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Oncogenic Potential of Persistent Human Papillomavirus Infection

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Abstract

Human papillomaviruses (HPVs) are a family of small, DNA-based viruses that can cause either benign conditions or contribute to the development of cancerous tumors in humans. Some of the oncogenic strains, as supported by existing research, primarily infect epithelial cells and can be found in various areas of the skin and mucous membranes, including the genital, anal, oral, and respiratory tracts. Persistent HPV infection is a major risk factor for the development of numerous malignant tumors in humans that can occur in various anatomical areas. Among these, HPV16 and HPV18 are the most extensively studied due to their significant carcinogenic potential. The E6 and E7 oncoproteins of these strains play an important role in cell transformation and carcinogenesis, as they are integral to the cellular immortalization process. This review synthesizes the current literature and provides an in-depth analysis of the structure and organization of the HPV genome, the viral infection cycle, and the functional roles of the E6 and E7 oncoproteins. These proteins play a pivotal role in driving abnormal cell proliferation, detecting precancerous conditions, and determining the necessary interventions, including prevention and treatment strategies for HPV infections.

Keywords: Therapeutics against HPVs, E6 E7 HPV oncoproteins, Human papillomavirus, Oncogenic potential risk

Introduction

The family of Papillomaviridae is composed of a diverse range of small DNA viruses with a double-stranded, circular genome (< 10 kb), primarily affecting squamous epithelial cells in humans and animals, often resulting in papillomas [1]. Over 300 distinct papillomavirus strains are identified in both human and animal populations, with the family comprising 49 genes (source: http://pave.niaid.nih.gov/). HPV is categorized into five main phylogenetic groups, defined by their DNA sequence and specific life cycle characteristics [2]. These groups—alpha, beta, gamma, mu, and non-HPV—have distinct genetic profiles and biological behaviors. Molecular diagnostic methods are used to study these viruses since in vitro cultivation is not feasible. Out of the 150 known HPV strains, approximately 40 are capable of infecting the epithelial tissues in the anogenital tract and other mucosal surfaces in humans.

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HPV types can be divided into high-risk (HR-HPV) and low-risk (LR-HPV) categories, with HR-HPV strains being more commonly associated with malignant anogenital lesions. Some high-risk types, such as HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68, have oncogenic potential, while LR-HPV strains like HPV 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, and 81 are generally linked to benign growths, including papillomas in the anogenital, cervical, and laryngeal areas [3]. Types 6 and 11 are among the most prevalent and often cause benign hyperproliferative lesions. The International Agency for Research on Cancer (IARC) has classified HPV types such as 16, 18, and others as carcinogenic to humans (group 1), while HPV 68 is likely carcinogenic (group 2A). HPV 16 and 18 are recognized for their high oncogenic potential, with other genotypes, like HPV 26, 53, 66, 67, and others, being possibly carcinogenic [4]. The majority of genital warts are caused by LR-HPV types 6 and 11, which have a minimal risk of progressing to malignancy [5].

Globally, HPV types 16 and 18 are the most commonly found strains, and these are strongly correlated with cervical cancers, making up around 70% of all cervical cancer cases, originating from both premalignant and malignant lesions [6]. High-risk HPV types are also linked to a significant percentage of oral cancers and contribute to malignancies in the anal, penile, vulvar, and head and neck regions [7]. Several studies have found high-risk HPV in benign lesions, while low-risk types are seen in more severe lesions. Mucosal HPV types typically affect the anogenital and respiratory tracts, while cutaneous HPV types primarily target the skin, including the hands and feet. Persistent HPV infection remains a major factor in the development of various cancers across different anatomical areas in humans [8]. While only a small subset of HPV strains are associated with cancer, these infections account for approximately 15% of all human cancers, with over one-third of these cases being attributed to HPV [9]. HPV infection is strongly associated with cervical cancer and other malignancies in the vagina, vulva, anus, rectum, penis, and oropharynx. CDC data from 2008-2012 indicated that of 38,793 new cancer cases across different body sites (cervix, vagina, vulva, penis, anus, and oropharyngeal), approximately 30,700 were linked to HPV infection, with 24,600 attributed to types 16 and 18, and 3,800 to types 31/33/45/52/58 [10].

