

HPV Update

Overview

Genital Human Papillomavirus (HPV) is the most common sexually transmitted infection in the United States today. There are over 100 types of HPV; however, only about 30-40 of these types are sexually transmitted and cause genital HPV. The double-stranded DNA HPV virus can infect the skin and mucous membranes of the genital areas of men and women, including the skin of the penis, anus and rectum, vulva, vagina, and cervix. These infections can present as genital warts or subclinical infections that are found during routine pap smear screening.

Most sexually active people in the United States will have HPV at some time in their lives. The virus is often asymptomatic; the majority of people who become infected with HPV do not know they have it. There are about 6.2 million new HPV cases per year, or about 1/3 of all new STD infections. Approximately 20 million Americans are currently infected with HPV. About half of those who are infected with HPV are sexually active adolescents and young adults ages 15-24 years old. Discovering the true incidence of the disease is difficult, as many people do not realize that they have been exposed or have the disease. HPV is not a reportable disease; it can be transient, and therefore come and go before being discovered at the time of exam.

Persistent HPV infections are now known to be the major cause of cervical cancer. In 2007, an estimated 11,000 women in the United States were diagnosed with cervical cancer, and nearly 4,000 died from it. Cervical cancer occurs in nearly a half-million women every year worldwide, claiming a quarter of a million lives. Other HPV related cancers estimated for 2008 include approximately 3500 women with vulvar cancer, 2200 women with vaginal and other female genital cancers, 1250 men with penile and other male genital cancers, and 3000 women and 2000 men with anal cancer.

Transmission

Genital HPV is spread through skin-to-skin contact, not through an exchange of bodily fluid. Most HPV is transmitted during penetrative genital contact (vaginal or anal sex). The absence of penetration, with genital contact, such as oral-genital, manual-genital, or genital-genital, can lead to HPV infection, but much less commonly than with sexual intercourse. Although evidence is lacking that condoms offer complete protection from HPV infection, condom use may reduce the risk of HPV related disease, such as genital warts and cervical neoplasia. There is some evidence that condom use may help in the clearance of HPV or HPV associated lesions.

Sexual behavior is the most constant predictor of the acquisition of HPV infection. Factors strongly associated with HPV infection in women include that of a young age (less than 25 years), numbers of sex partners, early age at first sexual intercourse (16 years or younger), and a male partner who has or has had

multiple sexual partners. The number of sexual partners is proportionately linked to the risk of HPV infection. Having sex with a new partner may be the strongest risk factor for initial HPV infection than having sex with a steady partner.

HPV infections are also commonly seen in same-sex sexual partners. HPV DNA can be detected in swabs from the anal canal in over 50% of male-male sexual partners. HPV virus can be found on inanimate objects, such as clothing or other surfaces; however, transmission is not known to occur by this route.

HPV Types

The genital HPV viruses have been divided into two groups based on their odds of causing cancer. The groups are thus called the “low risk” types (non-oncogenic) and the “high risk” types (oncogenic or cancer-associated).

Common high-risk types are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 82. These are considered high risk because they are found in association with invasive cancers of the cervix, vulva, penis or anus, as well as other sites. HPV-16 is the most common high-risk type, found in nearly 50% of all cervical cancers. It is also one of the most common types found in women without cancer. The presence of HPV-16 does not mean that a cancer will develop, but it does mean that the likelihood is increased over other HPV viral types.

HPV-18 is also a common high-risk virus, found in both squamous and glandular lesions of the cervix. HPV 18 accounts for an estimated 10-12% of cervical cancers. HPV types 16 and 18 together cause about 70% of cervical cancers. The other high-risk viral types are associated with cervical cancer, but at a much lower frequency. HPV types 31,33,45,52,and 58 each account for approximately 2-4% of cervical cancers, with other high-risk types accounting for less than 1% of cervical cancers. High-risk types of HPV are associated with pre-invasive squamous lesions of the penis, penile cancer, and anal intraepithelial neoplasia and cancer. Penile cancer is very rare, especially in circumcised men, with an incidence of 0.8/100,000 men in 2002. Anal cancer risk is increased, however, in male-male sexual relationships, but currently no screening methods have been recommended.

While this information is concerning, it is important to remember that the majority of high-risk HPV infections go away on their own and do not cause cancer.

Common low-risk types of HPV virus are 6, 11, 40,42, 43, 44, 54, 61, 72, 73, and 81. These types can cause benign or low-grade cervical cell changes and genital warts (or condyloma accuminata), but rarely are found in association with invasive cancers. HPV-6 and HPV-11 are low-risk viral types found most commonly in association with genital warts.

