CIN 3 without prior CIN 1 lesions. Foci of CIN 1 and CIN 3 with different HPV types have been reported in the same cervical lesion, which raises the possibility that concomitant development of different grades of CIN may occur (37). A few cases of invasive cancer of the cervix have been reported despite continuous and appropriate screening.

Multiple longitudinal studies have attempted to document rates of "progression" and "regression" of CIN. A review of the literature since 1950 reported that 57% of patients with CIN 1 and 32% with CIN 3 undergo spontaneous regression (38). However, the same review reported that 1.7% of all patients with CIN of any grade progress to invasive cancer, ranging from 1% for CIN 1 to more than 12% for CIN 3. Progression from CIN 3 to invasive cancer has been reported in up to 36% of cases (29). A review of 30 years of the literature calculated pooled rates of progression from LSIL and HSIL to invasive cancer to be 0.15% and 1.44%, respectively, over 24 months (39). In that analysis, 47% of LSIL and 35% of HSIL regressed to normal during the 2-year observation period. Conclusions from reviews of multiple natural history studies must be interpreted with caution. The studies included in these reviews used varying diagnostic criteria (biopsy or cytology or both), populations, and duration of follow-up. Moreover, they did not account for the poor reproducibility inherent in both cytologic and histologic diagnoses (14).

# Clinical Considerations and Recommendations

### ▶ *When should screening begin?*

Cervical neoplasia develops in susceptible individuals in response to a sexually transmitted infection with a high-risk type of HPV (28, 29, 31, 40). The cervix is especially vulnerable to this infection during adolescence when squamous metaplasia is most active. Human papillomavirus infections are commonly acquired by young women (34, 35), but, in most, they are cleared by the immune system within 1–2 years without producing neoplastic changes. The risk of neoplastic transformation increases in those women whose infections persist (35, 41). Most cervical squamous intraepithelial lesions do not progress to cervical cancer (29, 38, 39). The small proportion of women who do develop invasive squamous cancer generally do so over many years, and the transition from CIN to cancer takes longer in younger women (29). Cervical cancer screening in adolescents within the first 3 years after initiation of sexual intercourse is not likely to result in the identification of HSIL or cancer. In addition, earlier onset of screening may increase anxiety, morbidity, and expense from increased follow-up procedures. Furthermore, squamous cell cervical cancer is exceedingly rare in the first two decades of life (4). Therefore, it seems reasonable to begin cervical cancer screening approximately 3 years after initiation of sexual intercourse, but no later than age 21 years. Recognizing the time course in the progression of CIN and the unpredictable nature of follow-up in younger women, cytologic screening may be initiated earlier at the discretion of the clinician.

### ▶ *What is the optimal frequency of cervical cytology screening?*

The optimal number of negative cervical cytology test results needed to reduce the false-negative rate to a minimum has not been demonstrated (3, 42). Several studies have shown that in an organized program of cervical cancer screening, annual cytology examinations offer little advantage over screening performed at 2- or 3-year intervals (43–45). These studies showed minimal difference in the acquisition of cervical cancer or HSIL at screening intervals of 1, 2, or 3 years in women who had at least one prior normal screening result and who were enrolled in health care programs that provided and monitored cervical cytology screening.

Several practical considerations must be examined before biennial or triennial screening can be adopted as a national standard. Published studies have assumed a program of cervical cancer screening and follow-up. In the current U.S. practice climate, a woman's care provider may change frequently, as employment and insurance carriers change. Consequently, the physician may be unable to determine a woman's screening history—ie, the date of her last cervical cytology test, frequency and results of her prior tests, or prior abnormal test results and their management. Patients are frequently inaccurate

in recalling the timing and results of recent screening, more often underestimating the time elapsed and incorrectly recalling abnormal results as normal (46–49). In addition, the high false-negative rate of cytology screening remains a concern, as does the relatively poor reproducibility inherent in cervical cytology (14). Performing multiple screening tests at regular intervals remains the best way to ensure existing premalignant cervical disease has been ruled out before extending the interval between screenings. This is especially true for young women who have a high likelihood of acquiring a high-risk type of HPV (34, 35).

There is room to individualize screening frequency in a woman who is known to have a negative history and several recent annual cervical cytology tests. The chance such a patient will develop CIN 2 or CIN 3 is extremely low, and screening at intervals of every 2–3 years is a safe, cost-effective approach. It is important to educate patients about the nature of cervical cytology, its limitations, and the rationale for prolonging the screening interval. Physicians also should inform their patients that annual gynecologic examinations are still appropriate even if cervical cytology is not performed at each visit.

Annual cytology screening should be recommended for women younger than 30 years. Women aged 30 years and older who have had three consecutive cervical cytology test results that are negative for intraepithelial lesions and malignancy may be screened every 2–3 years. Certain risk factors have been associated with CIN in observational studies; women with any of the following risk factors may require more frequent cervical cytology screening:

- Women who are infected with human immunodeficiency virus (HIV)
- Women who are immunosuppressed (such as those who have received renal transplants)
- Women who were exposed to diethylstilbestrol in utero

Women infected with HIV should have cervical cytology screening twice in the first year after diagnosis and annually thereafter (22, 50). Women treated in the past for CIN 2 or CIN 3 or cancer remain at risk for persistent or recurrent disease and should continue to be screened annually (51, 52). Women with previously normal cervical cytology results whose most recent cervical cytology sample lacked endocervical cells or transformation zone components and those with partly obscuring red or white blood cells should be rescreened in 1 year (30).

### ▶ *When is it appropriate to recommend discontinuing screening?*

Although the rate of new-onset cervical cancer plateaus at age 65 years in U.S. women in general, among certain subsets—most notably, African-American women—the incidence increases steadily across the age spectrum (2, 7). Most new cases are seen in unscreened or infrequently screened women. It is difficult to set an upper age limit for cervical cancer screening. Postmenopausal women screened within the prior 2–3 years have been shown to have a very low risk of developing abnormal cytology (53, 54).

The American Cancer Society recommends that screening may be discontinued at age 70 years in low-risk women (5). The U.S. Preventive Services Task Force has set age 65 years as the upper limit of screening (55). An older woman who is sexually active and has had multiple partners may be at lower risk for new-onset CIN than a younger woman because of her decreased rate of metaplasia and less accessible transformation zone; however, she is still at some risk for acquiring HPV and CIN. A woman with a previous history of abnormal cytology also is at risk; women in both of these categories should continue to have routine cervical cytology examinations.

Primary vaginal cancer represents a very small fraction of gynecologic malignancies (5). The vaginal mucosa lacks a transformation zone. Women who have had a hysterectomy and have no history of CIN are at very low risk of developing vaginal cancer. Cytologic screening in this group has a low rate of diagnosing an abnormality and a very low positive predictive value. In a study of 9,610 Pap tests performed among women who had a hysterectomy for benign indications an average of 19 years previously, only 1.1% had cytologic abnormalities. Biopsies of these women showed no vaginal intraepithelial neoplasia grade 3 or cancer (54). Continued routine vaginal cytology examinations in such women are not cost-effective and may cause anxiety and overtreatment. Thus, women who have had a total hysterectomy and have no prior history of high-grade CIN may discontinue screening.

Women who had high-grade cervical intraepithelial lesions before hysterectomy can develop recurrent intraepithelial neoplasia or carcinoma at the vaginal cuff several years postoperatively (56, 57). Women who have had a hysterectomy and have a history of CIN 2 or CIN 3—or in whom a negative history cannot be documented—should continue to be screened annually until three consecutive satisfactory negative cervical cytology results are obtained. Routine screening may then be discontinued. A woman who has had three consecutive satisfactory negative examinations following treatment for

CIN 2 or CIN 3 before she had a hysterectomy also may discontinue screening.

Before considering whether a woman who has had a hysterectomy should continue regular cytology screening, the provider should be sure the woman's cervical cytology history is accurate. The history should confirm that she had benign findings at the time of hysterectomy and that her cervix was removed as part of the hysterectomy. However, when a woman's past cervical cytology and surgical history are not available to the physician, screening recommendations may need to be modified.

### ▶ *How do the various methods of cervical cytology compare in terms of effectiveness?*

Cervical cytology is the basis of the most effective and cost-effective cancer screening program ever implemented. Cervical cytology, however, is not a diagnostic test (1). The sensitivity of cervical cytology recently has been reported to be lower than the previously estimated 60–85% (29). A recent comprehensive review of the literature evaluated the accuracy of screening cervical cytology in screened populations with a low prevalence of cervical disease (42). For inclusion in this review, a study was required to have sufficient verification of both negative and positive cervical cytology to calculate sensitivity and specificity. Only three studies met the inclusion criteria to evaluate the standard preparation for cervical cytology at a threshold of ASCUS or worse and estimate its ability to diagnose CIN 1 or more severe lesions. At these thresholds, the standard preparation had a sensitivity of 51% and a specificity of 98%. The authors also calculated performance measures based on nine studies that permitted evaluation at the cytologic threshold of LSIL. The mean sensitivity was 47%, and specificity was 95% (58).

Studies comparing the accuracy of liquid-based thin-layer cervical cytology with the standard preparation have used 1 of 2 study designs. The split sample design prepares the specimen by first placing cells on a glass slide for a standard preparation, then suspending the remaining cells in liquid medium for liquid-based cytology. This design has the potential to falsely decrease the sensitivity of the liquid-based preparation. The direct-to-vial technique, however, prepares the entire specimen for liquid-based cytology but compares a screened population with historic controls. Although most studies have included confirmation of positive test results with colposcopy and biopsy, which allows an estimate of sensitivity, few have used sufficient verification of negative cervical cytology to determine specificity. With both study designs, liquid-based cytology diagnosed from 36% to more than 200% more cases of LSIL and from 26% to 103% more cases of HSIL than the conventional method (59–63). True-positive rates documented with biopsy were improved with the use of liquid-based cytology in some but not all studies (60–64).

Although liquid-based thin-layer cervical cytology appears to have increased sensitivity for detecting cancer precursor lesions over the conventional method, the degree to which sensitivity is increased is unknown. Equally important, the difference in specificity between the liquid-based and conventional tests has not been determined. Although an increase in sensitivity will permit earlier detection of cancer precursor lesions, any decrease in specificity can result in increased cost and morbidity from false-positive diagnoses. The conventional test, although disappointing in its documented sensitivity, has proved effective in reducing cervical cancer rates where screening programs exist. Liquid-based products can be effective in population screening as well. Their reported increase in sensitivity may make them especially useful in women who are screened infrequently. Providers selecting a cervical cytology method should consider the screening history of their patient, the cost of the test, and the possible effects of false-negative or false-positive results.

### ▶ *Is the recommended frequency of screening affected by the method of screening?*

The American Cancer Society recommends that women younger than 30 years undergo cervical cancer screening annually if the conventional method is used or every 2 years if a liquid-based method is used (5). However, there are very limited data to support this approach. The recommendation of biennial cytology using the liquid-based method discounts the possibility of false-negative results, a consideration with both liquid-based and conventional methodologies. Moreover, the increased sensitivity of liquid-based methods over conventional methods is small with studies showing overlapping confidence intervals. According to FDA-required labeling, the ThinPrep technique may be marketed as better able to detect LSIL and HSIL than the conventional Pap test, and the SurePath technique may be marketed as equivalent to the conventional Pap test (17).

### ▶ *When is HPV testing appropriate?*

Although it is estimated that up to 100% of women with histologic CIN 2 or CIN 3 will test positive for a high-risk type of HPV, many women harbor the virus in their lower genital tracts without showing cytologic or histologic changes (31, 32, 34, 40, 65). Currently, only one product, Hybrid Capture II, is FDA-approved for testing for cervical HPV DNA. It assesses exfoliated cervical cells for the presence of 1 or more of 13 high- and inter-

mediate-risk HPV types. Although the test appears to be very sensitive, rare cross-reactivity with low-risk HPV types and HPV types of undetermined significance has been reported. The clinical implications of this finding are unknown (66).

Its utility has been well demonstrated for the primary triage of cervical cytology tests read as ASC-US (23, 67–70). In this setting, high-risk HPV DNA testing has been shown to have a sensitivity ranging from 78% to 96% for the detection of CIN 2 or CIN 3, with rates of referral for colposcopy ranging from 31% to 56%. The use of "reflex" HPV testing has been recommended as a convenient and cost-effective approach to evaluating ASC-US (68, 71, 72). The technique involves collecting a sample for high-risk HPV DNA testing at the same time as cervical cytology screening and evaluating it only if the cytology is read as ASC-US. Reflex HPV testing may be done by testing from residual preservative if liquid-based cytology is used or by performing a separate HPV DNA test at the same time as cervical cytology and storing it for use if ASC-US is the result.

High-risk HPV DNA test results would be expected to be positive when cervical cytology results indicate HSIL, so the test has little utility in this setting. Likewise, up to 83% of women with LSIL diagnosed by cervical cytology have been shown to be positive for high-risk HPV types, thus limiting the usefulness of the test in this setting as well (73). Because HPV is more prevalent in younger women and the rate of CIN 2 and CIN 3 increases with age, it has been suggested that HPV DNA testing might be a more selective test in older women (68). However, stratifying results by age demonstrated only minimal differences in the sensitivity of HPV DNA testing when used as a triage test for ASCUS results (74). The rate of referral to colposcopy decreased with age, however, from 68% in women younger than 29 years to 31% for women aged 29 years and older (74).

Another clinical setting in which HPV DNA testing may be useful is in the secondary triage of women with a cytologic diagnosis of ASC-US, ASC-H, or LSIL in whom colposcopy is negative or biopsy fails to reveal CIN. A protocol of follow-up in 1 year with HPV DNA testing has been suggested as an alternative to repeat cytology in this group, with repeat colposcopy for those with positive test results (71).

### ▶ *When cervical cytology and HPV DNA testing are used together, can women be screened less frequently?*

The FDA has recently approved the combination of cervical cytology and HPV DNA testing for primary screening for cervical cancer for women aged 30 years and older. This new indication for the use of HPV DNA testing was based on information from several large studies (71, 75–78). These studies demonstrated that women aged 30 years and older who had both negative cervical cytology test results and negative high-risk type HPV DNA test results were at extremely low risk of developing CIN 2 or CIN 3 during the next 3–5 years. This risk was much lower than the risk for women who had only cytology and tested negative. Because the FDA approval for the use of HPV DNA as a primary screening modality was based on clinical study data, whether the combination of virus screening and cytology will perform equally well when applied to population-based screening practice is unknown.

Any woman aged 30 years or older who receives negative test results on both cervical cytology screening and HPV DNA testing should be rescreened no more frequently than every 3 years. The combined use of these modalities has been shown to increase sensitivity but also decrease specificity and increase cost. However, it has been estimated that the increase in screening interval will offset the cost of this new screening regimen (79).

It is important to note that the FDA approval for use of this approach is only for the panel of high-risk HPV types. In addition, the combination of cytology and HPV DNA screening should be restricted to women aged 30 years and older because transient HPV infections are common in women younger than 30 years, and a positive test result may lead to unnecessary additional evaluation and treatment. Routine testing using cytology alone remains an acceptable screening plan.

## Summary of Recommendations

***The following recommendations are based on good and consistent scientific evidence (Level A):***

- Annual cervical cytology screening should begin approximately 3 years after initiation of sexual intercourse, but no later than age 21 years.
- Women younger than 30 years should undergo annual cervical cytology screening.
- Women aged 30 years and older who have had three consecutive negative cervical cytology screening test results and who have no history of CIN 2 or CIN 3, are not immunocompromised and are not HIV infected, and were not exposed to diethylstilbestrol in utero may extend the interval between cervical cytology examinations to every 2–3 years.

- Evidence-based data indicate both liquid-based and conventional methods of cervical cytology are acceptable for screening.
- Women who have undergone hysterectomy with removal of the cervix for benign indications and who have no prior history of CIN 2 or CIN 3 or worse may discontinue routine cytology testing.

***The following recommendations are based on limited and inconsistent scientific evidence (Level B):***

- Women previously treated for CIN 2 or CIN 3 who have completed their posttreatment follow-up should be monitored annually until at least three consecutive negative cytology screening results are documented.
- The use of a combination of cervical cytology and HPV DNA screening is appropriate for women aged 30 years and older. If this combination is used, women who receive negative results on both tests should be rescreened no more frequently than every 3 years.
- Women who have undergone hysterectomy with removal of the cervix and have a history of CIN 2 or CIN 3 should continue to be screened annually until three consecutive negative vaginal cytology test results are achieved.

***The following recommendations are based primarily on consensus and expert opinion (Level C):***

- Physicians should consider individualization in determining the time to begin screening, the interval between cervical cytology examinations, the age at which cervical cytology testing is no longer needed, and the testing methodology to be used. In addition to considering risk factors for cervical cancer, the provider ideally should be able to determine the patient's past screening history and reliably monitor the patient in the future.
- Evidence is inconclusive to establish an upper age limit for cervical cancer screening. If screening is discontinued, risk factors should be assessed during the annual examination to determine if reinitiating screening is appropriate.
- Yearly testing using cytology alone remains an acceptable screening plan.
- Regardless of the frequency of cervical cytology screening, women should be counseled that annual examinations, including pelvic examination, are still recommended.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and May 2003. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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## CURRENT ISSUES

*Section Editor: Suzanne M. Selvaggi, M.D.*

# ASC-US and HPV Testing in Women Aged 40 Years and Over

Kathy S. Bruner, M.D., and Diane D. Davey, M.D.*

*High-risk human papillomavirus (HPV) DNA triage is commonly performed for cervical cytology specimens interpreted as atypical squamous cells of undetermined significance (ASC-US), but little is known about testing results in women ≥40 yr of age. The extent to which clinical follow-up after HPV testing reflects the most recent management guidelines is unknown also. Data from 108 patients ≥40 yr of age with concurrent (93 patients) or recent (15 patients) ASC-US interpretations and HPV testing were reviewed. Twenty-five (23.1%) of these patients were positive for high-risk HPV. The HPV⁺ rate was higher in women with a current interpretation of ASC-US (26.9%) compared with those with a previous ASC-US result (0%). Many patients were not managed exactly according to the "2001 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities." The majority (52.6%) of women with HPV⁺ ASC-US did not receive colposcopy in our institution, and 41.3% of women with HPV⁻ ASC-US received follow-up testing within 8 mo. These results show the potential for inadequate evaluation of women with HPV⁺ ASC-US, as well as unnecessary early repeat cytology in HPV⁻ ASC-US patients. Therefore, additional clinician education and reminders to correlate cytology and HPV test results may be warranted to optimize patient care.* Diagn. Cytopathol. 2004;31:358–361.
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*Key Words:* atypical squamous cells; human papillomavirus; management guidelines; cervical cytology; Papanicolaou test; dysplasia

The "2001 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities"[1] recommend reflex human papillomavirus (HPV) DNA testing as the preferred triage for patients with atypical squamous cells of undetermined significance (ASC-US) interpretations on liquid-based cytology. A few studies have looked at the results of HPV DNA testing across age groups, and most indicate that the rate of high-risk HPV positivity decreases with age.[2–4] In fact, Bolick et al. reported that the rate of oncogenic HPV decreases fourfold from age <20 to >50 yr for ASC-US Pap tests.[5] However, many of these studies had small numbers of patients in the >40-yr age group and did not specifically look at the elderly population. The aim of this study was to specifically evaluate the rate of high-risk HPV positivity in women ≥40 yr of age who had a concurrent ASC-US interpretation or an ASC-US interpretation within the last year. We also wanted to evaluate the clinical follow-up of these patients and determine to what extent the clinicians in our medical center are following the most recent management guidelines.

## Materials and Methods

Data were obtained by searching the University of Kentucky Medical Center (UKMC) cytopathology files for women ≥40 yr of age who had HPV testing during the 13-mo period of January 1, 2002 to January 13, 2003. HPV testing was performed on the residual Cytyc ThinPrep liquid vial by the Digene Hybrid Capture II method (Digene Corporation, Gaithersburg, MD). Cases were selected that had a concurrent ASC-US interpretation or an interpretation of ASC-US within the last year. The latter group had concurrent negative cytology exams, but HPV testing was ordered on the basis of the previous ASC-US result. Patients were divided into the following age ranges: 40–49 yr, 50–59 yr, 60–69 yr, and ≥70 yr. Then, these groups were subdivided into those who were negative for high-risk HPV and those who were positive for high-risk HPV. Patients with equivocal HPV results were included in the positive high-risk HPV group. The type of clinical follow-up the patients received was evaluated by searching the UKMC cytopathology and surgical pathology files. This was done to determine if clinicians in our institution are following the "2001 Consensus Guidelines for the Management of Women with Cervical Cytological Abnormalities," which was published in JAMA in April 2002.[1] The types of follow-up received were divided into the following groups: repeat Papanicolaou (Pap) test at 3 mo (±1 mo), repeat Pap test at 6 mo (±2 mo), repeat Pap test at 1 yr (±2 mo), cervical biopsy, and no follow-up to date. The minimum follow-up time was 14 mo. Charts of patients who were

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Table I. Age Groups of Patients

| Age (yr) | Total patients | Current ASC-US | ASC-US within the last year | High-risk HPV$^+$ (%) |
|---|---|---|---|---|
| 40–49 | 64 | 54 | 10 | 13 (20.3%) |
| 50–59 | 32 | 27 | 5 | 6 (18.8%) |
| 60–69 | 11 | 11 | 0 | 6 (54.5%) |
| ≥ 70 | 1 | 1 | 0 | 0 (0%) |
| Total | 108 | 93 | 15 | 25 (23.1%) |

Table II. HPV Results According to Cytology Interpretation

| | High-risk HPV$^+$ (%) | High-risk HPV$^-$ (%) | Total |
|---|---|---|---|
| Current ASC-US | 25 (26.9%) | 68 (73.1%) | 93 |
| ASC-US within last year | 0 (0%) | 15 (100%) | 15 |
| Total | 25 (23.1%) | 83 (76.9%) | 108 |

positive for high-risk HPV but did not have a cervical biopsy were reviewed to determine if these patients had been taken to colposcopy. For patients who had a cervical biopsy, the biopsy slides were pulled and reviewed. This study was approved by the University of Kentucky Institutional Review Board.