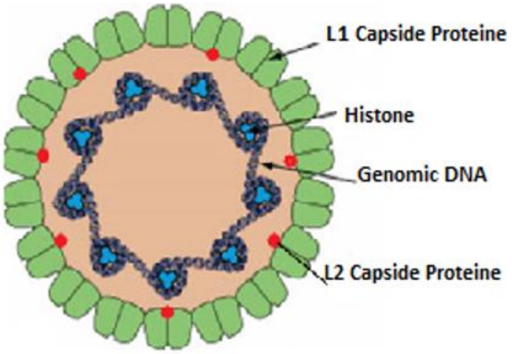
This review synthesizes current literature, offering an in-depth analysis of the HPV genome's structure and organization, the viral infection cycle, and the functional roles of the E6 and E7 oncoproteins.

Results and Discussion

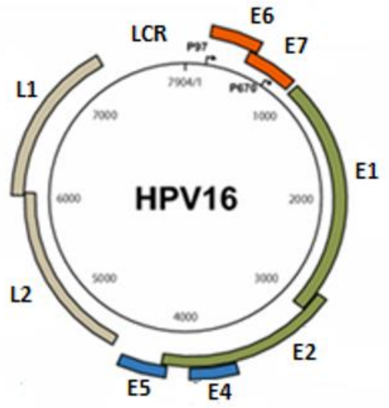
Human papillomavirus structure and genome organization

Human papillomaviruses (HPV) are classified as epitheliotropic DNA viruses, characterized by a circular double-stranded DNA genome ranging from 8 to 10 kilobases in size and 50-60 nanometers in diameter. These viruses are associated with histone-like proteins and are encased in two distinct capsid layers, termed L1 and L2 **(Figure 1a)**. The L1 protein forms the major capsid, arranged in a pentameric structure with 72 capsomeres, each consisting of five monomeric subunits, each approximately 55 kDa. The L1 capsid's stability is reinforced by disulfide bonds between the capsomers. In contrast, the L2 protein (75 kDa), a minor component, plays a crucial role in assembling the capsid by blocking or sealing the central opening of each pentameric unit [11].

Carcinogenic types of human papillomavirus (HPVs) are known to express auxiliary proteins such as E4, E5, E6, and E7, in addition to capsid proteins L1 and L2, and replication factors like E1 and E2, which are conserved across papillomaviruses [12]. These proteins play a crucial role in evading the immune system and are involved in viral replication, which influences the cellular environment for optimal replication [13]. The promoter P670 controls the expression of the L1 and L2 late open reading frames (ORFs), with their activity occurring primarily in the upper layers of the epithelium due to intricate regulatory modifications. The six ORFs—E1, E2, E4, E5, E6, and E7—are expressed from different promoters at various stages of epithelial cell differentiation. The genome also contains a non-coding region known as the long control region (LCR) or upstream regulatory region (URR), which houses the replication origin and regulatory sequences necessary for gene expression [14]. The organization of the HPV16 genome and its structural components are depicted in **Figure 1b** [11].



a)



b)

Figure 1. a) structure of human papillomavirus, and b) genome organization of the high-risk alpha HPV 16 types

The early proteins associated with the viral structure and genome, as outlined in the literature [11, 15], perform the following roles:

- The E1 protein, which encodes a virus-specific helicase DNA, is crucial for the replication and amplification of the HPV genome, with its binding regions varying in length and sequence.
- The E2 protein is known for its ability to bind both viral and host genome sites, with conserved N- and C-terminal sequences across different papillomavirus types. E2 is involved in processes such as transcription, replication, and genomic partitioning, with its actions relying on interactions with host cell genetic products, often altering their typical functions for the virus's benefit.
- The E4 and E5 proteins exhibit significant sequence diversity across papillomavirus types, which contributes to the virus's varying tropisms and transmission pathways. These proteins are involved in the release of viral particles from epithelial cells.
- E2 also regulates the transcriptional activity of E6 and E7 proteins, which are critical for controlling the cell cycle in all HPV strains. This regulation allows for genome amplification in the middle layers of the epithelium and helps the virus evade certain innate immune responses.
- The L1 protein is central to HPV prevention vaccines because it induces immune responses by generating neutralizing antibodies, offering protection against the virus.
- The L2 protein assists in the virus's ability to bind to host cellular receptors, facilitating the viral particle's internalization, transport to the nucleus, and delivery of viral DNA to replication sites. Additionally, E2 contributes to the packaging of the viral DNA into new capsids.

