Chapter

# Association between Human Papillomavirus and Urological Cancers: An Update

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## Abstract

Human papillomavirus (HPV) is currently the most common sexually transmitted pathogen in the world, and as such imposes a substantial global burden due to its oncogenic properties. The significant association of HPV with anogenital and head and neck carcinomas is well established. In terms of urological malignancies, only the association between HPV and penile cancer has been well defined; despite close anatomical proximity, its relationship with bladder, prostate, kidney, and testicular cancers has remained unclear. With technological advances in the nucleic acid amplification tests used to detect HPV over the last two decades, the results of new studies have led to the need to reexamine these relationships. This brief review aims to evaluate the association between urological malignancies and HPV infection in light of recent data.

**Keywords:** HPV, penile cancer, prostate cancer, kidney cancer, bladder cancer, testicular cancer

## 1. Introduction

The human papillomavirus (HPV) is a double-stranded DNA virus whose only host is humans. It is the most common sexually transmitted pathogen in the world today. Epidemiological studies indicate the global prevalence of HPV is close to 12% [1]. The main reason for this high prevalence is that HPV infection is usually asymptomatic. The clinical course of HPV infection is divided into three periods—the latent, subclinical, and clinical phases [2]. Up to 90% of HPV infections are controlled by host adaptive immunity, thereby remaining in the latent phase and eventually becoming undetectable. However, 10% of cases progress to intraepithelial neoplasia or condylomatous lesions, and 1% transform into invasive cancer [3]. While over 200 HPV types have been identified to date, only 40 of them cause anogenital infections and HPV-associated malignancies [4]. Unlike many other viruses, HPVs are classified according to genetic sequence rather than antigenic structures. Therefore, instead of serotypes, they are numbered by genotype and in the order of discovery [5]. Despite its largely benign nature, HPV is a high-profile public health issue and poses a substantial socioeconomic burden due to its oncogenic properties. HPV and Epstein–Barr virus (EBV) are responsible for the most frequent virus-related cancers [6], with HPV linked to nearly 10% of cancers globally [7]. Based on their oncogenic potential, HPVs are divided into high-risk (HR-HPV) and low-risk (LR-HPV) types. HR-HPVs disrupt the cell cycle via their E6 and E7

oncoproteins, preventing progression from G1 to S phase [8]. The E6 oncoprotein inhibits the function of tumor suppressor protein p53. This increases the risk of cell transformation due to a lack of genetic stability and inhibition of apoptosis. The E7 oncoprotein inactivates another tumor suppressor protein, retinoblastoma (Rb). This results in the uncontrolled synthesis of the proteins necessary for cell cycle progression, and the cell enters a state of continuous proliferation [9]. Unlike HR-HPVs, the E6 and E7 oncoproteins of LR-HPVs do not inactivate p53 and Rb to the same degree [10].

Because HPV shows epithelial tropism, squamous cell carcinoma is the most common histologic type of HPV-related cancer. HPV association has been reported in 96% of cervical carcinomas, 75% of vulvar carcinomas, 41% of oropharyngeal carcinomas, and 36% of anal carcinomas [11–13]. The results of meta-analyses suggest that the presence of HPV is a favorable prognostic factor in anogenital and head and neck cancers [13–15]. Although it is not clear how the presence of HPV improves prognosis in these carcinomas, it was reported that HPV-negative primary cancers showed high metastatic potential and had more aggressive p53 mutations, resulting in more severe deregulation of normal growth control and poorer prognosis compared to HPV-positive cancers [16].

Considering the close anatomical proximity to anogenital carcinomas, researchers have investigated the relationship between HPV and urological malignancies for approximately three decades. Among these cancers, only penile cancer has been clearly associated with HPV. The relationship between HPV and other urological malignancies such as prostate, kidney, bladder, and testicular cancers remains controversial today. This lingering uncertainty is the result of limitations arising from methodological differences in past publications. These limitations can be summarized as small case series, lack of fresh tissue sampling, the use of serological tests for HPV detection, and the inadequacy of case–control studies [17–19]. In recent years, however, remarkable advances in polymerase chain reaction (PCR) assay technology have enabled the identification of more genotypes in a single sample, and DNA extraction from formalin-fixed, paraffin-embedded (FFPE) tissues, has become more efficient. Therefore, it is clear that results obtained two to three decades ago must be reevaluated.

