Review Article

Persistent Human Papillomavirus Infection: Immunological Mechanisms and Progression to Cancer

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Abstract

Persistent human papillomavirus infection is a multifactorial process shaped by viral, host, and environmental determinants that collectively promote immune evasion, persistence, and malignant progression. Infection begins in the basal epithelial cells, where viral attachment and entry are mediated by specific host receptors, followed by maintenance of viral DNA as episomes or, in some cases, integration into the host genome. This integration frequently disrupts viral regulatory genes and leads to overexpression of the E6 and E7 oncoproteins, which inactivate p53 and retinoblastoma protein, promote telomerase activation, and drive genomic instability. These events establish the molecular basis for cell immortalization and carcinogenesis. A central feature of persistent infection is the ability of human papillomavirus to evade both innate and adaptive immunity. The virus limits immune detection through low-copy replication, minimal cytopathic effects, suppression of interferon signaling, impairment of antigen-presenting cells, and evasion of natural killer cell activity. At the adaptive level, defective cytotoxic T cell responses, T helper imbalance, regulatory T cell infiltration, and T cell exhaustion further weaken viral clearance. Humoral immunity is also limited during natural infection, explaining why established infections are often not effectively eliminated. As persistence continues, oncogenic signaling pathways, genomic instability, and local immunosuppressive tumor microenvironments facilitate progression from intraepithelial neoplasia to invasive carcinoma. This process is influenced by genetic susceptibility, hormonal factors, microbiome alterations, immunosuppression, coinfections, and behavioral cofactors. Although prophylactic vaccines provide strong protection against new infections, established disease still requires therapeutic approaches such as therapeutic vaccines, immune checkpoint inhibitors, and emerging cell-based and viral immunotherapies.

Key words

Human papillomavirus, viral persistence, immune evasion, carcinogenesis, tumor microenvironment, therapeutic vaccines.

Introduction

Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections worldwide and a leading infectious cause of cancer-related morbidity and mortality. According to GLOBOCAN 2022, a total of 1,505,394 HPV-associated cancer cases were diagnosed globally, representing 7.5% of all cancers, with 755,303 deaths recorded in that year alone [1]. Cervical cancer remains the dominant HPV-related malignancy, accounting for 44% of this burden, with 662,044 new cases and an age-standardized incidence rate of 14.1 per 100,000 women; over 90% of cases and deaths occur in low- and middle-income countries, where access to screening and vaccination remains critically limited [1, 2]. Beyond the cervix, HPV drives a substantial proportion of oropharyngeal, anal, vulvar, vaginal, and penile cancers, collectively representing the remaining 56% of attributable cases [1]. Oropharyngeal cancer shows an inverse epidemiological pattern, being most prevalent in high-income countries and rising disproportionately among men due to the absence of established screening programs [3]. Projections based on GLOBOCAN 2022 and Global Burden of Disease 2021 data indicate that the incidence of all eight HPV-related cancer types will continue to increase across all continents through 2045, underscoring the urgency of global prevention efforts [4].

To understand why HPV infection so frequently progresses to malignancy, its molecular architecture must first be considered. HPV is a small, non-enveloped double-stranded DNA virus whose genome of approximately 8 kb is organized into three functional regions: the long control region (LCR), which governs transcription and replication; the early region (E), encoding regulatory and oncogenic proteins (E1, E2, E4, E5, E6, E7); and the late region (L), encoding the major (L1) and minor (L2) structural capsid proteins [5, 6]. More than 200 HPV genotypes have been identified and classified according to their oncogenic potential. High-risk types - principally HPV-16 and HPV-18 - account for approximately 70% of all cervical cancers worldwide, and also drive the majority of other HPV-associated malignancies [2, 7]. The central oncogenic mechanisms are mediated by the viral proteins E6 and E7, which are normally expressed at low levels from episomal viral DNA but become markedly upregulated following chromosomal integration, an event that disrupts the E2 repressor gene and releases these oncoproteins from transcriptional control [5, 6]. E6 promotes degradation of p53 via the ubiquitin–proteasome pathway and activates telomerase, while E7 inactivates the retinoblastoma protein (pRb), together driving cell cycle dysregulation, resistance to apoptosis, and progressive genomic instability [8, 9].