## Results

A total of 108 women who were ≥40 yr of age with ASC-US and HPV testing were identified. Of these, 93 patients had a current ASC-US interpretation and 15 patients had an interpretation of ASC-US within the last year (Table I). The largest number of patients was in the 40- to 49-yr age group. In the older age groups, all women were tested on the basis of a current ASC-US result (Table I).

Of the 108 total cases, 25 (23.1%) cases were positive for high-risk HPV and 83 (76.9%) cases were negative for high-risk HPV (Table II). Of the 93 patients with a concurrent ASC-US result, 25 (26.9%) patients were positive for high-risk HPV. All of the 15 patients with a previous ASC-US result within the last year were negative for high-risk HPV.

Some variation in HPV results was seen according to age group. In the 40- to 49-yr age group, 20.3% of cases was positive for high-risk HPV (Table I). Of those with a current ASC-US result, 24.1% were positive for high-risk HPV (Table III). The numbers were similar for the 50- to 59-yr age group, but the rate of HPV positivity was higher for the 60- to 69-yr age group with 54.5% of the ASC-US patients positive. The single woman >70 yr old was negative for high-risk HPV.

The 25 HPV$^+$ ASC-US patients should have been referred for colposcopic evaluation according to the 2001 Consensus Guidelines.[1] Of the 25 patients, 6 (24.0%) patients had their diagnosis and HPV testing before the 2001 Consensus Guidelines were published and 19 (76.0%) patients had their diagnosis and HPV testing after the guidelines were published. Of the 19 cases diagnosed and tested after the guidelines were published, 2 (10.5%) patients had colposcopy performed concurrently with their HPV$^+$ ASC-US results based on a prior abnormal Pap test; these patients then had follow-up Pap tests at 1 yr. Of the remaining 17 women, 1 (5.3%) patient had a repeat Pap test and concurrent biopsy at 1 mo, 1 (5.3%) patient had colposcopy and repeat Pap test at 3 mo with no biopsy, 5 (26.3%) patients had a cervical biopsy at 3 mo, 4 (21.1%) patients had only a repeat Pap test at 3 mo, 2 (10.5%) patients had a repeat Pap test at 6 mo, 2 (10.5%) patients had a repeat Pap test at 1 yr, and 2 (10.5%) patients have had no follow-up to date. Therefore, only 9 of these 19 (47.4%) patients received follow-up according to the guidelines. Eight (42.1%) patients had repeat Pap testing alone. If only the patients who received some sort of follow-up to date are considered, the number who received proper follow-up increases to 52.9%. Of those six patients who had a cervical biopsy, four patients had mild dysplasia, one patient had mild to moderate dysplasia, and one patient had no evidence of dysplasia. The patient with no evidence of dysplasia on biopsy had a repeat Pap test 2 mo later, which was negative.

Table III. HPV Status of Women With Current ASC-US Result

| Age (yr) | High-risk HPV$^+$ (%) | High-risk HPV$^-$ (%) | Total |
|---|---|---|---|
| 40–49 | 13 (24.1%) | 41 (75.9%) | 54 |
| 50–59 | 6 (22.2%) | 21 (77.8%) | 27 |
| 60–69 | 6 (54.5%) | 5 (45.5%) | 11 |
| ≥70 | 0 (0%) | 1 (100%) | 1 |
| Total | 25 (26.9%) | 68 (73.1%) | 93 |

The 83 patients who had a current ASC-US or ASC-US within the last year who were negative for high-risk HPV should have been followed with repeat cytological testing at 12 mo according to the 2001 Consensus Guidelines.[1] Of the 83 patients, 19 (22.9%) patients had their diagnosis and HPV testing before the 2001 Consensus Guidelines were published and 64 (77.1%) patients had their diagnosis and HPV testing after the guidelines were published. One of the latter patients had a negative history, but concern for a high-grade lesion was noted in the report and colposcopy was suggested regardless of the negative HPV result; the follow-up biopsy showed mild dysplasia. Of the remaining 63 cases diagnosed and tested after the guidelines were published, 11 (17.5%) patients had a repeat Pap test at 3 mo, 15 (23.8%) patients had a repeat Pap test at 6 mo, 15 (23.8%) patients had a repeat Pap test at 1 yr, 1 (1.6%) patients had a cervical biopsy at 3 mo, and 19 (30.1%) patients have had no follow-up to date. Two (3.2%) patients had hysterectomies for benign reasons after HPV testing. Only 15 of these 63 (23.8%) patients received follow-up exactly according to the guidelines. If only patients who received some sort of follow-up to date are considered and the hysterectomy patients are excluded, the number who

received proper follow-up increases to only 35.7%. The patient with a biopsy at 3 mo had a remote history of mild dysplasia; the follow-up biopsy was negative, but there was no evidence of transformation zone.

## Discussion

The largest study to date to look at HPV DNA testing as a triage for patients with ASC-US was the ASC-US/Low-Grade Squamous Intraepithelial Lesion Triage Study (ALTS). The patients enrolled in this study were predominantly a younger population with a median age of 29 yr. Nevertheless, this study did show that the rate of HPV positivity appears to decrease with age. Among women who were ≥29 yr of age, only 31.2% were positive for high-risk HPV compared with 65.2% in those aged 23–28 yr and 71% in those aged 18–22 yr. The total positive rate for all ages was 54%.[6]

Our study, which focuses on an older population with a median age of 47 yr, showed somewhat similar rates of HPV positivity. In our study, for all women ≥40 yr of age, the rate of high-risk HPV positivity was 23.1%. For women aged 40–49 yr, the rate was 20.3% and decreased to 18.8% for women aged 50–59 yr. The rate appeared to increase for the 60- to 69-yr age group; however, these numbers may be biased by small sample sizes in this age range. As expected, the $HPV^+$ rates were higher in women with a current interpretation of ASC-US (26.9%) compared with those with a previous ASC-US result (0%). For comparison, the rate of $HPV^+$ ASC-US for all patients in our laboratory averages 45%.

ALTS, as well as our study, evaluated HPV DNA testing as a triage for ASC-US. If HPV DNA testing is done in women ≥30 yr old as a primary screening modality, as included by ACOG in their August 2003 screening guidelines,[7] the prevalence of HPV positivity would be even lower than when done for triage.[8–10] Kulasingam et al. found that at least 20% of <25 yr old were $HPV^+$, and women ≥35 yr of age had only about a 6% positive rate.[9] Similarly, Petry et al. detected HPV in only 6.4% of women who were >29 yr old in a routine screening population in Germany.[10]

Our study had few women with squamous intraepithelial lesion (SIL) on biopsy, but other studies have confirmed that HPV testing has high sensitivity in detecting high-grade lesions and carcinoma.[11] Given the high sensitivity and negative predictive value, HPV testing clearly is helpful as a triage test in older women. Pap tests in this age group may be problematic to interpret, especially given the difficulty in distinguishing hormonal changes and postmenopausal atypia from SIL or cancer-related abnormalities.[12] Most of these conditions are characterized by nuclear enlargement with minimal nuclear hyperchromasia, and this can lead to an increased proportion of ASC-US to SIL cases in this age group. Also, these older women are less likely to acquire a transient HPV infection. For all of these reasons, the proportion of ASC-US cases positive for HPV is likely to be lower than in younger age groups.

The "2001 Consensus Guidelines for the Management of Women with Cervical Cytologic Abnormalities" recommend reflex HPV DNA testing as the preferred triage for patients with ASC-US results on liquid-based cytology.[1] The guidelines then go on to recommend colposcopic evaluation for those patients who are positive for high-risk HPV and repeat cytological testing at 12 mo for those patients who are negative for high-risk HPV. These guidelines were published in April 2002; however, they are not always followed in our institution. At our medical center, only 47.4% of patients with $HPV^+$ ASC-US received follow-up according to the guidelines, and only 23.8% of women with $HPV^-$ ASC-US received the indicated follow-up. Our study identified problems both with potential inadequate evaluation, which could lead to failure of early detection, and with too frequent repeat testing, which increases health care costs and patient anxiety. Of the patients who were positive for high-risk HPV, 42.1% received a repeat Pap test only rather than being taken for colposcopy. Of the patients who were negative for high-risk HPV, many of them (41.3%) received a repeat Pap test too soon and several did not receive a 12-mo repeat. There may be specific reasons for some patients to receive a Pap test earlier than 12 mo, but it is unlikely that most patients had such indications. For those women who did not receive colposcopy for a positive HPV test, follow-up and treatment at another institution can not be entirely excluded.

The results of this study suggest that additional clinician education may be useful in promoting optimal patient follow-up according to accepted guidelines. Clinicians in our community have readily accepted the concept of HPV triage testing for ASC-US, but many do not understand or choose not to follow accepted guidelines. Our laboratory provides the American Society for Colposcopy and Cervical Pathology (ASCCP) web site in all of the reports with epithelial abnormalities and alerts clinicians to correlate ASC-US results with HPV testing results. Newsletters also are sent to providers periodically, which explain the guidelines and provide references. However, a single report giving both cytology and HPV testing results and a follow-up recommendation is not given. Such a unified report might be ideal in promoting optimal patient follow-up, but it is difficult to manage in laboratories that send out their HPV testing. It is likely that management will improve over time, as clinicians are educated from a variety of resources. The Kentucky Cancer Program has just offered a free monograph on cervical cytology testing and follow-up to all pertinent health providers,[13] and this publication conforms to the ASCCP guidelines.[1] Our study suggests that health care systems will find it useful to monitor all phases of abnormal

cytology follow-up to find areas to educate providers and optimize patient care.

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# Screening for Cervical Cancer and Initial Treatment of Patients With Abnormal Results From Papanicolaou Testing

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**New techniques for cervical cancer screening and a better understanding of the natural history of human papillomavirus (HPV) and cervical neoplasia have inspired a quest for more rational screening strategies for cervical cancer. Often, screening intervals for women older than 30 years can be expanded safely to every 3 years, and experts now agree that screening may cease after hysterectomy and in elderly women (provided certain criteria have been met). Liquid-based cytology produces more satisfactory specimens than conventional testing and offers the valuable option of treating atypical squamous cells of undetermined significance by "reflex" testing for high-risk types of HPV on the original specimen. Testing for HPV as an adjunct to cervical cytology for primary screening is now considered reasonable for many women older than 30 years.**

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**ACS = American Cancer Society; AIS = adenocarcinoma in situ; ASCUS = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; DES = diethylstilbestrol; HIV = human immunodeficiency virus; HPV = human papillomavirus; LBC = liquid-based cytology; LSIL = low-grade squamous intraepithelial lesion; USPSTF = US Preventive Services Task Force**

In recent years, the array of options used in screening for cervical cancer has been expanded substantially by the development of new technologies such as liquid-based cytology (LBC) and by testing for human papillomavirus (HPV). Also, empirical data about the natural history of HPV and the effect of various strategies for screening and triage of abnormal cytology results have allowed for robust scrutiny of evidence-based screening algorithms. These changes have resulted in several organizations substantially revising their prior screening guidelines for cervical cancer.[1-4]

## EPIDEMIOLOGY OF CERVICAL CANCER

Cervical cancer mortality has decreased substantially by the detection of precursor lesions and earlier-stage cancers by means of Papanicolaou testing. However, invasive cervical cancer remains the cause of death for almost 4000 women each year in the United States, with most cases occurring in unscreened (and suboptimally screened) women. Virtually all cases of squamous cell cervical cancer arise in the context of prior infection with a high-risk type of HPV (ie, one known to increase the chance of cervical neoplasia). Cervical HPV infection is acquired sexually. The peak incidence and prevalence of HPV infection occur in women younger than 25 years, but most infections (70%-80%) in younger women are transient and do not progress to cervical neoplasia. When infection and cervical abnormalities progress, the vast majority do so in an orderly fashion from less severe to more severe lesions before transitioning to an invasive cancer. Glandular lesions may be an important exception to this rule. Reliable early detection of cervical adenocarcinoma or the precursor lesion, adenocarcinoma in situ (AIS), remains a challenge. Because glandular lesions follow a less predictable clinical course and because the sensitivity for detecting glandular lesions is believed to be decreased compared with squamous lesions, all interpretations of Papanicolaou test results suggesting a glandular cell abnormality require meticulous and cautious follow-up.

Behavioral risk factors for squamous cell cervical cancer include earlier age at onset of sexual intercourse and larger number of lifetime partners. Cigarette smoking is the most important nonsexual risk behavior, independently increasing the risk 2- to 4-fold in several studies.

## INITIATION AND FREQUENCY OF SCREENING

Screening is defined as testing of a healthy individual. It is important to remember that the following discussion should not be generalized to the evaluation of a patient with signs or symptoms of cervical disease or to the follow-up of a woman with prior abnormal results from Papanicolaou testing. Screening recommendations attempt to balance the potential for good (prevention of cancer) against the potential for harm, in this case needless worry, expense, or intervention.

Both the American Cancer Society (ACS) and the US Preventive Services Task Force (USPSTF) recommend that all women begin annual Papanicolaou testing approximately 3 years after onset of sexual activity or at age 21 years (whichever occurs first).[1,2] Although screening women who have never been sexually active has little value, this recommendation is based on the generally high prevalence of sexual activity by that age and on concerns that clinicians may not always obtain accurate sexual histories.

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A question-and-answer section appears at the end of this article.

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The standard recommendation for initial screening has been to perform conventional Papanicolaou testing every year until age 30 years. After 3 consecutive years of normal results and no dysplasia within the past 5 years, women may undergo less frequent screening at the discretion of the physician and the patient. Screening should be performed at least every 3 years. Papanicolaou test results described as "satisfactory but limited by lack of endocervical cells, obscuring inflammation, or blood" are generally followed up in 1 year.

Women with atypical squamous cells of undetermined significance (ASCUS) or a low-grade squamous intraepithelial lesion (LSIL) whose initial evaluation reveals no dysplasia should be screened again at 6 and 12 months for LSIL or at 12 months for ASCUS, followed by screening every year (or every 2 years if using LBC and following ACS guidelines) until 5 years from the last abnormal result. Women with a history of higher-grade lesions are considered under "surveillance" rather than being "screened" and should be monitored at shorter intervals under the guidance of a gynecologist.

The most recent ACS guidelines recommend different screening intervals (previously noted) for the conventional and the LBC Papanicolaou tests. The increased sensitivity of LBC methods results in improved detection of all categories of dysplasia, with potential for increased detection of lesions of questionable clinical significance (such as a transient low-grade dysplasia). The ACS guidelines recommend expanding the testing interval to every 2 years when using LBC screening for those women who would otherwise receive annual testing by the traditional method. With either method, screening should be performed at least every 3 years. Thus, when using LBC, a woman initially would be screened every 2 years and, after 3 consecutive normal test results (over 6 years), she would continue to be screened at 2- to 3-year intervals. (However, the recommendation for different testing intervals based on conventional vs LBC preparation of the slides has not yet been accepted universally.[2,3])

Women who are at high risk of cervical cancer should be screened more frequently. Specifically, immunocompromised women (including those with human immunodeficiency virus [HIV] or lymphoproliferative disorders or those taking long-term corticosteroids or organ transplant immunosuppression) generally should continue annual screening, as should women with intrauterine exposure to diethylstilbestrol (DES). Women with a history of recent cervical intraepithelial neoplasia (CIN) 2 or 3 or any prior diagnosis of invasive cervical cancer generally continue surveillance (no longer screening) Papanicolaou testing annually (or more frequently in some settings). Those with a history of CIN 2 or 3 may stop screening when criteria listed in the "When to Stop Screening" section are met.

## WHEN TO STOP SCREENING

Women older than 65 years (USPSTF recommendation) or 70 years (ACS recommendation) who are not at high risk may safely stop screening if they have had 3 or more documented, technically satisfactory normal results from Papanicolaou testing *and* have had no abnormal results within the past 10 years.

There are exceptions to these guidelines for women at higher risk. Women with a history of CIN 2 or 3 should continue screening regardless of age or history of hysterectomy until they have had 3 or more technically satisfactory normal results from Papanicolaou testing *and* have had no abnormal results within the past 10 years. Women with a history of cervical cancer or in utero DES exposure should continue screening indefinitely for as long as they are in reasonably good health, regardless of age or history of hysterectomy. Immunosuppressed women (including those taking corticosteroids or those infected with HIV) should continue screening indefinitely for as long as they are in reasonably good health, regardless of age, but may stop after hysterectomy if this would otherwise be appropriate (see next paragraph).

Should women be screened after hysterectomy? Women who have undergone total hysterectomy for benign disease and have documented surgical pathology showing normal cervical epithelium or at most low-grade dysplasia (CIN 1) and who were screened appropriately before hysterectomy need not be screened. This recommendation is based on the extremely low yield of significant disease and the potential harms of false-positive results in this population.[5] Women with a history of CIN 2 or 3 (or for whom prior pathology reports are unavailable) should continue screening until the criteria (discussed previously) associated with 3 consecutive normal results from Papanicolaou testing within 10 years have been met. Women with a history of cervical cancer or a history of in utero DES exposure should continue screening indefinitely. For various reasons, cervix-sparing hysterectomy (supracervical hysterectomy or subtotal hysterectomy) is once again in vogue in certain regions in the United States. Women who have undergone subtotal hysterectomy should continue (or discontinue) screening as would women in their risk group who have not undergone a hysterectomy.

## LIQUID-BASED CYTOLOGY

Options for Papanicolaou testing now include conventional (slide smear) or LBC analysis. Recommendations increasingly favor the LBC methods for reasons discussed subsequently.

With LBC, the sample is suspended in a liquid that is centrifuged, and then cells are recovered from the centri-

fuged sediment. This technique provides a cleaner, more accurate preparation for microscopic analysis than conventional Papanicolaou testing for various reasons (including improved transfer of cellular material, more uniform distribution on the slide, a decrease in obscuring background factors, and less air-drying artifact). In most studies, LBC preparation has a slightly higher sensitivity than does preparation based on the conventional method, with approximately equivalent specificity. The LBC preparation also has been found to result in a higher rate of "satisfactory" test results.[6,7] The ACS considered the higher sensitivity (more frequent detection of actual disease), increased cost, and chance of increased harm (patient anxiety and possible treatment of clinically insignificant lesions) with LBC Papanicolaou tests when formulating their recommendation to increase the screening interval for LBC methods to every 2 years.

Another advantage of LBC is the ability to perform HPV testing on the same sample when indicated (eg, for ASCUS).

It is important to note that optimal specimen collection for LBC Papanicolaou testing requires use of a plastic rather than a wooden spatula. The endocervix is sampled with the usual brush instrument or with a plastic spatula that incorporates an endocervical "broom." The collection device(s) must be swirled in the collection medium for the recommended 30 seconds and then discarded or the ends of the collection devices are cut or broken off and submitted in the collection medium, depending on manufacturer's directions. Physicians should review instructions for the particular test used in their own clinical settings.

## HPV DNA TESTING

Testing for high-risk types of HPV can help in the treatment of women with ASCUS by identifying those at higher risk of harboring or developing neoplasia. Most cytology laboratories are set up to allow this test to be performed on the same specimen already collected for LBC testing. This "reflex" testing is not available with traditional Papanicolaou testing. (Note that the types of HPV that cause genital warts are associated with only a minimal increase in cervical cancer risk and that testing for these low-risk types has no role in cervical cancer screening.) Currently, only 1 Food and Drug Administration–approved HPV test is available. The Hybrid Capture II assay (Digene Diagnostics, Gaithersburg, Md) tests for the 13 high-risk HPV types most commonly associated with high-grade dysplasia and cancer.

Recently, the Food and Drug Administration approved the use of HPV DNA testing as an adjunct to cytology for primary cervical cancer screening. This decision was based on several large studies that indicated increased sensitivity for detection of high-grade lesions compared with screening with cytology alone. Guidelines from both the ACS and the American College of Obstetricians and Gynecologists have noted this as a reasonable alternative screening strategy when used only in women aged 30 years or older and no more frequently than every 3 years. These restrictions take advantage of the extremely high negative predictive value (99%-100%) of combined cytology and HPV DNA testing for high-grade lesions while decreasing the costs and anxiety associated with overdiagnosis and overtreatment of women with transient HPV infections of no clinical consequence.[8]

The introduction of HPV testing in primary screening requires careful education of the patient and clinician. Much confusion in this early phase of implementation has centered on 2 misperceptions. First, HPV infection is common in all sexually active women, even in the absence of classic epidemiological risk factors for cervical disease. Women with positive HPV test results must be helped to understand that this is not an indicator of infidelity. Also, positive test results for high-risk HPV types do not mean that a cytologic abnormality is present. It is possible, and indeed common, to have high-risk HPV infection with no detectable cytologic abnormality. Such women should be regarded as being at higher risk of dysplasia and cancer, but dysplasia is not an inevitable consequence of HPV infection.

