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Cervical Cancer Screening in the Era of Improved Technology and HPV Vaccines

Milestones in Cervical Cancer Detection and Prevention: Significance in Clinical Practice

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Weighing the Costs and Benefits: Technologic Advances in Cervical Cancer Screening

Efficacy of HPV Screening Versus Liquid-Based Cervical Cytology and Imaging: What the Data Really Show

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Cervical Cancer Screening in the Era of Improved Technology and HPV Vaccines

Until a decade ago, the Papanicolaou smear—which had been introduced in the 1940s—was the only cervical cancer screening method available. New screening technologies have emerged since then that have improved cervical cancer detection substantially. These include the liquid-based, thin-layer Pap test, introduced in the mid-1990s; testing of Pap samples for human papillomavirus (HPV) DNA, and, more recently, computer-assisted screening.

When any pharmacologic or technologic advances become available, clinicians are faced with the challenge of evaluating data regarding the efficacy of those medications or technologies and with considering the cost-effectiveness of adopting them into their practices. For those specializing in obstetrics and gynecology and other clinical areas in which cervical cancer screening is performed, these evaluations have made liquid-based Pap testing the standard practice: approximately 90% of Pap tests in the United States are now done using liquid-based technology. Today, we must consider the implications of two other developments that may affect cervical cancer screening: the recent approval of a quadrivalent HPV vaccine and the emerging role of computer-assisted screening of liquid-based, thin-layer Pap specimens.

In this supplement to Ob.Gyn. News, four articles are presented that we hope will be both useful and thought-provoking.

—Mark H. Einstein, MD, MS, Chair

Milestones in Cervical Cancer Detection and Prevention: Significance in Clinical Practice

MARK H. EINSTEIN, MD, MS, CHAIR

Over the 10 years since liquid-based cytology was introduced for cervical cancer screening, clinical practice in this area has changed dramatically: 90% of Papanicolaou tests in the United States are now performed using the liquid-based Pap technology. Reflex testing for the presence of human papillomavirus (HPV) infection is now the practice standard for managing patients whose Pap test shows atypical squamous cells of undetermined significance (ASC-US).

Improvements in detection of cervical abnormalities achieved by the use of liquid-based, thin-layer technology have been thoroughly documented in the peer-reviewed literature, and these benefits are familiar to clinicians in women's health care settings. Additionally, significant advances in reducing cervical cancer incidence and mortality have been introduced more recently: computer-assisted screening in the United States for improving detection of cytologic abnormalities on Pap tests and the availability of a vaccine for the most problematic strains of HPV.

IMPROVING DETECTION OF CERVICAL CANCER

The conventional Pap smear represented a life-saving advance in women's health because it allowed early detection and treatment of cervical cancer and, thus, dramatically reduced mortality from this disease. However, the rate of reduction in cervical cancer in the United States gradually slowed; as early as the 1980s, the rate had approached a plateau.

There were two main reasons for this. First, cervical cancer screening has never been universal. The unscreened population includes women who have limited access to medical care as well as those who choose not to have Pap tests. Second, the conventional Pap smear is associated with a high rate of false-negative results, which has been reported to range between 1.5% and 55%.[1] The use of liquid-based Pap testing has decreased the incidence of false-negative Pap test results. With even broader use of liquid-based cytology, a continued decline in cervical cancer incidence has occurred.

However, although early detection and treatment of cytologic abnormalities have led to a decrease in cervical cancer in general, a disturbing trend has emerged, with the proportion of glandular lesions and cervical adenocarcinoma increasing. Part of the reason for this increase in adenocarcinoma is that conventional Pap smears are of limited value in detecting it. Data are available demonstrating that adequate sampling of the cervical canal combined with liquid-based, thin-layer Pap test technology improves detection of glandular lesions of the cervix. (This issue is discussed in greater detail in the article by Drs Lozano and Sauer on page 5.)

More recently, computer-assisted screening was developed with the goal of helping to identify positive Pap tests and further reduce false-negative results. Two types of systems currently are available, and these are described in "How Computer-Assisted Screening Works," page 4.

ROLE OF HPV VACCINES IN REDUCING CERVICAL CANCER INCIDENCE

In June 2006, the first HPV vaccine, Gardasil®, was introduced, which is effective against HPV types 6 and 11—which cause genital warts—as well as the oncogenic types 16 and 18.[2,3] The Advi-

sory Committee on Immunization Practices of the Centers for Disease Control and Prevention suggests routine vaccination for girls as young as 9 years of age.[4] Ideally, it should be given before the onset of sexual activity, but sexually active women still are likely to benefit—even if a woman is already infected with HPV, vaccination may protect her from acquiring infection with other HPV types that are covered by the vaccine. The quadrivalent vaccine is approved by the US Food and Drug Administration (FDA) for administration to females between 9 and 26 years of age.[3] Recently, the American College of Obstetrics and Gynecology published its recommendations that a Pap test be performed prior to the administration of HPV vaccine and that Pap tests be routinely performed even in women who have been vaccinated.[5]

Because of HPV's role in cervical dysplasia and carcinoma, a gradual decrease in HPV infections—and, therefore, in abnormal Pap test results—should result. However, the ultimate impact of HPV vaccination on cervical cancer incidence depends on a number of variables. The greatest and most obvious factor is the extent of vaccination in the population: until vaccination is widespread, with most women in the target age groups receiving the vaccine, statistics will not be significantly affected. As with immunization programs that have been introduced for protection against other diseases—notably, the communicable diseases of childhood—the greatest benefits will not be seen until vaccination is virtually universal. Such compliance with childhood vaccinations was achieved only when vaccinations became a requirement for school admission.