Despite this oncogenic potential, most HPV infections follow a benign and self-limited course. More than 90% of new infections, including those caused by high-risk genotypes, become undetectable within two years, with clearance frequently occurring within the first six months after acquisition [7, 10]. Only 10–20% of infected individuals develop persistent infection - defined as the continuous detection of the same high-risk HPV genotype across sequential testing intervals - and this subset carries virtually all of the cancer risk attributable to HPV [10, 11]. A meta-analysis including 656,555 participants found that the weighted mean duration of any persistent HPV infection was 13.29 months, with approximately 50% of infections resolving within two years; HPV-16 carried a uniquely elevated seven-year risk of progression to CIN3+ of 22%, far exceeding that of other high-risk genotypes [11, 12]. The factors determining whether an infection will clear or persist are multifactorial, encompassing viral genotype and load, the presence of multiple concurrent infections, older age, cigarette smoking, high parity, prolonged oral contraceptive use, and co-infection with other sexually transmitted pathogens such as herpes simplex virus type 2 and Chlamydia trachomatis [10, 13]. At the molecular level, persistent infection is accompanied by an impaired local cellular immune response, characterized by elevated IL-10, IL-6, and TGF-β1, reflecting a shift toward a Th2-dominant cytokine environment that facilitates viral integration, cellular transformation, and ultimately malignant progression [10].

This structured narrative review aims to provide an integrated analysis of the immunological mechanisms underlying persistent HPV infection and its progression to cancer, encompassing innate and adaptive immune evasion, molecular pathways of malignant transformation, host and environmental cofactors, and current prophylactic and therapeutic immunological strategies, with the purpose of establishing a practical framework for the prevention and management of HPV-associated malignancies.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of persistent human papillomavirus infection, with particular emphasis on the immunological mechanisms underlying viral persistence and progression to cancer. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the biological complexity of HPV-associated carcinogenesis and the heterogeneity of available evidence across immunological, molecular, and clinical domains, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate virological, immunological, and oncological considerations into a coherent and clinically applicable framework. Special attention was given to innate and adaptive immune evasion mechanisms, the tumor microenvironment in HPV-driven malignancies, host and environmental cofactors of viral persistence, and current prophylactic and therapeutic immunological strategies. The objective was to provide a structured synthesis capable of supporting evidence-based decision-making in the prevention and management of HPV-associated malignancies.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and December 2025. The final search was performed in April 2026. This timeframe was selected to capture contemporary advances in HPV immunology, immune checkpoint research, therapeutic vaccine development, and updated epidemiological data on HPV-related cancer burden. Foundational studies were incorporated when necessary to contextualize pathophysiological mechanisms or provide historical perspective on viral oncogenesis. The search strategy combined MeSH and free-text terms using Boolean operators related to human papillomavirus, persistent HPV infection, HPV immunology, innate immune evasion, adaptive immune response, T cell exhaustion, tumor microenvironment, HPV oncoproteins E6 and E7, cervical cancer, oropharyngeal cancer, anogenital cancer, HPV carcinogenesis, prophylactic vaccines, therapeutic vaccines, and immune checkpoint inhibitors. Searches were conducted across titles, abstracts, and indexed subject headings to maximize sensitivity.

The initial search yielded 199 records. After removal of duplicates, 150 articles remained for title and abstract screening. Of these, 95 underwent full-text evaluation, and 47 studies were included in the final synthesis. Selection was performed independently by two authors, with disagreements resolved through discussion and consensus. Exclusion criteria comprised non–peer-reviewed publications, isolated case reports, editorials without outcome data, studies exclusively addressing HPV diagnostics or screening without immunological or oncological content, redundant datasets, and publications not directly addressing immune mechanisms, molecular pathways, host cofactors, or therapeutic strategies in HPV-associated malignancies.

