Human papillomavirus (HPV) is a ubiquitous human pathogen that causes cervical and other anogenital cancers as well as genital warts and recurrent respiratory papillomatosis. Human papillomavirus infection is most common among young, sexually active individuals, and it is so prevalent that approximately 75% to 80% of sexually active individuals will become infected in their lifetime. Currently, options are limited for both prevention of infection of patients with HPV-associated disease: infection can only be prevented with complete abstinence from all forms of sexual activity because condoms do not offer complete protection from HPV and HPV can be transmitted by nonintromissive sexual activities. Treatment of patients with HPV-associated disease such as cervical intraepithelial neoplasia and genital warts consists of counseling, treatment if indicated, and monitoring for recurrence. Soon, however, prevention of these HPV-related diseases may be available in the form of a prophylactic HPV vaccine. Phase 3 studies of a quadrivalent vaccine that protects against both high- and low-risk types of HPV demonstrated the vaccine to be 100% effective in preventing HPV type 16– and type 18–associated cervical disease, suggesting that these vaccines, if made widely available, will dramatically reduce the burden of HPV-related disease.

Epidemiology of HPV Infection: Low- and High-Risk Types

Individuals aged 15 to 24 years are at highest risk for genital HPV infection because sexual debut typically occurs in the mid to late teen years, and HPV exposure generally occurs shortly thereafter. In a review of STDs among American youth, Weinstock et al report 4.6 million cases of HPV infection a year, compared with 640,000 cases of genital herpes and 1.5 million cases of chlamydia. Estimates of the prevalence of HPV infection are derived largely from studies in women because few studies have been conducted in men, and the data that are available for HPV infections in men are limited by the widely varied genital sampling and laboratory methods used. In more recent studies conducted in men, the prevalence of genital HPV infection appears to be at least as high as that among women of similar backgrounds.

Approximately 40 types of HPV infect the genital epithelium. Human papillomavirus types are classified as either oncogenic, “high-risk,” types, which are capable of causing dysplasia and cancer, or nononcogenic, “low-risk,” types, which cause low-grade mild dysplasia, genital warts, and respiratory papillomatosis. Human papillomavirus types 16 and 18 are the two most common high-risk types of HPV, whereas HPV types 6 and 11 are the two most common low-risk types. Infection with one type does not confer protection from another type. It is estimated that approximately 1% of Americans have genital warts, 4% have cervical dysplasia detected on colposcopic examination, 10% are infected with genital HPV without clinical symptoms or signs, and 60% are seropositive for one or more genital HPV types without evidence of current disease (Figure 1,2).

During the past two decades, it has become clear that infection with high-risk genital HPV is necessary for the development of cervical cancer.13-16 Human papillomavirus types 16 and 18 are implicated in approximately 70% of cervical cancers worldwide (Figure 2,17). Evidence that high-risk genital HPV types are associated with a subset of squamous cell carcinomas of the head, neck, and skin is also increasing.
Clinical Manifestations and Transmission of HPV

Clinical manifestations of genital HPV include condylomata acuminata (genital warts), dysplasia, and cancer of the cervix, anus, vulva, vagina, and penis, and recurrent respiratory papillomatosis. The occurrence of HPV-related disease is more common at the cervix than other sites likely because women have a transformation zone on the cervix. Dysplasia and cancer of the anus are just as common in men who have sex with men as cervical disease is in women; the anus has a transformation zone similar in some ways to that of the cervix.

The cervical transformation zone, located between the mature epithelium of the exocervix and the columnar epithelium of the endocervical canal, is particularly vulnerable to HPV because it is a site where immature squamous cells are turning over (ie, squamous metaplasia), thereby creating a clinical scenario for dysplasia to occur. Squamous metaplasia is a common finding among younger women with or without HPV infection. Squamous cell carcinoma also occurs at other transformation zones in the body, such as the esophageal junction where the esophagus meets the stomach, and at the dentate line in the anal canal, where the anus meets the rectum.

Genital HPV is transmitted by skin-to-skin contact, and sexual contact with an infected partner, regardless of the sex of the partner, is the most common route of transmission. Often, the infected partner has subclinical genital HPV and is not aware that he or she is infected. Risk estimates per sexual act are not known for acquisition of HPV.

Perinatal transmission from mother to child is rare and causes HPV type 6–or type 11–related recurrent respiratory papillomatosis in infants and young children when it occurs. In studies of women with a history of genital warts or current disease related to HPV type 6 or type 11, less than 2% of these women transmitted HPV to their children. Cesarean section does not seem to prevent perinatal transmission of HPV. Condom studies are limited and show that this method of prevention is not highly effective, likely because genital HPV is often found on areas not covered by a condom, such as the vulva and the scrotum. Some studies suggest that partners who are currently infected with the same HPV types may be more likely to have cervical or penile dysplasia regress if they use condoms regularly and effectively.

