Journal of Translational Medicine

REVIEW

Open Access

# Human papilloma virus (HPV) mediated cancers: an insightful update

Sadaf Khursheed Baba[1], Shahad Shahdad Eissa Alblooshi[2], Reem Yaqoob[1], Shalini Behl[3], Mansour Al Saleem[4], Emad A. Rakha[5,6], Fayaz Malik[7], Mayank Singh[8], Muzafar A. Macha[9], Mohammed Kalim Akhtar[1], Walid A. Houry[10,11], Ajaz A. Bhat[12], Asma Al Menhali[2], Zhi-Ming Zheng[13] and Sameer Mirza[1,14*]

## Abstract

Human papillomavirus (HPV), a DNA virus, is a well-documented causative agent of several cancers, including cervical, vulvar, vaginal, penile, anal, and head & neck cancers. Major factors contributing to HPV-related cancers include persistent infection and the oncogenic potential of particular HPV genotypes. High-risk HPV strains, particularly HPV-16 and HPV-18, are responsible for over 70% of cervical cancer cases worldwide, as well as a significant proportion of other genital and head and neck cancers. At the molecular level, the oncogenic activity of these viruses is driven by the overexpression of E6 and E7 oncoproteins. These oncoproteins dysregulate the cell cycle, inhibit apoptosis, and promote the accumulation of DNA damage, ultimately transforming normal cells into cancerous ones. This review aims to provide a comprehensive overview of the recent advances in HPV-related cancer biology and epidemiology. The review highlights the molecular pathways of HPV-driven carcinogenesis, focusing on the role of viral oncoproteins in altering host cell targets and disrupting cellular signalling pathways. The review explores the therapeutic potential of these viral proteins, and discusses current diagnostic and treatment strategies for HPV-associated cancers. Furthermore, the review highlights the critical role of HPV in the development of various malignancies, emphasizing the persistent challenges in combating these cancers despite advancements in vaccination and therapeutic strategies. We also emphasize recent breakthroughs in utilizing biomarkers to monitor cancer therapy responses, such as mRNAs, miRNAs, lncRNAs, proteins, and genetic markers. We hope this review will serve as a valuable resource for researchers working on HPV, providing insights that can guide future investigations into this complex virus, which continues to be a major contributor to global morbidity and mortality.

**Keywords** HPV, Cancer, E6, E7, Oncoproteins, Cell cycle, Apoptosis, Therapeutics

## Introduction

HPV infection is the most common sexually transmitted infection worldwide, carrying significant societal implications. It can be contracted by sexually active individuals, both men and women [1], and it is more prone in women, with an estimate suggesting that 80% of women could acquire genital HPV by the age of 50 [2]. Now, HPV has been recognized by the World Health Organization as the causative agent of several cancers. About 5% of all malignancies in humans, including those of the cervical, vulvar, vaginal, penile, anal, head and neck cancers, particularly oropharyngeal regions and oral cavity, are caused by HPV [3–5]. Over 400,000 lives are lost to these cancers each year [6]. It is estimated that about >90% of cervical cancers are caused by HPV infection [7]. The main contributors to HPV-related malignancies are the virus's persistent infection and the activity of its oncogenes [8–10]. Due to the lack of noticeable symptoms, HPV infection often appears to be clinically asymptomatic, yet a few lesions that may

*Correspondence:
Sameer Mirza
sameermirza@uaeu.ac.ae; mirzasam@gmail.com
Full list of author information is available at the end of the article

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

develop into invasive malignancies can be seen in the genital organs [11].

Currently, there are many HPV genotypes known, which are divided into high-risk HPV (HR-HPV) and low-risk HPV (LR-HPV) based on their ability to cause cancer [12, 13]. The International Agency for Research on Cancer (IARC) now recognizes 229 HPV genotypes, with the list growing [14]. HR-HPV genotypes are found to be responsible for the majority of HPV-related carcinoma [15, 16]. For instance, genotypes [16, 18, 26, 31, 33, 35, 39, 45, 51–53, 56, 58, 59, 66, 68, 72, 81] are known to cause oropharyngeal and anogenital malignancies in humans [17]. Furthermore, HPV16 and HPV18 are responsible for more than 70% of cervical cancer cases [18], whereas HPV16 contributes to 87% of global OPSCC cases [19, 20]. In contrast, LR- HPV strains, such as HPV 6 and 11, may induce warts on the genitalia, anus, mouth, and throat; nevertheless, they infrequently lead to malignancy [21]. A clear correlation exists between the severity of HPV infection and the intensity of lesions, as well as the prevalence of oncogenic HPV genotypes, suggesting a link between these genotypes and the development of cancers, including cervical cancer (CC), head and neck squamous cell carcinoma (HNSCC), anal cancer, and less common cancers such as penile, vaginal, and vulvar cancers [22]. Harald Zur Hausen's innovative work transformed the contemporary comprehension of cervical cancer by demonstrating a causal relationship with human papillomavirus (HPV). In 1976, he proposed his hypothesis that HPV is the causative agent of cervical cancer [23]. His meticulous research also improved the understanding of HPV's role in various cancers [24]. His discoveries facilitated the advancement of the HPV vaccine, an essential instrument in preventing cervical cancer and diminishing HPV-related worldwide morbidity and mortality [25, 26]. Substantial advancements have been achieved in the prevention of HPV-related cancers via vaccines and screening methods. Notwithstanding these gains, difficulties persist, such as low vaccination rates in low- and middle-income nations and the necessity for wider deployment of HPV preventive programs globally [27].

This review examines recent developments in HPV-related cancer biology and epidemiology, emphasizing HPV's role in carcinogenesis. It elucidates the mechanisms underlying HPV-induced carcinogenesis and the influence of viral oncoproteins on host cellular targets and signalling pathways.. Furthermore, we represented areas of HPVs association with various cancers, existing methods for diagnosis and treatment, therapeutic potential and strategies of targeting oncoproteins in cancers, various biomarkers, and vaccinations available. These prospective targets and biomarkers offer avenues to alleviate the worldwide burden of HPV-related diseases via early intervention, tailored treatment approaches, and maybe curative medicines. Further research in this domain is essential to achieve a thorough comprehension of the molecular mechanisms behind oncoprotein-mediated cancer metastasis and to formulate novel diagnostic and treatment approaches for patients with HPV- induced metastatic disease.

## HPV-induced cancer epidemiology

Men and women can both be affected by HPV infections. Studies estimate that over 80% of sexually active individuals will have contracted HPV by the age of 45 [28]. Ninety percent of HPV infections resolve within 2 years on average [29]. However, genital warts and malignancies are among the diseases that can result from persistent infections [4]. HPV-16 and 18 cause ninety percent of HPV-related malignancies; however, cases associated with HPV 31, 33, 45, 52, and 58 have been rising [30].

Geographically, there were significant regional differences in the frequency of HPV infection and related malignancies. Countries in Africa, South America, and parts of Europe have the highest prevalence of HPV infection globally (≥ 33.87%), followed by regions in Europe and Australia (16.93–33.87%), with lower rates observed in some countries in North and South America (< 16.93%) [31]. Asia exhibited a relatively lower overall HPV prevalence; however, a rising trend was observed between 2004 and 2017 [17]. Rates of HPV infection differ around the world, with developing nations having a higher prevalence (42.2%) than developed ones (22.6%) [32, 33].

Studies indicate that HPV is present in up to 99.99% of cervical cancer (CC) cases, demonstrating a strong correlation [34]. Every year, about 570,000 cases of cervical cancer are reported worldwide due to HPV infection, which accounts for 8.6% of all female malignancies [35]. Owing to the extensive implementation of screening and preventive measures, the prevalence of cervical cancer has significantly decreased [36]. However, low- and middle-income countries (LMICs), particularly those in South America, Africa, and Asia, face a disproportionately high burden of HPV-related CC [37]. This is due to limited access to healthcare in resource-constrained settings [38]. The World Health Organization (WHO) initiated the global Cervical Cancer Elimination Initiative in 2020 to expedite the elimination of cervical cancer (4 cases per 100,000 women-years) and has set targets to be accomplished by 2030 [39]. Moreover, cervical HPV infection has been associated with an increased prevalence of anal

carcinoma [36]. It has been demonstrated over the years that HPV infection, particularly anal infections, is quite prevalent among men [40]. Affluent nations are experiencing a rise in the proportion of head and neck squamous cell carcinomas (HNSCCs) associated with HPV, notably oropharyngeal squamous cell carcinoma (OPSCC) [37]. The burden of HPV-positive OPSCC is significantly higher in males from more developed countries [19]. Europe se to about 50%, but North America had the highest frequency, with an estimated rate of 65% [41]. HPV-related malignancies continue to be a major source of morbidity and death globally, particularly in less developed nations, despite the availability of prophylactic measures [42].

## Transmission

The most well-documented route of HPV transmission is sexual contact, primarily through skin-to-skin or skin-to-mucosa contact [43, 44]. Oral HPV transmission is linked mainly to sexual activity, with little evidence indicating transmission via saliva or routine encounters [43]. However, non-sexual transmission routes are also possible, including contact with fomites, self-inoculation, indirect transmission via hands, and vertical transmission from mother to child during direct contact with an infected mother's genital tract or through ascending infection, especially after premature rupture of membranes [44]. Additionally, studies have shown that HPV can be transmitted through blood [45]. Effective measures are essential in clinical settings to prevent unintentional HPV transmission, as the virus can persist on medical equipment even after standard disinfection [46]. Raising awareness and implementing proper disinfection protocols is crucial to reduce transmission and its associated health impact.

## HPV life cycle

### HPV genome organization

HPV is a non-enveloped virus and belongs to the papillomavirus genus of the *papovaviridae* family. All HPVs have a double-stranded circular DNA genome of about 7.9 kb (Fig. 1A). It is composed of: (1) early (E) region encodes E1, E2, E1^E4, E5, E6, E7, E8^E2 proteins that are linked to infection, viral replication, and oncogenesis; (2) late (L) region encodes L1, L2 proteins [47]. (3) an upstream regulatory region (URR), also known as the long non-coding control region (LCR), is responsible for viral early promoter transcription and DNA replication but not responsible for protein coding functions [47, 48]. The URR has the most diversity and contains the p97 promoter and regulatory motifs. This functionality, URR analysis, can be used for HPV classification [21, 49]. The key features of the expressed HPV genes are summarized in Table 1. The icosahedral shell encapsidating the

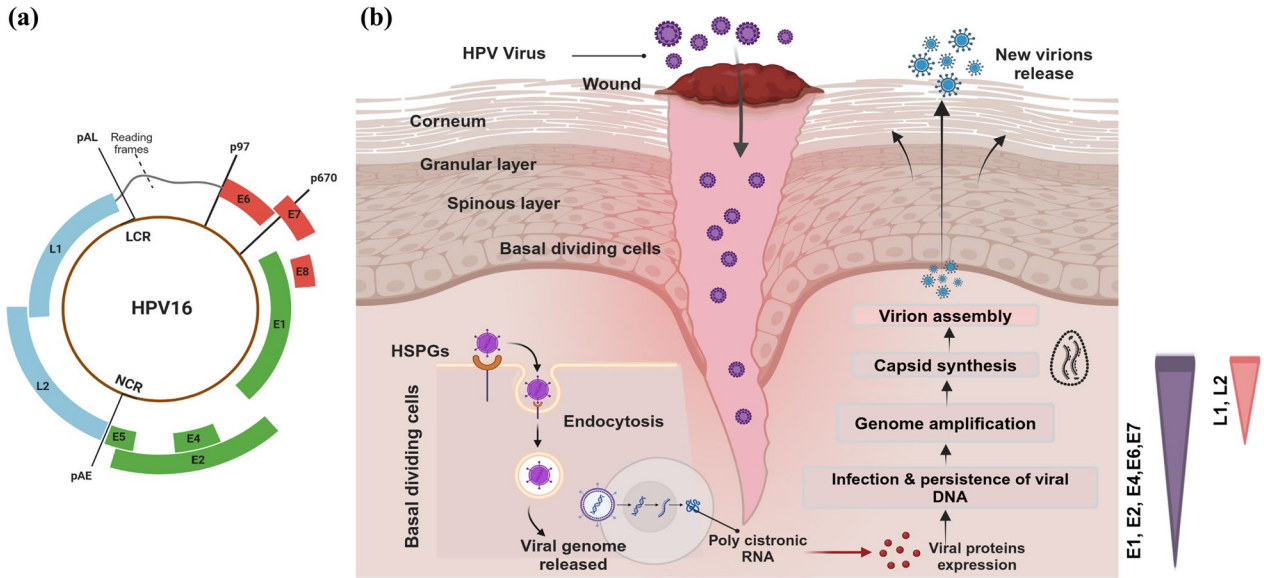


**Fig. 1** **A** HPV genome organization. The genome of HPVs, about ~7.9 kb circular double-stranded DNA, consists of approximately eight open reading frames (ORFs), which can be functionally categorized into three main regions: the E region, the L region, and the long control region (LCR). Early and late promoters (p) are denoted p97 and p670, respectively; early and late polyadenylation sites are denoted pAE and pALs, respectively with straight lines above the circular genome. **B** The HPV infection starts in the basal epithelial cells upon injury/trauma/permeability and ends with the assembly and virion release at the very top terminally differentiated epithelial cells. Early genes of E1, E2, E6, E7, E4, E5 and late genes of L1 and L2 are expressed in basal to superficial layers during the infection initiation, progression, and termination. Complete virions are then shed from the surface of the squamous epithelium in a non-lytic manner

**Table 1** Summary of the functions of Human Papilloma Virus genes. E, early genes and L, late genes

| Gene | Key functions | References |
|---|---|---|
| E1 | Helicase; involved in genome replication | [310] |
| E2 | Viral life cycle's master regulator, viral gene transcriptional regulator, partitioning viral genomes, reduces the expression of E6 and E7 | [311, 312] |
| E1^E4 | Expressed as late stage as a viral late gene, helps the virus escape the host cell via disruption host cytokeratin network | [313–315] |
| E5 | Small hydrophobic transmembrane proteins that are carcinogenic and contribute to the productive viral life cycle | [316] |
| E6 | Oncoprotein; inhibiting p53, counteracts the antiviral actions of E7 via preventing apoptosis | [317] |
| E7 | Oncoprotein inhibiting pRb,<br>Setting up the cellular conditions for immortalization and replication | [318] |
| E8^E2 | Suppressing the expression of genes and viral replication | [319] |
| L1 | key structural element of the viral capsid<br>Being shown following the differentiation of cells | [320] |
| L2 | A small capsid protein that actively contributes to the HPV virus's assembly throughout the infectious process | [321] |

genome is made up of 360 copies of a single protein, L1 arranged into 72 pentameric capsomeres most likely containing only one copy of L2 at the centre [50]. HPV also has early (PE) and late (PL) promoters and polyadenylation sites (pAE and pAL).

### Life cycle

The HPV life cycle is intricately tied to the differentiation of host keratinocytes in the epithelium. (Fig. 1B). The virus's productive phase and the random integration of its DNA into host chromosomes specifically target the basal of the epithelium [51, 52]. The virus needs microlesions/small breaks in the skin or mucosa to gain entry [53]. HPV L1 capsid protein attaches itself to cellular receptors on the surface of basal layer cells [54]. Heparin sulphate proteoglycans (HSPGs) appear to be the main receptor for the initial binding [55]. HPV entrance receptors include integrins (α6 integrin) [56–58], laminins [59], syndecan-1 [56, 60], annexin-A2 heterotetramer [61, 62], vimentin [63], and tetraspanin-enriched membrane microdomains [64]. The HPV genotype and cell type determine the receptor approach. Endocytosis drives the virus [65]. The virus travels within small vesicles through membrane-bound cytoplasmic components, the *trans*-Golgi network [66, 67], and the endoplasmic reticulum (ER) [67, 68]. The viral capsid is removed, and the viral genome is released in close proximity to the nuclear membrane due to a sequence of interactions and structural alterations in the vesicles [69]. Entry into the nucleus occurs through nuclear pores or mitosis when the nuclear membrane breaks down [70]. Upon nuclear entry into the dividing cells of the basal layer, the viral early promoter is activated to express a polycistronic RNA. This polycistronic RNA undergoes extensive alternative RNA splicing to express viral E6, E7, E1, E2. Early proteins help to sustain infection. E1 and E2 facilitate initial episomal viral genome replication. E6 and E7 proteins help to maintain replication via suppresses cellular differentiation, promote cell cycle progression, and prevent apoptosis in developing cells [53]. E4 proteins, the most common viral regulatory factor, may help differentiate keratinocytes, which promotes viral genome amplification in late phases of the viral life cycle [71]. Several thousand viral genomes are produced by late-stage DNA replication and it requires enhanced early proteins to complete and release virions [53]. Following cell's entry into the epithelium's outermost keratinized layer, freshly synthesized viral DNA is encapsidated with immunogenic capsid proteins L1 and L2 to create virion assembly which are subsequently released, and the life cycle is restarted. New virions are deposited in cornified layer that are continuously shed. HPVs do not induce complete cell lysis [72]. There is a lower limit on the duration of the viral life cycle since it takes around 3 weeks for a basal cell to differentiate and migrate to the epithelial surface [73].