Eligible studies included randomized controlled trials, large observational cohorts, systematic reviews, meta-analyses, expert consensus statements, and contemporary international guidelines from oncology, virology, gynecology, and immunology societies. Priority was assigned to multicenter investigations, studies with immunologically validated outcome measures, and research evaluating viral clearance, immune evasion mechanisms, malignant progression, or treatment response in HPV-positive populations. Extracted variables included study design, HPV genotype and anatomical site, immunological parameters assessed, molecular pathways implicated, host and environmental cofactors analyzed, therapeutic modality evaluated and reported clinical or immunological outcomes. Methodological quality and internal validity were assessed narratively, considering risk of bias, sample size, follow-up duration, consistency of genotyping methods, and reproducibility of immunological or oncological findings. In cases of conflicting evidence, greater interpretative weight was assigned to higher-level evidence and guideline-supported recommendations.

Reference lists of included studies were manually screened to identify additional relevant publications. Given its narrative design, this review is subject to potential selection bias and does not provide pooled quantitative estimates. Artificial intelligence–based tools were used exclusively to assist in literature organization and structural coherence, whereas critical appraisal, synthesis, and final interpretation were conducted independently by the authors to preserve methodological rigor.

Persistent Human Papillomavirus Infection

Human papillomavirus infection begins in the basal epithelial cells, where heparan sulfate proteoglycans and α-6 integrin play essential roles in viral entry and tropism, particularly in the cervical transformation zone [14]. In this process, the viral L1 and L2 proteins mediate internalization and allow the establishment of infection in the basal layer of stratified epithelia [15].

Once infection is established, human papillomavirus DNA is maintained as episomes within basal cells, allowing low-level replication and sustained persistence without the need for integration into the host genome [14]. However, integration into the host genome is a stochastic event that frequently leads to disruption of the E2 gene, which in turn causes overexpression of the E6 and E7 oncoproteins [15]. Although this integration is associated with genomic instability and is considered a dead end for viral replication, it represents a decisive mechanism in oncogenesis [16].

In this context, the E6 and E7 oncoproteins play a central role in cell immortalization. The E6 oncoprotein promotes the degradation of p53, a tumor suppressor protein, thereby preventing apoptosis, while E7 inactivates the retinoblastoma protein, leading to uncontrolled cell cycle progression. Together, both oncoproteins contribute to telomerase activation and genomic instability, thereby facilitating cell immortalization and carcinogenesis [14, 17].

In addition, viral persistence and latency mechanisms are modulated by epigenetic processes, including DNA methylation and histone modifications, which affect both viral and host genes [18]. Added to this are the roles of the vaginal microbiome and immune evasion strategies, since dysbiosis has been linked to an increased risk of progression to high-grade lesions [10]. At the same time, low-level replication of viral DNA in basal cells is sustained through the activation of DNA damage repair pathways, which are manipulated by the virus to evade the immune response [20].

Innate Immune Evasion by HPV

HPV employs a stealth infection strategy characterized by minimal activation of the innate immune system. This is facilitated by the absence of viremia, restricted cytopathic effects, and limited exposure of viral antigens to the immune system. In addition, the virus maintains a low copy number in basal keratinocytes, which further contributes to avoiding immune detection [14, 21].

A key mechanism underlying this process is the suppression of interferon signaling pathways. HPV proteins, particularly E6 and E7, interfere with essential components of these pathways, including IRF-3, STAT-1, and toll-like receptor signaling, leading to downregulation of interferon beta production [22, 23]. For example, the E6 protein of HPV16 directly interacts with IRF3, inhibiting its ability to mediate interferon beta expression [24]. This suppression of the interferon pathway is crucial for generating an immunotolerant environment that facilitates viral persistence [25].

At the same time, HPV infection impairs antigen presentation and pattern recognition. It induces dysfunction in Langerhans cells, which are critical antigen-presenting cells in the epithelium [20]. In parallel, the virus suppresses the cyclic GMP-AMP synthase-stimulator of interferon genes pathway and inhibits the NLRP3 inflammasome, further weakening the host’s capacity to recognize and respond to infection [26].

