Review: Human papillomavirus (HPV)

Dhuha Abdullah[1]

1 Jabir ibn Hayyan Medical University

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

The human papillomavirus, or HPV, is a virus that can infect both men and women in various body areas. There are more than a hundred varieties of HPV. There are high-risk and low-risk varieties. Infections with the human papillomavirus (HPV) are highly frequent. There are over a hundred varieties of HPV. On the hands and feet, several HPVs can result in warts. Other HPVs can cause genital warts, infections, or malignancies, such as cervical and genital cancer and cancer of the back of the throat. These diseases can also be contracted through sexual activity.

Dhuha Abdullah Kadhim*

Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Faculty of Medicine

*Corresponding author. E-mail: dhuha.a.kadhum@jmu.edu.iq

Keywords: HPV, Genital, Cervix, Papilloma.

Etiology

A member of the Papovaviridae family, HPV is a tiny, nonenveloped, epitheliotropic, ds, circular DNA with a diameter of 55 nm. Through disruption of the cutaneous and mucosa, the virus enters the epithelium and infects basal stem cells (mucosal epithelium), leading to benign lesions such as warts (cutaneous, plantar, flat, anal, genital, and laryngeal) or a variety of malignancies (uterus, penis, and vulva cancers). According to Araldi et al. (2018), the virus's genome includes two late (L) phase genes and seven early (E) phase genes. According to Soheili et al. (2021), HPVs are classified into 5 genera, namely alpha, beta, gamma, mu, and nu, rely on L1 protein. Those genera included more than 200 varieties that are dispersed throughout various geographic regions.

The words "papilla" and "oma" are combined to form the word "papilloma." The Latin word papilla (papilla on the tongue) refers to a rounded, tiny protuberance on an organ or part of the body, and the word oma (oma) refers to any irregular

development, including tumors (carcinoma).

The three regions that make up the HPV genome are the late (L) region, which encodes the structural proteins of the virus, the early (E) region, which encodes proteins necessary for viral gene expression, replication, and survival, and the long control region (LCR), which controls viral gene expression and replication. The first expression stage of these proteins is denoted by the labels E and L, which correspond to the viral life cycle stage. The HPV cycle primarily produces the oncogenic proteins E6 and E7. According to Surriabre et al. (2019), the products of these genes bind to tumor suppressor genes and inactivate them, disrupting the host cell cycle.

Types of Human papillomavirus

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection that can infect the vaginal areas, mouth and throat of females and males. There are over a hundred varieties of HPV. Depending on how likely they are to cause cancer, HPV may be categorized as high-, low-, and moderate-risk. It's critical to realize that HPV by itself cannot cause cancer; rather, it needs to be combined with other risk factors such as pregnancy, immunosuppression, UV radiation exposure, smoking, and folate deficiency (Hirth, 2019).

Fifteen HPV strains, including those listed as "high risk," have been linked to high-grade intraepithelial lesions that can develop into cancer or malignancies (18, 31, 16, 33, 39, 35, 52, 51, 45, 58, 59, 56, 82, 68, and 73). Three categories, 66, 26, and 53, are classified as "moderate risk." According to Doorbar et al. (2012), the 12 types are categorized as "lower risk" since they are associated with condylomata formation and low-grade precancerous lesions. These are 81, 61, 11, 70, 40, 44, 6, 43, 72, 54, CP6108, and 70.

HPV types 6 or 11, which result in genital warts, and kinds 1, which cause cutaneous warts. Furthermore, HPV strains 6 and 11 cause laryngeal papillomas, which are upper infections of the respiratory tract.Depending on when it first manifests, the condition can manifest as either juvenile or adult papillomatosis. According to Tamataki et al. (2007), contact with an infected mother's vaginal canal after childbirth is typically the means of transmission for the juvenile form. According to Bouvard et al. (2009), HPV "high-risk" varieties have been linked to the development of head and neck cancers as well as vaginal, anal, and penile cancers in both men and women.

Risk classification	HPV types
High-risk	16, 18, 31, 33, 35 39, 45, 51, 52, 56 58, 59, 68, 73, 82
Probable high-risk	26, 53, 66
Low risk	6, 11, 40, 42, 43, 44 54, 61, 70, 72, 81, CP6108
Undetermined risk	34, 57, 83

Table 1. HPV infection types (Munoz et al., 2003).