Human papillomavirus infectious cycle

HPV relies on a specific mode of transmission that involves penetration into the flattened epithelial layers of the skin and mucosal membranes. The virus's life cycle is driven by the host cell's biological processes, beginning with micro-abrasions that facilitate the infection of basal stem cells in the epithelium. Once inside, the virus targets these self-renewing cells, which are stimulated to proliferate as part of the wound healing process, leading to the viral infection. The sequence of HPV replication is detailed in the literature [11], and the cycle, illustrated in **Figure 2**, includes the following stages:

- After entry, the virus activates the E1 and E2 genes to regulate genome copy numbers, attracting essential proteins to the viral replication origin, which are required for DNA replication.
- Expression of E1, E2, E5, E6, and E7 genes occurs in the suprabasal layers, promoting viral genome stability and facilitating cell division. This increase in infected cells results in the production of infectious virions.
- As cells in the epithelium differentiate, promoter activation ensures sustained expression of E1, E2, E6, and E7 genes. This, in turn, leads to the simultaneous upregulation of L1 and L2 gene expression, as well as E4, which contributes to genome amplification and the replication of viral copies within the cell.
- In the granular layer, the major and minor viral capsid proteins, L1 and L2, are synthesized and released, assembling into virions that move to the stratum corneum of the epithelium, thus completing the viral capsid formation.

Cycle of life

HPV's lifecycle unfolds in two distinct phases: the maintenance phase and the differentiation phase. During the maintenance phase, viral proteins are produced at very low levels in undifferentiated cells, contributing to immune evasion and the persistence of the virus. As the virus progresses to the differentiation phase, HPV-infected cells move out of the basal layer, leading to a significant increase in viral protein production. This shift also delays the expression of infection markers in regions that are less susceptible to the host's immune system. Research indicates that this phase establishes a unique infection period for high-risk (HR) or low-risk (HL) HPV types: HR-HPV, particularly HPV-16, has a considerably higher likelihood of causing chronic infections with a prolonged clearance time (~6-12 months) [16].

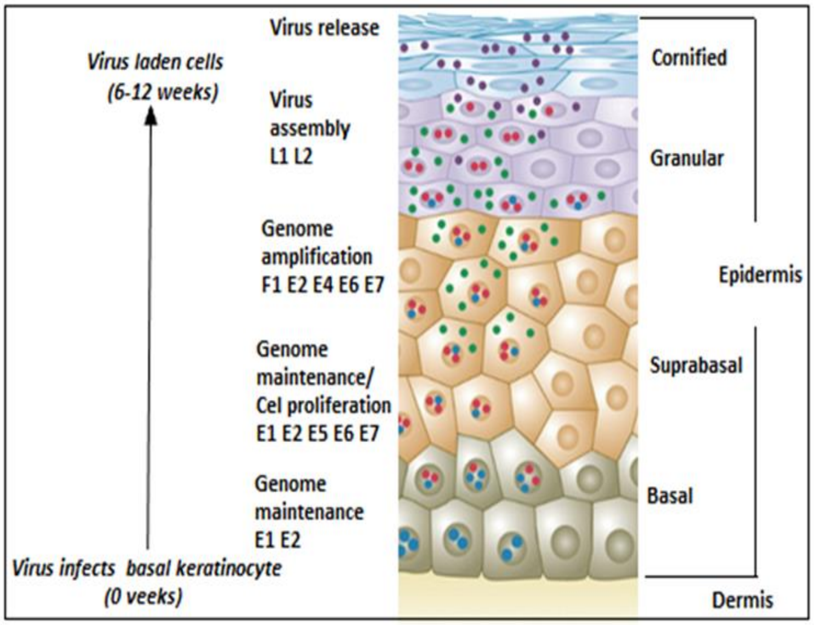


Figure 2. Life cycle of HPV infection (adapted: [11, 17])

