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Human papillomavirus infection among men and its role in the etiology of prostate cancer: A prospective study

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Introduction Human papillomavirus (HPV) has been implicated in the pathogenesis of several malignancies, including cervical, penile, and oropharyngeal cancers. Its role in prostate cancer (PCa), however, remains uncertain. The embryological structure known as the prostatic utricle – sharing histological features with the cervix – has been proposed as a potential reservoir for HPV in males. The aim of this study was to evaluate the presence of HPV DNA in the prostatic utricle and its possible association with prostate cancer.

Material and methods A prospective study was conducted between 2019 and 2022 among 50 men (median age: 64 years) undergoing radical laparoscopic prostatectomy for PCa. Biological samples were obtained from the prostatic utricle in all patients. Additionally, the population was randomly divided into two subgroups. In the first subgroup, swabs were collected from under the foreskin and the external urethral meatus. In the second subgroup, washings were obtained from random intraprostatic sites. All samples were analyzed for HPV DNA using polymerase chain reaction (PCR) and genotyping.

Results The HPV DNA was not detected in samples from the prostatic utricle or random prostate locations (0/50; 0%). Positive HPV DNA was found in two cases (7.69%) from external genital swabs. Both patients had high-risk PCa, reported no current sexual activity, and presented with relatively small prostate volumes.

Conclusions The absence of HPV DNA in prostatic and utricular tissue does not support a direct causal relationship between HPV infection and prostate cancer. However, a potential indirect role – such as promotion of chronic inflammation – cannot be excluded. These findings highlight the importance of HPV vaccination in both sexes, as well as the need for further research into the long-term impact of the virus on prostate carcinogenesis.

Key Words: human papillomavirus infections ‹› prostatic neoplasms ‹› prostatectomy ‹› polymerase chain reaction ‹› urogenital system ‹› sexually transmitted diseases ‹› viral

INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed malignant tumor in men in Poland, representing a significant challenge in uro-oncology. It is characterized by rising incidence and mortality rates, making it the second leading cause of cancer-related deaths in men, following lung cancer [1]. The increase in diagnoses is attributed to factors such as an aging population, the widespread use of prostate-specific antigen (PSA) testing, and greater public awareness of cancer-related diseases [2].

The incidence of prostate cancer varies geographically, ethnically, and environmentally. African Americans have a 2.5 times higher risk of developing PCa compared to Caucasians, while Asian populations

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exhibit the lowest incidence rates [3–5]. Hereditary prostate cancer typically manifests earlier in life; however, it does not necessarily follow a more aggressive course [6, 7]. Other important risk factors include diabetes, hypercholesterolemia, dietary deficiencies in micro- and macronutrients, and sexually transmitted infections. Among pathogens, only gonorrhea has been confirmed to be associated with the development of prostate cancer [3, 8]. Moreover, a recently published meta-analysis (2024) identified overweight and obesity as additional risk factors for PCa [9].

Interestingly, studies have shown that frequent ejaculation (over 21 times per month) can reduce the risk of prostate cancer by 20% [10, 11].

Chronic inflammation and infections of the genitourinary tract are also potential etiological factors for prostate cancer. By inducing oxidative stress and generating reactive oxygen species, they may lead to DNA damage and the selection of mutated cells, fostering the development of prostatic intraepithelial neoplasia (PIN) and malignant transformation [12]. In most patients, prostate cancer develops slowly, with a prolonged preclinical phase. At diagnosis, cancerous lesions are typically small, organ-confined, and of low-grade malignancy. However, over time, the disease may progress locally and develop distant metastases [13–16].

Human papillomavirus (HPV) is one of the most common sexually transmitted pathogens, affecting up to 80% of sexually active individuals [17]. Chronic high-risk HPV (HR-HPV) infection in women is strongly associated with cervical cancer, a relationship confirmed by research that earned Prof. Harald zur Hausen the Nobel Prize in 2008 [18]. In men, HPV is recognized as a risk factor for penile, anal, and oropharyngeal cancers. HPV DNA has been detected in 70–100% of penile intraepithelial neoplasia (PeIN) cases and in 40–50% of invasive penile cancers. The most frequently identified HPV types are the oncogenic types 16 (72%) and 18 (6%) [19]. A geographic correlation between penile and cervical cancers suggests a shared etiology among sexual partners [20].

