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Human Papillomavirus Infection: Epidemiology, Biology, Host Interactions, Cancer Development, Prevention, and Therapeutics

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Abstract

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide. It is caused by the human papillomavirus, a DNA virus that infects epithelial cells in various mucous membranes and skin surfaces. HPV can be categorized into high-risk and low-risk types based on their association with the development of certain cancers. High-risk HPV types, such as HPV-16 and HPV-18, are known to be oncogenic and are strongly associated with the development of cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers. These types of HPV can persist in the body for an extended period and, in some cases, lead to the formation of precancerous lesions that may progress to cancer if left untreated. Low-risk HPV types, such as HPV-6 and HPV-11, are not typically associated with cancer but can cause benign conditions like genital warts. Genital warts are characterized by the growth of small, cauliflower-like bumps on the genital and anal areas. Although not life-threatening, they can cause discomfort and psychological distress. HPV is primarily transmitted through sexual contact, including vaginal, anal, and oral sex. It can also be transmitted through non-penetrative sexual activities that involve skin-to-skin contact. In addition to sexual transmission, vertical transmission from mother to child during childbirth is possible but relatively rare. Prevention of HPV infection includes vaccination and safe sexual practices. HPV vaccines, such as Gardasil and Cervarix, are highly effective in preventing infection with the most common high-risk HPV types. These vaccines are typically administered to adolescents and young adults before they become sexually active. Safe sexual practices, such as consistent and correct condom use and limiting the number of sexual partners, can also reduce the risk of HPV transmission. Diagnosis of HPV infection can be challenging because the infection is often asymptomatic, especially in men. In women, HPV testing can be done through cervical screening programs, which involve the collection of cervical cells for analysis. Abnormal results may lead to further diagnostic procedures, such as colposcopy or biopsy, to detect precancerous or cancerous changes. Overall, HPV infection is a prevalent sexually transmitted infection with significant implications for public health. Vaccination, regular screening, and early treatment of precancerous lesions are key strategies to reduce the burden of HPV-related diseases and their associated complications. Education and awareness about HPV and its prevention are crucial in promoting optimal sexual health. This study aimed to carry out a literature review considering several aspects involving HPV infection: Global distribution, prevalence, biology, host interactions, cancer development, prevention, therapeutics, coinfection with other viruses, coinfection with bacteria, association with head and neck squamous cell carcinomas (HNSCC), and association with anal cancer.

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Abstract

Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide. It is caused by the human papillomavirus, a DNA virus that infects epithelial cells in various mucous membranes and skin surfaces. HPV can be categorized into high-risk and low-risk types based on their association with the development of certain cancers. High-risk HPV types, such as HPV-16 and HPV-18, are known to be oncogenic and are strongly associated with the development of cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers. These types of HPV can persist in the body for an extended period and, in some cases, lead to the formation of precancerous lesions that may progress to cancer if left untreated. Low-risk HPV types, such as HPV-6 and HPV-11, are not typically associated with cancer but can cause benign conditions like genital warts. Genital warts are characterized by the growth of small, cauliflower-like bumps on the genital and anal areas. Although not life-threatening, they can cause discomfort and psychological distress. HPV is primarily transmitted through sexual contact, including vaginal, anal, and oral sex. It can also be transmitted through non-penetrative sexual activities that involve skin-to-skin contact. In addition to sexual transmission, vertical transmission from mother to child during childbirth is possible but relatively rare. Prevention of HPV infection includes vaccination and safe sexual practices. HPV vaccines, such as Gardasil and Cervarix, are highly effective in preventing infection with the most common high-risk HPV types. These vaccines are typically administered to adolescents and young adults before they become sexually active. Safe sexual practices, such as consistent and correct condom use and limiting the number of sexual partners, can also reduce the risk of HPV transmission. Diagnosis of HPV infection can be challenging because the infection is often asymptomatic, especially in men. In women, HPV testing can be done through cervical screening programs, which involve the collection of cervical cells for analysis. Abnormal results may lead to further diagnostic procedures, such as colposcopy or biopsy, to detect precancerous or cancerous changes. Overall, HPV infection is a prevalent sexually transmitted infection with significant implications for public health. Vaccination, regular screening, and early treatment of precancerous lesions are key strategies to reduce the burden of HPV-related diseases and their associated complications. Education and awareness about HPV and its prevention are crucial in promoting optimal sexual health. This study aimed to carry out a literature review considering several aspects involving HPV infection: Global distribution, prevalence, biology, host interactions, cancer development, prevention, therapeutics, coinfection with other viruses, coinfection with bacteria, association with head and neck squamous cell carcinomas (HNSCC), and association with anal cancer.