## TREATMENT OF PATIENTS WITH ABNORMAL RESULTS FROM PAPANICOLAOU TESTING

To more effectively communicate results to clinicians, the National Cancer Institute issued a revision in 2001 of the "Bethesda System" terminology used to report cervical cytology.[9] The major types of intraepithelial lesions in that classification are listed in Table 1. A consensus conference also was convened that year to develop evidence-based guidelines for treating women with abnormal results from Papanicolaou testing.[4] These guidelines form the basis of the following discussion, and the consensus conference recommendations are summarized in Table 2.

### Specimen Adequacy

Cervical cytology reports often comment on limitations of the specimen. Fortunately, guidelines for these situations have been published.[10] Patients whose Papanicolaou test results are interpreted as "Negative for intraepithelial lesion but lacking endocervical or transformation zone component" generally have been found to be at no higher risk than those with the components present. Recheck in 1 year is advised. Also, women whose Papanicolaou test results are interpreted as "Negative but partially obscured by... (blood, inflammation, air drying artifact)" generally have been found to be at no increased risk. Again, recheck in 1 year is advised. (Note that LBC substantially decreases the frequency of this problem.) Women whose test results are

TABLE 1. Terminology Used in Reporting Cervical Cytology*

| Abbreviation | Expansion | Risk and follow-up† |
|---|---|---|
| AGC | Atypical glandular cells | Very high risk that cervical or endometrial cancer or precursor lesion is present |
| AIS | Adenocarcinoma in situ | Very high risk that cervical cancer or precursor lesion is present |
| ASC-H | Atypical squamous cells, cannot exclude HSIL | Higher risk; requires colposcopy |
| ASCUS | Atypical squamous cells of undetermined significance | Very low risk that cervical cancer is present, but requires follow-up |
| CIN | Cervical intraepithelial neoplasia | *Not* a Pap test result, but rather a histologic finding on biopsy; precancerous lesion of the cervix; grades range from 1 (low dysplasia) to 3 (severe dysplasia) |
| HSIL | High-grade squamous intraepithelial lesion | Rare, but high risk; requires vigilant follow-up |
| LSIL | Low-grade squamous intraepithelial lesion | Low to moderate risk; requires follow-up in most patients |

*Pap = Papanicolaou test; the Pap test is a method of detecting cervical cytopathologic abnormalities that may suggest cancer or cancer precursor lesions.
†Based on abnormal Pap test results.

interpreted as "Unsatisfactory for evaluation because of... [any reason]" are more likely than average to have a high-grade lesion present, and recheck in less than 6 months (preferably 2-4 months) is advised.

### Atypical Squamous Cells of Undetermined Significance

The most common abnormality on Papanicolaou testing is ASCUS. Approximately 5% of patients with ASCUS results will harbor CIN 2 or 3 (moderate to severe dysplasia) on biopsy, whereas 0.1% to 0.2% will have invasive cervical cancer. Thus, some type of follow-up or further testing is appropriate but need not be aggressive. Traditionally, options were limited to immediate colposcopy or repetition of Papanicolaou testing at 4- to 6-month intervals until 2 consecutive normal results were obtained, with immediate colposcopy if ASCUS reappeared (or more serious results appeared) on any subsequent tests. Immediate colposcopy has the advantage of prompt confirmation of the presence or absence of disease. However, it has the disadvantages of cost, discomfort, and the anxiety associated with being referred for specialty care (with the attendant implications of potential serious disease).

The ability to test for high-risk HPV types offers a third and arguably the best option for treating patients with ASCUS results. With this protocol, women who test positive for high-risk HPV types are referred for colposcopy, whereas those testing negative are advised to undergo screening again in 1 year. This method of triage for results that indicate ASCUS is highly sensitive, with a well-documented negative predictive value of 98% or more.[11] This method is preferable when it can be performed as a reflex test (initially LBC is used so that HPV testing is performed without an additional patient visit when ASCUS results are present).[4] A recent analysis showed that reflex HPV testing is more cost effective than alternative strategies for follow-up of ASCUS results.[12]

In the setting of reflex HPV testing for ASCUS cytology, should a woman infected with a high-risk HPV type ever be tested for HPV again? In young women (in whom HPV infection usually remits spontaneously), repeated HPV testing with subsequent Papanicolaou testing may continue to be useful for interpreting ASCUS results. Repeated HPV testing in older women (in whom the HPV infection is more likely to be chronic) is probably of less value, but a discriminating age cutoff has not been identified.

Postmenopausal women with clinical or cytologic evidence of atrophy who have ASCUS are at lower risk of clinically important neoplasia than are premenopausal women. Although use of reflex testing for HPV generally is preferred in this population as well, a reasonable alternative suggested by some guidelines is to treat with vaginal estrogen for 4 to 6 months and then repeat Papanicolaou testing 1 week after therapy is completed. The Papanicolaou test should be repeated again in 4 to 6 months. If results from both follow-up tests are normal, then routine screening can be resumed. If results are abnormal from either follow-up test, the patient should be referred for colposcopy.[4]

Another exception includes women who are immunosuppressed due to HIV, lymphoproliferative disorder, corticosteroid use, or posttransplantation immunosuppression. All immunosuppressed women with ASCUS results should be referred for colposcopy. In HIV-positive patients, colposcopy should be performed regardless of CD4 count, HIV viral load, or use or nonuse of antiretroviral therapy.

### Other Abnormalities on Papanicolaou Testing

Patients with abnormalities other than ASCUS on Papanicolaou testing should be referred for specialty care. The following brief summary is a supplement to specialty consultation for primary care physicians. (Most of this information is abridged from a report of a 2001 consensus

TABLE 2. **Guidelines for Treating Women With Abnormal Results From Papanicolaou Testing***

| Pathology report | Intermediate considerations | Action |
|---|---|---|
| Normal | | Continue regular screening |
| "Negative for intraepithelial lesion but lacking endocervical or transformation zone component" (or "No endocervical cells identified") | | Recheck in 1 year |
| "Negative but partially obscured by..." | | Recheck in 1 year |
| "Unsatisfactory for evaluation" | | Recheck within 6 months |
| Atypical squamous cells of undetermined significance | | |
| Most patients | Reflex test for high-risk HPV types—test is positive | Colposcopy |
| | Reflex test for high-risk HPV types—test is negative | Recheck in 1 year |
| | Other (less preferred) options | Either colposcopy now or repeat Pap test in 4 months |
| Special patient populations | Immunosuppression (HIV, lymphoproliferative disorder, or pharmacological) | Colposcopy |
| | Postmenopausal with vaginal atrophy | Consider intravaginal estrogen followed by repeated Pap test in 4-6 months (see text for details) |
| Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion | | Colposcopy |
| Low-grade squamous intraepithelial lesion | | Colposcopy |
| High-grade squamous intraepithelial lesion | | Colposcopy with endocervical assessment, aggressive follow-up |
| Atypical glandular cells and adenocarcinoma in situ | | Colposcopy and endocervical curettage, endometrial sampling, aggressive follow-up |

*HIV = human immunodeficiency virus; HPV = human papillomavirus; Pap = Papanicolaou testing.

conference sponsored by the American Society for Colposcopy and Cervical Pathology.[4])

**Low-Grade Squamous Intraepithelial Lesion.** On subsequent cervical biopsy, 15% to 30% of women with LSIL will have CIN 2 or 3. Referral for colposcopy is indicated for all premenopausal patients. Because 83% of women with LSIL test positive for high-risk HPV types anyway, HPV testing is not indicated in this setting. The only exception to this recommendation is that postmenopausal women with LSIL who have evidence of atrophy on examination may be treated in the same way as those with ASCUS.[4]

**Atypical Squamous Cells, Cannot Exclude High-Grade Squamous Intraepithelial Lesion.** The probability of finding CIN 2 or greater on biopsy ranges from 24% to 94% in such patients. Patients should be referred for prompt colposcopy.

**High-Grade Squamous Intraepithelial Lesion.** This cytologic interpretation is uncommon, accounting for only 0.45% of Papanicolaou test results. However, there is a 75% chance of having CIN 2 or 3 on biopsy and a 1% to 2% chance of invasive cancer. Thus, aggressive follow-up with colposcopy and endocervical evaluation is indicated. Because of the high risk of clinically important neoplasia, close follow-up is necessary, even if results from the initial colposcopic evaluation were negative.

**Atypical Glandular Cells and AIS.** This category is associated with a substantially greater risk of cervical neoplasia than ASC or LSIL, with up to 50% of results indicating CIN 2 or 3 on biopsy and 5% to 10% of results revealing AIS or invasive adenocarcinoma. Aggressive treatment is indicated, with immediate referral for colposcopy, endocervical curettage, and endometrial biopsy. This treatment often is followed by further procedures such as cone biopsy and dilation and curettage if the diagnosis remains uncertain.

## SUMMARY

Cervical cancer screening with Papanicolaou testing should begin at age 21 years (or within 3 years after onset of vaginal intercourse, if earlier) and cease after hysterectomy for benign conditions or after age 65 years (USPSTF recommendation) or 70 years (ACS recommendation) in women with adequate recent screening who are not otherwise at high risk of cervical cancer.

The maximum screening interval should be 3 years, with more frequent screening at onset and in high-risk situations (HIV, prior dysplasia, chronic immunosuppression).

Although more expensive, LBC has the advantages of improved sensitivity for LSIL and higher-grade lesions as well as fewer "unsatisfactory" and "obscured by blood/inflammation" readings and provides the ability to perform HPV testing on the same specimen (when indicated).

The use of HPV testing as an adjunct to cervical cytology for screening is an acceptable strategy, as long as it is restricted to women older than 30 years, and combined screening is done no more frequently than every 3 years.

When available, the preferred strategy for management of ASCUS in most situations is reflex HPV testing (high-

risk types only) on the original LBC specimen collected for the Papanicolaou test. When this is unavailable, other options include repeated Papanicolaou testing at 4- to 6-month intervals until 2 consecutive normal results are obtained, immediate colposcopy, and HPV testing at the next Papanicolaou testing.

Women with ASC-H (atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion) and LSIL test interpretations should undergo colposcopy.

Minimal follow-up requirements for women with high-grade squamous intraepithelial lesion, atypical glandular cells, and AIS interpretations include colposcopy and endocervical curettage.

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## Questions About Papanicolaou Test Screening

1. In a 50-year-old woman, which *one* of the following situations would *not* warrant performing Papanicolaou testing more frequently than the routine recommendation of every 3 years?
   a. HIV positive, undergoing treatment, and with normal CD4 count
   b. HIV positive, undergoing treatment, and with undetectable viral load
   c. Rheumatoid arthritis and taking long-term methotrexate and prednisone
   d. History of CIN 2
   e. Smoker with more than 4 lifetime sexual partners

2. Which *one* of the following is *not* an advantage of LBC compared with traditional cytology?
   a. Less artifact on microscopic examination
   b. Higher sensitivity
   c. Higher specificity
   d. More uniform distribution of cells on the slide
   e. Ability to perform testing for HPV on original specimen

3. A 67-year-old woman comes to your office for her annual examination. Seven years previously, results from conventional Papanicolaou testing showed ASCUS on 2 consecutive visits, after which colposcopic biopsy findings were normal. She has had 4 normal results from Papanicolaou testing since that time, the last being 3 years ago. She would like to stop screening if possible. Which *one* of the following is the *most appropriate* course of action?
   a. Discontinue Papanicolaou testing now
   b. Perform Papanicolaou test today, once more in 3 years, and then stop if results from both are normal
   c. Perform Papanicolaou test today, and continue testing every year indefinitely
   d. Perform Papanicolaou test today, and continue testing every 3 years indefinitely
   e. Perform Papanicolaou test today, and continue testing every 3 years until the woman reaches age 75 years

4. A 38-year-old woman undergoes routine Papanicolaou testing, and results show ASCUS. Reflex testing results for HPV high-risk types are negative. Which *one* of the following is the *most appropriate* course of action?
   a. Colposcopy
   b. Perform Papanicolaou test again in 4 months
   c. Perform Papanicolaou test again in 4 months with another test for high-risk types of HPV
   d. Perform Papanicolaou test again in 1 year
   e. Perform Papanicolaou test again in 3 years

5. Results from a conventional Papanicolaou test of a 33-year-old smoker indicate that the specimen was "unsatisfactory for interpretation due to obscuring blood and inflammation." The patient is asymptomatic, and results from multiple prior Papanicolaou tests have been normal, most recently from 3 years previously. Assuming that LBC will be used for the next Papanicolaou test, which *one* of the following is the *most appropriate* next step?
   a. Perform Papanicolaou test within 2 weeks
   b. Perform Papanicolaou test within 4 months
   c. Perform Papanicolaou test in 6 months
   d. Perform Papanicolaou test in 1 year
   e. Perform Papanicolaou test in 3 years

Correct answers: 1. *e*, 2. *c*, 3. *b*, 4. *d*, 5. *b*

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# The Elevated 10-Year Risk of Cervical Precancer and Cancer in Women With Human Papillomavirus (HPV) Type 16 or 18 and the Possible Utility of Type-Specific HPV Testing in Clinical Practice

*Michelle J. Khan, Philip E. Castle, Attila T. Lorincz, Sholom Wacholder, Mark Sherman, David R. Scott, Brenda B. Rush, Andrew G. Glass, Mark Schiffman*

***Background:*** **Human papillomavirus (HPV) types 16 and 18 cause 60%–70% of cervical cancer worldwide, and other HPV types cause virtually all remaining cases. Pooled HPV testing for 13 oncogenic types, including HPV16 and 18, is currently used in clinical practice for triage of equivocal cytology and, in conjunction with Pap tests, is an option for general screening among women 30 years of age and older. It is not clear to what extent individual identification of HPV16 or HPV18 as an adjunct to pooled oncogenic HPV testing might effectively identify women at particularly high risk of cervical cancer or its immediate precursor, cervical intraepithelial neoplasia 3 (CIN3).** ***Methods:*** **From April 1, 1989, to November 2, 1990, a total of 20810 women in the Kaiser Permanente health plan in Portland, OR, enrolled in a cohort study of HPV and cervical neoplasia. Women were tested for 13 oncogenic HPV types by Hybrid Capture 2 (HC2), and those women with a positive HC2 test were tested for HPV16 and 18. Enrollment Pap smear interpretation and HPV test results were linked to histologically confirmed CIN3 and cervical cancer (≥CIN3) occurring during 10 years of cytologic follow-up. We calculated cumulative incidence rates with 95% confidence intervals for each interval up to 122 months using Kaplan–Meier methods.** ***Results:*** **The 10-year cumulative incidence rates of ≥CIN3 were 17.2% (95% confidence interval [CI] = 11.5% to 22.9%) among HPV16+ women and 13.6% (95% CI = 3.6% to 23.7%) among HPV18+ (HPV16−) women, but only 3.0% (95% CI = 1.9% to 4.2%) among HC2+ women negative for HPV16 or HPV18. The 10-year cumulative incidence among HC2− women was 0.8% (95% CI = 0.6% to 1.1%). A subanalysis among women 30 years of age and older with normal cytology at enrollment strengthened the observed risk differences.** ***Conclusions:*** **HPV screening that distinguishes HPV16 and HPV18 from other oncogenic HPV types may identify women at the greatest risk of ≥CIN3 and may permit less aggressive management of other women with oncogenic HPV infections.** **[J Natl Cancer Inst 2005;97:1072–9]**

Infection with human papillomavirus (HPV) causes 95%–100% of all cervical cancer, which is the second most common cancer in women worldwide *(1–3)*. Of about 40 known sexually transmitted HPV types, approximately 15 have been established as oncogenic (high-risk) types in epidemiologic studies *(4–6)*. International case–control studies have demonstrated the approximate proportion of squamous cell cervical carcinoma for which each oncogenic HPV type is responsible: HPV16 causes more than 50% of cancers, HPV18 causes 10%–15%, HPV45 causes approximately 7%, and HPV31 causes approximately 3% *(7,8)*. Other oncogenic HPV types individually cause less than 2% of cervical squamous cell cancer *(5)*. HPV18 also causes more than 35% of cervical adenocarcinomas, which are difficult to detect by current cytologic screening methods *(8)*. HPV16 and 18 are two of the most common HPV types in women without cancer as well *(9)*.

The risk of cervical neoplasia associated with infection by individual HPV types has been examined in cross-sectional and case–control studies, but few studies have examined the prospective risks associated with individual HPV types in the general population. In a prospective cohort of 1075 women 15–19 years old, Woodman et al. *(10)* demonstrated that, compared with HPV-negative women, women infected with HPV16 and 18 have relative hazard ratios of 8.5% (95% confidence interval [CI] = 3.7 to 19.2) and 3.3% (95% CI = 1.4 to 8.1), respectively, for development of cervical intraepithelial neoplasia 2 (CIN2) or 3 (CIN3, equivalent to precancer) over a 3-year period after primary infection. In another prospective study of 603 female university students, Winer et al. *(11)* reported a cumulative incidence rate for high-grade CIN (CIN2 and CIN3) of 27.2% (95% CI = 16.3 to 43.3) after incident infection with HPV16 or 18. In the natural history of HPV, most infections are transient, especially among younger women; only the small fraction of infections that persist may progress to cervical cancer, usually after more than a decade. Therefore, HPV DNA testing for use in primary screening as an adjunct to cytology has only been approved by the Food and Drug Administration and recommended for women 30 years of age and older *(12–14)*. However, published prospective data regarding type-specific risks in this age group are still lacking.

The only HPV DNA test currently approved in the United States for co-screening with cytology, Hybrid Capture 2 (HC2), uses a pooled probe set for 13 oncogenic HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68); the test does not distinguish individual HPV types. We recently examined the performance of this test in more than 20000 women enrolled

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in a 10-year prospective cohort and found that HC2 demonstrated superior sensitivity and negative predictive value over 5–10 years compared with a single Pap smear *(15)*. However, we wondered whether the value of HPV testing could be further optimized by separate detection of the most important HPV types. Specifically, we used type-specific probes for HPV16 and 18 in this same cohort study, to clarify whether additional testing of oncogenic HPV-positive (HC2+) women for HPV16 and HPV18 could better predict the future development of cervical precancer (CIN3) and cancer. If so, the risks associated with these two HPV types might justify serious consideration of HPV16 and HPV18 type-specific testing as an adjunct to a pooled oncogenic HPV DNA test.

## Subjects and Methods

### Study Participants

From April 1, 1989, to November 2, 1990, 23 702 women receiving routine cytologic screening in a prepaid health plan at Kaiser Permanente in Portland, OR, were recruited for a cohort study of the natural history of HPV infection. Women were excluded as described previously *(15,16)*, and the remaining cohort of 20 810 women with satisfactory baseline cytology was followed prospectively by routine cytology for up to 122 months. The cohort was a demographically representative sample (mainly Caucasian) in which approximately 50% of women underwent cervical cytologic screening at Kaiser Permanente, which served about one-quarter of the women residing in Portland during this time.

After exclusion of 208 women with indeterminate baseline cytology, 51 women with high-grade squamous intraepithelial lesions (HSILs) or cancer cytology at baseline, and 37 women who tested positive for oncogenic HPV types but did not have HPV16 or HPV18 typing results, the current analysis was restricted to 20 514 women with negative, equivocal, or mildly abnormal baseline cervical Pap smears; suitable samples for HPV testing; and applicable type-specific HPV test results. Subjects were 16 years of age or older (median age = 34.0 years, standard deviation [SD] = 12.6 years). Separate analyses were performed on the subgroup of 13 229 women aged 30 years or older at enrollment to address current age–specific screening recommendations *(12,13)*.

### Enrollment Examination

Informed consent was obtained under the prevailing institutional review board guidelines at Kaiser Permanente and the National Institutes of Health. Participants underwent a routine pelvic examination. Experienced clinicians prepared a single ethanol-fixed Pap smear for each subject using an Ayre spatula and cytobrush. Next, the cervix was rinsed with 10 mL of sterile saline using a 3¼ inch flexible intracatheter extender. The pooled fluid was collected from the posterior vaginal fornix and processed for HPV testing as described below.

### Follow-Up

During the study period, annual cytologic screening of women at Kaiser continued as part of standard clinical practice. The then-current standard practice guidelines for management of abnormal cytology mandated treatment of patients with CIN2 or greater, but health plan physicians also treated some patients with CIN1 at their discretion (which is more aggressive treatment than current guidelines recommend) *(12,14)*. Once treated, women were censored and were not included in the denominator of women at risk in subsequent time intervals. HPV test results were not known by clinicians and were not used to direct patient management.

### Pathology

Pap smears were originally reported using a classification that predated the development of the Bethesda System; we converted these interpretations into Bethesda 2001 terminology for this study *(17)*. We reclassified women with smears reported as "normal" or "benign reactive atypia" as "negative for intraepithelial lesion or malignancy (negative)" according to the Bethesda 2001 classification *(17)*. Pap smears reported as "severe reactive atypia, possibly dysplasia" or "possible koilocytotic or condylomatous atypia" were reclassified as "atypical squamous cells" (ASCs). Cytologic interpretations of dysplasia were reclassified as low-grade squamous intraepithelial lesions (LSILs) or HSILs. Histologic diagnoses were converted into CIN nomenclature. Specifically, severe dysplasia and carcinoma in situ were categorized as CIN3.

