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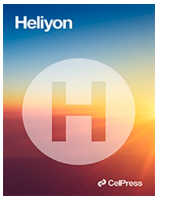

Review article

Unraveling HPV-associated cancer complexity: From molecular insights to innovative therapies

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ABSTRACT

Human papillomavirus (HPV) contributes to a high global incidence of sexually transmitted infections, predominantly associated with cervical cancer, as well as head and neck, penile, anal, vaginal, and vulvar cancers. Despite efforts through improved screening and HPV vaccination campaigns, challenges persist, influencing the frequency of HPV-related malignancies. Collaborative scientific endeavors strive to pioneer groundbreaking approaches, aiming to alleviate the adverse consequences of HPV-related malignancies on individuals and communities.

The present review is focused on exhaustively covering HPV-associated cancers, particularly cervical cancer. This study highlights the initiation, progression, immune invasion, and treatment strategies of HPV-associated cancers. The role of viral oncoproteins E6 and E7 responsible for immune evasion and subsequent latent infection is also elaborated. The article also sheds light on the pivotal role of HPV vaccination in averting high-risk HPV infections and associated cancers. The scope of this review encompasses HPV-associated cancer epidemiology, regional disparities, and the distinctive challenges faced in the context of India. This will be a value addition to the knowledge repertoire beneficial for creating awareness and designing health policies.

1. Introduction

A high incidence of Sexually Transmitted Infections (STIs) globally is attributed to human papillomavirus (HPV). It belongs to the group of non-coated, dsDNA viruses, with 52–55 nm diameter that infects the skin and mucous membrane epithelial cells. Due to their propensity to cause several malignancies, certain HPV strains are regarded as high-risk [1]. HPV infections are considered high-risk contributing to 90 % of all reported cervical cancers. In addition to cervical cancer, other cancers associated with HPV include head and neck, penile, anal, vaginal, and vulvar cancers. The geographical distribution of HPV-associated malignancies varies in low- and middle-income nations where access to prognosis and vaccination is restricted. According to WHO, "cervical cancer is the fourth most common cancer among women globally, with an estimated 604000 new cases and 342000 deaths in 2020. Over 90 % of these cases and deaths occurred in low- and middle-income countries" [2,3]. Women's mortality in India is high due to cervical cancer [4,5]. Numerous factors, such as lack of knowledge, restricted screening availability, and specific cultural and socioeconomic circumstances, are blamed for the high frequency [6,7]. Age-related incidences of cervical cancer in India is the highest in the world [5]. The oropharyngeal and oral cancers are two more HPV-related malignancies that are progressively being reported in India. There have

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been measures to address these problems, involving better screening systems and HPV vaccine campaigns. The frequency of HPV-associated malignancies in India is still impacted by issues like the huge population size, unequal access to healthcare, and social norms [8–10]. There is substantial scientific evidence to support the well-established link between HPV and cancer, especially cervical cancer. Nonetheless, the scientific debate continues to relate HPV with cancer genesis and the interplay of variables, such as genetic predisposition, environmental factors, and lifestyle choices. Furthermore, studies have suggested the connection of HPV with malignancies, but essentially not all HPV infections will result in cancer. While there are complexities in understanding cancer causality, the data strongly supports HPV as a causative component in various types of cancer, making it an important focus for preventive and treatment initiatives [1,3,11].

This review is a comprehensive coverage of HPV associated cancer complexities which consolidates the recent advancements in the area of its prevention and therapy. It certainly provides value addition for raising awareness about HPV management with translational impact on health policy design.

1.1. Global distribution of HPV subtypes and associated malignancies

The first disease linked to HPV that was reported to cause more than 500,000 cases worldwide each year was cervical cancer [11] (Table 1). The prevalence of HPV-associated cancers is depicted in Fig. 1. Developing countries have limited screening facilities thus causing a disproportionately large burden of cervical cancer instances accounting for approximately 88% of the cases [12]. The geographical distribution of HPV and its subtypes in women diagnosed with invasive cervical cancer is summarized in Table 2 [13,14]. Approximately over 200 types of HPV are reported, out of which 40 are known to infect mucosal membranes of the genitals [15–17]. The International Agency for Research on Cancer (IARC) has linked twelve HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) to various malignancies, including cervical cancer [18]. HPV 6 and 11 types are responsible for low-grade or benign cervical tumors, genital warts, and recurrent respiratory papillomatosis (RRP) [19]. High-risk HPV types (16 and 18) may cause malignancies and both low-grade and high-grade cellular abnormalities in the cervix [18]. Cervical, anal, penile, vulval, vaginal, and head and neck cancers are caused by a variety of high-risk HPV types, including HPV 16 [1,18]. Continuous exposure to high-risk HPV types, particularly HPV-16 and HPV-18, is a significant risk factor for cervical cancer development. Cervical cancer risk factors encompass HPV infection, early sexual activity initiation, engagement in multiple sexual relationships, smoking, compromised immune function, and limited access to routine cervical screening.

1.2. HPV biology and virus-host interactions

The viral genome is composed of a circular, dsDNA molecule approximately 8 kilobases in length. The early proteins encoded by this genetic material include E1, E2, E4, E5, E6, E7, and sporadically E8 (but E5 and E8 may not be present in some HPV strains), which play pivotal roles in virus replication and the alteration of host cell behavior. In contrast, the L1 and L2 late proteins serve as the building blocks of the viral capsid, facilitating virion attachment to cell surface receptors and aiding in the transport of the virus to the nucleus [20]. The viral genome relies on various proteins for its replication and transcription. E1 and E2 proteins play essential roles in these processes. E4 facilitates genome interactions and assists in the release of the virus. E5 contributes to genome amplification and promotes cellular proliferation. E6 and E7 are also considered to be important oncogenic factors during the early stages of carcinogenesis, and they are classified as oncoproteins [21]. The role of different HPV proteins is summarized in Table 3. The HPV reaches its host cells at the cellular level through microscopic lesions or abrasions in the skin or mucous membranes. The virus particles internalize inside the cell after adhering to particular receptors on the cell surface. After host cell attachment, various cellular processes are affected by viral spread. The endocytosed HPV vesicles are carried to the nucleus along microtubules after the egression of virion at the endosome is facilitated by L2. Thereafter, early transcription starts there, coupled with a fast but fleeting production of the early proteins. HPV may then enter the latency period. When basal cells begin to differentiate, they move in the direction of the tissue's surface. The expression of structural proteins in this region enables the assembly and release of virion, which takes place concurrently with tissue desquamation. HPV genome integration may occur as a result of viral persistence in basal cells, which encourages the development of cancer (Fig. 2).

Table 1
Global burden of malignancies linked to HPV.

Type of cancer	Average number of cases[a]			References
	In men	In women	Total	
Vagina	–	17908	17908	[96,100]
Penis	36068	–	36068	[96,101]
Vulva	–	45240	45240	[96,102]
Anus	21706	29159	50865	[96,97]
Oropharynx	79045	19367	98412	[94,95]
Nasopharynx	96371	36983	133354	[94,103]
Cervix	–	604127	604127	[14,96,104]

[a] Estimated global number of new cases in 2020, spanning all age groups and genders [retrieved from https://gco.iarc.fr/today/home (accessed on September 12, 2023)].

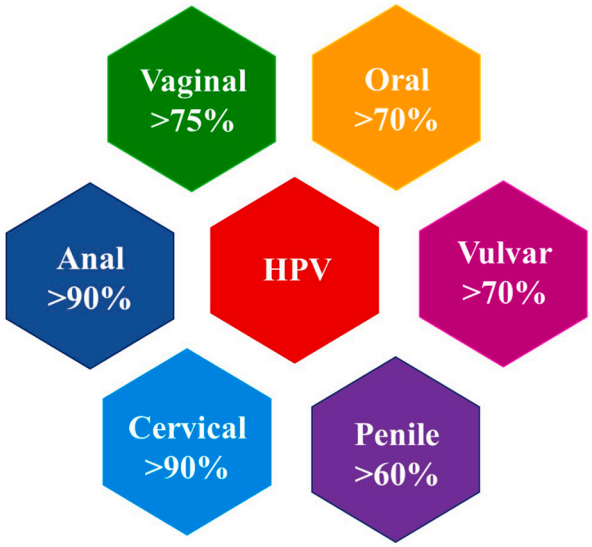

Fig. 1. Prevalence of HPV associated cancers.