Keywords: Human papillomavirus; cancers; screening; public health; sexual health; prevention.

Introduction

Papillomaviruses (PV) are a diverse group of viruses that belong to the Papillomaviridae family. They are small, non-enveloped viruses with a circular double-stranded DNA genome. PV are known to infect a wide range of vertebrate species, including humans.[1-6] PV are highly species-specific, meaning that different types of papillomaviruses typically infect specific animal species. For instance, human papillomaviruses (HPV) infect humans, bovine papillomaviruses (BPV) infect cattle, and canine papillomaviruses (CPV) infect dogs.[2,7-11]

HPV are the most extensively studied and clinically significant group of PV in humans. They have more than 200 identified types, and each type is designated with a number (e.g., HPV-16, HPV-18, etc.). HPV can be categorized into low-risk types and high-risk types based on their association with different diseases.[10-13] Low-risk HPV, such as HPV-6 and HPV-11, are associated with the development of benign warts, known as papillomas. These warts commonly occur on the skin and mucous membranes of the anogenital region, including the genitals and anus. They can also appear on other parts of the body, such as the hands and feet. Low-risk HPVs rarely lead to cancer.[3,12-17] High-risk HPV, including HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, and others, have the potential to cause various types of cancer. The most significant

cancer associated with high-risk HPV is cervical cancer, which is the fourth most common cancer in women worldwide. High-risk HPV can also cause other anogenital cancers, such as anal, vaginal, vulvar, and penile cancers. Additionally, they have been linked to a subset of head and neck cancers, particularly oropharyngeal cancer.[3,11,13,16,17]

Transmission of HPV occurs primarily through sexual contact, including vaginal, anal, and oral sex. However, other routes of transmission, such as vertical transmission from mother to child during childbirth or non-sexual skin-to-skin contact, can also contribute to HPV infection.[6,8] HPV infects the basal cells of epithelial tissues, where they establish a persistent infection. Most HPV infections are transient and resolve spontaneously within a couple of years without causing any symptoms or long-term health problems. However, persistent infections with high-risk HPV can lead to abnormal cellular changes, such as precancerous lesions, which may progress to cancer over time.[1,18-22]

Prevention of HPV infections primarily focuses on HPV vaccination and promoting safe sexual practices. HPV vaccines are highly effective in preventing infection with the most common high-risk HPV types and have the potential to reduce the incidence of HPV-related diseases, including cervical cancer.[23-27] Safe sex practices, including condom use and limiting sexual partners, can help reduce the risk of HPV transmission.[16,23-25,27-30] Regular screening, such as cervical cancer screening with Pap smears or HPV testing, is also important for the early detection of abnormal cellular changes and timely intervention.[24-28]

This study aimed to carry out a literature review considering several aspects involving HPV infection: Global distribution, prevalence, biology, host interactions, cancer development, prevention, therapeutics, coinfection with other viruses, coinfection with bacteria, association with head and neck squamous cell carcinomas (HNSCC), and association with anal cancer.

Search strategy

The keywords "HPV global distribution", "HPV prevalence", "HPV biology", "HPV host interactions", "HPV cancer development", "HPV prevention", "HPV therapeutics", "HPV coinfection with other viruses", "HPV coinfection with bacteria", "HPV association with head and neck squamous cell carcinomas", "HPV association with anal cancer" were used with Boolean combinations. The literature search and relevance evaluation were conducted with the databases PubMed, Web of Science, and Google Scholar. Articles found were considered potential reference sources. Searches were performed up to early june 2023.