Women who had received original histopathologic diagnoses of CIN3 or cancer (including endocervical adenocarcinoma in situ) on two different clinical specimens obtained on different dates (usually a diagnostic punch biopsy and a cone performed for treatment) were designated as cases, called ≥CIN3, and were not further reviewed. All other women who had a CIN2 or greater histopathology result underwent histologic specimen review. A single pathologist (DRS) performed the reviews. The review criteria for case definition were 1) an original histopathologic diagnosis of CIN2 reviewed as CIN3 or worse or 2) an original histopathologic diagnosis of CIN3 or worse confirmed as at least CIN2. This case definition, which required confirmation of a single CIN3 diagnosis as at least CIN2 by another pathologist, was more stringent than a disease endpoint defined by a single pathologist. For example, an original diagnosis of CIN3 that was reviewed as CIN1 would not have been a case in our analysis. We chose these criteria because we wished, by review, to exclude questionable precancer; however, the subtle histopathologic distinction between CIN2 and CIN3 has inadequate reproducibility, even among experts *(18)*. Therefore, in total, 131 (0.6%) of 20 514 women fulfilled this ≥CIN3 case definition, including 32 (0.2%) subjects with invasive carcinoma.

### HPV DNA Testing

Cervicovaginal lavage specimens were refrigerated within 1 hour of collection and transported to a laboratory for processing. A 1-mL aliquot was removed and frozen at −70 °C *(19)*. The remaining sample was divided roughly in half, cells were pelleted by centrifugation, the supernatant was separated from the pellet, and both were frozen.

We selected either frozen liquid aliquots or cell pellets for HPV testing, depending on availability. The vast majority of specimens were tested using cell pellets (92%). Separate analysis of the few specimens tested using liquid aliquots (8%) did not change our conclusions (data not shown). HPV testing (by laboratory personnel who were blinded to cytology and clinical outcome) was performed on enrollment specimens using the

HC2 microplate assay at a detection threshold of 1.0 pg/mL (approximately 5000 copies). The assay detected 13 oncogenic types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), as previously described (Digene, Gaithersburg, MD) *(20,21)*. As a method of secondary typing, we performed HPV16 and HPV18 testing using individual type-specific RNA probes coupled with type-specific capture of DNA:RNA hybrids using immobilized DNA oligonucleotides, as described previously *(22,23)*, on women who were HC2 positive ($n = 2853$). The Hybrid Capture (HC) genotyping method previously had been called the HC3 test and is described briefly as follows. Clinical specimens were denatured by heating in alkali to separate all DNA strands, as described previously for the HC2 test *(21)*. Then one almost-full–genome-length unlabeled RNA probe with short deletions in regions that correspond to two separate points of capture at least 3 kb apart on the genome of each target HPV type was combined with two small DNA capture oligonucleotides for each HPV type. The capture oligonucleotides exactly matched each target, and these were labeled with biotin. The purpose of the deletions in the RNA probes was to allow free access of the capture oligonucleotides to any HPV DNA targets that may have been present in the clinical specimens. These two kinds of probes, along with two pairs of short corresponding blocking oligonucleotides designed to suppress any residual cross-reactivity, were allowed to hybridize to target HPV DNA. The capture and corresponding blocking oligonucleotide pairs were chosen to hybridize only to specific unique regions of the HPV target to minimize or eliminate unwanted cross-reactivity. These multipart hybrid complexes were then captured on streptavidin-coated plates, washed to remove unreacted molecules, and detected by supplying a dioxetane substrate as in the HC2 test.

To examine the sensitivity of the initial HC2 testing for detection of HPV16 and HPV18 infections, we analyzed additional available type-specific results using HPV16 and HPV18 RNA probes in a nonrandomly chosen group of women who were HC2 negative ($n = 1381$). Many of these women had some other evidence of cervical cancer risk factors or HPV infection using other testing methods *(23)*, and we used their HPV16 and HPV18 type-specific results as well as their final diagnosis to assess the analytic and clinical sensitivity of the initial HC2 test for oncogenic HPV types and clinically relevant infection.

### Statistical Analysis

First, we divided the entire analysis cohort of 20 514 women into risk-stratified groups based on their HPV status at enrollment. Using HC2 results and HPV16 and HPV18 type-specific probe results, HPV infection was defined hierarchically: positive for HPV16 (HPV16+); else positive for HPV18 (HPV18+; 30 women with HPV16 coinfection were called HPV16+); else HPV16 negative, HPV18 negative, and HC2 positive (HPV16−/HPV18−/HC2+); else HC2 negative (HC2−). Of the 20 514 women, we classified 460 (2.2%) as HPV16+, 157 (0.8%) as HPV18+, 2,236 (10.9%) as HPV16−/HPV18-/HC2+, and 17 661 (86.1%) as HC2−.

Enrollment Pap smears were grouped by cytology: negative, ASCs, and LSILs. Of the 20 514 women, 19 919 (97.1%) had negative cytology at enrollment, 471 (2.3%) had ASCs, and 124 (0.6%) had LSILs.

We purposely de-emphasized exact time of diagnosis of ≥CIN3, because our experience strongly indicates that even repeated screening or expert colposcopic evaluation may miss many cases that, when detected at a later time, may be substantially misclassified as to time of development *(24,25)*. Therefore, after excluding women who had cytologic evidence of CIN2–3 or cancer at baseline, we included all subsequent cases of histologically confirmed ≥CIN3 through 122 months to examine the cumulative risk for ≥CIN3 over a 10-year period without attempting to assign exact date of occurrence. Instead, follow-up time was crudely divided into an initial period of 0–9 months (Pap smears that were rapidly repeated, presumably prompted by a previous cytologic abnormality or suspicious symptoms), followed by yearly intervals for a total time of 122 months. These intervals roughly paralleled the intervals at which women returned for annual smears.

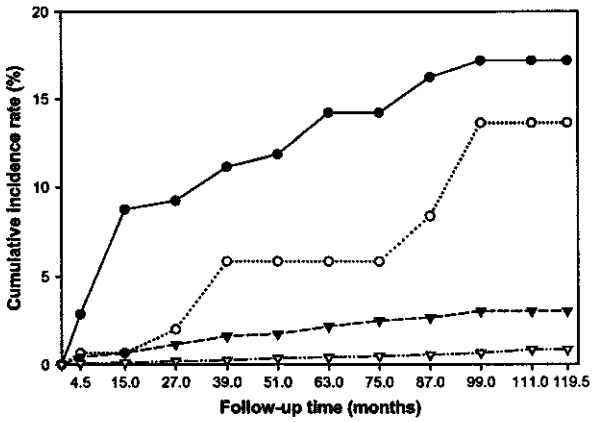
The risk of ≥CIN3 in each of the four HPV groups (HPV16+, HPV18+, HPV16−/HPV18−/HC2+, and HC2−) for each time interval was computed by dividing the number of cases diagnosed in that interval by the number of women at risk (i.e., who had undergone routine cytology screening) during that interval. Using Kaplan–Meier methods *(26)*, we calculated cumulative incidence rates (CIRs) with 95% confidence intervals for each interval up to 122 months. The CIR among women with positive screening tests is the positive predictive value (i.e., number of cases of ≥CIN3 among women with positive tests, divided by total number of positive tests, multiplied by 100%), adjusted for person-time and censoring. Similarly, the negative predictive value, adjusted for person-time and censoring, is equal to 100% minus the CIR in women with negative screening tests. Graphs were plotted to show the trend in CIR over the 10-year period.

We repeated the analysis after stratifying by age (<30 years versus ≥30 years) to evaluate the clinical application of HPV genotyping among older women for whom HPV and cytology co-testing is an option *(12–14)*. To the extent possible, given the limited numbers of women in each group, we also considered possible modifications of results by enrollment Pap smear result (negative, ASCs, or LSILs).

## Results

The overall CIRs of ≥CIN3 in 20 514 women according to HPV status at enrollment are shown in Fig. 1. Over a period of 10 years, 39 women who were HPV16+ at enrollment developed CIN3 or cancer (CIR = 17.2%, 95% CI = 11.5% to 22.9%), as did seven HPV18+ women (CIR = 13.6%, 95% CI = 3.6% to 23.7%), 30 HPV16−/HPV18−/HC2+ women (CIR = 3.0%, 95% CI = 1.9% to 4.2%), and 55 HC2−women (CIR = 0.8%, 95% CI = 0.6% to 1.1%). HPV16+ and HPV18+ women were at increased risk for ≥CIN3 in each time interval up to 8 years after enrollment. Of the 32 women who developed cancer, 12 (37.5%) were HPV16+ at enrollment, one (3.1%) was HPV18+, eight (25.0%) were HPV16−/HPV18−/HC2+, and 11 (34.4%) were HC2−. Of the 99 women who developed CIN3, 27 (27.3%) were HPV16+, 6 (6.1%) were HPV18+, 22 (22.2%) were HPV16−/HPV18−/HC2+, and 44 (44.4%) were HC2− at enrollment. An examination of the absolute risk of ≥CIN3 in each follow-up interval by HPV status also demonstrated that HPV16 and 18 were associated with higher risks than non-HPV16/18 oncogenic types and oncogenic HPV negativity (Supplementary Table 1, available at http://jnci cancerspectrum.oxfordjournals.org/jnci/content/vol97/issue14).

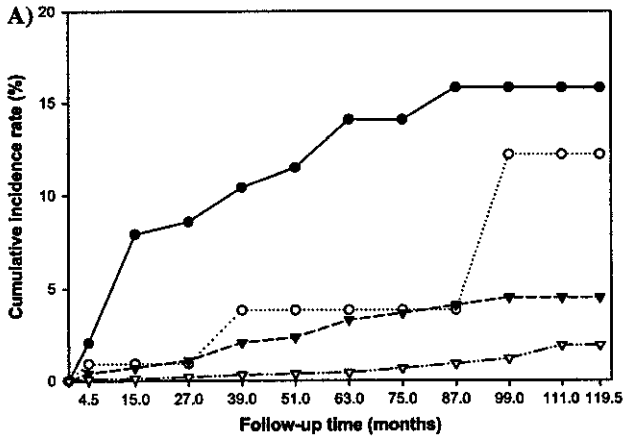
We then stratified the analysis by age and enrollment cytology to examine the risks in subgroups of women who might be




No. of women seen during follow-up interval

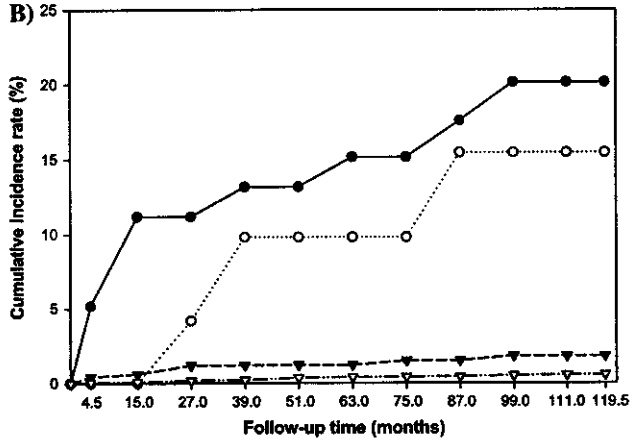
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HPV16+ | 455 | 247 | 190 | 144 | 125 | 112 | 94 | 84 | 89 | 35 | 3 |
| HPV18+ | 154 | 85 | 74 | 51 | 43 | 41 | 36 | 37 | 35 | 16 | 1 |
| HC2+ | 2211 | 1208 | 1016 | 862 | 755 | 701 | 600 | 528 | 547 | 256 | 17 |
| HC2- | 17391 | 9759 | 8672 | 7813 | 7136 | 6479 | 5960 | 5551 | 5278 | 2621 | 156 |

**Fig. 1.** Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (≥CIN3) over a 10-year period in 20 514 women according to oncogenic human papillomavirus (HPV) status at enrollment. HPV status is defined hierarchically as: positive for HPV 16 (**closed circles**), else positive for HPV18 (**open circles**), else positive for the non-HPV16/18 oncogenic types in Hybrid Capture 2 (**closed triangles**), else oncogenic HPV negative (**open triangles**).




No. of women seen during follow-up interval

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HPV16+ | 339 | 184 | 140 | 99 | 84 | 68 | 61 | 49 | 57 | 21 | 1 |
| HPV18+ | 110 | 62 | 50 | 34 | 26 | 26 | 26 | 21 | 23 | 13 | 1 |
| HC2+ | 1249 | 663 | 514 | 407 | 352 | 312 | 261 | 228 | 229 | 112 | 7 |
| HC2- | 5498 | 2896 | 2349 | 1957 | 1695 | 1493 | 1285 | 1214 | 1083 | 543 | 23 |




No. of women seen during follow-up interval

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| HPV16+ | 116 | 63 | 50 | 45 | 41 | 44 | 33 | 35 | 32 | 14 | 2 |
| HPV18+ | 44 | 23 | 24 | 17 | 17 | 15 | 10 | 16 | 12 | 3 | 0 |
| HC2+ | 962 | 545 | 502 | 456 | 403 | 389 | 339 | 300 | 318 | 144 | 10 |
| HC2- | 11893 | 6863 | 6323 | 5856 | 5441 | 4986 | 4675 | 4337 | 4195 | 2078 | 133 |

**Fig. 2.** Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (≥CIN3) over a 10-year period in **A)** 7285 women younger than 30 years of age and **B)** 13 229 women 30 years old and older, according to oncogenic human papillomavirus (HPV) status at enrollment. HPV status is defined hierarchically as: positive for HPV 16 (**closed circles**), else positive for HPV18 (**open circles**), else positive for the non-HPV16/18 oncogenic types in Hybrid Capture 2 (HC2) (**closed triangles**), else oncogenic HPV negative (**open triangles**).

targeted for different clinical management strategies. The CIRs for the 7285 women younger than 30 years of age and the 13 229 women 30 years of age and older are shown (Fig. 2, A and B, respectively). HPV DNA co-screening with cytology is now an option for some women aged 30 years or more (i.e., the women in Fig. 2, B). The overall rate of ≥CIN3 was 0.4% in the women aged 30 years and older and 1.0% in the women younger than 30 years of age (data not shown). The mean ages of women with CIN3 and cancer were 29.7 (SD = 9.4; range = 16–62) years and 36.8 (SD = 14.2; range = 19–78) years, respectively. Of the 32 women who developed cancer, nine were younger than 30 years of age at baseline and 23 were 30 years of age or older. After stratifying by age, the risks of ≥CIN3 for HPV16+ and HPV18+ women were still substantially elevated above those of HPV16−/HPV18−/HC2+ and HC2− women. However, non-HPV16/18 oncogenic types appeared to contribute more to the development of CIN3 and cancer in younger women ($n$ = 20 of 73 total cases, CIR = 4.5%, 95% CI = 2.3% to 6.6%) than in older women ($n$ = 10 of 58 total cases, CIR = 1.8%, 95% CI = 0.6% to 3.0%).

When we excluded women with ASC or LSIL cytology, we found that the risks of ≥CIN3 for 19 919 women who were cytologically negative at enrollment were similar to those for the entire cohort; the risks of ≥CIN3 in HPV16+ ($n$ = 25, CIR = 17.3%, 95% CI = 10.5% to 24.1%) and HPV18+ ($n$ = 5, CIR = 11.8%, 95% CI = 1.9% to 21.7%) women were substantially higher than those for HPV16−/HPV18−/HC2+ ($n$ = 22, CIR = 3.0%, 95% CI = 1.7% to 4.2%) women and HC2− ($n$ =46, CIR = 0.8%, 95% CI = 0.5% to 1.0%) women. Although the cumulative risk of ≥CIN3 for women with non-HPV16/18 oncogenic types was relatively low, the overall large number of women with other oncogenic infections produced a substantial number of cases ($n$ = 22).

We then focused on women who would be co-tested with HPV and cytology for general screening based on recently published guidelines, i.e., women 30 years of age and older *(12–14)*. Among the 12 976 women in this group and with negative cytology, the cumulative incidence rates of ≥CIN3 for the HPV groups were as follows: HPV16+, $n$ = 10, CIR = 20.7%, 95% CI = 8.6 to 32.8; HPV18+, $n$ = 3, CIR = 17.7%, 95% CI = 0.0 to 36.0; HPV16−/HPV18−/HC2+, $n$ = 6, CIR = 1.5%, 95% CI = 0.3 to 2.7; and HC2−, $n$ = 26, CIR = 0.5%, 95% CI = 0.3 to 0.7 (Fig. 3).

The risks for 471 women with an ASC cytology at enrollment were less clear than the risks for women with negative cytology due to small numbers (data not shown), although HPV16 positivity did appear to confer a higher 10-year risk ($n$ = 7, CIR = 12.1%, 95% CI = 3.4% to 20.9%) than the other risk groups. In the women with ASC cytology at enrollment, all 20 cases of CIN3 or cancer occurred within the first 2 years after enrollment.

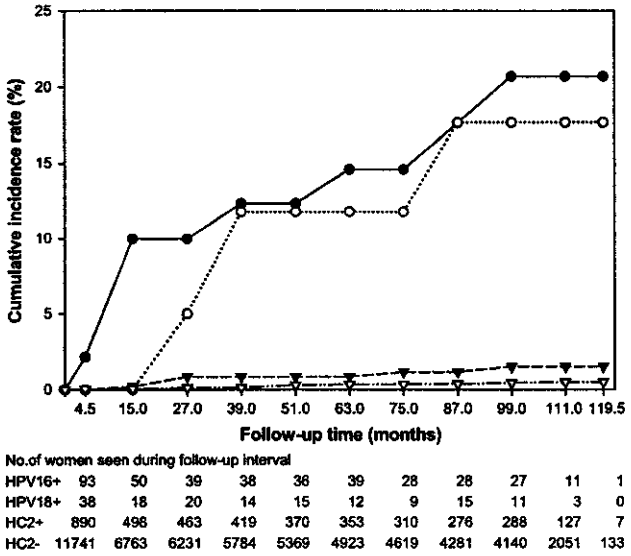



**Fig. 3.** Cumulative incidence of cervical intraepithelial neoplasia grade 3 and cancer (≥CIN3) over a 10-year period in 12976 women 30 years old and older with negative cytology at enrollment, according to oncogenic human papillomavirus (HPV) status at enrollment. HPV status is defined hierarchically as: positive for HPV 16 (**closed circles**), else positive for HPV18 (**open circles**), else positive for the non-HPV16/18 oncogenic types in Hybrid Capture 2 (HC2) (**closed triangles**), else oncogenic HPV negative (**open triangles**).

Because of very small numbers, the cumulative incidence rates for 124 women with LSIL cytology had wide confidence intervals and therefore could not be reliably interpreted (data not shown).

An examination of the relative contribution of baseline HPV typing and cytology to prospective detection of disease revealed that type-specific HPV testing was a potentially stronger long-term predictor of cervical disease than cytology in women aged 30 years and older (Table 1). A higher cumulative incidence rate of ≥CIN3 was associated with HPV16 positivity among the total group of women with negative, ASC, or LSIL baseline cytology (CIR = 20.1%, 95% CI = 9.7% to 30.6%) than with LSIL cytology among women with HPV-positive or -negative results (CIR = 11.1%, 95% CI = 1.5% to 20.7%). These results revealed that, among women 30 years of age or older, type-specific testing for HPV16 or HPV18 alone had a higher positive predictive value (i.e., number of cases among women with positive tests) than LSIL cytology alone.

To avoid a potential conservative bias, we initially excluded 37 women who tested positive for the 13 oncogenic HPV types (HC2+) but who did not have separate HPV16 and HPV18 typing results. A subanalysis including these women within the HPV16−HPV18−/HC2+ group did not alter our findings (data not shown).

To examine the analytical and clinical sensitivity of the initial HC2 test for detection of HPV16 and HPV18 and clinically relevant infection, we analyzed 1381 HC2− women who also had HPV16 and HPV18 type-specific results. Of these women, only 19 (1.4%) tested positive for HPV16, 5 (0.4%) tested positive for HPV18, and 1 (0.1%) tested positive for both HPV16 and HPV18 by the RNA probes. There were two cases of CIN3 among the 19 women who tested positive for HPV16 by the RNA probes but negative by HC2; these two women also tested positive for HPV16 by MY09/11 polymerase chain reaction (PCR) using

**Table 1.** The cumulative incidence rates (CIRs) and 95% confidence intervals (CIs) of ≥CIN3 during a 10-year prospective cohort study, according to HPV status and Pap smear diagnosis at enrollment in women ≥30 years old*

| | CIR (95% CI) by HPV status and Pap smear diagnosis | | | |
|---|---|---|---|---|
| HPV status | Negative | ASCs | LSILs | Total |
| HPV16+ | 20.7 (8.6 to 32.8) | 7.7 (0.0 to 22.2) | 30.0 (1.6 to 58.4) | 20.1 (9.7 to 30.6) |
| HPV18+ | 17.7 (0.0 to 36.0) | 0.0 | 0.0 | 15.4 (0.0 to 31.7) |
| Non-HPV16/18 oncogenic+ | 1.5 (0.3 to 2.7) | 6.4 (0.0 to 13.4) | 4.0 (0.0 to 11.7) | 1.8 (0.6 to 3.0) |
| Oncogenic HPV− | 0.5 (0.3 to 0.7) | 3.3 (0.1 to 6.6) | 9.1 (0.0 to 26.1) | 0.5 (0.3 to 0.8) |
| Total | 0.8 (0.5 to 1.0) | 4.2 (1.3 to 7.1) | 11.1 (1.5 to 20.7) | |

*A total of 13229 women aged 30 years and older were tested for HPV status by Hybrid Capture 2. ≥CIN3 = cervical intraepithelial neoplasia grade 3 (CIN3) or cervical cancer; HPV = human papillomavirus; ASC = atypical squamous cell; LSIL = low-grade squamous intraepithelial lesion; oncogenic HPV types = 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. CIRs and 95% CIs were calculated using the Kaplan–Meier method.

type-specific probes, indicating that they were most likely true HPV16 positives who were not detected by HC2. No HC2− women who developed CIN3 or cancer tested positive for HPV18 in this subanalysis.