Table 2
Geographical distribution of HPV and its subtypes in individuals with invasive cervical cancer.

HPV subtypes	Prevalence of invasive cervical cancer (%)					References
	Africa	Asia	Europe	Latin America & Caribbean	North America	
HPV6	–	<0.1	0.1	<0.1	–	[13,14]
HPV11	–	<0.1	–	<0.1	–	[13,14]
HPV16	47.6	60.5	65.5	59.2	71.9	[13,14]
HPV18	22.6	11.2	7.3	9.1	6.9	[13,14]
HPV26	–	0.4	0.1	0.5	–	[13,14]
HPV30	0.6	0.3	0.2	0.4	–	[13,14]
HPV31	1.8	3.0	3.4	4.9	3.1	[13,14]
HPV33	1.5	3.5	5.7	3.5	3.1	[13,14]
HPV35	5.0	1.0	2.2	2.1	–	[13,14]
HPV39	0.6	1.2	1.3	2.2	1.3	[13,14]
HPV45	9.9	5.5	3.9	6.8	5.6	[13,14]
HPV51	2.4	0.7	1.4	1.6	1.3	[13,14]
HPV52	2.6	3.8	1.9	2.7	3.1	[13,14]
HPV53	–	<0.1	0.5	0.3	0.6	[13,14]
HPV56	0.7	0.7	1.6	0.6	0.6	[13,14]
HPV58	0.7	3.9	1.3	2.0	1.9	[13,14]
HPV59	0.2	1.4	0.7	1.2	–	[13,14]
HPV66	0.4	<0.1	<0.1	<0.1	–	[13,14]
HPV68	0.2	0.9	0.6	0.6	–	[13,14]
HPV70 -		0.2	<0.1	<0.1	–	[13,14]
HPV73	0.2	0.5	0.8	0.4	–	[13,14]
HPV82	–	<0.1	–	0.1	–	[13,14]

Table 3
Role of early and late proteins of HPV.

Protein	Role
E1	Regulation of viral DNA replication
E2	Regulation of transcription
E4	Virus maturation and release
E5	Regulation of the growth factor signaling pathway
E6	Degradation of p53
E7	Degradation of retinoblastoma protein, pRb; stimulation of cell proliferation
L1	Major capsid protein; required for virus assembly and stability
L2	Minor capsid protein; important for the binding of virion in the cell receptor, transport to the nucleus

HPV has created complex escape mechanisms to avoid the host's immunological response. By minimizing the synthesis of antigen proteins while the virus is in its vegetative stage, HPV can also avoid immune detection [22]. When infection first begins, HPVs only express a small number of proteins, which are swiftly transported to the cell nucleus [23] reducing their exposure to the host's defense system. There is a noticeable development of capsid protein expression later in the infection phase. A small number of antigen-presenting cells are present in the outer epithelial layer, which quickly releases these proteins. This phenomenon is recognized as a passive immune evasion strategy. Additionally, HPV employs active immune evasion tactics through the generation of onco-proteins E6 and E7 [22]. These oncogenic proteins employ their robust binding affinity with cellular immune regulatory proteins to inhibit the activation of immune-related genes and signaling pathways within infected keratinocytes. Toll-like receptor 9 (TLR9) is essential for detecting viral dsDNA molecules and subsequently activating signaling pathways that lead to inflammation [24]. TLR9 expression in keratinocytes is decreased by diverse mechanisms used by HPV oncoproteins. Specifically, at the TLR9 promoter region, the HPV38 E7 interacts with EZH2, an enzyme that alters histones, resulting in histone methylation and thus preventing production of TLR9 [25]. In a similar manner, HPV16 E7 binds the histone demethylase JARID1B and the histone deacetylase HDAC1 to the TLR9 promoter regulatory region, resulting in TLR9 downregulation [26]. Existing research on the relationship between TLR9 expression and cervical cancer is ambiguous. It has been discovered, however, that cervical epithelial cells with elevated TLR9 levels are less vulnerable to HPV infection than cells with reduced TLR9 expression [27]. In contrast, other investigations have found increased TLR9 expression in cervical cancer patients [28,29]. Immune system dysfunction in infected cells reduces their ability to alert neighboring immune cells, creating a widely immunosuppressive environment that encourages the growth of cancer [22]. HPV can endure within the host cell for an extended period, evading complete elimination by the immune system and resulting in a latent or chronic infection [30,31]. When the immune system is compromised or weakened, as seen in immunosuppressed individuals, the latency period for HPV may be extended. Low-risk HPV types like HPV 6 and 11 often cause benign warts and have a shorter latency period than high-risk HPV types 16 and 18, which are associated with the onset of cervical and other malignancies. Some HPV infections might last for years with no outward signs of a problem. The virion's capacity to elude the immune system and create a latent or subclinical infection is typically linked to its persistence [31,32]. The likelihood of developing cancer over the long run is increased by this persistence [33]. The duration of infection necessary to elevate cancer risk remains unclear, complicating the understanding of the infection's natural history. This uncertainty extends to the HPV vaccine, where debates persist over its long-term efficacy and whether booster doses are necessary to maintain immunity. The variability in immune responses to persistent HPV infections, influenced by factors like genetics and co-infections, adds another layer of complexity.

The goal of this field of research is to elucidate the molecular processes by which HPV oncoproteins alter host cell signaling pathways, elude immune surveillance, and drive cell transformation. Determining new treatment strategies to thwart HPV's carcinogenic effects may result from a thorough understanding of these mechanisms. Researchers are also looking into the possibility of utilizing immune-based therapy to destroy HPV-infected cells or targeting viral proteins [34,35]. Insights acquired from researching the interplay between the HPV virus and its hosts may also have larger implications for comprehending the pathophysiology of other

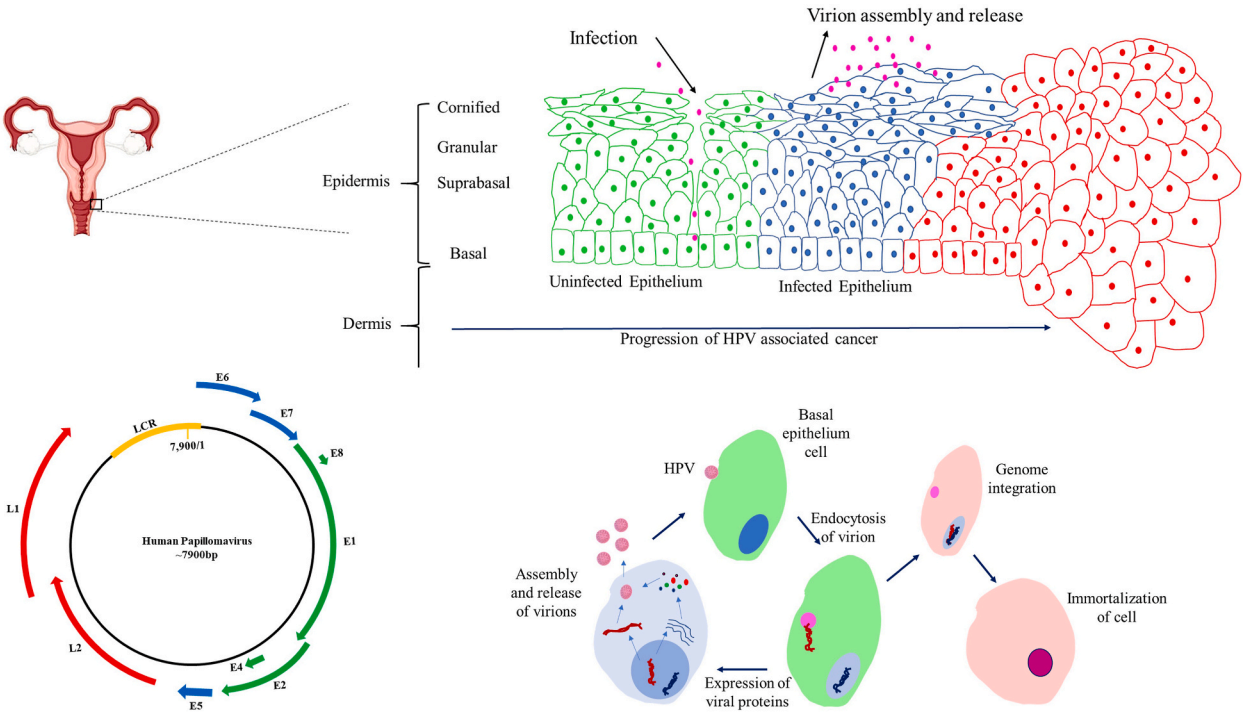

Fig. 2. Life cycle of HPV and Immortalization of host cells.

viral infections and their links to cancer.