Life cycle HPVs

Life cycle Because HPVs are epitheliotropic in particular, Within stratified squamous epithelia, their life cycle takes place. Entry It is believed that HPV enters the body through piercing microtraumas in the epithelia, with the basal cells acting as the virus's intended target cells. How the virus accesses the basal cells is still a mystery to us. The subsequent phases of life cycle are categorized as production, maintenance, and establishment. Viral DNA replication requires the transcription of genes encoding the E1 and E2 proteins, which are transcribed once HPVs enter the cell through endocytosis and are delivered to the nucleus. Six proteins are produced as a result of this: E1, E2, E4, E5, E6and E7. Tumor suppressor proteins p53 and retinoblastoma protein (pRb) are suppressed during carcinogenesis due to the production of E6 and E7. Cancer may also develop spontaneously as a result of episomal expressions E2, E4, and E5. (Graham, 2017).

The HPV replication cycle is thought to start when the virus enters the basal layer cells of the epithelium, typically through a microtrauma or slight abrasion of the epidermis. Once within the host cell, basal cells develop and move toward the surface of the epithelium, where HPV DNA replicates. Because HPVs only encode 8–10 proteins, host cell factors are needed to control the transcription and replication of HPV. Host cell factors interact with HPV genome's LCR region to initiate transcription of the virus's E6 and E7 genes, which starts HPV replication (Syrjänen & Syrjänen, 1999).

Transmission

HPV is a widespread pathogen that affects both sexes, with HPV infections thought to be the majority common STD. But during childbirth, the virus can also spread vertically, from mother to child. Even if a person does not exhibit any symptoms, skin-to-skin contact with an infected individual can transmit the majority of HPV strains. During vaginal, penile, oral, or anal sex, the HPV kinds that cause cancer are frequently transmitted (Merckx et al., 2013). Seminal fluid, placenta, amniotic fluid, umbilical blood, breast milk and spermatozoa have all been linked to HPV (Araldi et al., 2018).

Although HPV 16 remains infectious on wet surfaces for 7 days (Petca et al., 2020). HPV have been discovered in raw

and sewage sludge, there has never been evidence of HPV transmission by water. In 50% of the home bathing water samples, HPV was found (Di Bonito et al., 2015).

Immunity

HPV infection causes both humoral and cellular immune responses, and the development of anti-HPV antibodies is necessary to prevent the virus's propagation and reinfection. Furthermore, research has demonstrated that most HPV infections were eradicated by the cell-mediated immune response within a year and a half of exposure (Deligeoroglou et al., 2013).

Clinical Feature of HPV

Infection with HPV is symptomatic of genital warts. Genital warts are flat growths or lumps that resemble little cauliflowers. They can occur weeks or months after sexual contact with an infected partner and are often painless, itchy, and occasionally bleed. They are located in the anus or vagina, the buttocks, the groin, and the genitalia. Seldom do they reside in the mouth. The majority of HPV infections don't cause any symptoms or clinical illness. Clinical manifestations of HPV infection include anogenital warts, recurrent respiratory papillomatosis, cervical intraepithelial neoplasia, and cancers such as oropharyngeal, cervical, anal, vaginal, vulvar, and penile. Three weeks to eight months is the incubation phase, and two to three months is the clinical manifestation (Stanley, 2010).

Types of infections caused by HPV

1. Oropharyngeal Cancer

   The majority of throat malignancies, including those of the tonsils and base of the tongue, are linked to HPV. These are the most prevalent malignancies in men linked to HPV. Oropharyngeal cancers are also known to be caused by HPV ranging from 6- 71 percent (Stein et al., 2015).
2. Anal Cancer

   It is more prevalent among men who engage in male-to-male sexual relations, those who have experienced vulvar or cervical cancer, those who are HIV-positive, and those who have undergone organ transplantation. Eighty to ninety percent of anal squamous cell malignancies are linked to HPV infection, and most anal cancers linked to HPV are associated with HPV strains 16 and 18. According to de Martel (2017), HPV infection is responsible for almost half of penile cancer cases.
3. Penile Cancer

   guys with HIV and those who have intercourse with other guys are more likely to experience it. According to de Martel (2017), HPV infection is responsible for almost half of penile cancer cases.
4. Cervical Cancer

HPV infectivity is cause of all forms of cervical cancer. Both, HPV18 and HPV16 infections are determined to cause of 70% of cervical malignancies. remains one of the most frequent malignancies affecting women globally, with an expected 570,000 new cases and 311,000 deaths in 2018 (Arbyn et al., 2020). The most common HPV-related neoplasm among women under 65 is cervical cancer, which ranks second in terms of tumor death among these women, accounting for approximately 300,000 deaths yearly (WHO, 2021).Cervical cancer is the second most frequent cancer in women worldwide after breast cancer, accounting for over 500.000 cases. It is also the fifth most deadly cancer in women, resulting in about 275.000 deaths annually worldwide (Schiffman et al.,2007)