## 2. Penile cancer and HPV

Penile cancer is rare, accounting for approximately 0.5% of all cancers in men, with a peak prevalence in the sixth decade of life [20]. The incidence of penile cancer varies by geographical region depending on the hygienic, cultural, and religious characteristics of the population. Its incidence is between 0.3 and 1 per 100,000 in developed countries, while it reaches 4 per 100,000 in developing countries [1]. At present, the main known risk factors are phimosis, chronic inflammation of the penis, poor personal hygiene, smoking, polygamy, and HPV infection. Histopathologically, 95% of penile cancers are different variations of squamous cell carcinoma [21]. The fact that HPV-associated cancers are of squamous histology led to the early discovery of the relationship between HPV and penile carcinomas. Although there are methodological differences in HPV detection among published studies, the prevalence of HPV in penile cancers is reported to be between 39.7% and 59.3% [22]. According to a recent meta-analysis evaluating 2531 patients in 270 studies, the prevalence of HPV-DNA in patients with penile cancer was 48% (confidence interval [CI]: 40.0%–57.0%) [7]. HPV type 16 is the dominant type identified in HPV-associated penile cancers, with more than half of cases attributed

to this type alone [23]. The second most common strain detected in penile carcinomas is HPV type 18, and together these two types are responsible for more than 70% of HPV-associated penile carcinomas [24].

Penile intraepithelial neoplasia (PIN) is a penis cancer precursor lesion similar to cervical intraepithelial neoplasia (CIN). The extent to which the natural course of PIN mirrors that of CIN is unclear, and its clinical management is less standardized compared to CIN [25]. However, the link between PIN and HPV is noteworthy. Studies have indicated 70–100% association between HPV and PIN, much stronger than its relationship with penile carcinoma [26]. An important biomarker currently being studied in HPV-associated carcinomas is $p16^{INK4a}$, a protein whose expression is stimulated by the E7 oncoprotein [27]. Numerous recent studies suggest that $p16^{INK4a}$ expression can be used as an alternative marker of infection in cervical and other HPV-associated carcinomas due to its association with HR-HPV carcinogenesis [27]. Martins et al. reported that the expression of $p16^{INK4a}$ was significantly associated with the presence of HR-HPV in penile cancers, and could serve as a marker of HPV in penile cancer [28]. A recent meta-analysis by Olesen et al. investigating $p16^{INK4a}$ positivity in penile cancers and PIN yielded the interesting finding that the rate of $p16^{INK4a}$ positivity was 79.6% in HPV-positive patients with penile cancer but only 49.5% among those with PIN [29]. In this meta-analysis, of the histological subtypes of HPV-related penile squamous cell carcinomas, the highest prevalence of HPV was reported to be 84% in basaloid squamous cell carcinoma, followed by 75.7% in warty-basaloid squamous cell carcinoma.

There is little information in the literature regarding the relationship between HPV and tumor grade in penile squamous cell carcinoma. However, tumor grade and lymph node metastasis are the most important prognostic factors for disease-free survival [30]. Hölters et al. observed an association between HPV and histological grade in their study, reporting that the prevalence of HR-HPV types was higher in poorly differentiated grade 3 tumors [31]. Similarly, a recent study also demonstrated a positive correlation between HR-HPV and high-grade penile squamous cell carcinoma, especially in HPV-related basaloid and warty-basaloid carcinomas [32]. In light of these findings, it can be speculated that unlike cervical, anal, and oropharyngeal carcinomas, the presence of HPV may be a negative prognostic factor in penile carcinomas.

Circumcision is known to be an important protective factor against penile cancer, though it is not clear whether circumcision protects against HPV infection. Van Howe et al. determined that the prevalence of HPV did not differ between circumcised and uncircumcised men but reported a longer HPV clearance time in men who were uncircumcised [33]. In a study by Lu et al., viral clearance was higher for HR-HPV types in circumcised men than uncircumcised men, while there was no significant difference between the two groups in the clearance of LR-HPV types [34]. Gray et al. showed that circumcision reduced transmission of both HR-HPV and LR-HPV types [35]. In the latest report from Davis et al., male circumcision was found to reduce HR-HPV viral load in female partners, leading the authors to recommend circumcision for the reduction of HPV infection in both men and women [36].

