Overview

HPV infection is a viral infection that commonly causes skin or mucous membrane growths (warts). There are more than 100 varieties of human papillomavirus (HPV). Some types of human papillomavirus (HPV) infection cause warts, and some can cause different types of cancer.

Most HPV infections don't lead to cancer. But some types of genital HPV can cause cancer of the lower part of the uterus that connects to the vagina (cervix). Other types of cancers, including cancers of the anus, penis, vagina, vulva and back of the throat (oropharyngeal), have been linked to HPV infection.

These infections are often transmitted sexually or through other skin-to-skin contact. Vaccines can help protect against the strains of HPV most likely to cause genital warts or cervical cancer.

Symptoms

In most cases, your body's immune system defeats an HPV infection before it creates warts. When warts do appear, they vary in appearance depending on which kind of HPV is involved:

- **Genital warts.** These appear as flat lesions, small cauliflower-like bumps or tiny stemlike protrusions. In women, genital warts appear mostly on the vulva but can also occur near the anus, on the cervix or in the vagina.

In men, genital warts appear on the penis and scrotum or around the anus. Genital warts rarely cause discomfort or pain, though they may itch or feel tender.

- **Common warts.** Common warts appear as rough, raised bumps and usually occur on the hands and fingers. In most cases, common warts are simply unsightly, but they can also be painful or susceptible to injury or bleeding.
- **Plantar warts.** Plantar warts are hard, grainy growths that usually appear on the heels or balls of your feet. These warts might cause discomfort.
- **Flat warts.** Flat warts are flat-topped, slightly raised lesions. They can appear anywhere, but children usually get them on the face and men tend to get them in the beard area. Women tend to get them on the legs.

- **Flat warts.** Flat warts are flat-topped, slightly raised lesions. They can appear anywhere, but children usually get them on the face and men tend to get them in the beard area. Women tend to get them on the legs.

Common warts

Common warts can grow on your hands or fingers. They're small, grainy bumps that are rough to the touch.

Plantar warts

Plantar warts are caused by the same type of virus that causes warts on your hands and fingers. But, because of their location, they can be painful.

Flat warts

Flat warts are smaller and smoother than other warts. They generally occur on the face or legs and are more common in children and teens than in adults.

Female genital warts

Genital warts are a common sexually transmitted infection. They can appear on the genitals, in the pubic area or in the anal canal. In women, genital warts can also grow inside the vagina.

Male genital warts

Genital warts are a common sexually transmitted infection. They can appear on the genitals, in the pubic area or in the anal canal.

Cervical cancer

Nearly all cervical cancers are caused by HPV infections, but cervical cancer may take 20 years or longer to develop after an HPV infection. The HPV infection and early cervical cancer typically don't cause noticeable symptoms. Getting vaccinated against HPV infection is your best protection from cervical cancer.

Because early cervical cancer doesn't cause symptoms, it's vital that women have regular screening tests to detect any precancerous changes in the cervix that might lead to cancer. Current guidelines recommend that women ages 21 to 29 have a Pap test every three years.

Women ages 30 to 65 are advised to continue having a Pap test every three years, or every five years if they also get the HPV DNA test at the same time. Women over 65 can stop testing if they've had three normal Pap tests in a row, or two HPV DNA and Pap tests with no abnormal results.

Human papillomavirus infection (**HPV infection**) is caused by a DNA virus from the *Papillomaviridae* family.[5] Many HPV infections cause no symptoms and 90% resolve spontaneously within two years.[1] In some cases, an HPV infection persists and results in either warts or precancerous lesions.[2] These lesions, depending on the site affected, increase the risk of cancer of the cervix, vulva, vagina, penis, anus, mouth, tonsils, or throat.[1][2][3] Nearly all cervical cancer is due to HPV, and two strains – **HPV16** and **HPV18** – account for 70% of all cases.[1][7] **HPV16** is responsible for almost 90% of HPV-positive oropharyngeal cancers.[3] Between 60% and 90% of the other cancers listed above are also linked to HPV.[7] **HPV6** and **HPV11** are common causes of genital warts and laryngeal papillomatosis.[1]

An HPV infection is caused by the *human papillomavirus*, a DNA virus from the papillomavirus family.[8][9] Over 200 types have been described.[10] An individual can become infected with more than

one type of HPV,[11] and the disease is only known to affect humans.[5][12] More than 40 types may be spread through sexual contact and infect the anus and genitals.[4] Risk factors for persistent infection by sexually transmitted types include early age of first sexual intercourse, multiple sexual partners, smoking, and poor immune function.[1] These types are typically spread by sustained direct skin-to-skin contact, with vaginal and anal sex being the most common methods.[4] HPV infection can also spread from a mother to baby during pregnancy.[11] There is no evidence that HPV can spread via common items like toilet seats,[13] but the types that cause warts may spread via surfaces such as floors.[14] HPV is not killed by common hand sanitizers and disinfectants, increasing the possibility of the virus being transferred via non-living infectious agents called fomites.[15]

HPV vaccines can prevent the most common types of infection.[4] To be most effective, inoculation should occur before the onset of sexual activity, and are therefore recommended between the ages of 9–13 years.[1] Cervical cancer screening, such as the Papanicolaou test ("pap smear"), or examination of the cervix after applying acetic acid, can detect both early cancer and abnormal cells that may develop into cancer.[1] Screening allows for early treatment which results in better outcomes.[1] Screening has reduced both the number of cases and the number of deaths from cervical cancer.[16] Genital warts can be removed by freezing.[5]

Nearly every sexually active individual is infected by HPV at some point in their lives.[4] HPV is the most common sexually transmitted infection (STI), globally.[5] High-risk HPVs cause about 5% of all cancers worldwide and about 37,300 cases of cancer in the United States each year.[10] Cervical cancer is among the most common cancers worldwide, causing an estimated 604,000 new cases and 342,000 deaths in 2020.[1] About 90% of these new cases and deaths of cervical cancer occurred in low- and middle-income countries.[1] Roughly 1% of sexually active adults have genital warts.[11] Cases of skin warts have been described since the time of ancient Greece, but it was not until 1907 that they were determined to be caused by a virus.[17]

HPV types

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HPV is a group of more than 200 related viruses, which are designated by a number for each virus type.[10] Some HPV types, such as HPV5, may establish infections that persist for the lifetime of the individual without ever manifesting any clinical symptoms. HPV types 1 and 2 can cause common warts in some infected individuals.[18] HPV types 6 and 11 can cause genital warts and laryngeal papillomatosis.[1]

Many HPV types are carcinogenic.[19] About twelve HPV types (including types 16, 18, 31, and 45) are called "high-risk" types because persistent infection has been linked to cancer of the oropharynx,[3] larynx,[3] vulva, vagina, cervix, penis, and anus.[10][20][21] These cancers all involve sexually transmitted infection of HPV to the stratified epithelial tissue.[1][2] HPV type 16 is the strain most likely to cause cancer and is present in about 47% of all cervical cancers,[22][23] and in many vaginal and vulvar cancers,[24] penile cancers, anal cancers, and cancers of the head and neck.

The table below lists common symptoms of HPV infection and the associated types of HPV.

Disease	HPV type
Common warts	2, 7, 22
Plantar warts	1, 2, 4, 63

Flat warts	3, 10, 28
Anogenital warts	6, 11, 42, 44 and others[25]
Anal dysplasia (lesions)	16, 18, 31, 53, 58[26]
Genital cancers	• Highest risk:[25] 16, 18, 31, 45 • Other high-risk:[10][25] 33, 35, 39, 51, 52, 56, 58, 59, 66, 68 • Probably high-risk:[27] 26, 53, 73, 82
Epidermodysplasia verruciformis	more than 15 types
Focal epithelial hyperplasia (mouth)	13, 32
Mouth papillomas	6, 7, 11, 16, 32
Oropharyngeal cancer	16[3]
Verrucous cyst	60
Laryngeal papillomatosis	6, 11

Available HPV vaccines protect against either two, four, or nine types of HPV.[28] There are six prophylactic HPV vaccines licensed for use: the bivalent vaccines *Cervarix*, *Cecolin*, and *Walrinvax*; the quadrivalent vaccines *Cervavax* and *Gardasil*; and the nonavalent vaccine *Gardasil 9*.[28] All HPV vaccines protect against at least HPV types 16 and 18, which cause the greatest risk of cervical cancer. The quadrivalent vaccines also protect against HPV types 6 and 11. The nonavalent vaccine Gardasil 9 provides protection against those four types (6, 11, 16, and 18), along with five other high-risk HPV types responsible for 20% of cervical cancers (types 31, 33, 45, 52, and 58).[28]

Signs and symptoms

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Warts

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PapillomaA sample DNA test report for HPV genotype from a laboratory

Skin infection ("cutaneous" infection) with HPV is very widespread.[29] Skin infections with HPV can cause noncancerous skin growths called warts (verrucae). Warts are caused by the rapid growth of cells on the outer layer of the skin.[30] While cases of warts have been described since the time of ancient Greece, their viral cause was not known until 1907.[17]

Skin warts are most common in childhood and typically appear and regress spontaneously over weeks to months. Recurring skin warts are common.[31] All HPVs are believed to be capable of establishing long-term "latent" infections in small numbers of stem cells present in the skin. Although these latent infections may never be fully eradicated, immunological control is thought to block the

appearance of symptoms such as warts. Immunological control is HPV type-specific, meaning an individual may become resistant to one HPV type while remaining susceptible to other types.[*citation needed*]

Types of warts include:

- Common warts are usually found on the hands and feet, but can also occur in other areas, such as the elbows or knees. Common warts have a characteristic cauliflower-like surface and are typically slightly raised above the surrounding skin. Cutaneous HPV types can cause genital warts but are not associated with the development of cancer.[*citation needed*]
- Plantar warts are found on the soles of the feet; they grow inward, generally causing pain when walking.
- Subungual or periungual warts form under the fingernail (subungual), around the fingernail, or on the cuticle (periungual). They are more difficult to treat than warts in other locations.[32]
- Flat warts are most commonly found on the arms, face, or forehead. Like common warts, flat warts occur most frequently in children and teens. In people with normal immune function, flat warts are not associated with the development of cancer.[33]

Common, flat, and plantar warts are much less likely to spread from person to person.

