Zolfi *et al. Virology Journal* (2025) 22:53
https://doi.org/10.1186/s12985-025-02682-1

Virology Journal

REVIEW Open Access

A review of the carcinogenic potential of human papillomavirus (HPV) in urological cancers

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Abstract

Direct skin-to-skin contact during intimate sexual contact with a human papillomavirus (HPV)-positive individual is often the cause of HPV infection. In addition, many studies have been written up to date that look at the role of HPV in the growth of other types of tumors. Not all urological cancers are associated with HPV. However, penile cancer (PC) is often caused by HPV, especially high-risk types. HPV-16 has been the most frequent (68.3%), followed by HPV-6 (8.1%) and HPV-18 (6.9%). An increased risk of getting certain types of urinary cancers like prostate, bladder, testicular, and kidney has also been linked to these infections. Additionally, HPV may play a part in continuous inflammation and cancer progression in different organs and tissues. So, making HPV vaccine programs available to more people of the male sex around the world could significantly lower the number of urinary cancers caused by HPV. The critical effects of HPV on different types of urologic cancers (UCs), such as testicular, prostate, penile, and kidney cancer, and the importance of HPV vaccination have been seen in this study.

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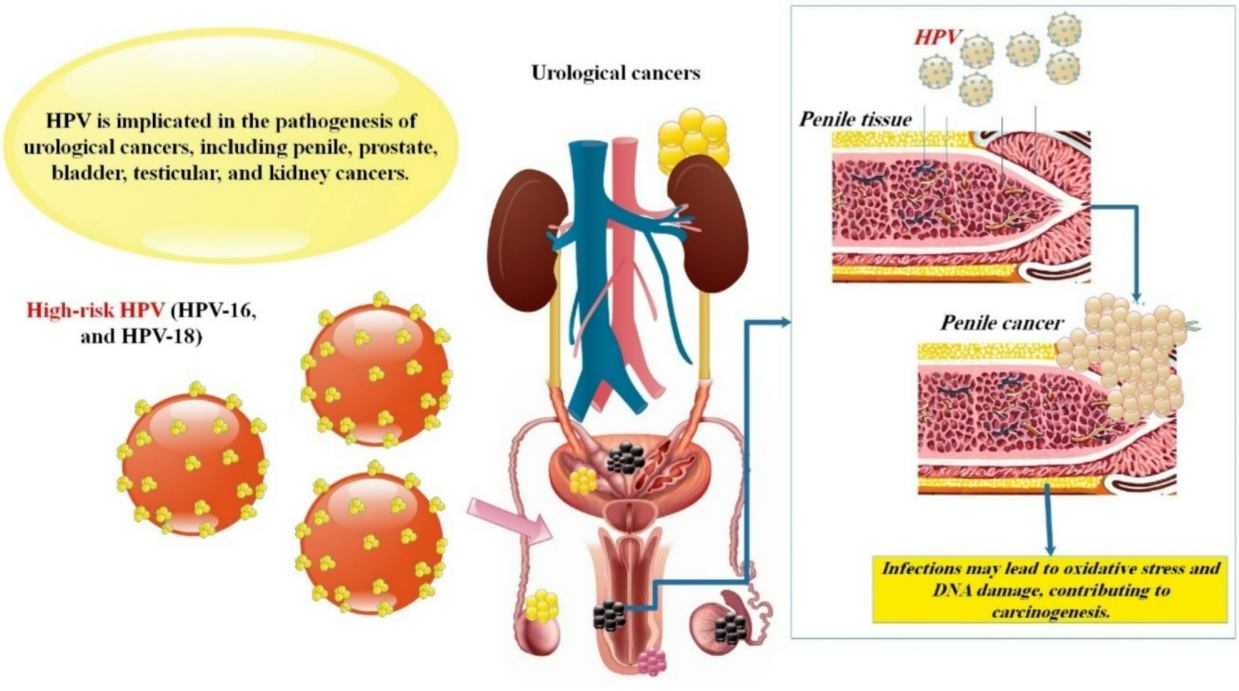
Graphical Abstract



Keywords Human papillomavirus (HPV), Urological cancer, HPV vaccine, Prostate cancer, Penile cancer

Introduction

Urological cancers (UCs), including prostate cancer (PCa), bladder cancer (BC), kidney cancer (KC), testicular cancer (TC), and penile cancer (PC), are common cancers that account for approximately a quarter of all malignant diseases in men [1]. They are responsible for more than 30% of all cancer cases and 10% of all cancer deaths in men. BC and KC are more likely to happen to male than to female persons [2]. Several things must work together to make cancer more likely. If apoptosis is stopped and the defense system doesn't get rid of the changed cell, the cellular genome may change after being exposed to something that can cause cancer. Infectious agents can use these traits to change a target cell. "Tumor viruses" are viruses that are linked to cancer in humans. Most of them can work with the host DNA and make the target cell eternal so that they can make more copies of themselves. The affected cell produces the viral genes, which can cause cells to grow and divide and stop them from dying (apoptosis) [3]. For instance, PCa development is affected by both genetic and external factors. We still don't fully understand the molecular events that cause PCa to grow or spread. A new body of research documents the part that virus illnesses play in starting or spreading PCa. In this case, some viruses have been shown to interact with host proteins and cause changes in genetics, the immune system, and inflammation that can start or spread PCa. The prostate can get sick from many things, including viruses. Viruses like human papillomavirus (HPV), cytomegalovirus (CMV), human herpes simplex virus type 2 (HSV2), human herpesvirus type 8 (HHV8), Epstein-Barr virus (EBV), polyomavirus BKV, and xenotropic murine leukemia virus-related virus (XMRV) have been found in the prostate in several studies. But it's still not clear how often infections happen or if they cause an inflammatory response or have a direct link to PCa development [4].

Sexually transmitted diseases are most often caused by HPV around the world. This infection causes about 5% of all cancers in the world each year, hitting about 625,600 women and 69,400 men [5, 6]. The number of people getting HPV infections is going up around the world, especially young people who are sexually active. As a result, these infections have become more common in urology practice over the past few years as incidental results and main concerns [7]. Most HPV infections only last a short time, but the chance of spreading the virus depends on things like age, gender, social position, and the type of HPV virus. HPV is divided into low-risk (LR)-HPV and high-risk (HR)-HPV types. HPV-16 and HPV-18 show different population trends [8]. HPVs are a big group of dsDNA viruses that attack human epithelial cells and

use the machinery of epithelial cells to make more copies of themselves [9]. They are about 55 nm across and have a double-stranded circular DNA genome with about 8,000 nucleotide base pairs. In general, HPV can lead to a variety of diseases, from harmless sores to cancerous growths that invade other parts of the body [10]. Furthermore, HPV's complicated pathogenesis includes genetic and epigenetic interactions. HPV oncogenes (E6 and E7) and their transfer into host DNA are key to causing cancer [11]. Benign tumors in the anogenital area, like condyloma acuminatum, are caused by HPV. However, HPV is also highly linked to cervical, anal, vulvar/vaginal, and PC carcinomas. In addition to being a cancer-causing virus, HPV is a big problem for society and the economy because mild sores keep coming back. No treatment completely cures the virus, which is costly [12].

Researchers showed that viral infections might influence PC and PCa growth by triggering long-term inflammatory processes that result in cancer and DNA damage. The E6/E7 oncoproteins of HPV-16 and −18 have been shown to eternize prostate epithelial cells (PECs) above and beyond (moreover, on the other hand, etc.). Remarkably, HPV has been found in both healthy and malignant prostate tissues in several epidemiological and biological investigations. Consequently, there is ongoing debate over the link between HPV infections and PCa development [13, 14]. The PC, additionally, burden varies around the world according to the incidence of alcohol use, human immunodeficiency virus (HIV) infection, hazardous sexual practices, and circumcision. PC is becoming more common among younger people, which is a cause for concern and highlights the need for measures to diagnose the disease early and prevent it [15].

HR-HPV infection, particularly HPV-16, may contribute to the development of BC too [11]. Implications for diagnosis, treatment, and prevention may arise from a better understanding of HPV's function in BC. The current research provides further evidence that HPV may have a role in BC development, lending indirect support to the worldwide recommendation that both sexes should implement basic preventative measures. More epidemiological investigations are required to validate these results and evaluate the function of diagnostic and preventative measures for HPV-related BC [16].

Western nations have seen an increase in the prevalence of TC over the last 20 years, making it the most prevalent malignancy among males aged 14–44. Both hereditary and environmental factors may influence the development of TC; the most pervasive of these is cryptorchidism [17, 18]. Infecting the male gametes directly in the testis is one way that HPV reduces fertility. This is because HPV causes aneuploidy and increased DNA fragmentation in sperm. Like other viruses that infect sperm, HPV is believed to adhere to spermatozoa at two separate locations along the equatorial domain of the spermatozoon's head. On the other side, there is a dearth of information about the link between HPV and TGCTs. It is doubtful that HPV does not have a role in testicular carcinogenesis, given the virus's well-documented carcinogenic potential and its specificity for this organ. Further evidence of high quality is still required to elucidate the matter further [19, 20].

Most of the time, HPV is spread by people touching their sex parts directly, which can cause diseases on the mucous membranes and keratinized epithelial cells [21]. Most illnesses don't cause any symptoms, but some, like penile, prostate, bladder, testis, and KC, can last for a long time. For example, HR and LR HPV were found in the cervixes of boys and men who didn't have any symptoms and who were getting circumcised, but the rates of finding were different based on the HPV detection method used [22]. Researchers recommend that people who have been diagnosed with TC get screened for HPV at the time of diagnosis, especially after additional treatments. This is because HPV exposure raises the risk of getting cancer and may also make it harder to get pregnant [23]. The focus should be on health development and prevention methods for men. To avoid getting urological cancer, people, especially guys, need to be protected against HPV [24]. One may argue that the need to strengthen current HPV vaccination programs is growing due to the potential link between HPV and UCs. Further analysis of the relationship between HPV and cancer risk and its effect on disease prognosis requires research based on high carcinogenic risk HPV type and virological markers such as viral load and viral physical condition [14]. Subunit vaccinations known as prophylactic HPV vaccines have been created to lessen the incidence of cervical cancer linked to HPV. The first vaccine, tetravalent, contains virus-like particles (VLPs) of HPV-16, HPV-18, HPV-6, and HPV-11; the second vaccine is bivalent and contains VLPs of HPV-16 and 18. Both vaccinations are "prophylactic," meaning they protect the recipient from catching HPV but don't treat an existing infection. Phase 3 clinical studies are now being conducted to examine the long-term effectiveness of bivalent and tetravalent vaccinations [25]. Therapeutic applications of targeted treatment, radiation, chemotherapy, and surgery are extensive. At this time, there is no one-size-fits-all solution for treating HPV infections. Immunotherapy, a new treatment approach for HPV infection, restores local immune cell activity to accomplish therapeutic objectives. However, many papers on this topic are only now coming to light. It has also led to the suggestion of therapeutic HPV vaccinations that target the E6 and E7 proteins; these vaccines can boost the immune response of T cells. When it comes to treating illnesses caused by HPV, there are a variety of vaccinations that have shown promise. These

include genetic, dendritic cell, peptide, protein-based options, and live-vector vaccines. Despite the lack of an authorized vaccination for clinical usage at this time, the therapeutic HPV vaccine shows great promise as a future therapy option [26].

This study examined the features of the HPV virus and investigated how this virus might be causing more types of urinary cancer. Lastly, we discussed the different vaccines and ways to avoid and treat HPV to lower UC.

Characterization of HPV infections

The most common sexually transmitted infection (STI) in the world is HPV [27]. Most people who get sick don't have any symptoms and get rid of the infection, but some people may have benign lesions that don't go away or that come back, and others may get precancerous lesions and cancer [28].

Three parts can be found in the HPV genome: E (early), L (late), and LCR (long control region). The E region codes for early proteins (E1–E2, E4–E7 genes), which are in charge of viral release (E4 gene), replication (E1 and E2 genes), and making an environment that is good for viral replication, such as avoiding the immune system of the host and keeping epithelial cell growth going (E5, E6 and E7 genes). Extra proteins E6–E7, E1–E4, and E8–E2 (E8 is a piece of E1) are made from intragenic promoters during transcription. The E8^E2 protein can do the job of the E5 protein. The L region makes the L1 and L2 capsid proteins, and the LCR (long control region) doesn't code for anything. It has cis-regulatory elements that control virus replication and gene expression [29] (Fig. 1).

The International Agency for Research on Cancer (IARC) divides HPV into five groups: those that are likely to cause cancer (group 1), those that may cause cancer (group 2), those that pose a low risk of cancer (group 3), and those that have not been categorized based on their ability to cause cancer2. HPV-16 is the most likely to cause cancer. Other types of HPV, including HPV-18, -31, -33, -35, -39, -45, -51, -52, -56, -58, and – 59, are known to cause human cancer. HPV-68 is also likely to cause cancer, as are HPV-26, -30, -34, -53, -66, -67, -69, -70, -73, -82, -85, and – 97. Finally, HPV-6, -11, -42, -43, and – 44 are known as LR HPV genotypes. Even though most infections are cleared up by the host's immune system within two years, about 10% of HPV infections will stay in people who have them later on [30].

It's important to note that most mucosal HPV infections don't cause any signs and are naturally cleared by the body's immune system. However, some infections last a long time and can eventually cause cancer in the affected area. Mucosal HPV genotypes are either LR or HR-HPV. LR genotypes can sometimes cause harmless warts but not dangerous tumors, while HR genotypes can cause cancer [31]. Most guys who have any HPV never have any signs or health issues. Genital warts can be caused by some types of HPV [32]. HR-HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) cases cause most penile and head and neck cancers [33]. On the other hand, only a small percentage of lesions caused by HPV infections turn into high-grade lesions or cancer. Genetic and immune system factors aren't the only things that can affect the chance of getting cancer. HR-HPV, viral

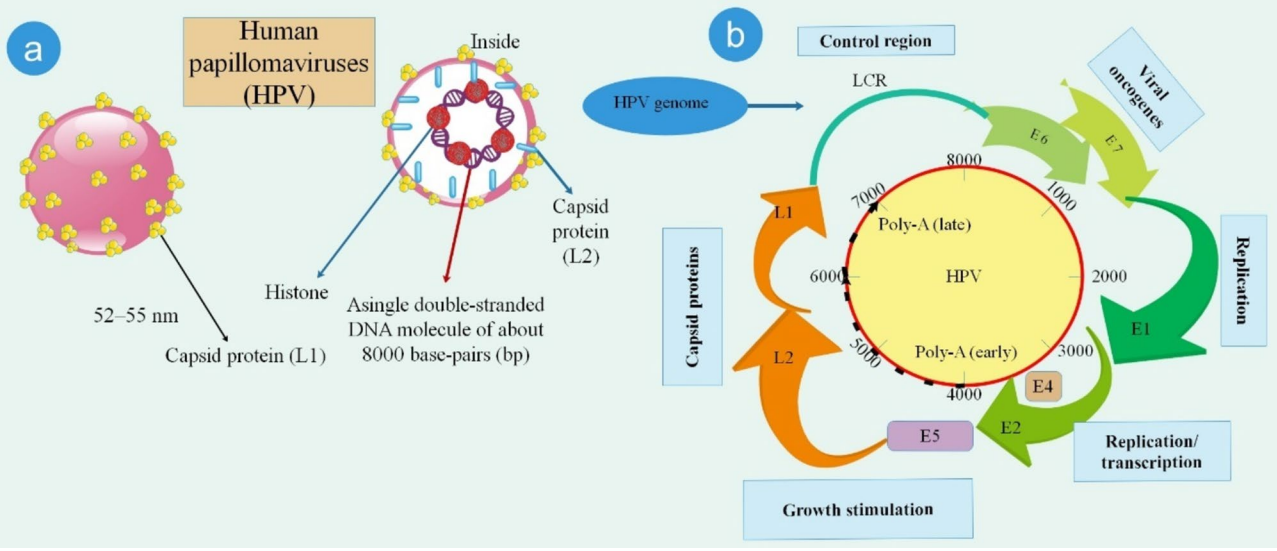


Fig. 1 (**a**, **b**) The structure and DNA of HPV. Early and late genes in the eight thousand base pairs comprise the HPV genome. In the late genome, L1 and L2 are encoded. In the early genome, E1, E2, E4, E5, E6, and E7 are encoded. The oncoproteins E6 and E7 break down tumor suppressors p53 and retinoblastoma tumor suppressor protein (pRb), respectively. L1 and L2 build the shape of the HPV capsid protein. LCR stands for "long control region" [37]

load, and viral integration are some viral factors that can cause this [34].