The role of HPV in the development of prostate cancer remains the subject of ongoing research. Studies, primarily based on histopathological analysis of prostate tissue and serological tests, indicate a possible correlation between HPV and PCa [21]. Chronic prostatitis caused by HPV may initiate oncogenic processes by generating reactive oxygen species, which damage DNA and inhibit anti-cancer mechanisms. Inflammatory conditions in the prostate occur in approximately 17% of PCa cases [22, 23].

Additionally, a meta-analysis suggested that sexually transmitted infections, including HPV, may play a significant role in the initiation of PCa [24]. Research by Russo et al. [25] indicated a strong association between HPV type 16 and increased PCa risk, although no such correlation was found for HPV type 18. Furthermore, HPV DNA has been detected in the semen of approximately 10% of men, predominantly type 16, suggesting a potential role of HPV in prostate carcinogenesis [26]. While HPV is a well-established key risk factor for cervical cancer, its role in prostate cancer development requires further investigation [27, 28].

The aim of this study was to:

- examine the presence of human papillomavirus (HPV) DNA in the prostatic utricle of men with prostate cancer who underwent radical laparoscopic prostatectomy;
- identify HPV infection within the study group and evaluate the correlation between HPV infection and the occurrence of prostate cancer.

MATERIAL AND METHODS

Study group characteristics

The study prospectively included 50 men who underwent radical laparoscopic prostatectomy in our clinic between 2019 and 2022 due to previously diagnosed prostate cancer.

During the study, clinical data were collected, including patient age, sexual activity, PSA levels, smoking status, presence of current urinary tract infections, and prostate MRI (mpMRI) findings assessing tumor extent and prostate volume. Additionally, clinical staging of prostate cancer was assessed based on physical examination, histopathological evaluation of tumor advancement in the resected prostate, and the morphology of the prostatic utricle in the postoperative specimen.

In the present study, a population of 50 men who underwent radical laparoscopic prostatectomy for prostate cancer were randomly divided into two subgroups, based on the scope of biological material collection for HPV DNA analysis. In all patients, a swab was taken from the prostatic utricle. Additionally, one subgroup underwent swabbing from the foreskin and external urethral meatus, while the other subgroup underwent sampling of washings from random prostate sites (Figure 1).

First subgroup (26 patients): Additional tests for HPV DNA were performed on swabs taken from under the foreskin and the external urethral meatus.

In the second subgroup (n = 24), testing for the presence of HPV DNA was performed on material

collected during radical laparoscopic prostatectomy. Washout samples were obtained from the interstitial structures of the prostate by puncturing with a fine needle during surgery. The material was collected both from randomly selected areas of the prostate and – in cases where a tumor was macroscopically visible – from the immediate surroundings of the lesion. After the puncture, a small volume of sterile saline solution (0.9% NaCl) was injected, which was then aspirated after gentle rinsing into a sterile syringe and submitted for PCR analysis. The aim of this approach was to increase the likelihood of detecting HPV presence, both in cancerous tissue and in seemingly unaffected prostatic parenchyma.

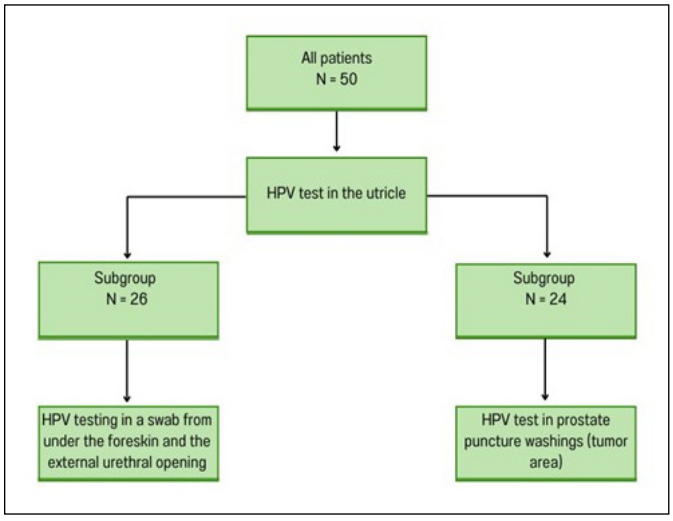

Figure 1. *Flowchart of the study. Division of the entire population into specific study groups.*