2. Cell transformation and cancer development

It is well recognized that HPVs have a role in the emergence of several malignancies, mostly through cell transformation. It is a complex process that occurs when healthy cells start to resemble malignant ones, resulting in uncontrolled growth causing tumor formation. The mucosal surfaces of the cervix, anus, and oral cavity are among the epithelial cells that HPV predominantly targets after infection. Through microscopic wounds or abrasions in the epithelium, the virus enters the cells inducing the expression of viral genes. The expression of genes like E6 and E7 and the components they produce are essential for cell transformation [36]. These oncoproteins obstruct vital cellular processes that regulate cell proliferation and differentiation. E6 prevents cells from undergoing cell cycle arrest and death in reaction to DNA damage by specifically directing the p53 (tumor suppressor protein) degradation [37,38]. As a result, there is a higher chance of mutations and transformations occurring in cells with damaged DNA. This raises the possibility of mutations and transformations by allowing cells with damaged DNA to continue to divide. The E7 interferes with the regulation of cell cycle progression by inactivating the retinoblastoma (Rb) protein. The cell cycle's restrictions are removed by Rb inactivation, resulting in unrestrained proliferation [39,40]. E7 interferes with how the Rb protein controls cell cycle progression. The cell cycle is uninhibitedly proliferated as a result of Rb inactivation [39,40]. Another oncoprotein, E5 plays a pivotal role in the progression of cancers associated with HPV types 16 and 18, which are strongly linked to cervical and other anogenital cancers. E5 contributes to cancer progression by enabling infected cells to evade the immune system, primarily through the downregulation of MHC class I molecules, that prevents cytotoxic T lymphocytes from recognizing and destroying the virus-infected cells. Additionally, E5 enhances oncogenic signaling by interacting with and activating growth factor receptors like Epidermal Growth Factor Receptor (EGFR), leading to sustained activation of pathways that promote cellular proliferation and survival. The oncoprotein also disrupts cellular homeostasis by altering the pH of intracellular organelles, affecting protein processing, and inhibiting apoptosis, allowing infected cells to survive despite oncogenic stress. Furthermore, E5 promotes angiogenesis by inducing the expression of VEGF (Vascular Endothelial Growth Factor), which supports tumor growth by supplying nutrients through new blood vessels. Although significant oncogenic properties have been potentially linked to E5 that synergizes with E6 and E7, driving the transformation of normal cells into malignant ones. This plays a crucial role in HPV-associated cancer progression [41]. Another critical stage in the progression of cancer is the insertion of HPV DNA into the genome of the host cell. It's crucial to remember that not all HPV infections lead to DNA integration, but when it does, the chance of developing cancer is greatly increased. This integration can disrupt cellular functions by upsetting regular gene expression patterns [42–44]. As a result of this mechanism, cancer cells may develop chromosomal instability [45]. A recent study suggests that the intron and promoter regions contained a significant concentration of HPV integration breakpoints. Further, the gene pathway analysis revealed that the HPV-integrated genes were highly prone to chemical carcinogenesis, steroid hormone biosynthesis, and cytochrome P450 pathways of xenobiotic metabolism [46]. Another study observed that HPV integration is more frequent within gene regions than intergenic regions, which may disrupt normal gene function and contribute to cancer progression. It was observed that there are distinct integration hotspots for cervical adenocarcinoma (AC) and squamous cell carcinoma (SCC), with STARD3 and ERBB2 being frequently integrated genes in AC, and RNA45S rDNA and MIR3648-1 in SCC. The differences in the integration patterns and associated genomic features between AC and SCC suggest that HPV-driven carcinogenesis might operate through different mechanisms in these two types of cervical cancer [47]. HPV integration into the host genome is a critical event in the development of cervical cancer, but the precise mechanisms by which this integration leads to malignancy are still debated. Some researchers argue that only specific integration events significantly increase cancer risk, while others believe that any integration poses a considerable threat.

Cellular signaling pathways can become dysregulated due to HPV infection and oncoprotein production. Cell growth, survival, differentiation, and apoptosis are just a few of the biological processes that are regulated by these pathways. A modified phenotype is developed as a consequence of changes in these pathways brought on by HPV.

Mechanisms for eluding immune surveillance are present in HPV-induced cell transformation. Some viral proteins can suppress the immune response, allowing infected cells to survive without being detected and destroyed by immune cells. The altered cells may also secrete substances that inhibit immunological responses, aiding in their survival and growth. Developing targeted therapeutics requires an understanding of how viral oncoproteins affect host cell functions and contribute to the emergence of cancer. Possible therapeutic approaches include increasing the immune response to infected and altered cells, targeting the oncoproteins E6 and E7, and restoring regular cell-cycle control [48].

3. Prevention and therapeutics

Preventing and managing HPV-associated malignancies is crucial for public health. Vaccination is a key strategy, shown to be

Table 4
A few of approved prophylactic HPV vaccines.

Vaccine	Vaccine type	Target HPV types	Approved/Authorized by	References
Gardasil 9	Nonavalent	6, 11, 16, 18, 31, 33, 45, 52, and 58	USFDA and EC	[53,54]
Gardasil	Quadrivalent	6, 11, 16, and 18	USFDA and EC	[53,54]
Cervarix	Bivalent	16 and 18	USFDA and EC	[53,54]
Cervavac	Quadrivalent	6, 11, 16, and 18	CDSCO, India	[55,105]

effective in preventing HPV infections, precancerous lesions, and cancers [49]. HPV vaccinations target high-risk strains linked to cancers like anal and cervical. Widespread vaccination is key to herd immunity and reducing cancer rates, especially in low- and middle-income countries, where raising awareness and promoting vaccination among young girls is vital [50,51]. Regular monitoring is advised for women over 50 who have had high-risk HPV infection for more than a year [52]. A few of prophylactic HPV vaccines, Cervavarix, Gardasil, Gardasil 9 approved by the USFDA [53] and European Commission [54] are commercially available (Table 4). In 2022, the Indian drug regulatory authority has given marketing authorization to Cervavac [55], a quadrivalent HPV vaccine of Indian origin manufactured by Serum Institute of India [56], that protects against HPV strains 6, 11, 16, and 18. Prophylactic vaccines aim to develop neutralizing antibodies against the virus effectively prevent HPV transmission but can't treat existing infections. While, therapeutic HPV vaccines trigger immune responses to target and destroy infected cells. Thus, these offer a potential solution for treating established HPV infections and related conditions [57–59]. Therapeutic vaccines encompass a diverse range of candidates, including proteins, peptides, live vectors, cell-based formulations, and nucleic acids, have been extensively studied in preclinical and clinical trials [60].