HPV types global distribution

HPV types have a global distribution, with varying prevalence rates in different regions and populations. Here are some key points regarding the global distribution of HPV types:

High-risk HPV types, particularly HPV-16 and HPV-18, are responsible for the majority of HPV-related cancers worldwide. These include cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers. HPV-16 is the most prevalent high-risk type and accounts for a significant proportion of HPV-associated cancers globally.[11,16,17,29]

The prevalence of specific HPV types can vary across regions due to factors such as geographical location, population demographics, cultural practices, and healthcare infrastructure. For example, certain HPV types may be more prevalent in regions with higher rates of cervical cancer, such as sub-Saharan Africa, parts of Asia, and Latin America. In contrast, other regions may have higher rates of HPV-associated oropharyngeal cancers, such as North America and Western Europe.[3,13-17]

Low-risk HPV types, such as HPV-6 and HPV-11, are commonly associated with genital warts. The prevalence of specific low-risk types can also vary geographically, but they are generally less frequently studied compared to high-risk types due to their lower association with cancer.[3,12,16,29]

HPV vaccination programs have been implemented in many countries to prevent HPV infections and related diseases. The impact of vaccination on HPV type distribution is influenced by several factors, including the vaccine coverage rate, targeted HPV types, and vaccine efficacy. HPV vaccines primarily target the most

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common high-risk types, including HPV-16 and HPV-18. As vaccination programs continue to expand, the distribution of HPV types may shift over time.[23,24,26,30-35]

HPV-related diseases, particularly cervical cancer, pose a significant global burden. Cervical cancer is a leading cause of cancer-related mortality among women in many low- and middle-income countries. The burden of HPV-associated diseases extends beyond cervical cancer to include other HPV-related cancers and genital warts. Efforts to increase HPV vaccination coverage and improve access to screening and treatment services are crucial for reducing the global burden of HPV-related diseases.[12,16,29,36]

HPV prevalence worldwide

The prevalence of specific HPV types can vary across countries and regions (**Figure 1**) due to various factors, including population demographics, sexual behavior, healthcare infrastructure, and vaccination programs.[12] Here is a general overview of HPV types' prevalence in different countries:

HPV-16 and HPV-18 are the most prevalent worldwide and are responsible for the majority of HPV-related cancers. They are commonly found in cervical, anal, vaginal, vulvar, penile, and oropharyngeal cancers.[14,17,37,38]

Sub-Saharan Africa has some of the highest cervical cancer incidence rates in the world, with HPV-16 and HPV-18 being the most prevalent types. Other high-risk types, such as HPV-31, HPV-35, and HPV-45, are also commonly found.[14,17,37,38]

The prevalence of HPV types in Asia can vary across countries. HPV-16 and HPV-18 are generally the most prevalent high-risk types in cervical cancer cases. However, some countries may have a higher prevalence of other high-risk types, such as HPV-58 in China and HPV-52 in Japan.[1,13,14,17,35,37,38]

HPV-type distribution in Europe can vary between countries. HPV-16 and HPV-18 are the most prevalent types in cervical cancer cases, but there can be variations in the prevalence of other high-risk types. For example, HPV-31, HPV-33, and HPV-45 are also commonly found in some European countries.[1,13,14,37,38]

HPV-16 is the most prevalent type of HPV-related cancer in North America, including cervical and oropharyngeal cancers. HPV-18 is also common but to a lesser extent. Other high-risk types, such as HPV-31, HPV-33, and HPV-45, are prevalent but less frequent compared to HPV-16 and HPV-18.[13,14,35,37,38]

The prevalence of HPV types in Latin America varies across countries. HPV-16 and HPV-18 are generally the most common types of cervical cancer cases. However, other high-risk types, such as HPV-31, HPV-33, and HPV-45, can also be prevalent in certain countries.[13,14,37,38]

Australia and New Zealand have implemented successful HPV vaccination programs. As a result, the prevalence of HPV-16 and HPV-18 has decreased significantly, contributing to a reduction in HPV-related diseases, including cervical cancer.[14,17,37,38]