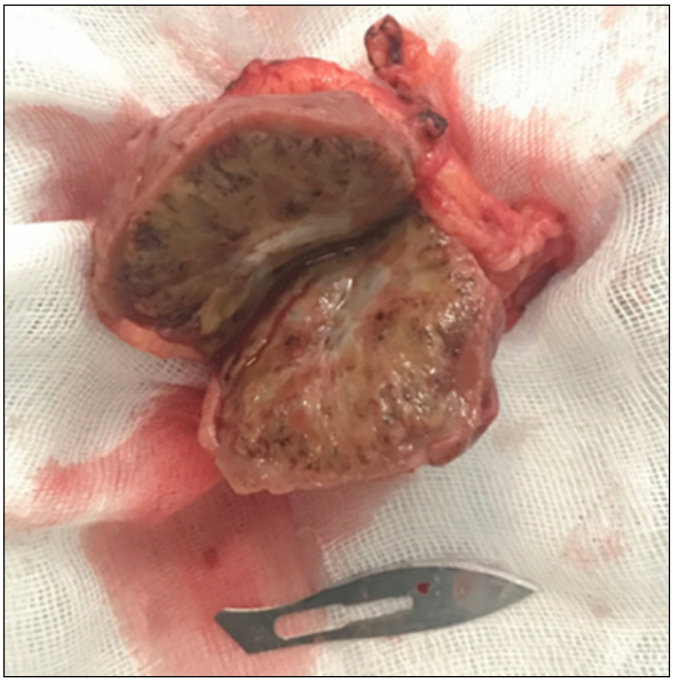

Figure 2. *Sectioned prostate. Exposure of the posterior wall of the urethra. Original material.*

Initially, only patients reporting sexual activity (38; 76%) were included in the study

However, individuals not currently sexually active (12; 24%) were later included, considering data suggesting that HPV can persist in the body for up to two years after infection [29].

A positive smoking history was noted in 41 patients (82%): 13 (26%) current smokers, 28 (56%) former smokers, and 9 (18%) never-smokers. Current urinary tract infections were identified in 3 patients (6%). Additional characteristics in the study population included a coexisting bladder cancer (1 patient; 2%) and a Yemeni-origin patient (1; 2%). One patient had a positive family history of prostate cancer, and another underwent palliative prostatectomy due to an invasive tumor.

Material collection procedure

Following radical laparoscopic prostatectomy, the prostatic utricle opening was identified in the resected specimen. The prostate specimen was dissected longitudinally along the anterior surface, from the base to the apex, to expose the posterior wall of the prostatic urethra (Figure 2).

The opening of the prostatic utricle was localized macroscopically, and in some cases microscopically, at the apex of the spindle-shaped seminal colliculus. A swab was then collected from the utricle using a thin cytobrush (Rovers EndoCervex-Brush), which was carefully inserted into the lumen of the utricle.

The collected material was stored at 4°C and transported to a laboratory specializing in HPV DNA analysis using the real-time PCR method, adhering to the recommended 30-day time frame for testing. Additionally, for comparison, samples were collected from random prostate sites (considering tumor localization), the external urethral meatus, and under the foreskin. None of the samples were deemed insufficient or unusable.

Human papillomavirus DNA detection method

The Anyplex II HPV HR Detection method was used to identify human papillomavirus (HPV) DNA. This technique employs real-time multiplex polymerase chain reaction (RT-PCR), allowing for the simultaneous detection and genotyping of 14 high-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56,

58, 59, 66, and 68. The method complies with international guidelines for cervical cancer screening and is widely used in virological diagnostics [30–32].