Clinical Manifestations

Sometimes, certain low-risk types of HPV can cause overt genital warts in men and women. Only about 1% of sexually active adults have visible genital warts at

any point in time. Genital warts, or condyloma accuminata, appear as small flesh colored bumps or groups of bumps. They can be raised, flat, single or multiple, small or large, and sometimes cauliflower shaped. Warts appear on the vulva/perineum/anal areas (external genitalia), the cervix and vagina areas in the female, and also on the penis, scrotum and anal areas of a male. Most genital warts are due to the 'low-risk' types of HPV, 6 and 11. Warts can appear within several weeks after sexual contact with a person who is infected with HPV, or they may take months or years to appear, or they may never appear. Condyloma accuminata are diagnosed easily by visual inspection; but occasionally a biopsy is warranted to confirm a diagnosis. If left untreated, genital warts may resolve, remain unchanged, or grow in size and number. They are not generally painful, but are cosmetically bothersome and can interfere with vaginal deliveries.

Rarely, genital HPV infections can be transmitted from mother to baby during delivery. This perinatal transmission with low-risk HPV types can result in respiratory tract warts in children, a condition called respiratory papillomatosis (RRP). The incidence of this is extremely rare, approximately 0.4-1.1 cases/100,000 live births to women with a genital wart history. Cesarean section delivery is not recommended for women with condyloma, as it is unclear that Cesarean prevents RRP.

Women with persistent high-risk HPV infection are at greatest risk for developing high-grade cervical dysplasia and cervical cancer. While infection with high-risk HPV (most commonly types 16 and/or 18) is necessary for the development of cervical cancer, most infections do not result in cancer. There currently are no data on the natural history of HPV infection in men.

Factors influencing HPV persistence and progression appear to be related to the immune system, and also to screening. The single most important factor associated with an increased risk of invasive cervical cancer is that of never or rarely being screened for cervical cancer. Screening for cervical cancer involves a visual inspection of the cervix, and a pap smear. The NIH estimates that 50% of the women who receive cervical cancer diagnoses have never been screened for cervical cancer, and an additional 10% have not received screening in the previous five years. Immunosuppression from any cause increases the likelihood of HPV persistence and increases the risk of development of cervical cancer. Cigarette smoking has a very significant association with HPV persistence and elevated risk of cervical cancer. Other epidemiologic factors associated with an increased risk of cervical cancer include long-term use of oral contraceptives, other genital infections such as Chlamydia, parity and nutritional factors.

Most HPV infections, both low and high risk, are transient and subclinical. Approximately 70% of women with HPV infections become HPV-DNA negative within one year; 91% become HPV-DNA negative within two years. The median duration of infection is about 8 months. Only about 10% of women develop persistent HPV infection.

It is thought that the gradual development of an immune response is the mechanism for HPV-DNA clearance. It is possible, however, that the HPV virus becomes dormant, and undetectable, reactivating many years later. This may be part of the mechanism allowing some women to appear to be disease free, and then suddenly show up with HPV on a pap smear, despite a long-term monogamous relationship. Many couples go through tremendous anxiety, anger and finger pointing regarding the possibility of infidelity in these situations, when actually it is their immune system and the HPV virus being inconstant. Even with knowledgeable guidance and information from physicians and counselors, many couples wrestle with the diagnosis of HPV, and continue to wonder how they got it and who gave it to them. Reassurance that least 75% of sexually active men and women acquire genital HPV infection during their lifetime is not always helpful.

Diagnosis

Detection of HPV can be done via direct inspection for condyloma or genital warts, pap smear with HPV testing, or pure HPV high-risk virus detection via molecular testing. The only currently FDA approved test for HPV is Digene's Hybrid Capture II HPV Test. This test, which uses cytology specimens from exfoliated cervical cells collected with a specially designed brush, is designed to detect high-risk types of HPV. It can tell whether one or more types of HPV are present; it does not identify the individual HPV types. The main use of the Hybrid Capture test is to help identify women with high-risk HPV who are at risk for developing pre-cancerous (dysplastic) or cancerous changes in the 36 months following initial testing.

There currently is no FDA approved HPV DNA test for males, nor is HPV testing of males recommended. Infection does not indicate increased risk of disease for the man or his partner. While HPV is common in men, HPV-associated cancers are rare.

There are no routine methods for culturing HPV. Serology tests are available, but these tests are only used in research.