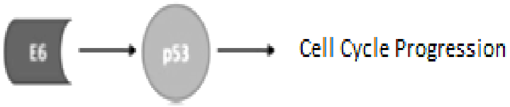
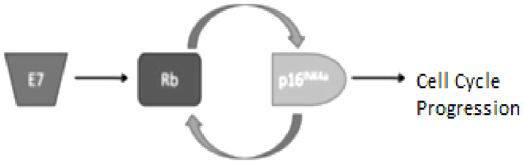
The Role of E6 and E7 oncoproteins in carcinogenesis

Studies have revealed that specific alpha-HPV strains target the mucosal epithelium, reaching the basal epithelial cells via microabrasions [18]. Unlike many viruses, HPV does not have its replication machinery, relying on host cell division and layering for viral replication. As the virus progresses from the basal to the suprabasal layers, the HPV oncoproteins E6 and E7 become crucial players in the process. These proteins orchestrate the regulation of cellular pathways that control cell maintenance, proliferation, and differentiation, particularly in the differentiated suprabasal area, where viral genome amplification takes place. This process not only influences the cell cycle but also affects apoptosis, facilitating viral persistence [8]. The productive viral cycle of HR-HPV alpha strains is a precisely regulated sequence, but during chronic infection, the viral DNA integrates unpredictably into the host genome, contributing to cellular immortality and eventually leading to malignancy.

In contrast to the virus's primary structural proteins, the oncoproteins E6 and E7 exhibit a high degree of variability and low conservation. These oncoproteins promote viral replication and cellular proliferation in differentiated cells by disrupting critical cell cycle checkpoints and interacting with various cellular proteins [19]. Several key interactions, such as E6's regulation of telomerase, E7's degradation of hypophosphorylated retinoblastoma proteins (pRb) and PDZ domain proteins, and E6's degradation of the tumor suppressor protein p53, are essential to their oncogenic action [20-22]. **Table 1** outlines the oncogenic pathways influenced by HPV E6 and E7, along with the properties of these oncogenes [13, 23].

HPV infections are a major cause of cervical cancer, with the E6 and E7 oncoproteins playing direct roles in both initiating and sustaining tumor growth. However, there is still debate about the specific actions of E6 and E7 in basal cells infected by low-risk HPV types (such as HPV 6 and 11), which typically do not lead to cancer but can cause lesions through infection at the site of a wound or micro-injury. For high-risk strains, particularly those affecting the cervix, the E6 and E7 proteins significantly enhance the proliferation of basal and parabasal cells, potentially leading to neoplastic transformations [24].

Table 1. Major properties and oncogenic pathways of HPV E6 and E7.

Major properties	Oncogenic pathways of E6 and E7.
E6 • Promotion of p53 degradation via the proteasome • Stimulation of telomerase expression • Breakdown of PDZ domain proteins involved in maintaining cell polarity • Suppression of innate immune responses	
E7 • Reprogramming of cells at the epigenetic level through increased KDM6A and KDM6B expression • Disruption of the pRb/E2F pathway by promoting pRb degradation • Induction of the DNA damage response (DDR) in differentiated cells to enhance viral genome replication • Suppression of innate immune responses	

Research findings emphasize that altering the expression of E6 and E7 complicates the accurate grading of neoplastic lesions [20], which is based on how far basal cells infiltrate the underlying epithelial layers [25]. Oncoproteins E6 and E7, predominantly produced by high-risk HPV types, interact with the tumor suppressors p53 and pRb, eventually leading to genetic instability and mutation accumulation. E6, in particular, drives the degradation of p53, a critical guardian of the genome, whereas E7 binds to and disables the tumor-suppressive function of the retinoblastoma protein family [26]. These two oncoproteins, abundantly present in both early and advanced cervical neoplastic lesions linked to high-risk HPV, play a pivotal role in tumor development. The expression of E6 and E7 is governed by the E2 gene. When HPV's circular DNA becomes integrated into the host genome—a fundamental event in malignant conversion—this integration often disrupts the E2 gene, leading to uncontrolled transcription of E6 and E7. In addition to undermining apoptotic pathways and fostering chromosomal instability, E6 and E7 interfere with the pro-apoptotic protein Bax. E6 also extends the life span of infected cells by promoting telomerase activity, effectively contributing to cellular immortality. E7, on the other hand, modifies the phosphorylation status of pRb, disabling its regulatory capacity. Under normal circumstances, pRb controls the transcription factor E2F by sequestering it, thereby preventing premature cell cycle progression. However, once E7 binds pRb and inhibits its function, E2F is liberated, allowing it to bind DNA and facilitate the transition from the G1 to S phase, a process tightly linked to cyclins and cyclin-dependent kinases. Furthermore, the transition governed by p53 is mediated by the p21 protein, which acts as a brake on the G1/S checkpoint [27]. In cells expressing E7, the formation of a non-functional E7-pRb complex prevents the retention of E2F, thus driving cell cycle progression and proliferation. HPV strains differ in their oncogenic potential depending on their ability to produce these proteins; for instance, HPV types 6 and 11 cannot inactivate p53 and pRb, whereas HPV 16 and 18 show a high propensity to initiate malignant transformation.