Genital warts

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HPV infection of the skin in the genital area is the most common sexually transmitted infection worldwide.[34] Such infections are associated with genital or anal warts (medically known as condylomata acuminata or venereal warts), and these warts are the most easily recognized sign of genital HPV infection.[*citation needed*]

The strains of HPV that can cause genital warts are usually different from those that cause warts on other parts of the body, such as the hands or feet, or even the inner thighs. A wide variety of HPV types can cause genital warts, but types 6 and 11 together account for about 90% of all cases.[35][36] However, in total more than 40 types of HPV are transmitted through sexual contact and can infect the skin of the anus and genitals.[4] Such infections may cause genital warts, although they may also remain asymptomatic.[*citation needed*]

The great majority of genital HPV infections never cause any overt symptoms and are cleared by the immune system in a matter of months. Moreover, people may transmit the virus to others even if they do not display overt symptoms of infection. Most people acquire genital HPV infections at some point in their lives, and about 10% of women are currently infected.[34] A large increase in the incidence of genital HPV infection occurs at the age when individuals begin to engage in sexual activity. As with cutaneous HPVs, immunity to genital HPV is believed to be specific to a specific strain of HPV.[*citation needed*]

Laryngeal papillomatosis

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In addition to genital warts, infection by HPV types 6 and 11 can cause a rare condition known as recurrent laryngeal papillomatosis, in which warts form on the larynx[37] or other areas of the

respiratory tract.[38][39] These warts can recur frequently, may interfere with breathing, and in extremely rare cases can progress to cancer. For these reasons, repeated surgery to remove the warts may be advisable.[38][40]

Cancer

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Case statistics

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Cervical cancer is among the most common cancers worldwide, causing an estimated 604,000 new cases and 342,000 deaths in 2020.[1] About 90% of these new cases and deaths of cervical cancer occurred in low- and middle-income countries, where screening tests and treatment of early cervical cell changes are not readily available.[1]

In the United States, about 37,300 cases of cancer due to HPV occur each year.[10]

The number of HPV-associated cancers in the period of 2008–2012 in the U.S.[41]

Cancer area	Average annual number of cases	HPV attributable (estimated)	HPV 16/18 attributable (estimated)
Cervix	11,771	10,700	7,800
Oropharynx (men)	12,638	9,100	8,000
Oropharynx (women)	3,100	2,000	1,600
Vulva	3,554	2,400	1,700
Anus (women)	3,260	3,000	2,600
Anus (men)	1,750	1,600	1,400
Penis	1,168	700	600
Vagina	802	600	400
Rectum (women)	513	500	400
Rectum (men)	237	200	200
Total	38,793	30,700	24,600

Cancer development

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Genome organization of human papillomavirus type 16, one of the subtypes known to cause cervical cancer (E1-E7 early genes, L1-L2 late genes: capsid)

In some infected individuals, their immune systems may fail to control HPV. Lingering infection with high-risk HPV types, such as types 16, 18, 31, and 45, can favor the development of cancer.[42] Co-factors such as cigarette smoke can also enhance the risk of HPV-related cancers.[43][44]

HPV is believed to cause cancer by integrating its genome into nuclear DNA. Some of the early genes expressed by HPV, such as E6 and E7, act as oncogenes that promote tumor growth and malignant transformation.[17] HPV genome integration can also cause carcinogenesis by promoting genomic instability associated with alterations in DNA copy number.[45]

E6 produces a protein (also called E6) that simultaneously binds to two host cell proteins called p53 and E6-Associated Protein (E6-AP). E6AP is an E3 Ubiquitin ligase, an enzyme whose purpose is to tag proteins with a post-translational modification called Ubiquitin. By binding both proteins, E6 induces E6AP to attach a chain of ubiquitin molecules to p53, thereby flagging p53 for proteosomal degradation.[46][47] Normally, p53 acts to prevent cell growth and promotes cell death in the presence of DNA damage. p53 also upregulates the p21 protein, which blocks the formation of the cyclin D/Cdk4 complex, thereby preventing the phosphorylation of retinoblastoma protein (RB), and in turn, halting cell cycle progression by preventing the activation of E2F. In short, p53 is a tumor-suppressor protein that arrests the cell cycle and prevents cell growth and survival when DNA damage occurs.[48] Thus, the degradation of p53, induced by E6, promotes unregulated cell division, cell growth and cell survival, all characteristics of cancer.[49]

It is important to note, that while the interaction between E6, E6AP, and p53 was the first to be characterized, there are multiple other proteins in the host cell which interact with E6 and assist in the induction of cancer.[50]

Squamous cell carcinoma of the skin

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Studies have also shown a link between a wide range of HPV types and squamous cell carcinoma of the skin. In such cases, *in vitro* studies suggest that the E6 protein of the HPV virus may inhibit apoptosis induced by ultraviolet light.[51]

Cervical cancer

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Artist's impression of cervical cancer caused by HPV.

Nearly all cases of cervical cancer are associated with HPV infection, with two types, HPV16 and HPV18, present in 70% of cases.[1][7][22][52][53][54] In 2012, twelve HPV types were considered carcinogenic for cervical cancer by the International Agency for Research on Cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[55] One study found that 74% of squamous cell carcinomas and 78% of adenocarcinomas tested positive for HPV types 16 or 18.[56] Persistent HPV infection increases the risk for developing cervical carcinoma. Individuals who have an increased incidence of these types of infection are women with HIV/AIDS, who are at a 22-fold increased risk of cervical cancer.[57][58]

The carcinogenic HPV types in cervical cancer belong to the alphapapillomavirus genus and can be grouped further into HPV clades.[59] The two major carcinogenic HPV clades, alphapapillomavirus-9 (A9) and alphapapillomavirus-7 (A7), contain HPV16 and HPV18, respectively.[60] These two HPV clades were shown to have different effects on tumour molecular characteristics and patient prognosis, with clade A7 being associated with more aggressive pathways and an inferior prognosis.[61]

In 2020, about 604,000 new cases and 342,000 deaths from cervical cancer occurred worldwide. Around 90% of these occurred in the developing world.[1]

Most HPV infections of the cervix are cleared rapidly by the immune system and do not progress to cervical cancer (see below the Clearance subsection in Virology). Because the process of transforming normal cervical cells into cancerous ones is slow, cancer occurs in people having been infected with HPV for a long time, usually over a decade or more (persistent infection).[38][62] Furthermore, both the HPV infection and cervical cancer drive metabolic modifications that may be correlated with the aberrant regulation of enzymes related to metabolic pathways.[63]

Non-European (NE) HPV16 variants are significantly more carcinogenic than European (E) HPV16 variants.[64]

Anal cancer

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The risk for anal cancer is 17 to 31 times higher among HIV-positive individuals who were coinfected with high-risk HPV, and 80 times higher for particularly HIV-positive men who have sex with men.[65]

Anal Pap smear screening for anal cancer might benefit some subpopulations of men or women engaging in anal sex.[66] No consensus exists, though, that such screening is beneficial, or who should get an anal Pap smear.[67][68]

Penile cancer

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HPV is associated with approximately 50% of penile cancers. In the United States, penile cancer accounts for about 0.5% of all cancer cases in men. HPV16 is the most commonly associated type detected. The risk of penile cancer increases 2- to 3-fold for individuals who are infected with HIV as well as HPV.[65]

Head and neck cancers

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See also: HPV-mediated oropharyngeal cancer

Oral infection with high-risk carcinogenic HPV types (most commonly HPV 16)[41] is associated with an increasing number of head and neck cancers.[69][53][70][71] This association is independent of tobacco and alcohol use.[71][72][73]

The local percentage varies widely, from 70% in the United States[74] to 4% in Brazil.[75] Engaging in anal or oral sex with an HPV-infected partner may increase the risk of developing these types of cancers.[70]

In the United States, the number of newly diagnosed, HPV-associated head and neck cancers has surpassed that of cervical cancer cases.[69] The rate of such cancers has increased from an estimated 0.8 cases per 100,000 people in 1988[76] to 4.5 per 100,000 in 2012,[41] and, as of 2021, the rate has continued to increase.[77] Researchers explain these recent data by an increase in oral sex. This type of cancer is more common in men than in women.[78]

The mutational profile of HPV-positive and HPV-negative head and neck cancer has been reported, further demonstrating that they are fundamentally distinct diseases.[79]

Lung cancer

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Some evidence links HPV to benign and malignant tumors of the upper respiratory tract. The International Agency for Research on Cancer has found that people with lung cancer were significantly more likely to have several high-risk forms of HPV antibodies compared to those who did not have lung cancer.[80] Researchers looking for HPV among 1,633 lung cancer patients and 2,729 people without the lung disease found that people with lung cancer had more types of HPV than noncancer patients did, and among lung cancer patients, the chances of having eight types of serious HPV were significantly increased.[81] In addition, expression of HPV structural proteins by immunohistochemistry and *in vitro* studies suggest HPV presence in bronchial cancer and its precursor lesions.[82] Another study detected HPV in the exhaled breath condensate (EBC), bronchial brushing and neoplastic lung tissue of cases, and found a presence of an HPV infection in 16.4% of the subjects affected by nonsmall cell lung cancer, but in none of the controls.[83] The reported average frequencies of HPV in lung cancers were 17% and 15% in Europe and the Americas, respectively, and the mean number of HPV in Asian lung cancer samples was 35.7%, with considerable heterogeneity between certain countries and regions.[84]

Skin cancer

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In very rare cases, HPV may cause epidermodysplasia verruciformis (EV) in individuals with a weakened immune system. The virus, unchecked by the immune system, causes the overproduction of keratin by skin cells, resulting in lesions resembling warts or cutaneous horns which can ultimately transform into skin cancer, but the development is not well understood.[85][86] The specific types of HPV that are associated with EV are HPV5, HPV8, and HPV14.[86]

Cause

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Transmission

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Sexually transmitted HPV is divided into two categories: low-risk and high-risk. Low-risk HPVs cause warts on or around the genitals. Type 6 and 11 cause 90% of all genital warts and recurrent respiratory papillomatosis that causes benign tumors in the air passages. High-risk HPVs cause cancer and consist of about twelve identified types.[10] Types 16 and 18 are responsible for causing most of HPV-caused cancers. These high-risk HPVs cause 5% of the cancers in the world. In the United States, high-risk HPVs cause 3% of all cancer cases in women and 2% in men.[87]

Risk factors for persistent genital HPV infections, which increase the risk of developing cancer, include early age of first sexual intercourse, multiple partners, smoking, and immunosuppression.[1] Genital HPV is spread by sustained direct skin-to-skin contact, with vaginal, anal, and oral sex being the most common methods.[4][20] Occasionally, it can spread from manual sex or from a mother to her baby during pregnancy.[88][89] HPV is difficult to remove via standard

hospital disinfection techniques and may be transmitted in a healthcare setting on re-usable gynecological equipment, such as vaginal ultrasound transducers. The period of communicability is still unknown, but probably at least as long as visible HPV lesions persist. HPV may still be transmitted even after lesions are treated and no longer visible or present.[90]

Perinatal

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Although genital HPV types can be transmitted from mother to child during birth, the appearance of genital HPV-related diseases in newborns is rare. However, the lack of appearance does not rule out asymptomatic latent infection, as the virus has proven to be capable of hiding for decades. Perinatal transmission of HPV types 6 and 11 can result in the development of juvenile-onset recurrent respiratory papillomatosis (JORRP). JORRP is very rare, with rates of about 2 cases per 100,000 children in the United States.[38] Although JORRP rates are substantially higher if a woman presents with genital warts at the time of giving birth, the risk of JORRP in such cases is still less than 1%.[*citation needed*]

Genital infections

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Genital HPV infections are transmitted primarily by contact with the genitals, anus, or mouth of an infected sexual partner.[91]

Of the 120 known human papillomaviruses, 51 species and three subtypes infect the genital mucosa.[92] Fifteen are classified as high-risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), three as probable high-risk (26, 53, and 66), and twelve as low-risk (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89).[19]

Condoms do not completely protect from the virus because the areas around the genitals including the inner thigh area are not covered, thus exposing these areas to the infected person's skin.[93]

Hands

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Studies have shown HPV transmission between the hands and genitals of the same person and sexual partners. Hernandez tested the genitals and dominant hand of each person in 25 heterosexual couples every other month for an average of seven months. She found two couples where the man's genitals infected the woman's hand with high-risk HPV, two where her hand infected his genitals, one where her genitals infected his hand, two each where he infected his own hand, and she infected her own hand.[94] Hands were not the main source of transmission in these 25 couples, but they were significant.[*citation needed*]

Partridge reports men's fingertips became positive for high-risk HPV at more than half the rate (26% per two years) as their genitals (48%).[95] Winer reports 14% of fingertip samples from sexually active women were positive.[96]

Non-sexual hand contact seems to have little or no role in HPV transmission. Winer found all fourteen fingertip samples from virgin women negative at the start of her fingertip study.[96] In a separate report on genital HPV infection, 1% of virgin women (1 of 76) with no sexual contact tested positive for HPV, while 10% of virgin women reporting non-penetrative sexual contact were positive (7 of 72).[97]

Shared objects

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Sharing of possibly contaminated objects, for example, razors,[90] may transmit HPV.[98][99][100] Although possible, transmission by routes other than sexual intercourse is less common for female genital HPV infection.[91] Fingers-genital contact is a possible way of transmission but unlikely to be a significant source.[96][101]