HPV biology

HPV are a group of small, double-stranded DNA viruses that infect the epithelial cells of the skin and mucous membranes in humans and animals. They are named after the warts (papillomas) that can form as a result of infection. HPV infections are extremely common, with over 200 different types of HPV identified to date.[12,39]

HPV has a non-enveloped icosahedral capsid composed of proteins called capsomeres. The viral genome is a circular, double-stranded DNA molecule.[12,39,40] The viral life cycle begins when the virus enters the host cell through a microtrauma or breach in the epithelial barrier. The virus attaches to the host cell surface receptors and enters the cell by endocytosis. Once inside, the viral genome is released into the host cell's nucleus.[10,12,40]

HPV replicate their DNA in synchrony with the host cell's DNA replication. The viral genome is replicated by the host cell machinery, using viral proteins. Viral DNA replication is tightly regulated to ensure that viral

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gene expression occurs at specific stages of the host cell cycle.[7,12,39,40] HPV has a limited coding capacity and relies on the host cell's machinery for gene expression. They produce two types of genes: early genes and late genes. Early genes are expressed during the initial phase of infection and are involved in regulating viral replication and modulating host cell functions. Late genes are expressed later in the infection cycle and encode structural proteins that form the viral capsid.[39,40]

Most HPV infections are cleared by the immune system without causing any symptoms. However, certain high-risk HPV types can establish persistent infections, which can lead to the development of various types of cancer, including cervical, anal, penile, vaginal, and oropharyngeal cancers. The expression of viral oncoproteins, such as E6 and E7, plays a crucial role in the transformation of infected cells and the development of cancer.[7,12,39,40]

HPV-host interactions

HPV enters the host cells through microtraumas or breaches in the epithelial barrier. The virus attaches to the host cell surface receptors, which can include heparan sulfate proteoglycans and specific cellular receptors such as alpha-6 integrin. These interactions facilitate the internalization of the virus into the host cell.[12,19,20,22,40-42]

HPV has evolved strategies to evade the host immune response. The virus can inhibit interferon signaling, interfere with antigen presentation, and modulate immune cell functions. By evading immune detection and clearance, HPV can establish persistent infections and increase the risk of disease progression.[12,19,22,42]

Once inside the host cell, HPV relies on the host cell machinery for gene expression. The viral genome is replicated and transcribed using host cell enzymes. The expression of viral genes is tightly regulated to ensure that specific viral proteins are produced at different stages of the infection cycle.[9,19,20,40-44]

High-risk HPV types, such as HPV16 and HPV18, can cause cellular transformation, leading to the development of cancer. The viral oncoproteins E6 and E7 play a critical role in this process. E6 proteins can bind and degrade p53, a tumor suppressor protein that regulates cell cycle arrest and DNA repair. E7 proteins bind and inactivate retinoblastoma (Rb) protein, which regulates cell cycle progression. Dysregulation of these key cellular processes by viral oncoproteins can lead to uncontrolled cell proliferation and the formation of tumors.[9,12,20,22,40-44]

HPV replicates its DNA in synchrony with the host cell's DNA replication machinery. The viral genome utilizes host cell factors and enzymes to replicate its DNA during S phase of the cell cycle. The virus has mechanisms to ensure proper timing and coordination between viral and host DNA replication.[7,9,12,21,39]

HPV infections are typically associated with the differentiation of epithelial cells. As infected cells move toward the upper layers of the epithelium and differentiate, viral gene expression changes. Late viral genes, which encode structural proteins, are expressed, leading to the production of new viral particles.[2,9,20-22,41-43]

The host immune response plays a critical role in controlling HPV infection. Both innate and adaptive immune responses are involved in recognizing and eliminating HPV-infected cells. Immune cells, such as cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and antigen-presenting cells (APCs), are involved in recognizing and clearing infected cells.[9,12,22,29,42,44]

HPV cancer development

HPV are known to play a significant role in the development of certain types of cancer. Persistent infection with high-risk HPV types, particularly HPV16 and HPV18, is strongly associated with the development of cervical, anal, penile, vaginal, vulvar, and oropharyngeal cancers.[18,45,29,45-48]