The integration of HPV genetic material into the host cell's DNA is closely associated with structural changes in the cervical squamous epithelium, beginning with low-risk intraepithelial lesions in individuals predisposed to high-risk infections. These lesions exhibit features such as nuclear irregularities and heightened mitotic activity. While integration sites can vary across chromosomes, they often lie within regions vital for cellular survival. Notably, the insertion of the full viral genome is not required for carcinogenesis; incorporation of the E6 and E7 genes alone is sufficient to drive malignant transformation. Cells harboring integrated HPV DNA display accelerated growth and diminished ability to differentiate. Moreover, this integration halts the productive viral replication cycle, preventing the formation of intact virions. Although this marks the functional endpoint of the virus, it enables continuous synthesis of oncogenic proteins.

Typically, integration of HPV DNA is absent in low-grade squamous intraepithelial lesions (LSIL) but is frequently observed in high-grade squamous intraepithelial lesions (HSIL), reinforcing the irreversible nature of the integration process. Without therapeutic intervention, HSIL can progressively advance into cervical carcinoma over extended periods, sometimes spanning several years or decades.

Interestingly, in approximately one-quarter of cervical cancers caused by HPV 16, the viral DNA remains episomal rather than integrated. In contrast, HPV types 18, 31, and 35 are nearly always detected in integrated form in associated cancers. In cases where HPV DNA persists in episomal form, mutations have been identified in the YY1 regulatory sequences—elements that serve as binding sites for the YY1 transcription factor, which governs the expression of numerous cellular genes. These YY1 mutations disrupt transcription factor attachment, thereby facilitating unchecked expression of E6 and E7 oncogenes, which in turn promotes abnormal cell proliferation and unregulated progression through the cell cycle [28].

Prevention and therapeutic opportunities

Prevention

In 1972, Stefania Jabłońska proposed a link between verruciform epidermodysplasia and skin cancers associated with HPV, laying the early groundwork for understanding viral oncogenesis. Five years later, Harald zur Hausen introduced a pivotal hypothesis implicating HPV as a critical factor in cervical cancer pathogenesis. This theory gained substantial support when Zur Hausen and his team, in 1983 and 1984, identified HPV types 16 and 18 as being directly involved in cervical tumorigenesis [29]. Over the following decade, mounting data confirmed the carcinogenic roles of these HPV types, including their involvement in malignancies of the oropharynx and oral cavity, as further substantiated by the IARC [30].

In immunocompetent individuals, HPV infections tend to resolve naturally, with around 70% clearing the virus within one year, and approximately 90% doing so within two years. However, infections caused by oncogenic HPV strains can persist due to inadequate immune responses, elevating the likelihood of progression to malignancy [31]. The importance of both innate and adaptive immunity is especially evident in immunocompromised populations, where persistent HPV infections and related cancers occur more frequently. Chronic infection can lead to squamous intraepithelial lesions, which often precede the development of premalignant and eventually invasive cervical cancer over a period ranging from 12 to 15 years [32].

Preventive strategies, including both vaccination and screening, are central to reducing the burden of cervical cancer. Studies have demonstrated that early detection through cervical screening enables better risk stratification for women infected with high-risk HPV types, particularly those at greatest risk of malignant transformation.