In another ancillary analysis, we explored the type specificity of the HPV16 and HPV18 RNA probes compared with available MY09/11 PCR data from previously published case–control studies that were conducted during the earlier years of the Kaiser Portland cohort study *(19,27)*. We did this to examine whether the type-specific probes were cross-reactive with other untargeted HPV types. We found that the single type RNA probes were highly type specific, in that women with other HPV types detected by PCR tested negative (411 of 424 non-HPV16/18 single type infections) for HPV16 and HPV18 using the RNA probes (Supplementary Table 2, available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol97/issue14). Among women who were HPV16+ by the RNA probes and also had PCR results ($n$ = 217), there was very little cross-reactivity with other carcinogenic HPV types (3%), and 85% of the infections were confirmed as HPV16+ by PCR (Supplementary Table 3, available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol97/issue14).

## Discussion

In this cohort study of 20514 women, the 10-year cumulative incidence rate of CIN3 or cancer was 17% among women who tested positive for HPV16 at enrollment. Among HPV18-positive, non-HPV16/18 oncogenic HPV-positive, and oncogenic HPV-negative women, the 10-year cumulative incidences of ≥CIN3 were 14%, 3%, and 1%, respectively. When we limited the analysis to women aged 30 years and older, for whom HPV testing and co-testing with cytology are an option, the 10-year cumulative incidences of ≥CIN3 among HPV16- and 18-positive women were 20% and 15%, respectively, whereas the 10-year cumulative incidence of ≥CIN3 among women with LSIL cytology at enrollment was 11%.

Recent cervical cancer screening guidelines suggest that oncogenic HPV DNA detection can be usefully introduced into

screening of women 30 years of age and older *(13)*. However, the large number of cytologically normal women with HPV has led to uncertainty regarding proper follow-up. Interim management guidance to repeat cytologic and HPV DNA screening at 6–12 months was recently proposed because of lack of sufficient data to make a confident decision on the discrete time interval at which follow-up would be appropriate *(12)*. We believe that too early repetition of HPV testing would mistakenly characterize as persistent many HPV infections that are destined to resolve. However, a long interval before the follow-up repeat examination can create clinician and patient concern and possible a loss to follow-up.

Based on our data, we suggest that separating HPV16 and HPV18, the two most risky oncogenic HPV types, from the other oncogenic HPV types would help to identify, among HPV positive women, the majority destined to progress to ≥CIN3, justifying immediate colposcopy of this subset of infected women and providing reassurance regarding the safety of a 12-month interval without colposcopy if other oncogenic HPV types are detected. Studies have shown that HPV persistence is more likely with HPV16 than with other oncogenic HPV types *(28–31)*. Women with non-HPV16/18 oncogenic HPV infections will still need to be followed more carefully than women without oncogenic HPV infections, but perhaps more conservatively than women with HPV16 and HPV18 infections. This new screening strategy could help to reduce the number of women who are referred to colposcopy for a positive HPV test (Fig. 4).

In this prospective cohort study of 20 514 women, 10-year cumulative incidence rates revealed considerably higher risk in women positive for HPV16 or HPV18 at enrollment compared with women positive for non-HPV16/18 oncogenic types and oncogenic HPV-negative women. These findings are consistent with those of other studies in the literature *(32,33)* and added the strengths of ≥CIN3 outcomes and a more than 20 000-woman prospective study with a large number of older women.

Stratification by age (<30 years versus ≥30 years) demonstrated the high risks associated with HPV16 and HPV18 in both younger and older women. Stratification by enrollment cytology (negative, ASCs, or LSILs) showed that high risks are associated with HPV16 and HPV18 in women with negative cytology; the risks for women with ASCs and LSILs were less clear, owing to small numbers. In particular, the lower rate of ≥CIN3 among women with ASCs in this study (4.2% of women with ASCs at enrollment developed ≥CIN3 over 10 years) compared with another cohort *(24)* may be due to the slightly different and possibly lower risk definition of ASCs that we used. An accompanying manuscript by Castle et al. *(34)* demonstrated the high risk of CIN3 over a 2-year follow-up associated with HPV16 infection among 5060 women with atypical squamous cells of undetermined significance (ASCUS) or LSILs at enrollment into the ASCUS-LSIL Triage Study; the absence of an elevated risk for HPV18 infection in that study may be the result of an insufficient follow-up period.

Our data (Table 1) suggest that HPV DNA screening of the general population of women aged 30 years and older, with separate typing of HPV16 and HPV18, might be a more powerful predictor of future CIN3 and cancer than ASC or even LSIL cytology. Among women with negative, ASC, and LSIL cytology we observed that a positive HPV16 test alone predicted a higher risk of CIN3 and cancer (20.1%) than a Pap smear with LSIL cytology alone (11.1%). According to current clinical guidelines, any woman with LSIL cytology is referred to colposcopy. Based on our data, it logically follows that women with HPV16 should be referred to colposcopy.

The data in Table 1 touch on a topic under debate by experts in cervical cancer screening—whether cytology or HPV DNA testing should be the primary screening tool for cervical cancer. Although the Pap smear has been used for over 50 years, data from research during the past 20 years has validated the use of HPV testing as an adjunct to primary screening *(35)*. Although requiring confirmation in other large screening populations, our prospective results support the notion that cervical cancer screening might gradually turn to a virologic rather than a cytomorphologic paradigm, in which viral type and persistence are key clinical parameters *(36)*. However, given that the sensitivity of both methods is imperfect, for situations in which caution is most important, the currently recommended combination of cytology and HPV testing is probably the preferred method.

Our previous study on 20 810 women in the Kaiser Portland cohort, which included women with HSIL cytology at enrollment, showed the 10-year risk of CIN3 or cancer to be approximately 7% for women who tested positive at enrollment by HC2 *(15)*. Our present study demonstrates the improvement in positive predictive value that could be achieved with type-specific HPV16 and HPV18 testing adjunctive to a pooled probe HPV test. It is worth considering the possible specific uses of a type-specific test for HPV16 and HPV18 in clinical practice. Women 30 years of age and older could be sampled for cytology, pooled probe HPV DNA testing, and type-specific HPV DNA testing as part of primary screening. Management of cytology and HPV results could proceed as outlined in Fig. 4. Typing for HPV16 and HPV18 would permit risk stratification of cytologically normal, HPV infected women, a group for whom the length of the repeat screening interval has been unclear. A positive test for HPV16 or HPV18 with any cytology result would warrant referral to colposcopy, whereas cytologically negative women who test positive only for non-HPV16/18 oncogenic types could be retested at 12 months and subsequently referred to colposcopy for repeat LSIL cytology or worse or a repeat positive oncogenic HPV test. Based on current guidelines *(13,14)*, women who are oncogenic HPV negative with negative cytology can be safely returned to screening every 3 years.

Our study has several limitations. It is likely that our findings in the Kaiser Portland cohort underestimate the true cumulative incidence rates, owing to aggressive management and censoring. Our study was performed in a setting in which participants were screened and treated according to clinical practice that would now be considered aggressive; that is, women were treated at first evidence of CIN2 and, in some cases, CIN1. Treated women were then censored and not followed up further to assess development of ≥CIN3. When we examined the censoring rates among women in our analysis who were not case patients in our analysis, we found that oncogenic HPV-positive women (HPV16+, 12.8% censored; HPV18+, 8.0%; HPV16−/HPV18−/HC2+, 7.0%) were differentially censored ($P<.001$) compared with oncogenic HPV-negative women (HC2−, 2.7% censored), although HPV status was not known by clinicians. We presume there would have been many more cases of CIN3 and cancer if this censoring mechanism had not been in place. If so, our calculated estimates of CIR thereby underestimate the true risks associated with HPV16, HPV18, and the other oncogenic HPV types.

Another limitation of our study design was our inability to examine synergy of various oncogenic HPV types. Specifically,

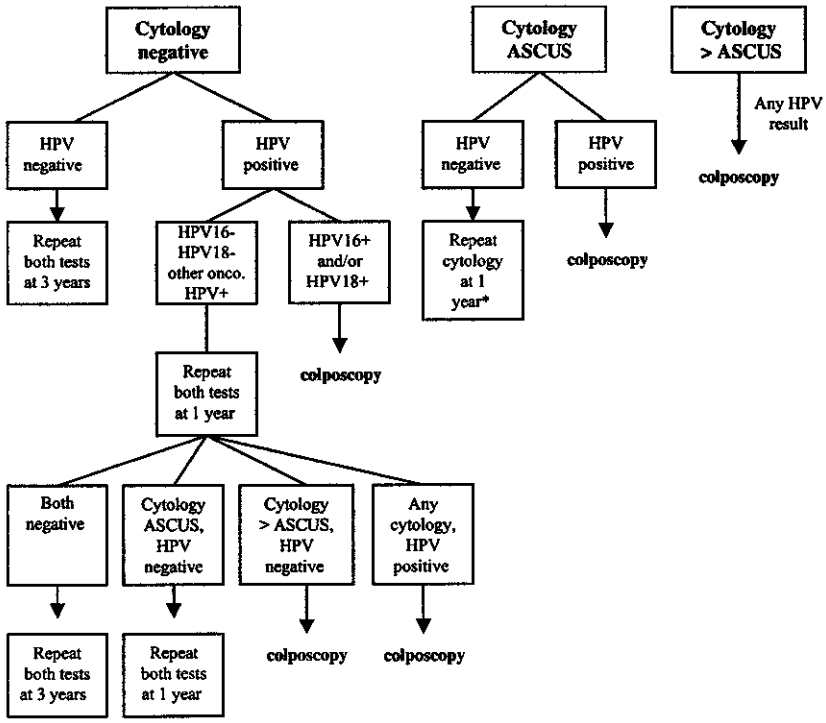



**Fig. 4.** Proposed algorithm for the management of women 30 years of age and older in primary cervical cancer screening using a combination of cervical cytology, pooled probe HPV DNA testing, and type-specific HPV16/18 testing. HPV = human papillomavirus; onco = oncogenic; ASCUS = atypical squamous cells of undetermined significance. Adapted from Wright et al. *(12)*.

we wondered whether inclusion of multiple infections within the HPV16+ group would produce an overestimate of the risks associated with HPV16. The only combination for which we had sufficient HPV typing data to examine possible additive effects was the group of 30 women infected with both HPV16 and 18 at enrollment, three (10.0%) of whom went on to develop ≥CIN3 over 10 years (CIR = 22.3%, 95% CI = 0 to 48.3). This risk did not differ from the risks for all women with HPV16 (CIR = 17.2%) and women with HPV18 without HPV16 (CIR = 13.6%).

Our method of grouping by HPV status assumed that the initial HC2 testing of the entire prospective cohort detected HPV16 and HPV18 infections with reasonable accuracy and with an analytical sensitivity level that was clinically relevant. To test this assumption, we looked at additional available type-specific results using the HPV16 and HPV18 RNA probes in women who had tested negative by HC2 but had HPV infection found by MY09/11 PCR and/or other cervical cancer risk factors. Of these 1381 HC2− women, 1.4%, 0.4%, and 0.1% tested positive for HPV16, HPV18, and both HPV16 and HPV18, respectively, with two cases of ≥CIN3 (3.6% of the 55 HC2− cases in total). Therefore, we believe that HC2 detected the great majority of clinically relevant HPV16 and HPV18 infections and that our HPV typing results are robust.

In conclusion, this prospective Kaiser Permanente cohort study demonstrated that HPV16 and HPV18 are clearly more dangerous than the other oncogenic HPV types, a conclusion consistent with the findings of other cohort studies *(10,11,37)*. Given that HPV16 and HPV18 are estimated from cross-sectional data to cause approximately 70% of cervical cancers worldwide and that the cumulative 10-year risk of ≥CIN3 in women with HPV16 or HPV18 ranges from 10% to 20%, we conclude that these two HPV types are potent carcinogens and should be more effectively targeted in clinical practice. If cost-utility analyses, which are in progress, show single-type tests for HPV16 and HPV18 adjunctive to a pooled HPV test to be cost-effective, then co-testing or triage by HPV16 and HPV18 typing may be a way to focus our clinical attention on a group of HPV-infected women at higher risk for progression to cervical precancer and cancer.

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## NOTES

A. Lorincz is the Senior Vice President of Research and Development and Chief Scientific Officer of Digene Corp., the maker of the Hybrid Capture 2 test, and owns stock in the company. M. Sherman has previously received research funding from Digene Corp. D. Scott holds stock in Tripath.

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# The Role of Human Papillomavirus in Screening for Cervical Cancer

Column Editor: Lorna Schumann, PhD, RNCS, NP-C, CCRN, ARNP, FNP, ACNP

Susan E. McFadden, RN, M.Nurs
Lorna Schumann, PhD

**PURPOSE**
To review the options for effectively screening for cervical cancer, including human papilloma virus (HPV) identification, cytologic screening, colposcopy, or a combination approach. Current pathophysiology, diagnostic criteria, treatment approaches, and patient preparation and education related to cervical cancer screening and prevention are also included.

**DATA SOURCES**
Comprehensive review of current literature, including research and review articles.

**CONCLUSION**
Because the Papanicolau (Pap) smear is a screening tool, not a diagnostic tool, further studies must be done to identify the actual nature of discovered abnormalities. Of particular concern is the classification of atypical squamous cells of undetermined significance (ASCUS), which may simply indicate inflammation, or may be the first indicator of serious pathology. Following ASCUS Pap smears with HPV screening will allow for a clarification of the best approach to treatment. A screening algorithm supported by a review of the literature is proposed.

**IMPLICATIONS FOR PRACTICE**
Cervical cancer is a preventable disease caused by certain forms of HPV. Current screening protocols are based on the use of the Pap smear; and in areas where this test is routine and available, morbidity and mortality rates have dropped dramatically. Many women throughout the world and in underserved regions of the U. S. do not have adequate access to routine screening with Pap smear technology. As long as women continue to die

## INTRODUCTION

Cervical cancer is the second most common type of cancer found in women worldwide. It is the leading form of cancer death in most developing countries (Richart, 1995). With the advent of strong screening protocols based on the use of the Papanicolaou (Pap) smear test, the cervical cancer death rate in comparison to other cancer deaths in the U. S. has dropped from over 30% in 1930 to less than 8% in 1994 (Cancer Statistics, 1998). Similar declines have been seen in other developed countries where the Pap smear is readily available. Since the development of the Pap smear in the 1940s, screening has relied on the use of the Pap smear for identification of abnormal pre-invasive cells, known as dysplasia, which are the precursor cells to cervical cancer. Where Pap smear screening has been properly implemented, cervical cancer death rates have dropped 50% to 70% (Cuzick, 1998). However, in a retrospective review of 312 laboratories, Montes, Cibas, DiNisco, and Lee (1999) found that false-negative Pap smears in women with subsequent pathology were identified in 19.7% of the cases reviewed.

In 1998, over 12,000 women in the U. S. were diagnosed with cancer of the uterine cervix, and 4,800 women died of the disease (Cancer Statistics, 1998; Canavan, & Doshi, 2000). Many women throughout the world and in underserved regions of the U. S. do not have adequate access to Pap smear testing. As long as women worldwide and in the U.S. continue to die needlessly of cervical cancer, more comprehensive and accessible screening methods must be explored.

Cervical cancer is the leading form of cancer death in most developing countries (Apgar, & Brotzman, 1999). Because of the potential for underlying malignancy, many experts recommend following all reports of atypical squamous cells of undetermined significance (ASCUS) with a colposcopy. This approach is often impractical and expensive, as many of these early irregular smears are benign (Jones, 1995). Other approaches to dealing with minor cytologic abnormalities include serial repeat Pap smears and testing for the human papillomavirus (HPV), the virus that has been implicated in the evolution of cervical cancer.

Although a variety of factors may cause cervical dysplasia, the primary risk of dysplasia advancing to cervical cancer is the presence of HPV (Kjellberg et al., 1998). Van Muyden and colleagues (1999) identified HPV in 100% of their study population of women with invasive cervical cancer. However, Tabrizi's group (1999) found HPV DNA in only 90% of cases of cervical cancer. Those women with HPV-negative carcinoma had a better prognosis, leading the researchers to conclude that HPV-negative cancers are different from those with detectable HPV-DNA. Van Muyden's

needlessly of cervical cancer, more comprehensive and accessible screening methods must be explored. (Cutting the unnecessary worldwide and in the U. S.)

**KEY WORDS**

Human papilloma virus; Papanicolau smear; ASCUS; Bethesda system; cervica dysplasia; CIN.

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group theorized that the failure to find HPV in cervical carcinoma simply indicates a lack of sensitivity of the HPV testing method. This strong correlation between HPV and cervical cancer opens the door for new methods of screening through the identification of HPV in the cervix.

This article explores the options for effectively screening for cervical cancer: HPV identification, cytological screening, or a combination approach, including a visual examination with the colposcope. The advantages and disadvantages of each of the three approaches, with an emphasis on efficacy, costs, and benefits, as well as a brief review of the current treatment recommendations for cervical cancer and patient preparation information is also included.

## PATHOPHYSIOLOGY

In contrast to most cancers that are treatable only after the cancer has been identified, cervical cancer is a preventable disease. Cervical cancer can be prevented either through avoidance of HPV, the causative agent, or through the identification and treatment of pre-invasive lesions. The dysplastic precursor lesions to cervical carcinoma are frequently referred to as cervical intraepithelial neoplasia (CIN) or, more specifically, squamous intraepithelial lesions (SIL), a term that identifies the area where abnormal cells proliferate.

Most cervical dysplasia occurs in the area of the squamocolumnar junction of the cervix, an area of active squamous cell proliferation. Until puberty, this junction is located on the exposed vaginal portion of the cervix and is relatively stable. At puberty, with the accompanying increase in estrogen, the squamous margin encroaches on the single-layered, mucous-secreting epithelium—the columnar epithelium—forming an area of metaplasia known as the transformation zone (MacKay, 1999). In young women and in women on oral contraceptives, this transformation zone is visible surrounding the cervical os and is called ectopy. Ectopy recedes into the endocervical canal with age and with the onset of sexual intercourse (Celum, Wilch, Fennell, & Stamm, 1998). Dysplasia is most commonly identified within the transformation zone, thus requiring that cell samples be obtained from this area when a Pap smear is obtained.

Various types of HPV have been identified as the cause of cervical cancer (Van Muyden et al., 1999). Studies indicate that cervical HPV types infect the squamous epithelium of the cervix. A number identifies each type of HPV. Human papillomavirus DNA can be identified in more than 80% of women with biopsy-confirmed SIL, with HPV types 6 and 11 predominating in low-grade SIL. High-grade lesions are most frequently associated with type 16. (Park, Fujiwara, & Wright, 1995). The HPV DNA incorporates itself into the cellular DNA, activating oncogenes and suppressing the host cell's immune response. Cervical cells are particularly prone to this type of damage during puberty and pregnancy, when the high levels of estrogen are promoting rapid change (Cothran, & White, 1995).

Papillomaviruses are epithelialtrophic, often causing focal epithelial proliferation, commonly known as warts. More than 70 different types of human papillomaviruses have now been identified (Schiffman, & Brinton, 1995). These variations, although similarly structured, are anatomically specific, with lesions always located in the same epithelial region and with a consistency in the type of lesion that they produce. Research has identified 23 different types of HPV that infect the female and male anogenital tracts, all of which are transmitted sexually. These various HPV types are associated with a range of anogenital diseases, from the common genital wart, condyloma acuminata, to invasive squamous cell carcinoma (Park, Fujiwara, & Wright, 1995).

Human papillomaviruses associated with the anogenital region include HPV 6, 11, 16, 18, 30, 31, 33, 35, 39, 40, 42-45, 51-58, and 61 (van Muyden et al., 1999). These HPV types are also classified according to their oncogenic potential. Most are classified as low-oncogenic-risk, are associated with condyloma acuminata and low-grade SIL (CIN 1), and are rarely found in association with invasive cancer. Intermediate-risk HPV includes types 33, 35, 39, 51, 52, and 59. Intermediate types are uncommonly detected in invasive anogenital cancers, but are associated with high grade SIL (CIN 2, 3). Types 16, 18, 31, 45, 56, and 58 are the high-oncogenic-risk types and are commonly found in women with high grade SIL (CIN 3) and with invasive cancer of the cervix and vulva. Type 16 is the most commonly found high-risk virus, detected in 30% to 77% of women with high grade SIL (Park, Fujiwara, & Wright, 1995). However, HPV 16 is also common in minor grade lesions and in ASCUS. High-risk HPV types, particularly type 16, are commonly detected in ASCUS smears and in condyloma (Autillo-Touati et al., 1998); and ASCUS samples that had high-risk HPV detected were significantly more likely to have high-grade dysplasia or cancer (Lin, Tseng, Lai, Hsueh, Huang, Law, 2000). Therefore, when facing a confusing ASCUS Pap smear, screening for the presence of high-risk HPV may provide a strong prognostic barometer, indicating the need for further diagnostic testing.

