Online publication ahead of print, AJMHS Vol 68, 2025

# Human Papillomavirus: A Comprehensive Overview of Infection, Cancer Risks, and Prevention Through Vaccination

Amarda Gica[1], Ergita Nelaj[2,3*], Kei Xhixhabesi[2], Irida Kecaj[3]

[1] University of Technical Science "Aleksandër Xhuvani", Elbasan, Albania
[2] Faculty of Medicine, University of Medicine, Tirana, Albania
[3] Department of Internal Medicine, UHC "Mother Teresa". Tirana, Albania

**Abstract**

Human papillomavirus (HPV) is a prevalent sexually transmitted infection with over 200 distinct strains, most of which are benign. However, persistent infection with high-risk HPV types, particularly HPV 16 and 18, is a leading cause of various cancers, including cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancers. HPV infects the skin and mucosal membranes, and in some cases, high-risk strains can lead to malignancies by interfering with cell cycle regulation and inhibiting tumor suppressor proteins. The development of the HPV vaccine has been a significant advancement in preventing HPV-related cancers. Current vaccines, such as Gardasil and Cervarix, target both high-risk and low-risk HPV types, protecting against strains linked to cancer and genital warts. Vaccination is most effective when administered before exposure to the virus, typically recommended for boys and girls between the ages of 9 and 15. Screening methods, including Pap smears and HPV testing, play a crucial role in the early detection of precancerous changes, particularly in cervical cancer. While the immune system usually clears HPV infections, those with weakened immunity are at higher risk of persistent infections and subsequent cancers. The combination of vaccination and regular screening can significantly reduce the burden of HPV-related diseases. Ongoing public health campaigns promoting vaccination and screening are essential for decreasing the incidence of

**Address for correspondence:** Ergita Nelaj*, Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirana, Albania. Address: Dibra's Street, No 370, Tirana, Albania. Email: dr_ergi@yahoo.com

preventable cancers worldwide. This article explores the characteristics, infection mechanism, and cancer association of HPV, emphasizing the importance of vaccination and early detection.

**Keywords**: papillomavirus, cancer, prevention, infection, vaccine.

## INTRODUCTION

Human papillomavirus (HPV) is a widespread sexually transmitted infection with over 200 different strains, most of which are harmless (1). It's estimated that nearly everyone will be exposed to HPV during their lifetime. More than 42 million people in the United States are living with HPV types known to cause health issues, and around 13 million new infections occur annually, including in teenagers (2). HPV affects the skin and mucous membranes, commonly targeting areas such as the genital region, mouth, throat, and oropharyngeal areas. While most HPV infections are symptomless and resolve without treatment, persistent infections with high-risk HPV strains can lead to serious health complications, including several types of cancer (3). The development of the HPV vaccine has significantly contributed to preventing these infections and the cancers they may cause.

This article explores the characteristics of HPV infection, its association with cancer, and the importance of vaccination in preventing these risks.

## HPV INFECTION: MECHANISM AND TYPES

HPV is a non-enveloped virus with a double-stranded DNA genome, belonging to the Papillomaviridae family. The virus features an icosahedral capsid structure, which is a symmetrical arrangement of protein subunits. The HPV genome comprises approximately 8,000 base pairs and encodes six early proteins (E1 to E7) along with two late proteins (L1 and L2) (4).

- E1 and E2 proteins help the virus replicate inside the host cell (5).
- E4, E5, E6, and E7 proteins play roles in viral replication and can interfere with the host cell's normal function, potentially leading to cancer in the case of high-risk strains (6). Elevated activity of E6 and E7 can promote cell proliferation, block cellular differentiation, and trigger chromosomal instability, ultimately leading to tumor development (7).

The L1 protein is the major capsid protein responsible for the formation of the viral capsid, while L2 assists in the virus's entry into the host cell (8).

Out of approximately 200 distinct HPV genotypes, 40 specifically target the anogenital region through direct skin-to-skin or mucosal contact. These strains are categorized as either low-risk or high-risk (HR) based on their potential to cause cancer (9).

