Reducing Patient Risk for Human Papillomavirus Infection and Cervical Cancer

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The majority of cervical cancers result when the human papillomavirus (HPV) is transmitted from a man to a woman during vaginal intercourse. Several factors, including vaginal intercourse at an early age or with multiple sex partners, place women at increased risk for infection with HPV. It is important for physicians to be aware of these risk factors and to screen for them in all of their female patients. It is also important for physicians to be familiar with the new HPV vaccinations that are becoming available, such as Gardasil, which in June 2006 became the first vaccine approved by the US Food and Drug Administration to protect patients against cervical cancer. The widespread use of routine HPV screening and cervical cancer vaccines can be expected to decrease the incidence of new HPV infection and cervical cancer worldwide.

Cervical cancer is the second leading cause of cancer mortality among women, killing more than 250,000 women worldwide each year.1 The World Health Organization (WHO) estimates that 500,000 new cases of cervical cancer are diagnosed each year.1 More than 80% of these cases occur in developing countries, where population-based routine screening, the Papanicolaou (Pap) smear, and optimal treatments are not available.1 In the United States, there are an estimated 10,500 cases of cervical cancer diagnosed annually—and these cases result in approximately 3700 deaths per year.2

More than 90% of cervical cancers are caused by the human papillomavirus (HPV), which is spread by skin-to-skin contact during sexual intercourse.1-3 This virus may be present on the anus, vulva, and cervix of women and on the anus and penis of men.4 The US Centers for Disease Control and Prevention (CDC) estimate that there are more new cases of HPV infection per year than of any other sexually transmitted disease (STD).5 Individuals who are infected with HPV may be unaware of it because most infections are subclinical in nature and diagnosable only with specialized DNA testing—that is, examination of genital or anal cells for the presence of HPV DNA.3 Only 4% of women with HPV infections have mild cytologic signs at presentation, and only 1% of such women have visible lesions at presentation.2 Studies have demonstrated that screening patients with combined Pap smear and Genital Human Papillomavirus (HPV DNA) testing can increase the clinical sensitivity for detecting high-grade cervical disease, including cancer, by greater than 99%.3

Epidemiologic studies in the United States have shown that 75% of women aged 15 to 50 years become infected with HPV in the genital tract sometime during their lives.1 In addition, according to a February 2007 report by the CDC, approximately 27% of women aged 14 to 59 years in the United States are currently infected with HPV—a rate that is higher than many previous estimates.6 If HPV infection is as prevalent as indicated by these statistics, why don’t more women actually have cervical cancer? Fortunately, more than 90% of genital HPV infections are transient, meaning that they are spontaneously cleared from the body within 2 years by natural humoral and antibody responses.5 However, 10% of genital HPV infections are persistent, as confirmed by detection of HPV DNA in consecutive genital tissue samples taken from patients.5

More than 100 different types of HPV have been documented, 40 of which have been isolated from anogenital epithelium.3-5 The various types of HPV are classified into low- and high-risk groups based on their oncogenic potential (Figure 1). The low-risk group (eg, common HPV types 6 and 11) is associated more often with genital warts and benign lesions than with cervical cancer.4 The high-risk (ie, oncogenic) group (eg, HPV types 16, 18, 31, 33, and 45) is associated most commonly with cervical cancer.4 Human papillomavirus types 16 and 18 have been isolated from more than half of cervical cancer biopsies worldwide.4 All HPV types are spread by skin-to-skin contact during sexual intercourse.4

When an HPV infection is not cleared with the body’s own immune system, a patient develops what is known as a persistent infection.3 Persistent infection with high-risk HPV types is an important determinant in the pathogenesis of cervical cancer.3 Therefore, positive tests for high-risk HPV types in women aged 30 years or older who get regular Pap testing and have been in monogamous relationships for more than

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3 years are more likely to represent persistent infection—and increased risk of cervical disease.

The human papillomavirus is a double-stranded DNA papillomavirus that encodes 10 viral proteins—two late gene products and eight early gene products.3 The late gene products consist of structural proteins for the viral capsid.3 The early gene products are proteins involved in viral replication and oncogenesis and are, thus, important in determining whether an HPV infection is active or latent.3 Proteins E6 and E7 from the high-risk HPV types, such as HPV 16 and 18, can bind to and inactivate the cellular tumor suppressor gene protein products p53 and pRb (ie, retinoblastoma protein), respectively, leading to malignant transformation.3 This transformation is a crucial process in the pathogenesis of cervical cancer.