Three important potential barriers to widespread acceptance of and compliance with HPV vaccination recommendations are cost, the potential for side effects, and parents' acceptance of the concept of vaccinating their preadolescent and adolescent daughters against a sexually acquired infection.

Furthermore, clinicians and patients should remain aware of the fact that the vaccine covers HPV types 16 and 18, which are responsible for about 70% of cervical cancers.[6] However, the remaining 30% of cervical cancers are caused by HPV types that are not covered by this vaccine. In addition, it is not yet known how long immunity against the covered HPV types persists following vaccination.

All of these are important reasons supporting the recommendation that women undergo vaccination and continue regular cervical cancer screening. Awareness is widespread among the general public about the availability of the quadrivalent vaccine, and the message is justifiably welcome. However, clinicians must provide patients with a factual context for the expectations about vaccination: cervical cancer can develop despite vaccination, and adherence to a regular cervical cancer screening program is still as important as ever.

Reimbursement for vaccination by Medicare and Medicaid and some health insurance companies has not yet been determined. A decision from the Centers for Medicare and Medicaid Services (CMS) regarding reimbursement is pending. Some health insurance companies will follow the lead of CMS, but even without the CMS determination, many companies already are providing partial reimbursement and

Continued on page 12

How Computer-Assisted Screening Works

Computer-assisted screening with an automated microscope was developed to prescreen slides and identify those that contain cells of interest.

To date, two such systems have been approved by the US Food and Drug Administration: the ThinPrep® Imaging System (TPIS) and the FocalPoint™ Slide Profiler (FPSP). Both work on the principle of morphometry. Both are approved for use with liquid-based Pap slides, and FPSP also is approved for prescreening conventional Pap smear slides. The FPSP is approved only for screening specimens from low-risk patients, as specifically defined in the product labeling.[1] TPIS is approved for screening low-risk as well as physician-designated high-risk patients, such as those with a previous tissue or Pap diagnosis of HPV, those with multiple sex partners, and patients with HIV infection or a history of cervical dysplasia.[2]

The FPSP works with image analysis software that makes algorithmic judgments about whether a slide specimen is normal or abnormal and categorizes it as requiring either: no further review (these are reported as negative for intraepithelial lesions or malignancy), review (requires evaluation by a cytotechnologist), quality control review (slides that have the highest probability of containing abnormal cells are selected for rescreening), or process review (slides that require review by a cytotechnologist because they could not be successfully processed by the system).

In addition to evaluating only slides prepared using liquid-based, thin-layer technology, the TPIS differs in several more ways. The most significant is that it scans slides and identifies cells of interest. Therefore, when a cytotechnologist and cytopathologist review such slides, the areas of special interest are clearly marked.

Specifically, a quantitative DNA stain is used to stain cervical cell nuclei. Abnormal cells have increased amounts of molecular DNA and tend to be larger and irregularly shaped; also, the nuclei in abnormal cells take up more stain than the nuclei in normal cells. The presence of irregularly shaped, large, and darkly stained cells indicates that the sample may be abnormal.

The TPIS imager scans each slide and identifies 22 fields that contain cells of interest, as described above. The cytotechnologist then reviews those 22 fields using an automated microscope and reports "no intraepithelial lesion" if all fields are judged to be normal. If the cytotechnologist judges cells in any field to be suspicious, the entire slide is reviewed and abnormal cell groups are marked. These slides are then evaluated by a pathologist.

Sources: 1. *FocalPoint™ Slide Profiler.* Available at: http://www.tripathimaging.com/nonus_fp_bpi.htm. Accessed November 30, 2006. *FocalPoint* is a trademark of TriPath Imaging, Inc. 2. *ThinPrep® Imaging System.* Available at: http://www.thinprep.com/pap-test/thinprep-imaging.html. Accessed November 30, 2006. *ThinPrep* is a registered trademark of Cytyc Corporation.

Improving HSIL and Glandular Disease Detection: What the Recent Data Show

RICHARD LOZANO, MD, AND HAROLD J. SAUER, MD, FACOG

The incidence of cervical cancer has declined dramatically since the glass-slide Papanicolaou test was introduced in the early 1940s. An estimated 9,700 new cases of invasive cervical cancer will have occurred and the disease will have claimed the lives of about 3,700 women in the United States during 2006.[1] However, although the overall incidence of cervical cancer has decreased, a shift has occurred in the frequency of the subtypes—the proportion of adenocarcinoma has been increasing (**Figure** on page 6).[2]

DETECTION OF LSILs, HSILs, GLANDULAR LESIONS, AND INVASIVE CANCER

The first liquid-based Pap test was approved by the US Food and Drug Administration (FDA) a decade ago, and since that time, scores of independent studies have been published in peer-reviewed journals documenting the advantages of this liquid-based, thin-layer cytology for detecting precancerous lesions or cervical cancer. The improvement over the conventional Pap smear has become widely recognized, and about 90% of clinicians in this country now are performing Pap tests using liquid-based technology.[3]

The detection of atypical squamous cells of undetermined significance (ASC-US) and low-grade squamous intraepithelial lesions (LSILs) is important because it allows clinicians to follow patients appropriately. Many of these lesions regress spontaneously, but it is not possible to predict which will regress and which will persist or progress. Thus, the improved visualization of cervical samples made possible by liquid-based cytology—resulting in a reduction in false-negative readings—is crucial to aid in treatment decisions and to avoid overtreatment.

