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Human Papillomavirus and Prostate Cancer: A Review of Epidemiological, Molecular, and Preventive Insights

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Abstract **Review Article**

This review shows the possible link between Human Papillomavirus (HPV) and prostate cancer, combining evidence from epidemiological, molecular, and clinical studies. High risk HPV types, particularly HPV 16 and HPV 18, have been seen in normal, benign, and malignant prostate tissues, which can suggest a potential oncogenic role via E6 and E7 proteins and interactions with APOBEC enzymes. Detection methods like PCR, in situ PCR, genome sequencing, and immunohistochemistry, confirm HPV presence in prostate tissues globally. Unlike other pathogens linked to prostate cancer, HPV is vaccine preventable, underscoring the importance of vaccination campaigns and safe sexual practices. Epidemiological data support a significant association (22.6% HPV prevalence in prostate cancers vs. 8.6% in benign tissues), inconsistencies in detection methods and regional HPV subtype variations highlight the need for standardized approaches and large-scale studies. This review highlights HPV's role in prostate oncogenesis, urges for enhanced public health strategies, and identifies research gaps to guide future investigations.

Keywords: Human Papillomavirus (HPV), Prostate Cancer, HPV 16 and 18, E6 and E7 Proteins, HPV Vaccination.

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INTRODUCTION

Human Papillomavirus (HPV) is a naked, double stranded DNA virus from the *Papillomaviridae* family, known for causing epithelial lesions and cancers (cervical, anal, and oropharyngeal) (Bradbury *et al.*, 2019). Globally, HPV is a recurring sexually transmitted infection, with about 80% of sexually active individuals exposed to getting it (CDC, 2024). Recent studies propose that high risk HPV, mainly HPV 16 and HPV 18, may add to prostate cancer development, a theory that was supported by their presence in prostate tissues (Lawson & Glenn, 2020). Unlike other pathogens linked to prostate cancer, such as Epstein-Barr virus and *Propionibacterium* acnes, HPV is the only vaccine preventable infectious agent, emphasizing the importance of vaccination campaigns (Lawson & Glenn, 2020). Low risk HPV subtypes cause benign conditions like genital warts, while persistent high risk HPV infections are associated with premalignant and invasive lesions in anogenital and oropharyngeal regions (Ntanasis *et al.*, 2020). In prostate cancer, high risk HPVs may commence oncogenesis directly through oncogenic proteins E6 and E7 or indirectly via contact with APOBEC enzymes, potentially collaborating with other pathogens (Lawson & Glenn, 2020). This complex role identifies and differentiates HPV's involvement in prostate cancer from its recognized mechanisms in cervical cancer.

Prognosis of Human Papillomavirus

Most HPV infections (90%) resolve spontaneously within two years without symptoms, but asymptomatic carriers can still transmit the virus (Jemal *et al.*, 2019). Long lasting infections with high-risk HPV subtypes can lead to serious conditions, including genital warts, recurrent respiratory papillomatosis, and genital cancers (head, neck, throat) (Jemal *et al.*, 2019). Low risk HPV types which cause warts do not usually lead to cancer. HPV related cancers often remain asymptomatic until advanced stages, underscoring the need for regular screenings to improve early detection and survival rates (CDC, 2024).

Pathogenesis of Human Papillomavirus

Papillomaviruses have co evolved with their hosts, showing high specificity for surface tissues (Van Doorslaer *et al.*, 2018). The Papillomaviridae family

includes alpha papillomaviruses (α-HPV), linked to mucosal cancers; beta papillomaviruses (β-HPV), associated with skin tumors in immunosuppressed individuals; and gamma, mu, and nu-papillomaviruses, primarily causing subclinical or skin lesions (Van Doorslaer *et al.*, 2018). Cancerous α-HPV types (HPV 16 and HPV 18), drive oncogenesis through E6 and E7 proteins, which disrupt cell cycle regulation by targeting TP53 and RB1, respectively (Janiszewska *et al.*, 2024). HPV's 50 nm non enveloped capsid contains a double stranded DNA genome of 5,748-8,607 nucleotides, infecting a lot of species (Van Doorslaer *et al.*, 2018).