When cervical cancer develops, the disease generally progress-

es over the course of several years from initial exposure to HPV, to low-grade SIL, to high-grade SIL, to carcinoma in situ, to invasive cervical carcinoma. Spontaneous regression of this process back to cytologically normal cervical tissue typically occurs at or before the low-grade SIL level. Low-grade SIL is common, usually benign and self-limiting; high-grade SIL, in contrast, is quite rare but, if left untreated, will generally progress to cancer. For this reason, when screening is dependent exclusively on Pap smear technology, high-grade SIL is considered the only true precursor to cervical cancer (Adam et al., 2000). High-oncogenic-risk HPV (types 16 and 18) positive dysplastic lesions carry the greatest risk for eventual advancement to cervical cancer.

## RISK FACTORS

Cervical dysplasia is essentially an asymptomatic condition that may result from previous exposure to HPV. A majority of women who are diagnosed with HPV will develop low-grade SIL within 4 years of infection (Schiffman, & Brinton, 1995). Other causes of dysplasia include other infectious or inflammatory agents or exposure to other reactive irritants. Most low-level dysplasia spontaneously regresses to normal. However, there is a 15% to 25% risk of low-grade SIL progressing to high-grade within two to four years. The asymptomatic nature of cervical dysplasia requires recognition of risk factors for likely exposure and contraction of HPV, particularly the HPV of high oncogenic potential (types 16, 18, 31, 45, 56, and 58).

All sexually active women are at risk for HPV (Reed, Zazove, Gregoire, Gorenflo, Lancaster, & Ruffin, 1993), the single most common sexually transmitted disease, found in as many as 65% of the general population (Adam et al., 2000). The peak prevalence of HPV occurs in women between 16 and 25 years of age. The prevalence rate drops sharply in women over the age of 30, possibly because of immunologic clearance or suppression of existing infection, or because of fewer new sexual partners resulting in less exposure to new HPV types (Schiffman, & Brinton, 1995). Women over 30 may also have a maturational protection as the vulnerable transformation zone regresses on the face of the cervix with aging. Levels of HPV remain high in women with high-grade lesions. Thirty-eight percent of HPV-positive women aged 35-39 have high-grade SIL, compared with 13.4% of women less than 19 years old (Adam et al., 2000). Low-grade SIL and HPV infection are usually diagnosed in women in their late teens and early twenties; high-grade SIL in 25-35 year-olds; and invasive cervical cancer after the age of 35-40. On average, approximately 15% of HPV positive cases will progress to high-grade SIL or carcinoma in situ within 9 years (Daley, 1998).

Since most HPV infections disappear within months of the initial diagnosis, other factors must also play a role in advancement to cervical cancer. High-oncogenic type HPV is the single most predictive co-factor for cancer progression (Schiffman, & Brinton, 1995; Adam et al., 2000). High levels of HPV and the length of time since the initial infection are also linked to higher grade lesions. A higher degree of dysplasia is often seen with a longer duration of infection. Immune-compromised women have a much greater likelihood of developing progressive SIL. In a study of HIV-positive women with no documented cervical disease (Ellerbrock et al., 2000), dysplasia was diagnosed in 20% of the study participants within three years of their HIV diagnosis. Invasive cervical cancer is a definitive diagnosis for AIDS in women who are HIV positive (Hollander, & Katz, 1999).

Other risks associated with the sexually transmitted nature of HPV include women who have known their current sexual partner less than 24 months, women with multiple sexual partners or non-monogamous partners, and women who began sexual activity at a younger age (Reed et al., 1993). Svare and colleagues (1998) compared the HPV prevalence between Danish women, where cervical cancer rates are extremely low, and Greenlandic women, where rates are nearly 4 times higher. Overall, the HPV rates were similar. In Greenland, HPV infections tended to be peak in women less than 19 years of age, followed by a dramatic drop in infection rates in women in their early 20s; whereas, HPV rates for Danish women were significantly lower in the first decades of life. The primary difference between the two groups was the age at initial onset of intercourse, indicating that early exposure to HPV increases the risk of the eventual development of cervical cancer.

Independent risk factors for the progression to cervical cancer include smoking, low income, and the use of oral contraceptives (Adam et al., 2000). Nicotine, a potential carcinogen, is concentrated in the cervical tissue of women who smoke. Smoking also presumably lowers the immune response, increasing the likelihood of progressive damage. There is a correlation between low-income level and a higher incidence of invasive cervical cancer, possibly related to a lower use of preventive care, lack of appropriate screening, and a higher incidence of HPV (Sanjose et al., 1996). Kruger-Kjaer's group (1998) explored the relationship of long-term oral contraceptive (OC) use and the progression of dysplasia. They found a correlation with OC use and the development of high-grade lesions; however, there was no relationship to the development of low-grade SIL. The estrogenized state of OC users may prevent the ectopy of the cervix from receding into the cervical canal, leaving the vulnerable area exposed.

## CLINICAL SIGNS AND SYMPTOMS

Physical symptoms associated with cervical dysplasia are rare, but include complaints of vaginal itching, odor, swelling, or visible lesions. These symptoms may be related to concomitant sexually transmitted diseases, such as *Chlamydia trachomatis* or bacterial vaginosis, which are another significant risk factor (Reed et al., 1993; Schiffman, & Brinton, 1995). Women or their male partners may present with visible condyloma, typically of the low-oncogenic-risk type, most often types 6 and 11. However, often multiple HPV types are present, requiring further typing if diagnosed visually (Cothran, & White, 1995).

The most common clinical sign of actual cervical carcinoma is a visible lesion appearing as a tumor or ulceration. Women may present with irregular or excessive vaginal bleeding or post-coital spotting; bloody or purulent, odorous, non-pruritic dis-

charge may indicate cervical ulceration and invasive lesions. Late invasive symptoms may include bladder and rectal dysfunction or fistulas and pain in the lower pelvic region (MacKay, 1999).

## DIFFERENTIAL DIAGNOSIS: THE BETHESDA SYSTEM

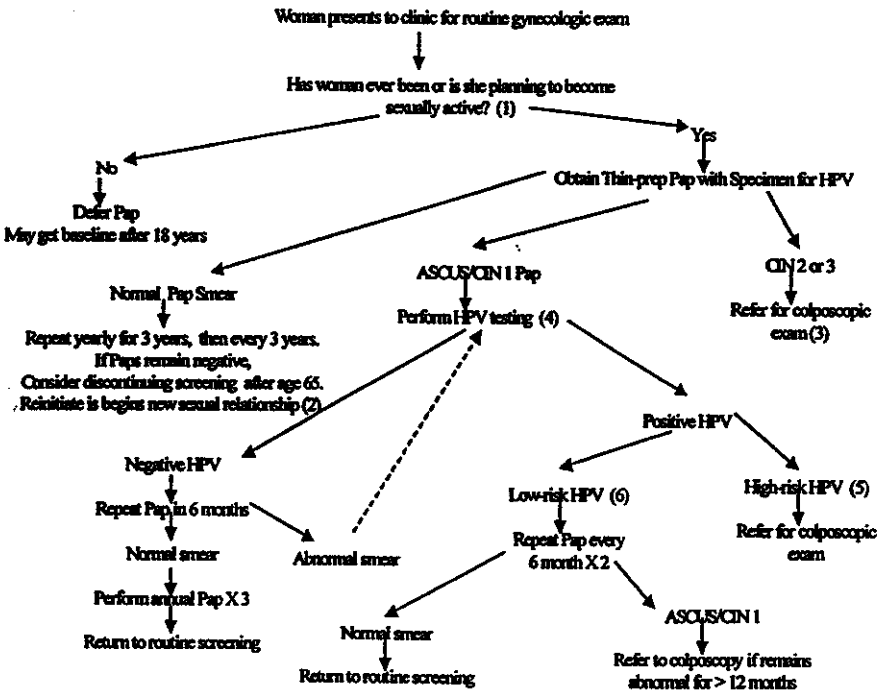
In an effort to clearly delineate the various possible cytological findings associated with the Pap smear, thus strengthening its value as a screening tool, a 1988 National Cancer Institute panel developed a standardized classification and diagnostic system known as the Bethesda System (Lunberg, 1988; Table 1). This classification system, although modified in 1991, continues to provide a useful, standardized format for the differentiation of Pap smears and the accompanying clinical diagnosis (Kurman, Henson, Herbst, Noller, & Schiffman, 1994). The Bethesda System utilizes the following descriptive diagnoses: benign cellular changes associated with infection, reactive changes, epithelial cell abnormalities, and finally, other malignant neoplasms. Evaluation of benign changes of infection include fungal, bacterial, protozoan, and viral, such as HPV. Definitive diagnoses of infectious etiology often require further confirmatory studies, such as cultures, or in the case of HPV, DNA hybrid screening. Reactive changes occur in response to inflammation, atrophy, or exposure to irritants such as chemotherapeutic agents, intrauterine contraceptive devices (IUDs), or the effects of treatment therapy.

Epithelial cell abnormalities are related to the advancement of cervical cancer. These cellular abnormalities include squamous and glandular cell changes. Squamous cell changes are classified in the Bethesda System as atypical squamous cells of undetermined significance (ASCUS), squamous intraepithelial lesion (SIL), or squamous cell carcinoma. Squamous intraepithelial lesions are further classified as low-grade or high-grade. Low-grade SIL encompasses mild dysplasia or cervical intraepithelial neoplasia grade 1 (CIN 1) and HPV. High-grade SIL includes moderate dysplasia (CIN 2), or severe dysplasia or carcinoma in situ (both graded CIN 3). Glandular cells are similarly differentiated between atypical glandular cells of undetermined significance (AGCUS), endometrial cells present when not histologically expected, adenocarcinoma, or other epithelial malignant neoplasm. Nonepithelial malignant neoplasms require a specification as to the type of malignancy (Lunberg, 1988).

The Bethesda system also includes a statement as to the adequacy of the specimen, with a recommendation for repeating the smear if it is deemed unsatisfactory. A hormonal evaluation confirms if the hormonal pattern is compatible with the woman's age and history, requiring that the clinician provide this historical information to the pathologist.

The Bethesda system has led to greater clarity and differentiation of the diagnoses of Pap smears. However, since its inception, the number of equivocal Pap smears, the ASCUS category, has grown. The potential for morbidity associated with over-read

**Figure 1.**




**Footnotes to algorithm:** This algorithm is referenced and supported with the numbers in parentheses at the end of key sections:

(1) Cervical cancer is caused by HPV, a sexually transmitted virus (Van Muyden et al., 1999). Therefore, women who are not sexually active are not at risk. Note: The practitioner must maintain a high level of suspicion and recommend the Pap smear if the sexual history is ambiguous.

(2) Women who receive screening every 3-5 years are not at significantly greater risk for invasive cervical cancer than are women who are tested annually (Wolff, 1996; Richart, 1995).

(3) High-grade SIL, CIN 2 or 3, is considered the only true precursor to cervical cancer (Adam et al., 2000; Daley, 1998).

(4) Testing of low-grade SIL and ASCUS Pap smears for HPV is a cost-effective and safe approach to avoid unnecessary colposcopic examinations (Apgar, & Brotzman, 1999).

(5) For the purpose of this algorithm, both intermediate- and high-risk-oncogenic HPV are considered "high-risk" with recommendation that colposcopy be performed. These include HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 (Park et al., 1995).

(6) Low-risk HPV include 6, 11, 30, 40, 42-44, 52-55, 57, and 61 (Park et al., 1995).

**Table 1.** Bethesda System for Reporting Cervical/Vaginal Cytological Diagnoses

Adequacy of the Specimen
Satisfactory for evaluation
Satisfactory for evaluation but limited by: (specify reason)
Unsatisfactory for evaluation: (specify reason)

General Categorization (optional)
Within normal limits
Benign cellular changes: See descriptive diagnosis
Epithelial cell abnormality: See descriptive diagnosis

Descriptive Diagnosis: Benign Cellular Changes
Infection
*Trichomonas vaginalis*
Fungal organisms morphologically consistent with *Candida* sp
Predominance of coccobacilli consistent with shift in vaginal flora
Bacteria morphologically consistent with *Actinomyces* sp
Cellular changes associated with Herpes simplex virus
Other
Reactive Changes-cellular changes associated with:
Inflammation (Includes typical repair)
Atrophy with inflammation ("atrophic vaginitis")
Radiation
Intrauterine Contraceptive Device (IUD)
Other

Descriptive Diagnosis: Epithelial Cell Abnormalities
Squamous Cell
Atypical squamous cells of undetermined significance (ASCUS): Qualify
Low-grade squamous intraepithelial lesion (SIL): HPV, mild dysplasia/CIN 1
High-grade SIL: Moderate and severe dysplasia, CIS/CIN 2 and CIN 3
Squamous Cell Carcinoma
Glandular Cell
Endometrial cells, cytologically benign, in a postmenopausal woman
Atypical glandular cells of undetermined significance (AGUS): Qualify
Endocervical adenocarcinoma
Endometrial adenocarcinoma
Extrauterine adenocarcinoma
Adenocarcinoma, not otherwise specified

Descriptive Diagnosis: Other Malignant Neoplasms

Descriptive Diagnosis: Hormonal Evaluation: (Applies to vaginal smears only)
Hormonal pattern compatible with age and history
Hormonal pattern incompatible with age and history: Specify
Hormonal pattern not possible due to: Specify

(National Cancer Institute, 2000)

**Table 2.** Sensitivity and Specificity of Pap Smears and HPV Screening

| Types of Tests | Sensitivity | Specificity |
|---|---|---|
| Pap smear—ASCUS (~5% of all Paps) | 77.7% (Schiffman et al., 2000)<br>85% (Bergeron et al., 2000)<br>66% (Cox, 1998) | 94.2% (Schiffman et al., 2000) |
| Repeat Pap smears | 76.2% (Manos et al., 1999) | |
| ASCUS Pap+ HPV—CIN 2, 3 | 89.2% (Manos et al., 1999) | 64.1% (Manos et al., 1999) |
| HPV (Digene Hybrid® Capture II)—CIN 2, 3 | 88.4% (Schiffman et al., 2000) | 89.0% (Schiffman, 2000) |
| Pap smear + HPV testing | 96.9% (Manos et al., 1999) | |

Pap smears has led some to question the value of using the Pap smear as an end-stage screening tool (Jones, 1995).

***Algorithm***

The optimal screening protocol for the prevention of cervical cancer remains controversial. However, because of the typically slow nature of the advancement from initial HPV infection to advancing dysplasia, and because low-grade lesions often regress without treatment, a reasonable and safe protocol would involve recognizing women at higher risk of dysplastic advancement and screening those women aggressively, while monitoring lower risk women with a conservative, watchful waiting approach. Women with high-grade lesions, CIN 2 or 3, require more aggressive follow-up with immediate colposcopic evaluation. If a woman has a normal Pap smear, it is reasonable to forgo HPV screening and monitor her with serial smears. The low-grade Pap smears, CIN 1 and ASCUS, remain the most confusing clinical problem. Screening for HPV in the presence of a marginal Pap smear provides objective data for further recommendations. Figure 1 is an algorithm developed by the authors and supported by a review of the literature that is based upon the screening strategy outlined above.

***Sensitivity/Specificity***

Table 2 lists the sensitivities and specificities of cervical cancer screening methods, including the Pap smear, HPV testing, and a combination approach. The slow nature of dysplastic advancement is well suited to a conservative monitoring of ambiguous or low-grade SIL (ASCUS, CIN 1). Repetitive Pap screening and/or confirmation of irregularities with HPV-typing allows for accurate diagnosis over time. The high-degree of sensitivity associated with a combination of Pap and HPV testing (96.9 %) provides a viable alternative to widespread colposcopic examinations.

Screening for HPV may also provide a first-line approach to screening for women when the Pap smear is not a feasible option. Wright, Denny, Kuhn, Pollack, and Lorincz (2000) explored this option in a study comparing the accuracy of self-collected HPV samples to that of Pap smears for cervical cancer screening. They concluded that the HPV screening is less specific but just as sensitive as the Pap smear. This demonstration that HPV self-collection may be a viable alternative to screening opens doors to the successful screening of women who were previously neglected.

***Cost Analysis***

Table 3 is an estimate of the costs for procedures related to cervical cancer screening and the time frame for receiving the results of these procedures. Colposcopies typically are scheduled shortly after an irregular Pap smear is identified, meaning that the cost of the colposcopy is additive to that of the Pap smear. Therefore, slowing decisions while monitoring dysplasia with serial screening, rather than immediate colposcopic treatment, will often allow the body to heal itself, resulting in further cost savings. The Thin-Prep™ Pap Test is significantly more expensive than the standard slide. This added cost is offset by the advantage of collecting the HPV sample at the same time as the Thin-Prep™ Pap Test. If the HPV sample is not needed, it may be discarded without further expense; if it is needed, a second collection fee will not be incurred. Forgoing annual screening in women who are at low-risk of cervical cancer would be an effective cost-control measure.

## MANAGEMENT

***Patient Education and Preparation***

Women need to understand that the Pap smear and HPV testing are screening tools used to identify pre-cancerous and cancerous cervical lesions. Table 4 is an information sheet, outlined in a question and answer format, which will help women understand how best to prevent contracting HPV and how to prepare for screening tests and treatment procedures.

**Table 3.** Cost Analysis and Timing of Tests

| | |
|---|---|
| Pap smear slide: | Negative— ~$25.00 plus office visit cost of ~$50.00-$75.00<br>Abnormal— ~$28.00 plus office visit cost of ~$50.00-$75.00 |
| Thin-Prep® Pap Test™: | ~$33.50 plus office visit cost of ~$50.00-$75.00<br>Evaluation of Pap smear takes approximately 5 days. |
| HPV testing<br>(Digene Hybrid® Capture II): | ~$67.50 (Obtained from Thin-Prep® Pap Test™ collection)<br>HPV results are obtained within 2 weeks of lab receiving specimen. |
| Colposcopy: | ~$110.00 without biopsy<br>~$135.00 with biopsy |

Results of colposcopy without biopsy are immediate. Most biopsy results are back in 2 to 3 days, although it may take up to 2 weeks to obtain results.

Note: Costs of all tests will vary with location and practice site. These estimates and time frames were obtained from personal communication with the virology lab technician, Harborview Medical Center, Seattle, WA; the senior coding analyst, Patient Accounting, Group Health Cooperative, Spokane, WA; and the cytology technician, Pathology Associates, Spokane, WA, October, 2000).

***Treatment Plan***

Invasive cervical cancer is a preventable disease. Advanced invasive cervical cancer has only a 14 % five-year survival rate (Wolff, 1996); prevention is the key to effective treatment. The 5-year survival rate is 99 % for women with localized cervical cancer, also known as CIS. On average, CIS will advance to invasive disease within two to ten years (MacKay, 1999). This slow progression allows for identification and treatment before the cancer advances.

The method of treatment is dependent upon the results of cervical screening. Early changes such as CIN 1 may be monitored for progression; these lesions often regress back to normal without treatment (Schiffman, & Brinton, 1995). As the primary prognostic indicator of cervical carcinoma, a CIN 2 or 3 diagnosis requires colposcopic evaluation, and if abnormal cells are visualized, biopsy (Daley, 1998).

Small, high-grade dysplastic lesions may be treated with ablative therapies, such as cauterization or cryotherapy (MacKay, 1999). Visible lesions may also be excised using a wire loop. For this procedure, known as a "large loop excision," to be successful, clear healthy margins surrounding the removed tissue must be present (Paraskevaidis et al., 2000). The treatment of choice for pre-invasive cancer, CIN 3 or CIS, is complete surgical removal of the transformation zone, known as conization of the cervix. Ablative therapies must be followed with regular screening, especially the first 2 years after treatment, to quickly identify recurrence (MacKay, 1999).

The treatment for advanced cervical carcinoma is dependent upon the grade of the lesion. A simple hysterectomy is the recommended treatment for CIS (stage 0) for women who have completed childbearing; however, ablative therapies as outlined above may be appropriate for women who wish to retain the uterus. Regular follow-up with Pap smears every 4 months for the first year, every 6 months for the second, and annually thereafter is vital to quickly identify recurrence in women who still have a uterus (MacKay, 1999).

Micro-invasive carcinoma (stage IA) is treated with a simple hysterectomy. Lesions extending past the cervix but not yet invading the pelvic wall (stages IB and IIA) may be treated with radical hysterectomy or radiation. Cancerous lesions that have extended past the pelvic wall (stages IIB, III, and IV) require radiation treatment (MacKay, 1999).

## CONCLUSION

Invasive cervical cancer is a needlessly deadly disease. Effective measures exist to prevent the unnecessary morbidity and mortality associated with cervical cancer. In developed countries, where established screening and treatment protocols exist, the incidence of cervical cancer has been dramatically reduced (Cuzick, 1998). However, cervical cancer remains the leading cause of cancer death in women in most developing countries (Richart, 1995). Even in the U. S., a significant portion of the population is left unscreened or inadequately screened, leading to thousands of deaths from cervical cancer each year (Cancer Statistics, 1998).