However, the more important target in cervical screening is high-grade squamous intraepithelial lesions (HSILs) and high-grade glandular lesions, with the goal of identifying patients with high-grade preinvasive lesions and invasive cancer as early as possible in the course of the disease. Two analytical comparisons of US studies involving the first liquid-based cytology system (introduced in 1996) demonstrated that liquid-based cytology improves detection of both LSIL and HSIL.

The first of the comparisons, by Bernstein and colleagues,[4] was a meta-analysis of 25 prospective studies involving 221,864 patients. Some of these were split-sample studies, meaning that a conventional Pap smear was prepared first and the rest of the sample was used for liquid-based cytology. These authors concluded that liquid-based cytology improved the adequacy of samples and was associated with improved detection of both LSILs and HSILs.

The second, by Abulafia and colleagues,[5] was a quantitative analysis of 24 studies. Seventeen of the studies compared liquid-based cytology with conventional Pap smears for 35,172 patients; 10 articles compared cytology with histologic or other "gold-standard" diagnoses for 21,752 patients; three studies used both types of comparisons. The investigators noted that the liquid-based technique demonstrated greater sensitivity and specificity than conventional Pap smears and concluded that the sensitivity of liquid-based cytology led to an increase in the detection of cervical atypia, LSILs, HSILs, and invasive cervical carcinoma.

In addition, multiple peer-reviewed publications have shown improved detection and classification of glandular lesions with liquid-based cytology (in these studies, ThinPrep was used) compared to conventional Pap smears.[6-11] The first of these was a study by Ashfaq and colleagues,[6] who studied results with liquid-based cytology compared with historical controls. This group demonstrated that ThinPrep was more sensitive and specific in identifying glandular lesions.

Bai and coworkers[7] and Carpenter and Davey[8] conducted similar studies, comparing liquid-based cytology results with historical controls, but also confirmed their findings with histologic studies. Biopsy confirmation of glandular lesions was better than that found with conventional Pap smears. Guidos and Selvaggi[9] studied endometrial tissue, specifically. In this study, the authors found that use of liquid-based cytology improved detection of endometrial carcinoma fivefold compared with conventional Pap smears, a conclusion supported by biopsy confirmation.

Finally, Schorge et al[10] compared conventional Pap smears collected from 1996 to 1998 with ThinPrep tests from 1998 to 2000, a total of almost 200,000 samples. These investigators reported that ThinPrep yielded a higher pickup of combined atypical glandular cells of undetermined significance (AGUS) and adenocarcinoma (0.17% of the liquid-based samples versus 0.09% of the conventional smears; $P<0.001$). In addition, the sensitivity for AGUS/adenocarcinoma was found to be significantly greater with the liquid-based test (72.0% versus 41.5%; $P<0.001$).

In August 2005, the FDA approved labeling referencing these studies,[6-11] which reported on the improved ability of the ThinPrep system to detect glandular disease as compared to conventional Pap testing.

INCREASING INCIDENCE OF CERVICAL ADENOCARCINOMA

Improved detection of cervical adenocarcinoma is crucial to reducing morbidity and mortality from this disease. This is of increasing importance because whereas the rate of squamous cell cancer is decreasing, the proportion of cervical adenocarcinoma—in both relative and absolute terms—is increasing. Cervical adenocarcinoma once accounted for approximately 5% of cases, but since the early 1970s, the proportion has grown dramatically; it was estimated to be as high as 20% to 25% in the year 2000[12] and has continued increasing (**Figure** on page 6).[2]

Several reasons for this shift have been proposed. One is increased detection, resulting from both the use of liquid-based

cytology and improvement in sampling devices and techniques.[13,14] In addition, an increased incidence of human papillomavirus (HPV) infection, especially type 18—the oncogenic HPV type most commonly associated with cervical cancer—has been suggested as an underlying cause.[15] Other possible cofactors include multiple sexual partners,[16] the use of oral contraceptives,[16] and obesity.[17]

ROLE OF TESTING FOR HIGH-RISK HPV

The role of HPV in the development of squamous cell cervical carcinoma has been recognized for a number of years and has been definitively demonstrated.

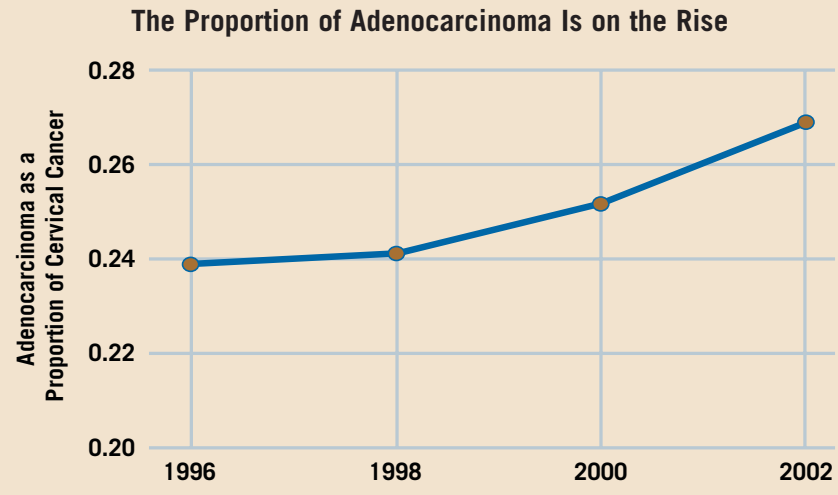
The value of liquid-based cytology combined with high-risk (HR)-HPV reflex testing is that patients with ASC-US results can be triaged. Reflex HR-HPV testing from a liquid-based Pap test (direct-to-vial sampling) is FDA approved only with the ThinPrep Pap Test. With reflex testing, the presence of an HR-HPV infection can be identified.