In the male population, HPV cases often present as anogenital warts, which not only cause a significant burden of complications but also contribute significantly to the increased rate of HPV transmission [35]. Furthermore, the most common epidermal manifestation of epidermotropic HPV is genital warts, which are caused mainly by non-oncogenic HPVs (types 6 and 11) in both men and women. With a peak age of less than 30, genital warts affect millions of men every year. Even though genital warts are harmless, sufferers experience a great deal of anxiety and embarrassment. After an HPV infection, genital warts typically take two to three months to incubate. These very contagious tumors spread quickly to sex partners. The most significant rise in sexual transmission is caused by flat penile warts, which are known to carry the most crucial quantity of HPV. Furthermore, on dry surfaces, anogenital warts often appear as smooth keratotic papular warts; on wet surfaces, they typically form cauliflower-like condylomata accuminata. They may be found under the prepuce, on the glans, coronal sulcus, scrotum, base or shaft of the penis, or in the pubic and rectal region in males. Approximately one-third of genital warts go away on their own, but they often come back; still, some of them develop into cancer within a few years [35].

HR-HPV infections can also cause penile, anal, and oropharyngeal cancers. To make sure that public health policies and interventions work, it is essential to have a complete knowledge of all of HPV's different forms [26]. Few published studies have looked into the frequency, pathogenesis, and distribution patterns of HPV infection in guys, making these essential issues less clear. A recent global review found that the general frequency of HPV among men is thought to be between 15% and 45%, with differences depending on location, age group, and testing method. Also, having multiple sexual partners, having oral and anal sex, and not having a strong immune system all have a significant effect on the number of HPV infections guys get [36].

HPV in cancer development

It is known that HPVs can cause many types of cancer (Fig. 2) by changing many signaling pathways by integrating oncogenes into the host genome and affecting gene expression [38] (Fig. 3).

Upstream DNA damage repair (DDR) kinases in mammalian cells include ataxia-telangiectasia mutated (ATM), ATM- and Rad3-Related (ATR), and DNA-dependent protein kinase (DNA-PKcs). As phosphatidylinositol-3-kinase-like kinases (PIKKs), these considerable serine/threonine kinases are involved in metabolism. The DDR signaling pathway is at the heart of this network's reaction to DNA damage, which is regulated by the ATR and ATM kinases. Although DNA replication stress and DNA damage activate ATM and ATR, the two proteins' DNA damage specificities differ and do not perform duplicate activities. When DNA damage is detected, ATM and ATR often collaborate to control subsequent events [39].

In addition, HR-HPV must activate cellular pathways to replicate successfully. These pathways include those for development and DDR. Amplification happens in G2/M and depends on the ATM and ATR circuits being turned on. When DNA double-strand (ds) breaks (DSB), the ATM pathway reacts by turning on several downstream effectors, such as pCHK2, changed histone H2AX, BRCA1, and RAD51. The ATR pathway is turned on when replication stress and single-stranded DNA (ssDNA) at replication forks that have stopped moving happen. When turned on ATR, it phosphorylates downstream effectors like CHK1, H2AX, and FANCD2. These are essential parts of the Fanconi Anemia (FA) pathway, along with BRCA1 and RAD51. The ATR pathway is critical to copying viruses in cells that haven't changed yet and making more copies of viruses in those that have changed. Scientists are still unsure how these DNA damage factors help HR genes grow, but they might help break up concatemers or work directly on replication. These factors rise similarly in tissues of both OPSCC and cervical cancers. New research suggests that some DDR members, like those in the FA pathway, become less effective when HPV causes cancer to spread. This might help explain why HR-HPV-positive cancers have many mutations: DNA damage repair pathways may not work as well [40].

When HPV E5, E6, and E7 oncoproteins are expressed, they can change several communication pathways that lead to cancer. Researchers summarized the signaling pathways these oncoproteins trigger and discussed targeted treatment against key signaling molecules [41]. The phosphatidyl inositol 3-kinase (PI3K)/AKT signaling is essential to cancer cell migration, invasion, and proliferation. Evidence suggests that the E6/E7 viral proteins directly activate this signal transduction pathway, which accelerates the evolution of HPV-positive cervical cancer [42]. Furthermore, E6 may activate the PI3K/Akt, Wnt, and Notch pathways while inhibiting tumor protein 53 and PDZ (postsynaptic density protein–drosophila disk big tumor suppressor–zonula occludens-1 proteins). E7 may accelerate the PI3K/Akt pathway and inhibit the function of retinoblastoma protein [43]. Both E6 and E7 can disable the mechanisms that regulate the synthesis of microRNA in cells, which may alter the communication between cells. The PI3K/Akt and mitogen-activated protein kinase pathways may function more quickly when E5 increases the epidermal growth factor receptor (EGFR)'s

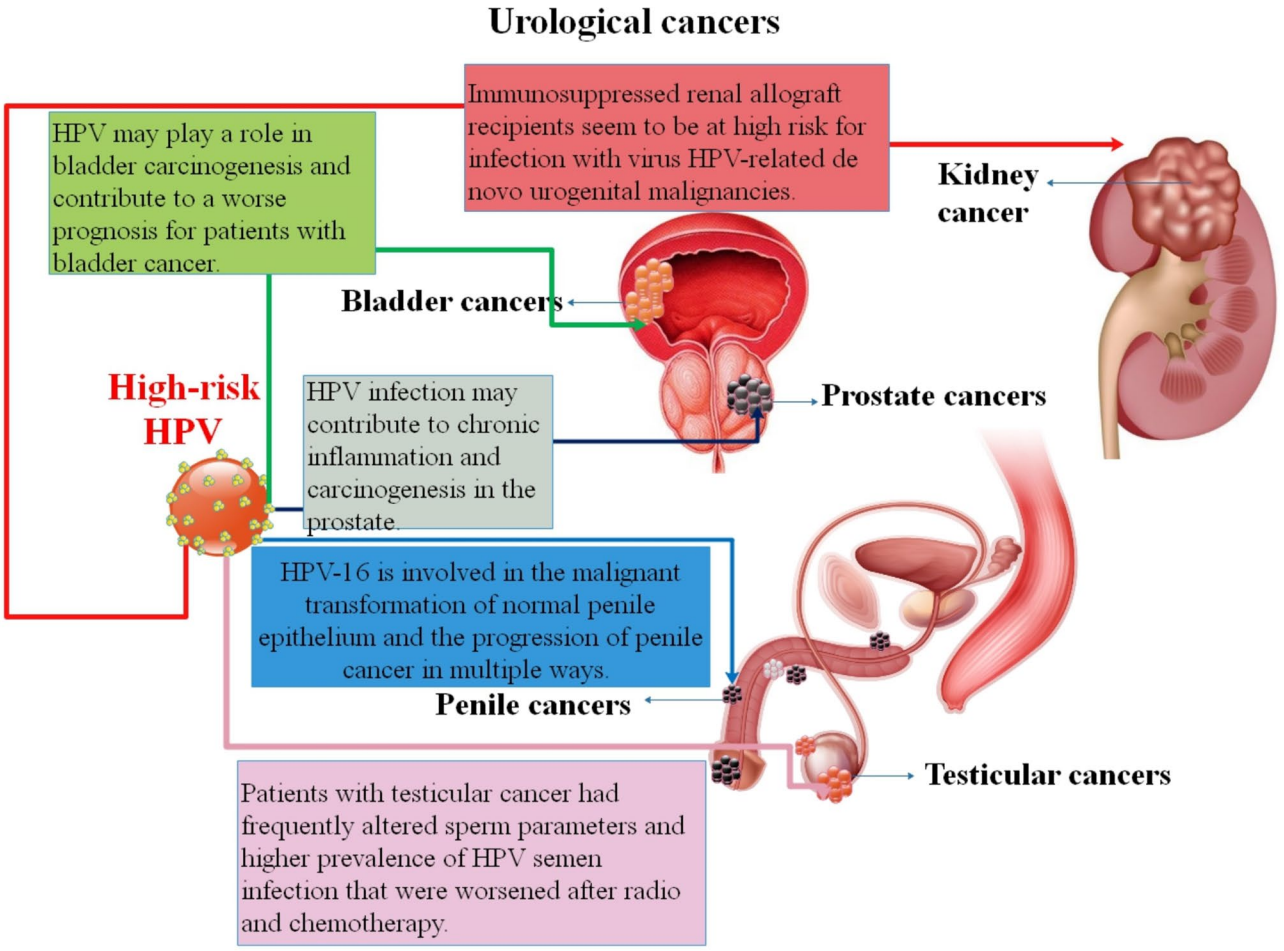


Fig. 2 The carcinogenic potential of HPV in urological cancer, including penile, prostate, bladder, testicular, and kidney cancers

sensitivity to the epidermal growth factor. E5 may also stop the subsequent apoptotic process. These altered signaling pathways could be crucial for the initiation and progression of HPV-related malignancies. There are potential medical benefits to treating the main signaling molecules specifically [44]. The oncoproteins E6 and E7 from the HPV virus break down p53 and pRb, which lets the cell move into the S phase without stopping in G1. Oncoproteins made by HR-HPV mess up a lot of crucial cellular signaling pathways. In particular, E5, E6, and E7 proteins mess up signaling pathways that include p53, pRb, PI3K/Akt/mammalian target of rapamycin (mTOR), EGFR, mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK), and Wnt/β-catenin. This makes HPV-mediated cancer more likely to happen [45].

Beyond its effects on tumor suppressors p53 and Rb, E6 and E7 expression also modifies other signaling pathways that might play a significant role in transformation. The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling cascade is one of these pathways that acts via several molecular and cellular processes and plays a crucial role in HPV-induced carcinogenesis. Researchers reviewed the literature on HPV-induced malignancies and how oncogenes E6, E7, and E5 stimulate the PI3K/Akt/mTOR signaling pathway to control tumor initiation, progression, and patient fate. Researchers also outline the common amplification of these signals in HPV-induced cancers. To better prevent and cure HPV-induced malignancies, their knowledge of how the PI3K/Akt/mTOR signaling pathway plays a role in immortalizing and carcinogenesis of HPV-transduced cells must be enhanced [46].

Additionally, malignancies linked to HPV have been linked to the deregulation of the Wnt/β-catenin pathway, which is present in many types of tumors. Researchers suggested that HPV oncoproteins activate the canonical Wnt/β-catenin pathway, which might play a role in transforming cells' beginning, development, and upkeep [47].

Many cell types, particularly the squamous epithelium that lines mucosal and skin surfaces, rely on the NOTCH pathway for their growth. One of the first stages in committing basal keratinocytes to terminal differentiation in genetically modified mice models is Notch1. Similarly,

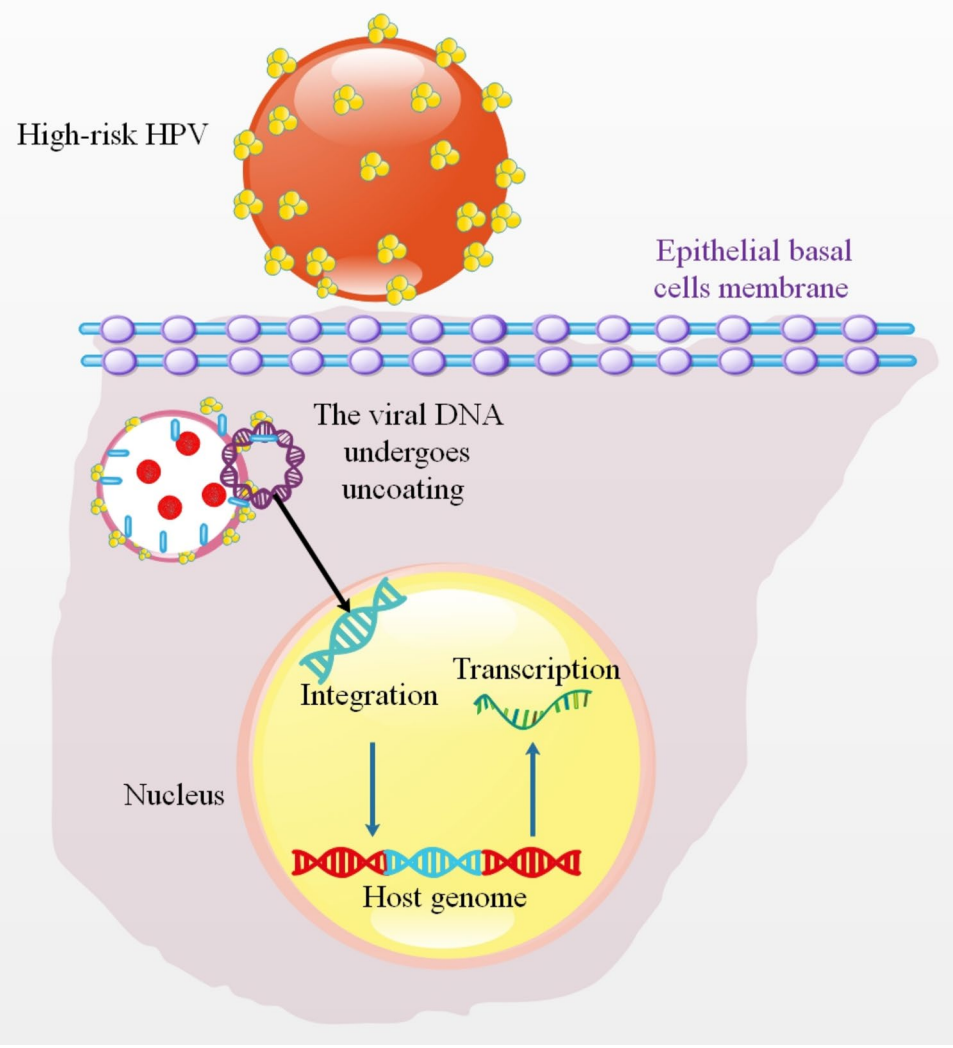


Fig. 3 HPV and developing cancer. High-potential viruses have fine-tuned adaptations that allow them to take advantage of the host's basal cells in the cutaneous and mucosal epithelium. Once the viral replication cycle is complete, the viral particles are released during cell division by desquamation from infected cells, which serve as a reservoir for the virus. Cervical epithelial cells in the transformation zone develop lesions when infected with HR-HPV for an extended period. Due to viral integration and cell change, lesions can disappear or advance to the first, second, and third phases of cervical intraepithelial neoplasia (CIN) (CIN1, CIN2, and CIN3). The CIN lesions are categorized according to their degree of severity. Invasive carcinoma develops from low-grade squamous intraepithelial lesions (LSIL), progressing to high-grade intraepithelial lesions (HSIL) [62]

NOTCH1 is often absent in head and neck squamous cell cancers (HNSCCs), which is in line with its crucial function in preventing tumor growth and starting keratinocyte differentiation. Consistent with NOTCH1's function as an oncogene in other malignancies, including T-cell acute lymphoblastic leukemia, constitutive NOTCH1 activation in the epithelium causes the spinous keratinocyte layers to expand and terminal differentiation to be impeded. The mutational setting of the tumor determines NOTCH1's dual activity as an oncogene and tumor suppressor. To be more specific, HPV-associated malignancies are more likely to progress when NOTCH1 activity is increased or decreased. The extra oncogenes from HPV likely prevent NOTCH from suppressing tumor development and allow the oncogenic pathways it activates to drive tumor growth. Researchers examined the function of the NOTCH pathway in malignancies of the head and neck, particularly those that are linked to HPV [48].