Blood

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Though it has traditionally been assumed that HPV is not transmissible via blood – as it is thought to only infect cutaneous and mucosal tissues – recent studies have called this notion into question. Historically, HPV DNA has been detected in the blood of cervical cancer patients.[102] In 2005, a group reported that, in frozen blood samples of 57 sexually naive pediatric patients who had vertical or transfusion-acquired HIV infection, 8 (14.0%) of these samples also tested positive for HPV-16.[103] This seems to indicate that it may be possible for HPV to be transmitted via blood transfusion. However, as non-sexual transmission of HPV by other means is not uncommon, this could not be definitively proven. In 2009, a group tested Australian Red Cross blood samples from 180 healthy male donors for HPV, and subsequently found DNA of one or more strains of the virus in 15 (8.3%) of the samples.[104] However, it is important to note that detecting the presence of HPV DNA in blood is not the same as detecting the virus itself in blood, and whether or not the virus itself can or does reside in blood in infected individuals is still unknown. As such, it remains to be determined whether HPV can or cannot be transmitted via blood.[102] This is of concern, as blood donations are not currently screened for HPV, and at least some organizations such as the American Red Cross and other Red Cross societies do not presently appear to disallow HPV-positive individuals from donating blood.[105]

Surgery

[edit]

Hospital transmission of HPV, especially to surgical staff, has been documented. Surgeons, including urologists and/or anyone in the room, are subject to HPV infection by inhalation of noxious viral particles during electrocautery or laser ablation of a condyloma (wart).[106] There has been a case report of a laser surgeon who developed extensive laryngeal papillomatosis after providing laser ablation to patients with anogenital condylomata.[106]

Virology

[edit]

Cryo-electron microscopy structure of the HPV type 16 viral capsid protein. Rendered from PDB: 5KEQ[107]

HPV infection is limited to the basal cells of stratified epithelium, the only tissue in which they replicate.[108] The virus cannot bind to live tissue; instead, it infects epithelial tissues through micro-abrasions or other epithelial trauma that exposes segments of the basement membrane.[108] The infectious process is slow, taking 12–24 hours for initiation of transcription. It is believed that involved antibodies play a major neutralizing role while the virions still reside on the basement membrane and cell surfaces.[108]

HPV lesions are thought to arise from the proliferation of infected basal keratinocytes. Infection typically occurs when basal cells in the host are exposed to the infectious virus through a disturbed epithelial barrier as would occur during sexual intercourse or after minor skin abrasions. HPV infections have not been shown to be cytolytic; rather, viral particles are released as a result of degeneration of desquamating cells. HPV can survive for many months and at low temperatures without a host; therefore, an individual with plantar warts can spread the virus by walking barefoot.[36]

HPV is a small double-stranded circular DNA virus with a genome of approximately 8000 base pairs.[20][109] The HPV life cycle strictly follows the differentiation program of the host keratinocyte. It is thought that the HPV virion infects epithelial tissues through micro-abrasions, whereby the virion associates with putative receptors such as alpha integrins, laminins, and annexin A2[110] leading to the entry of the virions into basal epithelial cells through clathrin-mediated endocytosis and/or caveolin-mediated endocytosis depending on the type of HPV.[111] At this point, the viral genome is transported to the nucleus by unknown mechanisms and establishes itself at a copy number of 10-200 viral genomes per cell. A sophisticated transcriptional cascade then occurs as the host keratinocyte begins to divide and become increasingly differentiated in the upper layers of the epithelium.[*citation needed*]

Evolution

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The phylogeny of the various strains of HPV generally reflects the migration patterns of *Homo sapiens* and suggests that HPV may have diversified along with the human population. Studies suggest that HPV evolved along five major branches that reflect the ethnicity of human hosts, and diversified along with the human population.[112]

Researchers initially identified two major variants of HPV16, European (HPV16-E), and Non-European (HPV16-NE).[113] More recent analyses based on thousands of HPV16 genomes show that indeed two major clades exist, that are further subdivided into four lineages (designated A-D) and even further subdivided into 16 sublineages (A1–4, B1–4, C1–4 and D1–4).[114][115] The A1-A3 sublineages constitute the European variant, A4 the Asian variant, B1-B4 the African type I variant, C1–C4 the African type II variant, D1 the North American variant, D2 the Asian American type I variant, D3 the Asian American type II variant.[114] The various lineages and sublineages have different oncogenic capacity, where overall, the non-European lineages are considered to increase the risk for cancer.[116] Although HPV16 is a DNA virus, there are signs of recombination among the different lineages.[115][117] Based on an analysis of more than 3600 genomes, between 0.3 and 1.2% of them could be recombinant.[115] Thus, ideally, genotyping (for cancer-risk assessment) of HPV16 should not be based only on certain genes, but on all genes from the entire genome.[115]

A bioinformatics tool named HPV16-Genotyper performs i) HPV16 lineage genotyping, ii) detects potential recombination events, iii) identifies, within the submitted sequences, mutations/SNPs that have been reported (in literature) to increase the risk for cancer.[115]

E6/E7 proteins

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Structure of the HPV type 16 oncoprotein E6 (purple), as obtained by X-ray crystallography, shown bound to the LxxLL peptide motif of the human protein UBE3A (cyan). Rendered from PDB: 4GIZ.[118]

The two primary oncoproteins of high-risk HPV types are E6 and E7. The "E" designation indicates that these two proteins are early proteins (expressed early in the HPV life cycle), while the "L" designation indicates that they are late proteins (late expression).[53] The HPV genome is composed of six early (E1, E2, E4, E5, E6, and E7) open reading frames (ORF), two late (L1 and L2) ORFs, and a non-coding long control region (LCR).[119] After the host cell is infected viral early promoter is activated and a polycistronic primary RNA containing all six early ORFs is transcribed. This polycistronic RNA then undergoes active RNA splicing to generate multiple isoforms of mRNAs.[120] One of the spliced isoform RNAs, E6*I, serves as an E7 mRNA to translate E7 protein.[121] However, viral early transcription subjects to viral E2 regulation and high E2 levels repress the transcription. HPV genomes integrate into the host genome by disruption of E2 ORF, preventing E2 repression on E6 and E7. Thus, viral genome integration into the host DNA genome increases E6 and E7 expression to promote cellular proliferation and the chance of malignancy. The degree to which E6 and E7 are expressed is correlated with the type of cervical lesion that can ultimately develop.[109]

Role in cancer

Sometimes papillomavirus genomes are found integrated into the host genome, and this is especially noticeable with oncogenic HPVs.[122] The E6/E7 proteins inactivate two tumor suppressor proteins, p53 (inactivated by E6) and pRb (inactivated by E7).[123] The viral oncogenes E6 and E7[124] are thought to modify the cell cycle so as to retain the differentiating host keratinocyte in a state that is favourable to the amplification of viral genome replication and consequent late gene expression. E6 in association with host E6-associated protein, which has ubiquitin ligase activity, acts to ubiquitinate p53, leading to its proteosomal degradation. E7 (in oncogenic HPVs) acts as the primary transforming protein. E7 competes for retinoblastoma protein (pRb) binding, freeing the transcription factor E2F to transactivate its targets, thus pushing the cell cycle forward. All HPV can induce transient proliferation, but only strains 16 and 18 can immortalize cell lines *in vitro*. It has also been shown that HPV 16 and 18 cannot immortalize primary rat cells alone; there needs to be activation of the ras oncogene. In the upper layers of the host epithelium, the late genes L1 and L2 are transcribed/translated and serve as structural proteins that encapsidate the amplified viral genomes. Once the genome is encapsidated, the capsid appears to undergo a redox-dependent assembly/maturation event, which is tied to a natural redox gradient that spans both suprabasal and cornified epithelial tissue layers. This assembly/maturation event stabilizes virions and increases their specific infectivity.[125] Virions can then be sloughed off in the dead squames of the host epithelium and the viral lifecycle continues.[126] A 2010 study has found that E6 and E7 are involved in beta-catenin nuclear accumulation and activation of Wnt signaling in HPV-induced cancers.[127]

Latency period

[edit]

Once an HPV virion invades a cell, an active infection occurs, and the virus can be transmitted. Several months to years may elapse before squamous intraepithelial lesions (SIL) develop and can be clinically detected. The time from active infection to clinically detectable disease may make it difficult for epidemiologists to establish which partner was the source of infection.[106]

Clearance

[edit]

Most HPV infections are cleared up by most people without medical action or consequences. The table provides data for high-risk types (i.e. the types found in cancers).[*citation needed*]

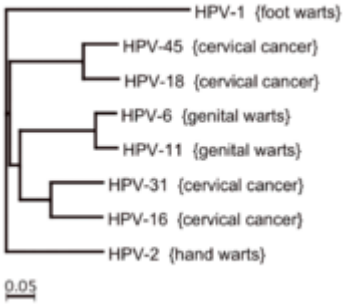
Clearance rates of high-risk types of HPV[128]

Months after initial positive test	**8 months**	**12 months**	**18 months**
% of men tested negative	70%	80%	100%

Clearing an infection does not always create immunity if there is a new or continuing source of infection. Hernandez' 2005-6 study of 25 couples reports "A number of instances indicated apparent reinfection [from partner] after viral clearance."[94]

Diagnosis

[edit]



Notable HPV[129] types and associated diseases

Over 200 types of HPV have been identified, and they are designated by numbers.[10][8][123] They may be divided into "low-risk" and "high-risk" types. Low-risk types cause warts and high-risk types can cause lesions or cancer.[130][131]

Cervical testing

[edit]

Main article: Cervical screening

Guidelines from the American Cancer Society recommend different screening strategies for cervical cancer based on a woman's age, screening history, risk factors, and choice of tests.[132] Because of the link between HPV and cervical cancer, the ACS currently recommends early detection of cervical cancer in average-risk asymptomatic adults primarily with cervical cytology by Pap smear, regardless of HPV vaccination status. Women aged 30–65 should preferably be tested every 5 years with both the HPV test and the Pap test. In other age groups, a Pap test alone can suffice unless they have been diagnosed with atypical squamous cells of undetermined significance (ASC-US).[133] Co-testing with a Pap test and HPV test is recommended because it decreases the rate of false-negatives. According to the National Cancer Institute, "The most common test detects DNA from several high-risk HPV types, but it cannot identify the types that are present. Another test is specific for DNA from HPV types 16 and 18, the two types that cause most HPV-associated cancers. A third test can detect DNA from several high-risk HPV types and can indicate whether HPV-16 or HPV-18 is present. A fourth test detects RNA from the most common high-risk HPV types. These tests can detect HPV infections before cell abnormalities are evident.[*citation needed*]

"Theoretically, the HPV DNA and RNA tests could be used to identify HPV infections in cells taken from any part of the body. However, the tests are approved by the FDA for only two indications: for follow-up testing of women who seem to have abnormal Pap test results and for cervical cancer screening in combination with a Pap test among women over age 30."[134]

Mouth testing

[edit]

Guidelines for oropharyngeal cancer screening by the Preventive Services Task Force and American Dental Association in the U.S. suggest conventional visual examination, but because some parts of the oropharynx are hard to see, this cancer is often only detected in later stages.[65]

The diagnosis of oropharyngeal cancer occurs by biopsy of exfoliated cells or tissues. The National Comprehensive Cancer Network and College of American Pathologists recommend testing for HPV in oropharyngeal cancer.[65] However, while testing is recommended, there is no specific type of test used to detect HPV from oral tumors that is currently recommended by the FDA in the United States. Because HPV type 16 is the most common type found in oropharyngeal cancer, p16 immunohistochemistry is one test option used to determine if HPV is present,[135] which can help determine course of treatment since tumors that are negative for p16 have better outcomes. Another option that has emerged as a reliable option is HPV DNA in situ hybridization (ISH) which allows for visualization of the HPV.[65]

Testing men

[edit]

There is not a wide range of tests available even though HPV is common; most studies of HPV used tools and custom analysis not available to the general public.[136][*needs update*] Clinicians often depend on the vaccine among young people and high clearance rates (see Clearance subsection in Virology) to create a low risk of disease and mortality, and treat the cancers when they appear. Others believe that reducing HPV infection in more men and women, even when it has no symptoms, is important (herd immunity) to prevent more cancers rather than just treating them.[137][138][*needs update*] Where tests are used, negative test results show safety from transmission, and positive test results show where shielding (condoms, gloves) is needed to prevent transmission until the infection clears.[139]