Prostate gland

Prostate, a walnut-sized (approximately 20 grams) male reproductive organ, surrounds the urethra below the bladder, producing seminal fluid to nourish and transport sperm, while also aiding in urine control and hormone production (Leslie *et al.*, 2022).

Prostate Cancer

Prostate cancer arises from uncontrolled cell growth in the prostate gland. It is the second most recurring cancer in men around the world, with around 1.4 million new cases and 375,000 deaths every year (Ferlay *et al.*, 2019). Prostatic intraepithelial neoplasia (PIN) is linked with an increased cancer risk. Prostate cancer types include adenocarcinoma, transitional cell carcinoma, neuroendocrine, basal cell, sarcoma, and castration-resistant forms (Marijike, 2020). Patients present with localized or advanced disease, with early detection improving treatability (Sekhoacha *et al.*, 2022).

Pathogenesis of Prostate Cancer

Prostate cancer has a complex cellular pathology, which involves multiple genes, environmental factors like diet, and inflammation (Hughes *et al.*, 2023). HPV may influence through direct oncogenic effects or indirect processes, such as APOBEC enzyme malfunction, differentiating its role from other cancers (Lawson & Glenn, 2020).

Prevalence of Prostate Cancer

Prostate cancer which is a recurring cancer affecting men over age 65, particularly in developed regions like Australia, North America, and Europe, with a 41% increase in incidence since 1993 due to PSA testing (Bray *et al.*, 2018). Incidence rises with age, though aggressiveness often decreases in older patients (Kaiser *et al.*, 2019).

Clinical Diagnosis of Prostate Cancer

Early-stage prostate cancer is highly treatable, but many cases are diagnosed at advanced stages (Cimadamore *et al.*, 2021). Diagnosis relies on prostate biopsy following abnormal PSA levels or digital rectal examination, supplemented by MRI or health screenings (Sekhoacha *et al.*, 2022).

Risk Factors

Prostate cancer risk increases with age (45-60 years), obesity, high fat diets, ethnicity, and family history of prostate or related cancers (Leslie *et al.*, 2022). Hereditary association to breast, ovarian, or cervical cancers and increased testosterone levels are also linked (Cimadamore *et al.*, 2021; Kaiser *et al.*, 2019). HPV's potential role shows the need for vaccination to reduce this modifiable risk factor (Morka *et al.*, 2022).

HPV AND CANCER DEVELOPMENT

Mechanisms of HPV Oncogenesis

HPV, which is among the most recurring sexually transmitted infections around the world, with around 80% of sexually active individuals exposed to it (CDC, 2024). While the immune system clears most HPV infections, infections with high-risk (HPV 16 and 18), can escape immune control and drive oncogenesis (Tornesello & Buonaguro, 2020). The oncoproteins E6 and E7, encoded by the viral genome, are key players in this process by targeting cellular pathways for cell cycle regulation and tumor suppression (Janiszewska *et al.*, 2024).

E6 attaches to the tumor suppressor protein TP53, which triggers its breakdown via E6AP ligase, which leads to cell cycle regulation and reduces proapoptotic protein expression, like BAX (Fischer, 2017; Janiszewska et al., 2024). Similarly, E7 binds to RB1, releasing the E2F/DP transcription factor, which is normally inactive in the G1 phase, mimicking physiological RB1 phosphorylation and driving G1–S transition, cell proliferation, and oncogenesis (Rubin, 2013).