Researchers demonstrated that HPV-positive (HPV+) cancer had a better prognosis than HPV-negative (HPV−) cancer patients and that the EGFR was downregulated in HPV + cancer. Additionally, researchers demonstrated that HPV E7 protein may modify TP53 and that the TP53 mutation rate is lower in HPV + cancer than in HPV-negative cancer. However, there was no discernible change between the two groups' wild-type TP53 expression levels. After building an HPV-human interaction network, researchers discovered that EGFR plays a crucial role. Researchers also observed from the network that hsa-miR-944 and the HPV E7 protein control EGFR.

Furthermore, there is no significant correlation between prognosis and EGFR total expression level. However, phosphorylated EGFR is linked to a worse prognosis. This suggests that individuals with HPV + cancer will have a poorer prognosis if EGFR activation occurs. Additional enrichment analysis revealed that HPV + and HPV-negative cancers had different activation patterns of the EGFR downstream pathway and the cancer-relative pathway. In conclusion, the HPV E7 protein inhibits EGFR, inhibiting phosphorylated EGFR and EGFR-related pathways, improving prognosis [49].

Cellular responses to stimuli that promote growth or differentiation are mediated by an intracellular signaling cascade known as the mitogen-activated protein kinase signal transduction system. In most cases, the activation of the MAP kinase pathway is a temporary response to one of many stimuli that vary in intensity depending on the cell type. Researchers believed that oncogenes like ras, src, raf, and mos undergo cell transformation in part by keeping components of this signaling pathway in their active state for longer. EGF and its absence did not prevent the E5 gene from increasing MAP kinase activity. E6 and E7 oncoproteins, on the other hand, do not affect MAP kinase activity, nor do they extend the EGF-induced MAP kinase activity. According to these results, E5 could help boost the cell response using the MAP kinase pathway. However, changes in the MAP kinase pathway are not linked to E6 and E7's transforming action. According to these results, all signs point to E5 amplifying the effect of growth factor stimulation [50].

Furthermore, HPVs have evolved to control their productive replicative cycles via the EGFR/MEK/ERK signaling pathway. According to mechanistic research, AP-1 factor knockdown lowers oncogene transcription, and EGFR/MEK/ERK signaling affects AP-1 transcription factor activity. Additionally, pharmacological inhibitors of EGFR, MEK, and ERK signaling diminish the neoplastic phenotype and HPV oncogene expression, suggesting a possible therapeutic approach to treat HPV neoplasia, restrict unchecked cell proliferation, and lower oncogene expression [51].

These HR-HPV oncogenes change many biological processes, such as DNA repair, angiogenesis, and/or apoptosis, which leads to cancer development. A thorough study of gene expression and changes in a group of DNA DSB repair genes in HPV-negative and HPV-positive HNC cancers also shows differences, suggesting that HPV affects the DNA repair processes in these cancers [52, 53].

R-loops are three-part RNA-DNA hybrids that play a significant role in controlling transcription in the body. However, when they form or change shape incorrectly, they cause DNA breaks and genetic instability. Cancers of the vaginal area and the throat and throat passages are caused by HR-HPV, which has more DNA breaks. Researchers found that R-loops were up to 50 times higher in cells with HR-HPV genomes. These loops were also easily found in squamous cell cervical carcinomas in vivo but not in normal cells. There were many R-loops in HPV-positive cells. These loops and the enzyme RNase H1, which regulates their removal, were discovered on the surfaces of the virus and cells. R-loop levels increased further when RNase H1 was removed from HPV-positive cells. This hindered the expression of DNA repair genes, including FANCD2 and ATR, which are essential for the virus to function and its ability to replicate. Researchers demonstrated that RNase H1 overexpression reduced the overall quantity of R-loop, which reduced DNA breaks by over 50%. Additionally, although increasing levels of components in the innate immune regulatory system, large amounts of RNase H1 prevented the virus from replicating and coding. Throughout the HPV life cycle, maintaining high R-loop levels is crucial. It was found that the E6 virus oncoprotein caused many R-loops by stopping p53 from doing its job of transcriptional activity. Investigators demonstrated that high amounts of R-loop are essential for HPV pathogenicity and that this depends on halting the p53 pathway [54].

Furthermore, miRs are non-coding regulatory RNAs that bind to complementary parts of the 5' and 3' untranslated regions of mRNAs to control the production and degradation of mRNAs. Several hundred genes in people have been found to code for up to 1,000 miRs [55]. These miRs control the production and activities of about a third of human genes. They are also involved in many critical cellular processes, such as cell division and death [56]. OncomiRs are oncogenes that MiRs may work as and are linked to cancer development, aggressive transformation, and spread [57]. Some oncomiRs are oncogenes, meaning that they cause cancer to grow when overexpressed. Other miRs, other hand, stop tumors from growing in healthy cells. But when the related genes aren't expressed enough, miRs, which generally help prevent tumors from growing, are misdescribed. This is one of the many ways that cancer starts [58].

MiR-34a is one of the oncomiRs linked to cancer and caused by HPV infections. In terms of transcription, MiR-34a is controlled by the tumor suppressor p53. The HPV oncogene E6 stops p53 from being expressed, which lowers the amounts of miR-34a. This causes more of the genes that miR-34a targets to be expressed. These genes are turned on more in HPV-related cancers, which makes cancer cells multiply, survive, and move around more [59].

When tumor cells lose PTEN, a well-known biological process called PI3K/Akt gets turned on. PI3K/Akt speeds up spread and growth. PI3K/Akt activity may also make cancer cells less susceptible to treatment because

it makes tumor cells more viable. PI3K/Akt activity also raises the amounts of Bcl-2 and XIAP, making tumor cells more likely to survive. PI3K/Akt raises the production of matrix metalloproteinases and EMT pathways, leading to more UC spread. Also, activating PI3K/Akt makes diseases immune to drugs and radiation, but blocking it with anti-tumor drugs stops the growth of tumors [60].

Urological tumors are solid tumors that create hypoxia because they grow too quickly and don't get enough food. Hypoxia-inducible factors (HIFs) control many molecular processes that start with insufficient oxygen. Two critical processes that need HIFs to work are angiogenesis and lymphangiogenesis. New blood vessels are made from old ones through these processes. These new vessels talk to stromal parts of the TME, which lowers the immune system. Much of the studies on angiogenesis in BC and PCa have focused on how HIF-1 affects VEGF and its targets. But little is known about the part HIF-2 and HIF-3 play in these cancers. There is evidence that HIF-1 and HIF-2 work together to help tumors grow, but more research is needed to fully understand how they are controlled dynamically, as seen in KC. HIFs are transcription factors that can do more than one thing. They can target many downstream pathways to help blood vessels grow. Angiopoietin 2 and VEGF bind to receptors on the surface of endothelial cells. Stem cell factor and stromal-derived factor 1 bind to receptors on bone marrow cells to help blood vessels grow. Angiogenesis in urologic tumors is mainly linked to the VEGF pathway, and these targets aren't given enough credit for their role in angiogenesis [61].

HPV and the immune system

For the development of new HPV therapies and tools, it is essential to have a better understanding of these basic immune processes in people who are at risk. A world goal is to stop at-risk groups from getting a persistent HPV infection and cancer from spreading [63].

To eradicate the infected cells and start an efficient acquired immune response, the innate immune system recruits innate immune cells to produce a pro-inflammatory milieu during HPV infections. Nonetheless, HPV uses a variety of tactics to elude immune monitoring, creating an anti-inflammatory microenvironment. By down-regulating several adhesion molecules and chemoattractants and activating keratinocytes, dendritic (DC), Langerhans (LC), natural killer (NK), or natural killer T (NKT) cells, new adjuvants like alpha-galactosylceramide and TLR (Toll-like receptors) agonists have been shown to reverse the anti-inflammatory microenvironment and promote a potent, targeted cytotoxic T cell response. Thus, these adjuvants can potentially treat HPV-generated lesions and might help clarify immune cells' unclear functions during HPV infection [64].

The capacity of HPVs, especially HR-HPVs, to undermine keratinocytes' function as innate immune sentinels is crucial to this accomplishment. In the immune system, keratinocytes mediate by responding to cell stress, damage, and infection [65].

Additionally, pathogen recognition receptors (PRRs), germ line-encoded innate immune system receptors, are expressed by eukaryotic cells and recognize invariant molecular motifs called pathogen-associated molecular patterns (PAMPs). Toll-like receptors (TLRs) are a significant class of PRRs that are expressed on the plasma membrane (TLR1, TLR2, TLR4, TLR5, TLR6) and endosomal membrane (TLR3, TLR9) by both vaginal and epidermal keratinocytes [64]. A second class of PRRs is the retinoic acid-inducible gene 1 (RIG 1)-like receptor (RLR) family that identifies cytoplasmic dsRNA, a trait of viral diseases. When TLRs and RLRs are activated, they start a series of signals that activate NF-κB. This leads to the production of pro-inflammatory molecules like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) and also triggers the expression of type I interferon genes through the activation of specific transcription factors called IRF3 and IRF7 [66]. To activate tissue-resident immune cells like Langerhans cells and macrophages and to recruit effector T cells, keratinocytes must secrete pro-inflammatory cytokines, chemokines, and their receptors, as well as antigen-processing and antigen-presenting molecules. These actions initiate adaptive immune responses to the local injury or infection. When HPV-16 or 18 episomes are preserved in the foreskin and cervical keratinocytes, genome-wide expression analysis reveals that HPV-16 suppresses these vital responses almost from the beginning of the infectious cycle [67].

Adjusting effector T cells has become a key aspect of immunotherapy for most cancers, including those linked to HPV. It's essential to understand how T-cells work in activation, response, repression, and fatigue in cancers related to HPV. Several studies have mentioned that HPV-positive tumors have a higher presence of tumor-infiltrating lymphocytes (TIL). Analysis of TILs from 12 cervical tumors showed that 9 of 12 had CD4 + T cells, and 8 of 12 patients had CD8 + T cells specific to HPV antigens when primed with overlapped peptides produced from E6 and E7 ex vivo. Most patients had polyclonal reactions [68, 69].

In HPV-16 + HNSCC, a more thorough investigation using peptides generated from all HPV genes revealed that HPV-antigen-specific T-cell responses were seen in 43 out of 66 patient samples and showed notable variability. Peptides covering all of the known early and late HPV genes were used to grow and restimulate T cells from patients both before and after therapy in vitro. Researchers demonstrated that CD4 + and CD8 + T lymphocytes reacted to peptides from all HPV genes, with E1 and L1

being the most common. Interestingly, the levels of activated T cells rose with the tumor stage and fell after curative treatment, indicating that the tumor burden, which acts as the antigen source, determines the predominance of HPV-antigen-primed cytotoxic T cells [69].

Throughout its life cycle, HPV employs very effective strategies to evade the immune system. The female genital tract's mucosal immune response against HPV consists of keratinocytes, Langerhans cells (LC), DC, tissue-resident macrophages, and intraepithelial gamma-delta T cells (γδ T cells). In the first line of defense against threats to the epithelial barrier, γδ T cells, which are the model for unconventional T cells, are crucial. The epithelium is protected from harm, including trauma and infections, by γδ T cells, which link the innate and adaptive immune systems. In the first stages of cervical carcinogenesis and chronic HPV infection, any alterations in the distribution and functional capacity of γδ T cells might play a role. Persistent HPV infection may result from inadequate stimulation and maturation of APCs (LC/DC), all of which highlight the crucial involvement of γδ T cells in HPV persistence. Potential therapies against HPV in infected people may use γδ T cells if this fascinating connection is confirmed [70].

Furthermore, HPV has a unique capacity to remain in the host's epithelium for an extended period—longer than other viruses do—which is required to finish its replication cycle. To do this, HPV has created several immune evasion strategies, which regrettably also facilitate the disease's development from infection to chronic dysplasia and ultimately to malignancy [71]. It is the keratinocyte differentiation pathway that HPV relies on for productive infection. Once within the basal keratinocytes that are dividing, HPV gene expression drops and vegetative replication speeds up significantly, but only in the more epithelial layers that will desquamate soon. It is believed that the absence of a viremic phase in the viral life cycle, together with the low levels of protein expression in the lower epithelial layers and the well-directed non-cytolytic amplification of the genome that occurs only in the differentiated layers, passively aid the virus in evading immune identification. In order to escape being detected by the immune system, HPV has successfully adapted to its hostile surroundings [72, 73].

Early on, HPV-infected cells inhibit immunological detection and acute epithelial inflammation. This makes it possible to evade viral persistence and immunosurveillance. When HPV-transformed cells develop into invasive malignancy, paracrine IL-6 orchestrates immunological deviation and persistent stromal inflammation. In stromal mesenchymal and invading immune cells, chemokine induction is caused via the IL-6/signal transducer and activator of transcription 3 (IL-6/STAT3) and IL-6/ CCAAT/enhancer binding protein (IL-6/C/EBP) pathways. Consequently, myelomonocytic cells that express T helper 17 (Th17) and protumorigenic matrix-metalloproteinase-9 (MMP-9) are recruited, further promoting inflammation. Myelomonocytic cells may develop into M2 macrophages or functionally compromised DC expressing programmed death-ligand 1 (PD-L1), suppressing cytotoxic T-cell responses. Because stromal DCs have a poor expression of the C-C chemokine receptor 7 (CCR7), they cannot move in response to lymph node-homing chemokines. IL-6 inhibits NF-κB activation in these cells. Instead, they create MMP-9 locally when immobilized inside the tumor stroma. Low levels of IL-12 expression cause T helper cell responses to change from Th1 to Th2. The development of invasiveness is facilitated by stromal inflammation and immunological deviation [74].