Studies have tested for and found HPV in men, including high-risk types (i.e. the types found in cancers), on fingers, mouth, saliva, anus, urethra, urine, semen, blood, scrotum and penis.[136]

The aforementioned Qiagen/Digene kit was successfully used off-label to test the penis, scrotum, and anus[140] of men in long-term relationships with women who were positive for high-risk HPV. Of these men, 60% were found to carry the virus, primarily on the penis.[140][*needs update*] Similar studies have been conducted on women using cytobrushes - an endocervical brush for sampling the cervix in females - and custom analysis.[141][142][*needs update*]

In one study researchers sampled subjects' urethra, scrotum, and penis.[141][142][*needs update*] Samples taken from the urethra added less than 1% to the HPV rate. Studies like this led Giuliano to recommend sampling the glans, shaft, and crease between them, along with the scrotum, since sampling the urethra or anus added very little to the diagnosis.[95] Dunne recommends the glans, shaft, their crease, and the foreskin.[136]

In one study the subjects were asked not to wash their genitals for 12 hours before sampling, including the urethra as well as the scrotum and the penis.[141] Other studies are silent on washing – a particular gap in studies of the hands.[*citation needed*]

One small study used wet cytobrushes, rather than wet the skin.[142] It found a higher proportion of men to be HPV-positive when the skin was rubbed with a 600 grit emery paper before being swabbed with the brush, rather than swabbed with no preparation. It's unclear whether the emery paper collected the virions or simply loosened them for the swab to collect.[*citation needed*]

Studies have found self-collection (with emery paper and Dacron swabs) as effective as collection done by a clinician, and sometimes more so, since patients were more willing than a clinician to scrape vigorously.[143][*needs update*][144] Women had similar success in self-sampling using tampons, swabs, cytobrushes, and lavage.[145][*needs update*]

Several studies used cytobrushes to sample fingertips and under fingernails, without wetting the area or the brush.[96][101][146][*needs update*]

Other studies analyzed urine, semen, and blood and found varying amounts of HPV,[136] but there is not a publicly available test for those yet.

Other testing

[edit]

Although it is possible to test for HPV DNA in other kinds of infections,[136] there are no FDA-approved tests for general screening in the United States[147] or tests approved by the Canadian government,[148] since the testing is inconclusive and considered medically unnecessary.[149]

Genital warts are the only visible sign of low-risk genital HPV and can be identified with a visual check. These visible growths, however, are the result of non-carcinogenic HPV types. Five percent acetic acid (vinegar) is used to identify both warts and squamous intraepithelial neoplasia (SIL) lesions with limited success[*citation needed*] by causing abnormal tissue to appear white, but most doctors have found this technique helpful only in moist areas, such as the female genital tract.[*citation needed*] At this time, HPV tests for males are used only in research.[*citation needed*]

Research into testing for HPV by antibody presence has been done. The approach is looking for an immune response in blood, which would contain antibodies for HPV if the patient is HPV positive.[150][151][152][153] The reliability of such tests has not been proven, as there has not been a FDA approved product as of August 2018;[154] testing by blood would be a less invasive test for screening purposes.

Prevention

[edit]

The HPV vaccines can prevent the most common types of infection.[4] To be effective they must be used before an infection occurs and are therefore recommended between the ages of nine and thirteen. Cervical cancer screening, such as with the Papanicolaou test (pap) or looking at the cervix after using acetic acid, can detect early cancer or abnormal cells that may develop into cancer. This allows for early treatment which results in better outcomes.[1] Screening has reduced both the number and deaths from cervical cancer in the developed world.[16] Warts can be removed by freezing.[5]

Vaccines

[edit]

Main article: HPV vaccine

Three vaccines are available to prevent infection by some HPV types: Gardasil, Gardasil 9 and Cervarix; all three protect against initial infection with HPV types 16 and 18, which cause most of the HPV-associated cancer cases. Gardasil also protects against HPV types 6 and 11, which cause 90% of genital warts. Gardasil is a recombinant quadrivalent vaccine, whereas Cervarix is bivalent, and is prepared from virus-like particles (VLP) of the L1 capsid protein. Gardasil 9 is nonavalent, having the potential to prevent about 90% of cervical, vulvar, vaginal, and anal cancers. It can protect for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58; the latter five cause up to 20% of cervical cancers which were not previously covered.[155]

The vaccines provide little benefit to women already infected with HPV types 16 and 18.[156] For this reason, the vaccine is recommended primarily for those women not yet having been exposed to HPV during sex. The World Health Organization position paper on HPV vaccination clearly outlines appropriate, cost-effective strategies for using HPV vaccine in public sector programs.[157]

There is high-certainty evidence that HPV vaccines protect against precancerous cervical lesions in young women, particularly those vaccinated aged 15 to 26.[158] HPV vaccines do not increase the risk of serious adverse events.[158] Longer follow-up is needed to monitor the impact of HPV vaccines on cervical cancer.[158]

The CDC recommends the vaccines be delivered in two shots at an interval of at least 6 months for those aged 11–12, and three doses for those 13 and older.[159] In most countries, they are funded only for female use, but are approved for male use in many countries, and funded for teenage boys in Australia. The vaccine does not have any therapeutic effect on existing HPV infections or cervical lesions.[160] In 2010, 49% of teenage girls in the US got the HPV vaccine.[*citation needed*]

Following studies suggesting that the vaccine is more effective in younger girls[161] than in older teenagers, the United Kingdom, Switzerland, Mexico, the Netherlands, and Quebec began offering the vaccine in a two-dose schedule for girls aged under 15 in 2014.[*citation needed*]

Cervical cancer screening recommendations have not changed for females who receive the HPV vaccine. It remains a recommendation that women continue cervical screening, such as Pap smear testing, even after receiving the vaccine, since it does not prevent all types of cervical cancer.[160][162]

Both men and women are carriers of HPV.[163] The Gardasil vaccine also protects men against anal cancers and warts and genital warts.[164]

Duration of both vaccines' efficacy has been observed since they were first developed, and is expected to be long-lasting.[165]

In December 2014, the FDA approved a nine-valent Gardasil-based vaccine, Gardasil 9, to protect against infection with the four strains of HPV covered by the first generation of Gardasil as well as five other strains responsible for 20% of cervical cancers (HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58).[166]

Condoms

[edit]

The Centers for Disease Control and Prevention says that male "condom use may reduce the risk for genital human papillomavirus (HPV) infection" but provides a lesser degree of protection compared

with other sexual transmitted infections "because HPV also may be transmitted by exposure to areas (e.g., infected skin or mucosal surfaces) that are not covered or protected by the condom."[167]

Disinfection

[edit]

The virus is unusually hardy and is immune to most common disinfectants. It is the first virus ever shown to be resistant to inactivation by glutaraldehyde, which is among the most common strong disinfectants used in hospitals.[168] Diluted sodium hypochlorite bleach is effective,[168] but cannot be used on some types of re-usable equipment, such as ultrasound transducers.[88] As a result of these difficulties, there is developing concern about the possibility of transmitting the virus on healthcare equipment, particularly reusable gynecological equipment that cannot be autoclaved.[169][170] For such equipment, some health authorities encourage use of UV disinfection[171] or a non-hypochlorite "oxidizing-based high-level disinfectant [bleach] with label claims for non-enveloped viruses",[172] such as a strong hydrogen peroxide solution[173][171] or chlorine dioxide wipes.[171] Such disinfection methods are expected to be relatively effective against HPV.[*citation needed*]

Management

[edit]

See also: Genital warts

There is currently no specific treatment for HPV infection.[174][175][176] However, the viral infection is usually cleared to undetectable levels by the immune system.[177] According to the Centers for Disease Control and Prevention, the body's immune system clears HPV naturally within two years for 90% of cases (see Clearance subsection in Virology for more detail).[174] However, experts do not agree on whether the virus is eliminated or reduced to undetectable levels, and it is difficult to know when it is contagious.[178][*needs update*]

Follow up care is usually recommended and practiced by many health clinics.[179] Follow-up is sometimes not successful because a portion of those treated do not return to be evaluated. In addition to the normal methods of phone calls and mail, text messaging and email can improve the number of people who return for care.[180] As of 2015 it is unclear the best method of follow up following treatment of cervical intraepithelial neoplasia.[181]

Epidemiology

[edit]

Globally, 12% of women are positive for HPV DNA, with rates varying by age and country.[182] The highest rates of HPV are in younger women, with a rate of 24% in women under 25 years.[183] Rates decline in older age groups in Europe and the Americas, but less so in Africa and Asia. The rates are highest in Sub-Saharan Africa (24%) and Eastern Europe (21%) and lowest in North America (5%) and Western Asia (2%).[182]

The most common types of HPV worldwide are HPV16 (3.2%), HPV18 (1.4%), HPV52 (0.9%), HPV31 (0.8%), and HPV58 (0.7%). High-risk types of HPV are also distributed unevenly, with HPV16 having a rate of around 13% in Africa and 30% in West and Central Asia.[183]

Like many diseases, HPV disproportionately affects low-income and resource-poor countries. The higher rates of HPV in Sub-Saharan Africa, for example, may be related to high exposure to human immunodeficiency virus (HIV) in the region. Other factors that impact the global spread of disease

are sexual behaviors including age of sexual debut, number of sexual partners, and ease of access to barrier contraception, all of which vary globally.[182][184]

United States

[edit]

HPV prevalence among women by age, including 20 low-risk types and 23 high-risk types[185]

Age (years)	**Prevalence (%)**
14 to 19	24.5%
20 to 24	44.8%
25 to 29	27.4%
30 to 39	27.5%
40 to 49	25.2%
50 to 59	19.6%
14 to 59	**26.8%**

HPV is estimated to be the most common sexually transmitted infection in the United States.[185] Most sexually active men and women will probably acquire genital HPV infection at some point in their lives.[22] The American Social Health Association estimates that about 75–80% of sexually active Americans will be infected with HPV at some point in their lifetime.[186][187] By the age of 50 more than 80% of American women will have contracted at least one strain of genital HPV.[185][188] It was estimated that, in the year 2000, there were approximately 6.2 million new HPV infections among Americans aged 15–44; of these, an estimated 74% occurred to people between ages of 15 and 24.[189] Of the STIs studied, genital HPV was the most commonly acquired.[189] In the United States, it is estimated that 10% of the population has an active HPV infection, 4% has an infection that has caused cytological abnormalities, and an additional 1% has an infection causing genital warts.[190]

Estimates of HPV prevalence vary from 14% to more than 90%.[191] One reason for the difference is that some studies report women who currently have a detectable infection, while other studies report women who have ever had a detectable infection.[192][193] Another cause of discrepancy is the difference in strains that were tested for.[*citation needed*]

One study found that, during 2003–2004, at any given time, 26.8% of women aged 14 to 59 were infected with at least one type of HPV. This was higher than previous estimates; 15.2% were infected with one or more of the high-risk types that can cause cancer.[185][194]

The prevalence for high-risk and low-risk types is roughly similar over time.[185]

Human papillomavirus is not included among the diseases that are typically reportable to the CDC as of 2011.[195][196]

Ireland

[edit]

On average 538 cases of HPV-associated cancers were diagnosed per year in Ireland during the period 2010 to 2014.[197] Cervical cancer was the most frequent HPV-associated cancer with on average 292 cases per year (74% of the female total, and 54% of the overall total of HPV-associated cancers).[197] A study of 996 cervical cytology samples in an Irish urban female, opportunistically screened population, found an overall HPV prevalence of 19.8%, HPV 16 at 20% and HPV 18 at 12% were the commonest high-risk types detected. In Europe, types 16 and 18 are responsible for over 70% of cervical cancers.[198] Overall rates of HPV-associated invasive cancers may be increasing. Between 1994 and 2014, there was a 2% increase in the rate of HPV-associated invasive cancers per year for both sexes in Ireland.[197]

