

Update on cervical cancer screening

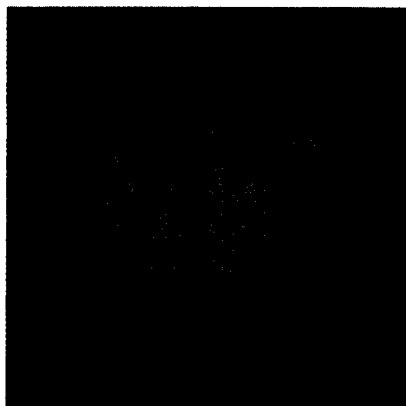
Current diagnostic and evidence-based management protocols

Carol Ball, MD Joan E. Madden, MD

PREVIEW

Growing evidence about the role of human papillomavirus (HPV) infection in the development of cervical cancer holds promise for prevention as well as early detection. At the same time, important advances in diagnostic techniques and management guidelines based on study evidence offer more effective tools for classification of disease severity and appropriate treatment options. In this article, the authors review the 2001 revision of the Bethesda System and the new evidence-based protocols for managing patients with abnormal Pap smears.

The Pap smear (ie, sampling of exfoliated cells from the uterine cervix for microscopic examination to detect underlying cancer or precursors) was developed by Papanicolaou and Trout in 1943. Since its introduction and widespread use, deaths from cervical cancer in the United States have been reduced by almost 75%.



cancer is not inevitable. In fact, up to 70% of cervical intraepithelial neoplasia grade 1 (CIN 1) lesions resolve spontaneously during follow-up of 1 to 2 years.²

The Pap smear

Despite its outstanding record of success as a screening tool for cervical cancer, the conventional Pap smear has an appreciable

Rationale for screening

The primary goal of cervical cytologic screening is to identify women in whom further evaluation with colposcopy is required to detect the presence of true cancer precursors. The development of cervical cancer proceeds in a predictable fashion over a long period, allowing ample opportunity for intervention at a precancerous stage. Progression from low-grade to high-grade dysplasia takes an average of 9 years, and progression from high-grade dysplasia to invasive cancer takes 3 months to 2 years.¹ More recent studies on the natural history of cervical dysplasia have shown that progression from low-grade changes to

false-negative rate. Among the causes are errors in sampling the cervix and in preparing the slide. Steps that patients should take to optimize conditions for Pap test collection are listed in the box on page 60.

The clinician should be careful to sample the transformation zone (T zone) of the cervix, where a majority of cervical cancers arise. The squamocolumnar junction is the most readily identifiable landmark of the T zone. Inclusion of endocervical glandular cells on the Pap smear slide indicates that the T zone has been adequately sampled. The cervical os and ectocervix should be completely visualized before the cell sample is taken. Either a spatula and endocervical brush or a broomlike collection device

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INFORMATION FOR PATIENTS

Preparing for a Pap smear

To improve the accuracy of your test results:

- Schedule your Pap smear appointment about 2 weeks (10 to 18 days) after the first day of your last menstrual period.
- Do not douche within 48 hours before the test.
- Do not use tampons, birth control foams, jellies, or other vaginal creams or vaginal medications for 48 hours before the test.
- Refrain from intercourse for 48 hours before the test.

can be used. In conventional Pap smear preparation, collected cells are spread directly on a glass slide and fixed. Fixation must take place rapidly in order to avoid drying artifact.

Liquid-based, thin-layer preparation techniques (eg, ThinPrep, SurePath) have been developed in an attempt to address some of the problems with cell collection and slide preparation that have resulted in high false-negative rates for the conventional Pap smear. Cells collected from the cervix are suspended in a liquid preservative solution, then spread in a thin layer on a slide by a processor in the laboratory. Blood, mucus, and inflammatory cells are removed during this process, resulting in a better preparation for examination under the microscope. Drying artifact is also eliminated by this technique, and a more representative sample of cells collected from the cervix is included on the slide.

Screening guidelines

According to the American College of Obstetricians and Gynecologists,³ cervical cytologic screening should begin at age 18 or at the time of initiation of sexual activity. ACOG and many other national medical organizations now recommend that a woman who

has had three normal Pap smears at 1-year intervals may, in consultation with her physician, decrease the frequency of screening to every 2 to 3 years. Three years is the maximum time that should elapse between Pap smears.

