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Human papillomavirus: what every provider should know

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Persistence of human papillomavirus (HPV) infection is necessary for the development of cervical cancer. Additionally, infection with HPV is implicated in the majority of cases of other genital tract malignancies including vulvar, penile, and vaginal cancer. HPV testing and vaccination are a routine part of obstetrical/gynecological clinical practice. With an enhanced public awareness of HPV infections, many patients turn to their obstetricians/gynecologists with questions about transmission, testing, and prevention. In this review, we will discuss the biology of HPV, epidemiology of disease, methods and indications for testing, and vaccination strategies.

Key words: cervical cancer screening, human papillomavirus, human papillomavirus biology, human papillomavirus testing, human papillomavirus vaccination

Prior to the 1970s, the prevailing theory on the cause for genital tract malignancies was infection with the herpes simplex virus. The scientific community initially doubted Dr Harald Zur Hausen,[1] a German physician and virologist, when he suggested that the same viral particles noted in genital warts might be the culprit for genital tract malignancies. Zur Hausen's work evolved and eventually in 1983, his laboratory isolated human papillomavirus (HPV) 16 and implicated its role in the development of cervical cancer.[2] One year later, his laboratory isolated HPV 18, thus discovering the two HPV types that today are known to cause approximately 70% of cervical carcinoma and many other invasive and preinvasive lesions of the vulva, vagina, penis, anus, and head and neck.[3-7]

Since the discoveries by Zur Hausen and his colleagues, our clinical and scientific knowledge of HPV has increased dramatically. In this review, we will discuss the biology of HPV, including transmission and viral life cycle as well as the epidemiology of disease, methods and indications for testing, and vaccination strategies.

The biology of HPV

Transmission

HPV infections are almost exclusively acquired from sexual exposure. Areas of microtrauma within the skin and mucosal surfaces are the proposed sites of infections. Early data confirm sexual transmission by noting that only sexually active women acquire HPV infections, and the rate of acquisition correlates with the number of sexual partners.[8] For reasons that are poorly understood, not all sexual partnerships result in HPV transmission. Concordance of HPV infection between sexual partners is variable and ranges from 40% to 60%.[9-12] Risk factors for concordance are still being elucidated. Length of sexual relationship, frequency of intercourse, condom use, and number of lifetime sexual partners may play a role.[9,12]

HPV has been detected in multiple anatomic sites including the penis, cervix, anus, and hands.[13,14] HPV has also been detected on areas of unprotected genital skin such as the vulva and scrotum, providing an explanation as to why condoms offer incomplete protection against HPV infection.[15] Although transmission has been documented to occur between many anatomic sites, the cervix is the most common site of transmission. In one study, transmission was almost 3 times as likely to occur from the cervix to penis than penis to cervix.[14]

Circumcision does play a role in reduction of HPV transmission, which has led some to suggest it as a method to reduce the disease burden in endemic communities in which vaccination and screening are not yet feasible or practical.[16]

Although the primary method of HPV transmission is through sexual exposure, transmission between mother and infant has also been documented. Transmission has been suggested via contact with vaginal and cervical mucosa during delivery, transplacental transmission, transmission via amniotic fluid, and horizontal transmission during infancy. The rate of vertical transmission to newborns varies dramatically between studies and may be a result of older, less reliable HPV tests. Newer studies suggest a vertical transmission rate of approximately 20-30%.[17-19] The majority of neonatal infections are cleared by the first year of life, with 1 study showing a 100% clearance rate.[18] More recent prospective data suggest that children of HPV-positive mothers are more likely to test HPV positive at the 6 week postpartum visit; however, a significant number of infants (~17%) born to HPV-negative mothers will also test HPV positive at some point in their first 2 years of life, suggesting other modes of horizontal infection play a crucial role.[19]

Life cycle

Upon entry into the cells at areas of microtrauma, HPV targets the actively proliferating basal cells of the epithelium. In normal squamous epithelium, the basal layer is the area of active cell division. After division, the daughter cells migrate away from the basal layer and no longer progress through the cell cycle. High-molecular-weight keratins are produced

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TABLE 1
HPV classification

High-risk	HPV types
Carcinogenic[a]	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
Probably carcinogenic[a]	68
Possibly carcinogenic[a]	26, 53, 66, 67, 70, 73, 82
Tested for in commercially available detection systems	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68
Low-risk	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, 89

HPV, human papillomavirus.