Risk Factors for Acquisition of HPV

One of the greatest risk factors for acquisition of HPV among both men and women is having a greater number of lifetime sex partners. In studies of women, risk for genital HPV infection seems to increase with earlier age of sexual debut, higher number of partners among their sex partners, increasing age, and smoking. In the few studies conducted in men, lifetime and recent number of sex partners and perhaps frequency of sex emerge as risk factors for acquisition of HPV.
decrease the risk of persistent infection.\textsuperscript{40} with men is higher than the incidence of anal cancer among men who have sex with other men, especially with advanced disease and human immunodeficiency virus (HIV) infection, especially with advanced disease and immunosuppression; and having a high number of lifetime sex partners.

Men and women who engage in receptive anal intercourse are at risk for anal HPV infection with clinical sequelae that may include anal warts and anal dysplasia or cancer. Other risk factors for anal HPV include having a current HPV infection at another genital site; having a history of cervical dysplasia or anal warts; having the human immunodeficiency virus (HIV) infection, especially with advanced disease and immunosuppression; and having a high number of lifetime sex partners.

In the United States, the incidence of anal cancer among men who have sex with men is higher than the incidence of cervical cancer among women.\textsuperscript{41} This difference is likely due to the fact that screening for anal cancer is not widely practiced in the United States, often because providers are not comfortable doing an anal Papnicolaou (Pap) test or reading anal Pap cytology (and HPV testing in some settings) is cost-effective in reducing anal cancer rates, though this seems likely given the success of cervical cytology screening programs in reducing cervical cancer rates.

## HPV-Related Disease of the Cervix

Cervical dysplasia is the most common clinical manifestation of genital HPV. In the United States, there are approximately 1 million women with low-grade dysplasia and 300,000 with high-grade dysplasia each year. It is estimated that each year about 10 million US women have HPV infection without detectable cytologic abnormalities.\textsuperscript{42} Worldwide estimates for the same clinical conditions are more than 300 million.\textsuperscript{42} Regression of mild or low-grade dysplasia is the norm with only a minority of women progressing to cancer. However, accurately predicting who will progress and who will regress is not easy; therefore, all women are followed up until the dysplasia resolves. Women with severe or high-grade dysplasia should be offered a diagnostic excisional procedure.\textsuperscript{43}

Although these challenges are likely to change in the future as providers may now receive training for anal cancer screening and treatment of patients with anal dysplasia through the American Society for Colposcopy and Cervical Pathology (ASCCP), it will be many years before this screening is widely practiced throughout the United States. It will also be many years before we know whether screening for anal cancer with anal cytology (and HPV testing in some settings) is cost-effective in reducing anal cancer rates, though this seems likely given the success of cervical cytology screening programs in reducing cervical cancer rates.

### HPV-Related Disease of the Uterine Cervix

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Cervical cancer remains the second leading cancer among women worldwide, mainly in countries where primary screening with Pap tests does not occur.\textsuperscript{44} However, even in the United States, where more than 50 million Pap tests are done on women every year, there are still approximately 10,370 new cases and 3710 deaths annually.\textsuperscript{45,46} The direct cost of cervical cancer screening in the United States is estimated at more than $5 billion each year.\textsuperscript{47} Direct costs associated with the management of high-grade dysplasias in the United States approximate $2350 per case, with an average of 6.9 office visits; management of low-grade dysplasia costs an average of $1275 and requires 4.5 treatment visits.\textsuperscript{48}

Much has been learned about the natural history of genital HPV infection during the past two decades, largely from studies in young women. Unfortunately, no long-term studies of the natural history of genital HPV infection in men have been published, so it is not known how, if at all, the disease cycle is different in men. Among women, exposure to genital HPV typically occurs soon after sexual debut and is followed by a 1- to 8-month period during which no symptoms or signs of the infection exist. Many infections are subclinical; neither condyloma nor dysplasia will develop. After this incubation period, a lesion (eg, cervical dysplasia or genital wart) may appear with a period of active growth that typically generates a sustained immune response during a 3- to 6-month period. After the immune response is initiated, there is a period of host containment, which is followed by either a sustained clinical remission or persistent or recurrent disease.