As HPV is known to be associated with anogenital warts, these are notifiable to the Health Protection Surveillance Centre (HPSC). Genital warts are the second most common STI in Ireland.[199] There were 1,281 cases of anogenital warts notified in 2017, which was a decrease on the 2016 figure of 1,593.[200] The highest age-specific rate for both male and female was in the 25–29 year old age range; 53% of cases were among males.[200]

Sri Lanka

[edit]

In Sri Lanka, the prevalence of HPV is 15.5% regardless of cytological abnormalities.[201]

Inner Mongolia

[edit]

In the Autonomous Region of Inner Mongolia overall HPV prevalence is 14.5% but shows substantial ethnical disparity, the prevalence in Mongolian women (14.9%) being much higher than that of Han participants (4.3%).[202] Urbanization, the number of sex partners, and PAP history appear as risk factors for HPV infection in Han, but not in Mongolian women. The region is thus an important example that the epidemiology of HPV is more related to cultural and ethnical factors and not to geography per se.[*citation needed*]

History

[edit]

In 1972, the association of the human papillomaviruses with skin cancer in epidermodysplasia verruciformis was proposed by Stefania Jabłońska in Poland. In 1976 Harald zur Hausen published the hypothesis that human papillomavirus plays an important role in the cause of cervical cancer. In 1978, Jabłońska and Gerard Orth at the Pasteur Institute discovered HPV-5 in skin cancer.[203] In 1983 and 1984 zur Hausen and his collaborators identified HPV16 and HPV18 in cervical cancer.[204]

The HeLa cell line contains extra DNA in its genome that originated from HPV type 18.[205]

Human papillomavirus and cancer

5 March 2024

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Key facts

- **Human papillomavirus (HPV) is the name of a group of 200 known viruses. They do not cause concerns in most people, but infection with some high-risk types is common and can cause genital warts or cancer.**
- **In 90% of people the body controls the infection by itself. Persistent HPV infection with high-risk HPV types is the cause of cervical cancer and is associated with cancers of the vulva, vagina, mouth/throat, penis and anus *(1)*.**
- **In 2019, HPV caused an estimated 620 000 cancer cases in women and 70 000 cancer cases in men *(1)*.**
- **Prophylactic vaccination against HPV can prevent these cancers. In addition, HPV-screening and treatment of pre-cancer lesions is an effective way to prevent cervical cancer.**

Overview

Human papillomavirus (HPV) is a common sexually transmitted infection. Almost all sexually active people will be infected at some point in their lives, usually without symptoms.

HPV can affect the skin, genital area and throat.

Condoms help prevent HPV but do not offer total protection because they do not cover all the genital skin.

HPV usually goes away on its own without treatment. Some HPV infections cause genital warts. Others can cause abnormal cells to develop, which go on to become cancer.

Cancers from HPV can be prevented with vaccines.

The vaccine does not contain any live virus or DNA from the virus so it cannot cause cancer or other HPV-related illnesses. The HPV vaccine is not used to treat HPV infections or diseases caused by HPV, but instead to prevent the development of cancers.

Currently, cervical cancer is the only HPV-caused cancer for which screening tests are available. Screening tests are used to check for disease when there are no symptoms. The goal of screening for cervical cancer is to find precancerous cell changes before they become cancer and when treatment can prevent cancer from developing. Screening for cervical cancer is an important part of routine health care for people who have a cervix. This includes women and transgender men who still have a cervix.

Cervical cancer is the most common type of cancer caused by HPV, other less common cancers affecting men and women, including anal, vulvar, vaginal, mouth/throat and penile cancers.

Scope of the problem

The highest prevalence of cervical HPV among women is in sub-Saharan Africa (24%), followed by Latin America and the Caribbean (16%), eastern Europe (14%), and South-East Asia (14%) *(2)*. Prevalence in men is highly variable based on sexual trends.

Evidence showed that prevalence of the virus is higher among women living with HIV, men who have sex with men, immunocompromised individuals, people with co-infection with other sexually transmitted infections (STI), people who receive immunosuppressive medications and children who have been through sexual abuse.

Globally, it is estimated that 620 000 new cancer cases in women and 70 000 new cancer cases in men were caused by HPV in 2019 *(1)*. Cervical cancer was the fourth leading cause of cancer and cancer deaths in women in 2022, with some 660 000 new cases and around 350 000 deaths worldwide *(3)*. Cervical cancers account for over 90% of HPV-related cancers in women *(1)*.

The highest rates of cervical cancer incidence and mortality are in low- and middle-income countries. This reflects major inequities driven by lack of access to national HPV vaccination, cervical screening and treatment services, and social and economic determinants.

Symptoms

Most people will not have any symptoms from an HPV infection. The immune system usually clears HPV from the body within a year or two with no lasting effects.

Some HPV infections cause small rough lumps (genital warts) that can appear on the vagina, penis or anus and rarely the throat. They may be painful, itchy or bleed or cause swollen glands.

HPV infection that does not go away on its own can cause changes to cervical cells, which lead to precancers that may become cervical cancer if left untreated. It usually takes 15–20 years for cervical cancer to develop after HPV infection.

The early changes in cervical cells and precancers mostly do not cause symptoms. Symptoms of cervical cancer may include bleeding between periods or after sexual intercourse or a foul-smelling vaginal discharge. These symptoms may be due to other diseases. People with these symptoms should speak to their healthcare provider.

Prevention

Being vaccinated is the best way to prevent HPV infection, cervical cancer and other HPV-related cancers. Screening can detect cervical precancers that can be treated before they develop into cancer.

HPV vaccines should be given to all girls aged 9–14 years, before they become sexually active.

The vaccine may be given as 1 or 2 doses. People with reduced immune systems should receive 2 or 3 doses. Check with your healthcare provider to determine what is best for you.

Using condoms during sex is an important way to prevent HPV infection. Voluntary male circumcision also reduces the risk of infection. Being a non-smoker or stopping smoking reduces the chances of developing persistent HPV infection.

Testing cells from a woman's cervix for HPV is used to screen women for cervical cancer. Women should be screened every 5–10 years starting at age 30. Women living with HIV should be screened every 3 years starting at age 25.

After a positive HPV test (or other screening method), a healthcare provider can look for changes on the cervix or precancers that could develop into cervical cancer if left untreated. Treatment of precancers prevents cervical cancer. Precancers rarely cause symptoms, which is why regular screening to check cervical health is important.

Learn more about vaccination of boys and older age groups: WHO position paper

Treatment

There is currently no treatment for HPV infection. Treatments exist for genital warts, cervical precancers and cervical cancer.

Non-cancerous genital warts and precancerous lesions in the cervix, vagina, vulva, anus or penis can be removed or treated by ablation (freezing or heating) or with surgery.

Currently, cancer of the cervix (cervical cancer) is the only HPV-caused cancer for which screening tests are available.

Treatments for cancers caused by HPV (including cervical cancer) are more effective if diagnosed early. Treatment should begin quickly after diagnosis.

Learn more about cervical precancer treatment here: WHO fact sheet on cervical cancer

Management pathways for invasive cancer care are important tools to ensure that a patient is referred promptly and supported as they navigate the steps to diagnosis and treatment decisions. A multidisciplinary team should ensure diagnosis and staging (histological testing, pathology, imaging) takes place prior to treatment decisions which could include surgery, radiotherapy and systemic therapy such as chemotherapy. Treatment decisions should be in line with national guidelines and interventions should be supported by holistic psychological, spiritual, physical and palliative care.

As low- and middle-income countries scale-up cervical screening, more cases of invasive cervical cancer will be detected, especially in previously unscreened populations. Therefore, referral and treatment strategies need to be implemented and expanded alongside prevention services.

WHO response

Giving the global public health burden of cervical cancer caused by HPV, the World Health Assembly (WHA. 73.2) adopted the Global strategy to accelerate the elimination of cervical cancer as a public health problem with the following targets:

- 90% of girls fully vaccinated with HPV vaccine by age 15;
- 70% of women are screened with a high-performance test by 35, and again by 45 years of age; and
- 90% of women identified with cervical disease receive treatment (90% of women with pre-cancer treated; 90% of women with invasive cancer managed).

Prevention of HPV-associated precancer and cancer is also a key element of WHO's Global health sector strategy on, respectively, HIV, hepatitis and sexually transmitted infections, 2022–2030 and the resolution WHA74.5 (2021) on oral health includes actions on mouth/throat cancers.

The joint work of the WHO at global, regional and national level, alongside UN sister agencies delivers to:

1. increase political commitment to formulate policy and support implementation
2. offer contextualized technical assistance, lessons learned and best practices
3. develop norms and standards based on latest evidence
4. lead the global health ecosystem to achieve the targets and improve quality of care.

Human papillomavirus (HPV)

Human papillomavirus (HPV) is the name of a very common group of viruses. They do not cause any problems in most people, but some types can cause genital warts or cancer.

HPV affects the skin. There are more than 100 different types.

Symptoms of human papillomavirus (HPV)

HPV does not usually cause any symptoms.

Most people who have it do not realise and do not have any problems.

But sometimes the virus can cause painless growths or lumps around your vagina, penis or anus (genital warts).

How human papillomavirus (HPV) is spread

Many types of HPV affect the mouth, throat or genital area. They're easy to catch.

You do not need to have penetrative sex.

You can get HPV from:

- any skin-to-skin contact of the genital area
- vaginal, anal or oral sex
- sharing sex toys

HPV has no symptoms, so you may not know if you have it.

It's very common. Most people will get some type of HPV in their life.

Important

You do not have to have sexual contact with a lot of people to get HPV. You can get HPV the first time you have sex.

Conditions linked to human papillomavirus (HPV)

Most of the time HPV does not cause any problems.

In some people, some types of HPV can cause:

- genital warts
- abnormal changes in the cells that can sometimes turn into cancer

HPV types linked to cancer are called high-risk types.

Cancers linked to high-risk HPV include:

- cervical cancer
- anal cancer
- penile cancer
- vulval cancer
- vaginal cancer
- some types of head and neck cancer

You can have HPV for many years without it causing problems.

You can have it even if you have not been sexually active or had a new partner for many years.

Testing for human papillomavirus (HPV)

HPV testing is part of cervical screening. There's no blood test for HPV.

During cervical screening, a small sample of cells is taken from the cervix and tested for HPV.

Screening is offered to all women and people with a cervix aged 25 to 64. It helps protect them against cervical cancer.

Some sexual health clinics may offer anal screening to men with a higher risk of developing anal cancer, such as men who have sex with men.

Find out more about cervical screening and how it helps protect against cervical cancer

How to protect yourself against human papillomavirus (HPV)

You cannot fully protect yourself against HPV, but there are things that can help.

- Condoms can help protect you against HPV, but they do not cover all the skin around your genitals, so you're not fully protected.
- The HPV vaccine protects against the types of HPV that cause most cases of genital warts and cervical cancer, as well as some other cancers. It does not protect against all types of HPV.

Find out more about the HPV vaccine and who can have it

Treating human papillomavirus (HPV) infections

There's no treatment for the HPV infection. Most HPV infections do not cause any problems and are cleared by your body within 2 years.

If HPV causes problems, such as genital warts or changes to cells in the cervix, you can have treatment for these.

Continuing Education Activity

The human papillomavirus (HPV) is a non-enveloped, double-stranded, circular DNA virus that is responsible for causing multiple epithelial lesions and cancers. It can manifest as cutaneous and anogenital warts, which depending on the subtype, may progress to carcinoma. This activity reviews

the evaluation and management of human papillomavirus infection and explains the role of the interprofessional team in improving care for patients with this condition.

Objectives:

- Identify the etiology of human papillomavirus infection.
- Review the role of E6 and E7 protein in the pathophysiology of human papillomavirus infection.
- Explain the management of human papillomavirus infection.

Access free multiple choice questions on this topic.