## 3. Bladder cancer and HPV

Bladder cancer is the fourth most common malignancy in men and the eighth most common in women, causing an estimated 400,000 new cases and 186,000 deaths per year worldwide [37]. Important known risk factors include age,

ethnicity, smoking tobacco, chemical exposure (aromatic amines and hydrocarbons), and in some regions, schistosomiasis. Histologically, more than 90% of bladder cancers are urothelial cell carcinoma. The incidence of bladder cancer has shown a marked increase over the last three decades, and despite extensive efforts, it is still difficult to predict tumor progression, optimal treatment, and final clinical outcomes [38]. Over the same period, the relationship between HPV and bladder cancer has also been investigated and two hypotheses have been proposed to explain their association. The first hypothesis is that the urethra is the first point of contact during sexual transmission of the virus and serves both as a viral reservoir and direct connection between the urinary bladder and genital area, possibly providing a natural route of viral migration. The second hypothesis is based on the natural epithelial tropism of HPV [39]. In a pooled meta-analysis of 2855 cases in 52 studies, the prevalence of HPV in bladder cancer samples ranged between 0% and 100% [40]. However, this extremely wide range of HPV prevalence is open to interpretation. In the past, extracting DNA from FFPE tissue was a challenge, and most publications stating that there is no relationship between HPV and bladder cancer were conducted in FFPE tissues using older technologies in HPV research [41–43]. Li et al. emphasized this in their meta-analysis, noting that the prevalence of HPV was higher in studies using fresh tissue than in studies using FFPE and suggesting that FFPE tissues may yield false-negative results. In the same meta-analysis, it was also determined that the HPV prevalence in patients with bladder cancer was 16.88% and HPV types 16 and 18 were the major types detected [40]. Another meta-analysis by Jimenez-Pacheco et al. including 20 controlled studies of HPV-DNA revealed a significant association between HPV presence and bladder cancer, with a pooled odds ratio (OR) of 2.19 (95% CI: 1.40–3.43) [44]. Most recently, Sarier et al. conducted a case–control study using fresh tissue and demonstrated a strong correlation between urothelial carcinoma of the bladder and HPV infection (OR: 4.24, 95% CI: 1.63–12.34) [45].

Although squamous cell carcinoma of the bladder accounts for 2% of all bladder cancers, scientific interest in its relationship with HPV has persisted due to its histological structure [46]. However, because it is rare cancer, published series are small and studies have yielded conflicting results [47–49]. In a recent study by Collins et al. investigating the presence of p16 and HR-HPV in 33 patients with squamous cell carcinoma of the bladder using in situ hybridization (ISH), P16 expression was detected in 28% of the patients, while HR-HPV was not detected in any patient [50].

Tumor grade is an important factor in terms of bladder cancer progression. However, the literature also includes conflicting reports regarding the relationship between tumor grade and HPV. An association between HPV and low-grade tumors was reported by Tenti et al. [51], while an association with high-grade tumors was observed by Cai et al. [52]. In contrast, Sarier et al. observed no significant correlation between tumor grade and HPV in their study [45].

Tumor recurrence is an important and common event in bladder cancer. Exposure to infectious agents is recognized as one of the risk factors for urological malignancies, especially those with a high tumor recurrence rate [53]. Although the literature data on the relationship between HPV and bladder tumor recurrence are limited, the results are impressive and largely consistent among studies. Badawi et al. reported a significant association between HPV type 16 and tumor recurrence rate [54]. Moghadam et al. found that HPV was significantly associated not only with tumor recurrence but also with tumor stage [55]. In their 2-year follow-up study, Sarier et al. observed higher tumor recurrence rates in patients with bladder tumors associated with HPV-DNA [56].

## 4. Prostate cancer and HPV

Prostate cancer is the second most common cancer and a fourth most common cause of cancer deaths in men and therefore poses a serious burden worldwide [57]. The most important risk factors are age over 50 years, ethnicity, family history of prostate cancer, diet, and infection, although the available data are limited. There is evidence to suggest that chronic inflammation of the prostate is quite common in adults and may directly contribute to the development and progression of prostate malignancy [58]. This inflammation forms the basis of the main hypothesis for the relationship between HPV and prostate cancer. Epithelial damage caused by chronic inflammation may result in loss of tolerance to normal prostate-associated antigens, thereby triggering a sustained autoimmune reaction [59]. The immune evasion strategies of viruses contribute to persistent viral infection and induce chronic inflammation through cytokines. This presents a mechanism by which HPV may trigger chronic inflammation of the prostate glandular epithelium [59].