In a study of young women with incident HPV infection, Winer et al\textsuperscript{49} report a 36-month cumulative incidence of cervical squamous intraepithelial
lesions (SIL) of 47.2% (95% confidence interval, 38.9%–56.4%). They report a median time to clearance of 5.5 and 4.7 months, respectively, for cervical and vaginal SIL. Thus, lesions can be expected to develop in about half of individuals with high-risk HPV infections.

Cervical intraepithelial neoplasia (CIN) does not develop in the majority of young women who acquire genital HPV. Among those women with incident HPV type 16 or 18 infection in their study, Winer et al found a 36-month cumulative incidence of 20% for CIN grade 2 (CIN 2) compared with 6.7% for CIN grade 3 (CIN 3). Furthermore, most mild cases of CIN and moderate to severe cases of CIN in young women resolve without treatment. A minority of mild cases of CIN either persists without further progression or progresses to cancer over several years.

**Cervical Cancer Screening Methods and Guidelines**

The biggest risk factor for cervical dysplasia and cancer is the presence of persistent oncogenic HPV infection. However, reliably predicting who among the persistently infected will progress to severe neoplasia or worse is challenging. Research of biological markers such as a p16 assay is under way in an effort to identify women at highest risk for progression. Until such a means is available, all women with cervical dysplasia should be followed up and treated in a manner similar to that outlined in guidelines of the ASCCP for the management of abnormal cytology.

Testing for oncogenic or high-risk types of HPV with the Hybrid Capture 2 (Digene Corporation, Gaithersburg, Md), which will be referred to as the HC2 test throughout the rest of this article, is approved for use by the US Food and Drug Administration in women with atypical squamous cells of undetermined significance (ASCUS) Pap test results and for primary cervical cancer screening in conjunction with a Pap test in women older than 30 years. The HC2 test provides a positive or negative result for one or more of 13 oncogenic HPV types. It does not provide a type-specific result. Although this technology is gaining in interest and use, the HC2 test has not replaced cervical cytology, which remains a useful screening test for detecting cervical dysplasia and cancer.

Reflex HPV testing refers to the practice of doing an HPV DNA test on the sample collected at the time of the liquid-based Pap test if the result of the Pap test is reported as ASCUS. The HPV result is then used as a means of triaging women with ASCUS into two groups: the HPV-negative group who may be triaged back to routine cervical cancer screening as recommended for her age group, and the HPV-positive group who may have significant disease warranting further diagnostic investigation such as colposcopic examination and biopsy. If the screening Pap test delivers a result that is anything other than ASCUS, the specimen is discarded.

Women who undergo conventional Pap tests may also be offered a reflex HPV test, but this test would require collection of an additional sample using a swab or cervical brush at the time of the Pap test and then storage of the sample at the laboratory to be used for the purpose of HPV DNA testing only if the Pap result is reported as ASCUS. Studies designed to assess the clinical utility of reflex HPV testing as a means of triaging women with different Pap test results have been done using liquid-based cytology. It is unclear if reflex HPV testing used in any other setting would deliver similar results.

Reflex HPV testing of women with cytologic evidence of low-grade SIL is not clinically useful or cost-effective because 82.9% (range, 79.1%–86.1%) of these women will have test results positive for HPV. The ASCCP has made available to providers detailed flowcharts of triage algorithms for different clinical scenarios of abnormal cytology; these flowcharts are available at www.asccp.org. Reflex HPV testing for the triage of ASCUS Pap tests does not generally apply to women with diethylstilbestrol (DES) exposure and women with HIV infection.

Practicing HPV-testing laboratories across the United States follow the Bethesda descriptive system for cervical cytology, and this system was most recently revised in September 2001. In addition, the guidelines for appropriate cervical cancer screening practices in different age groups and populations were revised in 2002. Guidelines for screening and treatment of adolescents for HPV-related cervical disease are also available.

It is important to remember to counsel women about the HPV test and how it will be used to inform their physicians about the significance of their Pap test result should they have some mild atypia on the Pap test. These counseling messages should include information about HPV, how it is transmitted, how common the infection is among women and men, and how cancer related to the virus is usually easily detected among women participating in screening programs.

**Treatment and Counseling Considerations for Women With Cervical Dysplasia**

Women with CIN 2 or CIN 3 should undergo a diagnostic excisional procedure, usually in an office setting. If there is any evidence that the cervical dysplasia extends into the cervical canal, cryotherapy is generally not recommended. Although excisional procedures are relatively simple procedures for providers with proper training, patients often feel significant anxiety over a diagnosis of CIN and the procedure used to treat the condition.