If a patient with an ASC-US result on liquid-based testing has a positive reflex HPV test, the standard of care now is for that patient to be more closely followed than one who has no evidence of a high-risk HPV infection. However, reflex HPV testing does not identify the specific type of HPV.

The availability of HR-HPV DNA testing from the vial has made it possible for HR-HPV–positive patients to be readily identified, so that patients who have infections with the low-risk HPV types—that is, types 6 and 11—can be classified as negative. HR-HPV infections are recognized as oncogenic—principally, types 16 and 18—and should be followed as high risk. To date, one liquid-based cytology method has received FDA approval for HPV DNA testing from the vial. However, as discussed in Dr Einstein's article on page 3, HPV testing is not a substitute for cervical cytologic testing.

Currently, the benefits of HPV testing in patients with glandular lesions are not clear because the association between HPV infection and glandular lesions is not completely understood. The literature demonstrates that many endocervical cancers are HPV-positive, and when HPV is found in patients with atypical glandular cells, it is most commonly type 18.[15,18,19] However, cervical adenocarcinoma without evidence of HPV infection has been found in certain populations of women (women more than 60 years of age and virginal women, including those in religious orders).[15,18,19] In a recent study, Andersson and colleagues[20] tested the potential utility of a DNA probe set for assessing glandular cells in Pap tests and noted that HPV DNA could not be detected in 4 (33%) of the 12 cases they examined. HPV DNA testing is not recommended by the FDA for following patients with atypical glandular cells.

FIGURE. Progressive Incidence of Adenocarcinoma Relative to Squamous Cell Carcinoma



Source: Surveillance, Epidemiology, and End Results (SEER) Program Database.[2]

COMPUTER-ASSISTED SCREENING FURTHER IMPROVES DISEASE DETECTION

Clearly, the early detection of HSIL and glandular lesions can be improved with liquid-based Pap testing.* The introduction of computer-assisted screening has been shown to increase detection rates even further.† (For a further overview of how this new technology works, see the sidebar in Dr Einstein's article on page 4.) To date, only one screening system—the ThinPrep Imaging System (TPIS)—has been approved by the FDA for evaluating slides in both low- and high-risk patients.

In a recent study, Dziura and colleagues[21] compared the results of ThinPrep Pap Tests screened only manually and with dual review using TPIS; almost 28,000 samples were reviewed in each group. The rates of increase in sensitivity of dual-reviewed compared with manual review alone were significant for four diagnostic categories: ASC-US; abnormal squamous cells, cannot rule out high-grade squamous intraepithelial lesion (ASC-H); low-grade squamous intraepithelial lesion (LSIL); and high-grade intraepithelial lesion (HSIL). Specifically, the increased sensitivity rates were 29.0% for ASC-US ($P<0.001$), 50.0% for ASC-H ($P<0.001$); 30.7% for LSIL ($P<0.001$); and 20.0% for HSIL ($P<0.05$). Specificity was also increased substantially for ASC-H (11.7%) and HSIL (8.9%).

In another recent paper,[22] investigators at a medium- to high-volume laboratory in Kentucky (Dr Lozano's laboratory) published their results from the first 6 months of use of the TPIS imager compared with manual screening alone of ThinPrep Pap Tests. The published results include 39,717 computer-assisted screens reported from May through October 2004 and 87,267 cases that had been manually screened and reported in the previous year.

The study shows a significant increase in detection rates over manual screening for HSILs and more severe lesions by 38% ($P<0.0001$). A 46% increase in the detection of LSILs was found with the im-

ager-assisted screening compared with manual screening ($P<0.0001$). The two methods yielded similar results in both the ASC-US to squamous intraepithelial lesion ratio and unsatisfactory specimens.

CONCLUSION

Improvements in the detection of significant lesions have been an important goal and, with the availability of liquid-based, thin-layer Pap testing, this has been accomplished. The development of computer-assisted screening that scans and identifies specific areas of diagnostic interest on Pap slides has further decreased the false-negative results that were seen with conventional Pap smears. These technologic advances have provided the opportunity for even greater benefit to women's health, especially in light of the increasing incidence of cervical adenocarcinoma. ■

FOOTNOTES

* In August 2005, the FDA approved labeling referencing multiple peer-reviewed studies,[6-11] which reported on the improved ability of the ThinPrep Imaging System (TPIS) to detect glandular disease as compared to conventional Pap testing.

† The TPIS clinical trial showed a statistically significant increase in ASC-US+ sensitivity of 6.4% [95% CI, 2.6-10.0] and a statistically significant increase in HSIL+ specificity of 0.2% [95% CI, 0.06-0.4].