In fact, numerous studies have investigated the relationship between infection and prostate cancer. Taylor et al. demonstrated a significant association between prostate cancer risk and infection with any sexually transmitted disease-related agents in their meta-analysis of 29 studies including 6022 prostate cancer patients and 7320 control cases [60].

As with bladder cancer, a wide range has been reported for the prevalence of HPV in prostate cancer (0–100%). Again, methodological approaches are the major limitation. The use of serology-based tests for HPV detection is controversial. These tests identify general exposure to HPV infection but are not able to identify HPV infection in specific organs, such as the prostate. Although ISH is an effective method for detecting HPV, PCR is considered the gold standard [61]. By using multiple degenerate primary pairs in the amplification reaction, the PCR assay can easily be adapted to detect most HPV types associated with anogenital tract disease. A recent meta-analysis by Lawson et al. is valuable in this regard. In the part of their study evaluating 14 serology-based studies including 5149 prostate cancer patients and 7794 benign prostate controls, HPV antibodies were detected in 20% of both groups. Based on this finding, they stated that when evaluated serologically, there is no difference in the prevalence of HPV antibodies between men with and without prostate cancer. However, in another part including only PCR-based studies conducted after the year 2000 (including 1071 prostate cancer patients and 1103 benign prostate controls), the HPV prevalence was found to be 21.6% in prostate cancer patients and 6.7% in controls ($p = 0.001$) [17]. The authors concluded from this meta-analysis that HR-HPV has a causal role in prostate cancer. Other meta-analyses conducted in the last decade using different parameters also showed similar results. In a meta-analysis by Sasidharanpillai et al. evaluating the relationship between HPV and oropharyngeal and anogenital cancers based on recent molecular studies (nine studies, 876 men), significant HPV association was reported in prostate cancer tissue specimens (19%, CI: 10–29%) [7]. Yin et al. also determined that HPV was associated with an increased risk of prostate cancer (OR: 2.27) in their meta-analysis of 24 case–controlled studies including 971 prostate cancer and 1085 benign prostate patients [62]. In a meta-analysis of 26 tissue-based case–control studies conducted by Yang et al., the prevalence of HPV infection was found to be 18.93% and overall HPV positivity in prostate tissues was associated with a significantly higher risk of prostate cancer (OR: 1.79, 95% CI: 1.29–2.49) [57]. Moghoofei et al. reported that the two major genotypes associated with prostate cancer were HPV types 16 and 18, respectively [63].

Gleason score is an important pathological parameter for the prognosis of prostate cancer. However, the data on the relationship between HPV and Gleason score are controversial. Singh et al. reported that Gleason score was high (≥ 8) in 74% of patients with HPV-related prostate cancer ($p = 0.003$), whereas Moghadam et al. found no significant difference in Gleason score in his patient group [64].

Glenn et al. published an interesting study regarding HPV and prostate cancer. The researchers identified HR-HPVs in the benign prostate tissue specimens of patients who developed prostate cancer 1–10 years later. A remarkable finding from their study was that E7 oncoprotein expression was detected in 82% of samples at the time of benign prostatic hyperplasia diagnosis but only 29% of prostate cancer specimens were from the same patients. The authors suggested that HPV has an oncogenic role in the early stage of prostate tumorigenesis [65].