Statistical analysis

Statistical analyses were conducted using the R software (version R-4.2.2) [33]. For continuous variables, medians and interquartile ranges (Q1–Q3) were calculated, while frequencies (percentages) were determined for categorical variables. Comparisons of continuous variables were performed using the Mann–Whitney U test, and categorical variables were analyzed using the chi^2 test or Fisher's exact test, depending on subgroup sizes. A significance level of $\alpha = 0.05$ was adopted.
Data visualization was performed using the ggplot2 library [34]. Boxplots displayed the median (bold line), first and third quartiles (box edges), and whiskers representing 1.5 times the interquartile range. Variable distributions were illustrated with points representing individual observations. Confidence intervals for proportions were calculated using the exact binomial method [35].

Bioethical standards

Patients were informed about the details of the study and provided written informed consent to participate. The Ethics Committee of Pomeranian Medical University in Szczecin issued a favorable opinion for this study (No. approval: KB-0012/13/19).

RESULTS

General characteristics

Histopathological analysis of postoperative specimens revealed that all tumors were adenocarcinomas, confirming the dominance of this histopathological type in prostate cancer. More than half of the patients (28; 56%) had organ-confined cancer (pT2a and pT2c), while 18 patients (36%) presented with capsular invasion (pT3a). Only one patient was diagnosed with tumor infiltration into adjacent organs (pT4).
Regarding lymph node involvement, the majority of patients (47; 94%) had lymph nodes free of metastasis (pN0), while regional lymph node involvement (pN1) was observed in three cases. These findings correlated with preoperative multiparametric magnetic resonance imaging (mpMRI) assessments, which were performed for most patients.
The mean PSA value was 7.89 ng/ml, and the mean prostate volume, as evaluated by mpMRI, was 34.5 ml. Detailed distributions of PSA levels and prostate volume in the study population are illustrated in Figures 3 and 4.
The overall characteristics of the study population aligned with the profile of typical patients with prostate cancer eligible for radical surgical treatment. The majority were men aged 60–70 years, sexually active, with low to moderate disease progression and PSA levels ranging from 6 to 12 ng/ml. The study group was predominantly classified as International Society of Urological Pathology (ISUP) grade 2, with a Gleason score (GS) of 3+4 observed in 20 patients (40%). The next largest group included patients with a GS of 3+3 (ISUP 1), accounting for 14 individuals (28%). The least common were advanced grades – ISUP 4 (4 patients, 8%) and ISUP 5 (3 patients, 6%). Details are presented in Table 1.

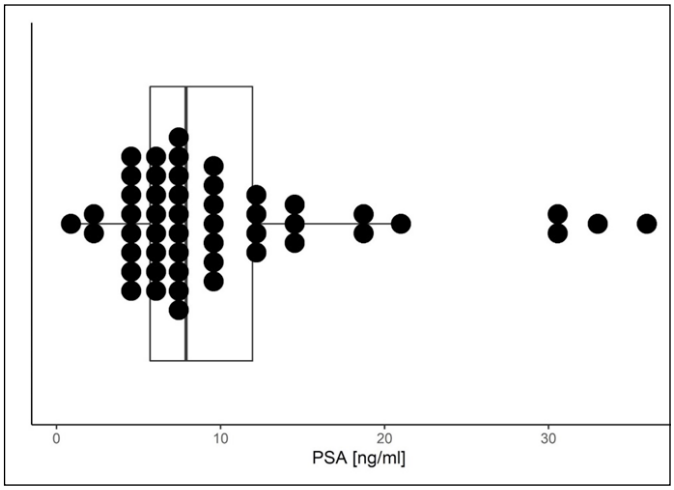

Figure 3. *Boxplot of PSA values [ng/ml] for the entire study population. Black dots represent individual observations.*