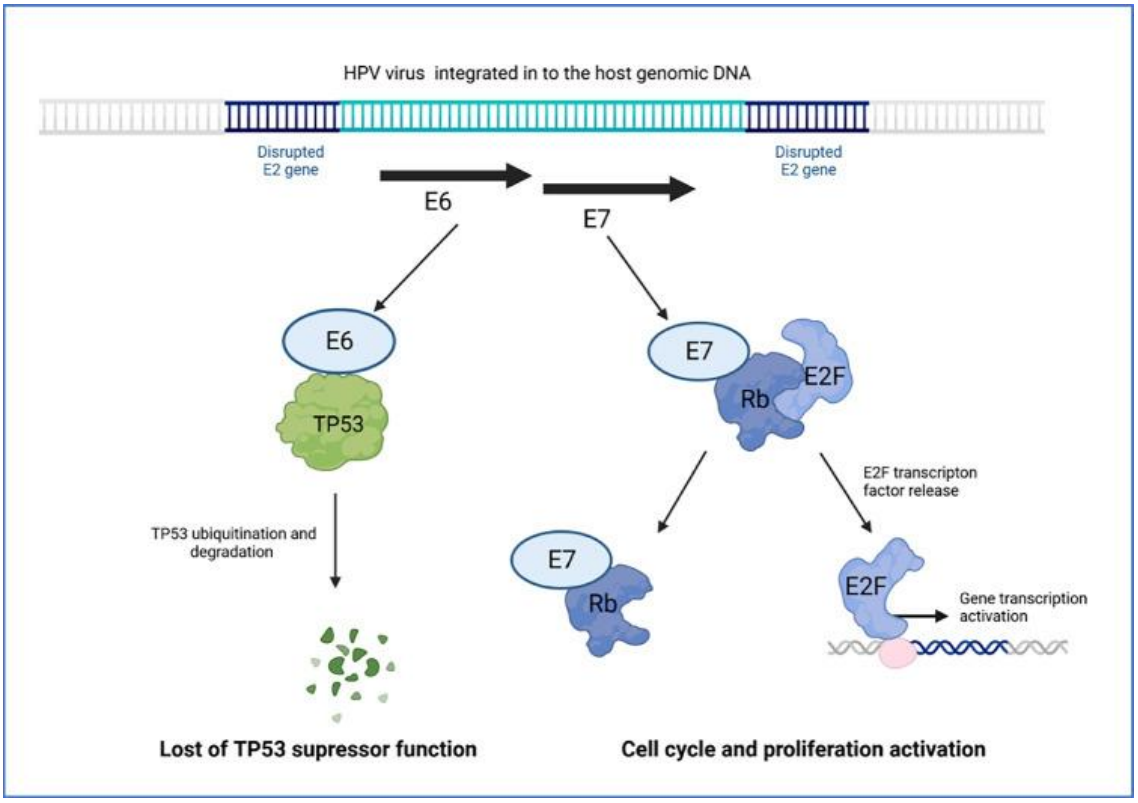

Fig 1: Activity of the E6 and E7 proteins driven by HPV 16 (Janiszewska *et al.,* 2024).

Human Papillomavirus related Cancers.

Persistent high-risk HPV infections cause cancers in infected tissues, they are responsible for most cases of cervical and ana cancers (90%), a lot cancers of the vagina and vulva (70%), 60% of penile cancers, and 60-70% of oropharyngeal cancers, often exacerbated by tobacco and alcohol use (CDC, 2024; Saraiya *et al.,* 2015). Cervical intraepithelial neoplasia (CIN) may advance to cervical cancer or regress, depending on viral and host factors, with no verified biomarkers to predict development (Taguchi *et al.,* 2020). Anal cancer studies have examined present tumor cells to track treatment and relapse, highlighting HPV's role in disease progression (Carter *et al.,* 2020). Oropharyngeal cancer, distinct from oral cavity cancer, is a major HPV related head and neck cancer (NCI, 2023).

EPIDEMIOLOGICAL AND MOLECULAR EVIDENCE FOR HPV IN PROSTATE CANCER

Direct and Indirect Oncogenic Roles

Multiple pathogens, including HPV, Epstein-Barr virus, and *Propionibacterium acnes*, have been detected in prostate cancer tissues (Tortorec *et al.,* 2020). High-risk HPVs exert both direct and indirect oncogenic effects in prostate cancer.