HPV also evades natural killer cell activity through multiple mechanisms. It downregulates major histocompatibility complex class I expression and suppresses NKG2D ligands, both of which are essential for natural killer cell recognition and activation. The virus creates an immunosuppressive microenvironment that restricts natural killer cell recruitment and impairs their function, as observed in aggressive juvenile-onset recurrent respiratory papillomatosis [27].

Adaptive Immune Response and Failure of Viral Clearance

$CD8^+$ cytotoxic T lymphocytes respond against HPV through the recognition of viral peptides presented by major histocompatibility complex class I molecules. However, defects in major histocompatibility complex class I presentation can impair this response and lead to cytotoxic insufficiency. Although the HPV oncoproteins E6 and E7 are considered immunodominant targets, their expression can alter antigen presentation and thereby reduce the effectiveness of $CD8^+$ T cell responses [28].

In parallel, persistent HPV infection is associated with dysfunction of $CD4^+$ T helper responses, particularly through an imbalance between Th1 and Th2 pathways. This imbalance is often characterized by suppression of Th1 activity and dominance of interleukin-10, which impairs effective T cell priming. As a result, the development of a robust cellular immune response necessary for viral clearance is compromised [29].

At the local level, regulatory T cells also contribute to immune evasion and persistence. These cells infiltrate HPV-associated lesions, express FOXP3, and produce immunosuppressive cytokines such as transforming growth factor beta and interleukin-10, thereby promoting a locally immunosuppressive microenvironment that favors persistence of infection. The presence of these regulatory T cells within HPV lesions suppresses the activity of effector T cells and further facilitates viral persistence [30].

Moreover, chronic HPV infection can induce T cell exhaustion, a state marked by the upregulation of inhibitory receptors such as programmed cell death protein 1, T cell immunoglobulin and mucin-domain containing-3, and lymphocyte activation gene-3. These exhaustion markers reflect both phenotypic and functional decline in T cell activity, ultimately reducing the immune system’s capacity to eliminate the virus [20].

Humoral immunity also shows important limitations in the context of natural HPV infection. These infections frequently result in low seropositivity rates and fail to generate sterilizing neutralizing antibody titers, which limits the effectiveness of the humoral response in clearing established infections. Although prophylactic vaccines are capable of inducing strong antibody responses, they are not effective against existing infections, which underscores the need for therapeutic vaccines [30].

Tumor Microenvironment in HPV-Driven Carcinogenesis

HPV-associated lesions and invasive carcinomas are characterized by an immunosuppressive cytokine landscape that includes interleukin-10, transforming growth factor beta, vascular endothelial growth factor, and interleukin-6. These cytokines collectively contribute to an immunosuppressive environment that facilitates tumor growth and immune evasion. In cervical cancer, their presence has been linked to modulation of immune responses in ways that promote tumor progression [15].

Within this tumor microenvironment, myeloid-derived suppressor cells and tumor-associated macrophages are actively recruited and play a central role in immune suppression. Myeloid-derived suppressor cells produce arginase-1 and reactive oxygen species, which suppress T cell activity and promote tumor growth. At the same time, tumor-associated macrophages frequently undergo M2 polarization, a phenotype associated with tissue remodeling and immunosuppression, thereby further supporting tumor progression [15].

Another major mechanism of immune escape in HPV-driven cancers is the activation of immune checkpoints. HPV oncoproteins, particularly E7, drive the upregulation of programmed death-ligand 1, a key immune checkpoint molecule that promotes T cell exclusion and contributes to an immune desert phenotype. This upregulation has been observed in multiple HPV-associated malignancies, including cervical and oropharyngeal cancers, and is closely associated with immune evasion. Consequently, immune checkpoint activation contributes to the poor antitumor immune response and supports the rationale for the use of immune checkpoint inhibitors in treatment [15, 31].

Despite these shared mechanisms of immunosuppression, important differences exist between HPV-positive and HPV-negative tumor microenvironments. HPV-positive tumors generally exhibit a more favorable pattern of immune infiltration, with increased presence of adaptive immune cells such as CD4-positive and CD8-positive T lymphocytes [32, 33]. These tumors also tend to have a lower mutational burden than HPV-negative tumors, which may contribute to their better prognosis. In contrast, HPV-negative tumors are characterized by a more immunosuppressive microenvironment, with higher levels of fibroblasts and capillary endothelial cells, features that contribute to a poorer prognosis [31, 34].