Risk Factors
It is important to keep in mind that a risk factor is anything that influences an individual’s chance of contracting a disease, including genetic, environmental, and behavioral factors. In assessing a patient’s risk, the physician should focus on those factors that the patient has the ability to change, such as sexual behavior. However, it is also important for the physician to ask the patient about risk factors that cannot be changed, such as family medical history, so that the most appropriate screening can be performed.

Although many factors can lead to the development of cervical cancer, HPV is the only factor associated with more than 90% of cervical cancers in the United States.2 In most cases of cervical cancer, the presence of HPV is necessary to prompt the cellular transformation that leads to cervical cancer. Moscicki et al7 reported in 1998 that women who had at least three positive test results for high-risk HPV types were 14 times more likely to have cervical cancer precursor cells than women who had negative test results for high-risk HPV types. Nevertheless, the presence of HPV is not sufficient to cause cancer in every woman who is infected. Therefore, other risk factors must be involved in the progression from viral incorporation to cell transformation and cancer.5

Certain sexual behaviors are closely linked with acquiring HPV infection. For example, multiple sexual partners and vaginal intercourse at an early age (<20 y) increase a woman’s chances for HPV exposure and infection.4 Thus, early education about these risk factors may decrease a woman’s risk for exposure to HPV infection.

Recent studies suggest that the most commonly recommended precaution against STDs may not be completely effective in preventing the transmission of HPV. Skin-to-skin transmission of HPV is still possible, even with the use of condoms.5 Based on this recent research evidence, the CDC reported in 2004 that “available scientific evidence is not sufficient to recommend condoms as a primary prevention strategy for the prevention of genital HPV infection.”5 Yet the CDC added, “There is evidence that indicates that the [consistent] use of condoms may reduce the risk of cervical cancer.”5 This beneficial effect of condoms is related to the fact that condoms protect against other STDs, such as AIDS, chlamydia, and genital herpes—STDs that may depress the body’s immune system, thereby increasing the risk of cervical cancer.5

According to the American Cancer Society (ACS), sexual intercourse with an uncircumcised man can also increase a woman’s risk of HPV infection.4 A study conducted in 2002 by Castellsagué et al8 concluded that uncircumcised men were more likely to contract penile HPV infection, thereby placing their sexual partners at higher risk for HPV infection and cervical cancer.

Certain personal behaviors are also sufficient to promote neoplastic change in cervical cells. Smoking has been identified as a possible cofactor in the progression of low-grade cervical lesions to high-grade cervical lesions.9,10 In 1998, Ho et al9 reported that the risk of cervical intraepithelial neoplasia (CIN) grade 3—called high-grade squamous intraepithelial lesion (HSIL) in the 2001 Bethesda System11—is substantially increased if a woman smokes more than 10 cigarettes per day—especially if she is infected with HPV type 16. McIntyre-Seltman et al10 concluded in 2005, “Women with oncogenic HPV and minimally abnormal Papanicolaou smears who smoke were up to three times more likely to be diagnosed with ≤CIN 3...than nonsmokers.” In 2006, the ACS2 noted, “Quitting smoking substantially decreases the risk of lung, laryngeal, esophageal, oral, pancreatic, bladder, and cervical cancers.” Smoking’s role as a risk factor for cervical cancer is related to the fact that it reduces the body’s ability to mount a sufficient immune response and may prevent effective clearing of HPV from the body.9,10 In addition, the carcinogens in cigarettes may cause oncogenic changes in cells where the DNA has already been infiltrated with HPV.9

Another behavioral influence on cervical cancer risk is a woman’s diet. Diets low in fruits and vegetables have been associated with an increased risk of cervical cancer.4 The etiologic factors involved in this association are thought to be secondary to a lack of certain vitamins and minerals, including vitamin C, copper, and zinc.12

A patient’s obstetric history is also important in assessing her risk status in regard to cervical cancer. For example, there is an increased risk of cervical cancer in women who have carried seven or more full-term pregnancies and in women who have
Since the 1980s, new cases of these adenocarcinomas have greatly decreased. DES-related cervical and vaginal clear-cell adenocarcinoma, "DES daughters" have aged beyond the average age of diagnosis of DES-related cervical and vaginal clear-cell adenocarcinoma. As "DES daughters" have aged beyond the average age of diagnosis of DES-related cervical and vaginal clear-cell adenocarcinoma, new cases of these adenocarcinomas have greatly decreased since the 1980s. Finally, some researchers believe that an inherited genetic condition may prevent the body from attacking HPV as well as it should, leading to persistent infection. However, the nature of the genetic defect and its precise mode of inheritance remain unknown.