## HPV carcinogenesis

Most of the HPV infections are asymptomatic and resolve on their own with time. The development of HPV infection to cancer is rare, despite of the overwhelming evidence linking HR-HPVs to several malignancies [74]. Persistent infection of basal and stem epithelial cells be the main factor leading to cancer development [75]. However, in rare cases, particularly with HPV types 16 and 18, reactivation of latent HPV infections may lead to malignancy [76, 77]. During persistent infection, there is an integration of the viral genome with the host genome that modifies the condition of host cells, facilitating the onset and progression of malignancies. Integration of the HPV genome typically involves the deletion of large segments of viral DNA and the disruption of the

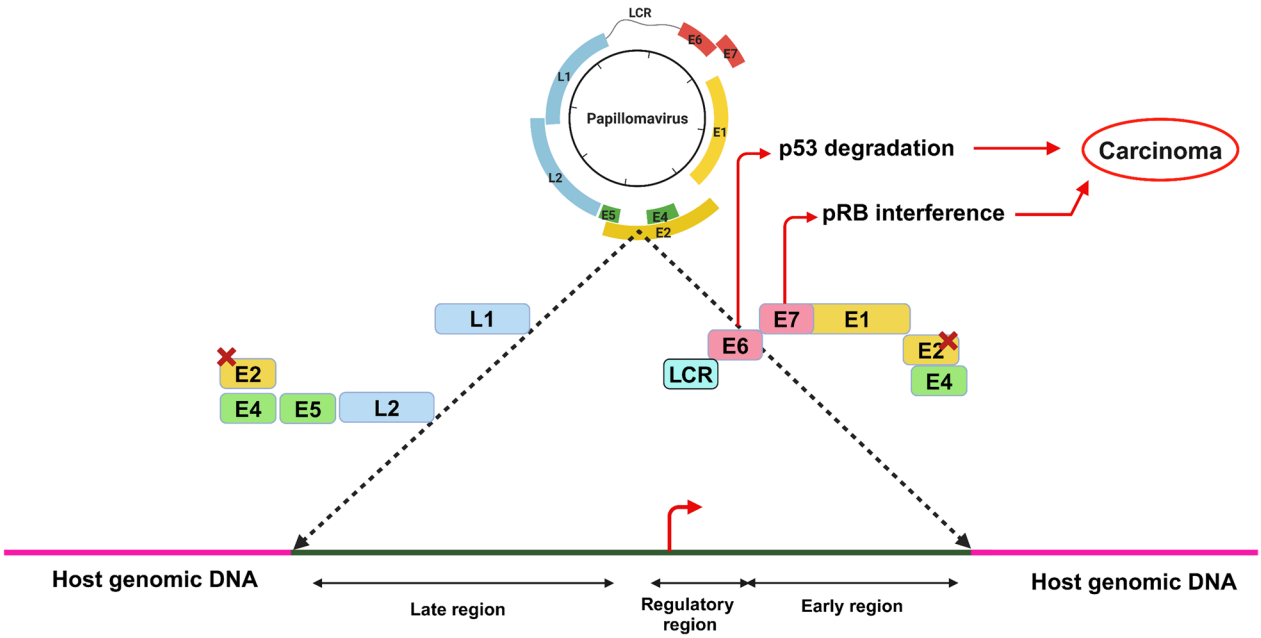


**Fig. 2** Integration of the HPV genome into the host genome induces disruption of the E2 gene, leading to the consecutive expression of the oncogenes E6 and E7, resulting in induced cellular immortalization, transformation, and, ultimately, carcinoma

E2 gene (Fig. 2). In this integrated form, the E6 and E7 genes remain intact and can be transcribed from the long control region (LCR) located upstream of the integration site. The disruption of E2 (and E2 repressor that negatively regulates E6 and E7 expression), and alterations to cellular promoter elements near the integration site can lead to increased E6 and E7 expression [78]. This increased expression is the critical alteration needed for the progression of infection to malignancy, regardless of the anatomical site infected [79, 80]. Overexpressed E6 and E7 activity interferes with the transcription of tumor suppressor genes (p53 and Rb), chromosomal instability, inhibits differentiation, and promotes cell proliferation, collectively increasing the risk of malignancies [53]. Moreover, progression of carcinoma is accelerated via dysregulated epigenetic modifications. For instance, HPV DNA and host cell genome causes the dysfunction of tumor suppressor genes, thereby accelerating the malignancies [81].

### Oncoproteins altering host cell targets

HPVs oncoproteins'best-known actions is to degrade important tumor suppressor proteins, leading to uncontrolled cell growth. E7 interacts with the tumor suppressor pRb, a retinoblastoma protein, to cause carcinogenesis [82] and other retinoblastoma pocket proteins, such as p107 and p130 [83, 84], resulting in the inhibition or proteasomal degradation of Rb's. Using the conserved and canonical LXCXE (L, leucine; C, cysteine; E, glutamic acid; X, any amino acid) based binding motif, E7 binds to unphosphorylated pRb [85]. Such binding enables ubiquitination and subsequent proteasome destruction, releasing the transcription factors E2 F, which causes active E2 F-dependent transcription that encourages the cell cycle's passage to the S phase, increasing proliferation and, coincidentally, the transcription of viral genes [84, 86]. E7 can further promote G1-S phase entry of the cell cycle [87, 88] by repressing or activating the expression of cell cycle regulatory proteins, such as cyclins A and E, and the cyclin kinase inhibitors p21 and p27 [75]. Additionally, E7 triggers the activation of DNA methyltransferase, which causes an uncontrollably high degree of DNA methylation. This perturbation additionally tampers with the epigenetic modulation of cellular processes [89–91]. Targeting Rb-E2 F and other cell cycle regulators can have the biological consequence of upregulating p53, another tumor suppressor that would ordinarily counterbalance these effects by preventing cell growth and triggering apoptosis [84]. To prevent this, another oncoprotein called E6 interferes with another tumor suppressor protein, p53 and BAK, a pro-apoptotic protein, inhibiting their function, preventing apoptosis, and allowing viral DNA replication to continue [92]. E6 binding to the ubiquitin ligase enzyme, referred to as E6 associated protein (E6 AP) results in proteasomal degradation and inhibition of p53 [89, 90]. As depicted in Fig. 3, there is a marked decrease in p53 levels in E6-expressing cells, which predisposes them to

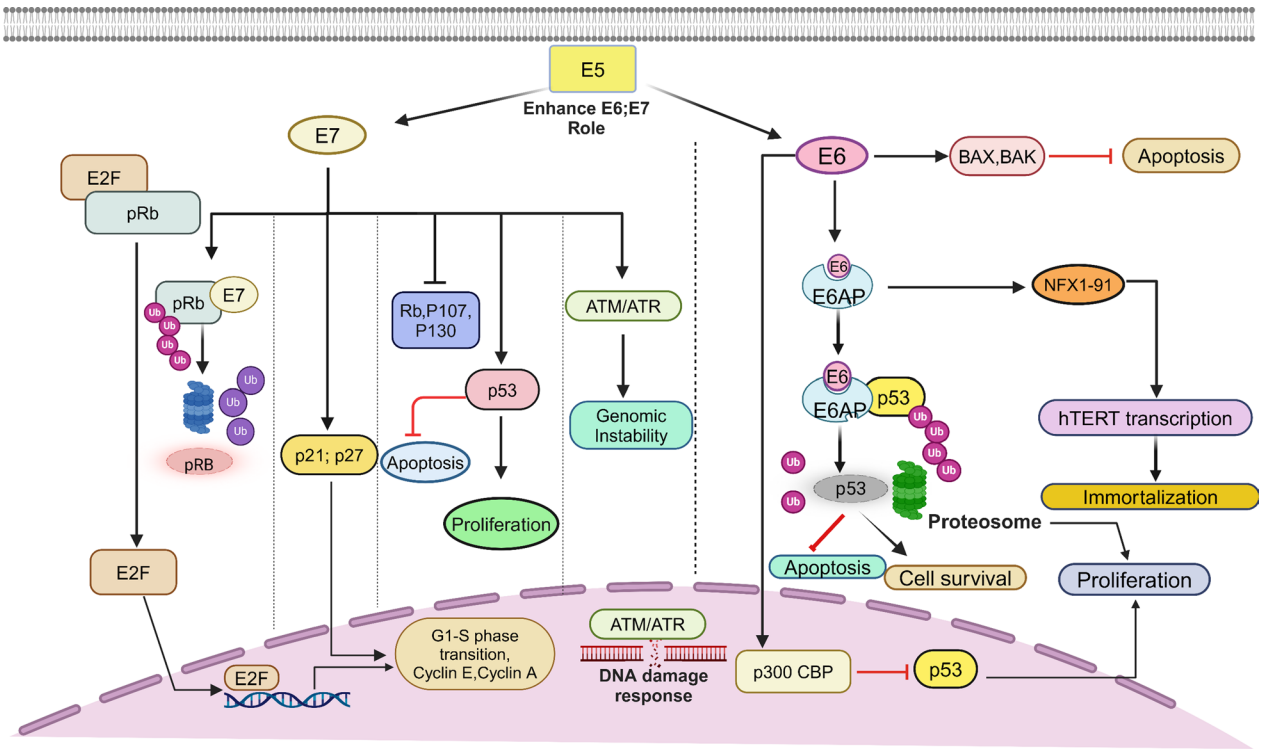


**Fig. 3** Events mediated and modulated by HPV E6/E7

the accumulation of mutations and chromosomal aberrations, resulting in greater chances of developing transformation, dysplasia, and cancer [93]. Other targets encompass a variety of important components, including proteins involved in apoptosis that regulate cell signalling and adhesion, as well as p300/CBP transcriptional activators that participate in differentiation regulation and cell cycle control [94]. In addition, E6 also triggers the transcription of telomerase reverse transcriptase (TERT), which is essential for cellular immortalization [95]. Due to impairment of DNA, the cells activate the DNA damage response (DDR) [96]. To encourage viral genome replication, HPVs also subvert the host DNA damage response, which raises replication stress and adds to genomic instability [97]. It is demonstrated that in the presence of single-strand or double-strand DNA breaks, E7 and E6 activate the ATM and Rad3-related (ATR) and ataxia telangiectasia-mutated (ATM) DNA damage repair pathways respectively [98]. Cell cycle arrest takes place due to the activation of these DNA damage repair pathways; E7, however, stops this from happening by causing claspin to degrade, a protein necessary for DNA damage checkpoint repair [99]. Head and neck cancer has also been linked to manipulation of DNA damage response, as HPV16 E7 causes DNA damage in an Rb-dependent manner that leads to tumor growth when combined with other DNA repair abnormalities [100]. As cervical squamous intraepithelial lesions progress in severity, the expression of DNA repair factors such as phospho-CHK1, pCHK2, FANCD2, and BRCA1 increases, suggesting a potential role for these pathways in the progression to malignancy [101]. Figure 3 lists the host cell targets for E6 and E7.

HR-HPVs'typical infectious life cycle depends on all of these interactions. Nonetheless, these cellular regulation networks and signalling pathways may be dysregulated due to elevated E6/E7 expression, which can lead to the advancement of tumors. Furthermore, the development of carcinogenesis may also be aided by the HPV E5 protein. E5 appears to enhance the roles of E6 and E7 in the growth of tumors, and it has numerous recognized activities that may aid in the transformation process [53, 102]. Studies have also shown that the HPV16 E5 oncoprotein is linked to cervical lesions and may influence apoptosis, cell proliferation, and differentiation in the process of carcinogenesis [103].

### Oncoproteins altering cellular signalling pathways

HPV early proteins aid in the malignant development of tumor cells via controlling the aberrant activation or inactivation of numerous tumor-related signalling pathways (Fig. 4). E5 is crucial in regulating cell proliferation,

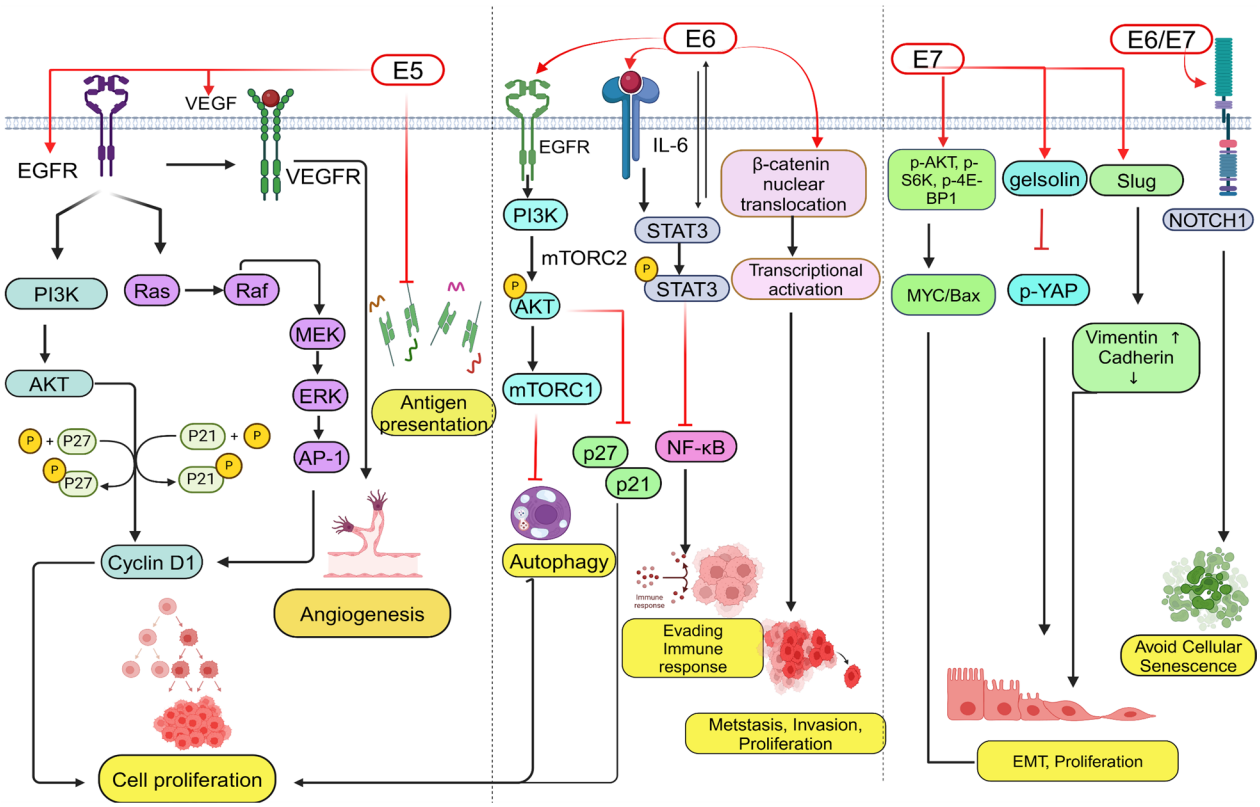


**Fig. 4** Tumor-associated signalling pathways regulated by HPV E6/E7

viral replication, and several signalling pathways that trigger oncogenesis. E5 can engage with the epidermal growth factor receptor (EGFR) and initiate MAPK/ERK and PI3 K/AKT pathways [104]. EGFR activates MEK 1/2 and PI3 K, which phosphorate ERK1/2 and AKT, respectively. Vascular endothelial growth factor (VEGF), a crucial element in angiogenesis, is ultimately elevated [105]. AKT activation leads to p21 and p27 phosphorylation, which gets accumulated in the cytoplasm and loses its ability to inhibit cyclin-dependent kinase (CDK) 4/6-cyclin D1 activity, facilitating the transition of cells from the G-phase to the S-phase. The S-phase is extended, resulting in increased basal layer cell proliferation and accelerated viral genome replication [106]. Furthermore, MAPK activation maintains the expression of cyclin D1, hence facilitating cell proliferation and activating activator protein 1 (AP-1) which is crucial for initiating and sustaining E6 and E7 expression, thereby amplifying viral expression [107]. It is demonstrated that in HPV-positive CC patients, high expression of c-Jun (AP-1 dimer) is associated with poor prognosis [108]. E5 also evades immune response via downregulating major histocompatibility complex (MHC)-I expression and inhibiting MHC II transporting to the cell surface for antigen presentation [17, 109].

E6 possesses the capability to induce uncontrolled cell proliferation. It has been reported that E6 controls the PI3 K/Akt/mTOR pathway. Akt phosphorylation by mTORC2 activates mTORC1, inhibiting autophagy and increasing viral replication and cell proliferation [110, 111]. It also leads to uncontrolled proliferation via downregulating the expression of cyclin inhibitor kinases such as p21 and p27 and CDKs [112]. E6/E7 has been shown to target Notch1 to avoid cellular senescence [113]. Activated neurogenic locus notch homolog protein 1 (Notch 1) keeps HPV16 E6 and E7-induced transformation intact and prevents p53-induced apoptosis [114]. E6 augments STAT3 signaling by promoting IL-6 production via the Ras-related C3 botulinum toxin substrate 1/NF-κB pathway. STAT3 can subsequently enhance the expression of E6. Activated STAT3 facilitates the transcription of genes associated with cell proliferation [115]. HPV-related malignancies also exhibit upregulation of the wnt/β-catenin pathway, another signalling pathway that is responsible for cell division, migration, and proliferation [116, 117]. E6 is reported to promote the production of Wnt signalling downstream target genes like cyclin D1 and C-myc and helps β-catenin nuclear translocation, which promotes cell growth and proliferation [118] E6 promotes

the expression of MZF1, leading to the subsequent transcription of NKX2-1 and FOXM1. FOXM1 augments the transcription and translocation of β-catenin [119]. Extracellular vesicular Wnt7b, which is increased by E6 in HPV-16 and HPV-18 positive cells, can notably boost β-catenin signaling to enhance angiogenesis and cancer invasion [120]. Interferon regulatory factor 3 interacting with E6 inhibits its phosphorylation, transcriptional activity, and translocation, suppressing downstream IFNβ production and allowing HPV to avoid immune responses [121].

E7, another oncoprotein, promotes the generation and progression of carcinoma, as it can trigger DNA damage and genomic instability. HR-HPV16 E7 has been found to stimulate PI3 K signalling. Increased AKT expression encouraged Pirin expression, which in turn activated NF-κB signalling cascade, which promotes cell migration and EMT in CC and oral cancer cells. EMT can also be induced by E7's ability to interact with gelsolin to drive cytoskeletal actin reorganization and encourage pYAP retention in the cytoplasm. YAP1 activation beyond the carcinogenic threshold thereby arises cervical cancer [122]. E7 may regulate the expression of EMT-associated transcription factors Slug, which increases vimentin expression and decreases E-cadherin expression, simultaneously contributing to EMT and migration [123]. HPV-16 E7 and E6 collaboratively enhances the accumulation of β-catenin in the nucleus, elevates the expression of c-Myc and transcription factors, and facilitates the onset of EMT [118]. HPV16 E7 is reported to prevents phosphorylation of p70S6 K, 4E-BP1, and AKT probably by enhancing expression of a long non-coding RNA lnc-FANCI-2 [124, 125]. Upregulates the expression of the c-MYC, Bax, and insulin receptors, leading to cell proliferation and cancer progression [126]. E7 also helps in immune evasion by suppressing RIG-1 and cGAS-STING pathway activation and IFN production and release [127]. These are the various oncogenic signalling pathways modulated by HPV oncoproteins to promote carcinogenesis.

