HPV, Warts and All...

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Human papillomavirus (HPV) infection has been implicated in a number of disease processes in humans, ranging from common skin warts to cervical dysplasia. Common warts (*verruca vulgaris*) are found in approximately 10% of children and young adults. It is also estimated that as many as 50% to 75% of sexually active people acquire a genital HPV infection at some point in their lives. Most genital HPV infections are asymptomatic (leading to higher transmission rates), but still carry a heavy burden of illness as they can lead to genital warts (*Condyloma acuminatum*) or squamous cell carcinoma of the anogenital tract.

What is HPV?

HPVs are nonenveloped viruses with double-stranded circular DNA. There are at least 100 types of papillomaviruses that fall into either the mucosal or the cutaneous groups. While the mucosal group infects the body's mucous membranes, such as the anogenital tract, the oral cavity and the respiratory tract, the cutaneous group infects only the skin and individual types are associated with specific clinical manifestations. Table 1 demonstrates the different types of HPV infections and their specific clinical manifestations. Although the

Table 1

Characteristics of an HPV infection

Clinical characteristics		Virus types	Mode of transmission
Cervical cancer	High risk	HPV-16, -18, -45, -31	Sexual
	Intermediate risk	HPV-33, -35, -39, -51, -52, -56, -59, -68, -73	
	Low risk	HPV-6, -11, -26, -42, -43, -44, -53, -54, -55, -62, -66	
Cancer of the vulva, vagina, anal canal and penis		HPV-16 and others	Sexual
Anogenital warts (*Condyloma acuminatum*)		HPV-6, -11	Sexual
Juvenile-onset recurrent respiratory papillomatosis		HPV-6, -11	Vertical; transmission at birth
Adult-onset recurrent respiratory papillomatosis		HPV-6, -11	Unknown
Focal epithelial hyperplasia of the oral cavity		HPV-13, -32	Nonsexual contact
Cutaneous warts	Common warts	HPV-1, -2, -4, -26, -27, -29, -41, -57, -65, -77	Nonsexual contact
	Plantar warts	HPV-1, -2, -4, -63	
	Flat warts	HPV-1, -2, -3, -4, -7, -10, -28	

natural history of HPV infection has long been ill defined, recent research has focussed on genital HPV infection found in women. According to these results, it has been found that the natural history is often self-limited (mean infection of six to 12 months and only 9% of women showed infection 24 months after initial infection). The incubation period can range from two to three weeks and last up to 18 months. The mean incubation period is three months. Persistent infection with high-risk types of HPV along with host factors, is believed to be responsible for genital HPV infection leading to neoplasm.

About warts

Warts are the cutaneous manifestation of an HPV infection. Warts may exist in different forms depending on the HPV type responsible and the epithelium involved.

Common warts (*verruca vulgaris*) usually occur on the hands, as flesh-coloured to brown, exophytic, and hyperkeratotic papules.

Plantar warts (*verruca plantaris*) occur on the soles of the feet and can be quite painful. They can be differentiated from calluses by removing the surface layer to reveal thrombosed capillaries.

Flat or planar warts (*verruca plana*) are most common among children and can occur on the face, neck, chest and flexor surfaces of the forearms and legs.

Genital warts (*condyloma acuminatum*) can be single or multiple and appear as soft, moist, flesh-coloured swellings of the skin. They can vary in size, are raised or flat or have the appearance of cauliflower. They can also be found internally on the vulva, perineum, perianal skin, penis and scrotum or internally in the vagina, urethra, anus and mouth. Warts tend to be fairly distinctive, but can be mistaken for calluses in the case of non-genital warts or as other sexually transmitted diseases, such as condyloma latum (a manifestation of syphilis) or molloscum contagiosum.

About mucosal HPV

Mucosal HPV refers to the group of HPV types that infect the mucous membranes of the body including the anogenital tract, the oral cavity, the respiratory tract and the genitals. The vast majority of mucosal HPV types (approximately 40) infect the genital tract. However, some infect the oral cavity (HPV-13 and HPV-32) and some cause both gential warts and recurrent respiratory papiliomatosis (RRP) (HPV-6 and HPV-11).

What is the connection between HPV and anogenital cancer?

Until now, the vast majority of research in the connection between HPV and cancer has focussed on cervical cancer. Despite this, penile, vaginal, vulvar and anal cancers are also associated with an HPV infection. In men, penile cancer is exceedingly rare and its connnection with genital HPV is not well established. Anal neoplasms, however, are quite common among men with a history of anal intercourse (the prevalence, 35 in 100,000 in this group, is similar to that of cervical neoplasia prior to routine Pap smear screening). Screening by anal cytology may be beneficial in this group, although no official recommendations have been issued.