Molecular Pathways of Malignant Progression

The progression from persistent HPV infection to intraepithelial neoplasia is reflected in the grading of cervical intraepithelial neoplasia, which is based on the extent of epithelial abnormality. Cervical intraepithelial neoplasia grade 1 corresponds to mild dysplasia, whereas cervical intraepithelial neoplasia grade 3 represents severe dysplasia or carcinoma in situ. The transition from these precursor lesions to invasive cancer is strongly influenced by persistent infection with high-risk HPV types, particularly HPV16 and HPV18 [35]. Although many HPV infections regress spontaneously, persistent infections may progress to high-grade lesions and, ultimately, cancer. This progression is influenced by factors such as viral load, host immune response, and genetic predisposition [14, 36]. At the molecular level, key checkpoints in this process involve disruption of cell cycle regulation by the HPV oncoproteins E6 and E7, which inactivate the tumor suppressor proteins p53 and retinoblastoma protein, thereby promoting uncontrolled cellular proliferation [4].

As this neoplastic process advances, HPV also activates several oncogenic signaling pathways that further promote malignant transformation. The phosphatidylinositol 3-kinase/protein kinase B/mechanistic target of rapamycin pathway is frequently activated in HPV-related cancers and supports cell growth and survival, with HPV oncoproteins contributing directly to this activation. Likewise, activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway increases cellular proliferation and survival, further driving cancer progression [37]. In addition, HPV can activate the Wnt/beta-catenin pathway, which is involved in cell proliferation and differentiation, and cross-talk among these pathways may enhance the overall oncogenic potential of the virus [36].

Persistent HPV infection is also associated with genomic instability and the accumulation of somatic mutations. One important mechanism is apolipoprotein B messenger RNA editing enzyme catalytic polypeptide-like mediated mutagenesis, which introduces mutations into the host genome and contributes to genomic instability [20]. Furthermore, integration of HPV into the host genome can induce chromosomal aberrations that favor cancer progression. In this context, common driver mutations in HPV-related cancers include alterations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha and tumor protein p53, both of which are critical for tumor development [37].

The carcinogenic process also varies according to the anatomical site involved. In the cervix, HPV16 and HPV18 are the most prevalent types and show specific patterns of progression influenced by the cervical microenvironment. In the oropharynx, HPV-related cancers are increasing in incidence, with HPV16 as the predominant genotype, while the anatomical niche and immune evasion strategies play central roles in carcinogenesis [35]. In the vulva and anus, HPV-related cancers also display distinct progression patterns, with differences in genotype distribution and tissue-specific factors influencing malignant development [38].

Host and Environmental Factors Modulating Persistence and Progression

Genetic susceptibility plays an important role in the persistence of high-risk human papillomavirus infection and in progression toward cervical cancer. Specific human leukocyte antigen alleles, including HLA-

DRB113:02 and HLA-DQB105:02, have been associated with an increased risk of persistent high-risk human papillomavirus infections, whereas HLA-DRB1*15:03 has been linked to a decreased risk. These alleles influence the ability of the immune system to recognize and respond to viral antigens, thereby affecting infection persistence and disease progression. In addition, polygenic risk studies have identified genetic variants near genes such as TPTE2 and SMAD2 that are associated with persistent high-risk human papillomavirus infection, further supporting the role of host genetic predisposition in modulating viral persistence [39].

Hormonal influences also contribute to the regulation of human papillomavirus gene expression. Hormonal changes occurring during pregnancy or with the use of oral contraceptives can affect viral behavior, since estrogen and progesterone response elements in the viral genome may modulate replication and persistence, potentially increasing the risk of cervical cancer. Likewise, the hormonal milieu associated with pregnancy and oral contraceptive use can alter the local immune environment, which may facilitate viral persistence and progression [14].