Consensus regarding an upper age at which screening may be discontinued has been more difficult to reach. The US Preventive Services Task Force⁴ recommends that in patients who have had normal results on previous adequate screening, Pap smears can be discontinued at age 65. In contrast, until recently the American Cancer Society (ACS) recommended continued screening throughout a woman's life span. However, the latest ACS guideline⁵ advises that screening may be discontinued in women aged 70 years or older who have had three or more normal Pap test results and no abnormal results in the last 10 years. Women in whom invasive cervical cancer is diagnosed are often older than 50. However, about half of patients with newly diagnosed cervical cancer have never undergone cervical screening, and 60% to 80% have not been tested in the previous 5 years.¹

Conflicting guidelines also exist regarding screening in women who have had a hysterectomy for benign indications: some investigators⁶ recommend no further routine screening, whereas others state that screening should continue on the same schedule as before hysterectomy. A 1995 report of the ACOG Committee on Gynecologic Practice³ states: "The cost-effectiveness of cytologic screening for vaginal neoplasia after removal of the cervix for benign disease has not been demonstrated. Nonetheless, periodic cytologic evaluation of the vagina in [women with high-risk factors] is warranted."

Women who are immunocompromised, including those infected with HIV, are at high risk for cervical neoplasia and should be screened more frequently than the general population. HIV-positive women should be screened every 6 months for the first year after their diagnosis and at 1-year intervals thereafter. Pregnant women should be screened and

abnormal results evaluated in the same way as in women who are not pregnant.

Role of HPV in cervical cancer

HPV DNA can be identified in virtually all cervical cancers, and the virus is now accepted as a major causative factor in the development of cervical cancer and its precursor, cervical dysplasia.⁷ More than 100 types of HPV have been identified, and about one third of those result in genital infection. Genital HPV is transmitted almost exclusively by sexual contact and is arguably the most common sexually transmitted infection in the United States. Multiple risk factors for the development of cervical cancer have been identified (table 1). Many of the factors now appear to be surrogates for risk of exposure to HPV, and others probably are indicative of a decreased ability of the immune system to respond to the infection.

Genital HPV types are divided into high-risk and low-risk groups depending on the likelihood of development of significant cervical disease from exposure to a particular type. Low-risk types (ie, 6, 11, 42, 43, and 44) result in benign condyloma (ie, genital warts). The high-risk types (ie, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) are found in 99.7% of cervical cancers.^{7,8}

Epidemiologic studies have shown a high prevalence of HPV infection, especially in women younger than 25. At least 90% of these infections are cleared by the immune system, and HPV is no longer detected within 2 years of the initial infection. Persistence of DNA evidence of infection with high-risk viral types indicates significant risk for high-grade dysplasias and, ultimately, cervical cancer.² DNA probes for identifying HPV types have been developed and are now commercially available. The Hybrid Capture II Panel B probe identifies the 13 high-risk and intermediate-risk HPV types. The Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion Triage

continued

Table 1. Relative risks for cervical cancer by specific risk factor

Risk factor	Relative risk*
HIV infection	Very high
Moderate dysplasia on Pap smear within past 5 yr	Very high
Intercourse within 1 yr of menarche	16
No prior screening	10
HPV infection (depending on subtype)	2.5-30
Six or more lifetime sexual partners	5
Low socioeconomic class	5
Black race (compared with white race)	2.5
Smoking	2
Oral contraceptive use	1.2-1.5
Barrier contraceptive use	0.6

HPV, human papillomavirus.

*A relative risk of 1 indicates no increased probability of a negative outcome, whereas a relative risk of less than 1 means an actual protective effect may be present. A relative risk of 10 means a 10-fold increase. In the United States, the overall risk of cervical cancer in reproductive-age women who have not had a hysterectomy is about 1 in 5,200 per year, or 0.02%.

Adapted from Health care guideline: cervical cancer screening. Institute for Clinical Systems Improvement. June 2002. Available at: <http://www.icsi.org/guide/cervic.pdf>. Accessed Dec 11, 2002.

Table 2. The 2001 Bethesda System, simplified

Specimen adequacy

Satisfactory for evaluation

Unsatisfactory for evaluation

General categorization (optional)**Interpretation/result**

Negative for intraepithelial lesion or malignancy

- Organisms
- Other nonneoplastic findings

Other (eg, endometrial cells)

Epithelial cell abnormalities

- Squamous cell
 - ≈ Atypical squamous cells
 - Of undetermined significance (ASC-US)
 - Cannot exclude high-grade squamous intraepithelial lesion (ASC-H)
 - ≈ Low-grade squamous intraepithelial lesion (LSIL)
 - Human papillomavirus infection, mild dysplasia (ie, cervical intraepithelial neoplasia grade 1 [CIN 1])
 - ≈ High-grade squamous intraepithelial lesion (HSIL)
 - Moderate and severe dysplasia (ie, carcinoma in situ, CIN 2, and CIN 3)
 - With features suggestive of invasion
 - ≈ Squamous cell carcinoma
 - Carcinoma in situ
- Atypical glandular cells (AGC)
 - ≈ AGC not otherwise specified (NOS)
 - Endocervical, endometrial, or glandular cells
 - ≈ AGC favoring neoplasm
 - Endocervical or glandular cells
 - ≈ Endocervical adenocarcinoma in situ (AIS)
 - ≈ Adenocarcinoma
 - Endocervical, endometrial, extrauterine, or NOS