## 5. Kidney cancer and HPV

Kidney cancer is responsible for an estimated 2% of global cancer diagnoses and deaths, and its global burden is expected to increase [66]. The two most common subtypes are renal cell carcinoma and urothelial cell carcinoma. However, there are few studies on its possible association with HPV in the literature, and based on the evidence to date, the relationship between kidney cancers and HPV remains unclear. In a PCR-based study of 28 patients with kidney cancer, Grce et al. did not detect HPV in any patient [67]. Similarly, Hodges et al. did not detect HPV in any of their 62 patients with renal tumors by using ISH, leading the authors to conclude that HPV appears to have no oncogenic role in benign or malignant renal tumors [68]. In contrast, in their small case–control study (49 renal cell carcinoma cases, 16 controls), Salehipor et al. determined using PCR that the prevalence of HPV was 14.3% in the patient group and 0% in the control group [69]. Kamel et al. evaluated 56 patients with renal cell carcinoma using ISH and determined the prevalence of HPV to be 52% [70]. Although this is a remarkable finding, the fact that the study was not case-controlled can be seen as an important limitation. More recently, Farhadi et al. investigated the presence of HPV in 122 patients with renal cell carcinoma and demonstrated HPV association in 30.3%, with HPV type 18 being the most common type identified [71]. In terms of the case series, an important study by Koury et al. based on the Cancer Genome Atlas Database, which includes 3775 malignant neoplasms, indicated that there was no relationship between HPV infection and kidney cancer [72].

## 6. Testicular cancer and HPV

Although testicular cancers represent only 1% of all malignancies in men, they are the most common organ malignancy in men between 20 and 40 years of age [73]. The main known risk factors for testicular cancer are undescended testes, a family history of testicular cancer, and the presence of germ cell cancer in the opposite testicle [74]. While testicular tumors are still relatively uncommon, there has been an unexplained increase in their incidence over the last two decades [75]. Researchers have recently focused on the potentially important role of inflammation in the formation and progression of testicular cancer, as seen in the pathogenesis of other cancers [76]. In fact, the relationship between viral infections and testicular cancer was first investigated approximately 40 years ago [77]. Unfortunately, few studies have been published on the relationship between HPV

and testicular cancer in the intervening period. In their study of 39 testicular cancer and 48 control cases, Strickler et al. determined the prevalence of HPV to be 5% in testicular cancer specimens and 4% in the control group [78]. A PCR-based study evaluating the presence of HPV in 19 testicular cancer patients and one control case was not able to demonstrate a relationship between HPV infection and testicular cancer [79]. Similarly, Bertazzoni et al. reported that HPV was not detected by PCR in any specimens from 61 seminomas and 23 control cases [80]. Finally, in a meta-analysis of 20 studies and 265,057 patients to evaluate the relationship between testicular cancer and viral infections, Garolla et al. determined that testicular cancer was not associated with HPV, cytomegalovirus, or parvovirus b-19 infections, whereas EBV and HIV infections were significantly associated with a higher risk of developing testicular germ cell tumors (OR: 7.38, 95% CI: 1.89–28.75, OR: 1.71, 95% CI: 1.51–1.93, respectively) [81]. An important point to keep in mind when evaluating the relationship between testicular germ cell neoplasms and HPV is that HPV shows epithelial tropism, and germ cell neoplasms of the testicle do not arise from the epithelium.

## 7. Conclusion

The link between penile cancers and HPV is now well known. In this regard, the significant relationship between HPV and tumor grade should be taken into consideration and further studies should be conducted to elucidate the prognostic significance of HPV presence in penile cancers. The association between HPV and urothelial carcinoma of the bladder has become clearer in recent years with the use of molecular tests in HPV diagnosis and the findings of studies conducted with fresh tissue. In bladder cancer, the significant relationship between HPV and tumor recurrence should be kept in mind. The development of PCR technology has had a major impact on our understanding of the link between HPV and prostate cancer. Compared to previous serology-based studies, the results obtained using nucleic acid amplification tests such as PCR are noteworthy and show that a reevaluation of this relationship is needed. A key point here may be studied on the relationship between HPV and inflammation in the pathophysiology of prostate cancer. In contrast, it is premature to talk about an association between kidney cancer and HPV based on the limited evidence available today. Case-controlled studies with larger patient series will be elucidating. The existing evidence regarding testicular cancer indicates no association with HPV infection.

## Abbreviations

| | |
|---|---|
| CI | Confidence interval |
| EBV | Epstein–Barr virus |
| FFPE | Formalin-fixed, paraffin-embedded |
| HR | High-risk |
| HPV | Human papillomavirus |
| ISH | in situ hybridization |
| LR | Low-risk |
| OR | Odds ratio |
| PCR | Polymerase Chain Reaction |
| PIN | Penile intraepithelial neoplasia |
| Rb | Retinoblastoma |

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