During persistent infection, the HPV genome can integrate into the host cell's DNA. Integration disrupts the viral life cycle and alters the expression of viral genes. Integration often occurs in regions of the viral genome that encode the E6 and E7 oncoproteins (Aksoy et al., 2017). The E6 oncoprotein of high-risk HPV types has several functions that contribute to cancer development. E6 binds to and degrades the p53

tumor suppressor protein, which is involved in cell cycle regulation, DNA repair, and apoptosis. Loss of p53 function allows infected cells with damaged DNA to survive and proliferate.[12,43,46-48] The E7 oncoprotein of high-risk HPV types interacts with and inactivates the retinoblastoma (Rb) tumor suppressor protein. Rb normally prevents cell cycle progression from G1 to S phase. Inactivation of Rb by E7 disrupts cell cycle regulation and promotes uncontrolled cell proliferation.[12,43,47,48]

The combined effects of E6 and E7 oncoproteins can lead to cell transformation, characterized by uncontrolled cell growth and the formation of precancerous lesions. Infected cells lose their ability to undergo normal differentiation and acquire genetic and epigenetic alterations that contribute to malignant progression.[43,48-50] HPV oncoproteins can interact with various host cell factors and signaling pathways, promoting cell survival, proliferation, and immune evasion. For example, E6 and E7 can modulate the activities of cellular proteins involved in DNA repair, apoptosis, cell adhesion, and immune response.[2,19,20,40,43,44]

HPV infection triggers an immune response, including the recruitment of immune cells to the site of infection. However, high-risk HPV types have developed mechanisms to evade immune detection and clearance. Persistent infection can lead to chronic inflammation, which promotes the survival and growth of infected cells and contributes to cancer development (**Figure 2**).[2,44,43,48]

HPV-associated precancerous lesions, such as cervical intraepithelial neoplasia (CIN), can progress to invasive cancer if left untreated. The accumulation of additional genetic alterations, such as mutations in tumor suppressor genes or activation of oncogenes, can drive the progression from premalignant lesions to invasive cancer.[12,29,46-48]

HPV prevention

HPV vaccines are highly effective in preventing infection with the most common high-risk HPV types that cause cervical and other HPV-related cancers. Vaccines are typically administered in a series of doses, and it is recommended to receive the vaccine before becoming sexually active. The vaccines are most effective when given to individuals who have not been exposed to the virus. Vaccination is recommended for both males and females. It is important to consult with healthcare professionals to determine the appropriate vaccination schedule and options.[24-26,31-35]

Practicing safe sex can reduce the risk of HPV transmission. Consistent and correct use of male or female condoms can provide some protection, although they may not cover all potentially infected areas. It's important to note that HPV can infect areas not covered by condoms, so the risk of transmission can still exist. Limiting the number of sexual partners and engaging in a mutually monogamous relationship with an uninfected partner can also help reduce the risk of HPV transmission.[16,23-25,27-30]

Regular screening for HPV-related cancers, such as cervical cancer, is crucial for early detection and treatment. Pap smears, also known as Pap tests, are commonly used to detect abnormal cervical cells. HPV DNA testing can also be used as a screening tool. Individuals need to follow the recommended screening guidelines and consult with healthcare professionals for appropriate screening options and schedules.[24-28]

Raising awareness and providing accurate information about HPV, its transmission, associated diseases, and prevention methods is essential. Educating individuals, parents, and healthcare professionals about the benefits of HPV vaccination, safe sexual practices, and regular screening can help promote prevention efforts and reduce HPV-related diseases.[16,24-28,34]

HPV vaccination is most effective when administered before exposure to the virus. Vaccination programs often target preadolescents and adolescents, generally between the ages of 9 and 14. The immune response to the vaccine is typically stronger and more effective in this age group. However, vaccination can still be beneficial for individuals who are older or have already been exposed to HPV, as they may not have been infected with all vaccine-preventable HPV types.[25,31-35,52-54]