## HPV and various cancers

The main risk factor for the development of HPV-associated malignancy is HPV infection. HPV infections are often under the immune system's control and disappear in your body in a year or two. Long-term, high-risk HPV infections can cause alterations in the cells that, if left untreated, might worsen over time and eventually develop into precancerous and cancerous conditions. Six cancer forms are associated with HPV: these are cervical

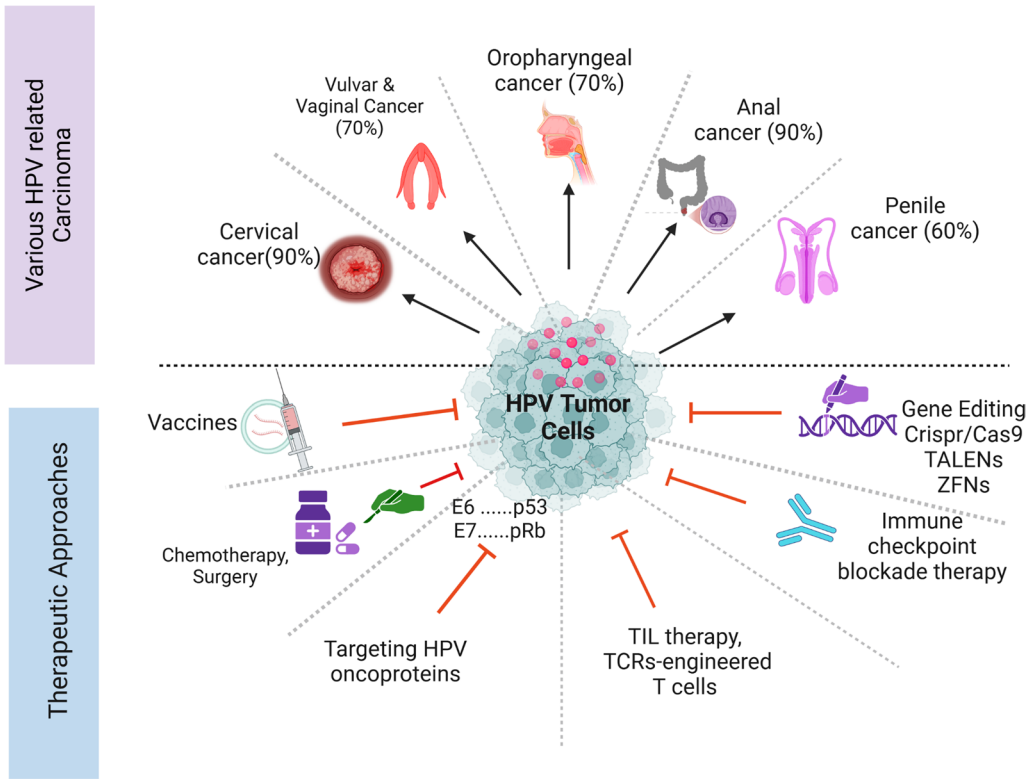


**Fig. 5** Depiction of HPV-related cancers comparing percentages of HPV-associated and other causes

[15, 128], vulvar, penile, vaginal, oropharyngeal and anal cancers [129–131]. As shown in Fig. 5, it is estimated that chronic, high-risk HPV infection is the cause of 90% of cervical and anal cancers, 70% of vulvar and vaginal cancers, 60% of penile cancers, and 70% of oropharyngeal cancers [132, 133]. These organs'interior surfaces are lined by squamous, thin, flat cells infected with HPV. Most HPV-related cancers are called squamous cell carcinomas. Certain malignancies of the cervix, known as adenocarcinomas, are caused by HPV infection of glandular cells.

#### Cervical cancer

Eighty percent of women who engage in sexual activity will, at some point in their lives, contract HPV [6]. A viral clearance has been confirmed in roughly 90% of affected women. However, the virus can continue to infect 10% of infected women, resulting in E5, E6, and E7-mediated mutations that can initiate cancer, as predicted by the stochastic model [134]. Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the two histological subtypes that make up cervical cancer. SCC, which arises from squamous cells in the ectocervix, is responsible for 75–83% of cases globally, whereas AC, which comes from glandular cells that create mucus in the endocervix, causes 12–25% of instances [135–137]. Subsequent to HPV infection during SCC progression, a dysplastic alteration occurs in the cervical epithelium's squamous cells, and these lesions are known as cervical intraepithelial neoplasia (CIN) [137]. Semi-quantitatively, the epithelial changes that makeup CIN have been categorized into three groups: CIN1 through CIN3. CIN1 lesions, also referred to as low-grade CIN, are flat warts that retain the ability to produce virus particles and complete the HPV life cycle. Proliferation is low in this instance, occupying the bottom third of the epithelium. Basaloid cells that occupy one to two -thirds of the lower epithelium are characteristic of CIN2 lesions. Finally, CIN3 lesions are a prelim stage of cervical cancer since they contain two-thirds of the epithelium's thickness. Given their propensity to develop cervical cancer, CIN2, and CIN3 are regarded as high-grade CINs [138, 139]. Only 10% to 20% of persistent HPV infections have the potential to progress to cervical cancer, with the majority of infections clearing up a few years after exposure [29]. If a persistent infection has been established, HPV can integrate into the host genome, which plays a critical part in the development of cancer, with HPV-human fusion transcripts being the primary driver of malignant transformation [78, 140]; viral integration is seen in 80% of HPV-16- and 100% of HPV-18-positive cervical carcinomas [141, 142]. Surgical procedures, radiation therapy, and chemotherapy are the current treatments used, but innovative immunotherapies have the potential for better prognosis and patient survival [143]. Over the years, a better understanding of HPV biology has led to the identification of several biomarkers, which could help develop more potent treatments and better prognoses [144].

#### Head and neck squamous cell carcinoma (HNSCC)

Head and neck cancers account for 47,813 new cases and 10,492 deaths annually, or about 3% of all new cancer cases in the US [145]. HNSCC can develop in various parts of the upper aerodigestive tract, including the oral cavity, nasopharynx, paranasal sinuses, oropharynx, hypopharynx, and larynx. Among these, OPSCCa in men has the highest prevalence and is increasing due to HPV, whereas cervical cancer was previously the most common HPV-associated cancer [146]. At least 85% of all HPV-positive OPSCCa have been reported to be related to HPV-16 [147]. According to predictions, the number of cases will increase over the next ten years, surpassing 30,000 cases annually by 2029 [148]. It is due to oral sexual behaviors have risen over the past 50 years, especially among younger people. The pathogenesis of HPV-related HNSCC has been found to be influenced by intratumor heterogeneity, including genetic, epigenetic, and histopathologic variations. The range of treatment responses seen in both clinical trials and established clinical practice is influenced by this heterogeneity [149].

#### Anogenital cancer

HPV is also found to be associated with 40–85% of all anal, penile, vaginal and vulvar carcinomas. In this instance, anogenital infections can serve as viral reservoirs for cervical infections, which can serve as HPV reservoirs for anogenital infections [150].

##### *Anal cancer*

HPV infection is significantly linked to 90% of anal cancer cases, with HPV16 being the most common form identified in 75% of cases [151, 152]. Anal cancer is becoming more common in both genders; however, it is more common in high-risk populations, including HIV-positive individuals and homosexual men. Precancerous lesions precede HPV-related anal cancer, and the two diseases have comparable etiologies [151]. Squamous cell carcinoma (SCC) is the most common histological type of malignancy observed in the anorectal region [153]. Anal SCC patients (20–30%) usually do not experience many symptoms therefore diagnosis becomes difficult or delayed [154]. Recent studies have shown that treating anal high-grade squamous intraepithelial lesions (HSIL) significantly lowers the risk of developing anal cancer compared to active surveillance in patients with a history

of anal HSIL [155]. The early acquisition of anal HPV is substantially prevented by HPV vaccination [156]. Using anal cytologic test (or anal swab), samples are taken into tests through high-resolution anoscopy (HRA) [157]. HRA is the gold standard for the screening and diagnosis of anal dysplasia and cancer. It is generally used after an abnormal cytology result [158]. However, anal cytologic analysis and anal HPV testing have limitations, and high-resolution anoscopy is not a practical screening method due to its expensive nature and restricted availability [159]. Therefore, more investigations are required to enhance screening algorithms for the detection of anal HSIL.

#### *Vulvar and vaginal cancer*

Although vaginal and vulvar cancers are relatively rare tumors, however, their occurrence is rising globally [160]. This has been partly linked to the acceleration of the epidemiology of HPV infection [161]. High- income countries tend to have greater rates of both cancers [162]. A higher percentage, 78% of vaginal cancers, are linked to HPV infection; in contrast, only 25% of vulvar cancers are HPV positive [163]. Two different routes lead to invasive squamous cell carcinoma in the vulva (VSCC); one-third of vulvar SCC is HPV-associated, whereas the other pathway is HPV-independent. This difference can be seen in the lesions that precede it, known as differentiated vulvar intraepithelial neoplasia (dVIN) and HSIL, respectively [6]. Compared to HSIL, dVIN has a larger chance of developing into cancer. Precursors and vulval malignancies positive for HPV are associated with younger ages and smoking.

On the other hand, aging and persistent inflammatory conditions like Lichen Sclerosis (LS) are linked to HPV-negative vulval cancer and precursor lesions [6]. Patients with advanced vulvar cancer have poor treatment outcomes despite having a better prognosis if diagnosed in the early stages of the disease [164]. Improved vulvar cancer prognosis is therefore crucial, particularly for patients whose disease has progressed to an advanced stage. While far less common than cervical cancer, vulvar cancer is discovered to be more common than vaginal cancer. Therefore, the low frequency of vulvovaginal malignancies may be one factor contributing to the lack of evidence on this topic [162]. Compared to cervical recurrence, which has a larger body of evidence, the effectiveness of HPV vaccination in preventing vulvovaginal recurrence remains largely unexplored, and currently, no screening program exists. Therefore, further research is needed to provide stronger evidence to support preventive measures for protecting women's health [160].

#### *Penile cancer*

Penile cancer (PC) is a rare malignant tumor in the male genitourinary system, with an estimated 36,068 new cases and 13,211 deaths worldwide in 2020, according to the Global Cancer Statistics (GLOBOCAN) [162]. PC is mostly developed from genital warts and precancerous lesions. Penile intraepithelial neoplasia (PeIN) occurs in mucosal epithelial areas, commonly in glans and foreskin in the penis, with a 45.5% HPV DNA prevalence [165, 166]. It has also been demonstrated that there are two possible routes for malignant transformation in penile cancer development, depending on whether HPV infection is present or not. Like vulvar cancer, PeIN, the precursor to penile cancer, is HPV-positive in the majority of cases (up to 90%), with HPV 16 being the most prevalent genotype (40%).

In contrast, a lower number (50%) of penile carcinomas is associated with HPV. Phimosis, chronic inflammation, obesity, smoking, UVA phototherapy, immunosuppression, multiple sexual partners, and socioeconomic factors are associated with HPV-negative penile cancer and its precursor lesions [167]. HPV vaccines are a primary strategy for preventing cancers induced by the HPV. These vaccines are particularly injected into young people to reduce the likelihood of HPV infections. Studies indicated that the vaccinations are highly effective against related precancerous and cancerous conditions induced by high-risk HPV subtypes like HPV 16 and 18 [168]. Regular screening and HPV testing are important for adults as well as high-risk patients who can suffer from abnormalities. Circumcision status can suggest the risk of being infected with sexually transmitted diseases like HPV, as uncircumcised men can commonly develop genital warts due to greater exposure of genital mucosa to HPV [169]. All age groups appear to have a high prevalence of HPV infection; however, the incidence of HPV-associated vulvar and penile cancer is significantly lower than the incidence of cervical cancer, indicating that the vulvar and penile epithelium may be more receptive to productive HPV infections, which support the viral life cycle to generate viral progeny with appropriate control of viral gene expression (or be more likely to be controlled by host immunity), rather than abortive/non-productive infections, which are more likely to progress to malignant transformation [14]. Vaginal cancer would also fall under these principles.

## Diagnosis

To prevent and manage HPV infection and stop the spread of cancer, early diagnosis of HPV is essential. Due to the complicated nature of HPV infections, regular

**Table 2** Diagnostic approaches to characterize HPV

| Test method | Strengths | Limitations | Refs. |
|---|---|---|---|
| Cytology or Pap smear test | Early detection of precancerous lesions in CC,<br>Simple to operate,<br>easy to learn,<br>cost-effective,<br>performed in any laboratory | Limited sensitivity, low specificity,<br>inadequate repeatability | [172, 173] |
| Visual inspection test with acetic acid (VIA) | Higher detection rate for high-grade lesions,<br>Fast results, less follow-up visits | False positive results | [175] |
| Colposcopy | Non-invasive, painless,<br>High sensitivity,<br>Cost-effective | Low specificity | [176] |
| Thinprep cytologic test (TCT) | Enhanced quality of TCT slides,<br>Higher detection rate,<br>Non-invasive, | – | [177] |
| HPV DNA PCR | High sensitivity and specificity | Not prognostic marker | [181, 182] |
| mRNA PCR | High sensitivity and specificity<br>Reflects virus's active transcription,<br>Prognosis of illness | Required technical expertise | [183] |

screening is essential for monitoring HPV-related lesions [17, 46] (Table 2).

## Cytological screening

The principal approach to identifying precancerous and cancerous lesions arising from HPV infections has been cytological screening, including the Papanicolaou stain (Pap smear), colposcopy, or visual inspection analysis.

### *Cytology or Pap smear*

It is used to find aberrant cervical epithelial cells, which could be a sign of cervical carcinoma or precancerous lesions, and serves as a routine CC screening. Pap smear has led to a significant decrease in the incidence of CC and death [170]. This decrease has been ascribed to increased coverage and the execution of effective Pap-based screening programs [171]. Nonetheless, the primary clinical limitations of the Pap smear include its limited sensitivity, low specificity, inadequate repeatability, and an annual or triennial testing schedule [172, 173].

### *Visual inspection test with acetic acid (VIA)*

It is a good substitute for cytology. Since Pap screening method entails multiple steps, requiring a cytopathology laboratory equipped with qualified experts to identify cancer facilitates timely treatment if necessary [3]. This 3–5% acetic acid solution is applied on the cervix for one to two minutes to complete the VIA. The cervix is then examined for a white colour change, which may indicate underlying pathology. Studies have shown that early diagnosis employing VIA can reduce cervical cancer incidence by 25% and mortality by 35% [174]. Despite its higher sensitivity, VIA has not been widely adopted in mass screening programs, likely due to its higher false-positive rates [175].

### *Colposcopy*

It functions as an intermediary diagnostic technique between visual inspection and low-magnification microscopy. This technique can identify subtle lesions imperceptible to the naked eye, precisely locate the lesion, and facilitate tissue sampling for histopathological analysis, improving diagnostic accuracy, especially for asymptomatic early-stage cervical cancer. The examination is affordable, personnel training is easy, and the procedure is non-invasive and painless, leading to high patient adherence. However, it is associated with high sensitivity but low specificity [176].

### *Thin prep cytologic test (TCT)*

It is a thin-layer liquid-based cytological screening method for cervical lesions. The approval of liquid-based cytology by the FDA also represented a significant achievement, providing a uniform distribution of a monolayer of cells that was largely devoid of obscuring components [175]. It is superior to the Pap smear test for a higher detection rate of abnormal cervical cells and smears enhanced quality, attaining an effectiveness exceeding 95%. It facilitates early prevention, detection, and management of cervical cancer, hence decreasing the associated mortality rate. Owing to its non-invasive and convenient characteristics, this test is appropriate for routine gynaecological examinations [177].

### HPV testing

HPV testing has emerged as a promising screening method for cervical cancer as a more sensitive method than the Pap test alone with reduced false-negative rate for cervical lesions [178]. Numerous HPV testing techniques have been developed, such as Hybrid Capture II and PCR, which can identify high-risk HPV genotypes linked to cervical cancer [179]. In many affluent nations, HPV testing is being explored as an additional cervical cancerscreening technique [180]. Due to high sensitivity, specificity, and capacity to detect numerous HPV types simultaneously, PCR-based assays are frequently employed in the diagnosis of genital warts, cervical cancer screening, and other HPV-related illnesses [181, 182]. Although HPV DNA testing is used to confirm HPV infection, it does not show how the infection is progressing. Thus, additional assays were created, particularly those that focused on viral oncoproteins or E6/E7 mRNA, to ascertain the virus's active transcription in infected cells and to offer more precise information regarding the prognosis of the illness [183]. PCR-based tests, which are regarded as the gold standard, are frequently used to identify HPV at the nucleic acid level.

In recent years, more sophisticated analytical tools,such as isothermal amplification techniques (IATs) and CRISPR-Cas-based systems, have surfaced that may surpass them in terms of ease of use, affordability, or temporal efficiency [184]. For instance, in cervical cancer and oropharyngeal squamous cell carcinoma, loop-mediated isothermal amplification (LAMP) has become a viable method for the quick and affordable identification of high-risk HPV subtypes. It demonstrates high sensitivity and specificity comparable to PCR, the current gold standard [185, 186]. Furthermore, the AmpFire HPV assay,, showed similar sensitivity to PCR-based tests for identifying CIN2 + and CIN3 + in samples collected by the patient and clinician, qualifying it for use in mass screening initiatives [187]. Similarly, the CRISPR-Cas system has been employed in the detection of HPV [188–200]. Scientists have created CRISPR-Cas12a-based assays that show great sensitivity and specificity for identifying HPV16 and HPV18 DNA in a variety of clinical samples, such as plasma and anal swabs [201, 202]. These assays can yield results in 35–80 min without requiring costly equipment or a high level of technical competence by integrating CRISPR-Cas technology with isothermal amplification techniques like recombinase polymerase amplification (RPA) [192].

### Co-testing

There is a gradual shift from relying solely on cytological testing to adopting co-testing, which combines cytology and molecular testing to enhance screening efficacy [203, 204]. One study reported that co-testing detected CIN grade 3 or higher (CIN3 +) with high sensitivity (99.4%) [205]. Another study found that co-testing achieved a sensitivity of 93% for detecting AIN2 + [206]. However, co-testing is associated with a higher rate of false positives than using the Pap test alone [207]. These screening methods highlight the potential for addressing high-risk HPV (HR-HPV) infections and abnormal cell changes, such as precancerous lesions, before they progress to malignancy.