Low-risk HPV: These are typically associated with benign conditions like genital warts or warts in other parts of the body (e.g., hands or feet), and are called non-oncogenic types (10). The most common low-risk types are HPV 6 and HPV 11 (11). These types are not linked to cancer but can cause discomfort or cosmetic issues, such as genital warts.

High-risk HPV: These are associated with cancer development and are called oncogenic types. The most common high-risk types are HPV 16 and

HPV 18, which are responsible for approximately 70% of cervical cancers worldwide (12). Other high-risk types include HPV 31, HPV 33, HPV 45, HPV 52, and HPV 58 (13). Infections with high-risk HPV strains can lead to persistent cellular changes and, if left untreated, progression to cancer, especially in the cervix, anus, oropharynx, and genital areas.

HPV infects keratinocytes, the predominant cells in the skin and mucosal membranes. The virus typically enters the body through small cuts, abrasions, or mucosal disruptions.

HPV is estimated to be responsible for greater than 99% of cervical, 90% of anal, 69% of vulvar, 75% of vaginal, 40% of penile, and 70% of oropharyngeal cancers (1). Cervical cancer is the fourth most common cancer in women worldwide, with an estimated 604,000 new cases globally in 2020.

Here's how the infection process unfolds:

Entry: The HPV virus binds to specific receptors on the surface of basal epithelial cells (the deepest layer of the skin or mucosa). The L1 protein of the virus facilitates binding and the initial entry into the cell (14).

Replication: Once inside, HPV begins to replicate its DNA within the host cell's nucleus. The early HPV proteins (E1, E2) help with the replication and maintenance of the viral genome, while E6 and E7 proteins can interfere with the host cell's normal function (9,15). In particular, E6 and E7 inhibit tumor suppressor proteins like p53 and RB, allowing the infected cell to proliferate uncontrollably, which may eventually lead to cancer (7,9,16).

Latency: In most cases, the immune system clears the infection within 1-2 years. However, in some instances, the virus remains latent in the epithelium, and persistent infection may occur, particularly with high-risk HPV types.

Progression to Cancer: In cases of persistent infection with high-risk HPV types, the continuous expression of viral oncoproteins (E6 and E7) can disrupt normal cell function and lead to precancerous lesions (7,9,16). Over time, these lesions may evolve into invasive cancer if left untreated. This progression can take years or even decades.

## HPV AND CANCER DEVELOPMENT

Persistent infection with high-risk HPV can cause cellular changes that may eventually lead to cancer. The virus integrates its DNA into the host cell genome, producing oncoproteins E6 and E7, which can disrupt normal cell cycle regulation and prevent apoptosis (programmed cell death) (7,9,16). Over time, these changes can result in the development of malignancy.

Cervical cancer: Cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related deaths among women (17). High-risk HPV infection is the primary cause of cervical cancer, responsible for over 99% of all cases (18). Persistent infection with high-risk HPV strains—especially types 16 and 18—is the leading cause of most cervical

cancer cases (9). While non-sexual transmission has been reported, sexual contact remains the primary route of infection. On average, a persistent HPV infection can progress to high-grade cervical intraepithelial neoplasia and eventually invasive cervical cancer over 15 to 30 years (19). Regular screening through Pap smears and HPV testing helps detect precancerous changes early, reducing the incidence of cervical cancer.

Other cancers: HPV infection is also implicated in cancers of the anus, penis, vulva, vagina, and oropharynx. Viral infections by HPV are a well-known etiological factor for head and neck cancers, as HPV accounts for approximately 25% of all head and neck cancers (20). In oropharyngeal cancer, HPV 16 is the predominant strain, affecting the throat, tonsils, and back of the mouth (21). The rising incidence of HPV-related oropharyngeal cancer, especially in men, has prompted further research and public health efforts.

HPV infection is linked to a higher risk of penile cancer in men, particularly those with multiple sexual partners. Persistent infection with high-risk HPV strains, especially in individuals with compromised immune systems (e.g., HIV-positive individuals), increases the risk of anal cancer (22).

## HPV VACCINATION: A PREVENTIVE APPROACH

The immune system typically clears most HPV infections within 1 to 2 years. However, in some cases, the virus can evade immune detection, leading to persistent infection. People with weakened immune systems, such as those with HIV or those undergoing immunosuppressive therapy, are more likely to develop persistent infections and HPV-related cancers.