**Patient Screening**

Physicians should ask their patients about all possible risk factors for HPV exposure and cervical cancer during each gynecologic examination. Physicians should inquire whether patients have previously had an abnormal Pap smear result and whether they have had multiple sexual partners. A patient’s social history should always be updated to include a record of any unwanted sexual encounters, any possible exposure to hazardous chemicals, and her habits of alcohol consumption, tobacco use, diet, and exercise.

When interviewing a patient of minor age, it is helpful for the physician to request that her parent(s) or guardian(s) step out of the examination room before asking questions about the girl’s body, self-image, health status, or sexual behaviors. Parents should not be forced out of an examination room. If they are willing to step out, however, the patient may be more likely to provide honest answers and to ask questions on topics she would not feel comfortable asking about in the presence of parents. Teenagers who are pregnant or who have had children may legally be considered “emancipated minors,” in which case parental permission is not required in order for them to be seen by a physician. However, laws regarding emancipated minors vary across states, so physicians are advised to become familiar with their local legal requirements.

If a patient’s interview reveals risk factors for HPV infection or cervical cancer (Figure 2), the physician should conduct a nonjudgmental discussion with the patient about those risk factors and their possible consequences. In this discussion, the physician must be open and honest with the patient, allow the patient to ask questions, and offer advice on how to control the risk factors, especially if smoking is one of the risk factors.

Based on guidelines published by the ACS and the American College of Obstetricians and Gynecologists (ACOG), all women should be screened with a cervical cytologic test (ie, Pap smear) 3 years after their first vaginal intercourse or by age 21 years, whichever occurs first (Figure 3). Per ACS guidelines, women should be screened annually—or every 2 years if the liquid-based ThinPrep Pap Test (Cytyc Corporation, Marlborough, Mass) is used—until they reach 30 years of age. If, at age 30 years, the previous three Pap smears have had negative results, patients should continue undergoing cytologic screening every 2 to 3 years. If, at age 70 years, the patient has had at least three normal cytologic test results—including no abnormal test results within the previous 10 years—all cervical screening may be discontinued.

In addition, all cervical screening may be discontinued if a hysterectomy with cervical removal is performed for a benign condition (Figure 3). What Do the Screening Results Mean? Clinical management may depend on patient age, health status, and the oncogenic potential of any squamous abnormalities noted in cytologic testing. In recent years, liquid-based cytologic testing, a reflex test for HPV DNA—such as hybrid capture or polymerase chain reaction—has become adjunctive to traditional cytologic studies (Figure 4).

For women who are younger than 20 years, a “wait-and-see” approach is recommended when the results of a Pap smear are atypical squamous cells of undetermined significance (ASC-US). Such patients should be given the opportunity to clear the infection before more invasive intervention is undertaken. In other words, adolescent women with less than HSIL on a Pap smear should have repeat testing in 12 months. If the repeat test indicates ASC or greater, then these patients should be referred for colposcopy. Patients with HSIL or

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**Figure 2.** Risk factors for human papillomavirus (HPV) infection and cervical cancer. **Abbreviations:** DES, diethylstilbestrol; HIV, human immunodeficiency virus.
greater on initial Pap smear should proceed to colposcopy. Immediate loop electrosurgical excision is unacceptable.

Women aged 20 years to premenopausal age who have ASC-US results may be given the option of returning in 6 to 12 months for a repeat Pap smear or HPV DNA test—or referral for colposcopy. If repeat testing is chosen and the new results indicate continued ASC-US, atypical glandular cells of undetermined significance (ASG-US), HSIL, or low-grade squamous intraepithelial lesion (LSIL), referral for colposcopy is recommended. If repeat testing yields negative results, the patient may return to a routine screening schedule. If the result of an HPV DNA test is positive for high-risk HPV types, it is advisable to refer the patient for immediate colposcopy. If low-risk HPV types are present, cytologic testing should be repeated in 12 months.