### Screening criteria

Numerous societies have provided screening criteria for women at average risk, including those for cervical cancer and HPV screening, depending on age and HIV co-morbidity. These guidelines are based on recommendations from the WHO, USPSTF (United States Preventive Services Task Force), and CDC (Table 3) [3]. The CDC currently does not recommend routine screening for HPV infection in men, as no approved tests are available. However, anal Pap testing may be offered to men

**Table 3** CDC, USPSTF, and WHO recommendations for cervical cancer and HPV screening in women depending on age and HIV co-morbidity

| Female populations | WHO | CDC and USPSTF |
|---|---|---|
| < 21 | Not advised | Not advised |
| 21–30 | Not advised | Pap testing every three years |
| 30–65 | HPV DNA testing every 5–10 years; complete after 2 negative tests | Pap test every 3 years, Pap test with HPV co-testing every 5 years,or HPV testing every 5 years |
| Having HIV | HPV DNA test starting at age 25 every 3–5 years | Pap test or Pap test with co-testing starting at age 21 yearly for three years then every three years for life |

who engage in anal intercourse or are HIV-positive [208]. HPV screening primarily targets individuals at high risk, focusing on cervical and anal cancers. As a result, there are limited opportunities for screening HPV-associated oropharyngeal cancers [209]. Further research is needed to develop effective strategies for detecting and screening for HPV infection in other cancers, such as oropharyngeal cancer [157].

To support the cervical cancer elimination strategy, surveillance-based programs for effective cervical screening need to be expanded and strengthened. This includes utilizing survey-based methods, conducting population-based screening studies, encouraging women to participate in screening programs, implementing routine screening with cytology or VIA, and improving infrastructure and medical staff facilities in resource-limited areas [210]. Additionally, the WHO highlights that HPV DNA screening, which allows for self-sampling, can help increase screening rates, as some women may prefer self-sampling over traditional provider-administered methods [211].

## Biomarkers

Biomarkers play an important role in the detection and prediction of malignancies linked to HPV. These could improve clinical management choices and perhaps save lives by facilitating early diagnosis of HPV infections and their progression to cancer, especially in developing nations [212]. Table 4 shows several promising biomarkers for diagnosis and management of HPV infections.

### mRNA biomarkers

Over the years, it has been well established that messenger ribonucleic acid (mRNA) could be a precise indicator of gene transcription activity. HPV E6/E7 mRNA detection has been studied recently as a possible biomarker for cervical cancer screening. Various studies have evaluated the detection of mRNA transcripts in cervical scrapings to identify cervical precancers [213–217]. It has been shown that to identifying HSIL in women who are positive for HPV, E6/E7 mRNA detection in cervical exfoliated cells is performed similarly to cytology triage [218]. Another study reported 100% positivity for E6/E7 mRNA in high-grade lesions associated with lesion progression [219]. These findings suggest that detecting E6/E7 mRNA could serve as a valuable biomarker and screening tool for cervical cancer, potentially reducing unnecessary procedures and alleviating patient concerns.

Additionally, recent research found that CAPZB mRNA levels may serve as a complementary marker for HR-HPV infection [220]. One study reported that in HPV-positive HNSCC patients, high expression of the *KEAP1* gene and low expression of *NRF2*, *TP53*, and *NQO1* genes were significantly associated with better survival [221]. HPV-positive HNSCC patients with higher *ZNF540* mRNA expression had higher overall survival (OS) [222]. In another study increased expression of follicular dendritic cell secreted protein (FDCSP), a chemokine-associated prognostic biomarker are associated with improved HPV-positive HNSCC patients'prognosis [223].

### ncRNAs as biomarkers

Non-coding RNAs (ncRNAs) are important in HPV-driven malignancies [224, 225]. Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are among the classes of non-coding RNAs (ncRNAs) that are dysregulated in HPV-related malignancies and are associated with tumor prognosis and progression [226]. These are found to play a significant role in tracking different cellular functions in gynaecological malignancies, several clinical trials are being conducted to find biomarkers and potential therapeutic benefits of ncRNAs [227].

#### *miRNAs*

miRNAs have gained attention as possible biomarkers for cervical cancer diagnosis and HPV infections as aberrant expression of oncogenic and tumor-suppressive miRNAs is important for cervical carcinogenesis during HPV infection [228]. miRNA dysregulation may be a significant factor in the development of cervical cancer [228], and the assessment of particular miRNAs may offer novel potential markers for cancer screening and the assessment of patients'prognosis [229–231]. In the progression of invasive cervical carcinoma, the up-expression of miR-16, miR-21, miR-25, miR-92a, miR-378, and down-expression of miR-22, miR-27a, miR-29a, and miR-100 are reported as the most frequent miRNAs [230, 232]. Other findings revealed cervical cancer tissues with upregulated levels of several miRNAs, including miR-15a-5p, miR-17-5p, and miR-21-5p [233]. A substantial drop in miR-375 expression in 170 cervical cancer tissues when compared to 68 normal tissues has also been reported [234]. Moreover, there is an improved accuracy for the diagnosis of cervical cancer when a combination of six elevated miRNA markers are used (miR-20a, miR-92a, miR-141, miR-183*, miR-210, and miR-944) [235]. In HPV-positive OPSCC, the overexpression of miR-182-5p, miR-133a-3p and miR-205-5p has been documented and thus can be used as prognostic indicators [236, 237]. In patients with HPV-positive tonsil and base-of-tongue

**Table 4** Indicating biomarkers for cervical cancer and HR-HPV infection screening and diagnosis

| Biomolecule | Tumor type | Biomarker | Expression | Outcome | Refs. |
|---|---|---|---|---|---|
| mRNA | CC | E6/E7 | High | Lesion progression | [219] |
| | | CAPZB | High | Distinguish between cervical LSIL − and HSIL + | [220] |
| | HNSCC | TP53 | Low | Associated with improved survival | [221] |
| | | NRF2 | Low | | |
| | | KEAP | High | | |
| | | NQO1 | Low | | |
| | | *ZNF540* | High | Improved OS | [222] |
| | | FDCSP | High | Improved OS | [223] |
| miRNA | CC | miR-21 | High | Depicts Cancer Progression | [232] |
| | | *miR-29a* | Low | | |
| | | miR-15a-5p<br>miR-17-5p<br>miR-21-5p | High | More in HPV-infected cervical cancer than in normal tissues | [233] |
| | | miR-218 | Low | Its downregulation involved in cervical cancer pathogenesis | [322] |
| | | miR-375 | Low | Advancement of Cervical cancer | [234] |
| | OPSCC | miR-182-5p<br>miR-133a-3p<br>miR-205-5p | High | prognostic indicators | [236, 237] |
| | TSCC/BOTSCC | miR-155 | High | increased OS and PFS | [238] |
| lncRNA | CC | RUSC1-AS1<br>LINC01411<br>LINC01990<br>LINC02099<br>LINC00452<br>ADPGK-AS1<br>C1QTNF1-AS1<br>H19 | High | Prognostic indicator | [240] |
| | | LINC01101 and LINC00277 | Low | Reduced expression with lesion and cancer progression | [241] |
| | HNSCC | *PRINS* | High | Associated with better OS and DFS | [242] |
| Protein biomarkers | CC | P16INK4a | High | Prognostic indicator | [243] |
| | | MCM2 | High | Prognostic marker | [249, 251] |
| | | CA-125 | High | Used in cervical cancer and ovarian cancer diagnosis | [245, 252, 253] |
| | | SCCAg | High | Poor response to treatment and lower survival rates | [254] |
| | OPSCC | P16INK4a | High | Prognostic marker | [244] |
| | Anal carcinoma | TOP2 A | High | Prognostic marker | [250] |
| DNA methylation markers | CC | DAPK1, RARB, TWIST1, EPB41L3, LMX1, and HPV16 L1 | Epigenetic modifications in DNA methylation patterns | Prognostic biomarkers and Potential diagnostic | [256, 259] |
| Genetic markers | CC | P53, PTEN,PIK3 CA,Kras mutation | Genetic alterations | Associated with resistance to therapy, poor prognosis, predicting response to treatment and overall survival | [245] |

cancer (TSCC/BOTSCC), increased overall survival and progression-free survival (PFS) have been reported, which has been associated to be significantly linked with increased expression of miR-155 [238].

#### *lncRNAs*

lncRNAs have also emerged as potential biomarkers and regulators in HPV-induced malignancies [239]. A study on cervical cancer prognosis identified the 8-lncRNA set (RUSC1-AS1, LINC01411, LINC01990, LINC02099, LINC00452, H19, ADPGK-AS1, C1QTNF1-AS1) as prognostic indicators [240]. LINC01101 and LINC00277 expression levels are also significantly linked to HPV presence. Their reduced expression is observed in cervical lesions and cervical cancer [241]. Another lncRNA, lnc-FANCI-2 expression has been reported as a potential biomarker for improved cervical cancer patient survival [124]. In HPV-positive HNSCC, lncRNAs, *MEG3*, and *H19* appeared downregulated, while *PRINS*, *CDKN2B-AS1*, *TTTY15*, and *TTTY14*, were found to be upregulated. High *PRINS* expression in HPV-positive HNSCC had significantly higher overall and disease-free survival due to the robust infiltration of immune cell [242].

### Protein markers

Several protein markers have shown potential as biomarkers for HPV-related carcinomas. P16INK4a is a tumor suppressor protein marker often used to identify high-grade cervical lesions and differentiate between benign and malignant cervical tissues [243]. It is also used to assess HPV status in HNSCC; its expression improves OPSCC survival [244]. Several other protein biomarkers are being studied for cervical cancer detection, including survivin, Ki-67, matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) [245]. Using p16 and Ki-67 staining in combination enhances diagnostic accuracy, especially in differentiating high-grade from low-grade lesions [246–248]. Others include minichromosome maintenance protein 2 (MCM2) and topoisomerase II alpha (TOP2 A), whose expression is associated with HPV-induced cervical lesions and anal carcinoma respectively [249, 250]. Both proteins can potentially serve as biomarkers for identifying precancerous and cancerous lesions. Notably, MCM2 shows strong expression in HSIL [249], and MCM2 expression is much higher in CIN and SCC than in normal cervical tissue [249, 251]. Cancer antigen (CA-125), is another protein biomarker that is elevated in cervical adenocarcinoma (ADC) [245, 252, 253]. SCCAg, an SCC tumor marker, increased levels suggest poor treatment response and diminished survival chances in CC patients [254]. Therefore, protein biomarkers possess significant potential in improving the early detection, diagnosis, and treatment of cervical cancer.

### DNA methylation

DNA methylation of human and HPV genes is a potential biomarker for cervical cancer screening and prognosis. Investigating changes in host and viral DNA methylation and their connection to cervical cancer development can provide valuable insights into the disease's mechanisms, aiding in both treatment and prevention efforts [255]. It has been shown that the severity of cervical lesions correlates well with increased frequency and level of methylation in both host and viral genes [256, 257]. Methylation biomarkers can identify early-stage modifications to differentiate between high-grade lesions and cancer and increase the effectiveness of cervical cancer screening [258]. Certain genes have demonstrated potential in differentiating between precancerous lesions, invasive malignancy, and normal tissue, including DAPK1, RARB, TWIST1, EPB41L3, LMX1, and HPV16 L1 [256, 259]. Accurate and timely triage of women with HSIL + cervical illness, both HPV-positive and HPV-negative, has been made possible by using very sensitive and specific hypermethylated DNA markers *FMN2*, *EDNRB*, *ZNF671*, *TBXT*, and *MOS* [260]. Before clinical deployment, specific biomarkers necessitate additional assessment and automation.

### Genetic markers

Genetic modifications in cervical cancer include several DNA sequence abnormalities that may function as indicators for detection, diagnosis, prognosis, and therapy response [261]. For instance, mutations in the p53 tumor suppressor gene most commonly mutated in cervical cancer at its aggressive stage may have prognostic significance. Mutation of another tumor suppressor gene, PTEN, promotes tumorigenesis via constitutive activation of the PI3 K/Akt pathway. Therefore, its assessment can provide prognostic information and guide therapeutic decisions in CC. Additional genetic alterations associated with cervical cancer encompass PIK3 CA and Kras mutations which may have implications for the targeted therapy. These genetic alterations function as significant biomarkers for the detection of cervical cancer, evaluation of risk, and selection of therapies [245]. However, further research is required to validate these biomarkers'therapeutic use and establish standardized testing protocols for their integration into standard clinical practice.

## Therapeutic approaches

### Targeting HPV early proteins

HR-HPV early (E) proteins play a major role in initiating HPV-mediated carcinoma. By developing novel therapeutic approaches directed towards targeting E proteins, it may be possible to eradicate all cancer

cells significantly. E6 and E7 proteins are recognized as primary oncogenes in cervical and head and neck cancers [262].

#### *Targeting E6 oncoprotein*

E6 leads to tumor suppressor protein p53 destruction via forming a complex with E6 AP [263]. Reactivating the action of p53 may be possible through the effective treatment strategy directed towards inhibiting the formation of this complex. Compound Cpd12 has demonstrated encouraging results by interfering with the E6/p53 interaction that blocks the E6-mediated degradation of p53 [264]. This method has extensive activity against cervical and head-and-neck cancer cells and is effective against several high-risk HPV strains, such as HPV16, HPV18, HPV45, and HPV68 [265]. Additionally, although attempts have been made to target p53 [266] or its negative regulators [267], no p53 drug discovery program has been approved by the food and drug administration (FDA) or European medicines agency (EMA) [268, 269]. To develop E6-directed therapies, numerous attempts have been performed, such as siRNAs [270–272], chemical matter, including affibodies, nanobodies [273, 274], intrabodies [275, 276], and small molecule inhibitors [277]. Furthermore, a viable approach for therapeutic intervention against many types of HPV is to target E6 interactions with cellular proteins that include PDZ binding motifs or acidic leucine-rich LxxLL motifs [278–280]. Polyhydroxy flavonoids, LxxLL-derived mini proteins, and LxxLL-based peptides have all been used to target the HPV16 E6 LxxLL binding groove [281–283].

#### *Targeting E7 oncoprotein*

E7 leads to the inactivation of tumor suppressor pRb, which also causes an increase in the free E2 F family of transcription factors (E2 F) in the cell. These events increase the cyclin-dependent kinase inhibitor p16 (p16INK4a) and abnormal proliferation, which is indicated by elevated Ki-67 expression [284]. This dependence on p16INK4a is dependent on its capacity to suppress CDK4/CDK6 activity and is mediated by the histone demethylase KDM6B. One possible therapeutic target in HPV-associated malignancies is the p16INK4a addiction. In p16-dependent cell lines, small molecule inhibitors of KDM6B, including a selective inhibitor of the histone demethylase JMJD3/UTX, GSK-J4, have demonstrated effectiveness in causing cell death [89]. Future treatments may benefit from the results of the interaction between E7 and HDAC inhibitors, which is a promising antiviral target. Recent clinical trials are investigating a variety of HDAC inhibitors to deactivate E7 since the overexpression of HDAC plays a major role in the advancement of cancer [285] Furthermore, phase I/IIa clinical trials have tested a p16INK4a peptide vaccination approach for patients with advanced HPV-associated malignancies, indicating the possibility of p16INK4a-targeted immunotherapy [286]. Additionally, the E2 protein has been studied as a possible therapeutic agent; VP22-E2 fusion proteins have been shown to be able to penetrate cells and cause apoptosis [287]. These oncoproteins represent promising therapeutic targets for HPV-related cancers.

### Treatment using genome editing technology

Recent research has exhibited diverse methods for utilizing genome editing technology to suppress E6/E7 expressions in cervical cancer associated with HR-HPVs. In vitro and in vivo studies have shown the effectiveness of local injection of CRISPR/Cas9, targeting both E6 and E7 concurrently in causing cell death and preventing tumor growth [288]. Silencing these genes resulted in the death of HPV18 and HPV16 cancer cells, inducing p53 and pRb expression [289, 290]. Moreover, p53/Rb protein overexpression and the inhibition of HeLa cell growth could be achieved by another method i.e., gene knockout chain reaction (GKCR) method, which targeted the HPV18 E6/E7. Thus, this technique may be promising for treating HPV infections and associated cervical cancer [291]. Transcription activator-like effector nucleases (TALENs) and zinc finger nucleases (ZFNs) are two more genome editing technologies that have also been investigated for cervical cancer treatment [292, 293].

### Other therapies

Depending on the clinical stage of the disease, treatment options for cervical cancer include surgery, chemotherapy and radiation therapy. Historically, cisplatin-based chemotherapy has been the standard of care. However, because of an increase in resistance to monotherapy, cisplatin-based chemotherapy has been found to be more effective when paired with other therapies such as bevacizumab, topotecan, paclitaxel, 5-fluorouracil or bleomycin [294, 295]. Moreover, Nocardia rubra cell wall skeleton, a New Drug in China, can mitigate T-cell exhaustion and augment local immunological responses in patients with HPV infection or diagnosed with CIN [296]. Additionally, immunotherapy like, immune checkpoint inhibitors (ICIs) such as tremelimumab, pembrolizumab, nivolumab, and durvalumab, alone or as combination therapies have gained attention recently as a treatment option for advanced or recurrent cervical cancer [297, 298]. In HPV-positive oropharyngeal cancer also, ICIs in combination with radiation therapy encouraging results are reported [298]. Therapeutic approaches focusing on the immune response against the

HPV proteins have been drawing attention. For instance, anti-tumor immunity offered by tumor-infiltrating lymphocyte therapy (TIL therapy), is expected to be effective in cervical cancer [299]. Moreover, engineered T-cell therapies with T cell receptors (TCRs)-engineered T cells targeting E7 are highly effective in the treatment of refractory HPV-related cancers, including cervical, vulvar, anal, and oropharyngeal cancers [299, 300]. In preclinical studies, E7-specific TCR-engineered T cells demonstrated high functional avidity and effectively killed HPV-16 + cancer cells in vitro and mouse models [301]. Similar approaches targeting HPV-16 E6 have also shown potential in preclinical studies [302]. These findings support the therapeutic potential of TCR-engineered T cells in treating HPV-related epithelial cancers. Additionally, topical medications such as imiquimod, podophyllotoxin, and cidofovir, as well as manual removal or destruction, are available therapies for genital warts [303].

### Vaccinations

A variety of vaccinations have been created and promoted to prevent HPV-associated cancers. Vaccinations tend to be combined with other therapies, including radiation, chemotherapy, and immunotherapy [27]. The widespread adoption of preventive vaccinations has significantly (54–83%) reduced the prevalence of HPV-related malignancies [304]. Bivalent, quadrivalent, and nine-valent are the three main vaccines available. The most recent vaccine, known as Gardasil®9, is a nine-valent that targets HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. The bivalent targets HPV 16 and 18, while quadrivalent vaccines targets HPV 6, 11, 16, and 18 [305]. Therapeutic vaccination seeks to eradicate subclinical HPV-associated illness by activating cellular immunity through dendritic cells (DCs) specific to antigen T-cell activity [306]. According to the CDC, the HPV vaccination offers sustained immunity against infection for at least 12 years [3]. It is due to the stimulation of memory B cells which are essential for preserving immunological memory [307]. The WHO recommends girls aged 9 to 14 to follow a one- or two-dose regimen. For girls and women between the ages of 15 and 20, a single or double dosage plan. For women over 21, two doses spaced 6 months apart. When it comes to vaccines, females between the ages of nine and fourteen— prior to the start of sexual activity—are the main target population. When possible and affordable, it is advised that secondary targets, such as older girls and boys, be vaccinated [308]. By using nine-valent HPV vaccine 3% of laryngeal cancer, 4% of oral cavity cancer, 21% of oropharynx cancer, 23% of vulvar cancer, 25% of penile cancer, 61% of vaginal cancer, 79% of anal cancer, and 90% of cervical cancer can be prevented [309]. Despite these advancements, vaccination rates are still low globally because of restricted access and knowledge, underscoring the need for better preventative measures and educational initiatives [3].