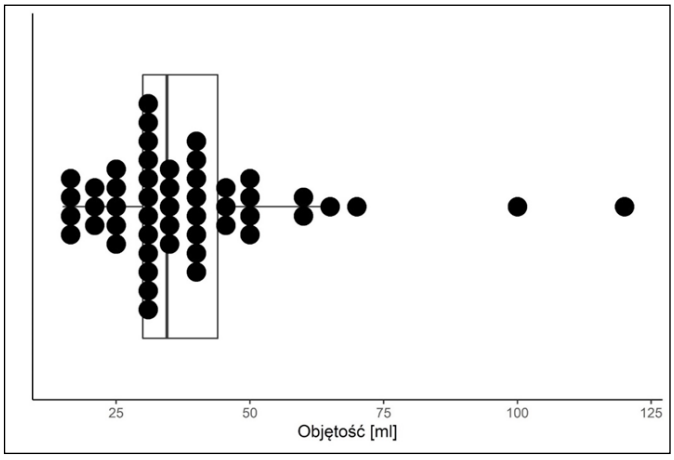

Figure 4. *Boxplot of prostate volume [ml] for the entire study population. Black dots represent individual patients.*

In subgroup 1, consisting of 26 patients, in addition to analyzing HPV DNA in the prostatic utricle, its presence was assessed in swabs taken from under the foreskin and the external urethral meatus. The median age of patients was comparable to the median age of the entire study population, with sexual activity reported by 17 individuals (65%). In terms of TNM classification, organ-confined changes (pT2c) predominated, consistent with the overall study group. A distinguishing feature of this subgroup was the presence of a patient with prostate cancer invading adjacent organs (pT4) and all patients with regional lymph node involvement (pN1). PSA levels and prostate volume did not differ significantly from the averages in the overall study group. Detailed data for subgroup 1 are presented in Table 2.

Results regarding Human papillomavirus

In none of the swabs collected from the prostatic utricle nor in the material obtained from random prostate punctures was HPV DNA detected.

Table 1. *Clinical characteristics and tumor stage of the entire study population*

Clinical characteristics	
N	50
Age	64.21 (59.47–66.62)
Sexual activity	38 (76%)
Urinary tract infection	3 (6%)
Cigarettes	Yes: 13 (26%) In the past: 28 (56%) No: 9 (18%)
Tumor stage	
pT	pT2a: 3 (6%) pT2c: 25 (50%) pT3a: 18 (36%) pT3b: 3 (6%) pT4: 1 (2%)
pN	N0: 47 (94%) N1: 3 (6%)
PSA	7.89 (5.7–11.95)
PV	34.5 (30–44)
cT	cT1c: 19 (38%) cT2a: 13 (26%) cT2b: 12 (24%) cT2c: 5 (10%) cT3: 1 (2%)
Gleason scale	6: 14 (28%) 7: 29 (58%) 8: 4 (8%) 9: 3 (6%)
ISUP	1: 14 (28%) 2: 20 (40%) 3: 9 (18%) 4: 4 (8%) 5: 3 (6%)
MRI PIRADS	PI-RADS 2: 3 (6%) PI-RADS 3: 4 (8%) PI-RADS 4: 27 (54%) PI-RADS 5: 16 (32%)
MRI lymph node involvement	N0: 45 (90%) N1: 5 (10%)
MRI prostate capsule invasion	No: 39 (78%) Possible: 4 (8%) Yes: 7 (14%)

PV – prostate volume; MRI – magnetic resonance imaging; ISUP – International Society of Urological Pathology; PI-RADS – Prostate Imaging–Reporting and Data System; PSA – prostate-specific antigen