Vaccination against HPV has proven to be a highly effective method for reducing the burden of HPV-related cancers and genital warts. The vaccines target the most common high-risk and low-risk HPV types, offering protection against strains that are most commonly associated with cancer and genital warts.

Available Vaccines: The primary vaccines in use are Gardasil (which protects against HPV types 6, 11, 16, and 18) (23) and Cervarix (which protects against HPV types 16 and 18) (24). Gardasil 9, the most recent version, protects against an additional five HPV types (31, 33, 45, 52, and 58), further expanding its ability to prevent cancer (25).

Efficacy and Safety: Clinical trials have shown that the HPV vaccine is highly effective in preventing infections with the targeted HPV types and associated cancers. Vaccination has been shown to reduce the incidence of cervical cancer precursors by more than 90% (26). The vaccine is generally safe, with side effects typically limited to mild reactions like pain at the injection site, dizziness, or fever.

Vaccination Recommendations: The HPV vaccine is most effective when administered before any exposure to the virus, why vaccination is recommended for both boys and girls between

the ages of 9 and 15, ideally before they become sexually active. Catch-up vaccination is recommended for individuals up to age 26, and in some cases, vaccination may be considered up to age 45 (27).

## SCREENING AND EARLY DETECTION

Despite the availability of the HPV vaccine, screening remains an essential tool in the early detection of HPV-related cancers. Regular Pap smears (cervical cytology) and HPV testing are recommended for women starting at age 21, with intervals varying based on age and previous test results. Early detection of precancerous changes can prevent the progression to full-blown cancer, particularly cervical cancer.

## CONCLUSION

HPV infection represents a significant public health concern due to its association with various cancers, including cervical, anal, and oropharyngeal cancers. Vaccination provides an effective preventive strategy against HPV infection and its related cancers. When combined with early detection through screening, vaccination can greatly decrease the global impact of HPV-related diseases. Continued public health efforts to promote vaccination and regular screening are crucial for lowering the incidence of these preventable cancers.

**Acknowledgement**: None declared

**Conflict of Interest Statement**: The authors declare that they have no conflict of interest.

## REFERENCES

1. Rosalyn E. Plotzker, Akanksha Vaidya, Utsav Pokharel, Elizabeth A. Stier, Sexually Transmitted Human Papillomavirus: Update in Epidemiology, Prevention, and Management, Infectious Disease Clinics of North America 2023;37,2:289-310, ISSN 0891-5520, ISBN 9780443183027, https://doi.org/10.1016/j.idc.2023.02.008 .

2. Centers for Disease Control and Prevention (CDC). (2024). HPV and Cancer. Retrieved from CDC Website.

3. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. Cervical cancer: Learn More – Human papillomaviruses (HPV): How can you be infected and what consequences can that have? [Updated 2025 Mar 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279260/

4. Sheila V. Graham; The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. Clin Sci (Lond) 2017; 131 (17): 2201–2221. doi: https://doi.org/10.1042/CS20160786.

5. Ozbun MA. Human papillomavirus type 31b infection of human keratinocytes and the onset of early transcription. J. Virol 2002; 76, 11291–11300.

6. Graham SV. Human papillomavirus: gene expression, regulation and prospects for novel diagnostic methods and antiviral therapies. Future Microbiol 2010;5, 1493–1506.

7. Pett M. and Coleman N. Integration of high-risk human papillomvirus: a key event in cervical carcinogenesis? J. Pathol 2007; 212, 356–367.

8. Buck C. and Trus B. The papillomavirus virion: a machine built to hide molecular achilles' heels. In Viral Molecular Machines (Rossmann M.G. and Rao V.B., eds) 2012:403–422, Springer, U.S.A. Google Scholar.

9. Fernandes Q, Allouch S, Gupta I, et al. Human Papillomaviruses-Related Cancers: An Update on the Presence and Prevention Strategies in the Middle East and North African Regions. Pathogens 2022;11(11):1380. Published 2022 Nov 19. doi:10.3390/pathogens11111380.

10. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. Vaccine 2006;24(3):S35–S41. doi: 10.1016/j.vaccine.2006.06.015.

11. Ouda AM, Elsabagh AA, Elmakaty IM, Gupta I, Vranic S, Al-Thawadi H, Al Moustafa AE. HPV and Recurrent Respiratory Papillomatosis: A Brief Review. Life 2021;11:1279. doi: 10.3390/life11111279.

12. Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, Clifford GM. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. Int J Cancer 2007;121:621–632. doi: 10.1002/ijc.22527.

13. Bernard HU, Burk RD, Chen Z, van Doorslaer K, Hausen H.z, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010;401:70–79. doi: 10.1016/j.virol.2010.02.002.

14. Bernard HU, Calleja-Macias IE, Dunn ST. Genome variation of human papillomavirus types: Phylogenetic and medical implications. Int J Cancer 2006;118:1071–1076. doi: 10.1002/ijc.21655.

15. Motoyama S, Ladines-Llave CA, Luis Villanueva S, Maruo T. The role of human papilloma virus in the molecular biology of cervical carcinogenesis. Kobe J Med Sci 2004;50:9–19.

16. Al Moustafa AE. E5 and E6/E7 of high-risk HPVs cooperate to enhance cancer progression through EMT initiation. Cell Adhes. Migr 2015;9:392–393. doi: 10.1080/19336918.2015.1042197.

17. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA A Cancer J Clin 2021;71:209–249. doi: 10.3322/caac.21660.

18. Yuan Y, Cai X, Shen F, Ma F. HPV post-infection microenvironment and cervical cancer. Cancer Lett 2021;497:243–254.

doi: 10.1016/j.canlet.2020.10.034.

19. Collins Y, Einstein MH, Gostout BS, Herzog TJ, Massad LS, Rader JS, Wright J. Cervical cancer prevention in the era of prophylactic vaccines: A preview for gynecologic oncologists. Gynecol Oncol 2006;102:552–562.
doi: 10.1016/j.ygyno.2006.07.022.

20. Joseph AW, D'Souza G. Epidemiology of human papillomavirus-related head and neck cancer. Otolaryngol. Clin. North Am 2012;45:739–764.
doi: 10.1016/j.otc.2012.04.003.

21. Laprise C, Madathil SA, Schlecht NF, Castonguay G, Soulières D, Nguyen-Tan PF, Allison P, Coutlée F, Hier M, Rousseau MC, et al. Human papillomavirus genotypes and risk of head and neck cancers: Results from the HeNCe Life case-control study. Oral Oncol 2017;69:56–61. doi: 10.1016/j.oraloncology.2017.03.013.

22. Fernandes Q, Gupta I, Vranic S, Al Moustafa AE. Human Papillomaviruses and Epstein-Barr Virus Interactions in Colorectal Cancer: A Brief Review. Pathogens 2020;9:300.
doi: 10.3390/pathogens9040300.

23. Monie A, Hung CF, Roden R, Wu TC. Cervarix™:A vaccine for the prevention of HPV 16, 18-associated cervical cancer. Biol. Targets Ther 2008;2:107–113.

24. Schwarz T.F. Clinical update of the AS04-adjuvanted human papillomavirus-16/18 cervical cancer vaccine, Cervarix. Adv Ther 2009;26:983–998. doi: 10.1007/s12325-009-0079-5.

25. Cuzick J. Gardasil 9 joins the fight against cervix cancer. Expert. Rev. Vaccines 2015;14:1047–1049.
doi: 10.1586/14760584.2015.1051470.

26. Alemany L, Saunier M, Alvarado-Cabrero I, Quirós B, Salmeron J, Shin HR, Pirog EC, Guimerà N, Hernandez-Suarez G, Felix A, et al. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. Int J Cancer 2015;136:98–107.
doi: 10.1002/ijc.28963.

27. Garbuglia AR, Lapa D, Sias C, Capobianchi MR, Del Porto P. The Use of Both Therapeutic and Prophylactic Vaccines in the Therapy of Papillomavirus Disease. Front. Immunol 2020;11:188. doi: 10.3389/fimmu.2020.00188.