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Weighing the Costs and Benefits: Technologic Advances in Cervical Cancer Screening

WARNER K. HUH, MD, FACOG, FACS

The introduction of technologic advances that hold promise for improving the health and well-being of patients generates two principal responses: optimism for better-quality patient care and concerns about whether implementing the new procedures is affordable and justified by clinical outcomes—that is, their cost-effectiveness.

FACTORS AFFECTING COST-EFFECTIVENESS

Assessments of cost-effectiveness for cervical cancer screening must consider several variables. These include the cost of screening (a labor-intensive process), the cost of the technologies used in screening, the cost of follow-up, avoidance of cervical cancer (including potential complications and death), and screening intervals.

In addition, three methods must be considered in a cost-effectiveness analysis: the conventional, glass-slide Papanicolaou smear, liquid-based, thin-layer Pap testing, and cytologic evaluation plus human papillomavirus (HPV) testing. The cost-effectiveness of these methods are affected by myriad issues, but mainly by their sensitivity, specificity, positive predictive value, and negative predictive value versus costs.

EXTENDING SCREENING INTERVALS: A PROPOSAL FOR REDUCING COSTS

In evaluating the cost-effectiveness of cervical cancer screening methods, it is important to keep in mind that cervical cancer rates in this country have decreased dramatically since the introduction of the conventional Pap smear because it came to be accepted as a test that must be administered yearly. However, with improved sensitivity associated with the new Pap testing technologies, annual testing actually may be overscreening, leading, in turn, to unnecessary treatment and costs.

Some experts have suggested extending the intervals between Pap tests from annually to every 2 years or more as a way to make improved technology more affordable, yet retain the advances that have been achieved in the rate of cervical cancer detection and the reduction in the rate of cervical cancer mortality. Several important studies have been published that explore both the economic and the health implications of this proposal.

Miller and colleagues[1] conducted a matched case-control study to determine whether increasing the time intervals between Pap tests would change the odds ratio for developing invasive cervical cancer. Screening intervals of more than 3 years were associated with dramatically increased risks for missing the diagnosis of cervical cancer.

Subsequently, Goldie and colleagues[2] published a complex analysis comparing the costs and sensitivity of cytologic screening at various intervals and using several strategies. The intervals considered were 1, 2, and 3 years, and the strategies were (1) conventional Pap testing, (2) liquid-based cytology and the use of HPV DNA testing when abnormal squamous cells of undetermined significance (ASC-US) were identified, and (3) liquid-based cytology combined with HPV DNA testing for all women 30 years of age or older (the US Food and Drug Administration has approved HPV DNA testing in primary screening only for women in this age group).

Goldie's group reported that, compared with annual conventional Pap testing, triennial liquid-based cytology administered to all women and the combination of liquid-based cytology/HPV DNA testing for women 30 years of age or older provide equal or greater benefits in terms of cervical cancer detection. The study further demonstrated that, compared with annual conventional Pap testing, the incremental cost-effectiveness ratios were $95,300 (for triennial liquid-based cytology) and $228,700 (for liquid-based cytology/HPV DNA testing) per year of life gained. Also important was the conclusion that annual primary screening with liquid-based cytology/HPV DNA has a cost-effectiveness ratio of more than $2 million per year of life gained, and the strategy increases life expectancy by only a few hours. Extending screening intervals beyond 3 years poses the risk for an unacceptable increase in the cervical cancer rate.

In 2006, Gemmen and colleagues[3] presented a model of the total cost of screening, treatment, and diagnosis, including a strategy in which liquid-based cytology plus ThinPrep® Imaging System was used.* These researchers reported that, according to this model, diagnosis represents the greatest cost when HPV testing is included, whether with conventional Pap smears or liquid-based cytology, and that the overall cost of screening increases sharply when HPV testing is used. Liquid-based cytology was determined to be the most cost-effective method when clinical efficacy is factored in. Computer-assisted imaging added a small amount to the cost of screening over liquid-based cytology without imaging, but yielded a small net reduction in overall costs when diagnosis and treatment were considered as well.

Bidus and colleagues[4] published an analysis similar to that of Goldie and colleagues[2] but used a population of women in the US military. In the armed forces, salaries are based on rank and job function, regardless of gender, which simplifies the calculation of time lost from the job and the actual associated costs. Another advantage to studying this population is that regular health care and follow-up are virtually assured.

In this study, the investigators used a model that considered both direct and indirect costs of health care.

The strategies compared in this study were: (1) liquid-based cytology (LBC) alone, (2) LBC with HPV testing regardless of cytologic results for women over the age of 30 (DNA/PAP), (3) LBC with HPV detection when a cytologic result of ASC-US was found (HPV reflex), and (4) all of the above compared at 1-, 2-, and 3-year intervals. As the **Table** shows, the strategies that were either more costly and

FOOTNOTE

* This study was supported by Cytyc Corporation, Marlborough, Mass., the manufacturer of the cytology/imager system evaluated.

less effective or that had a higher incremental cost-effectiveness ratio than an adjacent strategy were considered dominated (that is, less desirable) strategies.

Bidus and colleagues concluded that, in this military population, the most cost-effective among the strategies studied—especially when indirect costs are considered—was screening every 2 years with liquid-based cytology and reflex HPV testing when ASC-US was found.

The cost per year of life gained (also known as the incremental cost per life year)—that is, the cost of keeping an individual patient alive for 1 additional year—with an annual conventional Pap test plus HPV DNA testing was calculated to be almost $1.5 million. Biannual screening with liquid-based cytology and reflex HPV testing costs an additional $56,728 per year of life gained, and triennial screening with this strategy costs $5,140 per year of life gained. (Goldie and colleagues[2] note that a cost of $50,000 or less per year of life gained can be considered "cost-effective.")