Table 2. *Clinical characteristics and prostate cancer staging for subgroup 1*

Clinical characteristics	
N	26
Age	64.67 (60.72–68.43)
Sexual activity	17 (65.38%)
Urinary tract infection	1 (3.85%)
Cigarettes	0: 4 (15.38%) 1: 10 (38.46%) 2: 12 (46.15%)
Tumor stage	
pT	2c: 14 (53.85%) 3a: 10 (38.46%) 3b: 1 (3.85%) 4: 1 (3.85%)
pN	0: 23 (88.46%) 1: 3 (11.54%)
PSA	7.95 (5.32–12.44)
PV	33.5 (30–44)
cT	cT1c: 7 (26.92%) cT2a: 10 (38.46%) cT2b: 6 (23.08%) cT2c: 2 (7.69%) cT3: 1 (3.85%)
Gleason scale	6: 6 (23.08%) 7: 15 (57.69%) 8: 3 (11.54%) 9: 2 (7.69%)
ISUP	1: 6 (23.08%) 2: 10 (38.46%) 3: 5 (19.23%) 4: 3 (11.54%) 5: 2 (7.69%)
MRI PI-RADS	PI-RADS 2: 3 (11.54%) PI-RADS 3: 3 (11.54%) PI-RADS 4: 14 (53.85%) PI-RADS 5: 6 (23.08%)
MRI lymph node involvement	N0: 21 (80.77%) N1: 5 (19.23%)
MRI prostate capsule invasion	0: 21 (80.77%) 1: 5 (19.23%)

ISUP – International Society of Urological Pathology; MRI – magnetic resonance imaging; PI-RADS – Prostate Imaging–Reporting and Data System; PSA – prostate-specific antigen; PV – prostate volume

Positive results were observed exclusively in the first study subgroup, where the analyzed material consisted of swabs taken from under the foreskin and the external urethral meatus. Importantly, HPV infection in both of these patients was not linked to their current sexual activity, which may confirm the virus's ability to persist in the body for years after the initial infection.

Subgroup 2, comprising 24 patients, included the analysis of HPV DNA in washings from random prostate sites, particularly from areas with macroscopic changes, if present. The patients' age was comparable to other groups, but as many as 21 individuals (87.5%) reported active sexual activity, distinguishing this subgroup. Histopathologically, pT2c and pT3a classifications predominated, and no cases of lymph node involvement were noted in this subgroup. Detailed data for subgroup 2 are provided in Table 3.

Positive results detecting HPV DNA were obtained in only two cases (7.69%) within subgroup 1, which included 26 patients. The virus was identified in swabs taken from the foreskin and the external urethral meatus, but its presence was not detected in the prostatic utricle of the same patients (95% confidence interval: 0.95–25.13%). In the first patient, HPV-18 and HPV-51 subtypes were identified, while in the second patient, HPV-39 was detected. Both patients reported no current sexual activity, supporting the possibility that HPV infection may persist up to 2–3 years after acquisition. The statistical significance of this difference was estimated at $p = 0.054$. Neither patient presented with a concurrent urinary tract infection. Both were active smokers, and the tumors diagnosed were classified as high risk according to the EAU (European Association of Urology) guidelines (pT3a cN+ and pT2c). Interestingly, the tumors were identified in relatively small prostate glands (15 and 18 ml). The characteristics of the patients with positive HPV DNA results are summarized in Table 4.

Table 3. *Clinical characteristics and prostate cancer staging for subgroup 2*

Clinical characteristics	
N	24
Age	63.95 (59.05–65.78)
Sexual activity	21 (87.5%)
Urinary tract infection	2 (8.33%)
Cigarettes	0: 5 (20.83%) 1: 3 (12.5%) 2: 16 (66.67%)
Tumor stage	
pT	pT2a: 3 (12.5%) pT2c: 11 (45.83%) pT3a: 8 (33.33%) pT3b: 2 (8.33%)
pN	N0: 24 (100%)
PSA	7.75 (6.04–10.45)
PV	34.5 (28.75–41.25)
cT	cT1c: 12 (50%) cT2a: 3 (12,5%) cT2b: 6 (25%) cT2c: 3 (12.5%)
Gleason scale	6: 8 (33.33%) 7: 14 (58.33%) 8: 1 (4.17%) 9: 1 (4.17%)
ISUP	1: 8 (33.33%) 2: 10 (41.67%) 3: 4 (16.67%) 4: 1 (4.17%) 5: 1 (4.17%)
MRI PI-RADS	PI-RADS 3: 1 (4.17%) PI-RADS 4: 13 (54.17%) PI-RADS 5: 10 (41.67%)
MRI lymph node involvement	N0: 24 (100%)
MRI prostate capsule invasion	No: 18 (75%) Yes: 2 (8.33%) Possible: 4 (16.67%)