Other malignant neoplasms**Automated review and ancillary testing (include as appropriate)****Educational notes and suggestions (optional)**

Study (ALTS)⁹ showed that testing for the high-risk viral types can be helpful in identifying women with atypical Pap smear results who should receive further evaluation with colposcopy. Colposcopy involves examination of the cervix, the vagina and, at times, the vulva with magnification after the application of acetic acid. Biopsy samples are taken of any lesions identified that are suggestive of dysplasia or invasive cancer.

The Pap smear report

Most laboratories use The Bethesda System (TBS) or a modification thereof for reporting Pap smear results. TBS was first developed in 1988 at a workshop sponsored by the National Cancer Institute. The purpose of developing this system was to provide uniform diagnostic terminology that would facilitate communication between the laboratory and the clinician. TBS was further refined in 1991 and again in 2001. The latest revision includes important changes in the terminology used to report cytologic test results.¹⁰

Communication begins with the clinician. When a Pap smear is sent to the laboratory, it is important to provide information on the request that will facilitate interpretation of the smear by the cytologist-pathologist. Such information includes the patient's age, date of her last menstrual period, previous or current hormone therapy, previous abnormal Pap smears and any related treatment, history of radiation therapy or chemotherapy, and previous hysterectomy. The information provided to the clinician is divided into three broad categories: specimen adequacy, general categorization of cytologic findings, and interpretation/result (table 2).

Specimen adequacy

This section of the Pap smear report describes the technical interpretability of the slide received by the laboratory. Specimens are described as either "satisfactory for evaluation" or "unsatisfactory" with

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further comment about the presence or absence of endocervical cells or the reason that the slide was unsatisfactory. The description "satisfactory, but limited by" has been eliminated. Slides that previously would have been placed in this category are now called "satisfactory for evaluation" with further description of any limiting factors.

General categorization of cytologic findings

The general categorization section gives the overall interpretation of the smear without further description. This part of the report is optional and is meant to allow for rapid triage of results by the clinician or office staff. The term "within normal limits" has been replaced by "negative for intraepithelial lesion or malignancy." The general category of "benign cellular changes" has been eliminated. Such findings are now reported as "negative," and a more specific description of findings that are reportable but not indicative of an epithelial abnormality is included in the interpretation/result section of the report. These findings may include such things as evidence of specific infections, inflammation, and atrophy. The general category "other" has been added. The most frequent finding reported in this category is the presence of endometrial cells.

Interpretation/result

This section replaces the previous "diagnosis" report and gives a further description of any epithelial abnormality and other nonneoplastic findings. Significant changes were made in this area, especially in reporting the TBS 1991 categories of ASCUS and AGUS.

Findings formerly reported as ASCUS are still called atypical squamous cells (ASC) but are further divided into two types: (1) atypical squamous cells of undetermined significance (ASC-US) and (2) atypical

squamous cells, cannot exclude high-grade intraepithelial lesion (ASC-H).

The category called atypical glandular cells of undetermined significance (AGUS) has been eliminated because the term was too easily confused with ASCUS.

Glandular cell abnormalities are divided into four groups. Within these groups, the specific type of glandular cell (ie, endocervical, endometrial, or extrauterine) is reported when possible.

Initial management of epithelial cell abnormalities

Shortly after the 2001 revision of TBS, a separate consensus conference, sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP), was convened to develop evidence-based guidelines to assist clinicians in the management of women with abnormal or ambiguous Pap tests.¹¹ These management guidelines are the first standardized, evidence-based protocols for management of abnormal Pap smears that have been made available to clinicians and patients.

Squamous cell abnormalities

The ASCCP guidelines classify squamous cell abnormalities according to four categories.

ASC: This category of abnormalities is subdivided into two types, ASC-US and ASC-H.

ASC-US: A woman with ASC-US has a 5% to 17% chance of having CIN 2 or 3 (moderate or severe dysplasia).⁸ For this reason, a squamous intraepithelial lesion should be suspected whenever ASC-US is reported.

Three acceptable options for the initial management of ASC-US¹² are briefly discussed here.

1. Repeat the Pap smear in 4 to 6 months. If the result is ASC-US or a more advanced lesion, the patient should be referred for colposcopy.
2. Refer for immediate colposcopy. Women with

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negative results on colposcopic examination should undergo another Pap smear in 12 months.