To summarize, the evidence available to date indicates that it is cost-effective to extend cervical screening intervals to every 2 or every 3 years. However, the issue of extending Pap test intervals beyond 1 year should also be considered within the context of patient compliance. For example, screening intervals beyond every 3 years has been shown to be associated with an unacceptable increase in the rate of cervical cancer.[2,3] Therefore, patients who are told to receive biannual or triennial Pap tests must understand the risk associated with failing to adhere to this recommendation.

Agreement is growing among clinicians that screening every 2 to 3 years rather than annually is appropriate, but patients seem unconvinced. Sirovich and coworkers[5] conducted a random-digit-dialing telephone survey of a nationally representative sample of 360 women 40 years of age or older. Almost all (99%) had had at least one Pap test, and 59% had annual screenings. Only 43% reported hearing about recommendations for less-frequent screening, and half of all women surveyed said they believed these recommendations were based on cost considerations rather than on medical evidence.

An overwhelming majority of respondents (69%) said they would still try to obtain annual screening even if their clinicians advised less frequent intervals and reassured them that the benefits of annual and less frequent screenings were comparable. A shift in the "annual Pap test" paradigm will require further education and acceptance on the part of both medical professionals and patients.

TABLE. Health Care-Related Costs Related to Diagnosis and Treatment of HPV and Cervical Cancer in a US Military Population

Strategy	Mean Costs ($)	Incremental Costs ($)	Mean Life Expectancy (y)	Incremental Life Expectancy (y)	Incremental Cost Per Life Year ($)
No Pap test	402		25.8770		
LBC + reflex HPV every 3 y	665	264	25.9282	0.05127	5,140
LBC + reflex HPV every 2 y	832	166	25.9312	0.00293	56,728
LBC + reflex HPV every 3 y before age 30 y and then DNA/PAP every 3 y thereafter	1,032	200	25.9296	–0.0016	Dominated
LBC + reflex HPV every 2 y before age 30y and then DNA/PAP every 3 y thereafter	1,072	40	25.9304	0.0008	Dominated
DNA/PAP every 3 y	1,130	57	25.9307	0.0003	Dominated
LBC + reflex HPV every y before age 30 y and then DNA/PAP every 3 y thereafter	1,224	392	25.9315	0.0003	Ext Dom
LBC + reflex HPV every y	1,355	523	25.9342	0.0030	171,224
DNA/PAP every 2 y	1,515	160	25.9329	–0.0013	Dominated
DNA/PAP every y	2,675	1,320	25.9351	0.0009	1,472,416

LBC, liquid-based cytology; HPV, human papilloma virus; PAP, Pap test; Ext Dom, extremely dominated.
Strategies that are too costly and less effective or have a higher incremental cost-effectiveness ratio than an adjacent strategy are considered dominated. Mean life expectancy is the average discounted life expectancy (discounting is done in order to account for time preferences in cost-effective analysis).

Source: Bidus MA et al.[4] Reprinted with permission.

UNDERSERVED POPULATIONS

The cost-effectiveness of screening in special populations deserves mention: those women in Title X and Planned Parenthood clinics who are still being screened with conventional Pap tests. Cost-containment strategies still imposed on many clinical settings that serve the poor, the uninsured, and the underinsured do not permit these systems to implement cervical screening with technologies that have proved to have higher sensitivity and specificity as well as better positive predictive and negative predictive values.

However, the putative cost savings are reduced when one considers the problem of follow-up. With the conventional Pap smear, a patient with a result of ASC-US must return for an HPV test to determine appropriate subsequent management. The real cost of having patients return for an additional visit must be factored into the calculation. In medically underserved populations, poor compliance is a well-recognized deterrent to optimum health care, particularly when the services are prevention- and diagnosis-oriented rather than treatment-focused. An unknown proportion of ASC-US-positive patients who fail to return for follow-up evaluation and who have precancerous or early cancerous lesions may be lost to the system during the time when their conditions are potentially detectable and more easily—and less expensively—treated.

CONCLUSION

The majority of physicians who perform Pap testing now send their samples to laboratories that use liquid-based, thin-layer cytology and include reflex DNA testing in their diagnostic algorithms when ASC-US is found. In addition to an expected continued decrease in the incidence of high-grade lesions, we can hope to see a further decrease in the incidence of cervical cancer. Also important is the potential for a decrease in the overall cost of screening for cervical cancer, with the goal of implementing new technologies that improve cervical cancer detection at

Continued on page 12

Efficacy of HPV Screening Versus Liquid-Based Cervical Cytology and Imaging: What the Data Really Show

MICHAEL KARRAM, MD, FACOG, AND MICHAEL L. KRYCHMAN, MD

In the years since the connection between cervical cancer and human papillomavirus (HPV) was demonstrated, the considerable research focusing on this ubiquitous virus has yielded remarkable achievements: widely accessible molecular testing for HPV and a vaccine against the four most common sexually transmitted HPV types (including types 16 and 18, which have been associated with the overwhelming majority of cases of cervical dysplasia and cancer).

The availability of vaccination and HPV cervical screening has led to some challenging questions about cervical cancer screening. Some authors have advocated HPV testing as a primary screening method, either combined with or as a replacement for cervical cytology, and clinicians as well as patients wonder whether being vaccinated against HPV will make cervical cytology less important.