HPV DNA testing should NOT be used

For men

To check the HPV status of patients or their partners with genital warts or other sexually transmitted infections (STIs)

To check the HPV status of partners of women with cervical cancer

To check the HPV status of pregnant women

Treatment

There are several different types of treatments available for topical genital warts, including topical treatments such as podofilox, imiquimod, podophyllin, and trichloroacetic acid, or destructive treatments such as cryotherapy (freezing) laser, and surgical excision. There is no evidence that one therapy is more efficacious than another. In 90% of cases, the immune system will clear both high-risk and low-risk HPV infection naturally within two years.

Changes in the pap smear secondary to HPV can be treated according to ASCCP/Bethesda guidelines for abnormal pap smear management. These include procedures such as LEEP, cold knife conization of the cervix, and cryosurgery of the cervix. Treatment is dependant on the severity and extent of the lesion, and the childbearing status of the patient.

Prevention

The surest way to prevent HPV infection is to refrain from any genital contact with another individual. If sexually active, reducing the number of sexual partners may help reduce the risk of acquiring genital HPV.

While treatment of subclinical genital HPV infection is not recommended, there is some evidence to suggest that treatment of genital warts reduces the amount of HPV-DNA that can be found in the tissue. It is unknown however, whether treatment decreases the infectivity of partners.

To decrease the transmission likelihood, consistent use of a condom can reduce the risk of HPV transmission by 70%. However, HPV infection can occur in areas that are not covered by a condom (i.e., scrotum, vulva, or perianal areas), thus condom use is not an absolute guarantee of protection.

In June of 2006, the FDA licensed the first vaccine developed to prevent cervical cancer and other diseases in females caused by certain types of HPV. This quadrivalent vaccine, Gardasil, protects against the four HPV types (6,11, 16, and 18), which have been shown to cause 90% of the genital warts, and over 70% of cervical cancers. Also in June 2006, the Advisory Committee on Immunization Practices (ACIP) recommended the use of this vaccine in females ages 9-26 years old.

This prophylactic vaccine is made from non-infectious HPV-like particles (or virus-like particles, VLP). It does not contain thimerosal or mercury. The HPV vaccine has been tested in over 11,000 females around the world, demonstrating its safety. The most major side effect was that of mild injection site pain.

The vaccine is intended for 11-12 year old girls, but can be given to girls as young as 9 years of age up to the age of 26. Ideally, the vaccine should be administered before the onset of sexual activity; however, females who are sexually active who have not yet been infected with any or all of the four HPV types in the vaccine can potentially receive benefit from it. Females who have

already been infected with one or more HPV types will still get protection from the vaccine types they have not acquired. Unfortunately, there is no clinical test available to determine whether someone has had any or all of the four HPV types in the vaccine.

Clinical trials have demonstrated 100% efficacy in preventing cervical precancers caused by the specific HPV types in the vaccine. Nearly 100% efficacy was shown in preventing vulvar and vaginal precancers and genital warts caused by the targeted HPV types.

The vaccine is not a form of treatment for pre-existing HPV-related disease. If a female is already infected with one of the HPV types in the vaccine, the vaccine will not prevent disease from that type. The vaccine will not necessarily improve the pathology of a pre-existing lesion such as an abnormal pap smear, warts or condition caused by a previous HPV infection.

There are currently no data to support the vaccination of males. Efficacy studies in males are ongoing.

The Gardasil vaccine is administered through a series of three intra-muscular injections over a six-month period. The second and third doses should be given 2 and 6 months after the first dose, and can be given at the same time as other age-appropriate vaccines. Lactating women can receive the vaccine, but pregnant women should not. The vaccine has not been linked with any adverse fetal or pregnancy effects, but data on vaccination in pregnancy are limited.

The private-sector list price of the vaccine is \$119.75 per dose, or about \$360.00 for the complete series. The federal Vaccines for Children (VFC) Program will provide free vaccines to children and adolescents under the age of 19 years who are uninsured, Medicaid-eligible, American Indian, or Alaska Native. VFC vaccines are also available at over 45,000 sites in the US including hospital, private and public clinics, and through Federally Qualified Health Centers or Rural Health Centers. Some private insurance companies cover the vaccine. Another bivalent vaccine, protective against HPV types 16 and 18 was submitted to the FDA in 2007 and is awaiting approval.

While the HPV vaccine's potential for prevention of cervical and other HPV related cancer and disease is exciting, it does not protect against all types of HPV. It is important that vaccinated females continue to receive regular pap smears and cervical cancer screening, and that they practice safe sexual behavior if we are to continue to improve the tremendous burden of the cancers and diseases caused by HPV worldwide.

April 2008

Sources

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