## Conclusion

In summary, HPV's strong association with several malignancies, including cervical, head and neck, and genital cancers, highlights its significance as a major global health concern. Despite the availability of vaccines targeting the most common oncogenic strains, the incidence of HPV-related cancers continues to rise, emphasizing the need for ongoing research. A deeper understanding of the intricate molecular mechanisms of HPV-induced carcinogenesis, particularly the role of viral oncoproteins in disrupting host cell function, is crucial for developing more effective diagnostic and therapeutic strategies. Additionally, identifying novel biomarkers and targeted treatments holds great promise for improving outcomes in HPV-associated cancers. Sustained research into the virus's biology and its interactions with host cells remains vital to reducing the significant morbidity and mortality caused by HPV infections worldwide.

#### Abbreviations

| | |
|---|---|
| HPV | Human papillomavirus |
| HR | High Risk |
| LR | Low risk |
| LSIL | Low-grade squamous intraepithelial lesion |
| HSIL | High-grade squamous intraepithelial lesion |
| HNSCCs | Head and neck squamous cell carcinomas |
| LCR | Long non-coding control region |
| ORFs | Open reading frames |
| URR | Upstream regulatory region |
| HSPGs | Heparin sulphate proteoglycans |
| ATM | Ataxia telangiectasia-mutated |
| SOD2 | Superoxide dismutase isoform 2 |
| EMT | Epithelial-to-mesenchymal transition |
| CTHRC1 | Collagen triple helix repeat containing 1 |
| TALENs | Transcription activator-like effector nucleases |
| ZFNs | Zinc finger nucleases |
| SCJ | Squamocolumnar junction |
| SCC | Squamous cell carcinoma |
| AC | Adenocarcinoma |
| CIN | Cervical intraepithelial neoplasia |
| OPSCCa | Oropharyngeal squamous cell carcinoma |
| dVIN | Differentiated vulvar intraepithelial neoplasia |
| VSCC | Invasive squamous cell carcinoma in the vulva |
| GLOBOCAN | Global cancer statistics |
| PeIN | Penile intraepithelial neoplasia |
| PI3 K | Phosphoinositide 3-kinase |
| MAPK | Mitogen-activated protein kinase |
| MEK | Mitogen-activated extracellular signal-regulated kinase |
| LAMP | Loop-mediated isothermal amplification |

#### Acknowledgements

We thank our colleagues for their valuable suggestions, critical reading, and useful comments on this review. Figures were created with BioRender.com.

#### Author contributions

S.M. was involved in the conception and design of the review and critically edited the manuscript. S.K.B., S.A., and R.Y. researched the data for the article.

S.K.B wrote the original draft of the manuscript. S.B, A.A.B generated the idea for making figures and generated figures. We would like to thank M.S, M.A.M and F.M. for their assistance and for helpful comments especially in rearranging the tables. MAS and ER provided intellectual input to contribute towards manuscript preparation and edited the manuscript. W.A.H., M.K.A., A.A.M., and Z.Z critically revised the manuscript and edited the scientific content. All authors read and approved the content of the manuscript before final submission.

**Funding**
This work was primarily funded by grants from United Arab Emirates University (UAEU): Start-Up fund 12S134-Startup; UPAR fund 12S164-UPAR; SURE PLUS fund 12S204-Sureplus and, Mubadala-UAEU grant 21S117 to S.M. Research in the W.A.H. group is funded by a Canadian Institutes of Health Research project grant (PJT-173491). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Availability of data and materials**
Not applicable**.**

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

**Author details**
[1]Department of Chemistry, College of Science (COS), United Arab Emirates University (UAEU), P.O. Box 15551, Al Ain, United Arab Emirates. [2]Department of Biology, College of Science (COS), United Arab Emirates University (UAEU), Al Ain, United Arab Emirates. [3]Omics Centre of Excellence, M42 Health, Abu Dhabi, United Arab Emirates. [4]Department of Applied Medical Sciences, Applied College, Qassim University, Qassim, Saudi Arabia. [5]Histopathology Department, School of Medicine, University of Nottingham, Nottingham, UK. [6]Department of Pathology, Hamad Medical Corporation, Doha, Qatar. [7]Division of Cancer Pharmacology, CSIR-Indian Institute of Integrative Medicine, Srinagar, Jammu and Kashmir 190005, India. [8]Department of Medical Oncology (Lab), Dr. BRAIRCH, All India Institute of Medical Sciences (AIIMS), New Delhi 110029, India. [9]Watson-Crick Centre for Molecular Medicine, Islamic University of Science and Technology, Awantipora, Kashmir 192122, India. [10]Department of Biochemistry, University of Toronto, Toronto, ON M5G 1M1, Canada. [11]Department of Chemistry, University of Toronto, Toronto, ON M5S 3H6, Canada. [12]Metabolic and Mendelian Disorders Clinical Research Program, Precision OMICs Research & Translational Science, Sidra Medicine, Doha, Qatar. [13]Tumor Virus RNA Biology Section, HIV Dynamics and Replication Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, MD, USA. [14]Zayed Bin Sultan Centre for Health Sciences, United Arab Emirates University (UAEU), Al Ain, United Arab Emirates.

Received: 30 January 2025 Accepted: 7 April 2025
Published online: 29 April 2025

**References**

1. Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. Sex Transm Dis. 2014;41(11):660–4.
2. Hathaway JK. HPV: diagnosis, prevention, and treatment. Clin Obstet Gynecol. 2012;55(3):671–80.
3. Jensen JE, Becker GL, Jackson JB, Rysavy MB. Human papillomavirus and associated cancers: a review. Viruses. 2024;16(5):680.
4. Sehnal B, Rozsypal H, Nipčová M, Sláma J. The prevalence, incidence, persistence and transmission ways of human papillomavirus infection (HPV). Epidemiol Mikrobiol Imunol. 2017;66(4):198–209.
5. Haręża DA, Wilczyński JR, Paradowska E. Human papillomaviruses as infectious agents in gynecological cancers. Oncogenic properties of viral proteins. Int J Mol Sci. 2022;23(3):1818.
6. Egawa N. Papillomaviruses and cancer: commonalities and differences in HPV carcinogenesis at different sites of the body. Int J Clin Oncol. 2023;28(8):956–64.
7. Kombe Kombe AJ, Li B, Zahid A, Mengist HM, Bounda GA, Zhou Y, et al. Epidemiology and Burden of Human Papillomavirus and Related Diseases, Molecular Pathogenesis, and Vaccine Evaluation. Front Public Health. 2020;8:552028.
8. Hausen HZ. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst. 2000;92(9):690–8.
9. Boulet G, Horvath C, Vanden Broeck D, Sahebali S, Bogers J. Human papillomavirus: E6 and E7 oncogenes. Int J Biochem Cell Biol. 2007;39(11):2006–11.
10. Woodman CB, Collins SI, Young LS. The natural history of cervical HPV infection: unresolved issues. Nat Rev Cancer. 2007;7(1):11–22.
11. Mao C, Hughes JP, Kiviat N, Kuypers J, Lee SK, Adam DE, et al. Clinical findings among young women with genital human papillomavirus infection. Am J Obstet Gynecol. 2003;188(3):677–84.
12. McBride AA. Human papillomaviruses: diversity, infection and host interactions. Nat Rev Microbiol. 2022;20(2):95–108.
13. Aranda-Rivera AK, Cruz-Gregorio A, Briones-Herrera A, Pedraza-Chaverri J. Regulation of autophagy by high- and low-risk human papillomaviruses. Rev Med Virol. 2021;31(2): e2169.
14. Seyoum A, Seyoum B, Gure T, Alemu A, Alemayehu DH, Alemu A, et al. High rate of non-vaccine targeted high-risk HPV genotypes circulate among women in Eastern Ethiopia. Sci Rep. 2024;14(1):958. https://doi.org/10.1038/s41598-024-51594-7.
15. Bosch FX, Manos MM, Muñoz N, Sherman M, Jansen AM, Peto J, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. J Natl Cancer Inst. 1995;87(11):796–802.
16. Roden R, Wu TC. How will HPV vaccines affect cervical cancer? Nat Rev Cancer. 2006;6(10):753–63.
17. Jain M, Yadav D, Jarouliya U, Chavda V, Yadav AK, Chaurasia B, et al. Epidemiology, molecular pathogenesis, immuno-pathogenesis, immune escape mechanisms and vaccine evaluation for HPV-associated carcinogenesis. Pathogens. 2023;12(12):1380.
18. Tommasino M. The human papillomavirus family and its role in carcinogenesis. Semin Cancer Biol. 2014;26:13–21.
19. Lu Y, Xie Z, Luo G, Yan H, Qian HZ, Fu L, et al. Global burden of oropharyngeal cancer attributable to human papillomavirus by anatomical subsite and geographic region. Cancer Epidemiol. 2022;78:102140.
20. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer Epidemiol Biomarkers Prev. 2005;14(2):467–75.
21. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1–17.
22. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016;4(9):e609–16.
23. Hausen HZ. Condylomata acuminata and human genital cancer. Cancer Res. 1976;36:794.
24. Hausen HZ. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer. 2002;2(5):342–50.
25. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet. 2009;374(9686):301–14.
26. Michels KB, Hausen HZ. HPV vaccine for all. Lancet. 2009;374(9686):268–70.
27. Zhang Y, Qiu K, Ren J, Zhao Y, Cheng P. Roles of human papillomavirus in cancers: oncogenic mechanisms and clinical use. Signal Transduct Target Ther. 2025;10(1):44.

28. Tao Y, Shao H, Zhang T, Pu J, Tang C. Factors influencing men's attitudes toward HPV vaccination in males included in the chinese national immunization program. Vaccines. 2022;10(7):1054.
29. Shanmugasundaram S, You J. Targeting persistent human papillomavirus infection. Viruses. 2017;9(8):229.
30. Wei F, Georges D, Man I, Baussano I, Clifford GM. Causal attribution of human papillomavirus genotypes to invasive cervical cancer worldwide: a systematic analysis of the global literature. Lancet. 2024;404(10451):435–44.
31. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. ICO/IARC information centre on HPV and cancer (HPV information centre). Human papillomavirus and related diseases in the world Summary Report. 2019;17(6).
32. Alizon S, Murall CL, Bravo IG. Why human papillomavirus acute infections matter. Viruses. 2017;9(10):293.
33. Tan SC, Ismail MP, Duski DR, Othman NH, Ankathil R. Prevalence and type distribution of human papillomavirus (HPV) in Malaysian women with and without cervical cancer: an updated estimate. Biosci Rep. 2018. https://doi.org/10.1042/BSR20171268.
34. Filipić B, Rapajić-Moran I, Nikolić I, Oljačić S, Mandić A. Human papillomaviruses and cervical cancer from the perspective of the World Health Organisation initiative for cervical cancer elimination. Arch Pharm. 2024;74:56–75.
35. Tarnju AV. Global burden of cervical cancer. In: Rajkumar R, editor. Cervical cancer-a global public health treatise. London: IntechOpen; 2021.
36. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74(1):12–49.
37. Scott-Wittenborn N, Fakhry C. Epidemiology of HPV related malignancies. Semin Radiat Oncol. 2021;31(4):286–96.
38. Nweke MC, Okolo CA, Daous Y, Esan OA. Challenges of human papillomavirus infection and associated diseases in low-resource countries. Arch Pathol Lab Med. 2018;142(6):696–9.
39. Singh D, Vignat J, Lorenzoni V, Eslahi M, Ginsburg O, Lauby-Secretan B, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health. 2023;11(2):e197–206.
40. Farahmand M, Monavari SH, Tavakoli A. Prevalence and genotype distribution of human papillomavirus infection in different anatomical sites among men who have sex with men: a systematic review and meta-analysis. Rev Med Virol. 2021;31(6):e2219.
41. Stein AP, Saha S, Kraninger JL, Swick AD, Yu M, Lambert PF, et al. Prevalence of human papillomavirus in oropharyngeal cancer: a systematic review. Cancer J. 2015;21(3):138–46.
42. Serrano B, Brotons M, Bosch FX, Bruni L. Epidemiology and burden of HPV-related disease. Best Pract Res Clin Obstet Gynaecol. 2018;47:14–26.
43. Wierzbicka M, San Giorgi MRM, Dikkers FG. Transmission and clearance of human papillomavirus infection in the oral cavity and its role in oropharyngeal carcinoma - a review. Rev Med Virol. 2023;33(1):e2337.
44. Petca A, Borislavschi A, Zvanca ME, Petca RC, Sandru F, Dumitrascu MC. Non-sexual HPV transmission and role of vaccination for a better future (Review). Exp Ther Med. 2020;20(6):186.
45. Cladel NM, Jiang P, Li JJ, Peng X, Cooper TK, Majerciak V, et al. Papillomavirus can be transmitted through the blood and produce infections in blood recipients: Evidence from two animal models. Emerg Microbes Infect. 2019;8(1):1108–21.
46. Boccardo E. New approaches for infective HPV detection, quantification and inactivation: preventing accidental virus transmission in medical settings. EBioMedicine. 2021;64:103222.
47. Yu L, Majerciak V, Zheng ZM. HPV16 and HPV18 genome structure, expression, and post-transcriptional regulation. Int J Mol Sci. 2022;23(9):4943.
48. Graham SV. Human papillomavirus: gene expression, regulation and prospects for novel diagnostic methods and antiviral therapies. Future Microbiol. 2010;5(10):1493–506.
49. Bletsa G, Zagouri F, Amoutzias GD, Nikolaidis M, Zografos E, Markoulatos P, et al. Genetic variability of the HPV16 early genes and LCR. Present and future perspectives. Expert Rev Mol Med. 2021;23:e19.
50. Buck CB, Trus BL. The papillomavirus virion: a machine built to hide molecular Achilles' heels. Adv Exp Med Biol. 2012;726:403–22.
51. Mac M, Moody CA. Epigenetic regulation of the human papillomavirus life cycle. Pathogens. 2020;9(6):483.
52. Tabatabaeian H, Bai Y, Huang R, Chaurasia A, Darido C. Navigating therapeutic strategies: HPV classification in head and neck cancer. Br J Cancer. 2024;131(2):220–30.
53. Graham SV. The human papillomavirus replication cycle, and its links to cancer progression: a comprehensive review. Clin Sci (Lond). 2017;131(17):2201–21.
54. Raff AB, Woodham AW, Raff LM, Skeate JG, Yan L, Da Silva DM, et al. The evolving field of human papillomavirus receptor research: a review of binding and entry. J Virol. 2013;87(11):6062–72.
55. Schiller JT, Day PM, Kines RC. Current understanding of the mechanism of HPV infection. Gynecol Oncol. 2010;118(1 Suppl):S12–7.
56. Surviladze Z, Dziduszko A, Ozbun MA. Essential roles for soluble virion-associated heparan sulfonated proteoglycans and growth factors in human papillomavirus infections. PLoS Pathog. 2012;8(2):e1002519.
57. Abban CY, Meneses PI. Usage of heparan sulfate, integrins, and FAK in HPV16 infection. Virology. 2010;403(1):1–16.
58. Evander M, Frazer IH, Payne E, Qi YM, Hengst K, McMillan NA. Identification of the alpha6 integrin as a candidate receptor for papillomaviruses. J Virol. 1997;71(3):2449–56.
59. Culp TD, Budgeon LR, Marinkovich MP, Meneguzzi G, Christensen ND. Keratinocyte-secreted laminin 5 can function as a transient receptor for human papillomaviruses by binding virions and transferring them to adjacent cells. J Virol. 2006;80(18):8940–50.
60. Shafti-Keramat S, Handisurya A, Kriehuber E, Meneguzzi G, Slupetzky K, Kirnbauer R. Different heparan sulfate proteoglycans serve as cellular receptors for human papillomaviruses. J Virol. 2003;77(24):13125–35.
61. Woodham AW, Da Silva DM, Skeate JG, Raff AB, Ambroso MR, Brand HE, et al. The S100A10 subunit of the annexin A2 heterotetramer facilitates L2-mediated human papillomavirus infection. PLoS ONE. 2012;7(8):e43519.
62. Dziduszko A, Ozbun MA. Annexin A2 and S100A10 regulate human papillomavirus type 16 entry and intracellular trafficking in human keratinocytes. J Virol. 2013;87(13):7502–15.
63. Schäfer G, Graham LM, Lang DM, Blumenthal MJ, Bergant Marušič M, Katz AA. Vimentin modulates infectious internalization of human papillomavirus 16 pseudovirions. J Virol. 2017;91(16):17.
64. Scheffer KD, Gawlitza A, Spoden GA, Zhang XA, Lambert C, Berditchevski F, et al. Tetraspanin CD151 mediates papillomavirus type 16 endocytosis. J Virol. 2013;87(6):3435–46.
65. DiGiuseppe S, Bienkowska-Haba M, Guion LG, Sapp M. Cruising the cellular highways: how human papillomavirus travels from the surface to the nucleus. Virus Res. 2017;231:1–9.
66. Day PM, Thompson CD, Schowalter RM, Lowy DR, Schiller JT. Identification of a role for the trans-Golgi network in human papillomavirus 16 pseudovirus infection. J Virol. 2013;87(7):3862–70.
67. Lipovsky A, Popa A, Pimienta G, Wyler M, Bhan A, Kuruvilla L, et al. Genome-wide siRNA screen identifies the retromer as a cellular entry factor for human papillomavirus. Proc Natl Acad Sci U S A. 2013;110(18):7452–7.
68. Zhang W, Kazakov T, Popa A, DiMaio D. Vesicular trafficking of incoming human papillomavirus 16 to the Golgi apparatus and endoplasmic reticulum requires γ-secretase activity. MBio. 2014;5(5):e01777-e1814.
69. Urbanelli L, Buratta S, Tancini B, Sagini K, Delo F, Porcellati S, et al. The role of extracellular vesicles in viral infection and transmission. Vaccines (Basel). 2019;7(3):102.
70. Warburton A, Della Fera AN, McBride AA. Dangerous liaisons: long-term replication with an extrachromosomal HPV genome. Viruses. 2021;13(9):1846.
71. Middleton K, Peh W, Southern S, Griffin H, Sotlar K, Nakahara T, et al. Organization of human papillomavirus productive cycle during neoplastic progression provides a basis for selection of diagnostic markers. J Virol. 2003;77(19):10186–201.
72. Münger K, Basile JR, Duensing S, Eichten A, Gonzalez SL, Grace M, et al. Biological activities and molecular targets of the human papillomavirus E7 oncoprotein. Oncogene. 2001;20(54):7888–98.
73. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev. 2012;25(2):215–22.
74. Stanley M. Pathology and epidemiology of HPV infection in females. Gynecol Oncol. 2010;117(2 Suppl):S5-10.