PREVALENCE AND NATURAL HISTORY OF HPV

Unquestionably, HPV infection is extremely common. The US Centers for Disease Control and Prevention estimate that approximately 20 million Americans currently have a genital HPV infection, and about 6.2 million each year acquire a new genital HPV infection, making it the most common sexually transmitted viral infection in this country.[1] At least 80% of women will have had an HPV infection by age 50.[1]

Worldwide, the World Health Organization (WHO) estimates that 409,400 new cases of cervical cancer occur each year in developing countries and 83,400 new cases occur in developed countries. According to the WHO, an estimated 660 million people have a genital HPV infection.[2]

Most sexually active adults will acquire a genital HPV infection at some time in their lives, but the most serious disease caused by HPV, cervical cancer, is relatively rare when the prevalence of infection is considered. In addition, the rate of cervical cancer has declined considerably over the years since the Papanicolaou smear was introduced. The women most likely to develop cervical cancer are those who have never had a Pap test or who are screened rarely.[3]

The natural history of HPV cervical infections must be considered in any discussion of screening and risk management. Einstein and Burk[4] evaluated the available data and summarized the path that an HPV infection may follow (**Figure**). Three important studies of HPV in populations of young women demonstrated that most HPV infections are transient and cause either no changes or low-grade cervical intraepithelial neoplasia (ie, CIN 1) and that CIN 1—even those lesions associated with high-risk HPV types—will spontaneously regress in most young women.[5-7] Many health care professionals now advocate close surveillance with repeat cytologic evaluation of these types of lesions. High-grade lesions are most likely to occur when infection persists beyond 1 year; only 30% to 50% of HPV infections in young women fail to clear within that time.[4]

When high-grade lesions develop, the condition may progress to invasive cancer. Several factors have been identified that are thought to contribute to the progression from infection to cancer in patients with HPV. Some of the risk factors are tobacco use, infection with other sexually transmitted pathogens, and a compromised immune system (for example, in patients taking immunosuppressant medications following organ transplantation).[8]

Given what is currently known and understood about the natural history of HPV infection, it is apparent that the mere presence of HPV infection reveals little about its significance. It is not possible to determine whether the infection is new, persistent, or recurrent and, therefore, whether the patient is at high risk or not. Thus, the positive predictive value of HPV screening is limited by the natural history and the high prevalence of HPV infections. This is particularly true in women less than 30 years of age.

In addition, the role of HPV infection in the development of glandular lesions and adenocarcinoma is not yet clearly understood. HPV may or may not be present in these conditions, so the failure to identify HPV infection does not rule out the possibility of nonsquamous lesions. (See the article by Drs Lozano and Sauer on page 5 for further discussion of this topic.)

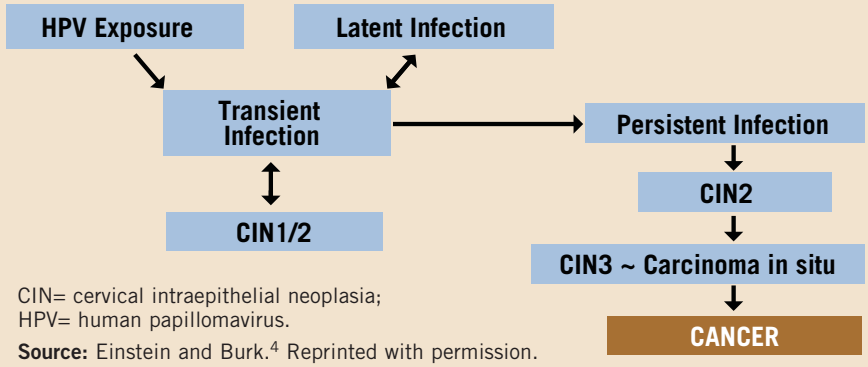
HPV TESTING VERSUS CERVICAL CYTOLOGY: REVIEWING THE DATA

It has been suggested that HPV screening is substantially more sensitive than cytologic screening, but it is important to recognize that such suggestions are based on comparisons between HPV testing and conventional Pap smears, not between HPV testing and liquid-based cytology or liquid-based Pap testing with computer-assisted imaging.

A well-designed study that provides reliable data is from the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) group,[9] which examined several strategies for identifying and evaluating women with clinically significant disease. The ALTS investigators conducted a randomized multicenter trial comparing three management strategies in patients with equivocal results on Pap testing: immediate colposcopy, triage to colposcopy based on HPV DNA testing and liquid-based Pap test results, or triage based on cytology alone.

The data indicated that, for women with a Pap test result of atypical squamous cells of undetermined significance (ASC-US), reflex HPV testing from the same liquid-based Pap test vial is more sensitive than colposcopy and conventional cytology in identifying women who have a cervical abnormality. The reported sensitivity for the liquid-based Pap test plus HPV reflex testing was 96%. In addition, the negative predictive value was 99%—that is, there was a 1% chance of a high-grade squamous intraepithelial lesion (HSIL) in a patient with an ASC-US result and a negative HPV test result.[9]

FIGURE. Pathway to Cervical Cancer



CIN= cervical intraepithelial neoplasia;
HPV= human papillomavirus.

Source: Einstein and Burk.[4] Reprinted with permission.