Go to:

Introduction

The Human Papillomavirus (HPV) is the initiating force behind multiple epithelial lesions and cancers, predominantly cutaneous and mucosal surfaces.[1][2][3]

There are more than 100 subtypes of HPV. Individuals with persistent HPV infection and those who have multiple sexual partners are at very high risk for acquiring more HPV subtypes. The current classification of HPV infection is as follows:

- Non-genital (Cutaneous)
- Mucosal or anogenital
- Epidermodysplasia verruciformis (EV)

The clinical lesions may be visibly obvious, but in some cases (latent lesions) may require testing for viral DNA. The majority of HPV infections are latent, and most clinical lesions present as warts rather than a malignancy.

Today, HPV has been implicated as a cause of laryngeal, oral, lung, and anogenital cancer. Subtypes 6 and 11 are low risk and usually present with the formation of condylomata and low-grade precancerous lesions. HPV subtypes 16 and 18 are high risk and are responsible for high-grade intraepithelial lesions that progress to malignancies. It is important to understand that HPV alone does not cause cancer but requires triggers like smoking, folate deficiency, UV light exposure, immunosuppression, and pregnancy.

Go to:

Etiology

HPV is a non-enveloped, double-stranded, circular DNA virus of the Papillomaviridae family. The virus enters the epithelium through disruption to the skin/mucosa and infects basal stem cells. Its genome contains seven early (*E*) and two late (*L*) phase genes required for viral propagation. The viral DNA may remain as an independent episome for a period before integrating into the host's genome. HPV preferentially integrates at fragile sites in the human DNA where the strand is prone to breakages.[4]

Risk factors:

- Sexual activity, age of first sexual intercourse, and number of sexual partners
- Smoking

- Use of oral contraceptives (more than 5 years)
- Chewing betel nut
- Exposure to radiation and UV light

Go to:

Epidemiology

HPV subtypes show a predilection for body sites they most commonly infect, and disease manifestations that result from infection may vary. Over 180 subtypes of HPV have been identified. Cutaneous warts of the hands and feet, such as verruca vulgaris or verruca plantaris, are most commonly caused by HPV subtypes 1, 2, 4, 27, or 57. Most anogenital warts, such as condyloma acuminatum, are caused by HPV subtypes 6 or 11 and termed low-risk HPV; these subtypes also are responsible for juvenile and adult recurrent respiratory papillomatosis. Pre-cancerous and cancerous lesions of the cervix, male and female anogenital areas, and oropharyngeal area are most commonly caused by HPV subtypes 16 and 18. However, subtypes 31, 33, 35, 45, 52, and 58 also fall in the high-risk HPV group as they are associated with cervical cancer development.

The HPV subtypes which cause cutaneous verrucae are spread by contact between skin with microscopic or macroscopic epidermal damage and a fomite-harboring HPV. The prototypical location for contracting warts of the feet is a locker room.

Both low-risk and high-risk HPV (sometimes referred to as alpha-papillomaviruses) are considered sexually transmitted but may be spread by other forms of intimate contact. According to the Center for Disease Control and Prevention (CDC), the most recent studies show the prevalence of genital HPV for adults aged 18 to 59 to be approximately 45.2% in men and 39.9% in women.[5][6]

Go to:

Pathophysiology

*E*6 and *E*7 are oncoproteins that inactivate p53 and pRb proteins, respectively; these inactivations lead to dysregulation of the cell cycle and neoplastic transformation of the affected tissue. The virus remains relatively inactive in early infection but keeps the cell from entering a resting (G0) state. As the infected cells grow and mature, *E*2 regulates the transition from early- to late-phase genes, and the virus increases the production of virions for dispersal. This increase in virion production in HPV-driven lesions typically manifests as hypertrophy of the infected tissue (discrete, thickened lesions, e.g., the common wart) with the potential for atypia and malignant transformation in those lesions infected with high-risk HPV.

Go to:

Histopathology

The wart histology may reveal hyperkeratosis, papillomatosis, and parakeratosis. The long rete ridges usually point to the wart center, and the capillaries are often thrombosed.

Go to:

History and Physical

Evaluation and treatment of HPV infection vary by body site and disease manifestation. For a more in-depth examination of each disease entity, please visit those specific topics.

History

- Cutaneous warts (verruca vulgaris, verruca plantaris): Ask about potential infectious contacts and hygiene habits (e.g., "Do you wear shower shoes when showering at the gym?" or "Are the lesions painful and/or prone to bleeding?")
- Anogenital warts (condyloma acuminatum): Providers should ask about:

1. Sexual history/infectious contacts
2. Duration and location of the wart(s)
3. Prior vaccination for HPV (Gardasil, Cervarix)
4. History of wart removal/treatment
5. History of diseases or medications that may cause them to be immunocompromised.

- Pap smears (cervical for females, anal Pap smear for males), HPV testing, and sexually transmitted infections.
- Cervical dysplasia (squamous and glandular): Providers should ask about:

1. Menses/prior Pap smears/HPV testing,
2. Sexually transmitted infections/sexual history/infectious contacts,
3. Prior vaccination for HPV (Gardasil, Cervarix), and
4. Associated symptoms, such as bleeding/spotting outside of menses, pelvic or genital pain, pain/bleeding during intercourse, and/or palpable lesions felt on the cervix.

Physical Examination

- Cutaneous warts (verruca vulgaris, verruca plantaris): Examine hands and feet thoroughly, including between digits and the underside of the toes.
- Anogenital warts (condyloma acuminatum): Examine the anogenital region. Patients may additionally require a speculum examination of the vaginal walls and/or anus. Men may require an examination of the urethra, depending on signs and symptoms. Depending on the history of sexual practices, an oropharyngeal examination may be prudent.
- Cervical dysplasia (squamous and glandular): Perform a speculum examination of the cervix. Depending on the patient's age and Pap smear history, an initial or repeat Pap smear may be warranted.

Epidermodysplasia verruciformis is an autosomal recessive trait that increases the susceptibility to specific warts that are not usually observed in the general population. EV is also seen in immunocompromised individuals and those who have undergone transplants. The condition starts in childhood and can affect any part of the body. The warts are flat and often mistaken for tinea versicolor. While warts have weak metastatic potential, they are locally destructive.

Go to:

Evaluation

Patients with cutaneous, anogenital, and/or oropharyngeal warts may have them excised and submitted for histopathological examination if there is any question about the diagnosis or concern for dysplasia.[6][7]

Screening for cervical dysplasia/malignancy is typically accomplished through speculum examination and Pap smear with concurrent or reflex HPV testing, an assay test performed on cervical cells to evaluate the most common HPV subtypes associated with dysplasia. Treatment protocols stratify patients by age, HPV status, and Pap smear results. Depending on treatment stratification, patients with results concerning intraepithelial squamous or glandular lesions may proceed to colposcopy (a procedure in which the cervix is coated with acetic acid, acetowhite areas are evaluated with a colposcope, and concerning areas are biopsied to examine for histopathologic evidence of dysplasia or malignancy).

Go to:

Treatment / Management

Individuals with cutaneous warts have numerous treatment options available, including surgical removal, cryotherapy (freezing the infected tissue), irritant or immunomodulating medications, and laser removal. Many of these treatments' overarching purpose is to manually or chemically irritate the area, thereby invoking a host immune response to assist in clearing the infected tissue.[8][9][10]

To prevent lower anogenital tract HPV infection by the most common high-risk and low-risk subtypes, the CDC recommends that boys and girls be vaccinated for HPV starting at ages 11 to 12. It is further recommended that women get vaccinated through the age of 26 and men through the age of 21.

Anogenital and oropharyngeal warts may be treated similarly to cutaneous warts as long as the patient is immunocompetent. Development of HPV-related carcinoma at these sites may require resection, chemotherapy, and/or radiation.

Cervical HPV-driven lesions may regress without any intervention. Young immunocompetent women with dysplasia are usually monitored at shortened intervals through Pap smears, HPV testing, and colposcopic examination. Persistent cervical dysplasia at any age, or high-grade dysplasia in older women, is treated with cryotherapy, loop electrosurgical excision procedure (LEEP), or cold knife cone (CKC) excision. Both surgical procedures (LEEP, CKC) involve resection of the cervical os and transformation zone. If the patient progresses to malignancy (e.g., squamous cell carcinoma, endocervical adenocarcinoma), further resection, chemotherapy, and/or radiation may be required.[11][12]

For a fuller explanation of the disease entities associated with HPV infection, please visit those topics specifically.

Go to:

Differential Diagnosis

- Corns & calluses
- Acrochordon
- Condyloma latum
- Keratoacanthoma

- Psoriasis
- Seborrhea
- Chancroid
- Herpes simplex
- Molluscum contagiosum

Go to:

Prognosis

The prognosis after an HPV infection is good, but recurrences are common. Even though there are many treatments for warts, none works well, and most patients require repeated treatments. The HPV infection can also result in vulvar intraepithelial dysplasia, cervical dysplasia, and cervical cancer. Some women remain at high risk for developing vaginal and anal cancer. The risk of malignant transformation is highest in immunocompromised individuals. Finally, when a patient has been diagnosed with HPV infection, there is a 5-20% risk of having other STDs like gonorrhea and/or chlamydia.

Go to:

Complications

- Poor cosmesis
- Depression, loss of self-esteem
- Genital warts may cause urethral obstruction.
- Condylomata may form ulcers and become infected.
- Progression to malignancy
- Transmission of HPV to others

Go to:

Postoperative and Rehabilitation Care

Long term follow up is essential as recurrence of warts is common. In addition, all treatments for warts have side effects that need to be monitored

The sexual partner also needs to be examined for condylomata.

Because of the risk of cancer, DNA testing and screening is required in high-risk patients.

Go to:

Consultations

- Infectious disease to manage HPV infection in immunocompromised individuals
- ENT to manage oropharyngeal papillomas
- Urologist to manage urethral/penile warts and penile cancer

- Colorectal surgeon to manage the anal disease
- Dermatologist to help manage warts and EV

Go to:

Deterrence and Patient Education

- Avoid multiple sexual partners.
- Use a condom
- Practice safe sex
- Undergo Pap smear screen

Vaccination

The 9 valent HPV vaccine is available to prevent certain cancerous lesions in males and females. The vaccine covers HPV subtypes 6,11,16,18,31,33,45,52 and 58. The effectiveness of the HPV vaccine has been inferred from several studies. It has been shown to prevent anal cancer, genital warts, cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, and anal intraepithelial neoplasia. The vaccine is most effective when administered before initiating sexual activity at ages 9-12.

Go to:

Pearls and Other Issues

- Boys and girls aged 11-12 should receive the HPV vaccine
- To be effective, the vaccination should be completed by age 13
- Studies show that the vaccine is effective after 2 doses in younger children

Go to:

Enhancing Healthcare Team Outcomes

HPV is known to cause lesions of the mucous membranes and skin. There are over 100 subtypes of HPV, and some are associated with an increased risk of malignancy. HPV diagnosis and treatment is best done with an interprofessional team.

For the most part, HPV is sexually acquired, and one of the best ways to decrease the morbidity of this infection is the patient's education. Both the nurse and the pharmacist are in a prime position to educate patients about safe sex, the use of condoms, and avoidance of multiple sex partners.

The pharmacist should provide information on the different treatments for warts, their benefits, and adverse effects. The pharmacist should also encourage the patients to be vaccinated against HPV.

Further, the primary care provider should encourage these women to undergo the Pap smear to screen for cervical dysplasia and the presence of HPV. More importantly, patients should be told that if they have genital warts, sexual activity should be avoided until the lesions have been treated or have resolved.

Finally, patients need to be educated that if they have HPV, they should be screened for other sexually transmitted infections. The sex partner's evaluation is vital if the cycle of spread is to be

broken.[13][14][15](Level II) Only through such collaboration between team members will the morbidity of HPV be reduced.

Outcomes

Once HPV is acquired, recurrences are common. However, for most patients with genital warts, there are treatments. In about 60% of cases, genital warts resolve spontaneously. Irrespective of the treatment of genital warts, the risk of cervical cancer is not altered.

The biggest concern with genital warts is the risk of cervical cancer. HPV is also known to be associated with anal and head and neck cancers. Individuals who are immunocompromised are also at risk for developing dysplasia or cancer of the vagina and vulva.