75. Moody CA, Laimins LA. Human papillomavirus oncoproteins: pathways to transformation. Nat Rev Cancer. 2010;10(8):550–60.
76. Chow LT, Broker TR. Human papillomavirus infections: warts or cancer? Cold Spring Harb Perspect Biol. 2013;5(7):17.
77. Letafati A, Taghiabadi Z, Zafarian N, Tajdini R, Mondeali M, Aboofazeli A, et al. Emerging paradigms: unmasking the role of oxidative stress in HPV-induced carcinogenesis. Infect Agent Cancer. 2024;19(1):30.
78. Yu L, Majerciak V, Lobanov A, Mirza S, Band V, Liu H, et al. HPV oncogenes expressed from only one of multiple integrated HPV DNA copies drive clonal cell expansion in cervical cancer. MBio. 2024;15(5):e0072924.
79. Münger K, Phelps WC, Bubb V, Howley PM, Schlegel R. The E6 and E7 genes of the human papillomavirus type 16 together are necessary and sufficient for transformation of primary human keratinocytes. J Virol. 1989;63(10):4417–21.
80. Liu H, Liang H, Li D, Wang M, Li Y. Association of cervical dysbacteriosis, HPV oncogene expression, and cervical lesion progression. Microbiol Spectr. 2022;10(5):e0015122.
81. Schreiberhuber L, Barrett JE, Wang J, Redl E, Herzog C, Vavourakis CD, et al. Cervical cancer screening using DNA methylation triage in a real-world population. Nat Med. 2024;30(8):2251–7.
82. Tomaić V. Functional roles of E6 and E7 oncoproteins in HPV-induced malignancies at diverse anatomical sites. Cancers (Basel). 2016;8(10):95.
83. Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. Virus Res. 2002;89(2):213–28.
84. Cosper PF, Bradley S, Luo L, Kimple RJ. Biology of HPV mediated carcinogenesis and tumor progression. Semin Radiat Oncol. 2021;31(4):265–73.
85. Münger K, Werness BA, Dyson N, Phelps WC, Harlow E, Howley PM. Complex formation of human papillomavirus E7 proteins with the retinoblastoma tumor suppressor gene product. Embo J. 1989;8(13):4099–105.
86. Chellappan S, Kraus VB, Kroger B, Munger K, Howley PM, Phelps WC, et al. Adenovirus E1A, simian virus 40 tumor antigen, and human papillomavirus E7 protein share the capacity to disrupt the interaction between transcription factor E2F and the retinoblastoma gene product. Proc Natl Acad Sci U S A. 1992;89(10):4549–53.
87. Jones DL, Alani RM, Münger K. The human papillomavirus E7 oncoprotein can uncouple cellular differentiation and proliferation in human keratinocytes by abrogating p21Cip1-mediated inhibition of cdk2. Genes Dev. 1997;11(16):2101–11.
88. Zerfass-Thome K, Zwerschke W, Mannhardt B, Tindle R, Botz JW, Jansen-Dürr P. Inactivation of the cdk inhibitor p27KIP1 by the human papillomavirus type 16 E7 oncoprotein. Oncogene. 1996;13(11):2323–30.
89. Munger K, Gwin TK, McLaughlin-Drubin ME. p16 in HPV-associated cancers. Oncotarget. 2013;4(11):1864–5.
90. Sano D, Oridate N. The molecular mechanism of human papillomavirus-induced carcinogenesis in head and neck squamous cell carcinoma. Int J Clin Oncol. 2016;21(5):819–26.
91. Sen P, Ganguly P, Ganguly N. Modulation of DNA methylation by human papillomavirus E6 and E7 oncoproteins in cervical cancer. Oncol Lett. 2018;15(1):11–22.
92. Hu Z, Ma D. The precision prevention and therapy of HPV-related cervical cancer: new concepts and clinical implications. Cancer Med. 2018;7(10):5217–36.
93. Duensing S, Münger K. Mechanisms of genomic instability in human cancer: insights from studies with human papillomavirus oncoproteins. Int J Cancer. 2004;109(2):157–62.
94. Mantovani F, Banks L. The human papillomavirus E6 protein and its contribution to malignant progression. Oncogene. 2001;20(54):7874–87.
95. Katzenellenbogen RA. Activation of telomerase by HPVs. Virus Res. 2017;231:50–5.
96. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009;461(7267):1071–8.
97. Sitz J, Blanchet SA, Gameiro SF, Biquand E, Morgan TM, Galloy M, et al. Human papillomavirus E7 oncoprotein targets RNF168 to hijack the host DNA damage response. Proc Natl Acad Sci U S A. 2019;116(39):19552–62.
98. Spriggs CC, Laimins LA. Human papillomavirus and the DNA damage response: exploiting host repair pathways for viral replication. Viruses. 2017;9(8):232.
99. Spardy N, Covella K, Cha E, Hoskins EE, Wells SI, Duensing A, et al. Human papillomavirus 16 E7 oncoprotein attenuates DNA damage checkpoint control by increasing the proteolytic turnover of claspin. Cancer Res. 2009;69(17):7022–9.
100. Park JW, Shin MK, Pitot HC, Lambert PF. High incidence of HPV-associated head and neck cancers in FA deficient mice is associated with E7's induction of DNA damage through its inactivation of pocket proteins. PLoS ONE. 2013;8(9):e75056.
101. Spriggs CC, Blanco LZ, Maniar KP, Laimins LA. Expression of HPV-induced DNA damage repair factors correlates with CIN progression. Int J Gynecol Pathol. 2019;38(1):1–10.
102. Bouvard V, Matlashewski G, Gu ZM, Storey A, Banks L. The human papillomavirus type 16 E5 gene cooperates with the E7 gene to stimulate proliferation of primary cells and increases viral gene expression. Virology. 1994;203(1):73–80.
103. Chen B, Zhao L, Yang R, Xu T. Advances in molecular mechanism of HPV16 E5 oncoprotein carcinogenesis. Arch Biochem Biophys. 2023;745:109716.
104. Ilahi NE, Bhatti A. Impact of HPV E5 on viral life cycle via EGFR signaling. Microb Pathog. 2020;139:103923.
105. Kim SH, Juhnn YS, Kang S, Park SW, Sung MW, Bang YJ, et al. Human papillomavirus 16 E5 up-regulates the expression of vascular endothelial growth factor through the activation of epidermal growth factor receptor, MEK/ ERK1,2 and PI3K/Akt. Cell Mol Life Sci. 2006;63(7–8):930–8.
106. Yang Z, Wang T, Wu D, Min Z, Tan J, Yu B. RNA N6-methyladenosine reader IGF2BP3 regulates cell cycle and angiogenesis in colon cancer. J Exp Clin Cancer Res. 2020;39(1):203.
107. Mahata S, Bharti AC, Shukla S, Tyagi A, Husain SA, Das BC. Berberine modulates AP-1 activity to suppress HPV transcription and downstream signaling to induce growth arrest and apoptosis in cervical cancer cells. Mol Cancer. 2011;10:39.
108. Thakur K, Janjua D, Aggarwal N, Chhokar A, Yadav J, Tripathi T, et al. Physical interaction between STAT3 and AP1 in cervical carcinogenesis: implications in HPV transcription control. Biochim Biophys Acta Mol Basis Dis. 2023;1869(8):166817.
109. Ashrafi GH, Brown DR, Fife KH, Campo MS. Down-regulation of MHC class I is a property common to papillomavirus E5 proteins. Virus Res. 2006;120(1–2):208–11.
110. Bossler F, Hoppe-Seyler K, Hoppe-Seyler F. PI3K/AKT/mTOR signaling regulates the virus/host cell crosstalk in HPV-positive cervical cancer cells. Int J Mol Sci. 2019;20(9):2188.
111. Zhang L, Wu J, Ling MT, Zhao L, Zhao KN. The role of the PI3K/Akt/mTOR signalling pathway in human cancers induced by infection with human papillomaviruses. Mol Cancer. 2015;14:87.
112. Tavakolian S, Goudarzi H, Faghihloo E. Cyclin-dependent kinases and CDK inhibitors in virus-associated cancers. Infect Agent Cancer. 2020;15:27.
113. Kagawa S, Natsuizaka M, Whelan KA, Facompre N, Naganuma S, Ohashi S, et al. Cellular senescence checkpoint function determines differential Notch1-dependent oncogenic and tumor-suppressor activities. Oncogene. 2015;34(18):2347–59.
114. Nair P, Somasundaram K, Krishna S. Activated Notch1 inhibits p53-induced apoptosis and sustains transformation by human papillomavirus type 16 E6 and E7 oncogenes through a PI3K-PKB/Akt-dependent pathway. J Virol. 2003;77(12):7106–12.
115. Johnson DE, O'Keefe RA, Grandis JR. Targeting the IL-6/JAK/STAT3 signalling axis in cancer. Nat Rev Clin Oncol. 2018;15(4):234–48.
116. Rahmani F, Hashemian P, Tabrizi AT, Ghorbani Z, Ziaeemehr A, Alijannejad S, et al. Regulatory role of miRNAs on Wnt/β-catenin signaling in tumorigenesis of glioblastoma. Indian J Cancer. 2023;60(3):295–302.
117. Zhu GX, Gao D, Shao ZZ, Chen L, Ding WJ, Yu QF. Wnt/β-catenin signaling: causes and treatment targets of drug resistance in colorectal cancer (Review). Mol Med Rep. 2021. https://doi.org/10.3892/mmr.2020.11744.
118. Chakraborti S, Karmakar A, Guha R, Ngan C, Kumar Das R, Whitaker N. Induction of epithelial to mesenchymal transition in HPV16 E6/E7 oncogene transfected C33A cell line. Tissue Cell. 2023;82:102041.
119. Bello JO, Nieva LO, Paredes AC, Gonzalez AM, Zavaleta LR, Lizano M. Regulation of the Wnt/β-catenin signaling pathway by human papillomavirus E6 and E7 oncoproteins. Viruses. 2015;7(8):4734–55.

120. Qiu JJ, Sun SG, Tang XY, Lin YY, Hua KQ. Extracellular vesicular Wnt7b mediates HPV E6-induced cervical cancer angiogenesis by activating the β-catenin signaling pathway. J Exp Clin Cancer Res. 2020;39(1):260.
121. Poirson J, Suarez IP, Straub ML, Cousido-Siah A, Peixoto P, Hervouet E, et al. High-risk mucosal human papillomavirus 16 (HPV16) E6 protein and cutaneous HPV5 and HPV8 E6 proteins employ distinct strategies to interfere with interferon regulatory factor 3-mediated beta interferon expression. J Virol. 2022;96(10):e0187521.
122. Matarrese P, Vona R, Ascione B, Paggi MG, Mileo AM. Physical interaction between HPV16E7 and the actin-binding protein gelsolin regulates epithelial-mesenchymal transition via HIPPO-YAP axis. Cancers (Basel). 2021;13(2):353.
123. Srivastava K, Pickard A, Craig SG, Quinn GP, Lambe SM, James JA, et al. ΔNp63γ/SRC/Slug signaling axis promotes epithelial-to-mesenchymal transition in squamous cancers. Clin Cancer Res. 2018;24(16):3917–27.
124. Liu H, Xu J, Yang Y, Wang X, Wu E, Majerciak V, et al. Oncogenic HPV promotes the expression of the long noncoding RNA lnc-FANCI-2 through E7 and YY1. Proc Natl Acad Sci U S A. 2021. https://doi.org/10.1073/pnas.2014195118.
125. Liu H, Yu L, Majerciak V, Meyer T, Yi M, Johnson PF, Cam M, Lowy DR, Zheng Z-M. The long noncoding RNA lnc-FANCI-2 intrinsically restricts RAS signaling and phosphorylation of Akt and Erk in HPV16-infected cervical cancer. eLife. 2024;13:RP102681. https://doi.org/10.7554/eLife.102681.1.
126. Strickland SW, Vande PS. The human papillomavirus 16 E7 oncoprotein attenuates AKT signaling to promote internal ribosome entry site-dependent translation and expression of c-MYC. J Virol. 2016;90(12):5611–21.
127. Lo Cigno I, Calati F, Borgogna C, Zevini A, Albertini S, Martuscelli L, et al. Human papillomavirus E7 oncoprotein subverts host innate immunity via SUV39H1-mediated epigenetic silencing of immune sensor genes. J Virol. 2020;94(4):13.
128. Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine. 2012;30:F24-33.
129. Serrano B, de Sanjosé S, Tous S, Quiros B, Muñoz N, Bosch X, et al. Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. Eur J Cancer. 2015;51(13):1732–41.
130. Gillison ML, Alemany L, Snijders PJ, Chaturvedi A, Steinberg BM, Schwartz S, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine. 2012;30(Suppl 5):F34-54.
131. Bonanni P, Boccalini S, Bechini A. Efficacy, duration of immunity and cross protection after HPV vaccination: a review of the evidence. Vaccine. 2009;27(Suppl 1):A46-53.
132. Szymonowicz KA, Chen J. Biological and clinical aspects of HPV-related cancers. Cancer Biol Med. 2020;17(4):864–78.
133. HPV and Oropharyngeal Cancer|CDC. https://www.cdc.gov/cancer/hpv/basic_info/hpv_oropharyngeal.htm. Accessed 14 Apr 2025.
134. Ryser MD, Myers ER, Durrett R. HPV clearance and the neglected role of stochasticity. PLoS Comput Biol. 2015;11(3):e1004113.
135. Wang M, Huang K, Wong MCS, Huang J, Jin Y, Zheng ZJ. Global cervical cancer incidence by histological subtype and implications for screening methods. J Epidemiol Glob Health. 2024;14(1):94–101.
136. Campos-Parra AD, Pérez-Quintanilla M, Martínez-Gutierrez AD, Pérez-Montiel D, Coronel-Martínez J, Millan-Catalan O, et al. Molecular differences between squamous cell carcinoma and adenocarcinoma cervical cancer subtypes: potential prognostic biomarkers. Curr Oncol. 2022;29(7):4689–702.
137. Small W Jr, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: a global health crisis. Cancer. 2017;123(13):2404–12.
138. Pett M, Coleman N. Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? J Pathol. 2007;212(4):356–67.
139. Wilting SM, Steenbergen RD, Tijssen M, van Wieringen WN, Helmerhorst TJ, van Kemenade FJ, et al. Chromosomal signatures of a subset of high-grade premalignant cervical lesions closely resemble invasive carcinomas. Cancer Res. 2009;69(2):647–55.
140. Liu M, Han Z, Zhi Y, Ruan Y, Cao G, Wang G, et al. Long-read sequencing reveals oncogenic mechanism of HPV-human fusion transcripts in cervical cancer. Transl Res. 2023;253:80–94.
141. Pirami L, Giachè V, Becciolini A. Analysis of HPV16, 18, 31, and 35 DNA in pre-invasive and invasive lesions of the uterine cervix. J Clin Pathol. 1997;50(7):600–4.
142. Cullen AP, Reid R, Campion M, Lörincz AT. Analysis of the physical state of different human papillomavirus DNAs in intraepithelial and invasive cervical neoplasm. J Virol. 1991;65(2):606–12.
143. Polten R, Kutle I, Hachenberg J, Klapdor R, Morgan M, Schambach A. Towards novel gene and cell therapy approaches for cervical cancer. Cancers (Basel). 2022;15(1):263.
144. Ojha PS, Maste MM, Tubachi S, Patil VS. Human papillomavirus and cervical cancer: an insight highlighting pathogenesis and targeting strategies. Virusdisease. 2022;33(2):132–54.
145. U.S. Cancer Statistics Working Group. U.S. cancer statistics data visualizations tool. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. 2022. https://www.cdc.gov/cancer/dataviz.
146. McBride AA. Human malignancies associated with persistent HPV infection. Oncologist. 2024;29(6):457–64.
147. Lechner M, Liu J, Masterson L, Fenton TR. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. Nat Rev Clin Oncol. 2022;19(5):306–27.
148. Rettig EM, Sethi RKV. Cancer of the oropharynx and the association with human papillomavirus. Hematol Oncol Clin North Am. 2021;35(5):913–31.
149. Dong H, Shu X, Xu Q, Zhu C, Kaufmann AM, Zheng ZM, et al. Current status of human papillomavirus-related head and neck cancer: from viral genome to patient care. Virol Sin. 2021;36(6):1284–302.
150. Araldi RP, Sant'Ana TA, Módolo DG, de Melo TC, Spadacci-Morena DD, de Cassia SR, et al. The human papillomavirus (HPV)-related cancer biology: An overview. Biomed Pharmacother. 2018;106:1537–56.
151. Monsonego J. EUROGIN 2010: roadmap on cervical cancer prevention. Gynecol Obstet Fertil. 2011;39(7–8):462–7.
152. Wang CJ, Sparano J, Palefsky JM. Human immunodeficiency virus/AIDS, human papillomavirus, and anal cancer. Surg Oncol Clin N Am. 2017;26(1):17–31.
153. Assarzadegan N, Brooks E, Voltaggio L. HPV-driven anal neoplasia: review and recent developments. Pathology. 2022;54(2):184–94.
154. Morton M, Melnitchouk N, Bleday R. Squamous cell carcinoma of the anal canal. Curr Probl Cancer. 2018;42(5):486–92.
155. Palefsky JM, Lee JY, Jay N, Goldstone SE, Darragh TM, Dunlevy HA, et al. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. N Engl J Med. 2022;386(24):2273–82.
156. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED Jr, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576–85.
157. Dahlstrom KR, Day AT, Sturgis EM. Prevention and screening of HPV malignancies. Semin Radiat Oncol. 2021;31(4):297–308.
158. Hillman RJ, Gunathilake MP, Jin F, Tong W, Field A, Carr A. Ability to detect high-grade squamous anal intraepithelial lesions at high resolution anoscopy improves over time. Sex Health. 2016;13(2):177–81.
159. Clarke MA, Wentzensen N. Strategies for screening and early detection of anal cancers: a narrative and systematic review and meta-analysis of cytology, HPV testing, and other biomarkers. Cancer Cytopathol. 2018;126(7):447–60.
160. Bechini A, Moscadelli A, Velpini B, Bonito B, Orlando P, Putignano P, et al. Efficacy of HPV vaccination regarding vulvar and vaginal recurrences in previously treated women: the need for further evidence. Vaccines (Basel). 2023;11(6):1084.
161. Joura EA, Lösch A, Haider-Angeler MG, Breitenecker G, Leodolter S. Trends in vulvar neoplasia. Increasing incidence of vulvar intraepithelial neoplasia and squamous cell carcinoma of the vulva in young women. J Reprod Med. 2000;45(8):613–5.
162. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.

163. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer. 2017;141(4):664–70. https://doi.org/10.1002/ijc.30716.
164. Stroup AM, Harlan LC, Trimble EL. Demographic, clinical, and treatment trends among women diagnosed with vulvar cancer in the United States. Gynecol Oncol. 2008;108(3):577–83.
165. Guimaraes MJ, Macieira R, Azevedo F, Lisboa C. Association between HPV infection and penile cancer and penile intraepithelial neoplasia: a retrospective observational study. J Eur Acad Dermatol Venereol. 2024;38(1):186–90.
166. Hoekstra RJ, Trip EJ, Ten Kate FJ, Horenblas S, Lock MT. Penile intraepithelial neoplasia: nomenclature, incidence and progression to malignancy in the Netherlands. Int J Urol. 2019;26(3):353–7.
167. Iorga L, Dragos Marcu R, Cristina Diaconu C, Maria Alexandra Stanescu A, Pantea Stoian A, Liviu Dorel Mischianu D, et al. Penile carcinoma and HPV infection (Review). Exp Ther Med. 2020;20(1):91–6.
168. Chadha J, Chahoud J, Spiess PE. An update on treatment of penile cancer. Ther Adv Med Oncol. 2022;14:17588359221127254.
169. Sali AP, Prakash G, Murthy V, Joshi A, Shah A, Desai SB, et al. Updates in staging of penile cancer: the evolution, nuances, and issues. Hum Pathol. 2023;133:76–86.
170. Swanson AA, Pantanowitz L. The evolution of cervical cancer screening. J Am Soc Cytopathol. 2024;13(1):10–5.
171. Lyon F. IARC. Cervix cancer screening. Cancer IAfRo. 2005.
172. Polman NJ, Snijders PJF, Kenter GG, Berkhof J, Meijer C. HPV-based cervical screening: rationale, expectations and future perspectives of the new Dutch screening programme. Prev Med. 2019;119:108–17.
173. Yunes-Díaz E, Ruiz PA, Lazcano-Ponce E. Assessment of the validity and reproducibility of the pap smear in Mexico: necessity of a paradigm shift. Arch Med Res. 2015;46(4):310–6.
174. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 2007;370(9585):398–406.
175. Rajaram S, Gupta B. Screening for cervical cancer: choices & dilemmas. Indian J Med Res. 2021;154(2):210–20.
176. Bai A, Wang J, Li Q, Seery S, Xue P, Jiang Y. Assessing colposcopic accuracy for high-grade squamous intraepithelial lesion detection: a retrospective, cohort study. BMC Womens Health. 2022;22(1):9.
177. Li T, Lai Y, Yuan J. The diagnostic accuracy of TCT + HPV-DNA for cervical cancer: systematic review and meta-analysis. Ann Transl Med. 2022;10(14):761.
178. Suh DH, Lee KH, Kim K, Kang S, Kim JW. Major clinical research advances in gynecologic cancer in 2014. J Gynecol Oncol. 2015;26(2):156–67.
179. Zhu Y, Wang Y, Hirschhorn J, Welsh KJ, Zhao Z, Davis MR, et al. Human papillomavirus and its testing assays, cervical cancer screening, and vaccination. Adv Clin Chem. 2017;81:135–92.
180. Liang LA, Einzmann T, Franzen A, Schwarzer K, Schauberger G, Schriefer D, et al. Cervical cancer screening: comparison of conventional pap smear test, liquid-based cytology, and human papillomavirus testing as stand-alone or cotesting strategies. Cancer Epidemiol Biomarkers Prev. 2021;30(3):474–84.
181. Bonde JH, Sandri MT, Gary DS, Andrews JC. Clinical utility of human papillomavirus genotyping in cervical cancer screening: a systematic review. J Low Genit Tract Dis. 2020;24(1):1–13.
182. Stoler MH, Wright TC, Parvu V, Yanson K, Eckert K, Kodsi S, et al. HPV testing with 16, 18, and 45 genotyping stratifies cancer risk for women with normal cytology. Am J Clin Pathol. 2019;151(4):433–42.
183. Bruno MT, Ferrara M, Fava V, Rapisarda A, Coco A. HPV genotype determination and E6/E7 mRNA detection for management of HPV positive women. Virol J. 2018;15(1):52.
184. Bartosik M, Moranova L, Izadi N, Strmiskova J, Sebuyoya R, Holcakova J, et al. Advanced technologies towards improved HPV diagnostics. J Med Virol. 2024;96(2):e29409.
185. Livingstone DM, Rohatensky M, Mintchev P, Nakoneshny SC, Demetrick DJ, van Marle G, et al. Loop mediated isothermal amplification (LAMP) for the detection and subtyping of human papillomaviruses (HPV) in oropharyngeal squamous cell carcinoma (OPSCC). J Clin Virol. 2016;75:37–41.
186. Saetiew C, Limpaiboon T, Jearanaikoon P, Daduang S, Pientong C, Kerdsin A, et al. Rapid detection of the most common high-risk human papillomaviruses by loop-mediated isothermal amplification. J Virol Methods. 2011;178(1–2):22–30.
187. Zhang W, Du H, Huang X, Wang C, Duan X, Liu Y, et al. Evaluation of an isothermal amplification HPV detection assay for primary cervical cancer screening. Infect Agent Cancer. 2020;15:65.
188. Avelino KY, Oliveira LS, de Oliveira HP, Lucena-Silva N, Andrade CA, Oliveira MD. Impedimetric sensing platform for human papillomavirus and p53 tumor suppressor gene in cervical samples. J Sci Adv Mater Devices. 2022;7(1):100411.
189. Avelino K, Oliveira LS, Lucena-Silva N, Andrade CAS, Oliveira MDL. Flexible sensor based on conducting polymer and gold nanoparticles for electrochemical screening of HPV families in cervical specimens. Talanta. 2021;226:122118.
190. Ganbaatar U, Liu C. NEXT CRISPR: An enhanced CRISPR-based nucleic acid biosensing platform using extended crRNA. Sens Actuators, B Chem. 2022;369:132296.
191. Gao J, Wu L, Yang D, Gong W, Wang J. A one-pot CRISPR/Cas9-typing PCR for DNA detection and genotyping. J Mol Diagn. 2021;23(1):46–60.
192. Gong J, Zhang G, Wang W, Liang L, Li Q, Liu M, et al. A simple and rapid diagnostic method for 13 types of high-risk human papillomavirus (HR-HPV) detection using CRISPR-Cas12a technology. Sci Rep. 2021;11(1):12800.
193. Zhou H, Xu Z, He L, Wang Z, Zhang T, Hu T, et al. Coupling CRISPR/Cas12a and recombinase polymerase amplification on a stand-alone microfluidics platform for fast and parallel nucleic acid detection. Anal Chem. 2023;95(6):3379–89.
194. Li Z, Ding X, Yin K, Xu Z, Cooper K, Liu C. Electric field-enhanced electrochemical CRISPR biosensor for DNA detection. Biosens Bioelectron. 2021;192:113498.
195. Wang Q, Zhang B, Xu X, Long F, Wang J. CRISPR-typing PCR (ctPCR), a new Cas9-based DNA detection method. Sci Rep. 2018;8(1):14126.
196. Xu X, Luo T, Gao J, Lin N, Li W, Xia X, et al. CRISPR-assisted DNA detection: a novel dCas9-based DNA detection technique. Crispr j. 2020;3(6):487–502.
197. Xu Z, Chen D, Li T, Yan J, Zhu J, He T, et al. Microfluidic space coding for multiplexed nucleic acid detection via CRISPR-Cas12a and recombinase polymerase amplification. Nat Commun. 2022;13(1):6480.
198. Xue Y, Luo X, Xu W, Wang K, Wu M, Chen L, et al. PddCas: a polydisperse droplet digital CRISPR/Cas-based assay for the rapid and ultrasensitive amplification-free detection of viral DNA/RNA. Anal Chem. 2023;95(2):966–75.
199. Zamani M, Robson JM, Fan A, Bono MS Jr, Furst AL, Klapperich CM. Electrochemical strategy for low-cost viral detection. ACS Cent Sci. 2021;7(6):963–72.
200. Zhao Y, Chen D, Xu Z, Li T, Zhu J, Hu R, et al. Integrating CRISPR-Cas12a into a Microfluidic dual-droplet device enables simultaneous detection of HPV16 and HPV18. Anal Chem. 2023;95(6):3476–85.
201. Han J, Shin J, Lee ES, Cha BS, Kim S, Jang Y, et al. Cas12a/blocker DNA-based multiplex nucleic acid detection system for diagnosis of high-risk human papillomavirus infection. Biosens Bioelectron. 2023;232:115323.
202. Tsou JH, Leng Q, Jiang F. A CRISPR test for detection of circulating nuclei acids. Transl Oncol. 2019;12(12):1566–73.
203. Fontham ETH, Wolf AMD, Church TR, Etzioni R, Flowers CR, Herzig A, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA Cancer J Clin. 2020;70(5):321–46.
204. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. European guidelines for quality assurance in cervical cancer screening. Second edition–summary document. Ann Oncol. 2010;21(3):448–58.
205. Jin XW, Lipold L, Foucher J, Sikon A, Brainard J, Belinson J, et al. Cost-effectiveness of primary HPV testing, cytology and co-testing as cervical cancer screening for women above age 30 years. J Gen Intern Med. 2016;31(11):1338–44.
206. Clarke MA, Deshmukh AA, Suk R, Roberts J, Gilson R, Jay N, et al. A systematic review and meta-analysis of cytology and HPV-related biomarkers for anal cancer screening among different risk groups. Int J Cancer. 2022;151(11):1889–901.
207. Treatment CSTS. Health Professional Version—National Cancer Institute. USA: National Cancer Institute. 2018.

208. Jensen JE, Becker GL, Jackson JB, Rysavy MB. Human papillomavirus and associated cancers: a review. Viruses. 2024;16(5):680. https://doi.org/10.3390/v16050680.
209. Lyons KM, Butler SL. Anal intraepithelial neoplasia from a pathologists point of view. Clin Colon Rectal Surg. 2018;31(6):328–35.
210. Brotherton JML, Wheeler C, Clifford GM, Elfström M, Saville M, Kaldor J, et al. Surveillance systems for monitoring cervical cancer elimination efforts: focus on HPV infection, cervical dysplasia, cervical screening and treatment. Prev Med. 2021;144:106293.
211. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. https://www.who.int/publications/i/item/9789240030824. Accessed 14 Apr 2025.
212. Molina MA, Carosi Diatricch L, Castany Quintana M, Melchers WJ, Andralojc KM. Cervical cancer risk profiling: molecular biomarkers predicting the outcome of hrHPV infection. Expert Rev Mol Diagn. 2020;20(11):1099–120.
213. Cattani P, Zannoni GF, Ricci C, D'Onghia S, Trivellizzi IN, Di Franco A, et al. Clinical performance of human papillomavirus E6 and E7 mRNA testing for high-grade lesions of the cervix. J Clin Microbiol. 2009;47(12):3895–901.
214. Coquillard G, Palao B, Patterson BK. Quantification of intracellular HPV E6/E7 mRNA expression increases the specificity and positive predictive value of cervical cancer screening compared to HPV DNA. Gynecol Oncol. 2011;120(1):89–93.
215. Keegan H, Mc Inerney J, Pilkington L, Grønn P, Silva I, Karlsen F, et al. Comparison of HPV detection technologies: hybrid capture 2, PreTect HPV-Proofer and analysis of HPV DNA viral load in HPV16, HPV18 and HPV33 E6/E7 mRNA positive specimens. J Virol Methods. 2009;155(1):61–6.
216. Ratnam S, Coutlee F, Fontaine D, Bentley J, Escott N, Ghatage P, et al. Clinical performance of the PreTect HPV-Proofer E6/E7 mRNA assay in comparison with that of the Hybrid Capture 2 test for identification of women at risk of cervical cancer. J Clin Microbiol. 2010;48(8):2779–85.
217. Sorbye SW, Fismen S, Gutteberg TJ, Mortensen ES. HPV mRNA test in women with minor cervical lesions: experience of the University Hospital of North Norway. J Virol Methods. 2010;169(1):219–22.
218. Yao YL, Tian QF, Cheng B, Cheng YF, Ye J, Lu WG. Human papillomavirus (HPV) E6/E7 mRNA detection in cervical exfoliated cells: a potential triage for HPV-positive women. J Zhejiang Univ Sci B. 2017;18(3):256–62.
219. Fontecha N, Basaras M, Hernáez S, Andía D, Cisterna R. Assessment of human papillomavirus E6/E7 oncogene expression as cervical disease biomarker. BMC Cancer. 2016;16(1):852.
220. Cai X, Huang W, Huang J, Zhu X, Wang L, Xia Z, et al. CAPZB mRNA is a novel biomarker for cervical high-grade squamous lesions. Sci Rep. 2024;14(1):20047.
221. Ramesh PS, Bovilla VR, Swamy VH, Manoli NN, Dasegowda KB, Siddegowda SM, et al. Human papillomavirus-driven repression of NRF2 signalling confers chemo-radio sensitivity and predicts prognosis in head and neck squamous cell carcinoma. Free Radic Biol Med. 2023;205:234–43.
222. Sobocińska J, Nowakowska J, Molenda S, Olechnowicz A, Guglas K, Kozłowska-Masłoń J, et al. Zinc finger proteins in head and neck squamous cell carcinomas: ZNF540 may serve as a biomarker. Curr Oncol. 2022;29(12):9896–915.
223. Wu Q, Shao T, Huang G, Zheng Z, Jiang Y, Zeng W, et al. FDCSP is an immune-associated prognostic biomarker in HPV-positive head and neck squamous carcinoma. Biomolecules. 2022;12(10):1458.
224. Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. Nat Rev Cancer. 2018;18(1):5–18.
225. Tornesello ML, Faraonio R, Buonaguro L, Annunziata C, Starita N, Cerasuolo A, et al. The role of microRNAs, long non-coding RNAs, and circular RNAs in cervical cancer. Front Oncol. 2020;10:150.
226. Castro-Oropeza R, Piña-Sánchez P. Epigenetic and transcriptomic regulation landscape in HPV+ cancers: biological and clinical implications. Front Genet. 2022;13:886613.
227. Razavi ZS, Tajiknia V, Majidi S, Ghandali M, Mirzaei HR, Rahimian N, et al. Gynecologic cancers and non-coding RNAs: epigenetic regulators with emerging roles. Crit Rev Oncol Hematol. 2021;157:103192.
228. Wang X, Tang S, Le SY, Lu R, Rader JS, Meyers C, et al. Aberrant expression of oncogenic and tumor-suppressive microRNAs in cervical cancer is required for cancer cell growth. PLoS ONE. 2008;3(7):e2557.
229. Zheng ZM, Wang X. Regulation of cellular miRNA expression by human papillomaviruses. Biochim Biophys Acta. 2011;1809(11–12):668–77.
230. Wang X, Wang HK, Li Y, Hafner M, Banerjee NS, Tang S, et al. microRNAs are biomarkers of oncogenic human papillomavirus infections. Proc Natl Acad Sci U S A. 2014;111(11):4262–7.
231. Wang X, Meyers C, Guo M, Zheng ZM. Upregulation of p18Ink4c expression by oncogenic HPV E6 via p53-miR-34a pathway. Int J Cancer. 2011;129(6):1362–72.
232. Pardini B, De Maria D, Francavilla A, Di Gaetano C, Ronco G, Naccarati A. MicroRNAs as markers of progression in cervical cancer: a systematic review. BMC Cancer. 2018;18(1):696.
233. Gao D, Zhang Y, Zhu M, Liu S, Wang X. miRNA expression profiles of HPV-infected patients with cervical cancer in the uyghur population in China. PLoS ONE. 2016;11(10):e0164701.
234. Wang F, Li Y, Zhou J, Xu J, Peng C, Ye F, et al. miR-375 is down-regulated in squamous cervical cancer and inhibits cell migration and invasion via targeting transcription factor SP1. Am J Pathol. 2011;179(5):2580–8.
235. Liu SS, Chan KKL, Chu DKH, Wei TN, Lau LSK, Ngu SF, et al. Oncogenic microRNA signature for early diagnosis of cervical intraepithelial neoplasia and cancer. Mol Oncol. 2018;12(12):2009–22.
236. House R, Majumder M, Janakiraman H, Ogretmen B, Kato M, Erkul E, et al. Smoking-induced control of miR-133a-3p alters the expression of EGFR and HuR in HPV-infected oropharyngeal cancer. PLoS ONE. 2018;13(10):e0205077.
237. Weiss BG, Anczykowski MZ, Ihler F, Bertlich M, Spiegel JL, Haubner F, et al. MicroRNA-182-5p and microRNA-205-5p as potential biomarkers for prognostic stratification of p16-positive oropharyngeal squamous cell carcinoma. Cancer Biomark. 2022;33(3):331–47.
238. Bersani C, Mints M, Tertipis N, Haeggblom L, Näsman A, Romanitan M, et al. MicroRNA-155, -185 and -193b as biomarkers in human papillomavirus positive and negative tonsillar and base of tongue squamous cell carcinoma. Oral Oncol. 2018;82:8–16.
239. He J, Huang B, Zhang K, Liu M, Xu T. Long non-coding RNA in cervical cancer: from biology to therapeutic opportunity. Biomed Pharmacother. 2020;127:110209.
240. Zhong Q, Lu M, Yuan W, Cui Y, Ouyang H, Fan Y, et al. Eight-lncRNA signature of cervical cancer were identified by integrating DNA methylation, copy number variation and transcriptome data. J Transl Med. 2021;19(1):58.
241. Iancu IV, Anton G, Botezatu A, Huica I, Nastase A, Socolov DG, et al. LINC01101 and LINC00277 expression levels as novel factors in HPV-induced cervical neoplasia. J Cell Mol Med. 2017;21(12):3787–94.
242. Kopczyńska M, Kolenda T, Guglas K, Sobocińska J, Teresiak A, Bliźniak R, et al. PRINS lncRNA is a new biomarker candidate for HPV infection and prognosis of head and neck squamous cell carcinomas. Diagnostics (Basel). 2020;10(10):762.
243. Li J, Poi MJ, Tsai MD. Regulatory mechanisms of tumor suppressor P16(INK4A) and their relevance to cancer. Biochemistry. 2011;50(25):5566–82.
244. Sedghizadeh PP, Billington WD, Paxton D, Ebeed R, Mahabady S, Clark GT, et al. Is p16-positive oropharyngeal squamous cell carcinoma associated with favorable prognosis? A systematic review and meta-analysis. Oral Oncol. 2016;54:15–27.
245. Garg P, Krishna M, Subbalakshmi AR, Ramisetty S, Mohanty A, Kulkarni P, et al. Emerging biomarkers and molecular targets for precision medicine in cervical cancer. Biochim Biophys Acta Rev Cancer. 2024;1879(3):189106.
246. Bean SM, Eltoum I, Horton DK, Whitlow L, Chhieng DC. Immunohistochemical expression of p16 and Ki-67 correlates with degree of anal intraepithelial neoplasia. Am J Surg Pathol. 2007;31(4):555–61.
247. Chen C-C, Hsueh K-C, Shen C-H, Bai C-H, Wu C-C, Wang Y-H. The diagnostic value of p16/ki67 dual immunostaining for anal intraepithelial neoplasia: a meta-analysis. Am J Mens Health. 2020;14(6):1557988320977630.
248. Walts AE, Lechago J, Bose S. P16 and Ki67 immunostaining is a useful adjunct in the assessment of biopsies for HPV-associated anal intraepithelial neoplasia. Am J Surg Pathol. 2006;30(7):795–801.
249. Kaur G, Balasubramaniam SD, Lee YJ, Balakrishnan V, Oon CE. Minichromosome maintenance complex (MCM) genes profiling and MCM2 protein expression in cervical cancer development. Asian Pac J Cancer Prev. 2019;20(10):3043–9.