Table 2

Treatment options for an HPV infection manifestation

HPV infection	Preferred treatment options	Considerations
Common warts	Expectant	No cost, slow and uncertain results
	Salicylic acid	Inexpensive, slow results
	Cryotherapy	Easy, painful, scarring, expensive
Plantar warts	Expectant	No cost, slow and uncertain results
	Salicylic acid	Inexpensive, slow results
	Cryotherapy	Easy, painful, scarring, expensive
Flat warts	Expectant	No cost, slow and uncertain results
	Salicylic acid	Inexpensive, slow results
	Imiquod 5% cream	Easy at home use, erythema, pruritis, erosions, bacterial infections
Genital warts	Expectant	No cost, slow and uncertain results
	Imiquod 5% cream	Easy at home use, erythema, pruritis, erosions, bacterial infections
	Cryotherapy	Easy, painful, scarring, expensive
HPV-related premalignant or malignant conditions	Loop electrode excision of the transformation zone, laser vaporization, cryotherapy, cone biopsy of cervix, surgical excision of vulvar or vaginal lessions	Referral to a gynecologist is recommended

Genital HPV transmission is predominantly through sexual transmission. The risk of contracting warts from sexual contact with a partner with obvious genital warts is 60% to 85%. The asymptomatic carrier, however, is also infectious because the wide range of vulnerable epithelium. Prior infection appears to confer type-specific immunity.

Can a patient have more than one kind of HPV?

Simultaneous infection rates with multiple types are very high, with more than 80% of one group of HPV-positive patients testing positive for more than one type of HPV. Persistent infection with high-risk types of HPV confers a high risk of developing high-grade neoplasias and cancer. Furthermore, immunosuppression significantly increases the risk of persistent infection. For example, one study showed that the prevalence of HPV in women infected with HIV was double that of women with comparable risk factors, but were free of HIV.

About cutaneous HPV

Cutaneous HPV can be transmitted through direct contact with infected tissue or with contaminated objects. Furthermore, HPV appears to have some specificity with regard to site and

morphology of warts. Plantar warts most often yield HPV-1, common warts HPV-2 and flat-warts HPV-3 and HPV-10. Although several types of HPV DNA sequences have been extracted from non-melanoma skin cancers, the oncogenic role of HPV in these cancers remains unclear.

How is HPV diagnosed?

Cutaneous warts are typically fairly distinctive and can be diagnosed on history and routine physical examination. Similarly, genital warts are visible on routine exam. Colposcopy is invaluable in assessing vaginal and cervical lesions and can also be helpful in the diagnosis of oral HPV infection.

Pap smears prepared from cervical scrapings can also reveal cytologic evidence of an HPV infection. Pap smear results should comment on:

- The adequacy of the sample
- A general categorization statement
- A descriptive diagnosis regarding benign or reactive changes, low- or high-grade intraepithelial cell abnormalities, glandular cell abnormalities or the presence of malignant cells.

Polymerase chain reaction (PCR), hybridization in situ and hybridization assay are techniques that have been used to diagnose and type HPV infection in the laboratory. These can be used in combination with Pap smear screening to increase sensitivity, to help evaluate the significance of atypical smears of undetermined significance and to guide further evaluation or treatment.

What is the connection between HPV and cervical cancer?

Immunosuppression (as in the case of infection with HIV) increases the risk of persistent infection with HPV. Persistent (>12 months with the same HPV-type) infection with high-risk HPV types is considered a necessary factor for invasive cervical cancer. Although necessary, persistent infection does not appear to be a sufficient condition, co-factors (in order of importance) include: smoking, multiparity, long-term (> 5 years) use of oral contraceptives, co-infection with other sexually transmitted diseases and inflammation. Progression from dysplasia to invasive cancer averages 10 years, although high-risk types (HPV–16, -18, -31, -45) progress in as little as three to six years.

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It is estimated that as many as 50% to 75% of sexually active people acquire a genital HPV infection at some point in their lives.

FAQ

How are HPV infections treated?

No treatment of HPV infections is 100% successful at preventing relapses. In addition, nearly all treatments are expensive (with the exception of over-the-counter preparations of salicylic acid) and are often associated with side-effects (pain, scarring, bacterial infections, unknown teratogenicity and flu-like symptoms in some cases). Furthermore, many HPV infections resolve spontaneously (roughly 40% of cutaneous warts in children will resolve spontaneously after two years while up to 90% of anogenital HPV infections will resolve spontaneously over the same time frame). Table 2 outlines some treatment options for various types of HPV infection. With regards to cervical dysplasia, low-grade lesions have a 60% regression rate and a 15% progression rate to high-grade abnormality, and thus can be treated conservatively or with surgical excision. High-grade lesions should be treated aggressively with destruction or excision of the transformation zone of the cervix.

Can an HPV infection be prevented?

Although research continues towards the development of vaccines against the types of HPV implicated in cervical cancer, genital warts and RRP, none of these are currently available for widespread use. Currently, avoidance of contact with infectious lesions is the only effective preventive measure available. While this can include the use of barrier method contraceptives to reduce the risk of contracting genital warts and other HPV-related diseases of the genital tract, this method has limited effectiveness. Although not preventative of HPV infection, screening for cervical dysplasia by regular Pap smears remains an excellent method for reducing HPV-related morbidity. Comparative studies have shown up to a 10-fold decrease in cervical cancer mortality in populations undergoing regular screening. The guidelines for screening are:

1. Initiation of Pap smear screening at 18 years of age or at onset of sexual activity and continuing until menopause.
2. Annual screening for high-risk patients smoking, multiparity, early first intercourse, multiple and/or high-risk partners, immunosuppression.
3. Two to five year interval screening for low-risk patients with three consecutive negative annual Pap smears.
4. Patients with Pap smears showing atypical cells of undetermined significance should undergo HPV testing.
5. Patients with smears showing low-grade or high-grade quamous intraepithelial lesions, carcinoma in situ or positive HPV testing should be referred to a gynecologist for colposcopy.