Finally, in at least one-third of patients with HPV, there is the presence of other sexually transmitted infections.[16][1][17](Level II)

Your doctor might be able to diagnose human papillomavirus (HPV) infection by looking at your warts.

If genital warts aren't visible, you'll need one or more of the following tests:

- **Vinegar (acetic acid) solution test.** A vinegar solution applied to HPV-infected genital areas turns them white. This may help in identifying difficult-to-see flat lesions.
- **Pap test.** Your doctor collects a sample of cells from your cervix or vagina to send for laboratory analysis. Pap tests can reveal abnormalities that can lead to cancer.
- **DNA test.** This test, conducted on cells from your cervix, can recognize the DNA of the high-risk varieties of HPV that have been linked to genital cancers. It's recommended for women 30 and older in addition to the Pap test.

More Information

- Pap smear

Treatment

Warts often go away without treatment, particularly in children. However, there's no cure for the virus, so they can reappear in the same place or other places.

Medications

Medications to eliminate warts are typically applied directly to the lesion and usually take many applications before they're successful. Examples include:

- **Salicylic acid.** Over-the-counter treatments that contain salicylic acid work by removing layers of a wart a little at a time. For use on common warts, salicylic acid can cause skin irritation and isn't for use on your face.
- **Imiquimod.** This prescription cream might enhance your immune system's ability to fight HPV. Common side effects include redness and swelling at the application site.

- **Podofilox.** Another topical prescription, podofilox works by destroying genital wart tissue. Podofilox may cause burning and itching where it's applied.
- **Trichloroacetic acid.** This chemical treatment burns off warts on the palms, soles and genitals. It might cause local irritation.

Surgical and other procedures

If medications don't work, your doctor might suggest removing warts by one of these methods:

- Freezing with liquid nitrogen (cryotherapy)
- Burning with an electrical current (electrocautery)
- Surgical removal
- Laser surgery

Treatment for HPV in the cervix

If you have an abnormal HPV or Pap test, your gynecologist will perform a procedure called a colposcopy. Using an instrument that provides a magnified view of the cervix (colposcope), your doctor will look closely at the cervix and take samples (biopsy) of any areas that look abnormal.

Any precancerous lesions need to be removed. Options include freezing (cryosurgery), laser, surgical removal, loop electrosurgical excision procedure (LEEP) and cold knife conization. loop electrosurgical excision procedure (LEEP) uses a thin looped wire charged with an electric current to remove a thin layer of a section of the cervix and cold knife conization is a surgical procedure that removes a cone-shaped piece of the cervix.

Preparing for your appointment

You'll likely start by seeing your primary care provider. Depending on where your warts are located, you may be referred to a doctor who specializes in disorders of the skin (dermatologist), feet (podiatrist) or reproductive organs (gynecologist or urologist).

Here's some information to help you get ready for your appointment.

What you can do

Before your appointment, make a list of:

- **Your symptoms,** including any that seem unrelated to the reason for your appointment

- **Key personal information,** including major stresses, recent life changes and your sexual history
- **All medications, vitamins or other supplements** you take, including the doses
- **Questions to ask** your doctor

For HPV infection, questions to ask your doctor include:

- What's the most likely cause of my symptoms?
- Are there other possible causes?
- Do I need to have any tests?
- How can I prevent HPV infection in the future?
- Are there brochures or other printed material that I can have? What websites do you recommend?

Don't hesitate to ask other questions.

What to expect from your doctor

Your doctor is likely to ask you questions, such as:

- When did your symptoms begin?
- Are you in a monogamous sexual relationship? Is your partner?
- Where have you found lesions?
- Are the lesions painful or itchy?
- Does anything seem to improve your symptoms?
- What, if anything, appears to worsen your symptoms?

What is human papillomavirus (HPV)?

Medically reviewed by Meredith Goodwin, MD, FAAFP — Written by Lori Smith, MSN, BSN, WHNP-BC — Updated on November 16, 2023

- Risk factors
- Diagnosis
- Prevention

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How we vet brands and products

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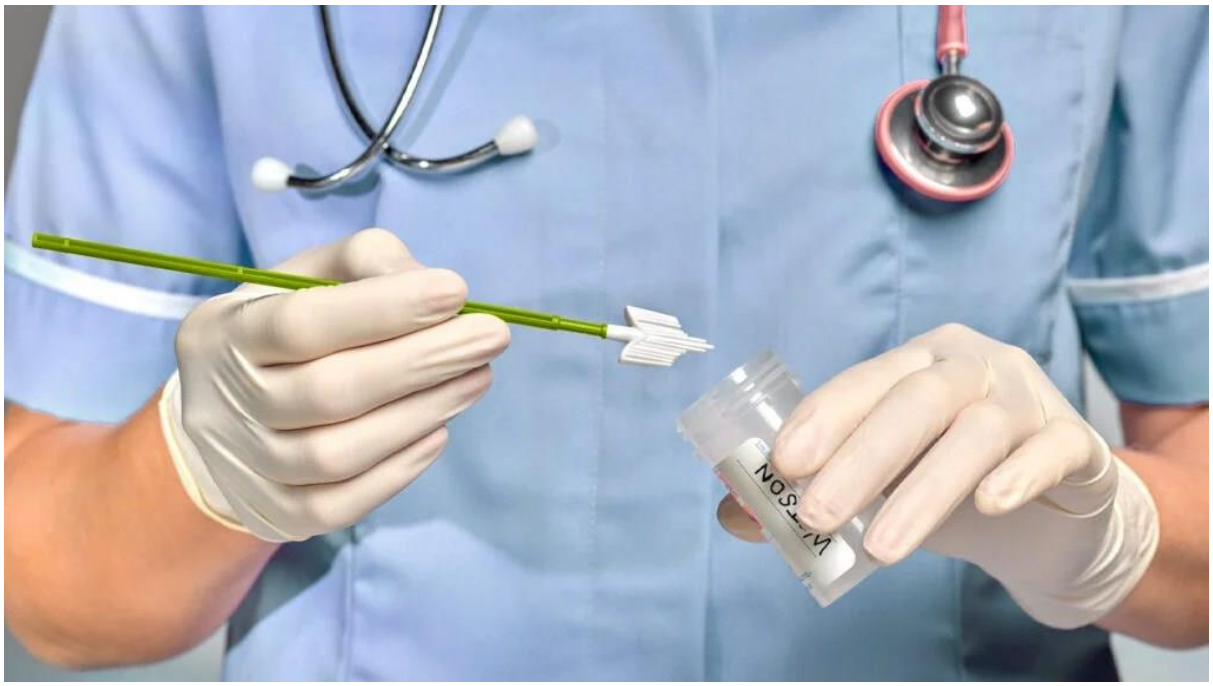
The human papillomavirus (HPV) causes an infection, typically through sexual contact. Warts are a common symptom, but HPV can also increase the risk of some types of cancer. Vaccines can help prevent HPV infections.

In the United States, around 79 millionTrusted Source people have HPV, and doctors diagnose around 14 million new cases every year.

There are different types of HPV, and some can increase the risk of cancer. Each year, around 19,400 females and 12,100 males in the U.S. develop cancers that stem from HPV.

In this article, learn what HPV is, how it spreads, the symptoms it causes, and their treatments. We also explore HPV vaccines and other ways to protect against the infection.

Treatments



Share on PinterestCredit Image: Peter Dazeley/Getty Images

There is no wayTrusted Source to cure HPV, to remove the virus from the body.

However, a person can take various steps to remove the warts that HPV can cause. It is also worth noting that these warts often go away without treatment.

Common warts

Over-the-counter salicylic acid products can treat common warts. Do not use these products on warts in the genital area, however.

For some people, a doctor may prescribe one of the following medications:

- imiquimod (Aldara, Zyclara)
- podofilox (Condylox)
- trichloroacetic acid
- podophyllin

Also, surgical intervention may be necessary.

Genital warts

Do not use over-the-counter products on genital warts. A doctor may recommendTrusted Source:

- **Cryotherapy:** This involves using liquid nitrogen to freeze off warts.
- **Electrocautery:** This involves using an electrical current to burn away the warts.
- **Laser or light therapy:** This involves using a high-powered, targeted beam to remove the unwanted tissue.
- **Surgical removal:** A surgeon can cut away warts in an outpatient procedure that involves a local anesthetic.

The best option will depend upon the type and location of the wart. Treatments can remove warts, but the virus will remain in the body and remain transmissible.

Symptoms

Symptoms of HPV may appear years after the initial infection. Some types of the virus cause warts to form, while others can increase the risk of cancer. Specifically, HPV can cause:

Genital warts

A person may haveTrusted Source one small skin bump, a cluster of bumps, or stem-like protrusions. These warts can range in size and appearance, and they may be:

- large or small
- flat or cauliflower-shaped
- white, pink, red, purplish-brown, or skin-colored

They can form on the:

- vulva
- cervix

- penis or scrotum
- anus
- groin area

These warts can cause itching, burning, and other discomfort.

Other types of warts

HPV can also cause common warts, plantar warts, and flat warts.

Common warts are rough, raised bumps that tend to form on the hands, fingers, and elbows.

Plantar warts are hard, grainy growths that often form on the feet, usually on the heels or balls of the feet.

Flat warts, meanwhile, are flat-topped, slightly raised lesions that are darker than the surrounding skin and often appear on the face or neck.

How HPV can lead to cancer

Most people with HPV do not develop cancer, but the infection can increase the riskTrusted Source, especially in people with weakened immune systems.

A high-risk strain of HPV can change the way that cells communicate with each other, and this can cause them to grow in an uncontrolled way.

In many people, the immune system defeats the unwanted cells. However, if the immune system is unable to do this, the cells can stay in the body and continue to grow. In time, this can lead to cancer.

It may take 10–20 years Trusted Sourcefor a tumor to develop, according to the National Cancer Institute (NCI).

In the U.S., around 3% of all cancers in females and 2% of all cancers in males stem from HPV.

The infection can increase the risk of developing cancer of the:

- cervix
- vulva
- vagina
- penis
- anus
- oropharynx, includng the base of the tongue and the tonsils

Routine screening can lead to an early diagnosis, and receiving prompt treatment can prevent the cancer from spreading.

The best course of treatment will depend on the type of cancer, its stage, and the age and overall health of the person.

Causes

HPV is a virus that transmits through skin-to-skin contactTrusted Source, often sexual contact. The infection can develop in anyone who is sexually active.

There may be no symptoms, or the symptoms may appear and disappear. HPV can passTrusted Source from person to person regardless of whether symptoms are present.

The strains of HPV that cause warts are different from those that increase the risk of cancer.

In children

HPV can transmit to an infant during birth. However, researchTrusted Source suggests that this risk is relatively low, as the immune system usually takes care of the infection in this situation.

SignsTrusted Source of an HPV infection in an infant include genital warts or lesions in the mouth.

If a young child develops HPV symptoms, it may indicate child sexual abuse.

Risk factors

Factors that increase the riskTrusted Source of HPV include:

- having several sexual partners
- having sex with someone who has had several sexual partners
- having sex without using barrier protection, such as a condom or dental dam
- having areas of broken or damagedTrusted Source skin
- having contact with warts or surfaces where HPV exposure has occurred
- not having the HPV vaccination

The risk of cancerTrusted Source is higher if a person has HPV and:

- has other sexually transmitted infections, such as chlamydia
- delivered their first baby at a young age
- has given birth to many children
- smokes tobacco products
- has a weakened immune system

Diagnosis

If warts or lesions are visible, a doctor can usually diagnose HPV with a visual examination. Also, tests can confirm the presence of the virus.

When to get tested for HPV?

TestsTrusted Source for HPV or related cervical cellular changes include:

- a Pap smear
- a DNA test
- a biopsy

A Pap smear, also called a cervical smear, involves collecting and testing cells from the surface of the cervix or vagina. It can reveal any cellular abnormalities that may lead to cancer.

A DNA test can evaluate for high-risk types of HPV, and a doctor may use it alongside a Pap smear.

