

# Human papilloma virus

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The human papilloma virus (HPV) plays a vital role in the pathogenesis of cervical disease. Here follows a detailed discussion on the virus and its effects.

The recognition of condylomata dates back to Roman times. Today HPV represents the most common symptomatic viral sexually transmitted disease (STD) in the United States. HPV belongs to the family of papouaviruses and is composed of a nonenveloped icosahedral, doublestranded DNA virus. The papillomaviruses are highly host specific and are characterized by an ability to infect and transform epithelial cells, producing characteristic histologic features.

The annual incidence of HPV infections has risen dramatically over the past three decades. The exact incidence and prevalence are unknown, since this is not a reportable disease, but there are thought to be at least 500,000 cases per annum. The rise could be attributed in part to increased hormonal versus barrier method use, as well as the lack of specific antiviral therapy.

Up to 50% of sexually active young women and 60% to 80% of male partners are infected with HPV. HPV is ubiquitous, and the majority of the population may be exposed to it by adolescence or early adulthood when sexual activity begins. Unfortunately, there is less partner tracing done than for other STDs. HPV is a chronic contagious disease, which is marked by dormant stages with intermittent reactivation. The virus exhibits latency patterns within human tissue. Clinical disease represents only the tip of the iceberg! Subclinical disease is 10 times more common than the presence of overt lesions.

HPV has gained notoriety because of its role in causing cervical cancer. It is associated with an increased risk for dysplasia and neoplasia. Almost all women with cervical cancer are infected with HPV, but most women with HPV infections will not develop carcinoma. However, the knowledge that certain HPV types are causally linked to cervical cancer has been difficult to apply in the clinical setting. When the link between HPV and cervical cancer was first described, it appeared important to treat low-grade cervical lesions aggressively. Now it is clear that most of these lesions either remain stable or eventually regress.

More than 80 distinct HPV types have been identified. Types are differentiated based on DNA homology or sequence and are broadly categorized as to their ability to cause malignant changes. Patients are often infected with more than one subtype. Each of the HPV genotypes has a predilection for a number of mucosal sites and is associated with a particular set of clinicopathologic entities. HPV 1 and 2 subtypes are associated with plantar and digital warts. HPV 3 and 10 subtypes are often found in association with flat warts. The most frequent subtypes found in genital disease include 6, 11, 16, and 18. HPV 6 and 11 are linked to genital warts/condylomata acuminata, low-grade squamous intraepithelial lesion (LGSIL) and respiratory papillomatosis in neonates. High-risk types include 16, 18, 31, and 45 and are associated with high grade squamous intra-epithelial lesions (HGSIL) and cervical cancer. DNA from high-risk HPV subtypes is present in more than 85% of squamous cell carcinomas of the cervix. Testing kits are being developed for HPV typing and tissue demonstration via DNA hybridization techniques (polymerase chain reaction) to facilitate appropriate risk stratification.

Other factors almost certainly act with HPV to produce cervical cancer. These include tobacco abuse, early onset of sexual activity, birth control pill use, pregnancy, ethnicity (e.g., Hispanics), number of sexual partners, alcohol or drug abuse, steroid use, poor nutrition (decreased folic acid intake), and other non-HPV STDs. Immunosuppression apparently favors the persistence of precursor lesions and, if cancer develops, may accelerate its course.

The incubation period of HPV is about 3 months, although it can be much longer in certain cases. The classic lesion, the genital wart, can be located on the vulva, vagina, perineum, cervix, anus, or penis glans and in the periclitoral region. Other variations of lesions exist and may be papillomatous, macular, erosive, pigmented, and erythematous in appearance. Most lesions are painless and often inobtrusive. Meisel's earlier classification of colposcopic appearances of HPV infections in the lower genital tract divided condylomata into the following classes:

#### Exophytic/florid

Detected with the naked eye

Epithelium has thick white surface with fingerlike projections showing irregular surface contours

Regular capillary loops seen in each of these projections—the most reliable diagnostic feature!

#### Early/spiked

Not usually visualized with naked eye

Irregular surface containing tiny spikes of tissue, called asperities (projections)

These projections reflect light from the colposcope

No capillary loops seen in asperities, but punctation may be present

Irregular surface with sharp border between it and the surrounding normal tissue

May resemble cervical intraepithelial neoplasia (CIN).

#### Flat/inverted

Most HPV infections of lower genital tract are flat, acetowhite lesions

Impossible to distinguish from intraepithelial neoplasia

Mosaicism or punctation, usually of fine type, may be present

If coarse vascular patterns are found, highly suspect for intraepithelial neoplasia

Reid scoring system helpful in distinguishing HPV infection from CIN

A further histologic typing differentiates between papillary, spiked, flat, inverted, and atypical condylomata.

The diagnosis of HPV-associated exophytic lesions (condylomata) of the vulva, vagina, and cervix requires no great expertise and no special tests. However, confirmation that no intraepithelial neoplasia is present should be sought by biopsy. Some condylomata may be readily confused with true malignant lesions because of their associated vascular changes. Subclinical HPV lesions of the vagina and cervix are usually detected by cytology.

Transmission occurs mainly via sexual contact. The diagnosis is based on cervical changes on the Papanicolaou (Pap) smear, visual identification of condylomata on the genitalia, or the typical HPV appearance on colposcopy. Autoinoculation may potentially take place, but nonvenereal transmission is extremely rare. Vertical transmission from mother to infant is possible during parturition.

The LGSIL category includes cytoplasmic manifestations of HPV infection previously called koilocytosis, koilocytotic atypia, and condylomatous atypia, as well as mild dysplasia. Koilocytosis refers to the specific cytopathic effect seen with HPV, namely hyperchromatism, nuclear shrinkage, and perinuclear vacuolization. Koilocytosis is the most specific

histologic marker for HPV infections, except in HPV subtypes 16 and 18, where koilocytosis may be absent. Although many experts suggest colposcopic evaluation of LGSIL, some advocate watchful waiting and repeat Pap smears. The patient's history and risk factors, as well as her degree of compliance, should be taken into account when deciding on the appropriate mode of evaluation and follow-up.

The approach to HGSIL is generally less controversial. Colposcopy, biopsy, and endocervical curettage (ECC) are recommended. A possible loop electrical excision procedure (LEEP) cone biopsy may be considered in certain cases. A number of recent studies suggest that women with high-grade dysplasia of the cervix are also at risk for invasive cancer of the vagina, vulva, and anus, probably because of the contiguous spread of HPV.

The natural history of HPV is even more obscure in men than in women. Male partners of women with lesions caused by HPV may have very small penile lesions, and partners often—but not always—share HPV types. It is unclear whether HPV-infected males have a significantly elevated risk of penile cancer.

Treatment options are influenced by the size, extent, and site of the lesions, as well as the individual's underlying conditions. Spontaneous regression takes place in 20% to 30% of cases. Treatment modalities for condylomata include cryotherapy, application of podophyllin, trichloroacetic acid, or Aldara cream, electrocautery, surgical removal, or laser therapy. Warts often proliferate during pregnancy and may be treated with trichloroacetic acid, but not with podophyllin.

No treatment modality succeeds in eradicating the virus, and no form of treatment is consistently effective. The risk for future development of dysplasia and neoplasia should not be overlooked, and regular follow-up evaluations (e.g., Pap smears, colposcopies, and possibly biopsies) should be strongly encouraged. Condoms may offer some protection against transmission, but partners may need to be evaluated too.

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