To stop HPV infection, your immune system needs the right natural and adaptive reactions and effective immune control mechanisms. There is a way for HPV to get around the defensive response, though. Since HPV can replicate in host cells without causing cytolysis, which doesn't speed up the inflammatory process or show viral antigens, it can spread. The E6 and E7 proteins of HPV-16 lower the amounts of type-I IFNs in host cells. This creates an immune tolerance stage when costimulatory factors are not present. This is done through inflammatory cytokines. In addition, its E5 protein controls the lower production of class 1 HLA, which stops the CTL attack even more. These ways for the immune system to get around may help HPV infections stay alive and spread, which is related to cancer development. In most cases, HPV infection is clinically quiet because it doesn't cause any significant signs. HPV plays a part in starting and spreading cancer. It can take many years for a squamous cell to turn into a carcinoma, with the help of different steps encouraging tumor growth, such as E6/E7 proteins that link with cell proteins. Ultimately, this turns healthy cells into abnormal cells that can live forever, divide, and cause cancer [65, 75–77].

Viral infections affect on urological cancers

UC are cancerous growths that start in parts of the urine system like the prostate, penile, kidney, ureter, bladder, or urethra. They are some of the most common types of cancerous tumors in the world. HPV plays a role in the growth of PCa. The three most common types of UC are kidney, bladder, and PCa. Both the number of cases and deaths from these three types of UC are going up. Most of the time, traditional treatments for UC include surgery to remove the cancer, chemotherapy, and radiation therapy. Although these methods can limit the progression of UC to a certain extent, the efficacy of these therapies is extremely limited for advanced and recurrent tumors, and patients have a low survival rate and poor prognosis.

Also, radiotherapy's ability to kill a lot of cells at once can have very bad effects on patients, lowering their chances of surviving and quality of life [78].

The numbers showed that UC was responsible for 13.1% of new cases of cancer and 7.9% of all cancer deaths. This type of cancer most often affects the testicles, the prostate, the kidney cells, and the kidney pelvis. The number of people with UC has grown by 2.5 times since 1990, and the number of deaths has grown by 1.6 times. In the United States in 2022, there were an extra 17,100 deaths from BC, 34,500 deaths from PCa, and 13,920 deaths from renal cell and renal pelvis cancer. TC is uncommon; it only makes up 0.4% of new cancer cases. UC grows more slowly than other types of cancer, and it is easy to cure if it is found and treated early. However, the early signs of UC aren't always easy to spot. Imaging tests, cystoscopy, and tissue samples aren't often used for large-scale screening because they are invasive, expensive, and use ionizing radiation. So, it's essential to find new targets that can be used for large-scale UC screening and protection [79].

Researchers suggested that virus illnesses may change the risk of getting cancer and how it develops, even in solid tumors [80]. A project called the Cancer Genome Atlas of urothelial BC suggests that viral diseases may play a part in the growth of some urothelial carcinomas [81]. Potential risk factors for BC include HPV and EBV infections, which have strong links with the disease. While the exact molecular mechanism by which viruses contribute to the development of BC has yet to be determined, potential pathways include oncogenic protein expression, cell cycle promotion, persistent viral infection, inhibition of apoptosis, and disruption of signaling pathways in bladder tissue [82].

Most men will get benign prostatic hyperplasia (BPH) or PCa at some point in their lives. Many people have said that virus infections are a big part of how PCa starts. To find out how virus illness and PCa are related and the differences between BPH and PCa regarding their appearance and how they work. This means that HSV-6 and human cytomegalovirus (HCMV) are more common in people with PCa than those with BPH. This means that more research needs to be done on viruses in prostate diseases with a larger group of people. This will help us understand the multi-stage process of turning benign into cancer and may lead to new ways to prevent and treat it [83].

In the PCa group, HCMV was much more common than in the control group, but this difference wasn't significant. Because HCMV can cause cancer, more research is needed to find out if there is a link between it and PCa. While there were close familial links between Iranian HCMV isolates and several reference genotypes, including KR 534,207 and MT 044483, the KR 534,207 genotype had the strongest genetic link [84]. A case-control study was done in Iran to look at the presence of the BK virus (BKV) and the EBV DNA in prostate samples from people with benign prostatic hyperplasia (BPH) and PCa. Out of the 121 samples, 90 (73%) were taken by prostatectomy, and 31 (27%) were taken by transurethral removal (TUR) of the prostate. There was no BKV in any of the tests, and one sample did show EBV. These results add to the proof that BKV and EBV do not cause PCa [85].

Polyploid giant cancer cells (PGCCs) and genetic instability are thought to be what make cancer spread. Researchers assessed how HCMV infection can change PECs. They compared their cellular and molecular characteristics to two HR clinical strains of HCMV that researchers previously isolated. HCMV infection has been linked to several different types of cancer. HCMV-induced PGCC creation, upregulation of Myc and EZH2, as well as stemness and epithelial-mesenchymal transition traits, all of which showed that PECs were changing. Investigators' research should be shared with other scientists because it opens the door for future studies to look into the possible role of HCMV and PGCCs in the growth and treatment of PCa [86].

HPV, EBV, CMV, Parvovirus B-19, and HIV have all been suggested by various writers as potential viruses involved in the formation of TGCTs in recent times. Finally, there is sufficient proof that HIV and EBV cause cancer of the testis in humans. In contrast, there is a lack of consensus among the current data about the risk of HPV and TGCTs, and further research is required to make definitive findings. Lastly, there is no proof that CMV and Parvovirus B-19 contribute to TC at this time [20].

The risk of PC, an extremely uncommon disease, seems to be higher in those with HIV. People living with HIV have a far higher chance of developing PC compared to those who do not have the virus. PC mortality is four times higher in those with HIV, suggesting that HIV affects disease features overall. In addition, males living with HIV advance from intraepithelial neoplasia six years earlier than men living without the virus. Infection with HPV is more common in males who are HIV-positive. Researchers also showed that a greater incidence of cancer is seen in Hispanics compared to Caucasian, HIV-positive males, suggesting that ethnicity modulates the link between HIV and PC [87]. Some underdeveloped nations have a higher incidence of penile squamous cell carcinoma (PSCC) than industrialized nations. One of the risk factors for the development of PC is an infection with HIV and/or HR-HPV. Possible prognostic and therapeutic target information comes from the tumor microenvironment (TME) of PSCC. Through histological evaluation, researchers ascertained if and how HIV and/

or HR-HPV infections impact the immune microenvironment of penile malignancies. Finally, it seems that the penile squamous cell carcinoma TME is affected by both HPV and HIV infections. One possible therapeutic target in PCa patients with HR-HPV infections is T cell immunoglobulin and mucin domain-containing protein 3, or TIM3 [88].

HPV in prostate cancer

PCa is the most common cancer in men in 112 countries and accounts for 15% of cancers. Researchers reported projections of PCa cases in 2040 based on data for demographic changes worldwide and rising life expectancy. Researchers suggested that the number of new cases annually will increase from 1.4 million in 2020 to 2.9 million by 2040 [89]. In addition, PCa is the fifth most common cause of cancer-related mortality and the second most common solid tumor in men. Incidence and mortality rates are significantly influenced by geographic location. In addition to genetic susceptibility, family history, and race/ethnicity, various individual, environmental, and occupational risk factors have been proposed to explain differences in the epidemiological burden of the disease. Modifiable risk variables may impact the likelihood of developing PCa and passing away from the disease itself, even if there is little evidence to support any apparent prophylactic method other than early diagnosis to lessen PCa mortality [90]. Using the polymerase chain reaction assay (PCR), McNicol and Dodd discovered HPV DNA in prostatic tissues for the first time in 1990 [91]. In addition, PCa is still a big problem for healthcare worldwide. It is still the most common type of non-dermatologic cancer in men, with about 233,000 new cases each year in the US. It is also the second most common cause of cancer-related death [92]. Unfortunately, there isn't much information about how this sickness works. In this way, genetic and external factors are thought to be very important in developing PCa. There is also more and more proof that there may be a link between HR-HPV infection and a higher chance of PCa [93].

Researchers assessed a possible link between PCa and HPV cases. Researchers showed that people who had HPV infections in the past had a 2.321 higher chance of getting PCa compared to people who had never had HPV infections. Notably, people who were first diagnosed with chronic prostatitis were also more likely to be later diagnosed with PCa, which makes sense in this situation. Researchers found a strong link between PCa and HPV infections, adding to the growing amount of data that points to a likely link between the two [94].

Moreover, the nuclear transcription factor "kappa-light-chain-enhancer" of B-cells, called NF-kB, is a specific link between inflammation and cancer. Many toxins can make this protein work. It manages genes that are often linked to cancer growth. NF-kB is turned on by almost all viral agents related to cancer. In a study with mice, this was proven by turning off NF-kB, which decreased inflammation and slowed cancer growth. Pathogens that cause infections can set off inflammation processes that can damage DNA in tissue cells, turning those cells into cancerous ones. It has been proven that HPV, human herpes virus, and EBV can turn on NF-kB. Anti-inflammatory drugs like aspirin have been shown to lower the chance of getting cancer, which backs up this proof [95].

In addition, researchers checked the levels of expression of virus genes (E2, E6, and E7) and cellular factors, such as tumor suppressor proteins (Rb and p53), anti-apoptotic mediators (Bcl-2 and survivin), and some mediators that play a role in inflammation and angiogenesis. Twenty-nine of the 58 cases (32.7%) and five of the 32 controls (15.6%) had the HPV genome found. There was, however, no statistically significant link between having the HPV genome and PCa. It was also found that HPV-16 and −18 were present in 47.4% and 31.6% of HPV-infected PCa cells. Moreover, Rb and p53, two proteins that help stop tumors from growing, were much less abundant in the HPV-infected samples compared to the HPV-negative samples. However, the levels of anti-apoptotic factors and factors involved in angiogenesis and inflammation were significantly higher in the HPV-infected PCa group compared to the HPV-negative PCa group and the control group [96].

Moreover, in another study, researchers checked the levels of expression of HPV genes (E2, E6, and E7) and cellular genes such as survivin and Bcl-2, proteins that stop cells from dividing (Rb and p53), and E-cadherin, N-cadherin, Twist, PTPN13, and SLUG, which play a role in anoikis resistance and invasiveness. In 36.1% of cases and 15.9% of control samples, the HPV genome was found. There was also a statistically significant link between HPV and PCa. Most of the people in both the PCa group and the control group had HPV genotypes 16 and 18. The amounts of the tumor-suppressing proteins Rb and p53 and the anti-apoptotic proteins Bcl-2 and Survivin were significantly lower and higher in the HPV-positive samples compared to the HPV-negative samples. Also, the average expression level of N-cadherin, SLUG, and TWIST genes was higher in HPV-positive samples compared to HPV-negative samples. On the other hand, the average expression level of PTPN-13 and E-cadherin genes was lower in HPV-positive samples compared to HPV-negative samples. Investigators showed that HPV infection may play a role in the growth of PCa tumors by changing genes related to anoikis resistance [97].

A study looked at how the levels of specific cellular miRNAs (miR-19a, miR-21, miR-23b, miR-34a, miR-150–5p, and miR-155) and the genes they target (P53,

Rb, c-Myc, TIMP-1, MMP-2, MMP-9, PDCD4, Bcl-2, and Survivin) in PCa tissue samples were related to the levels of HPV genes. HPV identification and genotyping were done on 39 healthy people and 112 people with PCa samples. These results showed that the HPV genome was found in 17.94% (7/39) of control samples and 28.7% (21/73) of PCa tissue samples. A strong link was not found between having an HPV infection and PCa. The researchers discovered that the mean levels of miR-19a and − 21 were much higher in PCa tissue samples compared to control tissue samples. On the other hand, the levels of miR-23b and − 34a were much lower. The current study showed that HPV-positive PCa has a different miRNA makeup than HPV-negative PCa [98].

In addition, the DNA differences between HPV-positive and HPV-negative PCa were looked at, as well as the state and genotyping of HPV infection. Researchers found the HR-HPV genome in 16.9% of the research group, and HPV-16 was the most common gene. The total number of mutations in HPV-positive and HPV-negative PCa was about the same, at 2.68/Mb and 2.58/Mb, respectively, in the selected whole-exome area. HPV-negative tumors had a mutational range that matched published PCa studies. There were more changes in SPOP, FOXA1, and MED12 than in other genes. There were more changes in KMT2C, KMT2D, and ERCC2 in HPV-positive cancers. The two groups had about the same copy number changes per sample. The two groups' highly amplified or deleted areas did not fully match. Researchers found that only in HPV-negative cancers did they find losses of tumor suppressors like CCNC and RB1 and additions of oncogenes like FCGR2B and CCND1. When HPV was present in tumors, specific losses of tumor suppressors like NTRK1 and JAK1 were found [99].

Researchers assessed if co-infection with HPV and EBV could be a cause of PCa. There were 50 and 30% of HPV/EBV-coinfected PCa cases that HPV-16 and 18 caused. There was no significant link found between PCa and HPV/EBV coinfection. The PCa group that had both HPV and EBV, on the other hand, had the highest rate of HPV genome integration (8/10; 80%). In addition, the total amounts of inflammatory factors (IL-17, IL-6, TNF-α, NF-κB, VEGF, ROS, and RNS), anti-apoptotic mediators (Bcl-2 and survivin), and anti-anoikis factors (Twist and N-cadherin) were much higher in the PCa cases that were co-infected with HPV and EBV compared to the PCa cases that were not co-infected with HPV/EBV. However, the levels of tumor-suppressor proteins (p53 and pRb) and E-cadherin (which blocks anoikis resistance) were significantly lower in the PCa group that was infected with both HPV and EBV compared to the PCa cases that were not infected with both viruses. This suggests that HPV/EBV coinfection may play a role in the development of PCa by changing the way cells behave [100].

So far, many studies have been done to look into how common HR-HPV is in PCa, but the results have been very different. In turn, this means that many people don't know how chronic HPV infection can lead to PCa. While this has been investigated in a few other countries, no studies have been done in the United Kingdom (UK) before. HPV-35 was found to be the most common type. Also, the HR-HPV positivity rate was higher in prostate tissues that were not working normally (adenocarcinoma and benign with prostatitis) compared to tissues that were working normally. Researchers have used immunohistochemistry (IHC) to show that prostate cells with HPV DNA also have HPV E7 protein. It indicates that HPV being in prostate tissue may be linked to the development of some types of PCa [101].

Deep knowledge of the biology of viruses that cause cancer and the host's defensive systems can make therapeutic methods easier. Based on these results, targeting HPV oncoproteins might be a good way to treat cancers linked to HPV. Now that we have a better understanding of how cancer viruses work, we are getting new and vital information about how apoptosis works at the molecular level [102]. It is important to note that HPV infection is still a possible risk factor for PCa, even if there is a lack of consensus in the existing research about the best ways to detect HPV in men who have the disease. Using normal prostate tissue as a reference, the current meta-analysis demonstrates that HPV infection is associated with PCa and that there is a considerable incidence of HPV infection in samples of prostate tumor tissue. This bodes well for future research along these lines. Specifically, further research is required to establish the involvement of HPV in the progression of PCa [14].