Public health measures such as practicing safe sex help reduce HPV transmission rates. Moreover, prophylactic vaccines—Cervarix, Gardasil, and Gardasil 9—offer significant protection against high-risk HPV strains. The nonavalent HPV vaccine (Gardasil 9 or 9vHPV), available in the United States since 2014 and subsequently adopted in Canada, Australia, and the European Union by 2015, targets seven high-risk types (16, 18, 31, 33, 45, 52, and 58) along with low-risk types 6 and 11 [33]. This expanded formulation, V503, includes virus-like particles (VLPs) representing five additional HPV strains (31/33/45/52/58), providing broader coverage. Vaccination with 9vHPV can prevent approximately 90% of cases involving genital warts and cancers of the cervix, vagina, anus, and other HPV-associated sites globally [34].

While the Pap smear remains an effective method for detecting cervical abnormalities associated with HPV, especially in regions that are difficult to access clinically, it is less reliable for identifying lesions in the oropharyngeal region, where HPV-related cancers also occur.

Diagnostic methods

A wide range of diagnostic strategies are currently employed to detect high-risk HPV infections. Traditional histological assessment remains a cornerstone in identifying cervical infections, focusing on tissue abnormalities rather than molecular markers specific to HPV. These histological examinations are guided by morphological changes, as illustrated in the grading of cervical intraepithelial neoplasia (CIN), where the extent of atypical cell involvement across the epithelial layer distinguishes CIN1, CIN2, and CIN3 stages. **Figure 3** illustrates the increasing abnormal cellular proliferation characteristic of these grades. Among them, a histopathologically confirmed CIN3 is considered a critical threshold that warrants surgical intervention [35].

One promising innovation in HPV screening is the use of DNA methylation profiling, particularly for high-risk

HPV types. This method is gaining attention as a viable alternative to cytological tests, largely due to its reproducibility, even when performed with brush-based self-sampling tools, and its alignment with expert cytology interpretations. Comparative studies have indicated that molecular HPV detection methods—including various PCR-based tests—outperform signal amplification assays such as s-LA and m-LA in identifying HPV-positive clinical samples [21].

For direct detection of viral oncogenic proteins, immunoassays like the Sca Rapid Test have emerged, showing notable specificity for the E6 protein. This test targets E6/E7 oncoproteins associated with HPV types 16, 18, and 45. Since HPV cannot be propagated in cell culture, diagnostic protocols have relied heavily on the identification of viral genetic material within infected tissues. Most of these rely on amplification techniques to detect viral DNA, which confirms the presence of infection in cervical epithelial cells. However, a major limitation of DNA-based diagnostics lies in their low predictive value for high-grade lesion development, as many HPV infections are transient and do not lead to cancer.

To address this, diagnostic assays have shifted focus toward mRNA-based technologies, particularly those detecting E6/E7 transcripts. These assays are capable of identifying oncogenic activity from five specific high-risk HPV types—namely 16, 18, 31, 33, and 45—as well as a broader panel of 14 oncogenic HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Unlike DNA tests, RNA-based diagnostics offer a more accurate reflection of active viral replication and cellular transformation. Research shows a correlation between elevated E6/E7 mRNA expression and the severity of cervical lesions, suggesting that these markers may provide superior prognostic information compared to DNA alone, thus improving screening precision and disease prediction [22].

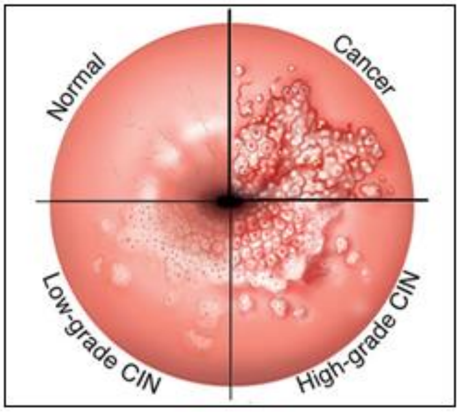


Figure 3. Stages of HPV infection

Therapeutics

Although human papillomavirus (HPV) has a well-established link to oncogenesis, there is currently no direct antiviral treatment specifically capable of eradicating HPV infections. While certain molecular pathways and potential inhibitory targets have been identified, there remains a pressing need for the development of novel therapeutic strategies that can act on these established mechanisms [23]. One promising avenue under clinical investigation involves the CRISPR/Cas9 gene-editing system, which has shown potential in suppressing the oncogenes E6 and E7. This method induces programmed cell death and halts cellular proliferation by reactivating key tumor suppressor proteins TP53 and pRb. A comparative overview of CRISPR/Cas9 and RNA interference approaches is provided in **Table 2**, highlighting their respective advantages and applications [23].