However, simultaneous liquid-based Pap testing plus HPV testing as a primary screening strategy does not seem to offer any advantages. Ferreccio and colleagues[10] tested several screening methods in more than 8,500 women, including cervicography, conventional Pap smear testing, liquid-based Pap testing, and HPV DNA testing. They evaluated these methods used alone as well as in various paired combinations for primary screening for cervical abnormalities. Regarding HPV DNA and liquid-based Pap tests, specifically, the authors found no differences between the two tests used alone or in combination in terms of negative predictive value and specificity.

Two other studies compared liquid-based Pap testing with HPV testing in detecting cervical intraepithelial lesions rated high-grade or greater (CIN 2+). In both studies, the negative predictive values were 100% or nearly 100% with both tests. Differences between the tests were found in positive predictive values. Belinson and colleagues[11] reported positive predictive values of 61% with liquid-based Pap test cytology and 23% with HPV testing for HSILs or higher-grade lesions. Clavel and coworkers[12] found that the liquid-based Pap tests had a positive predictive value of 15.1% versus 8.7% for HPV testing in women age 30 years or older.

It is not surprising that the HPV test methods now available show negative predictive values consistently approaching or reaching 100% in patients with cervical abnormalities. However, positive predictive value must also be considered, because the virus may be present without a cervical abnormality. A literature review by Bosch and colleagues[13] suggests that between 4% and 7% of cases of cervical carcinoma may occur without the presence of HPV.

LIQUID-BASED CYTOLOGY PLUS IMAGING

Cibas and colleagues[14] conducted a study* designed to compare high-risk HPV DNA testing with computer-assisted imaging in 857 women 35 years of age or older who had had liquid-based Pap testing. The subjects had negative results with liquid-based cytology, and computer imaging performed at the same time also showed negative results. The investigators then tested the cervical samples for HPV DNA. According to an interim analysis of data presented recently, high-risk HPV was present in 3.9% of these "double-negative" patients. (Interestingly, the younger women had a higher rate of HPV: 6.7% of women 30 to 34 years of age, 3% of those 35 to 39 years of age, and 2.6% of patients 40 to 45 years of age were HPV-positive.)

These results suggest that a negative result using a liquid-based Pap test with computer-assisted imaging is associated with a very low rate of high-risk HPV. Further studies are necessary, but if these findings are confirmed, liquid-based Pap testing with computer-assisted imaging may offer a more cost-effective screening strategy for women 30 years of age or older.

CONCLUSION

It is crucial that clinicians routinely screen for cervical disease using the most sensitive and reliable techniques currently available. HPV screening is helpful in that it provides a risk assessment regarding the likelihood that cervical disease will develop in a particular patient and is increasingly recognized as a valuable tool in determining the management of patients who receive an ASC-US reading with liquid-based Pap tests. However, cytology is the only screening method that allows the determination of whether a woman currently has cervical disease. Furthermore, cytology is the only test for which long-term data are available demonstrating an overwhelming benefit in decreasing the incidence of and mortality associated with cervical cancer. Computer-assisted screening, utilizing dual review (in which the imager directs the cytotechnologist's attention to cells of interest), allows the cytotechnologist to focus on interpretation of the slide thus improving sensitivity and specificity over manual screening.† ■

FOOTNOTES

* This study was supported by Cytyc Corporation, Marlborough, Mass., the manufacturer of the cytology/imager system evaluated.

† The TPIS clinical trial showed a statistically significant increase in ASC-US+ sensitivity of 6.4% [95% CI, 2.6-10.0] and a statistically significant increase in HSIL+ specificity of 0.2% [95% CI, 0.06-0.4].

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Milestones in Cervical Cancer Detection and Prevention: Significance in Clinical Practice

Continued from page 4

some are fully reimbursing for HPV vaccinations.

The clinical trial leading to FDA approval of the quadrivalent vaccine reported an excellent efficacy and safety profile, but the true incidence of toxicity for any new vaccine or drug is not apparent until it has been administered under real-world conditions to very large numbers of patients in the general population. Such data are not likely to be available for several years.

The acceptance of the vaccine for preadolescent and adolescent girls has been evaluated by means of parental questionnaires, in which adults were asked about their willingness to have themselves and their children vaccinated. The trend in these surveys is toward acceptance of vaccination.[7] The key here is education. The general public must be informed about HPV infection, its transmission, and the potential long-term health consequences of persistent infection with high-risk HPV types.

Even with widespread acceptance and use of HPV vaccines, it is estimated that a significant reduction in the number of cases of cervical cancer will not be seen for at least many decades. Clinicians and the public must be aware that vaccination is not a substitute for cervical cancer screening and that cervical cancer screening remains the standard of care.

CONCLUSION

Experience with liquid-based, thin-layer cytology with manual screening has demonstrated the efficacy of this technology in improving rates of detection of cervical cancer. The combination of liquid-based cytology and computer-assisted screening increases the likelihood of early detection even more. As HPV vaccination becomes more and more common and as the technologic advances in cervical cancer screening are increasingly more widely incorporated into clinical practice, the accumulating evidence is likely to support changes in screening recommendations. What will not change for some time, however, is the need for cervical cancer screening: the advent of HPV vaccination will not obviate the need for continued screening for at least several decades. Meanwhile, it is important for clinicians and patients alike to heed the advice to "vaccinate early, screen regularly." ■

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Weighing the Costs and Benefits: Technologic Advances in Cervical Cancer Screening

Continued from page 9

an affordable cost and without overscreening—and potentially overtreating—patients. ■

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