Conclusions are hard to draw because of the complexity of HPV transmission and carcinogenic pathways and the difficulties of assessing parameters like timing, biological gradient, and experiment in this setting. HR-HPV is probably involved in prostate carcinogenesis, either by inducing inflammation that might play a part in the oncogenic process at different points or by damaging the host DNA. We need further research on this subject, preferably with consistent study design methods and results analysis, to learn more about it. Hence, while there is some evidence that HPV may have a causative role in PCa, the evidence is not yet strong enough to use the phrase "highly likely" in the absence of more studies to back up this assertion [103].

HPV in the development of bladder cancer

Approximately 3% of all new cancer cases and more than 2% of cancer fatalities were predicted to occur in 2020 due to bladder cancer (BC), with over 573 thousand new cases and roughly 212 thousand BC deaths globally. Worldwide, BC is the tenth most frequent cancer diagnosed and the thirteenth leading cause of cancer death. Fortunately, it is highly treated when caught early, and the 5-year relative survival rates are reasonably high, with 77% in the US and 68% in Europe [104]. Moreover, BC is linked to significant effects on patient quality of life, morbidity, mortality, and healthcare system costs. It is still one of the major causes of cancer-related deaths globally. BC is often diagnosed after gross hematuria. Non-muscle-invasive bladder cancer (NMIBC) has a 90% overall survival rate. It is treated with transurethral resection of a bladder tumor (TURBT) first, then adjuvant intravesical (IVe) treatment based on risk. However, for several reasons, the cure rate for muscle-invasive bladder cancer (MIBC) is still lower [105]. A new era in diagnosing and treating BCa has begun thanks to recent findings, even if the clinical approach to the illness has been primarily unaltered for many years. In areas where people were more active, there was a drop in carcinogenic exposure and a rise in public knowledge of the risk factors, leading to decreased BCa-specific mortality. Overall, urologists are working to improve transurethral surgery by developing and implementing more stringent and high-quality methods [106]. Researchers from the Surveillance, Epidemiology, and End Results (SEER) program say there will be about 82,290 new cases of BC in 2023. The death rate has been slowly going down since 2016, but the incident rate has been going down since 2010. Men are three to four times more likely than women to get BC, and the average age at diagnosis is 73. About 90% of lower urinary tract tumors in the US are urothelial carcinomas, 5% are SCC, 2% are adenocarcinomas, and 1% are small-cell carcinomas [107–109]. Furthermore, viral infections linked to HPV are crucial to the development and outcome of BC. Researchers advised taking into account HPV as a possible risk factor for UC in terms of histological subtypes, even if the relationship between HPV infection and BC is still up for dispute for a variety of reasons. Furthermore, the quick creation of oncolytic viruses offers physicians and patients new therapeutic alternatives, and when combined with other anticancer techniques, they may present patients with several unanticipated advantages. However, researchers suggested more focus should be placed on virology research in developing BC and its possible use in therapeutic approaches [56].

Women were more likely to have HPV-16. HPV infection may play a part in the development of BC in both men and women. The HPV-18 genotype, followed by HPV-33, -16, and – 39 genotypes, maybe the most common types of oncogenes that can cause BC [110].

In addition, infectious agents like HPV are also now thought to raise the chance of BC. Researchers looked into whether there might be a link between HPV infection and the result of urothelial BC. Researchers examined 106 tissue samples from people with transitional cell cancer (TCC) of the urine bladder that were confirmed by histopathology. Out of the 106 people who were diagnosed with BC, 24 (22.6%) had an HPV infection. HPV-16 was found most often, followed by HPV-11, HPV-18, and HPV-6. The independent T-test showed that there was a strong link between mean age and HPV infection. Researchers showed that there was also a strong link between HPV infection and tumor stage, tumor grade, tumor invasion of muscle, and tumor return. The Chi-square Test showed a strong statistical link between the kinds of HPV and the growth grade. Researchers showed that having a family history of cancer and being infected with HPV may be able to predict tumor return in BC on their own. In general, researchers strongly suggested that there is a link between HPV infection and a worsening of the disease and a higher risk of return in people with BC [111].

To find out what kind of histology and grade of tumor differentiation people with primary and recurring clinically NMIBC who have a hazardous HPV infection have. Patients and ways. Formalin-fixed and paraffin-embedded bladder tumor tissue samples from 159 patients who had TUR of the bladder were checked for HPV DNA. Researchers can assume that there is a close link between finding BC in HPV patients with HR genotypes and finding BC with moderately differentiated or low-differentiated forms. Researchers showed that HPV infection may change the tumor differentiation level. Furthermore, this means that the HPV test could be used to figure out how the disease recurs or gets worse. A study found HR-HPV DNA in the tumor tissue of 59 out of 159 patients (37.1%). Of these, 52 patients (89.4%) had HPV type 16, 4 patients (6.7%) had HPV-18, and three patients (5.08%) had HPV-35. A study of the shapes and sizes of tissues from HPV-positive patients found that the tumor differentiation grade was G2 in 18 cases (30.5%), G3 in 37 blocks, and G1 only in 4 cases (6.7%). There is a 4.3 times greater chance of finding a stage G3 tumor when HPV is present [112].

Researchers found out how common HR-HPV is in primary BC and see if there is a link between HPV infection and the squamous cell part of bladder urothelial carcinoma [107]. In squamous cell carcinomas of the bladder, there was no link between having too much p16 and having an HPV infection. p16 shouldn't be used as a substitute to show that someone has HPV. Researchers revealed that HPV infection does not seem to be a cause

of BC and should not be used as an extra tool for diagnosis in these cases [113].

According to yet another report, HPV is a well-known cancer virus that is linked to anogenital carcinomas. Even though the bladder and the anogenital area are close to each other, there is still disagreement about the link between HPV and urothelial cancer of the bladder (UCB). This case-control study examined 69 people diagnosed with UCB between January and December 2018. The control group was made up of 69 people who went to the urology outpatient center during the study time for reasons other than cancer. Each patient was given a urethral swab and a sample of their first-void morning pee. The case group had a much higher rate of HPV-DNA positivity. There was no statistically significant link between HPV-DNA positivity and the grade of the tumor. There is a statistically significant link between HPV infection and UCB, no matter what grade the cancer is [114].

Researchers discovered thirteen key genes linked to HPV-related BC. These include the risk genes FLRT2, HOXC5, LDLR, SCD, GRM7, DSC1, EMP1, and HMGA1. Conversely, genes that are thought to have protective effects include LPA, SERPINA6, ZNF124, ETV7, and SCO2. Endothelial tumor adhesion is known to be mediated by the fibronectin leucine-rich transmembrane protein 2 (FLRT2), which may increase the invasiveness of colorectal cancer cells [115, 116]. One research found that FLRT2 inhibited BC development by inducing ferroptosis; however, another investigation found the opposite to be true [117]. This shows how closely HPV-related BC development is linked to the immune system. These genes may be used as immunotherapy, chemotherapy targets, and prognostic indicators. Researchers highlighted the close relationship between the immune microenvironment and HPV-driven BC growth, providing crucial new information about the disease's underlying processes and possible therapeutic intervention pathways [115].

Advanced bladder squamous cell carcinoma (aBSCC) is a type of BC that doesn't happen very often compared to urothelial carcinoma, which does. Researchers looked at the genetic alteration (GA) landscape in a group of aBSCC based on their link to the HPV to see if there would be changes in GA between the positive and negative groups. Out of all the aBSCC, 11 (6.4%) were found to have HPV genes (10 HPV-16 and 1 HPV-11). HPV + status was found a little more often in women (NS) and younger patients. Two of the female patients with aBSCC had had SCC before, one in the anus and one in the vaginal area. The HPV + aBSCC had fewer GA/tumor, more mutations that turned off RB1, and fewer GA that turned off CDKN2A, CDKN2B, TERT promoter, and TP53. Both the HPV + and HPV-aBSCC groups had similar levels of GA in genes linked to urothelial cancer, such as FGFR2 and FGFR3. It was found that none of the 11 HPV + aBSCC cases had MTAP loss (homozygous deletion), which has become a biomarker for PRMT5 inhibitor-based clinical studies. This was significantly lower than the 28% positive frequency of MTAP loss in the HPV- aBSCC group. The MTOR and PIK3CA pathways GA were not significantly different between the two groups. The two groups also had similar levels of MSI and TMB, which are thought to be immunotherapy (IO) reaction measures. There was PD-L1 expression data for some HPV + and HPV- cases, and it showed that a lot of them were positively stained. This was the case for both groups. Younger people are more likely to get HPV + aBSCC. As seen in other HPV-related squamous cell carcinomas, HPV + aBSCC has fewer mutations that turn off cell cycle control genes. These mutations are similar to those found in the MTOR and PIK3CA pathways. Researchers still don't know what role HPV plays in the development of BC, but it needs to be looked into more and proven in clinical trials [118].

Researchers found out if HPV was present in BC cells and see if it could be used as a biomarker [119]. Moreover, a significant link was found between HPV infection and critical clinical parameters such as tumor stage, tumor grade, and muscle invasion. HPV-16 was found in 11 (47.8%) BC cases, making it the most common. One HPV infection (18 cases, or 78.2%) was more common than co-infection (5 cases, or 21.7%). Still, there was no statistically significant link between the type of infection and the patient's clinical and molecular features. Investigators showed a strong link between HPV infection and advanced tumor features, significantly higher tumor grade, and pathological T-stage. This suggests that HR-HPV subtypes may affect how bladder tumors grow. These results show that HPV may play a role in the development of BC. They also indicate that infection with the virus, especially with HR types, could be a helpful sign for early diagnosis of BC and determining the risk of getting it. So, going after HPV in BC cells could lead to HPV-based tools for diagnosis and prognosis, as well as personalized treatment plans [120].

Researchers found that there are ethnic differences in the risk of BC in HPV infection. Researchers examined the likelihood of bladder tumor formation in HPV infection for various patient ethnic groups as well as the overall effect of papillomavirus infection on BC development. Although HPV cannot be identified as an etiological element in the development of BC, it is unquestionably a significant concurrent factor in the incidence of this oncopathology, according to the examination of literature data. It is essential to highlight that the data obtained supports the need to monitor papillomavirus infection in patients with bladder disease and the importance of HPV infection in establishing risk groups for developing the investigated oncopathology [121].

HPV in the development of testicular cancer

TC is the most frequent cancer among young men of European ancestry, accounting for 74,500 new cases globally in 2020, making it the 20th most common cancer type [122]. A five-year survival rate of 97% is achieved with proper therapy. Undescended testicles (cryptorchidism), a personal or family history of TC, advanced age, race/ethnicity, infertility, and other medical conditions all increase the likelihood of developing this malignancy [123]. Seminoma and non-seminoma testicular germ-cell tumors (TGCTs) comprise most TC cases [19, 20]. In many wealthy countries, the number of cases of TC has been slowly rising over the last few decades. On the one hand, better detection and treatment have shed light on this disease. On the other hand, few risk factors have been found that are different from other cancers. However the reasons for the rise in TC are unknown, and risk factors are still not well-understood [124]. There are two main types of TC: "non-germ cell," which makes up up to 95% of testis cancers, and "germ cell." TGCT starts in germ cells. There are two main types of TGCTs based on their histological features: seminomas and non-seminomas [125]. Cancers that begin in the testicles make up about 1% of all cancers. Among young guys aged 15 to 40, these tumors are the most common solid cancers, and the most common type is seminoma. The number of these tumors is rising. The exact cause of testicular germ cell tumors is still unknown. While cryptorchidism is thought to be the leading risk factor, there is evidence that genetic and environmental risk factors may also play a role [126]. There are only two kinds of juvenile tumors: teratomas and yolk sac tumors. Usually, TGCTs in young people are broken down into two groups: seminomas and non-seminomas. Each group makes up about half of all TGCTs [127]. While the seminoma is a pretty regular tumor, the non-seminomas are more violent and vary in type. These include embryonal cancer, choriocarcinoma, teratomas (which contain different types of somatic tissue), and yolk sac tumor. So, the standard pre-invasive CIS stage/cell can turn into a lot of various kinds of solid tumors so that it can be thought of as undifferentiated [128]. Researchers recommend that TC patients get screened for HPV when they are first diagnosed and especially after additional treatments. This is because HPV exposure raises the risk of getting cancer and may also make it harder to get pregnant [129].

Men aged 15 to 35 are most likely to get TC, which is a solid growth. In the last few decades, the number of cases has steadily increased. This is likely due to genetic and environmental factors. Even though being exposed to viruses like HIV, HCV, EBV, and HPV is often linked to cancer, there have been no studies that look at how viral diseases might play a role in the development of TC. Scientists looked at the characteristics of 155 TC patients' sperm and the amount of HPV on them at the time of discovery (T – 1), after an orchiectomy (T0), and 12 months after surgery or the end of additional treatments (T12). All of the cases had a much higher rate of semen infection than the controls (9.5% vs. 2.4%), and the properties of the sperm were different at both T1 and T0. Looking at sperm statistics, researchers saw a decrease in increasing motility at T – 1. Researchers demonstrated that after orchiectomy, patients had a reduction in sperm concentration and count, and motility got even worse. After surgery, the patients were split into three groups based on their treatment options: S (monitoring), R (radiotherapy), and C (chemotherapy plus or minus radiotherapy). At T12, sperm measures got better in the unaffected group but much worse in the R and C groups. It was also very common for people who had radiotherapy and/or chemotherapy to get an HPV semen infection. In the end, people with TC often had changed sperm statistics and a higher rate of HPV semen infections, which got worse after radiation and treatment. Researchers say that people with TC should be screened for HPV when they are first diagnosed, especially after additional therapies [130].

The TGCT, which can be either a seminoma or not a seminoma, is the most common type of TC. Moreover, a possible link between virus illnesses and TGCTs was first brought up almost 40 years ago, and people are still arguing about it. Recently, different writers have talked about how certain viruses, such as HPV, EBV, CMV, Parvovirus B-19, and HIV, might play a part in developing TGCTs. Researchers summarized how viral infections affect the chance of getting TGCTs. Only some viruses looked at showed a link with TGCTs in the meta-analysis. In particular, no link was found between HPV, CMV, and Parvovirus B-19 infection. On the other hand, people who had EBV or HIV had a much higher chance of getting TGCTs. In the end, researchers found enough data to show that HIV and EBV can cause cancer in the human testis. On the other hand, the information researchers have about the risks of HPV and TGCTs is mixed, and researchers need to do more research before they can say what they are. Finally, there is no proof that CMV and Parvovirus B-19 have an impact on the development of TC [20].

Numerous theories have been put out about the potential causes of TC development, including genetic predisposition, environmental factors, and exposure to endocrine disruptors during pregnancy and the prepubescent period. Although it is well known that some viral infections—such as EBV, HCV, HPV, HIV, and others—play a significant role in the development of several malignancies, testicular tumors have never been linked to this relationship. However, all tumors—including TC—can damage overall health and put patients at risk for infections. Additionally, adjuvant therapy showed a

substantial correlation with the susceptibility to HPV infection. Researchers discovered that 7% of patients had HPV semen infection during monitoring, which increased to 31% and 61% following chemotherapy and radiation treatment, respectively. Thus, in individuals with TC, drug-mediated immunosuppression seems to be exclusively associated with HPV seminal infection. Lastly, taking into account FISH analysis for HPV, researchers found that participants who had chemotherapy had a noticeably more significant proportion of infected sperm in addition to a tendency to rise in the R group. Rindicate that afflicted individuals had a higher prevalence of HPV infection than controls [130].