Widespread HPV vaccination can lead to herd immunity, which occurs when a significant proportion of the population is immune to the virus, reducing the overall transmission of HPV. By vaccinating a large portion

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of the population, including both males and females, the spread of the virus can be significantly reduced, protecting those who have not been vaccinated.[2,26,52,33,35,52]

HPV therapeutics

Various treatment modalities can be used to manage HPV-related lesions, such as genital warts or precancerous lesions. Topical medications, such as imiquimod, podophyllotoxin, or sinecatechins, can be applied directly to the affected area to help eliminate warts or reduce the size and appearance of lesions.[10,32,55-57]

Freezing the warts with liquid nitrogen can destroy the affected tissue. In some cases, surgical procedures like excision, electrocautery, or laser therapy may be performed to remove warts or precancerous lesions. Certain chemicals, such as trichloroacetic acid (TCA) or bichloroacetic acid (BCA), can be applied to the lesions to destroy the affected tissue.[55,57]

Surgical removal of the cancerous tissue is a common treatment approach. The extent of surgery depends on the stage and location of cancer. High-energy X-rays or other radiation sources are used to target and destroy cancer cells. Radiation therapy can be used alone or in combination with surgery or chemotherapy.[10,55-57]

Anti-cancer drugs can be administered systemically or directly to the affected area to kill cancer cells or inhibit their growth. Chemotherapy may be used alone or in combination with surgery or radiation therapy.[10,32,55-58] Targeted therapies, such as immune checkpoint inhibitors or specific molecular targeted drugs, may be used in certain cases to block the growth signals of cancer cells or enhance the immune response against the tumor.[59-62]

HPV-related cancers can be responsive to immunotherapy approaches. Therapies such as immune checkpoint inhibitors, which block proteins that inhibit the immune response, can help unleash the immune system's ability to recognize and attack cancer cells. Therapeutic vaccines are also being investigated to boost the immune response against HPV-infected cells. [59,62,63]

HPV coinfection with other viruses

HPV infections can occur concurrently with other viral infections. Coinfection refers to the presence of multiple viral infections in the same individual.[65,66] Here are some examples of HPV coinfection with other viruses:

Human Immunodeficiency Virus (HIV): HIV-positive individuals have a higher prevalence of HPV infection and are more susceptible to persistent and high-risk HPV infections. The weakened immune system in HIV-infected individuals increases the risk of HPV-related diseases, such as cervical cancer and anal cancer.[67-73]

Herpes Simplex Virus (HSV): Coinfection of HPV with HSV, particularly HSV-2, has been observed in some studies. Both HPV and HSV can cause genital lesions, and their presence together can complicate diagnosis and management.[67,73-75]

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV): Some studies have reported an association between HPV infection and chronic HBV or HCV infection. Coinfection with HPV and these hepatitis viruses may increase the risk of developing liver cancer.[73,76]

Epstein-Barr Virus (EBV): Coinfection of HPV with EBV has been observed in some cases, particularly in certain HPV-related cancers, such as nasopharyngeal carcinoma. The presence of both viruses may contribute to the development and progression of these cancers.[73,77-81]

Cytomegalovirus (CMV): Coinfection of HPV with CMV has been reported in various studies. Although the significance of this coinfection is not fully understood, it may influence the progression and severity of HPV-associated diseases.[73,81]

Human T-cell Lymphotropic Virus (HTLV): Coinfection of HPV with HTLV-1 has been documented in certain populations, particularly in areas with a high prevalence of HTLV-1 infection. The presence of HTLV-1 may influence the development and progression of HPV-related diseases.[73,76]

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It is important to note that coinfection with other viruses can impact the clinical course, treatment outcomes, and prognosis of HPV-associated diseases. It may also have implications for transmission dynamics and response to therapeutic interventions. Individuals with HPV infection should be screened and managed for other viral infections as appropriate, particularly if they have risk factors or belong to populations with a higher prevalence of these coinfections.[65]

HPV coinfection with bacteria

HPV infections can also occur concurrently with bacterial infections. Coinfection refers to the presence of multiple infections, in this case, both HPV and bacteria, in the same individual. While the focus of HPV infection is primarily on viral interactions, the presence of bacteria can influence the clinical course and outcomes of HPV-related diseases.[82-86]