HPV genetic material often integrates into the host genome in HPV-related lesions, potentially leading to cancer. This integration usually removes both early (E1, E2, E4, E5) and late (L1, L2) genes, making preventive vaccines ineffective. The loss of E2, a key suppressor of oncogenes E6 and E7, enhances their expression, promoting the development of malignant lesions [61,62]. Therapeutic vaccines focus on targeting E6 and E7 HPV oncoproteins to stimulate immune responses, particularly $CD4^+$ helper T cells and HPV antigen-specific $CD8^+$ cytotoxic T cells, by presenting these proteins to antigen-presenting cells (APCs) [63–65]. For $CD8^+$ T cell activation, E6 and E7 antigens are degraded by proteasomes, and only some of the resulting peptide fragments are presented on class I MHC molecules of APCs [63,66,67]. Only specific peptide fragments containing antigenic epitopes tightly bind to MHC molecules and interact with T cell receptors (TCRs) on antigen-specific T cells to trigger an immunological response. While both E6 and E7 are potential vaccine targets [58,67], most vaccines focus on E7 due to more extensive immunological characterization.in preclinical models than E6 [36].

The viral oncoproteins E6 and E7, which are important in cell transformation, are being carefully targeted by researchers [68,69]. The development of small compounds or biologics that block these oncoproteins may result in new therapeutic approaches. A viable therapeutic strategy is enhancing the body's immunological response to HPV-infected and malignant cells. Immune checkpoint inhibitors belong to the category of immunotherapy intended to improve the immune system's ability to detect and eliminate malignant cells. These therapies work by disabling the protective mechanisms that cancer cells use to escape immune surveillance. Recent advancements in immunotherapies for HPV-related cancers have shown promising potential, particularly through immune checkpoint blockade (ICB), therapeutic vaccination, and adoptive cell therapies. The ICB has become a cornerstone in the treatment of HPV-related cancers, particularly head and neck squamous cell carcinoma (HNSCC) and cervical cancer. The PD-1/PD-L1 pathway is dysregulated in HPV-related cancers to avoid immune detection. Monoclonal antibodies like -nivolumab and pembrolizumab target this pathway for cancer treatment [70]. The CHECKMATE-141 trial demonstrated that nivolumab significantly improved overall survival in patients with recurrent or metastatic HNSCC compared to standard therapy [71]. Similarly, the KEYNOTE-048 trial highlighted the effectiveness of pembrolizumab, either alone or in combination with chemotherapy, for improved outcomes in HNSCC

Table 5
Drugs approved for treatment of HPV associated cancers.

Treatment	Target	Approval	References
Pembrolizumab	CC, HNSCC	USFDA	[106,107]
Bevacizumab	CC	USFDA, CDSCO	[106,108]
Alymsys (Bevacizumab)	CC	USFDA	[106]
Avastin (Bevacizumab)	CC	USFDA	[106]
Zirabev (Bevacizumab)	CC	USFDA	[106]
Mvasi (Bevacizumab)	CC	USFDA	[106]
Keytruda (Pembrolizumab)	CC, HNSCC	USFDA	[106,107]
Tisotumab Vedotin-tftv	CC	USFDA	[106]
Tivdak (Tisotumab Vedotin-tftv)	CC	USFDA	[106]
Bleomycin Sulfate	CC, HNSCC, PC, VC	USFDA	[106,107,109,110]
Hycamtin (Topotecan Hydrochloride)	CC	USFDA	[106]
Topotecan Hydrochloride	CC	USFDA	[106]
Gemcitabine-Cisplatin	CC	USFDA	[106]
Carboplatin-Taxol	CC, HNSCC	USFDA	[106,107]
Cetuximab	HNSCC	USFDA	[107]
Erbitux (Cetuximab)	HNSCC	USFDA	[107]
Opdivo (Nivolumab)	HNSCC	USFDA	[107]
Nivolumab	HNSCC	USFDA	[107]
Hydrea (Hydroxyurea)	HNSCC	USFDA	[107]
Hydroxyurea	HNSCC	USFDA	[107]
Docetaxel	HNSCC	USFDA	[107]
Taxotere (Docetaxel)	HNSCC	USFDA	[107]
Trexall (Methotrexate Sodium)	HNSCC	USFDA	[107]
Methotrexate Sodium	HNSCC	USFDA	[107]
Libtayo® (Cemiplimab)	CC	EMA	[111]

CC, Cervical Cancer; PC, Penile Cancer; VC, Vulular Cancer; HNSCC, Head and Neck Squamous Cell Carcinoma.

patients, regardless of HPV status [72]. Among therapeutic vaccines, peptide-based vaccines like ISA 101, which uses synthetic long peptides from HPV16 E6 and E7, have shown the ability to stimulate robust T-cell responses. For instance, in clinical trials, patients with malignancies associated with HPV showed a 33 % response rate when ISA 101 and nivolumab were combined [71]. Further, vector-based vaccines, such as TG4001, utilize modified viral vectors engineered to express HPV antigens E6 and E7, and have shown promising results when injected with immune checkpoint inhibitors like avelumab [72]. Similarly, the DNA-based vaccines, GX188E and VGX-3100 which encode HPV16 and HPV18 E6 and E7 proteins have demonstrated efficacy in regressing high-grade cervical intraepithelial neoplasia and are being tested in combination with pembrolizumab for advanced cervical cancer [73]. Adoptive cell therapy is another innovative approach, which includes the adoptive transfer of tumor-infiltrating lymphocytes, chimeric antigen receptor (CAR)-T cells, and T cell receptor (TCR)-T cells have shown effective results in treating metastatic cervical cancer, with some patients experiencing durable complete responses [70]. Another potential immunotherapy such as CAR T-cells is still in the early stages of research for HPV-related cancers. It mainly targets surface antigens independent of MHC presentation, thus bypassing common immune evasion mechanisms. Questions about the efficacy of immunotherapies compared to traditional treatments, as well as concerns over severe immune-related side effects, spark ongoing debates. The high cost of immunotherapy raises ethical concerns regarding access, particularly in regions where cervical cancer is most prevalent. Moreover, the combination of immunotherapy with other treatments and the search for reliable biomarkers to predict patient response remain areas of active research and contention, reflecting the challenges in advancing cervical cancer prevention and treatment.

Advances in genetics have enabled the development of personalized cancer treatments. Understanding the genetic and molecular aspects of each tumor can guide treatment choices, making them more effective and reducing side effects [74,75]. Treatment options vary by cancer type and stage and include chemotherapy, surgery, radiation, and targeted therapies. Effectiveness depends on factors like cancer stage and patient health. Identifying and targeting biomarkers offers new therapeutic possibilities. The salient approved drugs available for the treatment of HPV associated cancers [76] is illustrated in Table 5. To improve results, combinatorial therapy approach is more successful. Combining standard chemotherapy, radiation therapy, or immunotherapy with targeted therapies can have synergistic effects that simultaneously targets many elements of cancer development [77]. Clinical trials are essential for evaluating the safety and effectiveness of new treatments, including those for HPV-related cancers. Participating in these trials gives patients access to innovative therapies and advances medical research.

Public education on HPV, its cancer risks, and prevention strategies can promote vaccination, regular screenings, and early detection. Raising awareness can also help reduce stigma and encourage open discussions about sexual health [78].

4. Coinfection with other viruses and bacteria

Even while HPV plays a big role in the emergence of several malignancies, it frequently works in conjunction with other factors. Numerous people with HPV infection also harbors other viruses and bacteria [79–81] that can affect the development of cancer. Other viruses, including human immunodeficiency virus (HIV) [80], Epstein-Barr virus (EBV) [81], herpes simplex virus (HSV) [82] etc., can infect people who are immunocompromised due to HPV infections. Recently, it is reported that the HPV & EBV influence cancer development through their interactions with the tumor microenvironment (TME). EBV influences the TME by expressing proteins like EBV nuclear antigen 1 (EBNA1) and latent membrane proteins (LMPs), which drive oncogenesis through immune evasion and modulation of the cellular environment. The TME comprises immune and stromal cells, blood vessels, and extracellular matrix components, which collectively regulate tumor behavior. In the TME, HPV impacts immune responses by expressing oncoproteins like E6 and E7, which modulate cell proliferation, migration, invasion, and inflammation. HPV-associated tumors often exhibit either a "hot" T-cell-inflamed TME, characterized by high levels of immune cell infiltration and pro-inflammatory mediators, or a "cold" non-T-cell-inflamed TME, marked by limited immune cell activity and more tumor-associated macrophages [83,84]. A 2023 study conducted in Qatar revealed that coinfection with multiple HPV subtypes is associated with advanced colorectal cancer (CRC) stages. The research showed that 17 % of CRC samples had both HPV and Epstein-Barr virus (EBV), and this coinfection was linked to more advanced stages of CRC. Furthermore, the presence of two or more HPV subtypes was a strong indicator of advanced CRC, with the presence of EBV further intensifying this association. These findings imply that HPV coinfection could play a critical role in CRC progression and potentially worsen the prognosis of colorectal cancer [85].