However, according to Bertazzoni et al., [131] this infection seems to be the result of a heightened vulnerability state brought on by the tumor rather than the cause of TC. Whether or not there is a cause-and-effect link between HPV and TC, or vice versa, will become more apparent with more extensive follow-up studies of individuals infected with HPV. Furthermore, researchers showed that chemotherapy, in particular, is a common treatment for TC patients and may significantly increase the incidence of HPV semen infection, most likely due to its immunosuppressive effects. In conclusion, as sperm HPV may cause cancer in several locations and further lower male fertility, researchers advised evaluating sperm HPV in patients with TC both before and especially after immunosuppressive therapy. More extensive research is required to validate these results in patients with additional malignancies [130].

HPV in the development of penile carcinoma

This is a rare type of cancer called PC. The International Agency for Cancer Research says 3,680 new cases were found worldwide in 2020. PC is primarily squamous cell cancer (more than 95%). PC mainly affects guys from low-income families who don't take care of their hygiene. The most significant numbers are in India, South America, and Africa. Infection with HPV-16-18, phimosis, and smoking are the biggest causes of PC and can make it happen a lot more often. PC usually happens to people in their later years, with the most significant rate seen in people over 60 [132, 133]. Furthermore, HPV is a recognized risk factor for the development of PC, which is a common health concern in developing nations. The warty and basaloid subtypes of SCC have the most significant detection rates. However, HR-HPV has been detected in as much as 40% of cases. The development of future prognostic indicators and a tailored therapy may depend on our ability to comprehend better the carcinogenesis associated with HPV. It is crucial to prioritize preventative strategies and enhance patient education since, at present, the only way to cure HPV infection is by removing skin lesions. There has been progress in reducing HPV-related malignancies in women because of efforts to increase HPV vaccine rates, but the same cannot be said for males [134]. Another thing is that about 60% of PC cases are caused by an HPV infection. Most people in PC get HPV types 16 and 18 [23]. Since the HPV vaccine guidelines for guys have been changed several times in the past 10 years, new information is still coming in on how to get more people to follow through with their shots [135].

Furthermore, poor socioeconomic level, phimosis, and HPV infection are risk factors for penile squamous cell carcinoma (PSCC), a disorder that is mainly overlooked and affects impoverished countries. Furthermore, researchers showed that T lymphocyte frequencies were lower in HPV-positive than in HPV-negative tumors. Furthermore, compared to healthy donors, individuals infected with HR-HPV showed lower maturation rates of mononuclear cells that were separated and differentiated into monocyte-derived dendritic cells (Mo-DCs) and lower expression of co-stimulatory molecules on these cells. Additionally, compared to controls, Mo-DCs from HR-HPV-positive patients showed a decreased capacity for lymphoproliferation. However, those HPV-negative patients showed a tendency toward a decrease in this capacity. In contrast to patients' lymphocytes, which demonstrated greater viability when cultivated with tumor supernatants, healthy donors' lymphocytes experienced apoptosis in the simulated TME. Our knowledge of the TME and the development of immunotherapy techniques will be significantly aided by researchers' findings, highlighting the effects of HPV infection on T lymphocyte infiltration, Mo-DC maturation, and lymphocyte survival in PSCC [136]. Furthermore, HPV DNA infection (mostly HPV-16) is linked to a significant number of penile malignancies and penile intraepithelial neoplasias, highlighting the potential advantages of HPV vaccination for both sexes [137].

Researchers discovered how common HPV DNA is and how different genotypes are spread among PCs in China. People who had positive HPV DNA were also tested for p16INK4a expression to make sure they had an HPV infection. PCR-RDB HPV test showed that 48.8% of people (166/340) had HPV, and 45.6% had p16INK4a expression. It was found that HPV-16 was the most common type of HPV found in cancers in this group of people (76.5%). In PC, 15.1% of people had HPV-18, which was the second most common type. Pathology tests showed that 307 cases were invasive PC, and 33 were non-invasive cancers. There was a lot of HPV DNA in the warty, basaloid, clear cell papillary, adenosquamous, and pseudohyperplastic histology groups. There were no statistically significant changes in the rates of invasive cancers based on the grade of the tumor, its stage, or the stage of the lymph nodes at detection. From 2006

to 2017, the number of HPV-positive PC cases went up a lot, while the number of phimosis cases went down a lot. About half of the PCs were linked to HPV infections. Researchers showed that the number of phimosis-related PC instances is decreasing. HPV is linked to PC development, and knowing how different regions have different HPV gene distributions is essential for controlling and preventing PC [138].

Investigators presented the first mouse model for PCs affected by HPV. IHC and quantitative PCR confirmed the expression of Ki67, cytokeratin 14, and the HPV-16 oncogenes E6 and E7. Mice transgenic for HPV-16 have problems inside the epithelium, like condylomas and penile intraepithelial neoplasia (PeIN). The lesions had high levels of cytokeratin 14 and the HPV-16 oncogenes E6 and E7. They also had cells multiplying out of control, as shown by Ki67-positive supra-basal cells. When HPV16-transgenic mice were exposed to DMBA, they got more PeIN and squamous cell cancer. Different histopathological aspects of the cancerous growths were similar to those found in HPV-associated human PC. Even after being introduced to dimethylbenz(a)anthracene (DMBA), wild-type mice showed no signs of cancer or precancerous growth. These findings are the first scientific proof that HPV-16 plays a part in the development of PC. In a significant way, this is the first mouse model that can accurately recreate key steps in the development of HPV-related PC and also show the same morphological and molecular traits as a human PC. This makes it possible to study PC biology in real life and make progress in both basic and applied research [139].

In a different study, the researchers looked into how common diseases are and the range of HPV types in foreskin tissue that had symptoms. Foreskins from 351 men who had symptoms were surgically removed and sent for histopathology analysis. As a clinical evaluation and reason for circumcision, phimosis was seen in 85.2% of people. 87% of the guys had inflammatory skin diseases on a histopathological level. Lichen sclerosis (LS), seen in 58.7% of cases, was the most common histopathological finding. PeIN was found in 2% of them without any prior clinical concern. In total, HPV was found in 17.1% of the guys, and there were 28 different types of HPV. It was found that 9.1% of people had HR-HPV kinds and that 2.3% had HPV-16. The chance of getting HPV went up if you were currently smoking. The risk of HPV went up if a person had more than 15 sexual partners in their lifetime. The risk went up even more when current smoking was taken into account. A histopathological study of circumcised affected foreskin showed that 2% of the men had PeIN, but there was no clinical evidence of cancer. Additionally, 87% of the men had treatable dermatological conditions, with LS being the most common and HR-HPV types being present in 9% [140].

According to another study, PC is standard in poor countries but uncommon in developed countries. The state of Maranhão in northeastern Brazil has the highest rate of PC cases ever reported. This is because of HPV infection, even though the state is socially and economically weak. Researchers used monoclonal antibodies against p16INK4a, p53, and ki-67 for IHC. The study found that patients from Maranhão had to wait 17 months for a diagnosis, had a high rate of penile removal (96.5%), and were infected with HPV (80.5%). Researchers used both histopathological and IHC research to show that PC had a high rate of HPV. Most of the patients (75.5% of them) had koilocytosis, which was linked to having had more than 10 sexual partners in their lives. IHC showed that p16INK4a overexpression was common (26.0%) in basaloid and high-grade tumors. Interestingly, researchers demonstrated that p16 doesn't seem to better predict disease-free mortality. Researchers also found that high levels of ki-67 and p53 were found in some cases. These levels were linked to worse prognostic factors, such as high-grade tumors, angiolymphatic and perineural invasion, and lymph node spread. It was found that high levels of ki-67 and p53 expression made patients less likely to survive, along with changes in grade, pT, stage, pattern, and depth of invasion. Researchers confirmed that there are a lot of PC cases in Maranhão that are infected with HPV. They also gave us new information about what might be causing so many PC cases in the area. Researchers pointed out that HPV might be linked to worse clinical outcome factors, which is different from what was seen in other areas. IHC data also supports the use of p16, ki-67, and p53 expression as essential biomarkers for diagnosis and/or prediction, which could be used in the clinical setting in developing countries like Brazil [141].

Researchers examined the pathologic traits and clinical results of invasive penile squamous cell carcinoma (SCC), along with the relationship between p16 IHC and HPV in situ hybridization (ISH). Researchers examined how pathologic traits, p16 IHC, and HPV ISH correlated with clinical results. There were 102 people in the study as a whole. The age range was 6313.3 years. The histology showed that 46% of tumors had an HPV-related subtype, and 52% of all cases tested positive for p16. The type of tumor had a strong relationship with p16 positivity, and p16 IHC correctly indicated the presence of HPV in 25 out of 26 cases (96%). Multivariate analysis showed that perineural invasion was linked to local disease return, while lymphovascular invasion was related to the disease spreading to other body parts and higher total mortality. Overall mortality was also higher in people who had urethral involvement. Also, HPV-related tumors that were identified by their molecular traits were linked to lower rates of disease spreading. Many people get penile SCC

from HPV. The tumor's anatomy and increase of p16 on IHC can both confirm the diagnosis [142].

Penile squamous cell cancer (PSCC) is a disease that is mainly ignored and mostly happens in areas that aren't well developed. It's more likely to occur in places where people don't have much money, have phimosis, or have HPV infection [143]. Unlike other urogenital cancers, its pathophysiology and therapeutic targets are still unknown. This is especially true when it comes to the immune system's reaction to the TME [144]. Researchers examined how immune cells enter and mature DCs and how lymphocytes die in HPV-positive and HPV-negative PSCC. Compared to HPV-negative tumors, HPV-positive tumors had smaller rates of T lymphocytes. In addition, people with HR-HPV had slower development rates of Mo-DCs and lower levels of co-stimulatory molecules in these cells compared to healthy donors. Also, Mo-DCs from HR-HPV-positive patients had lower lymphoproliferation capacity than controls, while HPV-negative patients tended to have lower lymphoproliferation capacity. These findings show how HPV infection affects the influx of T lymphocytes, the maturation of Mo-DCs, and the survival of lymphocytes in PSCC. They are essential for helping us learn more about the TME and developing new immunotherapy methods [145].

According to another study, squamous cell scrotal carcinoma (SCSC) is a rare type of skin cancer that has been linked to workplace chemicals in the past. While HPV DNA has been linked to SCSC, there is still no solid proof of its role in cancer. Researchers looked at HPV-DNA and–E6*I mRNA in six invasive SCSCs identified by their tissue type. LCM-PCR was used to find tumor cells that had HPV DNA. IHC was used to look at the expression of P16INK4a and p53.HPV-16-DNA and E6*I-mRNA were found in three warty or basaloid SCSCs. LCM-PCR showed that HPV-16 was in p16INK4a-positive cancer cells. Three normal-type SCSCs, on the other hand, were all harmful to HPV, and two produced p53 protein but not p16INK4a. HPV-16 was found in tumor cells and turned oncogenically in basaloid and warty SCSC. Normal SCSC, on the other hand, did not have HPV and showed immunostaining, which suggests a p53 mutation. The two ways that cancer starts and the link between the type of tissue in SCSC and HPV are the same as in PC [146]. PC is a common health problem in poor countries, and HPV is known to make it more likely to happen. HR-HPV has been found in as many as 40% of cases. The warty and basaloid types of SCC have the highest rates of finding. With a better understanding of how HPV-related cancer starts, researchers might be able to find better ways to diagnose and treat it. As of now, there is no cure for HPV infection other than treating skin sores. This is why finding ways to avoid it and teach patients more about it is essential. Even though encouraging women to get vaccinated against HPV has helped some cancers that are linked to HPV, the effects in men have not yet been fully explained [134].

Researchers assessed the relationship between survival and HPV DNA and p16 status in individuals with PC. In summary, men who have p16-positive or HPV-positive PC have a much better DSS than those who have p16-negative or HPV-positive PC. Researchers suggested that HPV and p16 testing may be used in clinical studies to determine the best course of treatment and follow-up [147]. Furthermore, according to the most recent EAU–ASCO recommendations, all patients with PSCC should have p16 testing done using IHC. This emphasizes the importance of evaluating p16 expression as a valuable diagnostic tool in treating PSCC. In the future, we hope that a forthcoming meta-analysis will shed more light and enhance our comprehension of this topic, expanding our awareness of the predictive relevance of p16 and HPV biomarkers in PSCC [148].

Generally speaking, HPV, and specifically genotype 16, plays several roles in the development of PC and the malignant alteration of healthy penile tissue. The E1 region is more often disturbed in PC regarding virus-host genome integration, and the integration sites in the PC genome typically show the corresponding control of different tumor suppressors or oncogenes. There are differences between the PC genome and HPV DNA regarding DNA changes. In PC, non-European variants are more prevalent and can have particular point mutations in the Af-1 region. Viral infection may impact DNA changes in the HPV + PC genome, including copy number alterations and point mutations (c-ras^{Ha}, P53, NOTCH1, etc.). Epigenetic modifications are also necessary in the development of PCs. Within the HPV L1 and LCR regions, such as the E2BS- and Sp1-binding sites, CpG methylation has been detected. By controlling the expression of relevant genes, certain methylation events and up-or-down-regulation of miRNAs in HPV + PC often cause tumor migration and resistance to treatment. According to the PC immunological microenvironment, the up-regulation of PD1 expression on T cells increases anti-tumor immune cell types, particularly CD8 + T cells. This improvement may make immunotherapy more effective for PC patients. Lastly, HPV vaccination may be a valuable method for avoiding HPV infection and the development of PC, as well as a therapeutic option for people with HPV + PC. There are undoubtedly some restrictions on this evaluation. First, because of the low frequency of PC, there isn't much relevant research in several parts (HPV DNA methylations and HPV DNA mutations), which might result in unsatisfactory findings. Second, there may be bias in the findings due to differences in PC populations and HPV–PC genome integration detection methodologies across studies. Third, only a small number

of research have identified the epigenetic consequences of HPV infection, which is insufficient to elucidate and confirm the role of methylation and miRNA/mRNA regulation in developing PC. To better understand the pathophysiology of HPV-related PC, future research should examine the integration patterns of the HPV–PC genome, PC gene methylation, and miRNA/mRNA regulation in greater detail. This will help to understand how host gene expression is regulated and how downstream molecular changes occur during HPV infection. Furthermore, studies aimed at creating therapeutic vaccinations that target certain HPV DNA sections are essential for providing PC patients with new therapy choices [149].

HPV in the development of kidney cancer in men

With 1.2 million common cases over five years, KC is the 12th most frequent cancer globally, according to the 2020 Globocan Registry [150]. Renal cell carcinoma (RCC) is one of the most common types of cancer in men. It affects 4.4% of men around the world. It wasn't until the early 1990s that HPV's possible role in the development of RCC was first studied. Since then, studies have examined whether this virus, usually found in men's private areas, raises the chance of RCC [151]. Farhadi et al., HPV was found in 30% of tumor samples from people with RCC. Because HPV's L1 capsid protein is missing and cells change in ways linked to the virus, like koilocytosis, in RCC patients, it was thought that HPV's life cycle is thrown off in its later stages [152]. Researchers showed that having HPV was also linked to having high-grade cancers. Another study used PCR to find that 14.3% of RCC samples had HR-HPV, but HPV was not found in any healthy kidney tissue in the control group. This suggests that HPV may play a part in the development of RCC. A different ISH study also found that 52% of RCC cells had HPV-DNA. However, Khoury et al.'s thorough study using data from the Human Genome Atlas did not find a link between RCC and HPV [153].