5. Warts

   Generally speaking, warts accompany all forms of HPV infections. People commonly have warts that are not malignant. Warts are caused by HPV2, HPV27, and HPV57, but not by types 2, 1, or 63. According to Koning et al. (2014), there are four different types of warts: flat warts, which are found in the foreheads, faces, and arms; plantar warts, which are located in the soles of the feet; and common warts, which are found in the hands, knees, elbows, and fingernails.

6. Respiratory Papillomatosis

   Respiratory papillomatosis is the name for the existence of warts in the respiratory tract, include the larynx. Respiratory papillomatosis is cause by HPV6 and HPV11. One way that respiratory papillomatosis spreads is through inhalation (Sinal and Woods, 2005).

7. Epidermodysplasia Verruciformis

   Tree man disease, also known as epidermodysplasia verruciformis, is caused by an autosomal recessive gene defect that, when combined with HPV infection, increases the likelihood of developing high-risk skin cancer (Lazarczyk et al., 2008).

8. Lung Cancer

   Both benign and malignant cancers in the upper respiratory tract can be brought on by HPV. Many cases of lung cancer include HPV antibody detection (AACR, 2011).

Epidemiology

Because many HPV infections are asymptomatic, diverse strains appear differently, and disease progression takes time, surveillance of HPV is complicated. Large cross-sectional studies provide data on the incidence of high-risk HPV infection before the HPV vaccination program was implemented in 2008. Women with abnormal cytology reported increased prevalence rates of all HPV types, especially HPV 16 and 18. (Howell-Jones et al., 2010).

Large cross-sectional studies provide data on the incidence of high-risk HPV infection before the HPV vaccination program was implemented in 2008. According to a UK prevalence research conducted on an unselected sample, HPV infections were quite rare in girls under the age of 14, but they started to rise dramatically in the mid-teens. According to Jit et al. (2007), among women aged 10 to 29, 11%, 3%, 12%, and 5%, respectively, exhibited serological evidence of HPV types 6, 11, 16, or 18. Geographical areas and demographic groupings exhibit significant variations in HPV infection

rates. At some point in their lives, 90% of the general population will get HPV. Young women are most likely to contract HPV shortly after starting a sexual relationship (Chesson et al., 2014).

In Australia, the frequency of anal and tonsillar cancers linked to HPV had been rising in men while being relatively consistent in women. Despite HPV-associated malignancies in males is lower than in females. Men who engage in sexual activity with other men are particularly vulnerable, as the prevalence of vaccine-type HPV is more than 4 times higher than heterosexual men. According to estimates, males who have sex with men in Australia are more likely to develop anal cancer than women who had cervical cancer before the cervical screening program was implemented (Wei et al., 2021).

According to reports, the prevalence of HPV types 16/18 in North America is 66% in men and 53% in women (Steinau et al., 2014). That an expected 570,000 new cases and 311,000 deaths from the disease in 2018, cervical cancer is one of majority common cancers among women worldwide (Arbyn et al., 2020). Less frequently, anogenital and head and neck malignancies are linked to HPV. About 1,550 instances of vaginal and vulval malignancies and 710 cases of penile cancer occur in England annually. In 2017, 510 men and 980 women were diagnosed with anal cancer (National Statistics, 2019).

Reservoir

The only natural HPV reservoir is humans. A variety of species are impacted by different members of the HPV family.

Risk Factors

The majority of risk factors for HPV infection are associated with sexual activity, such as having more lifetime and recent sexual partners. Other risk factors, such as co-infection with HIV, younger age at sexual initiation, greater number of pregnancies, genetic factors, smoking, age less than 25 years (in females only), and non-circumcision of the male partner, are less consistent with the findings of epidemiologic studies (Yanofsky et al., 2012).

Pathophysiology

The basal epithelium is the site of HPV infection. Despite a high prevalence of infection, most infections go away on their own in a year or two. The most significant risk factor for the development of cervical cancer is persistent infection, which affects only a tiny percentage of those who are infected.