However, the link between HPV and breast cancer (BC) remains controversial, a recent finding supports the hypothesis that HPV may play a role in the development and progression of BC, suggesting that HPV vaccination could potentially help prevent breast cancer [86].

Presence of one viral form enhances the possibility of another virus replication or activity resulting in coinfections with multiple clinical appearances. For instance, a compromised immune system brought on by HIV infection might result in recurrent HPV infections, raising the chance of cancer development [87]. About 5 % of all the cervical cancers that are reported attributed to HIV-infection [88]. The WHO states that "women living with HIV are six times more susceptible to develop cervical cancer compared to women without HIV" [2]. The coinfections, with multiple HPV types or other infectious agents can increase the severity and duration of HPV infections, which can increase the risk of oncogenic progression [89].

The microbiome, or the diverse community of microbes living in and on the body, has recently come to light as having a role in cancer progression. Changes in the microbiome's make-up can affect inflammatory reactions, immunological responses, and other cellular processes that advance cancer. Alterations in microbiota of the cervix, anal canal, or oral cavity may contribute to the local milieu that promotes cancer progression in the context of HPV-associated malignancies. There are numerous and intricate processes by which coinfecting viruses and bacteria interact with HPV to promote the growth of cancer [79–82,90]. The immune system can be weakened by some viruses, which enables HPV to survive. The cellular alterations that support the development of cancer may be

caused by other viruses and bacteria. Inflammation or metabolites that affect cancer growth may be produced by bacteria in the microbiome [91]. In addition to alterations in the immune system's response and nurturing a milieu that supports tumor formation, coinfections can affect the course of HPV infections naturally. They might also have an impact on how well treatments work and how a disease develops? The existence of coinfecting viruses and bacteria offers potential opportunities for cutting-edge therapeutic approaches. Researchers are investigating methods that focus on both HPV and the co-infecting pathogens. These treatments would have the potential to enhance treatment results and lessen cancer recurrence by addressing several relevant variables [92].

5. HPV-related HNSCC and anal malignancies

The Head and neck squamous cell carcinomas (HNSCC), a cluster of malignant conditions, develop in the mucosal lining of throat, oral cavity, and other structures in the head and neck region [93]. In recent times, there has been a noticeable rise in the incidence of HPV-related HNSCC, especially in the oropharynx (back of the throat) [94,95]. This increase is related to oral sexual activity spreading high-risk HPV strains. Similar to HNSCC, there has been an increase in anal malignancies linked to high-risk HPV infections, particularly in some populations [96,97]. Men and women both frequently contract anal HPV infections which can also lead to anal cancer sometimes when infected with high-risk strains for a long-term duration. The emergence of HPV-associated HNSCC and anal malignancies is influenced by a number of variables. These include participation in high-risk sexual activities, having several partners, using cigarettes or alcohol, suppressing the immune system (such as in HIV-positive people), and having other concurrent infections [98]. The molecular intricacies underlying HNSCC and anal cancers are complex. The HPV oncoproteins E6 and E7 disrupt the signaling pathways within host cells, resulting in uncontrolled cellular proliferation and the ability to evade the immune system. These cancers might respond differently to certain therapies compared to non-HPV-associated cancers. Molecular markers associated with HPV status can help in prognosis and therapy decisions. The rise in HPV-associated HNSCC and anal cancers underscores the importance of public health efforts in education, screening, and prevention. Encouraging public understanding of the connection between HPV and these types of cancers can motivate people to pursue routine screenings, embrace safer sexual practices, and contemplate HPV vaccination. Although the prognosis for HNSCC and anal cancers associated with HPV is typically better than that of malignancies not associated with HPV, treatment obstacles still persist. Research continues to be directed towards the creation of targeted medicines that take advantage of the distinct weaknesses of HPV-associated malignancies and reduce adverse effects [98,99].

6. Advance strategies for control and treatment

Public health initiatives aiming at preventing HPV infection and encouraging healthy habits will receive evidence-based direction from research on vaccine development, educational campaigns, and targeted interventions. Research on immune-based therapeutics, combination therapies, targeted therapies, and personalized medicine will all work together to help create more effective and accurate treatment plans. Early detection and precise prognosis depend critically on improved diagnostics. Our capacity to identify HPV-associated malignancies at an earlier stage will be strengthened implying novel diagnostic approaches, biomarkers, and imaging tools, allowing for prompt treatment and better patient outcomes.

7. Conclusion

In the course of their lifetime, 50%–80% of sexually active females will contract HPV. The primary concern associated with high-risk HPVs lies in their ability to potentially cause cancer. The HPVs starts the cell cycle, enabling the replication and assembly of viral particles. The oncoproteins E6, E7, and E5 from the virus have the capacity to interfere with the regular control of the cell cycle, preventing cell death triggered by unintended DNA replication. The proliferation of infected basal cells can also be fueled by the oncoproteins E6 and E7, which can result in neoplasia, an abnormal growth of tissue. Given that there is no proven cure for HPV, the high prevalence of genital HPV has been a major global health problem. The best strategy for treating and preventing HPV infection at the moment is vaccination. Future vaccines should be multivalent for all described oncogenic HPV strains if full efficacy of vaccination is anticipated. However, compared to present formulations, these vaccines will be significantly more expensive. We think that because there are so many uncertainties and concerns surrounding these vaccines, routine use of HPV vaccines requires much more consideration and evaluation. The increasing prevalence of HNSCC and anal cancers linked to HPV infection underscores the need for targeted research in these areas. Insights into their molecular pathogenesis, diagnosis, and treatment are vital for addressing these emerging challenges.

CRediT authorship contribution statement

Tara Chand: Writing – review & editing, Writing – original draft. **Ashwini Kumar Dubey:** Writing – review & editing, Writing – original draft. **Gauri Misra:** Writing – review & editing, Supervision, Conceptualization.