Researchers looked at 122 patients with histopathologically proven renal cell cancer and the tissues around the tumors fixed in formalin and then embedded in paraffin. Researchers used IHC to check the levels of p16INK4a and HPV L1 capsid proteins. The HPV genome was found in 37 (30.3%) tumor samples and the four (4.1%) tissues surrounding the tumors. The most common type of virus found was HPV-18, followed by HPV-16 and − 58. In 24 cases (20.3%), immunoexpression of p16INK4a was found. There was a strong link between the expression of p16INK4a and the presence of HR-HPV DNA in the data. CSAC-ISH research showed HR-HPV infection in 45% of tumors that had already been found to have HPV-DNA. Fifteen (83.3%) of the samples showed a diffuse signal pattern, but only three showed a pattern that was a mix of diffuse and punctate signals. The results show that certain kinds of HR-HPV are linked to renal cell cancer. It is thought that HPV infection in high-grade tumors might stop the disease from getting worse in some types of tumors, especially the papillary form [154].

Researchers found that out of the 2345 kidney replacements that have been done at this research center over the past 20 years, 16 had 20 genitourinary cancers, which were made up of 13 bladder/ureter carcinomas, 5 RCCs, and 2 prostate carcinomas. Researchers used immunohistochemical staining to look for polyomavirus large T antigen and p16. In p16 + cases, they then used ISH to look for HPV. Large T was found in four cases of high-grade invasive urothelial bladder carcinomas. At least eight years after the transplant, large T + urothelial carcinomas appeared in three young men who had a history of BK polyoma viremia. Two of them had native kidney failure due to reflux or obstruction. All tests that did ISH for HR-HPV came back negative. In total, three people died of cancer. Two PCa were p16 negative, and the other two were p16+/HPV negative. All five RCCs were negative for both big T and p16. Researchers showed that 31% of kidney donation patients have urothelial cancer but not RCC. Even though the sample size is small, young people with obstructive disease may be more likely to get significant T-positive urothelial cancer [155].

Through the ATM network-related DDR, HPV DNA integrations may influence how well cancer treatments function. Researchers investigated whether human HK-2 renal tubular cells immortalized by HPV-16 E6/E7 genes changed in response to cisplatin-induced DDR. Thiazolyl blue dye was used in cytotoxicity tests. DDR was detected by analyzing cell cycling and side population cells, ds-DNA breaks, ATM promoter activity, and variations in gene expression. Following cisplatin, HK-2 cells had increased ATM promoter activity, suggesting that this network was activated; nevertheless, DDR was inhibited since there were no DNA strand breaks, minimal γH2AX expression, and the cells continued to cycle. Cell growth was reduced, but cisplatin toxicity remained unchanged when HK-2 cells were exposed to the MDM2 antagonist, which triggers p53, nutlin-3, or p53 transcriptional activator, tenovin-1. On the other hand, arsenic trioxide synergistically increased cisplatin cytotoxicity, including loss of SP cells, by depolymerizing tubulin and blocking wild-type p53-induced phosphatase-1, which mediates reactions downstream of p53. Researchers showed that HPV-16 E6/E7 changed DDR by affecting p53-mediated cell growth controls. This may be fixed by focusing on WIP1 and other processes. Thus, it could help treat RCC [156].

The existence of viruses within the tumor, particularly in non-clear cell RCC, and the development of RCC in patients who already had long-term viral infections. According to several translational and clinical data that

have been gathered, the significant immunogenicity of sarcomatoid RCC may be caused by viruses, namely EBV. Furthermore, the potential involvement of endogenous retrovirus reactivation in RCC oncogenesis was disclosed, generating intriguing new theories on the immunogenicity of this tumor and its propensity to react to immune checkpoint inhibitors [157]. All HPV types that tested positive were HR genotypes (HPV-16 in three individuals and HPV-18 in four). Researchers showed that RCC may be linked to HPV infection, particularly HR genotypes. Nevertheless, further research is required to illustrate the molecular carcinogenic mechanisms behind this correlation [158].

HPV vaccine and treatment effects on urological cancer

It's still not clear what role HPV infection plays in UC [159]. The genetic makeup of UC has changed since variations that can be used to alter diagnosis, prognosis, and treatment plans have been found [160]. At the moment, scientists are looking into how viruses can affect cancer. In some types of cancer, HPV may be linked to the development of cancer [161]. Genitourinary (GU) cancers, like prostate, urothelial, kidney, testicular, penile, and adrenocortical cancers, make up a big part of all cancers in the world. There has been a lot of progress in the last ten years in how GU cancers are treated, but there is still a lot that can be done better [162]. miRNAs are noncoding RNAs that control how genes are expressed after they have been translated. They have been linked to several ways that cancer starts. So, they could change the way personalized cancer treatment is done. Several animal and clinical studies are currently being done to determine how well they work [163].

Researchers don't know much about the genetic changes that cause PC because most studies have been done on small groups of people with various causes. PSCC rates have gone up in developed countries over the last few decades because more people are being exposed to HPV. Even though surgery has helped treat locoregional PSCC, there aren't many effective ways to treat severe disease [164]. About one-quarter of people with invasive PSCC have changes in their genomes that can be used to treat them. These changes affect the mechanistic target of rapamycin, DNA repair, and receptor tyrosine kinase pathways [165]. It's possible that paired and sequential targeted treatments could help these people. Since PSCC is genetically similar to other cancers caused by HPV, getting vaccinated against it might be another way to treat it. Also, 40–60% of PSCC tumors have high levels of PDL1, and there aren't many mutational signs that point to immunotherapy resistance. This suggests that immunotherapy might help treat PSCC. Lastly, figuring out what kinds of bacteria live in the penile area and their biological function could lead to new ways to avoid and treat cancer [166].

For example, researchers compared the genetics of invasive penile SCC caused by HPV and SCC that HPV didn't cause in 156 patients from a single school in a low-incidence country. They used tailored next-generation sequencing to look at hotspots of 50 cancer-related genes. Seventy-nine of the 156 SCCs were thought to have been caused by HPV, while the other 77 were supposed to have happened without HPV. Only 28 (35%) of the 79 penile SCCs that HPV caused had somatic gene changes, but 69 (90%) of the 77 SCCs that were not caused by HPV did. The number of PIK3CA, FGFR3, and FBXW7 variants in both groups was about the same as in other human cancers. On the other hand, changes in the TP53 (44/77; 57%), CDKN2A (35/77; 45%), and HRAS (13/77; 17%) genes only happened in HPV-independent SCC in one HIV-positive patient, and TP53 and CDKN2A mutations often happened together (28/77; 42%). 9 (11%) of the 79 HPV-induced SCC cases had more than one gene change, compared to 47 (62%) of the 77 HPV-independent SCC cases. Fourteen (18%) of the 77 cases of HPV-independent SCC had more than one change per gene, while only three (4%) of the 79 cases of HPV-induced SCC did. There were 47 mutations in penile SCC caused by HPV, which is a lot fewer than the 143 mutations found in SCC not caused by HPV. The presence of somatic driver gene mutations was not linked to the age of the patients, the histology, or the stage of the primary SCC in either cause group. This suggests that driver gene mutations are acquired soon after invasion. Changes in tumor suppressor genes cause PC, which HPV doesn't cause. In HPV-induced SCC, malignant effects of E6 and E7 replace defects in these genes. Some people with advanced SCC may be able to benefit from targeted treatment and clinical studies, but most people with advanced penile SCC are still hard to treat [167].

Therapeutic HPV vaccines are being made to help people who have active HPV-associated PC. Oncoproteins E6 and E7 are very important for HPV's power to cause cancer. Therapeutic HPV vaccines use this dependence to make the immune system attack the oncoproteins by activating CD8 + T-cells to find and kill HPV-positive cells. Adoptive T-cell treatment can also be used to target these oncoproteins. Autologous tumor-infiltrating lymphocytes (TILs) are taken from the patient and grown to be re-infused into the patient. A T-cell receptor (TCR) that can connect to oncoproteins E6 and E7 is currently being developed. This will allow separate TILs to target HPV-infected tumor cells for more targeted delivery. Both ways of growing show the biological benefit that HPV-related markers have in PC growth. Nectin-4 and heat shock proteins (HSPs) are two examples of therapeutic targets still being studied. In the coming

years, they may lead to more treatment options. Patients can get a more effective and specific treatment plan with these new treatments and a better knowledge of the immune microenvironment around HPV-associated PC tumors [168].

While little study has focused on PC, it has been shown that non-HR-HPV penile tumors express more PD-L1, with low levels linked to a better prognosis and the absence of lymph node metastasis. A study of 148 penile SCCs revealed that HPV-positive tumors had greater HER3 expression, whereas HPV-negative tumors had more phosphorylated EGFR [143, 169, 170]. There may be a mechanism for EGFR overexpression in HPV-positive individuals, as another study discovered low levels of miRNA-146a, a downregulation of EGFR, in HPV-positive cancer. Other research has shown that penile tumors that were HPV-negative or positive had variable amounts of miRNA and mRNA, as well as abnormal DNA methylation, which might lead to the identification of other targets [143, 171–173]. Although several indicators are being studied, most research is currently focused on HPV-related malignancies other than penile SCC. Nonetheless, the promise is clear, and additional translational study and time will probably make diagnostic and treatment targets accessible soon [143].

A study conducted by Guiliano et al. (2011) found that when it comes to reducing external genital lesions in men aged 16 to 26, the quadrivalent HPV vaccination has a 90.4% effectiveness. The trial was randomized, placebo-controlled, and double-masked. Researchers showed that vaccination reduced anal intraepithelial neoplasia by 77.5% in a subset of 602 men who have intercourse with other men and are, therefore, not protected by herd immunity [174, 175]. Unfortunately, researchers revealed that the low frequency of PeIN and PC in the research group made it impossible to assess how efficiently the vaccination prevented these conditions. Given the low frequency of PC, using the male vaccine in its prevention will not be cost-effective. Because HPV causes oropharyngeal cancer, PC, anogenital cancer, and anogenital warts in men, it should be studied in a broader context. The gender-neutral HPV vaccine is economical when considering all illnesses linked to HPV. However, some research indicates cost-effectiveness declines if female immunization coverage exceeds 75%. More studies are required to assess the protective effect of HPV vaccination on PCs. However, because of the disease's rarity, the fact that HPV is present in only 50.8% of cases, and the amount of time that passes between HPV infection and the first discovery of lesions, evaluating this effect will be problematic and will need large research populations [175].

Even though there have been more genetic epidemiological studies in the past few years trying to find a link between HPV infection and the chance of BC, they have not yet concluded. When looking at studies, it's essential to consider their differences based on study area, histological type, HPV DNA specimen, release date, and detection method. HR-HPV types, especially HPV16, may play a part in setting off BC [23]. Few countries have told guys to get vaccinated because they think it is not worth the money [135]. However, vaccinations for both sexes have been suggested in the USA, Canada, Austria, and Australia. Before making these choices, careful cost-effective modeling was done to show that when the load of disease in men is taken into account, then, based on coverage, vaccine price, and other factors, immunization of men can become a cost-effective option [176].

Recurrent respiratory papillomatosis (RRP) is the most critical non-cancerous disease that is linked to HPV in the head and neck. When it comes to cancers, the number of head and neck cancers related to HPV has grown dramatically around the world. Also, it is now thought that HR-HPV infections cause about half of all cases of HNSCCs in the US. HPV is also important in the field of andrology. It was said to have a high HPV frequency, between 50 and 70%, in the male penile shaft, glans penis/coronal sulcus, semen, scrotum, perianal area, and anal area. In addition, the HPV virus has been linked to PC in male patients, along with other illnesses. It has been stated that about 10% of men in the general population and about 16% of men who can't get pregnant for no apparent reason are infected with HPV semen. However, based on clinical experience, these numbers are likely much lower than they are. It looks like HPV semen infection is mainly linked to asthenozoospermia and anti-sperm antibodies (ASAs). HPV virus is a health issue that negatively affects society and the people. Even with this proof, not much has been done to date to get a lot of young men vaccinated [177].

Men can also get HPV, which is terrible for their health [178]. HPV is a well-known oncovirus, and epidemiological studies have shown that the risk of cancer varies based on the type of cancer and the gene of HPV. Finding and identifying HPV is a key part of preventing and lowering the chance of cancers linked to HPV [179]. Direct identification of viral DNA sequences in tumor samples can be used to find HPV. It is also possible to find HPV DNA products in urine, blood, and biopsy samples, though these may not be as sensitive as tissue samples [180]. According to recent clinical studies, finding circulating DNA in the blood generated from malignant tumor cells may confirm the return of certain malignant tumors sooner than identifying elevated tumor marker levels. Consequently, the identification of tumor-derived circulating HPV genes in the blood may demonstrate the return of HPV-related infectious, malignant tumors sooner than the detection of rising tumor marker

levels. Specifically, circulating HPV DNA originating from tumors is a valuable indicator for distinguishing between tumor marker increase and malignant tumor recurrence [156]. According to a meta-analysis of cross-sectional research, PCa is linked to HPV-16 infection. Despite the diversity of evidence in the literature today about HPV diagnostic methods in PCa patients, HPV infection should be regarded as a possible risk factor for Pca [181]. There is no formal early detection program for extragenital symptoms. Meanwhile, research on HPV vaccinations demonstrates that their major utility should be in preventing illnesses that are reliant on HPV. Further study is necessary to determine the actual benefits and drawbacks of vaccinations [182].

The HPV vaccine is a good way to avoid getting diseases related to HPV. The World Health Organization (WHO) says that the HPV vaccine should be given to both men and women. Studies have shown that getting an HPV vaccine is a good way to avoid getting HPV and also to stop precancerous growths in the anogenital tract and genital warts. Males are not very aware of or open to [183]. Overall, guys were less likely to accept the HPV vaccine, though men who identified as the same gender were a little more likely to do so. Most of the time, people don't want to get vaccinated because they don't know enough about the disease or the vaccine, or it costs too much [184]. At the moment, there are successful preventative medicines against the most common oncogenic HPV types, 16 and 18, but not many people are getting them. It is currently recommended that surgery, chemotherapy, or local radiation therapy be used to treat cervical cancer. However, advanced cervical cancer can't be cured, so new treatment methods are needed. Targeted treatment is now being tried by going after chemo radiosensitized cancer stem cells, which are the leading cause of disease recurrence. Even though screening programs have been successful, cervical cancer is still not being found in enough people, especially those who are not getting screened or who are not getting tested enough. Current research includes studying the spread of HPV, the molecular changes during infection, and the natural history and molecular biology of the E6/E7 oncogene. Also, learning the molecular signaling pathways in cervical cancer can help create new treatments for people who already have the disease and also new ways to stop it from happening in the first place [185].