Diagnosed of HPV

HPV is not cultivated using traditional techniques. The most popular test for identifying abnormal cells on the cervix and HPV infection is the Pap test. Your doctor may diagnose you with genital warts based on a physical examination and your medical history. Although HPV nucleic acid testing is less specific than cytology, it is more sensitive than the latter. The

mainly utilized HPV serologic assays are enzyme immunoassays based on virus-like particles (VLPs). Furthermore, histological data from a cervical biopsy guided by a colposcopy can be used to inform treatment decisions (Saraiya et al., 2013).

Prevention by Vaccines

Though not all genotypes are linked to cancer, HPV infections typically resolve on their own after a year or two. The most efficient and economical means of prevention are vaccinations. There are three different vaccines available to stop HPV infections. Cervarix, Gardasil, and Gardasil 9 are these. They can provide protection against HPV16 and HPV18, and the recombinant vaccine Gardasil can also provide protection against HPV6 and HPV11. Targeting HPV 16 and 18, cervarix (bivalent type) is made from the protein present in the capsid (L1) by VLPs, or virus-like particles that resemble viruses but lack viral genomes. With the ability to protection against HPV16, HPV18, HPV31, HPV45, HPV52, HPV58, HPV6, and HPV11, Gardasil 9 (4vHPV) was the first vaccine to be approved by the Food and Drug Administration in 2006. As a result, these vaccines can help prevent over 90% of genital cancers, including cervical, anal, vaginal, and vulvar cancers (Rosalik et al., 2021). When it comes to women who have previously expose to HPV16 and HPV18, these vaccinations have very little effect. Later, Gardasil created a nine-valent (9vHPV) version that, in comparison to 4vHPV, also carries five L1 VLPs, including HPV carcinogenic strains 31, 33, 45, 52, and 58 (Soca Gallego, 2023).

All individuals between the ages of 9 and 25 should have HPV vaccination. The HPV vaccine should be given in two doses to all preteens who are 11 or 12 years old; the second dose should be given six to twelve months following the first. A three-dose series is advised if the first HPV dose is given on or after the age of 15. Those with specific immune-suppressive medical disorders are also advised to follow the 3-dose plan. According to Meites et al. (2019), the third dose ought to be given six months following the first dose, and the second ought to be given one to two months after the first.

Conclusion

In conclusion, human papillomaviruses (HPVs) represent a diverse group of viruses with significant implications for human health. The characteristics of HPV, including its small size, epitheliotropic nature, and circular DNA composition, contribute to its ability to infect basal stem cells in cutaneous and mucosal epithelia. This, in turn, leads to a spectrum of clinical outcomes ranging from benign lesions, such as various types of warts, to more severe consequences, including the development of cancers in different anatomical sites.

References

- Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30(Suppl. 5):F55–70.
- de Sanjosé S, Quint W, Alemany L, Geraets D, Klaustermeier J, Lloveras B, et al. Human papillomavirus genotype

attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol 2010;11(11):1048–56. 26 Z. Al-Lawati et al. / International Journal of Infectious Diseases 93 (2020) 22–27