3. **Test for high-risk HPV.** Testing for high-risk HPV is a highly sensitive method of identifying which patients with ASC-US are at risk for significant lesions, therefore needing immediate attention, and which patients can be monitored with cytologic testing. It is important to test only for intermediate-risk or high-risk HPV. Patients with a result of "ASC-US, HPV positive" are referred for colposcopy. Those with a result of "ASC-US, HPV negative" should undergo follow-up cytologic testing in 12 months.

Two protocols have been described for "reflex" HPV testing for women with ASC-US. One method is co-collection. At the time a conventional Pap smear is taken, a second cervical sample is collected and reserved for intermediate-risk and high-risk HPV-DNA testing if the Pap smear result is ASC-US. If the result is other than ASC-US, the reserved sample is discarded. When a liquid-based system is used for Pap smear collection, HPV testing can be done on the residual fluid medium. Both protocols avoid the need to call patients back for HPV testing, and both make it possible to integrate the results of the cytologic and HPV testing in a single report.

ASC-H: Women who have a Pap smear result of ASC-H should be referred for colposcopy without HPV testing. CIN 2 or 3 is identified in 20% to 94% of patients with ASC-H.⁹

Low-grade squamous intraepithelial lesion (LSIL): Women with LSIL should be referred for colposcopy. HPV testing is not indicated, because

83% of such patients are positive for high-risk HPV.⁹

High-grade squamous intraepithelial lesion (HSIL): Referral for colposcopy is also indicated in women with HSIL. They have a 70% to 75% chance of having CIN 2 or 3 and a 1% to 2% chance of having cervical cancer.⁹

Squamous cell carcinoma: Patients whose Pap smear results indicate squamous cell carcinoma should undergo immediate colposcopy.

Glandular cell abnormalities

Atypical glandular cells found on cervical cytologic testing, classified as either "not otherwise specified" or "favor neoplasia," are highly significant and require immediate further evaluation with colposcopy, endocervical curettage, cervical biopsy when appropriate and, in some cases, endometrial biopsy. Studies have shown much higher rates of severe underlying pathologic conditions in women with atypical glandular cells on Pap smear than in those with either ASC or LSIL. In addition, Pap smear reports indicating adenocarcinoma in situ or invasive adenocarcinoma necessitate immediate further evaluation.

Summary and conclusion

Pap smear screening for cervical cancer has been a preventive health success. Although improved technology is increasing the accuracy of this technique, more women who have never been tested will need to undergo screening in order to further decrease the incidence of cervical cancer in the United States.

The establishment of infection with high-risk genital HPV types as a causative factor in cervical cancer is a major breakthrough in understanding of this disease. Testing for the presence of high-risk HPV DNA should increase the ability to identify women who are truly at risk for cancer and true cancer precursors and to more efficiently plan further diagnostic evaluation.

The 2001 revisions in TBS reflect our improved understanding of the epidemiology and natural

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history of cervical epithelial abnormalities and cervical cancer. These revisions are designed to facilitate communication between the clinician and the laboratory and to improve the clinician's ability to accurately interpret the cytology report and plan initial management of any abnormalities. **PGM**

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References

1. Sawaya GF, Brown AD, Washington AE, et al. Clinical practice: current approaches to cervical-cancer screening. *N Engl J Med* 2001;344(21):1603-7
2. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr* 1998;132(2):277-84
3. ACOG committee opinion. Recommendations on frequency of Pap test screening. No. 152, March 1995. Committee on Gynecologic Practice. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 1995;49(2):210-1
4. US Preventive Services Task Force. Guide to clinical preventive services: report of the US Preventive Services Task Force. 2nd ed. Baltimore: Williams and Wilkins, 1996. Available at: <http://www.ahrq.gov/clinic/cpsix.htm>. Accessed Nov 15, 2002
5. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002;52(6):342-62
6. Pearce KF, Haefner HK, Sarwar SF, et al. Cytopathological findings on vaginal Papanicolaou smears after hysterectomy for benign gynecologic disease. *N Engl J Med* 1996;335(21):1559-62
7. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189(1):12-9
8. Unger ER, Duarte-Franco E. Human papillomaviruses: into the new millennium. *Obstet Gynecol Clin North Am* 2001;28(4):653-66
9. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93(4):293-9
10. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002;287(16):2114-9
11. Wright TC Jr, Cox JT, Massad LS, et al. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;287(16):2120-9
12. Richart RM. A sea change in diagnosing and managing HPV and cervical disease—part 1. *Contemp OB/GYN* 2002;5:42-56