A biopsy, which involves taking a sample of affected skin, may be necessary if a test reveals unusual cell changes.

There is currently no routine screening for HPV in males, and the range of testing options is limited. Some experts have called for more testing, especially for men who have sex with men.

How does HPV specifically affect males?

If a person has receptive anal sex, a doctor may recommend an anal Pap smear.

A person can also test for HPV at home, but it is important to see a doctor to confirm the diagnosis. The home test cannot detect cancer.

Home HPV kits are available for purchase online.

Prevention

To reduce the riskTrusted Source of contracting HPV, a person can:

- Get the HPV vaccine.
- Use barrier protection every time they have sex.
- Limit their number of sexual partners.
- Not have sex while genital warts are present.

To help prevent the warts from spreading:

- Avoid touching the wart unnecessarily.
- Wash the hands after touching a wart.
- Avoid shaving over a wart.
- Use footwear in public areas, such as pools and locker rooms, if warts are present on the feet.
- Treat and cover a wart until it disappears.
- Avoid sharing towels and other personal items.

Vaccination

The Centers for Disease Control and Prevention (CDC)Trusted Source recommend vaccination at the age of 11–12 years to reduce the risk of cervical and other forms of cancer.

This type of vaccine comes in two stages, 6–12 months apart. Currently, three HPV vaccinesTrusted Source are available:

- Gardasil
- Cervarix

- Gardasil 9

People aged up to 26 yearsTrusted Source who have not received the vaccine should ask their doctors about it.

People aged 27–45 yearsTrusted Source who have not had the vaccine are eligible for vaccination with Gardasil 9.

Speak with a doctor to see whether vaccination is appropriate. Anyone who is pregnant should wait until after delivery to have the vaccination.

Human papillomavirus (HPV) infects epithelial cells. Most of the > 100 subtypes infect cutaneous epithelium and cause skin warts; some types infect mucosal epithelium and cause anogenital warts. Skin or anogenital warts are diagnosed based on clinical appearance and are usually treated with topical medications or cytodestructive treatments. Genital warts may persist and spread widely in patients with decreased cell-mediated immunity (eg, due to pregnancy or HIV infection). Some types that infect mucosal epithelium can lead to anogenital or oropharyngeal cancer. Pap tests and/or HPV testing is recommended to screen for cervical cancer and anal cancer in high-risk patients. Vaccines are available to protect against many of the HPV strains that can cause genital warts and cancer.

Topic Resources

- 3D Models (0)
- Audios (0)
- Calculators (0)
- Images (5)
- Tables (0)
- Videos (0)

(See also Overview of Sexually Transmitted Infections.)

HPV is the most common sexually transmitted infection (STI). HPV is so common that 80% of sexually active unvaccinated people get the virus at some point in their life (1). In the US, about 14 million people become newly infected with HPV each year; before the HPV vaccine became available, each year roughly 340,000 to 360,000 patients sought care for genital warts caused by HPV.

Most HPV infections clear spontaneously within 1 to 2 years, but some persist.

General reference

a. 1. Centers for Disease Control and Prevention: Human papillomavirus (HPV). Accessed July 6, 2022.

Etiology of HPV Infection

There are > 100 known types of HPV. Some infect cutaneous epithelium and cause common skin warts. Some infect primarily the mucosa of the anogenital region, as well as the oropharyngeal and laryngeal areas.

Important manifestations of anogenital HPV include

- Genital warts (condyloma acuminatum)
- Intraepithelial neoplasia and carcinoma of the cervix, vulva, vagina, anus, or penis
- Laryngeal and oropharyngeal cancers
- Bowenoid papulosis

Some data suggest HPV plays a role in the pathogenesis of some bladder cancers.

Condylomata acuminata are benign anogenital warts most often caused by HPV types 6 and 11, as are laryngeal and oropharyngeal warts. Low- and high-grade intraepithelial neoplasia and carcinoma may be caused by HPV.

Virtually all cervical cancer is caused by HPV; about 70% is caused by types 16 and 18, and many of the rest result from types 31, 33, 45. 52, and 58 (1). HPV types that affect mainly the anogenital area can be transmitted to the oropharynx by orogenital contact; type 16 appears responsible for many cases of oropharyngeal cancer. HPV types 16 and 18 can also cause cancer in other areas, including the vulva, vagina, anus, and penis.

Pearls & Pitfalls

- Virtually all cervical cancer is caused by human papillomavirus (HPV).

HPV is transmitted from lesions during contact with skin or mucosa. The types that affect the anogenital region are usually transmitted sexually by vaginal or anal intercourse, but digital, oral, and nonpenetrative genital contact may be involved.

Genital warts are more common among immunocompromised patients. Growth rates vary, but pregnancy, immunosuppression, or maceration of the skin may accelerate the growth and spread of warts.

Reference

a. 1. Serrano B, Alemany L, Tous S, et al: Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. *Infect Agent Cancer* 7(1):38, 2012. doi:10.1186/1750-9378-7-38

Symptoms and Signs of HPV Infection

Warts caused by HPV appear after an incubation period of 1 to 6 months.

Visible anogenital warts are usually soft, moist, minute pink or gray polyps (raised lesions) that

- Enlarge
- May become pedunculated
- Have rough surfaces
- May occur in clusters

The warts are usually asymptomatic, but some patients have itching, burning, or discomfort.

In men, warts occur most commonly under the foreskin, on the coronal sulcus, within the urethral meatus, and on the penile shaft. They may occur around the anus and in the rectum, especially in men who have sex with men.

In women, warts occur most commonly on the vulva, vaginal wall, cervix, and perineum; the urethra and anal region may be affected.

HPV types 16 and 18 usually cause endocervical or anal intraepithelial lesions that are difficult to see and diagnose clinically.

Images of Genital Warts

Genital Warts

This photo shows small, soft, pink genital warts on the penile shaft.

Diagnosis of HPV Infection

- Physical examination
- HPV testing
- Cervical, and sometimes anal, cytology (Pap test)
- Sometimes colposcopy, anoscopy, or both

Genital warts are usually diagnosed with gross visual inspection. Their appearance usually differentiates them from condyloma lata of secondary syphilis (which are flat-topped) and from carcinomas. However, serologic tests for syphilis (STS) should be done initially and after 3 months. Biopsies of atypical, bleeding, ulcerated, or persistent warts may be necessary to exclude carcinoma.

Cervical and anal intraepithelial lesions can be visualized only by colposcopy and anoscopy. Applying a 3 to 5% solution of acetic acid for a few minutes before colposcopy causes lesions to whiten and enhances visualization and detection of small lesions. Screening for cervical cancer is discussed elsewhere in THE MANUAL.

In low-resource settings without access to routine Pap tests or colposcopy, screening and evaluation for cervical cancer include HPV testing and/or visual inspection with use of acetic acid or Lugol iodine (1, 2).

Nucleic acid amplification tests (NAATs) for oncogenic HPV subtypes are used as part of routine cervical cancer screening in women. Initial tests typical detect any one of 13 common high-risk types.

Follow-up HPV genotype tests may be done to detect the most high-risk types, typically 16, 18, or 45. No HPV testing for men is available for clinical use.

Clinicians should check for malignant oral lesions potentially caused by HPV during routine examination of the mouth and oral cavity.

Diagnosis references

a. 1. World Health Organization (WHO): Human papillomavirus (HPV) nucleic acid amplification tests (NAATs) to screen for cervical pre-cancer lesions and prevent cervical cancer; policy brief; 16 March 2022

b. 2. International Agency for Research on Cancer: A practical manual on visual screening for cervical neoplasia; Anatomical and pathological basis of visual inspection with acetic acid (VIA) and with Lugol's iodine (VILI). *IARC Technical Publication No. 41*, 2003. ISBN 92 832 2423 X

Treatment of HPV Infection

- Cytodestructive therapy or excision (eg, by caustics, cryotherapy, electrocauterization, laser, or surgical excision)
- Topical medications (eg, with antimitotics or interferon inducers)

No treatment of anogenital warts is completely satisfactory, and relapses are frequent and require retreatment. In immunocompetent patients, genital warts may resolve without treatment. In immunocompromised patients, warts may be less responsive to treatment.

Because no treatment is clearly more efficacious than others, treatment of anogenital warts should be guided by other considerations, mainly wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and the practitioner's experience (see the Centers for Disease Control and Prevention [CDC] 2021 Sexually Transmitted Infections Treatment Guidelines: Anogenital Warts).

Genital warts may be treated with

- Caustics
- Topical medications
- Cryotherapy
- Electrocauterization
- Laser
- Surgical excision

A local or general anesthetic is used depending on the size and number to be removed. Extensive vulvovaginal warts may require laser ablation. For anal warts, removal with a resectoscope may be the most effective treatment; a general anesthetic is used.

Topical treatments include antimitotics (eg, podophyllotoxin, podophyllin, 5-fluorouracil), caustics (eg, trichloroacetic acid), interferon inducers (eg, imiquimod), and sinecatechins (a botanical product

with an unknown mechanism). These are widely used but usually require multiple applications over weeks to months and are frequently ineffective. Before topical treatments are applied, surrounding tissue should be protected with petroleum jelly. Patients should be warned that after treatment, the area may be painful.

Interferon alfa (eg, interferon alfa-2b, interferon alfa-n3), intralesionally or IM, has cleared intractable lesions on the skin and genitals, but optimal administration and long-term effects are unclear. Also, in some patients with bowenoid papulosis of the genitals (caused by type 16 HPV), lesions initially disappeared after treatment with interferon alfa but reappeared as invasive cancers.

By removing the moist underside of the prepuce, circumcision may prevent recurrences in uncircumcised men.

Current sex partners of people with genital warts should be examined and, if infected, treated.

For **intraurethral lesions,** thiotepa (an alkylating medication), instilled in the urethra, is effective. In men, 5-fluorouracil applied 2 to 3 times a day is highly effective for urethral lesions, but rarely, it causes swelling, leading to urethral obstruction. Intraurethral lesions are typically managed by a urologist.

Cervical intraepithelial neoplasia (CIN) is monitored with excisional biopsy.

Vulvar and vaginal intraepithelial neoplasia are treated with surgical excision.

Sex partners of patients with cervical intraepithelial neoplasia or carcinoma and of patients with bowenoid papulosis should be counseled and screened regularly for HPV-related lesions. A similar approach can be used for HPV in the rectum.

Management of cancers caused by HPV is discussed elsewhere in THE MANUAL.

Prevention of HPV Infection

(For more information, see Childhood Vaccination Schedule and Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices.)

A **9-valent vaccine** and a **quadrivalent vaccine** protect against the 2 types of HPV (types 6 and 11) that cause > 90% of visible genital warts. These vaccines also protect against the 2 types of HPV (types 16 and 18) that cause most cervical cancers. The 9-valent vaccine also protects against other types of HPV (types 31, 33, 45, 52, and 58) that cause about 15% of cervical cancers. A **bivalent vaccine** protects against only types 16 and 18.

Only the 9-valent vaccine is available in the US.

The current recommendations from the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control are as follows:

For both females and males up to age 26 years: HPV vaccine is recommended at age 11 or 12 years (can start at age 9 years) and for previously unvaccinated or not adequately vaccinated patients up through age 26 years.

For adults 27 to 45 years: Clinicians should engage in a shared decision-making discussion with patients to determine whether they should be vaccinated.

Because HPV can be transmitted by skin-to-skin contact, condoms do not fully protect against infection.

Key Points

- **Anogenital warts are caused by human papillomavirus (HPV), most commonly types 6 and 11.**
- **HPV types 16 and 18 cause about 70% of cervical cancers and can cause cancer in other areas, including the vulva, vagina, penis, anus, and oropharynx.**
- **Diagnose warts by inspection; HPV testing is available to screen for cervical cancer.**
- **Treat warts with cytodestructive treatments, topical medications, or surgical excision.**
- **Treat cervical, vaginal, vulvar, or anal intraepithelial neoplasia with ablation or excision or manage with close surveillance.**
- **HPV vaccination is recommended for children and young adults.**