Screening has historically relied upon the Pap smear; however, Pap smear technology is not perfect. In addition to problems with Pap smear accuracy, women may not be adequately screened for a number of reasons, including lack of access to care, personal distaste for the invasive nature of the procedure, and a general misunderstanding of the preventive nature of the screening tool and the risk factors associated with cervical cancer.

Human papillomavirus is the primary cause of cervical cancer and has been identified in 90% to 100 % of cervical cancer

**Table 4.** Patient Education and Preparation

### What causes cervical cancer?

Cervical cancer is a progressive disease caused by the human papillomavirus (HPV). Because the cervix opens in the vagina, it is vulnerable to bacteria and viruses that may travel up the vagina and gather at the mouth of the cervix, sometimes causing sexually transmitted diseases. HPV is the most common of these diseases. Some types of HPV infection lead to cervical cell changes, called dysplasia. Dysplasia may eventually advance to cancer (Your Pap Exam, 1993).

### Am I at risk?

Almost all sexually active women run some risk of contracting HPV and subsequently, cervical cancer. For this reason, all sexually active women should be screened periodically, particularly within the first two years after initiating a new sexual relationship. More frequent screening may be necessary if a routine exam reveals early cervical changes or if signs of inflammation are evident.

### What is HPV?

Human papillomavirus is the virus that causes warts. To date, more than 68 different types of human papillomaviruses have been identified. Twenty-three different types of HPV have been identified that infect the genital region of men and women. These various HPV types are associated with a range of genital diseases, from the common genital wart, Condyloma, to invasive cancer of the cervix (Park et al., 1995).

### How is genital HPV spread?

As with all warts, genital HPV is spread through direct skin-to-skin contact. It is not transmitted through blood or body fluids. Genital HPV targets the moist mucous membranes surrounding the genitals. The most common form of transmission is direct contact between the infected skin on the penis, scrotum, vagina, vulva, or anus and the uninfected skin in the same areas of the partner's body (ASHA, 1995).

### How do I know if I have HPV?

Recognition of HPV can be difficult. Many people with HPV are asymptomatic, and the latency period for HPV (the time from date of infection to actual development of HPV) may be many months to years. Sometimes, you or your health-provider may see the HPV lesions. If your sexual partner has a definitive diagnosis, then you are likely to be carrying the virus as well. Without a visual confirmation of the disease, HPV may be identified through viral screening. Sometimes, the Pap smear will show changes indicative of HPV (ASHA, 1995).

### What is a Pap smear?

The Pap smear is a part of the pelvic exam used to examine the cells of the cervix to screen for signs of pre-cancerous lesions and cancer. Incidentally, Pap smears may identify cellular changes associated with infection. If these problems are caught early, they can usually be treated successfully. The Pap is not a specific test for HPV, although sometimes the results suggest that HPV may be present (Your Pap Exam, 1993).

### How is a Pap smear obtained?

You will need to undress from the waist down, lie on the exam table, and place your legs in the table stirrups. Your health-care provider will then open your vagina with an instrument called a speculum. She will then obtain samples from your cervix with a small spatula or swab, placing them on a slide to be sent to the lab for evaluation. She may also obtain samples for other testing, such as HPV or other infections (Your Pap Exam, 1993).

### When should I have a Pap smear?

All women should begin having Pap screening when they become or are preparing to become sexually active. After the initial screen, you and your provider will need to determine the frequency of future smears. Usually, yearly exams are recommended for 3-4 years, followed by screening every 3 to 5 years. Generally, women who have had a history of sexually transmitted infections should continue to have yearly screening. If abnormal cells are identified, more frequent screening, more in-depth testing to obtain a definitive diagnosis, or treatment may be necessary (Apgar, & Brotzman, 1999).

*Continued on next page*

### How should I prepare for the Pap smear?

1. Schedule the Pap smear between menstrual cycles. Menstrual blood may obscure any cells obtained, making them impossible to evaluate.
2. Avoid vaginal creams, foams, or suppositories for a week before the exam. Do not douche, use tampons, or have sexual intercourse the day before the exam.
3. Follow-up the results of your Pap smear with your health-care provider. Most offices will have a system of results notification. However, if you do not hear from the health-care office, call your provider; do not assume that no news is good news.
4. Discuss how frequently you should return for screening. The answer will probably depend on your medical history (A Patient Guide, 1995).

### Can I prevent HPV?

If you are sexually active, HPV can be difficult to prevent because it is often difficult to identify, and it is quite prevalent. HPV is contracted through body-to-body contact. Therefore, because a condom does not adequately cover the entire genital region, it is not an effective barrier to HPV. Use of the condom or the diaphragm may protect the cervix, because it is completely covered with these barrier methods. Obviously, condom usage remains extremely important as a tool for the prevention of most other sexually transmitted infections. The female condom, which covers the entire vulva, may be more protective (Cothran, & White, 1995).

The best protection against HPV is to limit your number of sexual partners and to know your partner's sexual history. Women who begin sexual activity at an older age are statistically less likely to develop problems associated with HPV. As the cervix matures, the vulnerable area becomes smaller.

### Is there a cure for HPV?

No. It may be possible for your body's own immune system to clear the virus. However, most often HPV is a virus that stays in your body once you have contracted it. Treatment can destroy the lesions, and for most women, the immune system will help keep the HPV under control. Over time, the chance of recurrent abnormalities from the HPV lessens.

### Is there anything else that I can do to protect myself?

Yes. The best protection is to keep your immune system as healthy as possible. In addition to not smoking this means eating well and protecting yourself against other sexually transmitted infections by limiting your number of sexual partners and by using condoms. Women who smoke have a higher rate of cervical cancer; smoking may inhibit the immune system, preventing or slowing repair of abnormal tissue.

lesions. The identification of high-oncogenic-risk HPV in the setting of a questionable Pap smear result supports aggressive treatment. Conversely, a negative HPV result provides objective evidence that a conservative watchful-waiting approach to treatment is appropriate. Screening for HPV as an adjunct to the traditional Pap smear assists in the determination of an appropriate, cost-effective treatment plan. The future of cervical cancer screening lies in the continued advancement of HPV testing. The key for the practitioner is to identify women at risk of cervical cancer, counsel them on measures to lower that risk, and screen appropriately.

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# Original Articles

## Periodic Abstinence From Pap (PAP) Smear Study: Women's Perceptions of Pap Smear Screening

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## ABSTRACT

**BACKGROUND The purpose of this study was to explore attitudes, beliefs, and perceived barriers to risk-based cervical cancer screening through focus group interviews of patients.**

**METHODS We conducted 8 focus group interviews of women using semistructured interviews. The investigators independently reviewed the focus group transcripts and identified the overall themes and themes unique to each question using an immersion and crystallization approach.**

**RESULTS Women are in agreement that cervical cancer screening is important and that women should get Pap smears regularly as an important way of protecting their health. They are not open to the idea of reducing the frequency of Papanicolaou (Pap) smears, however, because they perceive annual screening to be successful in reducing cervical cancer mortality. Additionally, they have concerns about test accuracy. Women are distrustful of the rationale for reducing the frequency of Pap smears. Women's previous bad experiences have reinforced their need for self-advocacy.**

**CONCLUSION Women are reluctant to engage in risk-based cervical cancer screening. In this environment, risk-based cervical cancer screening recommendations are likely to be met with resistance.**

**Key words:**

Attitude to health

cervix neoplasms/diagnosis

community health care

health promotion

mass screening

Papanicolaou test

practice-based research

public health

qualitative research

## INTRODUCTION

Each year approximately 16,000 women in the United States have cervical cancer diagnosed and about 4,800 die of this disease.[1] Many groups, including the American Cancer Society[2] [3] and the American College of Obstetricians and Gynecologists,[4] recommend annual Papanicolaou (Pap) testing, because this practice might have contributed to the declining incidence of invasive cervical cancer during the past 40 years.[5] Recommendations for Pap smear frequency are in conflict, however. Some groups, including the US Preventive Services Task Force[5] and the Canadian Task Force,[6] suggest that low-risk women need Pap smears only every 3 years after 3 consecutive normal Pap smear results. These recommendations are based upon data from 8 cervical cancer screening programs with more than 1.8 million women.[7] These programs show that the cumulative incidence of invasive cervical cancer was reduced 64.1% when the interval between Pap tests was 10 years, 83.6% at 5 years, 90.8% at 3 years, 92.5% at 2 years, and 93.5% at 1 year.

Putting risk-based screening recommendations into practice, however, presents difficulty for health care providers and patients. Inquiring about risk factors, such as sexual habits, is often embarrassing (to providers and patients), and depending upon how the risk factors are assessed, the findings can have questionable validity.[8] [9] [10] [11] [12] [13] [14] [15] [16] Additionally, some risk factors (race, for example[17] ), can be poor predictors compared with other factors (such as number of sexual partners), and no adequate models exist for predicting cervical cancer. Finally, concerns have been raised about compliance with other screening procedures, such

as mammography, clinical breast examinations, and fecal occult blood testing, if the frequency of cervical cancer screening is reduced.[18] [19] [20] [21] [22]

We designed a study to assess the feasibility of risk-based cervical cancer screening and to develop an instrument to facilitate the assessment of cervical cancer risk factors. If providers are to adopt recommendations for risk-based screening, it is critical to understand the perceptions, barriers, and concerns of the women they serve. Rolnick and colleagues[23] assessed the perceptions of patients about the frequency of Pap smears. Their study surveyed 673 women in a large health maintenance organization. More than one half of the women did not know that the recommendations for cervical cancer screening had changed. Of these women, 20% were skeptical and 50% made negative comments. These data raise concerns about women's willingness to engage in risk-based screening. The purpose of this study was to explore attitudes, beliefs, and perceived barriers to risk-based cervical cancer screening through focus group interviews of patients from a wide range of backgrounds.

## METHODS

### *Overview*

This study was conducted as part of a larger study to assess the feasibility of risk-based cervical cancer screening and to develop an instrument to facilitate the assessment of cervical cancer risk factors. We conducted focus group interviews with women seeking care from their primary care physician who were enrolled in a study of risk-based cervical cancer screening. We used semistructured interviews to identify important ideas and concerns about implementing risk-based cervical cancer screening. The instruments and procedures used in this study were reviewed and approved by the Michigan State University Committee on Research Involving Human Subjects and the Sparrow Health System Human Subjects Committee.

### *Subjects and Setting*

We consecutively recruited women older than 18 years from 8 practices located in 3 different settings: urban practices serving a large percentage of indigent women, a university health center serving mostly middle-class women, and a rural family practice residency. These practices in aggregate serve diverse groups of women. For the focus group interviews, we planned to enroll approximately 60 participants to ensure adequate representation from several potential strata. Several institutional review boards approved the study, and we obtained consent from all participants. We included women aged between 18 and 65 years regardless of the reason for their visit. We excluded women who had had a hysterectomy and those with a history of cervical cancer.

### *Procedures*

For purposes of the larger study, we used a stratified sampling strategy to ensure the recruitment of at least 200 women of minority race from 600 potential subjects. We approached 2,106 consecutive women attending the offices of the participating practices and asked them to complete a brief questionnaire that asked about demographics, smoking status, sexual practices and partners, previous sexually transmitted diseases, and abnormal Pap

smear results. After completing the screening questionnaire, the women who met the eligibility criteria listed above (n = 1,271) were asked about their willingness to participate in a focus group. Of the 812 (64% of those eligible) women who expressed interest in the focus group, we attempted to contact all by telephone with a follow-up mailed invitational letter.

For the focus group interviews, we recruited patients from all 8 participating practices. We invited women consecutively until 20 women agreed to participate in each group. We anticipated that of these 20 women, 6 to10 would actually attend the session at the specific time and location. We purposefully sampled each stratum to achieve 8 focus groups that were homogeneous for at least one of the following characteristics: age (younger than 40 years and 40 years and older), education (12 years or less and more than 12 years), and race (white and nonwhite). We used 40 years of age as a cutoff because of transitions in competing health issues, including sexually transmitted diseases, reproduction, and other preventive health measures that change around 40 years. We used high school education as a proxy for socioeconomic status and race strata to ease potential communication barriers that might occur within heterogeneous groups.

We held the focus group interviews in locations convenient to each of the practices: local school library, community health center meeting room, and conference rooms at clinical sites. We held each session after normal clinical hours. We compensated the participants for their time and provided food and beverages during the sessions.

A trained African American female moderator conducted the focus group interviews using semistructured methods (described in an online supplemental Appendix at http://www.annfammed.org/cgi/content/ full/1/4/203/DC1) based upon the Patient Path Model[24] and on the Behavioral Change Model.[25] She began each session with a brief orientation to the topic of health screening. She also developed with the group the rules for conduct of the session that would ensure privacy, respect, and flow of discussion. She then proceeded with specific questions and prompts to explore further issues raised by the group in response to the items.

We made tape recordings of all the sessions, and field notes were taken by a second research associate who was present during the focus group interviews. The field notes summarized major themes from the note taker's perspective and provided the observer's insights into the emotional content, personality, demeanor, and feelings of the focus group participants.

### *Data Analysis*

We transcribed tape recordings of the focus group interviews. From these transcripts and the notes taken at the time of the focus group interview, the 3 senior investigators independently identified the overall themes and themes unique to each question using an immersion and crystallization approach.[26] We held meetings with the senior investigators to reach consensus on themes and used the audiotapes to assist in resolving discrepancies. We then categorized the themes and coded the data collected in the focus groups. We had no a priori coding scheme but identified codes from within the transcripts themselves. After summarizing the results, we returned to the field notes to assess the comprehensiveness and accuracy of our data extraction.

## RESULTS

The focus groups included between 4 and 21 women (Table 1) . There were 4 groups homogeneous for race (1 including only African American women, 1 with only Hispanic women, and 2 with only white women); 2 groups with women either younger than 40 years or 40 years and older; 4 groups of women with high school or less education, and 4 groups with women who had more than a high school education.

**TABLE 1 – Demographic Characteristics of Focus Group Participants**

| Group | Number of Participants | Age (Years) | Race | Education |
|---|---|---|---|---|
| 1 | 6 | Diverse<br>Mean: 43.8<br>Range: 32–64 | Black, African American | 12 years plus some college |
| 2 | 4 | Less than 40<br>Mean: 27.8<br>Range: 22–33 | White | Less than 12 years |
| 3 | 8 | Less than 45<br>Mean: 34.9<br>Range: 23–43 | Diverse | Some college education 87.5% minimum of bachelor's degree |
| 4 | 13 | 40 and older<br>Mean: 48.1<br>Range: 40–63 | White | 12 years or higher<br>Range: 12 years to postgraduate degree |
| 5 | 7 | Diverse<br>Mean: 41.9<br>Range: 26–54 | Diverse | 12 years or less |

| | | | | |
|---|---|---|---|---|
| 6 | 5 | Diverse<br>Mean: 42.8<br>Range: 23–61 | Hispanic | Diverse<br>80% less than 12 years<br>Range: 10 years to 1 year of college |
| 7 | 21 | Diverse<br>Mean: 38.7<br>Range: 20–61 | Diverse | 12 years or higher |
| 8 | 4 | 39 and older<br>Mean: 43<br>Range: 39–53 | Diverse | Diverse<br>Range: 9 years to some college |

***Pap Smear Screening***

Women across all 8 groups were consistent in support of routine cervical cancer screening with Pap smears. Most women in each group believed strongly that yearly screening was important, although not all women were actually screened yearly, and a few had not had a Pap smear within the preceding 3 years. Sample comments from women included: "Well, I know that I have to have one, you know, if it is the difference between life and death ...," and "You cannot tell me one reason that would be good enough to not have one." Reasons provided by women for yearly screening included fear of rapid disease progression, worry about inaccuracy of Pap smears, an appreciation of the decrease in death rates from cervical cancer associated with increases in Pap testing, and a strong conviction that obtaining Pap smears was doing something important for one's health and one's family.

When asked about the possibility of risk-based cervical cancer screening (supplemental Appendix, questions 6 and 7), most women in each group were firmly set against this practice. Phrases such as "Russian roulette" and "feel cheated" were used to describe these convictions. One or two women in each group were willing to consider risk-based screening if advised by their health provider. Only 1 woman, who was willing to consider risk-based screening, obtained Pap smears at a lesser frequency of 2-year intervals.

A few women believed that reducing the frequency of Pap smears was warranted for women who had a hysterectomy, were older, or were not sexually active, but these opinions provoked a great deal of discussion in support of yearly testing for these groups of women as well. In fact, women, in several different groups independently were in support of increasing testing to every 6 months as women aged or in the presence of risk factors or a previous abnormal Pap smear finding. In support of their position for routine yearly testing, many women related stories about friends or family who had abnormal Pap smear findings or cervical cancer diagnosed.

Women also discussed when it was appropriate to begin screening Pap smears. Some women, across 5 groups and representing different racial mixes and the full spectrum of educational attainment, believed that Pap smears should begin at the onset of menses. Women in 5 of the 8 groups believed that the onset of sexual activity or upon reaching a certain age threshold (16 to 20 years of age, 6 groups) was the optimal time to begin testing.

### *Test Characteristics*

When asked about the perceived accuracy of Pap smears, women in 7 of the 8 groups reported concerns about false-negative and false-positive test results. One woman's concern about the overall accuracy is reflected in the following statement, "Because, sometimes they're right and sometimes they're wrong. You can go in and get a wrong one, and then you're all scared, then like 2 days later, or whatever, you can go in and get a right one. So they're not really adequate." Only 3 women across 3 different groups believed that the test was highly accurate. A few women in each of 4 different groups reported that a normal Pap test result was reassuring about one's general health. One woman said, "I think they are very effective, because they check for more than just cancer. I mean, us women can have yeast infections, and different kinds of things, and those Pap smears, when they check you, they will let you know whatever's wrong with your body. So I think they're very effective." Most women, however, understood that Pap smears for cervical cancer screening represented only one component of preventive health care.

### *Risk Factors*

Women expressed particular confusion about cervical cancer progression (mentioned in 5 groups), the role of family history (mentioned in 6 groups), and the terminology used to describe abnormalities. For example, several women used such terms as "high normal" smears in describing their own abnormal reports. From the 3 groups of women with more than high school education, human papilloma virus and its association with cervical cancer was mentioned, but these women appeared equally uncertain as to what it meant with respect to screening.

Risk factors for cervical cancer that were mentioned included sexually transmitted diseases, sexual activity, multiple partners, age, smoking, and having a previous abnormal Pap smear finding. There were a number of misconceptions about other potential risk factors. For example, some women also mentioned being overweight and using birth control pills or tampons as potential risk factors.

### *Barriers, Enablers, and Information Sources*

The women also identified a number of barriers and enablers to obtaining Pap smears, which are summarized in Table 2 .

**TABLE 2 -- Barriers and Enablers to Pap Test Screening Identified by Focus Group Participants**

| Barriers | Enablers |
|---|---|
| Economic, insurance | Physician-based |
| Patient factors | Female |

| | |
|---|---|
| Low personal priority | Generalist |
| Fear | Specialist |
| Embarrassment and discomfort (the "yucky" factor) | Good skill in communication and listening |
| Fatalism | Reminder systems |
| Time/scheduling | Insurance |
| Confidentiality | Office-based |
| Prior sexual abuse | Patient |
| Physician and staff factors | Free clinics, health department |
| Reluctance/not approachable | Contraception prescribing |
| Scheduling | Parent encouragement |
| Time constraints | Public education |
| Lack of continuity | Books |
| | Media |

Note: the items in this table are presented in no particular order.

*Self Advocacy*

Women from 7 of the 8 groups were quite vocal about taking responsibility for obtaining health information and cancer-screening information and testing. This important self-advocacy theme represented a consensus within the 7 groups and is reflected in the following statements: "I think that sometimes you have to be able to do research on your own. That's the key to me for having good health because you cannot just depend on the doctor to give you all the information."

Some women spoke of the need to work in collaboration with their physician. "But I think we are partners with our doctor ... we know our body better than they do. But they kind of need to hear from us so that they can kind of determine what it is they need to do to help us." Other women, however, reported bad experiences during a particular visit, which resulted in a lack of trust. Others stated a need to be assertive to get the information that they need from their physicians. Some women believed that doctors might misinform them because of "kickbacks" or money obtained from Pap smear screening.

Some women were suspicious that recommendations for Pap smear screening intervals were driven by organized medicine and the insurance industry, which were not looking out for their interests. "I don't think HMOs are looking for quality. They're looking to save their pocket, and that's a fact." Even when women are in trusting relationships with health providers, a previous experience often resulted in taking greater self-advocacy roles. "I don't take what my doctor says as gospel because I've had breast cancer and I firmly believe that if I had followed my original doctor's recommendations, I'd be dead now. I learned at that point that you have to take control, do the research and find what's going on."

***Powerful Narratives***

Two major themes emerged from the most powerful stories shared by these women: abuse by

clinicians and the role of personal experiences with advanced cancers detected at late stages. One woman shared the following story. "I think that a lot of the male men (sic), they don't care if they go in there and take your guts out. ... One time, I went in there and he started yelling at me because I moved. ... I jumped because he didn't tell me what he was going to do. ... He threw down his utensils and was swearing at me."