Evidence supporting the therapeutic potential of CRISPR/Cas9 has been steadily accumulating. For example, CRISPR-mediated targeting of E6 mRNA leads to a reduction in its expression, which in turn results in an upsurge of TP53 protein levels [36]. Similarly, disrupting the function of E7 via this gene-editing approach has demonstrated efficacy in impeding cervical cancer progression [37]. Moreover, precise editing of E6/E7 transcript regions—specifically targeting their promoter and open reading frames (ORF)—has led to significant reductions in E6 and E7 mRNA expression, elevation of TP53 protein, suppression of RB protein, induction of apoptosis, and inhibition of proliferation in SiHa cells. In vivo models have also shown diminished tumor growth following Cas9-mediated interventions. The first successful editing of HPV16 and HPV18 mRNAs through CRISPR/Cas9 technology was reported in 2014, signifying a pivotal step in the exploration of genome-editing therapeutics for HPV-driven cancers [38].

Further, in vivo applications have demonstrated that delivering CRISPR/Cas9 directly into tumors activates apoptotic pathways and curbs tumor growth, laying the foundation for potential adjuvant therapies in cervical cancer management. Beyond HPV, CRISPR/Cas9 systems are being tested across a spectrum of biomedical applications, such as genome-wide screening, gene disruption in various organisms, and targeted elimination of other pathogens like HBV and HIV.

Despite advancements in molecular therapies, clinical treatment of cancer remains standardized for both HPV-negative and HPV-positive individuals, often based on tumor stage and classification. Therapeutic options typically include surgery, radiotherapy, chemotherapy, or their combinations. When addressing precancerous cervical abnormalities, several procedures are available. These include loop electrosurgical excision procedure (LEEP), cryotherapy (freezing abnormal tissue), conization techniques using surgical tools or lasers to excise a cone-shaped sample from the cervix, and laser vaporization methods, which utilize focused light energy to eliminate dysplastic cervical tissues.

Table 2. CRISPR/Cas9 approach compared to RNAi

Targets	CRISPR/Cas9	RNAi
Loss-of-function mechanism	Frameshift DNA mutation	Post-transcriptional RNA degradation
Result	Permanent knockout	Reversible knockdown
Transgenes	Cas9 nuclease gRNA	si/shRNA
Guiding sequence	gRNA	si/shRNA
Required sequence information	Transcriptome	Transcriptome
Off-target space	Cuts as monomer	Transcriptome Genome
Transcript variants region	All variants	All variants

Conclusion

Among the wide spectrum of human papillomaviruses (HPVs), certain strains are directly implicated in the development of malignancies such as cervical cancer in women, penile cancer in men, and oropharyngeal cancers across both genders. Infectious pathogens are responsible for about 15% of all human cancers, with HPV alone contributing to nearly a third of those cases [9].

While low-risk oncogenic HPV strains are known to induce genital warts (condylomata) and mild epithelial changes, it is the high-risk oncogenic types that are associated with more severe pathological conditions, such as cervical intraepithelial neoplasia grade 2 and above—an early warning indicator of cervical cancer. The viral oncoproteins E6 and E7 are key drivers of HPV-mediated carcinogenesis, primarily by inactivating tumor suppressor proteins p53 and pRb. One promising therapeutic strategy for addressing cervical cancer is RNA interference targeting E6 and E7, which has shown the capacity to disrupt molecular functions critical to the virus's oncogenic mechanism. Silencing these oncogenes has demonstrated favorable outcomes in experimental cancer treatment models.

Despite the promise of prophylactic vaccination, its implementation remains complex and is still in the early stages of widespread adoption. As a result, therapeutic approaches remain essential for managing HPV-related conditions. Ongoing research has played a pivotal role in enhancing diagnostic and preventive strategies for HPV-induced diseases. Nonetheless, continued scientific investigation is crucial to better understand the molecular biology and epidemiological behavior of diverse HPV genotypes, which will be instrumental in evaluating the risks associated with persistent infection and its potential to progress toward malignancy.

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Ethics Statement: None

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