Direct evidence includes the presence of koilocytes large cells with perinuclear halos indicative of early HPV infection in benign and malignant prostate tissues, similar to early cervical oncogenesis (Medel-Flores *et al.,* 2018).

Indirectly, HPV may alter APOBEC3B enzymes, which normally protect against viral infections, this leads to host genome instability and cancer progression (Cheng *et al.,* 2018). HPV's role in prostate cancer likely involves early commencement, with reduced influence towards the later stages, and may require inflammatory, apoptotic, and angiogenic processes (Sadri *et al.,* 2020).

Evidence from Epidemiological Studies.

Epidemiological studies show a clear link between high-risk HPV and prostate cancer, though findings vary due to methodological differences. A systematic review of 26 case-control studies found high risk HPV in 22.6% of 1,284 prostate cancers compared to 8.6% of 1,313 benign or normal prostate tissues ($p = 0.001$) (Lawson & Glenn, 2020). Another meta-analysis reported a positive association (OR = 1.281, $p = 0.026$), with HPV-16 more prevalent in prostate tumors (Moghoofei *et al.,* 2019). A combined odds ratio of 2.27 (95% CI = 1.40-3.69) in HPV positive men further supports this link (Yin *et al.,* 2017). A study by Emerson et al. (2023) had inconclusive results on HPV L1 protein in prostate tissues, maybe due to small sample volume, low viral load, or PCR primers lacking high sensitivity.

Table 1: Reviews and Meta Analyses on HPV and Prostate Cancer

Author (Reference)	Studies	Findings
Russo *et al.*, 2020	30	Increased odds of prostate cancer in HPV 16 positive men (OR = 1.37, $p < 0.01$), but not HPV 18.
Lawson & Glenn, 2020	26	High-risk HPV in 22.6% of prostate cancers vs. 8.6% of benign tissues ($p = 0.001$).
Yin *et al.*, 2017	24	Combined Odds Ratio = 2.27 (95% CI = 1.40–3.69) for prostate cancer in HPV-positive men.
Moghoofei *et al.*, 2019	24	Positive association between HPV and prostate cancer (OR = 1.281, $p = 0.026$), higher HPV-16 incidence.

(Morka *et al.*, 2022)

No. *– Number,* ***HPV****- Human Papillomavirus,* ***p****-probability,* ***CI****-confidence interval.*

Detecting HPV in Prostate Tissues.

Detecting HPV in prostate tissues involves identifying viral DNA, RNA, or proteins using various techniques (Lawson & Glenn, 2020). Here are some methods used

- **a.** Polymerase Chain Reaction (PCR): This is the most common method, PCR amplifies HPV DNA (e.g., L1 or E6/E7 genes) for detection (Whitaker et al., 2013).
- **b.** In Situ PCR: Reduces contamination risks by localizing HPV DNA in formalin fixed tissue sections (Whitaker *et al.*, 2013).
- **c.** Genome Sequencing: Genome Sequencing looks at all the DNA in a tissue sample to find Human Papillomavirus (Glenn *et al.*, 2017). It is not as good as PCR as it has shown that gene sequencing techniques are unlikely to detect viruses with very low concentrations in cancers as compared to techniques in PCR (Vinner *et al.*, 2015).
- **d.** Immunohistochemistry: Detects HPV proteins like E7, found in 82% of benign prostate specimens and 29% of prostate cancers (Pascale *et al.*, 2013). Discrepancies in detection rates may stem from variable viral loads, tissue preparation, or assay sensitivity, necessitating standardized protocols (Lawson & Glenn, 2022).