Chlamydia trachomatis is a bacterial pathogen that can cause sexually transmitted infections. Studies have reported an association between HPV infection and concurrent *Chlamydia trachomatis*infection. Coinfection with *Chlamydia trachomatis* may enhance HPV persistence and increase the risk of HPV-related complications, such as cervical dysplasia and cervical cancer.[82-85,87]

Mycoplasma genitalium is another bacterial pathogen associated with sexually transmitted infections. Some studies have suggested an association between *Mycoplasma genitalium* infection and HPV infection, particularly in individuals with persistent HPV infections. Coinfection with *Mycoplasma genitalium* may influence the persistence and progression of HPV-related diseases.[87,88]

Group B Streptococcus (GBS) is a bacterium commonly associated with genital tract colonization and infections in women. Limited studies have suggested an association between GBS colonization and HPV infection. However, the clinical significance and impact of this coinfection on HPV-related diseases are not well established.[87,89]

Bacterial vaginosis (BV) is characterized by an imbalance of vaginal microbiota, with a decrease in *Lactobacillus species* and an increase in various bacteria. Some studies have shown an association between BV and HPV infection, particularly high-risk HPV types. BV may create an environment that favors HPV persistence and progression to cervical dysplasia.[87,90,91]

While less studied, other bacterial infections, such as *Neisseria gonorrhoeae* and *Haemophilus ducreyi* , have been reported in association with HPV infection. These coinfections may impact the clinical course, progression, and treatment outcomes of HPV-related diseases.[87,92]

HPV associated HNSCC

HPV infection is a known risk factor for a subset of head and neck squamous cell carcinomas (HNSCC). HNSCC refers to cancers that arise in the squamous cells lining the mucosal surfaces of the head and neck region, including the oral cavity, oropharynx, larynx, and hypopharynx.[93-103] HPV-associated HNSCC primarily involves the oropharynx, which includes the tonsils, base of the tongue, and the soft palate. The most prevalent HPV types associated with HNSCC are HPV16 and, to a lesser extent, HPV18. These high-risk HPV types are known to have oncogenic potential and can contribute to the development of cancer.[100-103] The incidence of HPV-related HNSCC has been increasing over the past few decades, particularly in younger individuals and those without traditional risk factors such as tobacco and alcohol use. It is estimated that approximately 70-80% of oropharyngeal cancers are associated with HPV infection.[100-104]

HPV-associated HNSCC is primarily linked to sexual transmission, particularly through oral-genital contact. It has been suggested that performing oral sex on an HPV-infected individual may increase the risk of acquiring HPV infection in the oral cavity and subsequently developing HPV-related HNSCC.[93-103]

The oncogenic potential of HPV in HNSCC is mainly attributed to the expression of the viral oncoproteins E6 and E7. These oncoproteins interfere with cellular regulatory mechanisms, promoting uncontrolled cell growth, inhibiting cell cycle control, and evading immune responses. The disruption of tumor suppres-

sor proteins, such as p53 and pRb, by HPV oncoproteins contributes to the malignant transformation of cells.[102-104]

HPV-related HNSCC often presents with distinct clinical and pathological characteristics compared to non-HPV-related HNSCC. Patients with HPV-associated tumors tend to be younger, have a better response to treatment, and have a more favorable prognosis compared to those with non-HPV-related HNSCC.[100-103]

HPV status in HNSCC is typically determined by detecting HPV DNA or by assessing the expression of specific viral proteins, such as p16. The presence of HPV in the tumor is associated with improved overall survival and disease-free survival rates in patients with HNSCC, particularly in oropharyngeal cancers. HPV status is considered an important prognostic factor and may influence treatment decisions.[100,103]

The treatment of HPV-related HNSCC follows similar principles as non-HPV-related HNSCC. Treatment options may include surgery, radiation therapy, chemotherapy, or a combination of these modalities, depending on the stage and extent of the disease. HPV-positive tumors may have a better response to treatment and may require less aggressive therapy compared to HPV-negative tumors.[100,103,105]