Another woman was particularly touched by her experience caring for another. "I worked at hospice and saw this woman on the last day of her life. She had cervical cancer that had spread through her body. That was one of the most horrific things I had ever seen ... she was like 55 or 60, so ... why risk it? It is not a big deal."

### *Field Notes*

On review of the field notes, we found that all major themes were addressed in the primary analysis. A few additional triggers for initiating Pap smears were mentioned, including becoming pregnant and discovering menstrual problems. In one group there was a sense from the women that Pap smear examinations were not as comprehensive as they should be. Women in one group were particularly concerned about waiting for their Pap smear results. There was a strong impression from the moderator about the importance of women's stories and their impact on their health concerns and decisions.

## DISCUSSION

The women who participated in these focus group interviews strongly believed that annual (or even more frequent) screening is very important. The messages of the 1960s that, among other things, linked contraception and getting Pap smears have been extremely effective. The habit of having an annual visit to a clinician for a Pap smear appears to be firmly entrenched. We speculate that the years of socialization by the media and various organizations promoting Pap smears as an integral part of women's health care will be difficult to overcome. It is not surprising, then, that women in this study are reluctant to consider risk-based cervical cancer screening. In part, their reluctance appears to be based on a lack of knowledge about the risk factors for cervical cancer, its natural history, and the effectiveness of annual compared with triennial screening.

To overcome the misperceptions and concerns expressed will require considerable education, communication, and reassurance. The women in this study prefer a proactive approach, in part because of mistrust of physicians, test characteristics, and the perceived success of yearly strategies in reducing cervical cancer. Whereas some women were aware of the shifting recommendations for Pap smear screening, they were unaware of the underlying rationale. Women are suspicious that changes in the recommended screening intervals are motivated by economic factors and not by science. Although the discussion included potential health information sources for women, the opposition to less frequent screening prevented the groups from providing strategies to implement risk-based cervical cancer screening.

We were especially impressed with the role of narratives about their personal experiences and those of loved ones in accessing health care. These stories had common themes, including impersonal providers and staff, poor communication, limited access, and abuse. Although these experiences were indirectly related to the research, they were prominent in the women's

memories and colored their willingness to change their beliefs or alter their practices.

We identified several limitations in this study. We recruited women who were seeking care from their usual health caregiver and were willing to participate in a study; therefore, their views might not represent those of women in the community. The consistency of themes across groups is striking, however, and these themes are likely to represent important issues for women who are already obtaining care from a health clinician. The group dynamics, while facilitating discussion in some instances, might have suppressed more timid members from contributing, especially as we had groups that were quite large. Although we used an experienced mediator to try to draw out alternate viewpoints, it is possible that some opinions were missed. We held some group sessions that were homogeneous and others that were heterogeneous with respect to ethnicity, age, and educational level. We noted no differences in themes across the groups with the exception of issues related to access to health care.

The authors are struck by the parallels of women's reluctance to reduce or abandon screening using a method that is perceived to be highly effective and the secular trends toward the use of more screening modalities without regard to their effectiveness. The Star Trek Tricorder total body evaluation that gives perfect health information is an image we have difficulty abandoning. "I wouldn't mind if there were more screenings. I know they have whole body scans, so I can just stand there and they can tell me if there is anything hiding." In contradistinction, health caregivers have difficulty abandoning questionable practices. Many ineffective modalities, such as the routine antenatal sonogram and electron beam computerized tomography, have reached boutique status because clinicians cannot agree on their appropriate use. It should be no surprise that women are reluctant to reduce the use of Pap smears.

We identified a number of important themes shared by the women in this study about cervical cancer screening. Women are reluctant to risk adversely affecting a successful approach by reducing the frequency of Pap smears. Women are distrustful of the rationale for reducing the frequency of Pap smears, but they are also empowered to get the information they need to make decisions. This latter point provides an opportunity to influence their belief systems. We encourage future investigators and policy makers to include the opinions and concerns of women before or in concert with changing guidelines or in planning future research in this area.

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# 2001 Consensus Guidelines for the Management of Women With Cervical Cytological Abnormalities

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for the 2001 ASCCP-Sponsored Consensus Conference

**Objective** To provide evidence-based consensus guidelines for the management of women with cervical cytological abnormalities and cervical cancer precursors.

**Participants** A panel of 121 experts in the diagnosis and management of cervical cancer precursors, including representatives from 29 professional organizations, federal agencies, and national and international health organizations, were invited to participate in a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP).

**Evidence and Consensus Process** Guidelines for the management of women with cervical cytological abnormalities were developed through a multistep process. Starting 6 months before the conference, working groups developed draft management guidelines based on formal literature reviews of English-language articles published in 1988-2001, as well as input from the professional community at large, obtained using interactive Internet-based bulletin boards. On September 6-8, 2001, the ASCCP Consensus Conference was held in Bethesda, Md. Guidelines with supporting evidence were presented and underwent discussion, revision, and voting.

**Conclusions** Management of women with atypical squamous cells (ASC) depends on whether the Papanicolaou test is subcategorized as of undetermined significance (ASC-US) or as cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H). Women with ASC-US should be managed using a program of 2 repeat cytology tests, immediate colposcopy, or DNA testing for high-risk types of human papillomavirus (HPV). Testing for HPV DNA is the preferred approach when liquid-based cytology is used for screening. In most instances, women with ASC-H, low-grade squamous intraepithelial lesion, HSIL, and atypical glandular cells should be referred for immediate colposcopic evaluation.

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EACH YEAR APPROXIMATELY 50 million women undergo Papanicolaou testing in the United States.[1] Of these, approximately 3.5 million (7%) are diagnosed with a cytological abnormality requiring additional follow-up or evaluation.[2] Determining which women with cytological abnormalities are at risk for significant cervical disease, performing appropriate diagnostic workups, and treating cancer precursors present a major public health challenge.

There are a number of reasons why comprehensive, evidence-based guidelines are needed for the management of women with cervical cytological abnormalities. One reason is that a National Cancer Institute workshop recently revised the criteria used by cytologists to render certain cytological interpretations, as well as the terminology used for reporting cervical cytology results (ie, the Bethesda System).[3] Other reasons include a better understanding of the pathogenesis and natural history of human papillomavirus (HPV) and cervical cancer precursors, and the availability of data from the National Cancer Institute's randomized Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion (ASCUS/LSIL) Triage Study (ALTS) (D. Solomon, MD, written communication, September 6-8, 2001). Moreover, existing guidelines were developed before sensitive molecular methods for detecting high-risk types of HPV and liquid-based cytology methods became widely available. Data are now available suggesting that these new technologies, when used together, are attractive alternatives to older approaches for managing women with cer-

See also pp 2114 and 2140.

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tant to recognize that these guidelines should never be a substitute for clinical judgment. Clinicians need to practice clinical discretion when applying a guideline to an individual patient since it is impossible to develop guidelines that apply to all situations.

The guidelines use the 2001 Bethesda System for cytological classification that uses the terms LSIL and HSIL to refer to cervical cancer precursors.[3] We have adopted a 2-tiered terminology for the histopathological classification of cervical intraepithelial neoplasia (CIN): CIN 1 denotes low-grade precursors and CIN 2,3 denotes high-grade precursors.[8] Detailed algorithms describing the 2001 Consensus Guidelines, and a glossary of terms used in the guidelines, are available at the ASCCP Web site (glossary also available at http://jama.ama-assn.org).

## ATYPICAL SQUAMOUS CELLS

The 2001 Bethesda System subdivides atypical squamous cells (ASC) into 2 categories: atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells, cannot exclude HSIL (ASC-H).[3] Several considerations underlie the consensus guidelines for the management of ASC. First, even among expert cytologists, the interpretation of a cervical cytology result as ASC is poorly reproducible.[9-11] Second, a woman with a cervical cytology result interpreted as ASC has a 5% to 17% chance of having CIN 2,3 confirmed by biopsy, while CIN 2,3 is identified in 24% to 94% of those with ASC-H.[5,12-20] However, the risk of invasive cervical cancer in a woman with ASC is low (approximately 0.1% to 0.2%).[21,22] These considerations suggest that a woman with ASC requires some form of additional workup or follow-up, but that consideration should be given to preventing unnecessary inconvenience, anxiety, cost, and discomfort. Immunosuppressed women with ASC are at increased risk for CIN 2,3, and high-risk types of HPV are frequently detected in immunosuppressed women, suggesting that these women require special consideration.[23,24] Conversely, postmenopausal women with ASC appear to be at lower risk for CIN 2,3 than premenopausal women.[14,25,26]

### Approaches to Managing Women With ASC

Repeating cervical cytological testing at specified intervals, performing immediate colposcopy, HPV DNA testing for high-risk types, or combining a single repeat cervical cytological test with another adjunctive method are all widely used in the United States for managing women with ASC. Each of these approaches has advantages and disadvantages.

Although repeat cytological testing is widely used for managing women with ASC, the sensitivity of a single repeat test for detecting CIN 2,3 is relatively low (0.67-0.85) (TABLE 2).[4,5,12,27-30] To compensate for this, previous guidelines have recommended that testing be repeated at specified intervals until a patient has several consecutive "negative for squamous intraepithelial lesion or malignancy" results before returning to routine screening.[31-33] The most appropriate threshold for referring women for colposcopy has been evaluated in several studies and appears to be a repeat cytology result of ASC or greater.[12,34,35] Referral thresholds of LSIL and HSIL miss many women with biopsy-confirmed CIN 2,3. There is limited information available on key parameters (eg, timing of the repeat test, number of repeats necessary) needed to design a program of repeat cytological testing. Repeating cervical cytological testing has several disadvantages compared with other management options. It can delay the diagnosis of CIN 2,3 or cervical cancer and, even in populations with good access to health care, adherence to recommendations becomes a problem for any follow-up that requires multiple visits.

The advantage of colposcopy for the evaluation of women with ASC is that it immediately informs both the woman and the clinician of the presence or absence of significant disease. A meta-analysis of the performance of colposcopy reported that the weighted mean sensitivity for distinguishing normal cervical tissue from abnormal tissue by colposcopy was 0.96 and the weighted mean specificity was 0.48.[36] However, since most published studies have been performed by expert colposcopists and have not uniformly obtained histological samples from normal-appearing tissue, the sensitivity of colposcopy in the published literature may be higher than would be observed in routine clinical practice. The disadvantages of colposcopy are that many women consider the procedure to be uncomfortable, referral for colposcopy may raise false con-

**Table 2.** HPV DNA Testing for the Management of Women With ASC*

| Source, y | Patients, No. | Repeat Cytology | | HPV DNA Testing | |
|---|---|---|---|---|---|
| | | Sensitivity (95% CI) | % Referred (95% CI) | Sensitivity (95% CI) | % Referred (95% CI) |
| Ferris et al,[28] 1998; Ferris et al,[35] 1998† | 144 | 0.70 (0.42-0.98) | 56 (49-64) | 0.89 (0.69-1.00) | 43 (35-51) |
| Manos et al,[4] 1999† | 995 | 0.76 (0.65-0.87) | 38 (35-41) | 0.89 (0.81-0.97) | 39 (36-42) |
| Bergeron et al,[27] 2000 | 111 | 0.67 (0.50-1.00) | 32 (23-41) | 0.83 (0.62-1.00) | 43 (34-52) |
| Lin et al,[29] 2000 | 74 | NA | NA | 1.00 | 53 (42-64) |
| Shlay et al,[30] 2000 | 200 | NA | NA | 0.93 (0.81-1.00) | 31 (25-37) |
| Solomon et al,[12]† | 2324 | 0.85 (0.81-0.89) | 59 (57-61) | 0.96 (0.94-0.98) | 56 (54-58) |

*DNA testing for high-risk types of human papillomavirus (HPV) was performed using the Hybrid Capture II HPV DNA Assay (Digene Inc, Gaithersburg, Md). ASC indicates atypical squamous cells; CI, confidence interval; and NA, not applicable.
†HPV DNA testing was performed from liquid-based cytology specimens.


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who are found to have ASC or greater on their repeat cervical cytology tests or who subsequently test positive for high-risk HPV DNA should be referred for colposcopy.

## ATYPICAL GLANDULAR CELLS AND ADENOCARCINOMA IN SITU

The 2001 Bethesda System classifies glandular cell abnormalities less severe than adenocarcinoma into 3 categories[3]: atypical glandular cells, either endocervical, endometrial, or "glandular cells" not otherwise specified (AGC NOS); atypical glandular cells, either endocervical or "glandular cells" favor neoplasia (AGC "favor neoplasia"); and endocervical adenocarcinoma in situ (AIS).

The AGC category is associated with a substantially greater risk for cervical neoplasia than the ASC or LSIL categories.[38] Various studies have found that 9% to 54% of women with AGC have biopsy-confirmed CIN, 0% to 8% have biopsy-confirmed AIS, and less than 1% to 9% have invasive carcinoma.[21,38-44] The 2001 Bethesda System separated AGC NOS from AGC "favor neoplasia" because it was believed that these 2 categories represent women at different risk for having significant disease, either squamous or glandular. Although the risk of having a high-grade lesion in various studies overlap, studies from individual centers have usually reported a higher risk among women with AGC "favor neoplasia" than among those with AGC NOS. Biopsy-confirmed high-grade lesions including CIN 2,3, AIS, or invasive cancer have been found in 9% to 41% of women with AGC NOS compared with 27% to 96% of women with AGC "favor neoplasia."[21,38-46] The cytological interpretation of AIS is associated with a very high risk of a woman having either AIS (48%-69%) or invasive cervical adenocarcinoma (38%).[49,50]

### Approaches to Managing Women With AGC and AIS

**Initial Workup and Evaluation.** All 3 methods (ie, repeat cytology, colposcopy, and endocervical sampling) traditionally used to evaluate women with AGC or AIS have limitations. Screening cervical cytology has a sensitivity of only 50% to 72% for identifying glandular neoplasia, and CIN is the most common form of neoplasia identified in women with a cytological result of AGC.[38-44,51-54] Moreover, repeat cervical cytological testing has been shown to be less sensitive than colposcopy for detecting CIN 2,3 and glandular lesions in women with AGC.[52] This supports the inclusion of colposcopy in the workup of women with AGC. However, many cases of biopsy-confirmed AIS have had no observed colposcopic abnormalities, and even combinations of cytological testing and colposcopy can miss small endocervical adenocarcinomas and AIS localized in the endocervical canal.[55] Although the sensitivity of endocervical sampling for the detection of glandular neoplasia localized in the endocervical canal is not well defined, many cases of biopsy-confirmed AIS have had no colposcopic abnormalities and in some series endocervical sampling has detected glandular neoplasia that was missed at colposcopy.[52,55-57] Age is a key factor in determining the frequency and type of neoplasia found in women with AGC. There is a higher risk of CIN 2,3 and AIS in premenopausal women compared with postmenopausal women, and premenopausal women with AGC have a lower risk of endometrial hyperplasia or cancer.[44,58-60] Approximately half of women with biopsy-confirmed AIS have a coexisting squamous abnormality and therefore the presence of a coexisting squamous abnormality does not change the management of women with AGC or AIS.[61-63]

**Subsequent Workup and Evaluation of Women in Whom Lesions Are Not Identified.** Because of the poor sensitivity of colposcopy, cytology, and endocervical sampling for detecting glandular abnormalities, women with AGC who do not have cervical neoplasia detected at the initial workup continue to be at increased risk. Because the risk varies with the subclassification of AGC (ie, either NOS or "favor neoplasia"), the most appropriate form of follow-up depends on the specific subclassification of AGC. Women with AGC NOS who have a negative initial workup have been found in some studies to be at relatively low risk for having a missed significant lesion.[47] Therefore, some authors have recommended that these patients can be followed up with repeat cytological testing.[47,64] However, women who have persistent AGC are at high risk for significant glandular disease.[47,48] In some studies, women with a cytological result of AGC "favor neoplasia" or AIS who have a negative initial workup have been diagnosed subsequently with significant lesions, including invasive cancers.[39,44,52] Therefore, some authors have suggested that the risk of a significant lesion in such patients is too great to rely on repeat cervical cytological testing alone, and have suggested that a diagnostic excisional procedure be used in this situation to rule out a serious endocervical lesion.[47,64] Other studies have reported that thermal damage can preclude the assessment of margins in electrosurgical or laser conization specimens obtained from women being evaluated for glandular cytological abnormalities and have recommended that cold-knife conizations be used in this setting.[61,65] The management of glandular cytological abnormalities can be quite challenging and women with unexplained glandular cytological findings should be referred to a clinician experienced in the management of complex cytological situations.

### Recommendations for Managing Women With AGC or AIS

**Initial Evaluation.** Colposcopy with endocervical sampling is recommended for women with all subcategories of AGC, with the exception that women with atypical endometrial cells should initially be evaluated with endometrial sampling (AII). Endometrial sampling should be performed in conjunction with colposcopy in women older than 35 years with AGC and in younger women with AGC who have unexplained vaginal bleeding (AII). Colposcopy with endocervical sampling is also


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**Satisfactory Colposcopy.** Endocervical sampling is acceptable for nonpregnant women with satisfactory colposcopic findings and a lesion identified in the transformation zone (CII), but it is preferred for nonpregnant women in whom no lesions are identified (BII). If biopsy, with or without endocervical sampling, fails to confirm CIN and the colposcopy is satisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive for a high-risk type of HPV (BII).

**Unsatisfactory Colposcopy.** Endocervical sampling is preferred for nonpregnant women with unsatisfactory colposcopic findings (BII). If biopsy fails to confirm CIN and the colposcopy is unsatisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (BII).

Women with LSIL who are found to have biopsy-confirmed CIN should be managed according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities (Wright et al, unpublished data, 2001).

### LSIL in Special Circumstances

**Postmenopausal Women.** In postmenopausal patients, follow-up without initial colposcopy is an acceptable option using protocols of either follow-up with repeat cytological testing at 6 and 12 months with a threshold of ASC-US or greater for referral for colposcopy, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (CIII).

A course of intravaginal estrogen followed by a repeat cervical cytology test approximately a week after completing the regimen is acceptable for women with LSIL who have clinical or cytological evidence of atrophy, with a referral for colposcopy if a result of ASC-US or greater is obtained and there are no contraindications to using intravaginal estrogen (CIII). If the repeat cervical cytology test result is "negative for intraepithelial lesion or malignancy," cytological testing should be repeated in 4 to 6 months. If both repeat cytology test results are "negative for intraepithelial lesion or malignancy," the patient can return to routine cytological screening, whereas if either repeat result is reported as ASC or greater, the patient should be referred for colposcopy (CIII).

**Adolescents.** In adolescents, an acceptable option is follow-up without initial colposcopy using a protocol of repeat cytological testing at 6 and 12 months with a threshold of ASC for referral for colposcopy, or of HPV DNA testing at 12 months with a referral for colposcopy if testing is positive for high-risk HPV DNA (CIII).

**Pregnant Women.** For the recommended management of pregnant women with a diagnosis of LSIL, see the "HSIL in Special Circumstances" section, below.

## HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

A cytological diagnosis of HSIL is uncommon, accounting for only 0.45% of cytology interpretations in 1996.[2] Women with a cytological diagnosis of HSIL have approximately a 70% to 75% chance of having biopsy-confirmed CIN 2,3 and a 1% to 2% chance of having invasive cervical cancer.[2,58,75]

### Approaches to Managing Women With HSIL

A cytological result of HSIL identifies a woman at significant risk for having CIN 2,3 or invasive cancer; therefore, colposcopy with endocervical assessment has traditionally been considered the best approach to managing these patients.[31] Usually, a colposcopic evaluation will identify a high-grade cervical or vaginal lesion.[58,75,76] However, those women with HSIL in whom a high-grade cervical or vaginal lesion is not identified after colposcopy appear to be at considerable risk for having an undiagnosed CIN 2,3 lesion. In some studies, up to 35% of women with a biopsy diagnosis of CIN 1 and a cytological result of HSIL have been found, after additional workup, to have biopsy-confirmed CIN 2,3.[77,78] Therefore, additional steps are usually taken when a high-grade cervical or vaginal lesion is not identified in a woman with HSIL. One of the first steps that is often taken is to perform a careful review of the colposcopic findings, biopsy results, and initial cervical cytology results. Numerous studies have shown that cytopathologists and histopathologists frequently differ in their interpretation of both cytological and histological cervical abnormalities, and that such a review can sometimes resolve the discrepancy.[11,79-81]

Many colposcopists believe that a cytology test result of HSIL in a pregnant patient requires special consideration. Pregnancy accentuates both normal and abnormal colposcopic findings, and clinicians may not obtain appropriate cervical biopsies out of concern of increased bleeding.[82,83] Although cervical biopsy during pregnancy is associated with an increased risk of minor bleeding, it has not been associated with increased rates of major bleeding or pregnancy loss in the large studies, and a failure to perform cervical biopsies in pregnant women has been associated with missed cancers.[84] Because of the risk of potential injury to the fetus, endocervical sampling is proscribed during pregnancy.

The approach of managing nonpregnant women with HSIL by immediate LEEP of the transformation zone (ie, "see and treat") has been shown to be safe, efficacious, and cost-effective, particularly in the hands of expert colposcopists.[85-88] However, most studies of women undergoing immediate LEEP for cytological abnormalities have reported that a significant number of the excised specimens will lack histologically confirmed CIN.[71,72] Therefore this approach appears to be most appropriate for patients from populations at risk of loss to follow-up and for older pa-


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