Women in this same age group who have atypical squamous cells–“cannot exclude HSIL” (ASC-H) or LSIL should undergo colposcopic examination. Those with ASC-H who do not have CIN 2 or CIN 3 would then have repeat cytology at 6 and 12 months or repeat HPV DNA testing at 12 months. Cases with CIN 2 or CIN 3 should be managed following guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP). Women with LSIL-positive Pap smear results should have endocervical sampling during colposcopic examination.

For women who have LSIL Pap smear results while pregnant, clinical response is once again age-dependent. Adolescent women should have colposcopy deferred until 6-months postpartum. All other pregnant women should receive colposcopy immediately and their cases should be managed following ASCCP guidelines based on CIN status. A woman who is pregnant and has been found to have ASC-US should be placed on the same treatment and testing plan as women with ASC-US who are not pregnant.

Previously a woman who was postmenopausal and had cytologic or clinical evidence of cervical cell atrophy but no contraindications for estrogen therapy was provided a 3-week course of intravaginal estrogen with repeat cervical cytology. Recent revisions to clinical guidelines, however, now recommend that such cases be managed the same as women in the general population.

<table>
<thead>
<tr>
<th>Source</th>
<th>Initial Papanicolaou Smear</th>
<th>Continued HPV Screening</th>
<th>Discontinuation of HPV Screening</th>
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</thead>
<tbody>
<tr>
<td>American Cancer Society</td>
<td>3 y after first vaginal intercourse; no later than age 21 y</td>
<td>Annual screening with following exceptions: every 2 y with liquid-based cytologic test; every 2-3 y if three consecutive normal test results in women age ≥30 y</td>
<td>Total hysterectomy for benign disease; age ≥70 y with at least three normal Papanicolaou smear results and no abnormal test results in previous 10 y</td>
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<tr>
<td>American College of Obstetrics and Gynecology</td>
<td>3 y after first vaginal intercourse or age 21 y, whichever occurs first</td>
<td>Annual screening until age 30 y, then the following options: continue screening annually; continue screening every 2-3 y; HPV DNA test in addition to cytologic test (if negative results, repeat Papanicolaou smear no sooner than 3 y)</td>
<td>Difficult to set upper age limit; postmenopausal women screened within previous 2-3 y have low risk of abnormal Papanicolaou smear results</td>
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**Figure 3.** Screening guidelines for cervical cancer published by the American Cancer Society and the American College of Obstetricians and Gynecologists. **Abbreviation:** HPV, human papillomavirus.

**Figure 4.** In recent years, liquid-based cytologic testing, a reflex test for human papillomavirus DNA, has become adjunctive to traditional cytologic studies. When the Papanicolaou smear and the Genital Human Papillomavirus (HPV) DNA test are used side by side, three outcomes are possible. Recommended guidelines for clinical management are noted.
In addition, previously when woman were known to be immunosuppressed (eg, as a result of infection with the human immunodeficiency virus [HIV]) and had a Pap smear result that was positive for ASC-US, she was referred for immediate colposcopy. The reason for this step was that ASC-US, CIN, and HPV infection are each two to three times more common in women who are infected with HIV than in women who are not infected with HIV. However, current guidelines recommend that women who are immuno-compromised receive the same routine screening schedule as women in the general population.

In cases where Pap smear results indicate medical conditions more serious than ASC-US—including HSIL, LSIL, or ASC-H—patients should continue to be referred for immediate colposcopy and endocervical sampling. However, cases with HSIL-positive Pap smears may be managed with either immediate loop electrosurgical excision or by colposcopic examination with endocervical sampling and further investigation or treatment based on CIN status.

Patients whose results are consistent with atypical glandular cells (AGC) with atypical endometrial cells must undergo endocervical and endometrial sampling. Cases with all other subtypes of AGC (ie, those without atypical endometrial cells) should advance to colposcopy with HPV DNA testing and endocervical sampling.

Please refer to the American Society for Colposcopy and Cervical Pathology Web site (http://www.asccp.org/) for more information on cervical pathology as well as colposcopy guidelines and recommendations for clinical management.

Vaccinations

Studies testing the clinical efficacy of various HPV vaccinations are underway worldwide. As of mid-2007, only one vaccine, Gardasil (Merck & Co Inc, Whitehouse Station, NJ), had been approved by the US Food and Drug Administration (FDA) for use against cervical cancer. Gardasil, which received approval in June 2006, is a quadrivalent, recombinant vaccine that targets the strains of HPV that are most often responsible for causing cervical cancer and genital warts—HPV types 6, 11, 16, and 18. Gardasil not only protects against high-risk HPV infection and cervical cancer, but against genital condyloma as well.