HPV anal cancers

HPV infection is a significant risk factor for the development of anal cancer. Anal cancer refers to cancer that arises in the tissues of the anus, which is the opening at the end of the rectum.[106-113] The majority of anal cancers are caused by persistent infection with high-risk HPV types, particularly HPV16 and HPV18. These HPV types have oncogenic potential and can lead to the development of cancerous cells in the anal region.[106,108,113]

HPV-associated anal cancer is primarily linked to sexual transmission, including both heterosexual and homosexual activity. The risk of acquiring HPV infection and subsequent anal cancer is increased by engaging in anal sex, having multiple sexual partners, and having a history of other sexually transmitted infections.[108,113] Certain populations have a higher risk of developing HPV-associated anal cancer. This includes men who have sex with men (MSM), individuals with a history of receptive anal intercourse, individuals with a weakened immune system (such as those with HIV/AIDS), and individuals with a history of other HPV-related diseases, such as cervical or genital warts.[106-113]

Before the development of anal cancer, precancerous lesions known as anal intraepithelial neoplasia (AIN) may be present. AIN can progress from low-grade to high-grade dysplasia, indicating increasing severity of abnormal cell growth. If left untreated, high-grade AIN can progress to invasive anal cancer.[108,113] The symptoms of anal cancer may include anal bleeding, pain, itching, a lump or mass in the anal area, changes in bowel habits, and discharge. However, these symptoms can also be caused by other conditions, so it is important to consult a healthcare professional for accurate diagnosis.[108,111,113]

The diagnosis of anal cancer involves various tests, including a physical examination, anal cytology (Pap smear), and biopsy of suspicious lesions. Staging is important to determine the extent of the cancer and guide treatment decisions. Imaging tests, such as computed tomography (CT) scans and magnetic resonance imaging (MRI), may be performed to assess the spread of the cancer to nearby lymph nodes or other organs.[106-113] Treatment options for anal cancer may include a combination of surgery, radiation therapy, and chemotherapy. The specific treatment approach depends on the stage and location of the cancer. Multidisciplinary care involving oncologists, surgeons, and radiation oncologists is often recommended for optimal treatment outcomes.[106,108,113]

HPV vaccination, practicing safe sex, and regular screening are important preventive measures for anal cancer. HPV vaccination can help prevent HPV infection and reduce the risk of developing HPV-related cancers, including anal cancer. Safe sexual practices, such as using condoms and limiting the number of sexual partners, can help reduce the risk of HPV transmission. Regular screening, including anal Pap smears and high-resolution anoscopy (HRA) in high-risk individuals, can detect precancerous lesions and allow for early intervention.[25,27,28,113]

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Conclusion

HPV infection is a common sexually transmitted infection that can have serious health implications. It is caused by various types of HPV, with high-risk types being strongly associated with the development of certain cancers, particularly cervical cancer. Low-risk types are responsible for benign conditions like genital warts. Prevention is a crucial aspect of managing HPV infection. Vaccination against HPV is highly effective in preventing infection with the most common high-risk types and should be administered before individuals become sexually active. Safe sexual practices, such as consistent condom use and limiting the number of sexual partners, also play a role in reducing the risk of transmission.

Early detection through regular screening is vital in identifying and treating precancerous lesions or detecting cancer at an early stage. Cervical screening programs are particularly important for women, but it is essential to raise awareness about HPV and encourage both men and women to seek appropriate healthcare. Public health efforts should focus on education, awareness, and access to vaccination and screening programs. By implementing comprehensive strategies that encompass vaccination, safe sexual practices, and early detection, we can significantly reduce the burden of HPV-related diseases and improve overall sexual health. It is worth noting that while this information provides an overview of papillomaviruses, the specific details and scientific understanding of HPV continue to evolve as research progresses.

Authorship

Jonas Wolf designed the study. Jonas Wolf wrote the first draft of the manuscript and contributed to the literature review and discussion of the results.

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Conflicts of interest

The author declare no conflicts of interest.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study

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