Data availability

No data was used for this review article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] J. Gargano, E. Meites, M. Watson, E. Unger, L. Markowitz, Chapter 5: Human Papillomavirus' in 'Manual for the Surveillance of Vaccine-Preventable Diseases [Available from: https://www.cdc.gov/vaccines/pubs/surv-manual/chpt05-hpv.html, 2022.
[2] WHO, Cervical cancer [Available from: https://www.who.int/news-room/fact-sheets/detail/cervical-cancer, 2022.
[3] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, Global Cancer Statistics 2020: GLOBOCAL estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 71 (2021) 209–249.
[4] A. Reichheld, P.K. Mukherjee, S.M.F. Rahman, K.V. David, R.A. Pricilla, Prevalence of cervical cancer screening and awareness among women in an Urban community in South India—a cross sectional study, Annal Glob. Health 86 (1) (2020).
[5] M. Singh, R.P. Jha, N. Shri, K. Bhattacharyya, P. Patel, D. Dhamnetiya, Secular trends in incidence and mortality of cervical cancer in India and its states, 1990-2019: data from the Global Burden of Disease 2019 Study, BMC Cancer 22 (2022).
[6] S. Ghosh, S.D. Mallya, R.S. Shetty, S. Pattanshetty, D. Deeksha Pandey, S.P. Shama Prasada Kabekkodu, et al., Knowledge, attitude and practices towards cervical cancer and its screening among women from tribal population: a community-based study from Southern India, J. Racial Ethnic Health Disparit. 8 (2021) 88–93.
[7] J.G. T, Factors influencing utilization of cervical cancer screening services among women – a cross sectional survey, Clin. Epidemiol. Global Health 11 (2021).
[8] M.J. Park, E.C. Park, K.S. Choi, J.K. Jun, H.Y. Lee, Sociodemographic gradients in breast and cervical cancer screening in Korea: the Korean national cancer screening survey (KNCSS) 2005-2009, BMC Cancer 11 (1) (2011) 1–8.
[9] S. Krishnan, E. Madson, D. Porterfield, B. Varghese, Advancing cervical cancer prevention in India: insights from research and programs [Available from: https://openknowledge.worldbank.org/entities/publication/da8b2955-006c-5794-8891-dbd363fbaf82, 2013.
[10] S. Srinivasan, V. Johari, A. Jesani, Cervical cancer screening in India. Ethics Dumping: Case Studies from North-South Research Collaborations, 2018, pp. 33–48.
[11] E. Pešut, A. Đukić, L. Lulić, J. Skelin, I. Šimić, N. Milutin Gašperov, et al., Human papillomaviruses-associated cancers: an update of current knowledge, Viruses 6 (13) (2021).
[12] IARC-WHO, Human Papillomaviruses: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 90, 2007 [Available from: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Human-Papillomaviruses-2007.
[13] A.J.K. Kombe, B. Li, A. Zahid, H.M. Mengist, G.A. Bounda, Y. Zhou, et al., Epidemiology and burden of human papillomavirus and related diseases, molecular pathogenesis, and vaccine evaluation, Front. Public Health (2021) 552028.
[14] S. de Sanjose, W.G. Quint, L. Alemany, D.T. Geraets, J.E. Klaustermeier, B. Lloveras, et al., Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study, Lancet Oncol. 11 (11) (2010) 1048–1056.
[15] E.-M. de Villiers, Cross-roads in the classification of papillomaviruses, Virology 445 (1–2) (2013) 2–10.
[16] J. Doorbar, W. Quint, L. Banks, I.G. Bravo, M. Stoler, T.R. Broker, et al., The biology and life-cycle of human papillomaviruses, Vaccine 30 (2012) F55–F70.
[17] K. Institutet, HPV reference clones [Available from: https://www.hpvcenter.se/human_reference_clones/, 2023.
[18] IARC-WHO, Humans WgotEoCRt, Biological Agents : IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 100B [Available from: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Biological-Agents-2012, 2012.
[19] C.J. Lacey, C.M. Lowndes, K.V. Shah, Chapter 4: burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease, Vaccine 24 (2006) 35–41.
[20] J.W. Wang, R.B.S. Roden, L2, the minor capsid protein of papillomavirus, Virology 445 (2013) 175–185.
[21] R. Evande, A. Rana, E.E. Biswas-Fiss, S.B. Biswas, Protein–DNA interactions regulate human papillomavirus DNA replication, transcription, and oncogenesis, Int. J. Mol. Sci. 24 (10) (2023).
[22] C. Zhou, Z.K. Tuong, I.H. Frazer, Papillomavirus immune evasion strategies target the infected cell and the local immune system, Front. Oncol. 9 (2019).
[23] M. Stoler, C.R. Rhodes, A. Whitbeck, S.M. Wolinsky, L.T. Chow, R. Broker, Human papillomavirus type 16 and 18 gene expression in cervical neoplasias, Hum. Pathol. 23 (1992) 117–128.
[24] L.S. Miller, Toll-like receptors in skin, Adv. Dermatol. 24 (2008) 71–87.
[25] L. Pacini, C. Savini, R. Ghittoni, D. Saidj, J. Lamartine, U.A. Hasan, et al., Downregulation of Toll-like receptor 9 expression by beta human papillomavirus 38 and implications for cell cycle control, J. Virol. 89 (2015) 11396–11405.
[26] U.A. Hasan, C. Zannetti, P. Parroche, N. Goutagny, M. Malfroy, G. Roblot, et al., The human papillomavirus type 16 E7 oncoprotein induces a transcriptional repressor complex on the Toll-like receptor 9 promoter, J. Exp. Med. 210 (7) (2013) 1369–1387.
[27] I. Daud, M. Scott, Y. Ma, S. Shiboski, S. Farhat, A.B. Moscicki, Association between toll-like receptor expression and human papillomavirus type 16 persistence, Int. J. Cancer 128 (4) (2011) 879–886.
[28] F. Cannella, A. Pierangeli, C. Scagnolari, G. Cacciotti, G. Tranquilli, P. Stentella, et al., TLR9 is expressed in human papillomavirus-positive cervical cells and is overexpressed in persistent infections, Immunobiology 220 (3) (2015) 363–368.
[29] J.W. Lee, J.J. Choi, E.S. Seo, M.J. Kim, W.Y. Kim, C.H. Choi, et al., Increased toll-like receptor 9 expression in cervical neoplasia, Mol. Carcinog. 46 (11) (2007) 941–947.
[30] G.A. Maglennon, J. Doorbar, The biology of papillomavirus latency, Open Virol. J. 6 (2012) 190, 87.
[31] J. Doorbar, The human Papillomavirus twilight zone – latency, immune control and subclinical infection, Tumour Virus Res. 16 (2023).
[32] A. Hammer, J. Blaakaer, M.N.C. de Koning, T. Steiniche, E. Mejlgaard, H. Svanholm, et al., Evidence of latent HPV infection in older Danish women with a previous history of cervical dysplasia, Acta Obstet. Gynecol. Scand. (2022).
[33] M. Senba, N. Mori, Mechanisms of virus immune evasion lead to development from chronic inflammation to cancer formation associated with human papillomavirus infection, Onco Rev. 6 (2012) e17.
[34] R. Julian, M. Savani, J.E. Bauman, Immunotherapy approaches in HPV-associated head and neck cancer, Cancers 13 (23) (2021).
[35] R. Rosales, C. Rosales, Immune therapy for human papillomaviruses-related cancers, World J. Clin. Oncol. 5 (5) (2014) 1002–1019.
[36] A. Yang, E. Farmer, T.C. Wu, C.F. Hung, Perspectives for therapeutic HPV vaccine development, J. Biomed. Sci. 23 (1) (2016) 75.
[37] S. Li, X. Hong, Z. Wei, M. Xie, W. Li, G. Liu, et al., Ubiquitination of the HPV oncoprotein E6 is critical for E6/E6AP-mediated p53 degradation, Front. Microbiol. 10 (2019).
[38] G. Travé, K. Zanier, HPV-mediated inactivation of tumor suppressor p53, Cell Cycle 15 (17) (2016) 2231–2232.