Human Papillomavirus Vaccines

As of 2021, 107 countries have implemented HPV vaccination initiatives, widely implemented in developed countries like Australia but limited adoption in resource limited countries (Bruni *et al.*, 2021). Three vaccines: Cervarix R (HPV 16, 18), Gardasil R (HPV 6, 11, 16, 18), and Gardasil R9 (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) are safe and effective, with Gardasil 9 as the current standard (Kamolratanakul & Pitisuttithum, 2021). These vaccines are advised for boys to reduce the risk of genital warts and HPV related cancers, but it is still unclear if they work in the long term against prostate cancer, which can take decades to develop (Lawson & Glenn, 2022). Cost effectiveness analyses suggest that gender-neutral vaccination could reduce HPV related cancer burdens, including prostate cancer, in high-risk populations (Bruni *et al.*, 2021).

Limitations and Future Research

The current understanding of HPV's role in prostate cancer is limited due to inconsistent detection techniques, like variations in PCR sensitivity and serology issues (Whitaker *et al.*, 2013), small sample sizes in some studies, such as those failing to detect significant HPV presence (Emerson *et al.*, 2023), and a lack of long term data on the effectiveness of vaccines (Lawson & Glenn, 2020). Variations in HPV subtype prevalence across regions contribute to heterogeneous findings, as seen in differing detection rates globally (Yin *et al.*, 2017).

Future research should focus on standardizing detection protocols, such as improving PCR and immunohistochemistry techniques (Lawson & Glenn, 2022), and conducting large scale epidemiological studies in diverse populations to address regional disparities (Moghoofei *et al.*, 2019). Evaluating the long-term impact of HPV vaccination, such as Gardasil 9, on prostate cancer incidence is critical, given the unknown duration of vaccine efficacy (Lawson & Glenn, 2020). Integrating HPV testing into prostate cancer screening could enhance early detection (Morka *et al.*, 2022), while cost-effective vaccination strategies in low resource settings are needed to address global disparities, particularly in developing countries with low vaccine coverage (Bruni *et al.*, 2021).

Recommendations.

Based on the findings of this review, the following recommendations are proposed to advance research and public health strategies concerning HPV and prostate cancer:

i. Conduct Large-Scale Epidemiological Studies: Large scale, multi center epidemiological studies should be prioritized to provide robust evidence of the link between HPV and prostate cancer, particularly in diverse populations to address

regional variations in HPV subtype prevalence which should include long term studies to assess the temporal associations between HPV infection and prostate cancer development.

ii. Enhance Public Health Education: Comprehensive health education campaigns should be ran to teach people about safe sex, condom use and reducing sexual partners, to reduce HPV transmission. These campaigns should target both men and women, emphasizing HPV's potential role in prostate cancer and other cancers to increase awareness and promote proactive preventive measures.

iii. Improve Detection Methods: Focus should be placed on normalizing HPV detection methods, such as PCR and immunohistochemistry, in order to ensure consistent and accurate results across studies. Developing high sensitivity, prostate specific HPV assays and integrating them into routine prostate cancer screening protocols could help in early detection.

iv. Promote HPV Vaccination Awareness: Public health initiatives should educate communities about HPV related diseases, including their potential link to prostate cancer, to increase vaccine uptake. Gender neutral vaccination programs should be expanded, especially in low resource settings, to address global disparities in vaccine coverage.

CONCLUSION.

This review shows a strong link between Human Papillomavirus (HPV) and prostate cancer, with high-risk HPV types detected significantly more often in cancerous prostate tissues than in non-cancerous ones. The virus's produces proteins that interfere with normal cellular functions, causing both direct and indirect roles in prostate cancer development, which works differently from how HPV affects other cancers like cervical cancer. Various detection methods have confirmed HPV's presence in prostate tissues across diverse populations, though inconsistencies underscore the need for standardized approaches. HPV is the only virus that is linked to prostate cancer that can be prevented with vaccines like Gardasil 9, which targets the high-risk HPVs, but it is still not certain how these vaccines work in the long term in preventing prostate cancer because the cancer takes years to develop. This review calls for a worldwide effort to enhance HPV vaccination coverage, input HPV testing into prostate cancer screening, and address issues in low resource places. By improving the test methods, studying the vaccine effectiveness, and strengthening public health strategies, we can reduce HPV related prostate cancer and improve men's health worldwide.

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