[a] Data adapted from Bouvard V, Baan R, Straif K, et al.[23]

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by these terminally differentiated keratinocytes until the nuclear envelope breaks down and the cells become empty keratin-filled sacs.

In HPV-infected cells, keratinocytes do not undergo terminal differentiation. Once inside the basal epithelial cell, the viral genome begins to replicate. These HPV infected cells migrate away from the basal layer and are characterized by active viral replication. In the uppermost epithelial layer, HPV deoxyribonucleic acid (DNA) is assembled into infectious virions. Typical HPV-associated cytopathic changes such as koilocytosis, multinucleation, and nuclear enlargement are due to the assembly of the viral particles in the upper epithelial layers. The epithelium is then shed and HPV particles are released, which can then infect a new host.

Not all HPV infections lead to dysplasia or invasive carcinoma. The oncogenic potential of the HPV type is mediated primarily by the behavior of the E6 and E7 proteins. These proteins are transcribed early in the viral life cycle, hence abbreviated E. Their activity is complex and multifaceted. E6 binds to and degrades tumor-suppressor protein p53 in the host cell, inhibiting the expression of genes involved in apoptosis and cell cycle arrest. Thus, less apoptosis and growth arrest occurs, leading to cellular proliferation.[20]

The E7 protein in high-risk HPV infection is involved with cell immortalization through the retinoblastoma (Rb) protein family. Rb proteins regulate the cell cycle by controlling the transition at the G1/S phase. When E7 binds Rb, the Rb-E7 complex is degraded and the cell proceeds unregulated through the S phase.[21]

The prevalence of HPV

Infection with HPV is the most common of all sexually transmitted diseases. More than 40 HPV types specifically infect the anogenital tract,[22] and these types can further be separated based on their oncogenic potential. Currently, 12 HPV types are designated by the International Agency for Research on Cancer as being carcinogenic, and 8 additional types are designated as probably or possibly carcinogenic (Table 1).[23] Commercially available HPV tests are able to identify 14 of these designated high-risk HPV types.

Although race, geographic region, and other modifiable risk factors all correlate with HPV prevalence, age is the strongest predictor of HPV prevalence. As part of the 2011 National Health and Nutrition Examination Survey (NHANES) in the United States, more than 4000 females collected cervicovaginal specimens for HPV testing. The overall prevalence of 37 different types of HPV was 42.5%, which represents approximately 40 million infections. Specifically, the prevalence of high-risk HPV types was 29%. The prevalence of HPV was lowest among females 14-19 years of age (32.9%) and highest among women 20-24 years of age (53.8%). HPV prevalence varied by race with non-Hispanic blacks having the highest prevalence (59.2%), followed by Mexican Americans (44.2%) and non-Hispanic whites (39.2%) (Figure).[24]

In some studies, there appears to be a second peak of HPV prevalence among postmenopausal women.[25] Women can acquire new HPV infections later in life and, similar to trends seen in young women, HPV infection in older women is strongly associated with the number of new sexual partners.[26] Additionally, this second peak can also be explained by a reduced immune response associated with postmenopausal immunosenescence.[27]

Because it is a sexually transmitted infection, it is important to understand the epidemiology of HPV infections in men. The largest US population-based study demonstrated the prevalence of all HPV types in men to be 61%. The prevalence of high-risk HPV infections was 23%. In contrast to trends seen in women, the prevalence of HPV infection was not affected by age.[28]

Risk factors for HPV infection

Even before the link between HPV infection and genital tract malignancies was established, it was well recognized that the components of a woman's sexual history put her at risk for cervical cancer. Now that the link between HPV and malignancy is well defined, sexual history has specifically been correlated with risk of acquiring HPV infection. The number of both recent and lifetime male sexual partners increases the rate of HPV infection, particularly high-risk HPV infection.[29] The most recent data from the NHANES show that number of lifetime partners is an independent risk factor for all races except non-Hispanic black women, in whom no independent correlation is seen.[24] Early onset of sexual activity is an independent risk factor in some but not all studies.[24,29]

Coinfection with other sexually transmitted diseases and vaginal infections is associated with increased susceptibility to HPV infection. Bacterial vaginosis, trichomoniasis, herpes simplex virus infection, and vulvar warts all increase the risk of HPV infection, although the correlation with development of cervical intraepithelial neoplasia (CIN) is not as strong.[30-32] Chlamydial infection has long been implicated in the development of invasive squamous cell cervical cancer.[33] More recent cohort studies have found that chlamydial infection pro-