[39] R.J. Bourgo, W.A. Braden, S.I. Wells, E.S. Knudsen, Activation of the retinoblastoma tumor suppressor mediates cell cycle inhibition and cell death in specific cervical cancer cell lines, Mol. Carcinog. 48 (1) (2009) 45–55.
[40] K.J. Oh, A. Kalinina, S. Bagchi, Destabilization of Rb by human papillomavirus E7 is cell cycle dependent: E2-25K is involved in the proteolysis, Virology 396 (1) (2010) 118–124.
[41] A.C. de Freitas, T.H.A. de Oliveira, M.R.J. Barros, A. Venuti, hrHPV E5 oncoprotein: immune evasion and related immunotherapies, J. Exp. Clin. Cancer Res. 36 (71) (2017).
[42] A.A. McBride, A. Warburton, The role of integration in oncogenic progression of HPV-associated cancers, PloS Pathology 13 (4) (2017) e1006211.
[43] M. Kamal, S. Lameiras, M. Deloger, A. Morel, S. Vacher, C. Lecerf, et al., Human papilloma virus (HPV) integration signature in Cervical Cancer: identification of MACROD2 gene as HPV hot spot integration site, Br. J. Cancer 124 (2021) 777–785.
[44] A.C. Brant, A.N. Menezes, S.P. Felix, L.M. de Almeida, M. Sammeth, M.A.M. Moreira, Characterization of HPV integration, viral gene expression and E6E7 alternative transcripts by RNA-Seq: a descriptive study in invasive cervical cancer, Genomics 111 (6) (2019) 1853–1861.
[45] S.F. Bakhoum, L.C. Cantley, The multifaceted role of chromosomal instability in cancer and its microenvironment, Cell 174 (6) (2018) 1347–1360.
[46] W. Li, S. Tian, P. Wang, Y. Zang, X. Chen, Y. Yao, et al., The characteristics of HPV integration in cervical intraepithelial cells, J. Cancer 10 (12) (2019) 2783–2787.
[47] Y. Bi, J. Hu, L. Zeng, G. Chen, H. Cai, H. Cao, et al., Characteristics of HPV integration in cervical adenocarcinoma and squamous carcinoma, J. Cancer Res. Clin. Oncol. 149 (20) (2023) 17973–17986.
[48] R. Franconi, S. Massa, F. Paolini, P. Vici, A. Venuti, Plant-derived natural compounds in genetic vaccination and therapy for HPV-associated cancers, Cancers 12 (11) (2020).
[49] J. Lei, A. Alexander Ploner, K.M. Elfström, J. Wang, A. Roth, F. Fang, et al., HPV vaccination and the risk of invasive cervical cancer, N. Engl. J. Med. 383 (14) (2020) 1340–1348.
[50] T. Regasa, E.G. Sendo, J.T. Deressa, Human papillomavirus knowledge, perception, and willingness to receive vaccination among female university students in Addis Ababa University, Ethiopia, 2022: a cross-sectional study, SAGE Open Nurs 9 (2023) 23779608231193554.
[51] E.K. Vraga, S.S. Brady, C. Gansen, E.M. Khan, S.L. Bennis, M. Nones, et al., A review of HPV and HBV vaccine hesitancy, intention, and uptake in the era of social media and COVID-19, Elife 12 (2023).
[52] G. Tuerxun, G. Abudurexiti, G. Abulizi, Prevalence, persistence, clearance and risk factors for HPV infection in rural Uyghur women in China, BMC Womens Health 23 (1) (2023) 433.
[53] CDC, Human papillomavirus (HPV) vaccination: what everyone should know [Available from: https://www.cdc.gov/vaccines/vpd/hpv/public/index.html, 2021.
[54] European-Commission, Human Papillomavirus (HPV) [Available from: https://health.ec.europa.eu/vaccination/hpv_en, 2023.
[55] CDSCO, CERVAVAC® Quadrivalent Human Papillomavirus (Serotype 6, 11, 16 & 18) Vaccine Recombinant : Summary of Product Characteristics [Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadSmPC/qHPV%20-%20SmPC%202022.pdf, 2022.
[56] SII. CERVAVAC®, Quadrivalent Human Papillomavirus (Serotypes 6, 11, 16, and 18) Vaccine (Recombinant) [Available from: https://www.seruminstitute.com/product_ind_cervavac.php, 2023.
[57] D.M. Harper, K.B. Williams, Prophylactic HPV vaccines: current knowledge of impact on gynecologic premalignancies, Discov. Med. 10 (50) (2010) 7–17.
[58] B. Ma, B. Maraj, N.P. Tran, J. Knoff, A. Chen, R.D. Alvarez, et al., Emerging human papillomavirus vaccines, Expet Opin. Emerg. Drugs 17 (4) (2012) 469–492.
[59] N. Kash, M.A. Lee, R. Kollipara, C. Downing, J. Guidry, S.K. Tyring, Safety and efficacy data on vaccines and immunization to human papillomavirus, J. Clin. Med. 4 (4) (2015) 614–633.
[60] A. Yang, J. Jeang, K. Cheng, T. Cheng, B. Yang, T.-C. Wu, et al., Current state in the development of candidate therapeutic HPV vaccines, Expert Reviews of Vaccines 15 (8) (2016) 989–1007.
[61] H. zur-Hausen, Papillomaviruses and cancer: from basic studies to clinical application, Nat. Rev. Cancer 2 (5) (2002) 342–350.
[62] J. Doorbar, Model systems of human papillomavirus-associated disease, J. Pathol. 238 (2) (2016) 166–179.
[63] C.S. Rumfield, N. Roller, S.T. Pellom, J. Schlom, C. Jochems, Therapeutic vaccines for HPV-associated malignancies, ImmunoTargets Ther. 9 (2020) 167–200.
[64] A.M. Almeida, J.A. Queiroz, F. Sousa, A. Sousa, Cervical cancer and HPV infection: ongoing therapeutic research to counteract the action of E6 and E7 oncoproteins, Drug Discov. Today 24 (10) (2019) 2044–2057.
[65] M.A. Cheng, E. Farmer, C. Huang, J. Lin, C.F. Hung, T.C. Wu, Therapeutic DNA vaccines for human papillomavirus and associated diseases, Hum. Gene Ther. 29 (9) (2018) 971, 66.
[66] Y. Yao, W. Huang, X. Yang, W. Sun, X. Liu, W. Cun, et al., HPV-16 E6 and E7 protein T cell epitopes prediction analysis based on distributions of HLA-A loci across populations: an in silico approach, Vaccine 31 (18) (2013) 2289–2294.
[67] R. Malla, M.A. Kamal, E6 and E7 oncoproteins: potential targets of cervical cancer, Curr. Med. Chem. 28 (39) (2021) 8163–8181.
[68] S. Peng, L. Ferrall, S. Gaillard, C. Wang, W.Y. Chi, C.H. Huang, et al., Development of DNA vaccine targeting E6 and E7 proteins of human papillomavirus 16 (HPV16) and HPV18 for immunotherapy in combination with recombinant vaccinia boost and PD-1 antibody, mBio 12 (1) (2021) e03224, 20.
[69] A. Pal, R. Kundu, Human papillomavirus E6 and E7: the cervical cancer hallmarks and targets for therapy, Front. Microbiol. 10 (2020) 3116.
[70] S.M. Norberg, C.S. Hinrichs, Engineered T cell therapy for viral and non-viral epithelial cancers, Cancer Cell 41 (1) (2023) 58–69.
[71] L.G. Sousa, K. Rajapakshe, J. Rodriguez Canales, R.L. Chin, L. Feng, Q. Wang, et al., ISA101 and nivolumab for HPV-16+ cancer: updated clinical efficacy and immune correlates of response, J. Immunotherap. Cancer 10 (2) (2022) e004232.
[72] M.Y. Lee, C.T. Allen, Immunotherapy for HPV malignancies, Semin. Radiat. Oncol. 31 (2021) 361–370.
[73] L. Ferrall, K.Y. Lin, R.B.S. Roden, C.F. Hung, T.C. Wu, Cervical cancer immunotherapy: facts and hopes, Clin. Cancer Res. 27 (18) (2021) 4953–4973.
[74] E. Kudela, A. Liskova, M. Samec, L. Koklesova, V. Holubekova, T. Rokos, et al., The interplay between the vaginal microbiome and innate immunity in the focus of predictive, preventive, and personalized medical approach to combat HPV-induced cervical cancer, EPMA J. 12 (2) (2021) 1990220.
[75] G. Miserocchi, C. Spadazzi, S. Calpona, F. De Rosa, A. Usai, A. De Vita, et al., Precision medicine in head and neck cancers: genomic and preclinical approaches, J. Personalized Med. 12 (6) (2022).
[76] N. Khairkhah, A. Bolhassani, R. Najafipour, Current and future direction in treatment of HPV-related cervical disease, J. Mol. Med. (Berl.) 100 (6) (2022) 829–845.
[77] M. Vanneman, G. Dranoff, Combining immunotherapy and targeted therapies in cancer treatment, Nat. Rev. Cancer 12 (4) (2012) 237–251.
[78] E. Krokidi, A.P. Rao, E. Ambrosino, P.P.M. Thomas, The impact of health education interventions on HPV vaccination uptake, awareness, and acceptance among people under 30 years old in India: a literature review with systematic search, Front Reprod Health 5 (2023).
[79] O.A.G. Tantengco, Y. Nakura, M. Yoshimura, F. Nishiumi, E.F. Llamas-Clark, I. Yanagihara, Co-infection of human papillomavirus and other sexually transmitted bacteria in cervical cancer patients in the Philippines, Gynecol. Oncol. Rep. 40 (2022).
[80] A. Pérez-González, E. Cachay, A. Ocampo, E. Poveda, Update on the epidemiological features and clinical implications of human papillomavirus infection (HPV) and human immunodeficiency virus (HIV) coinfection, Microorganisms 10 (2022).
[81] R. Blanco, D. Carrillo-Beltrán, A.H. Corvalán, F. Aguayo, High-risk human papillomavirus and epstein-barr virus coinfection: a potential role in head and neck carcinogenesis, Biology 10 (12) (2021).
[82] D.G. Sausen, O. Shechter, E.S. Gallo, H. Dahari, Borenstein RjdcPPP, Herpes simplex virus, human papillomavirus, and cervical cancer: overview, relationship, and treatment implications, Cancers 15 (14) (2023).
[83] Q. Fernandes, G. Sher, K.S. Prabhu, S. Kuttikrishnan, M. Merhi, S. Dermime, et al., Beyond viral infections: the multifaceted roles of human papillomavirus and epstein-barr virus in shaping the tumor microenvironment, Discov. Med. 36 (180) (2024) 1–15.
[84] Q. Fernandes, I. Gupta, S. Vranic, A.E. Al Moustafa, Human papillomaviruses and epstein-barr virus interactions in colorectal cancer: a brief review, Pathogens 9 (4) (2020) 300.