250. Scapulatempo-Neto C, Veo C, Fregnani J, Lorenzi A, Mafra A, Melani AGF, et al. Characterization of topoisomerase II α and minichromosome maintenance protein 2 expression in anal carcinoma. Oncol Lett. 2017;13(3):1891–8.
251. Amaro Filho SM, Nuovo GJ, Cunha CB, Ramos Pereira Lde O, Oliveira-Silva M, Russomano F, et al. Correlation of MCM2 detection with stage and virology of cervical cancer. Int J Biol Markers. 2014;29(4):e363–71.
252. Ran C, Sun J, Qu Y, Long N. Clinical value of MRI, serum SCCA, and CA125 levels in the diagnosis of lymph node metastasis and parauterine infiltration in cervical cancer. World J Surg Oncol. 2021;19:1–11.
253. Charkhchi P, Cybulski C, Gronwald J, Wong FO, Narod SA, Akbari MR. CA125 and ovarian cancer: a comprehensive review. Cancers. 2020;12(12):3730.
254. Tony V, Sathyamurthy A, Ramireddy JK, Iswarya SJ, Gowri SM, Thomas A, et al. Role of squamous cell carcinoma antigen in prognostication, monitoring of treatment response, and surveillance of locally advanced cervical carcinoma. J Cancer Res Ther. 2023;19(5):1236–40.
255. Wijetunga NA, Belbin TJ, Burk RD, Whitney K, Abadi M, Greally JM, et al. Novel epigenetic changes in CDKN2A are associated with progression of cervical intraepithelial neoplasia. Gynecol Oncol. 2016;142(3):566–73.
256. Louvanto K, Franco EL, Ramanakumar AV, Vasiljević N, Scibior-Bentkowska D, Koushik A, et al. Methylation of viral and host genes and severity of cervical lesions associated with human papillomavirus type 16. Int J Cancer. 2015;136(6):E638–45.
257. Siegel EM, Riggs BM, Delmas AL, Koch A, Hakam A, Brown KD. Quantitative DNA methylation analysis of candidate genes in cervical cancer. PLoS ONE. 2015;10(3):e0122495.
258. Albulescu A, Plesa A, Fudulu A, Iancu IV, Anton G, Botezatu A. Epigenetic approaches for cervical neoplasia screening (Review). Exp Ther Med. 2021;22(6):1481.
259. Feng Q, Balasubramanian A, Hawes SE, Toure P, Sow PS, Dem A, et al. Detection of hypermethylated genes in women with and without cervical neoplasia. J Natl Cancer Inst. 2005;97(4):273–82.
260. Fackler MJ, Pleas M, Li Y, Soni A, Xing D, Cope L, et al. Discovery and technical validation of high-performance methylated DNA markers for the detection of cervical lesions at risk of malignant progression in low- and middle-income countries. Clin Epigenetics. 2024;16(1):56.
261. Liew PL, Huang RL, Wu TI, Liao CC, Chen CW, Su PH, et al. Combined genetic mutations and DNA-methylated genes as biomarkers for endometrial cancer detection from cervical scrapings. Clin Epigenetics. 2019;11(1):170.
262. Pang CL, Thierry F. Human papillomavirus proteins as prospective therapeutic targets. Microb Pathog. 2013;58:55–65.
263. Wang JCK, Baddock HT, Mafi A, Foe IT, Bratkowski M, Lin TY, et al. Structure of the p53 degradation complex from HPV16. Nat Commun. 2024;15(1):1842.
264. Celegato M, Messa L, Goracci L, Mercorelli B, Bertagnin C, Spyrakis F, et al. A novel small-molecule inhibitor of the human papillomavirus E6–p53 interaction that reactivates p53 function and blocks cancer cells growth. Cancer Lett. 2020;470:115–25.
265. Celegato M, Messa L, Bertagnin C, Mercorelli B, Loregian A. Targeted disruption of E6/p53 binding exerts broad activity and synergism with paclitaxel and topotecan against HPV-transformed cancer cells. Cancers (Basel). 2021;14(1):193.
266. Zhao J, Blayney A, Liu X, Gandy L, Jin W, Yan L, et al. EGCG binds intrinsically disordered N-terminal domain of p53 and disrupts p53-MDM2 interaction. Nat Commun. 2021;12(1):986.
267. Zhang J, Yu G, Yang Y, Wang Y, Guo M, Yin Q, et al. A small-molecule inhibitor of MDMX suppresses cervical cancer cells via the inhibition of E6–E6AP-p53 axis. Pharmacol Res. 2022;177:106128.
268. Hassin O, Oren M. Drugging p53 in cancer: one protein, many targets. Nat Rev Drug Discov. 2023;22(2):127–44.
269. Wang H, Guo M, Wei H, Chen Y. Targeting p53 pathways: mechanisms, structures, and advances in therapy. Signal Transduct Target Ther. 2023;8(1):92.
270. Chang JT, Kuo TF, Chen YJ, Chiu CC, Lu YC, Li HF, et al. Highly potent and specific siRNAs against E6 or E7 genes of HPV16- or HPV18-infected cervical cancers. Cancer Gene Ther. 2010;17(12):827–36.
271. Javadi H, Lotfi AS, Hosseinkhani S, Mehrani H, Amani J, Soheili ZS, et al. The combinational effect of E6/E7 siRNA and anti-miR-182 on apoptosis induction in HPV16-positive cervical cells. Artif Cells Nanomed Biotechnol. 2018;46(sup2):727–36.
272. Tang S, Tao M, McCoy JP Jr, Zheng ZM. Short-term induction and long-term suppression of HPV16 oncogene silencing by RNA interference in cervical cancer cells. Oncogene. 2006;25(14):2094–104.
273. Zhu J, Kamara S, Wang Q, Guo Y, Li Q, Wang L, et al. Novel affibody molecules targeting the HPV16 E6 oncoprotein inhibited the proliferation of cervical cancer cells. Front Cell Dev Biol. 2021;9:677867.
274. Zhang W, Shan H, Jiang K, Huang W, Li S. A novel intracellular nanobody against HPV16 E6 oncoprotein. Clin Immunol. 2021;225:108684.
275. Lagrange M, Boulade-Ladame C, Mailly L, Weiss E, Orfanoudakis G, Deryckere F. Intracellular scFvs against the viral E6 oncoprotein provoke apoptosis in human papillomavirus-positive cancer cells. Biochem Biophys Res Commun. 2007;361(2):487–92.
276. Griffin H, Elston R, Jackson D, Ansell K, Coleman M, Winter G, et al. Inhibition of papillomavirus protein function in cervical cancer cells by intrabody targeting. J Mol Biol. 2006;355(3):360–78.
277. Yuan CH, Filippova M, Krstenansky JL, Duerksen-Hughes PJ. Flavonol and imidazole derivatives block HPV16 E6 activities and reactivate apoptotic pathways in HPV$^+$ cells. Cell Death Dis. 2016;7(1):2060.
278. Manzo-Merino J, Thomas M, Fuentes-Gonzalez AM, Lizano M, Banks L. HPV E6 oncoprotein as a potential therapeutic target in HPV related cancers. Expert Opin Ther Targets. 2013;17(11):1357–68.
279. Huibregtse JM, Scheffner M, Howley PM. Localization of the E6-AP regions that direct human papillomavirus E6 binding, association with p53, and ubiquitination of associated proteins. Mol Cell Biol. 1993;13(8):4918–27.
280. Chen JJ, Hong Y, Rustamzadeh E, Baleja JD, Androphy EJ. Identification of an alpha helical motif sufficient for association with papillomavirus E6. J Biol Chem. 1998;273(22):13537–44.
281. Cherry JJ, Rietz A, Malinkevich A, Liu Y, Xie M, Bartolowits M, et al. Structure based identification and characterization of flavonoids that disrupt human papillomavirus-16 E6 function. PLoS ONE. 2013;8(12):e84506.
282. Malecka KA, Fera D, Schultz DC, Hodawadekar S, Reichman M, Donover PS, et al. Identification and characterization of small molecule human papillomavirus E6 inhibitors. ACS Chem Biol. 2014;9(7):1603–12.
283. Ramirez J, Poirson J, Foltz C, Chebaro Y, Schrapp M, Meyer A, et al. Targeting the two oncogenic functional sites of the HPV E6 oncoprotein with a high-affinity bivalent ligand. Angew Chem Int Ed Engl. 2015;54(27):7958–62.
284. Tornesello ML, Buonaguro L, Giorgi-Rossi P, Buonaguro FM. Viral and cellular biomarkers in the diagnosis of cervical intraepithelial neoplasia and cancer. Biomed Res Int. 2013;2013:519619.
285. Baleja JD, Cherry JJ, Liu Z, Gao H, Nicklaus MC, Voigt JH, et al. Identification of inhibitors to papillomavirus type 16 E6 protein based on three-dimensional structures of interacting proteins. Antiviral Res. 2006;72(1):49–59.
286. Reuschenbach M, Pauligk C, Karbach J, Rafiyan MR, Kloor M, Prigge ES, et al. A phase 1/2a study to test the safety and immunogenicity of a p16(INK4a) peptide vaccine in patients with advanced human papillomavirus-associated cancers. Cancer. 2016;122(9):1425–33.
287. Green KL, Gaston K. Development of a topical protein therapeutic for human papillomavirus and associated cancers. BioDrugs. 2006;20(4):209–18.
288. Ling K, Yang L, Yang N, Chen M, Wang Y, Liang S, et al. Gene targeting of HPV18 E6 and E7 synchronously by nonviral transfection of CRISPR/Cas9 system in cervical cancer. Hum Gene Ther. 2020;31(5–6):297–308.
289. Hsu PD, Lander ES, Zhang F. Development and applications of CRISPR-Cas9 for genome engineering. Cell. 2014;157(6):1262–78.
290. Kennedy EM, Kornepati AV, Goldstein M, Bogerd HP, Poling BC, Whisnant AW, et al. Inactivation of the human papillomavirus E6 or E7 gene in cervical carcinoma cells by using a bacterial CRISPR/Cas RNA-guided endonuclease. J Virol. 2014;88(20):11965–72.
291. Tian R, Liu J, Fan W, Li R, Cui Z, Jin Z, et al. Gene knock-out chain reaction enables high disruption efficiency of HPV18 E6/E7 genes in cervical cancer cells. Mol Ther Oncolytics. 2022;24:171–9.
292. Aghamiri S, Talaei S, Roshanzamiri S, Zandsalimi F, Fazeli E, Aliyu M, et al. Delivery of genome editing tools: a promising strategy for HPV-related cervical malignancy therapy. Expert Opin Drug Deliv. 2020;17(6):753–66.

293. Ernst MPT, Broeders M, Herrero-Hernandez P, Oussoren E, van der Ploeg AT, Pijnappel W. Ready for repair? Gene editing enters the clinic for the treatment of human disease. Mol Ther Methods Clin Dev. 2020;18:532–57.
294. Tewari KS, Sill MW, Penson RT, Huang H, Ramondetta LM, Landrum LM, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet. 2017;390(10103):1654–63.
295. Burmeister CA, Khan SF, Schäfer G, Mbatani N, Adams T, Moodley J, et al. Cervical cancer therapies: current challenges and future perspectives. Tumour Virus Res. 2022;13:200238.
296. Chen W, Zhang Y, Zhao C, Shao S, Zhang Y, Li X, et al. Nocardia rubra cell wall skeleton up-regulates T cell subsets and inhibits PD-1/PD-L1 pathway to promote local immune status of patients with high-risk human papillomavirus infection and cervical intraepithelial neoplasia. Front Immunol. 2020;11:612547.
297. Xie Y, Kong W, Zhao X, Zhang H, Luo D, Chen S. Immune checkpoint inhibitors in cervical cancer: current status and research progress. Front Oncol. 2022;12:984896.
298. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med. 2021;385(20):1856–67.
299. Stevanović S, Draper LM, Langhan MM, Campbell TE, Kwong ML, Wunderlich JR, et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. J Clin Oncol. 2015;33(14):1543–50.
300. Norberg SM, Nagarsheth N, Doran S, Kanakry JA, Adhikary S, Schweitzer C, et al. Regression of epithelial cancers following T cell receptor gene therapy targeting human papillomavirus-16 E7. Blood. 2018;132:492.
301. Jin BY, Campbell TE, Draper LM, Stevanović S, Weissbrich B, Yu Z, et al. Engineered T cells targeting E7 mediate regression of human papillomavirus cancers in a murine model. JCI Insight. 2018. https://doi.org/10.1172/jci.insight.99488.
302. Draper LM, Kwong ML, Gros A, Stevanović S, Tran E, Kerkar S, et al. Targeting of HPV-16+ epithelial cancer cells by TCR gene engineered T cells directed against E6. Clin Cancer Res. 2015;21(19):4431–9.
303. Leslie SW, Sajjad H, Kumar S. Genital Warts. Treasure Island: StatPearls Publishing; 2024.
304. González-Rodríguez JC, Cruz-Valdez A, Madrid-Marina V. Cervical cancer prevention by vaccination: review. Front Oncol. 2024;14:1386167.
305. HPV Vaccination: What Everyone Should Know|CDC. https://www.cdc.gov/vaccines/vpd/hpv/public/index.html. Accessed 14 Apr 2025.
306. Lee SJ, Yang A, Wu TC, Hung CF. Immunotherapy for human papillomavirus-associated disease and cervical cancer: review of clinical and translational research. J Gynecol Oncol. 2016;27(5):e51.
307. De Vincenzo R, Conte C, Ricci C, Scambia G, Capelli G. Long-term efficacy and safety of human papillomavirus vaccination. Int J Womens Health. 2014;6:999–1010.
308. Human Papillomavirus Vaccines: WHO Position Paper. 2022. https://www.who.int/publications/i/item/who-wer9750-645-672. Accessed 14 Apr 2025.
309. de Sanjosé S, Serrano B, Tous S, Alejo M, Lloveras B, Quirós B, et al. Burden of human papillomavirus (HPV)-related cancers attributable to HPVs 6/11/16/18/31/33/45/52 and 58. JNCI Cancer Spectr. 2018;2(4):pky045.
310. Bergvall M, Melendy T, Archambault J. The E1 proteins. Virology. 2013;445(1–2):35–56.
311. Rosenblum HG, Lewis RM, Gargano JW, Querec TD, Unger ER, Markowitz LE. Human papillomavirus vaccine impact and effectiveness through 12 years after vaccine introduction in the United States, 2003 to 2018. Ann Intern Med. 2022;175(7):918–26.
312. McBride AA. The papillomavirus E2 proteins. Virology. 2013;445(1–2):57–79.
313. Doorbar J. The E4 protein; structure, function and patterns of expression. Virology. 2013;445(1–2):80–98.
314. Doorbar J, Ely S, Sterling J, McLean C, Crawford L. Specific interaction between HPV-16 E1–E4 and cytokeratins results in collapse of the epithelial cell intermediate filament network. Nature. 1991;352(6338):824–7.
315. McIntosh PB, Laskey P, Sullivan K, Davy C, Wang Q, Jackson DJ, et al. E1–E4-mediated keratin phosphorylation and ubiquitylation: a mechanism for keratin depletion in HPV16-infected epithelium. J Cell Sci. 2010;123(Pt 16):2810–22.
316. DiMaio D, Petti LM. The E5 proteins. Virology. 2013;445(1–2):99–114.
317. Vande Pol SB, Klingelhutz AJ. Papillomavirus E6 oncoproteins. Virology. 2013;445(1–2):115–37.
318. Roman A, Munger K. The papillomavirus E7 proteins. Virology. 2013;445(1–2):138–68.
319. Kuehner F, Stubenrauch F. Functions of papillomavirus E8^E2 proteins in tissue culture and in vivo. Viruses. 2022;14(5):953.
320. Buck CB, Day PM, Trus BL. The papillomavirus major capsid protein L1. Virology. 2013;445(1–2):169–74.
321. Wang JW, Roden RB. L2, the minor capsid protein of papillomavirus. Virology. 2013;445(1–2):175–86.
322. Li Y, Liu J, Yuan C, Cui B, Zou X, Qiao Y. High-risk human papillomavirus reduces the expression of microRNA-218 in women with cervical intraepithelial neoplasia. J Int Med Res. 2010;38(5):1730–6.


## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.