As of now, 17 years after the first preventive HPV vaccine was approved, only 68% of countries have added the HPV vaccine to their national immunization programs. This means countries must develop plans, practices, and policies to reach and maintain higher levels of HPV vaccination coverage. Since HPV shots came out, there is a better chance that cervical cancer will be gone entirely in the next ten years. Several safe and successful vaccines have been approved for use around the world. These include the quadrivalent GardasilTM and nonavalent Gardasil9 vaccines made by Merck and the bivalent vaccine CervarixTM made by GlaxoSmithKline. However, the weak health systems of LMICs are not well-equipped to handle the difficult task of giving teenage girls two doses of the vaccine. To eliminate cervical cancer by 2030, the WHO has asked all countries to speed up the use of methods and policies that have already been tried and tested. There is no doubt, though, that the cervical cancer vaccine is not a quick fix because it cannot replace the most important thing, which is cervical carcinoma screening [186, 187].

The number of cases of HPV-associated oropharynx cancer (HPV-OPC) is rising, and it has unique clinical, pathologic, genetic, and epidemiologic traits. However, based on the data researchers now have, managing HPV-OPC is the same as managing HPV-negative OPC and requires complicated, multidisciplinary methods. The better outlook for HPV-OPC and the side effects of present multimodality treatment in young people are reasons to look into de-intensification treatment plans that aim to lower side effects while keeping therapy effective. Currently, clinical studies look at less harmful systemic treatment regimens or lower doses of radiation in HPV-OPC. Minimally invasive surgery methods are also being looked into for HPV-OPC patients whose tumors are still in an early stage. De-intensification strategies should only be used in clinical trials, and people with HPV-OPC should be allowed to participate in those studies. To make deintensification plans work, choosing the right patients is essential. To do this, we need to learn more about the risk factors in the HPV-OPC group, how HPV affects the body's response to specific therapies, and how HPV itself changes the body's reaction. It has been shown that a history of smoking and extensive nodal disease can make the outlook of HPV association worse. There aren't any validated biomarkers for the HPV-OPC community yet, but changes in the PI3K pathway and immune response markers may become necessary. New ways to treat cancer are badly needed, especially for HPV-OPC patients who don't respond to definitive treatment. Some patients with recurrent or metastatic disease may also benefit from more invasive methods [188].

VElumab is a monoclonal antibody that targets protein-programmed death-ligand 1 (PDL-1). It was recently cleared by the FDA to treat Merkel cell carcinoma, a type of skin cancer, as well as kidney and BC. More than 200 clinical studies examined how avelumab works on different kinds of cancer. In one of these studies, avelumab is being tested along with TG4001, a new vaccine made with HPV-16 proteins, for diseases linked to HPV (NCT03260023). Durvalumab is another human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody

cleared by the FDA. It stops PD-L1 from interacting with PD-1 and is used to treat different kinds of lung and BC. Along with MEDI0457, durvalumab is now being tried in a phase 2 clinical study (NCT04001413) on people with HPV-positive OPSCC. It comprises DNA plasmids that contain the E6/E7 genes of HPV-16 and – 18 (VGX-3100) and DNA plasmids that include the human IL-12 and INO-9012, which sets off the defense system. A new study showed that patients with cervical cancer who had chemoradiation did well with MEDI0457. This brought up the idea of using tumor-specific vaccines along with radiotherapy. MEDI0457 was also well tolerated by people with HPV-related HNC cancer who had high levels of antigen-specific T cells. Even though the safety studies look good, the real test of a vaccine's effectiveness won't come until phase 2 and 3 clinical trials are over. In addition, durvalumab is being studied with radiation in people who have HPV-related OPSCC (NCT03623646) [59].

UC is to blame for thousands of deaths around the world from cancer [189]. Even though there have been improvements in how cancer is treated, the lack of effective treatments is still a significant problem for doctors and academics. Also, regular medical treatments can cause several harmful side effects that patients don't want, which lowers their quality of life and shortens their living time [190].

One of the main reasons humans die from cancer around the world is BC. Some things that can make you more likely to get BC are your genes and the things you are exposed to in your surroundings. HPV may help BC grow and worsen the outlook for people with BCa. To avoid getting BC, people, especially guys, need to get protected against HPV [191]. Researchers found that having a family history of cancer and being infected with HPV can be separate predictors of tumor return in BC [11].

One big worry about male HPV cases, though, is the low rate of seroconversion after a normal infection. It has also been said that having HPV antibodies does not protect guys as much from getting diseases in the future as it does for women [192]. Luckily, the quadrivalent HPV vaccine is very effective in safeguarding guys ages 16 to 26 against HPV. Seroconversion starts in month 7 and stays high for 36 months, with titers similar to those in women [174]. A study done in 2011 with 4,065 boys ages 16 to 26 from 18 randomized, placebo-controlled, and double-masked countries found that the quadrivalent vaccine might help avoid external genital lesions [193]. Researchers demonstrated that the effectiveness seen in the intention-to-treat group was 60.2% and 83.8% in the per-protocol group. Only people in the control group had PeIN. Also, in a Phase II clinical study in men ages 27–45 in the U.S. and Mexico, the quadrivalent vaccine was shown to immunize them at the same level as it did with younger men [194]. People have known for a long time that vaccines used to stop diseases can also boost the immune system to fight cancer. For example, the Bacillus Calmette–Guérin (BCG) vaccine has been approved since the 1970s to treat BC [195]. Since immunotherapies were recently approved, this study area has become more active. For example, known vaccines for infectious diseases have been used to fight tumors, either by themselves or with immune checkpoint inhibitors [196]. However, the link between HPV infection and the chance of getting BCa is still debated and unclear [132].

Researchers looked through four sources of references that didn't limit the language used. Studies that looked at how HPV infection and the chance of BCa interacted from the beginning of time until May 21, 2022, were found and used by researchers [197]. Researchers used both Random Effects and Fixed Effects models to guess how common each type of HPV would be and give a 95% confidence interval. Researchers also found the pooled chances ratio and the pooled risk ratio with 95% CI to see how the HPV virus changes the risk and outlook for BC [110]. A two-sample Mendelian randomization (MR) study used genetic variants linked to the HPV E7 protein as auxiliary factors. In conclusion, HPV may play a part in the development of BC and make the outlook worse for people who have BCa. To avoid getting BC, people, especially guys, need to be protected against HPV [198].

Researchers discovered how common HPV-16, -18, and – 52 are in Egyptians with BC or recurring cystitis. Researchers also want to examine how type-specific HPV-immunoglobulin (Ig)G results relate to PCR results and other clinical and pathologic factors. Investigators reviewed 60 inpatients at the Theodor Bilharz Research Institute (TBRI) Urosurgery Department. They were divided into four groups based on their symptoms: BC (20 patients in group I), cystitis (24 patients in group II), BC with cystitis (16 patients in group III), and a healthy control group of 20 people who were used for serologic testing. Researchers tested patients for HPV-16 and – 18 DNA using PCR on bladder tissue samples (BTB) and buffy coat cells (BCC). Researchers also tested their blood IgG antibodies to L1 capsids of HPV-16 and – 52 IgG using an enzyme-linked immunosorbent assay (ELISA). HPV-16 and – 18 DNA were found in 30% and 10% of BTB cases, respectively. These numbers were much higher in BC cases (44.4%) than in cystitis cases (11.11%). There was a strong link between these numbers and schistosomal affection (78.6% and 25%, respectively) and relapse (48%, HPV-16). A strong link was found between TCC and HPV-16 in 69.2% of BCC cases and 61.1% of BTB cases. There were a lot more multiple HPV types (16, 18, and 52) than single types (79.2% vs. 20.8%). The direct link between HPV-52 (11.7%) and HPV-16 (26.7%) seropositivity was significantly linked to TCC in patient groups only. Investigators showed that HPV-16, -18, and

– 52 are strongly linked to BC in Egyptian patients. This suggests that the viruses may work together to cause BC. These types of HPV were strongly linked to TCC tumors of low grade and high stage, as well as schistosomes and a tendency to come back. HPV serology would make it easier to care for and keep track of patients and create and test the best HPV vaccines [199].

Squamous cell carcinomas of the anogenital tract, skin, and oral cavity are among the human malignancies linked to HR-HPVs, which are mainly sexually transmitted infections. Several investigations have examined the connection between HPV infection and UCs. According to available data, there is now only a strong correlation between HR-HPV infection and UCs, namely squamous cell carcinomas of the penis. Researchers supported that a link between HPV infection and kidney, bladder, or PCa has been mixed. A thorough correlation between viral infection and identifying viral DNA, viral gene products, immunological responses to the virus, and epidemiological data is necessary since PCR findings are particularly susceptible to contamination. However, as shown by the prevalence of HPVs in patients with neurogenic bladder and squamous urothelial carcinoma, changes in medical practice, such as increased use of immunosuppressive medications and co-morbidities, may potentially alter HPV-associated disease presentations. This idea is supported by the very high incidence of HPV-associated ASCC, another relatively recent HPV-associated illness in men, among HIV-positive men who have sex with men. HPV-16 was identified in the majority of cases (94.9% of positive cases), and HPV DNA was discovered in 80–100% of patients with anal cancer [200].

It's also important to highlight that, given the available data and good hand cleanliness practices, genital-to-hand transfer via urologists is relatively uncommon in everyday practice. HPV DNA has been detected on

Table 1 The role of HPV in UC development

Urological cancers	HPV Functions	Ref
PCa	The current study showed that HPV-positive PCa has a different miRNA makeup than HPV-negative PCa.	[98]
PCa	The HPV/EBV coinfection may play a role in developing PCa by changing how cells behave.	[100]
PCa	The levels of anti-apoptotic factors and factors involved in angiogenesis and inflammation were significantly higher in the HPV-infected PCa group compared to the HPV-negative PCa group and the control group.	[96]
PCa	people who had HPV infections in the past had a 2.321 higher chance of getting PCa compared to people who had never had HPV infections	[94]
PCa	The average expression level of PTPN-13 and E-cadherin genes was lower in HPV-positive samples compared to HPV-negative samples. Researchers showed that HPV infection may play a role in the growth of PCa tumors by changing genes related to anoikis resistance.	[97]
BC	Investigators showed that having a family history of cancer and being infected with HPV may be able to predict tumor return in BC on their own. In general, researchers suggested that there is a link between HPV infection and a worsening of the disease and a higher risk of return in people with BC.	[111]
BC	The HPV-18 genotype, followed by HPV-33, -16, and – 39 genotypes, is the most common type of oncogene that can cause BC.	[110]
BC	Researchers' results showed that HPV infection changes the tumor differentiation level. This means that the HPV test could be used to determine how the disease recurs or gets worse.	[112]
aBSCC	As seen in other HPV-related squamous cell carcinomas, HPV + aBSCC has fewer mutations that turn off cell cycle control genes.	[118]
TC	the information researchers have about the risks of HPV and TGCTs is mixed, and researchers need to do more research before researchers can say for sure what they are. Finally, there is no proof that CMV and Parvovirus B-19 impact the development of TC.	[20]
TC	people with TC often had changed sperm statistics and a higher rate of HPV semen infections, which got worse after radiation and treatment.	[130]
PC	HPV is linked to PC development, and knowing how different regions have different HPV gene distributions is essential for controlling and preventing PC.	[138]
PC	Different histopathological aspects of the cancerous growths were similar to those found in HPV-associated human PC.	[139]
SCC	Many people get penile SCC from HPV. The tumor's anatomy and increase of p16 on IHC can both confirm the diagnosis.	[142]
SCSC	Normal SCSC, on the other hand, did not have HPV and showed immunostaining, which suggests a p53 mutation. The two ways that cancer starts and the link between the type of tissue in SCSC and HPV are the same as in PC.	[146]
kidney cancer (KC)	The results show that certain kinds of HR-HPV are linked to renal cell cancer. It is thought that HPV infection in high-grade tumors might stop the disease from getting worse in some types of tumors, especially the papillary form.	[154]
KC	Researchers showed that 31% of kidney donation patients have urothelial cancer but not RCC. Even though the sample size is small, young people with obstructive disease may be more likely to get significant T-positive urothelial cancer.	[155]

condyloma treatment tools in a few investigations, but no active virus was discovered. Aerosolized live HPV particles during laser ablation of large condylomas seem to provide the greatest danger, according to some reports of potential transfer via unwashed specula in women [200, 201].

HPV infection is widespread and significantly impacts society and the economy. The prevalence of anogenital carcinomas and anogenital warts in urology patients is sure to remain high. To develop diagnostic and treatment options, it is essential to understand the function of HPV in these malignancies. If urologists want to help their patients the most, they need to learn more about this virus and get expertise in treating it. The involvement of men in transmitting the virus to females is significant. To decrease the prevalence of anogenital illness in males and the HPV load and HPV-associated disease in women, it is recommended that men be vaccinated against HPV. 2014 Gardasil 9 became the most recent HPV vaccination to get FDA clearance. There are no vaccinations on the market that the FDA has not authorized. A total of 87 nations have instituted national immunization programs; of these, 68 have opted to vaccinate exclusively females, while 19 have chosen to inject both sexes. According to the CDC, both sexes should have a vaccine between the ages of 9 and 26, with booster shots administered between the ages of 11 and 12. For those between the ages of 9 and 14, the suggested immunization schedule includes two shots spaced 6–12 months apart, while those 15 and above are advised to have three doses at 0, 1, and 6 months. To get the most out of the vaccine's preventative effects, it's recommended to start immunization from a young age, before a person has their first sexual encounter [43].

Conclusion and future perspective

Infections are significant for cancers like prostate and PC that cause long-term inflammation. If you have HPV for a long time, your genes will change in ways that can lead to cancer. The risk might be lower if people get vaccinated against HPV, have safe sexual encounters, and treat cases quickly. The link between HPV and UC, like KC, is unclear. Additionally, HPV may play a part in continuous inflammation and the development of cancer in prostate cells. Also, PC is highly linked to HPV infection. So, getting a shot against HPV can significantly lower the chance of getting urinary cancer. Getting vaccinated against HPV and getting treatment for it is essential for reducing the possibility of some cancers, especially in guys. For diseases highly linked to HPV, like penile and oropharyngeal cancers, the HPV vaccine is a powerful way to stay healthy. Many people getting vaccinated and quickly finding and treating HPV-related diseases can significantly lower the number of cases of male cancers, including some types of UC. Researchers are still trying to figure out what the link is between HPV and cancers of the prostate, bladder, and kidneys. If we knew more about these links, we might be able to vaccinate more people against HPV. More studies are needed to figure out how viruses and UC are connected. The future of HPV vaccines for preventing urinary cancer looks bright, as they could be used in treatment settings, cover more strains, and work with personalized medicine. Also, making medicines that protect against HPV and other cancer-causing viruses (like EBV, hepatitis B, and C) is essential for preventing UC. As the study goes further, these vaccines could become a key part of lowering the number of guys who get cancers linked to HPV around the world. We must invest money into education, creativity, and fair access to reach this promise. In conclusion, in Table 1 we have summarized the important effects of HPV on UCs.

Acknowledgements
Thanks to Iran University of Medical Sciences.

Author contributions
N.E., E.Z., S.M., and F. KH.,: Writing – original draft. N.E., E.Z., Conceptualization, Supervision, N.E., E.Z., S.M., and F. KH.,: Writing – review & editing. All authors participated in the manuscript in the critical review process of the manuscript. All authors read and approved the final manuscript.

Funding
This research received no external funding.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 22 December 2024 / Accepted: 24 February 2025
Published online: 28 February 2025

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