[85] Q. Fernandes, I. Gupta, K. Murshed, H. Abo Samra, H. Al-Thawadi, S. Vranic, et al., Coinfection of HPVs is associated with advanced stage in colorectal cancer patients from Qatar, Pathogens 12 (2023) 424.
[86] C. Karachalios, S. Petousis, C. Margioula-Siarkou, D. K, Human papillomaviruses and breast cancer: a systematic review and meta analysis, Oncol. Lett. 27 (2) (2023) 75.
[87] H. Onohuean, E.J. Aigbogun, B.E. Igere, Meta-synthesis and science mapping analysis of HIV/HPV co-infection: a global perspective with emphasis on Africa, Glob. Health 18 (1) (2022) 39.
[88] D. Stelzle, L. Tanaka, K. Lee, A.I. Khalil, I. Baussano, A.S.V. Shah, et al., Estimates of Global burden of cervical cancer associated with HIV, Lancet Global Health 9 (2) (2020. 2021) e161–e169.
[89] G. Ashok, S. Basu, P. Priyamvada, A. Anbarasu, S. Chintala, S. Ramaiah, Coinfections in human papillomavirus associated cancers and prophylactic recommendations, Rev. Med. Virol. 34 (2) (2024) e2524.
[90] S.M. Kumari, V.M. Bhor, A literature review on correlation between HPV coinfection with C. trachomatis and cervical neoplasia - coinfection mediated cellular transformation, Microb. Pathog. 168 (2022).
[91] A.P. Bhatt, M.R. Redinbo, S.J. Bultman, The role of the microbiome in cancer development and therapy, CA A Cancer J. Clin. 67 (4) (2017) 326–344.
[92] A.G. Mukherjee, U.R. Wanjari, A.V. Gopalakrishnan, S. Kannampuzha, R. Murali, A. Namachivayam, et al., Exploring the molecular pathogenesis, pathogen association, and therapeutic strategies against HPV infection, Pathogens 12 (2023) 25.
[93] D.E. Johnson, B. Burtness, C.R. Leemans, V.W.Y. Lui, J.E. Bauman, J.R. Grandis, Head and neck squamous cell carcinoma, Nat. Rev. Dis. Prim. 6 (1) (2020).
[94] X. Castellsagué, L. Alemany, M. Quer, G. Halec, B. Quirós, S. Tous, et al., HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients, J. Natl. Cancer Inst. 108 (6) (2016) djv403.
[95] IARC-WHO, Oropharynx: Number of new cases in 2020, both sexes, all ages [Available from: https://gco.iarc.fr/today/data/factsheets/cancers/3-Oropharynx-fact-sheet.pdf, 2020.
[96] C. de Martel, M. Plummer, J. Vignat, S. Franceschi, Worldwide burden of cancer attributable to HPV by site, country and HPV type, Int. J. Cancer 141 (4) (2017) 664–670.
[97] IARC-WHO, Anus: number of new cases in 2020, both sexes, all ages [Available from: https://gco.iarc.fr/today/data/factsheets/cancers/10-Anus-fact-sheet.pdf, 2020.
[98] Z. Sun, X. Sun, Z. Chen, J. Du, Y. Wu, Head and neck squamous cell carcinoma: risk factors, molecular alterations, Immunology and Peptide Vaccines, Int. J Peptide Res. Therap. 28 (1) (2022).
[99] F. Kordbacheh, C.S. Farah, Current and emerging molecular therapies for head and neck squamous cell carcinoma, Cancers 13 (2021).
[100] IARC-WHO, Vagina: Number of new cases in 2020, both sexes, all ages [Available from: https://gco.iarc.fr/today/data/factsheets/cancers/22-Vagina-fact-sheet.pdf, 2020.
[101] IARC-WHO, Penis: Number of new cases in 2020, both sexes, all ages [Available from: https://gco.iarc.fr/today/data/factsheets/cancers/26-Penis-fact-sheet.pdf, 2020.
[102] IARC-WHO, Vulva: Number of new cases in 2020, both sexes, all ages [Available from: https://gco.iarc.fr/today/data/factsheets/cancers/21-Vulva-fact-sheet.pdf, 2020.
[103] IARC-WHO, Nasopharynx: Number of new cases in 2020, both sexes, all ages [Available from: https://gco.iarc.fr/today/data/factsheets/cancers/4-Nasopharynx-fact-sheet.pdf, 2020.
[104] IARC-WHO, Cervix uteri: Number of new cases in 2020, both sexes, all ages [Available from: https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf, 2021.
[105] CDSCO, Details of manufacturing permissions of Human Vaccines approved by CDSCO (2009 to 2022) [Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadVaccineManufacture/Details%20of%20manufacturing%20permissions%20of%20Human%20Vaccines%20approved%20by%20CDSCO%20(2009%20-%206th%20Oct.%202022).pdf, 2022.
[106] NIH-NCI, Drugs Approved for Cervical Cancer: NIH, USA [Available from: https://www.cancer.gov/about-cancer/treatment/drugs/cervical, 2022.
[107] NIH-NCI, Drugs Approved for Head and Neck Cancer: NIH, USA [Available from: https://www.cancer.gov/about-cancer/treatment/drugs/head-neck, 2021.
[108] CDSCO, r-DNA based Drugs Approved in the Country [Available from: https://cdsco.gov.in/opencms/resources/UploadCDSCOWeb/2018/UploadBiologicalrDNA/rdnaform46.pdf, 2019.
[109] NIH-NCI, Drugs Approved for Penile Cancer: NIH, USA [Available from: https://www.cancer.gov/about-cancer/treatment/drugs/penile, 2019.
[110] NIH-NCI, Drugs Approved for Vulvar Cancer: NIH, USA [Available from: https://www.cancer.gov/about-cancer/treatment/drugs/vulvar, 2019.
[111] Regeneron, Libtayo® (CEMIPLIMAB) Approved by The European Commission as the First Immunotherapy in Second Line Recurrent Or Metastatic Cervical Cancer Irrespective of PD-L1 Expression Level or Tumor Histology [Available from: https://investor.regeneron.com/news-releases/news-release-details/libtayor-cemiplimab-approved-european-commission-first-0/, 2022.