Local immunity is also shaped by the cervicovaginal microbiome. A shift from a Lactobacillus-dominated vaginal microbiome toward one enriched with Gardnerella and Prevotella has been associated with increased viral persistence and a greater risk of cervical cancer. This dysbiotic state can disrupt mucosal immunity and promote persistence of infection. Restoration of a healthy Lactobacillus-dominated microbiome through probiotics or microbial engineering has been proposed as a potential therapeutic strategy to enhance immune responses and reduce viral persistence [19, 40].

Immunosuppression, coinfections, and behavioral cofactors can further favor persistence of infection. Immunosuppression associated with human immunodeficiency virus infection or other sexually transmitted infections can impair the capacity of the host to clear human papillomavirus, thereby increasing the risk of persistent infection and progression to cancer. At the same time, behavioral factors such as smoking, high parity, and poor nutritional status may exacerbate persistence by weakening immune responses or creating a cellular environment that favors viral maintenance [41]. Moreover, the presence of other infections can modulate the immune response in ways that may facilitate viral persistence and progression [20].

Prevention and Therapeutic Immunological Strategies

Prophylactic human papillomavirus vaccines are based on virus-like particles derived from the L1 major capsid protein, which induce type-specific neutralizing antibodies. These vaccines are primarily directed against high-risk human papillomavirus types, particularly HPV-16 and HPV-18, which are responsible for the majority of human papillomavirus-related cancers [42, 43]. The currently available bivalent, quadrivalent, and nonavalent vaccines differ in the number of viral types they cover, with the nonavalent vaccine providing the broadest protection by including additional oncogenic types beyond HPV-16 and HPV-18. These vaccines generate robust neutralizing antibody responses and offer long-term protection against new infections, although the duration of immunity and the potential need for booster doses continue to be investigated [44, 45].

In contrast to prophylactic vaccination, therapeutic vaccine strategies are designed to induce cellular immunity against already established infections and lesions by targeting the viral oncoproteins E6 and E7. Multiple platforms, including deoxyribonucleic acid, messenger ribonucleic acid, peptide-based systems, and viral vectors, are currently under clinical evaluation [45, 46]. Although preclinical findings have been encouraging, no therapeutic human papillomavirus vaccine has yet been licensed, largely because of persistent challenges related to efficacy and safety. Current clinical trials are therefore exploring the use of these vaccines in combination with other therapeutic modalities in order to improve outcomes [30, 47].

Immune checkpoint inhibitors have also emerged as an important therapeutic strategy in human papillomavirus-positive cancers. Agents targeting the programmed cell death protein 1 and programmed death-ligand 1 axis have shown efficacy by enhancing T-cell-mediated antitumor responses. In parallel, ongoing research is focused on identifying predictive biomarkers that may help determine which patients are more likely to respond to these therapies. Combination approaches, particularly with chemoradiation, are also being explored to optimize therapeutic benefit [46].

Additional immunotherapeutic strategies are now being investigated for the treatment of human papillomavirus-associated malignancies. Among these, adoptive cell therapies such as T cell receptor-engineered T cells and chimeric antigen receptor T cells directed against E6 and E7 antigens represent promising emerging approaches. Likewise, oncolytic viruses and interventions designed to stimulate innate immunity are under study as novel strategies to strengthen antitumor responses in human papillomavirus-related cancers [46].

Conclusions

Persistent human papillomavirus infection is not determined solely by the initial viral entry, but by a complex interaction between viral immune evasion mechanisms, alterations in the host innate and adaptive immune responses, and local factors such as the microbiome, inflammatory milieu, and genetic susceptibility, all of which promote viral persistence and hinder effective clearance.

The progression from persistent infection to intraepithelial neoplasia and cancer is driven by the oncogenic activity of the viral E6 and E7 proteins, the activation of proliferative signaling pathways, the accumulation of genomic instability and somatic mutations, and the development of an immunosuppressive tumor microenvironment that facilitates immune escape and malignant progression.

Although prophylactic vaccines have demonstrated strong effectiveness in preventing new infections caused by high-risk human papillomavirus types, their inability to eliminate established infections highlights the need for complementary therapeutic strategies, including therapeutic vaccines, immune checkpoint inhibitors, and other advanced immunotherapies targeting human papillomavirus-associated malignancies.

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