The general public lacks basic knowledge about HPV, which may contribute to the anxiety women feel when they test positive for HPV or have abnormal cytology. In their study of women in the United Kingdom, Maissi et al assessed the state of anxiety, distress, and concern and quality of life 6 months after HPV testing in women with mildly abnormal Pap screening tests. They compared these women with a group with normal Pap test results and a group with abnormal Pap test results who did not undergo HPV testing. They found that at 6 months, levels of concern remained high in all women who had an abnormal Pap test result and were highest among the women not tested for HPV. Some predictors of concern across all women with an abnormal Pap test result were the fear of the development of cancer, being
HPV positive, or not knowing their HPV status (ie, not tested).63 Also in this study, the authors found that women who were either HPV positive or not tested for HPV perceived their risks of the development of cervical cancer as significantly higher than women with normal Pap test results and women who tested negative for HPV. Thus, appropriate counseling messages for women are needed, particularly as HPV testing becomes more widely marketed and available.

Genital Warts

Human papillomavirus types 6 and 11 cause most of the genital warts worldwide.12 Approximately 500,000 to 1,000,000 new cases of genital warts occur per year in the United States.65 According to one study, the direct medical costs associated with the treatment of individuals with genital warts to complete clearance ranged from $285 to $6665 for medical or surgical therapy.66 Because genital warts are often recurrent despite the method of treatment and because the diagnosis often generates significant distress for the patient, repeated office visits are common so that treatment and counseling may be provided.

Genital warts usually do not cause symptoms and seem to occur most often at sites of friction, such as the penile shaft, the scrotum, the vulva, the vagina, the cervix, the urethra, and the perineum. Visualization of genital warts is possible with the naked eye and a bright light and does not exclude the presence of oncogenic HPV types, because patients are often infected with more than one HPV type.

Genital warts may appear as the classic cauliflower-like condylomata acuminatum, or as smooth, domed, or flat papules; as keratotic warts with a thick, horny layer; or, atypically, with pigmentation, in which case a biopsy is warranted to rule out carcinoma. Biopsy is not recommended routinely and is generally reserved for patients with atypical lesions, lesions not responding to therapy, and lesions that are friable, pigmented, bleeding, and/or fixated to underlying structures.67,68

Patient-applied and provider-applied treatment modalities for genital warts are available, and providers should be comfortable treating patients with at least one treatment modality from each category.

A diagnosis of genital warts is frequently accompanied by anxiety.60,69,70 In a multicountry survey of 80 men and 86 women with genital warts, 47% of whom were currently undergoing treatment, the authors report that most patients said the treatment was associated with pain and embarrassment. In addition, 60% reported a recurrence of warts after initial treatment and clearance.67

Preventing HPV Infection With Prophylactic Vaccination

The HPV genome is divided into early and late genes. The early genes, E6 and E7, are the oncogenic gene products that bind p53 and retinoblastoma proteins and disrupt normal cell cycle processes, allowing the epithelium to inappropriately proliferate.71 This proliferation leads to dysplasia and cancer of the stratified squamous epithelium if the HPV infection persists.20 The late genes, L1 and L2, are the major and minor capsid proteins that are being targeted for development of virus-like–particle prophylactic vaccine.18

Prevention of HPV infection is difficult. Infections are often asymptomatic, so individuals may transmit the infection to multiple partners without ever becoming aware of the infection. Human papillomavirus is so widely prevalent and easily and efficiently transmitted by skin-to-skin contact that even individuals who have had few lifetime sexual partners are likely to become infected. Condoms offer only partial protection against HPV infection. Furthermore, even if an individual has had a previous infection with one type of HPV, little to no cross-protection exists for different HPV types. Therefore, such an individual is not immune to future infections with different HPV types.

Comment

New preventive strategies may soon be available in the form of prophylactic HPV vaccines. In 2002, the first controlled trial of an HPV type 16 vaccine was published and showed 100% efficacy in preventing persistent HPV type 16 infection among vaccine recipients compared with placebo recipients.72 Subsequent studies of a bivalent vaccine,73 which protects against the two most common oncogenic types of HPV, and a quadrivalent vaccine that protects against both the two most common oncogenic types of HPV and the two most common warts-causing types of HPV have also demonstrated high efficacy for these vaccines. In addition, phase 3 trials of the quadrivalent vaccine64–75 demonstrated 100% efficacy in preventing HPV type 16- and type 18–associated cervical cancer, adenocarcinoma in situ, and CIN. If these vaccines become widely available, they promise to dramatically reduce the burden of HPV-associated disease, as well as the cost and psychosocial burdens associated with HPV infection.

References