- Hirth J. Disparities in HPV vaccination rates and HPV prevalence in the United States: a review of the literature. Hum Vaccin Immunother. 2019;15(1):146-155
- Araldi RP, Sant'Ana TA, Módolo DG, de Melo TC, Spadacci-Morena DD, de Cassia Stocco R, Cerutti JM, de Souza EB. The human papillomavirus (HPV)-related cancer biology: An overview. Biomed Pharmacother. 2018 Oct;106:1537-1556
- Stein AP, Saha S, Kraninger JL, *et al*. Prevalence of Human Papillomavirus in Oropharyngeal Cancer: A Systematic Review. *Cancer J*. 2015; 21(3):138-46.
- de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. Worldwide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. Hepatology 2015; 62: 1190–200.
- Steinau M, Saraiya M, Goodman MT, *et al*. Human Papillomavirus Prevalence in Oropharyngeal Cancer before Vaccine Introduction, United States. Emerging Infectious Diseases. 2014;20(5):822-828.
- Jit M, Vyse A, Borrow R *et al*. (2007) Prevalence of human papillomavirus antibodies in young female subjects in England. *Br J Cancer* **97**(7): 989-91.
- Stamataki S, Nikolopoulos TP, Korres S *et al*. (2007) Juvenile recurrent respiratory papillomatosis: still a mystery disease with difficult management. *Head Neck* **29**(2):155-62.
- Howell-Jones R, Bailey A, Beddows S *et al*. (2010) Multi-site study of HPV type-specific prevalence in women with cervical cancer, intraepithelial neoplasia and normal cytology, in England. *Br J Cancer*, **103**(2): 209-16.
- National Statistics Cervical Screening Programme, England - 2019-20 available at:https://digital.nhs.uk/data-and-information/publications/statistical/cervical-screening-annual/
- Surriabre P, Torrico A, Vargas T, Ugarte F, Rodriguez P, Fontaine V. Assessment of a new low-cost, PCR-based strategy for high-risk human papillomavirus DNA detection for cervical cancer prevention. *BMC Infect Dis*. 2019;**19**(1):842
- Munoz N, Castellsague X, Berrington de Gonzalez A, Gissman L. HPV in the etiology of human cancer. Vaccine 2006; 24(Suppl 3): S3/1-10
- Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents.*The Lancet Oncology* 2009;10:321-2
- Graham SV. The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. *Clin Sci* (Lond) 2017; 131(17): 2201–2221
- Syrjänen, S.M. and Syrjänen, K.J. **1999.** New concepts on the role of human papillomavirus in cell cycle regulation. *Annals of Medicine*. **31:** 175-187
- Merckx M, Liesbeth WV, Arbyn M, et al. Transmission of carcinogenic human papillomavirus types from mother to child: a metaanalysis of published studies. *Eur J Cancer Prev* 2013; 22(3): 277–285
- Deligeoroglou E, Giannouli A, Athanasopoulos N, Karountzos V, Vatopoulou A, Dimopoulos K, et al. HPV infection: immunological aspects and their utility in future therapy. Infect Dis Obstet Gynecol. 2013; 2013:540850
- Stanley M. Pathology and epidemiology of HPV infection in females.*Gynecol Oncol*. 2010 May;117(2 Suppl):S5–10

- Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007; 370:890-907
- Koning MN, Quint KD, Bruggink SC, Gussekloo J, Bouwes Bavinck JN, Feltkamp MC,*et al*. High prevalence of cutaneous warts in elementary school children and ubiquitous presence of wart-associated HPV on clinically normal skin. Br J Dermatol 2014;172:196-201.
- Sinal SH, Woods CR. Human papillomavirus infections of the genital and respiratory tracts in young children. Semin Pediatr Infect Dis 2005;16:306-16.
- Lazarczyk M, Pons C, Mendoza JA, Cassonnet P, Jacob Y, Favre M,*et al.* Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. J Exp Med 2008;205:35-42.
- American Association for Cancer Research (AACR). Lung Cancer Risk Rises in the Presence of HPV Antibodies; 2011. Available from: http://www.aacr.org/
- World Health Organization, National Agency for Research. Cancer Today [cited 05.11.2021.
- Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sexually Transmitted Diseases* 2014;41:660-4.
- Wei F, Gaisa MM, D'Souza G, et al. Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. *Lancet HIV* 2021;8:e531-e43.
- Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol 2012;5(61):25-36
- Saraiya M, Steben M, Watson M, Markowitz L. Evolution of cervical cancer screening and prevention in the United States and Canada: Implications for public health practitioners and clinicians. Prev Med 2013;57(5):426-433
- Soheili, M.; Keyvani, H.; Soheili, M.; Nasseri, S. Human papilloma virus: A review study of epidemiology, carcinogenesis, diagnostic methods, and treatment of all HPV-related cancers. *Med. J. Islam. Repub. Iran.* **2021**, *35*, 65.
- Petca, A.; Borislavschi, A.; Zvanca, M.E.; Petca, R.C.; Sandru, F.; Dumitrascu, M.C. Non-sexual HPV transmission and role of vaccination for a better future (Review). *Exp. Ther. Med.* **2020**, *20*, 186.
- Di Bonito, P.; Della Libera, S.; Petricca, S.; Iaconelli, M.; Sanguinetti, M.; Graffeo, R.; Accardi, L.; La Rosa, G. A large spectrum of alpha and beta papillomaviruses are detected in human stool samples. *J. Gen. Virol.* **2015**, *96*, 607–613.
- Rosalik, K.; Tarney, C.; Han, J. Human Papilloma Virus Vaccination. *Viruses* 2021, *13*, 1091
- Soca Gallego, L.; Dominguez, A.; Parmar, M. Human Papilloma Virus Vaccine. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
- Meites, E.; Szilagyi, P.G.; Chesson, H.W.; Unger, E.R.; Romero, J.R.; Markowitz, L.E. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb. Mortal. Wkly. Rep.* 2019, *68*, 698–702