Three doses of 0.5 mL of Gardasil are given to patients. The second and third inoculations are given 2 and then 6 months after the first. Gardasil is available to physicians in 0.5 mL vials and in prefilled syringes. The vaccine’s cost to physicians is approximately $120 per dose, or $300 to $400 per vaccine series. Merck recommends that its Gardasil vaccine be given to girls and women who are between the ages of 9 and 26 years. Because HPV infection is spread through sexual contact, they recommend that girls and women be vaccinated before becoming sexually active. However, even if female patients in this age group have tested positive for any type of high-risk HPV in the past, she should still be vaccinated to protect against other HPV types. Gardasil does not substitute for routine cervical cancer screening, so women who receive the vaccine should continue undergoing regular screening.

In March 2007, GlaxoSmithKline plc (London, England) announced that it had filed for FDA approval of its cervical cancer vaccine, Cervarix, an adjuvant vaccine that targets the cancer-causing HPV types 16 and 18. Paavonen et al reported in June 2007 that clinical trials indicated that Cervarix is both well-tolerated by patients and effective in preventing cervical cancer caused by HPV types 16 and 18. Both Gardasil and Cervarix have demonstrated very high efficacy in proof-of-principle studies, and their manufacturers have announced results showing almost 100% protection against high-grade cervical cancer precursors caused by HPV types 16 and 18 in women aged 16 to 25 years.

Giving young girls the HPV vaccine is somewhat controversial, however. Some parents are concerned that giving preteens and teenagers protection against an STD may lead girls to believe it is “okay” and “safe” for them to engage in sexual activity. Indeed, some parents believe administering the vaccine may encourage promiscuity. However, there have been no proven correlations between early sexual activity and early sex education or access to contraceptives.

A girl who has never engaged in sexual intercourse can still be exposed to the virus if her first sexual partner has had just one previous partner. Vaccine efficacy is improved when girls receive HPV vaccination before vaginal intercourse. For this reason, recommendations for routine administration of the new vaccine target girls who are 11 to 12 years of age—also the recommended age range for the now common diphtheria, tetanus, and pertussis vaccine as well as the meningococcal conjugate vaccine.

Early vaccination ensures that women are protected from HPV before they become sexually active. About half of all women who are diagnosed with HPV are between the ages of 35 and 55 years—probably many years after their initial exposure. Indeed, it is estimated that HPV is most commonly contracted during the late teens and early twenties.

It is advisable for physicians to talk to patients of minor age and their parents about the risk of intercourse and other forms of sexual activity. The more patients know, the more likely they are to protect themselves from harm.

At this time, most studies have been conducted for the effectiveness of the vaccine up to age 26 years, when the immune system is its strongest. Clinical investigations are currently underway to test the vaccine’s effectiveness in older women (>26 years) and in men.

Because studies have been of short duration, one unknown property of these vaccines is their longevity. Further study is currently underway to determine how long the vaccine’s protective effect will last.

Conclusion

Cervical cancer is a preventable disease if patients are routinely screened for it and if patients with precursors of the
disease are treated early. Knowledge of the association between HPV infection and cervical cancer as well as thorough screening measures for HPV risk factors are key tools in a physician’s armory for fighting cervical cancer. By taking a few minutes to evaluate a patient’s risk for HPV infection and to educate her about certain behaviors that can be modified, a physician can reduce her chances of infection with HPV—and the progression of infection to cervical cancer. With the advent and availability of HPV vaccines, the incidence of cervical cancer worldwide will almost certainly decline in exponential proportions.

References

Editor’s Notes: In March 2006, JAOA—The Journal of the American Osteopathic Association published a supplement on this topic, Human Papillomavirus Vaccines: A “Shot” at Preventing HPV-Related Disease, with an educational grant from the Merck Vaccine Division. Readers are encouraged to view it at the JAOA’s Web site (http://www.jaoa.org /content/vol106/suppl_1). In addition, please watch for another upcoming Supplement to the JAOA on this topic in spring 2008 sponsored by Merck & Co, Inc. This supplement will be posted at: http://www.jaoa.org/supplements.shtml.

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