ISUP – International Society of Urological Pathology; MRI – magnetic resonance imaging; PI-RADS – Prostate Imaging–Reporting and Data System; PSA – prostate-specific antigen; PV – prostate volume

Table 4. *Characteristics of patients with positive HPV DNA results in swabs from the foreskin and external urethral meatus*

	Case 1	Case 2
HPV subtype	18.51	39
N	1	1
Age	72.73	60.55
Sexual activity	No	No
Urinary tract infection	No	No
Cigarettes	Yes	Yes
pT	pT3a	pT2c
pN	No	No
PSA	14.06	12
PV	15	18
cT	cT1c	cT2a
Gleason scale	7	7
ISUP	2	2
MRI PI-RADS	PI-RADS 4	PI-RADS 2
MRI lymph node involvement	Yes	No
MRI prostate capsule invasion	No	No

ISUP – International Society of Urological Pathology; MRI – magnetic resonance imaging; PI-RADS – Prostate Imaging–Reporting and Data System; PSA – prostate-specific antigen; PV – prostate volume

DISCUSSION

In recent years, interest in the potential impact of HPV on the development of prostate cancer (PCa) has increased, but available data remain inconclusive. Previous studies, including a 2020 meta-analysis by Lawson and Glenn [36], reported the presence of HPV DNA in prostate tissues in 22.6% of prostate cancer cases and 8.6% of cases involving benign prostatic hyperplasia (BPH) or normal prostate tissue, which was statistically significant ($p = 0.001$). The most commonly identified HPV types were HPV-16 and HPV-18, known for their high oncogenic potential. However, eight studies included in the same meta-analysis did not detect HPV in cancerous prostate tissue, highlighting discrepancies in findings and variability in research methodologies.

Previous analyses primarily relied on detecting HPV DNA in biopsy specimens, post-prostatectomy tissue, or tissue obtained via transurethral resection of the prostate (TURP). Among studies with the highest HPV detection rates, Whitaker et al. [37] conducted a notable investigation in 2013, demonstrating HPV presence in 58% of prostate cancer cases and 16% of benign prostatic hyperplasia cases. This study, employing in situ PCR with a lower risk of sample contamination, remains one of the most significant contributions to understanding this association. A review of studies reporting a positive correlation between prostate cancer and HPV infection is presented in Table 5.

The anatomical and histological analysis of the prostate gland, along with an understanding of the oncogenic mechanisms of prostate cancer, led the authors to formulate the hypothesis that the prostatic utricle could represent a potential site for HPV persistence within the male genitourinary tract. This assumption was also based on the observation

Table 5. *Results of studies reporting a positive correlation between HPV infection and prostate cancer*

Study	Country	PCa	BPH	HPV subtype	p-value
McNicol and Dodd 1992 [29]	Canada	14/27 52%	35/61 57%	16, 18	0.396 ns
Anwar et al. 1992 [38]	Japan	28/68 41%	0/10 0%	16, 18, 33	0.221 ns
Ibrahim et al. 1992 [39]	USA	6/40 15%	2/29 7%	16	0.344 ns
Rotola et al. 1992 [40]	Italy	6/8 75%	14/17 82%	16	0.0815 ns
Dodd et al. 1993 [41]	Canada	3/7 43%	5/10 50%	16	0.0841 ns
Tu et al. 1994 [42]	USA	1/43	0/1	16	–
Moyret-Lalle et al. 1995 [43]	France	9/17 53%	7/22 32%	16	0.682 ns
Wideroff et al. 1996 [44]	USA	7/56 13%	4/42 10%	16, 18, 31, 33, 45	0.654 ns
Terris and Peehl 1997 [45]	USA	10/53 19%	12/58 20%	16	0.571 ns
Serth et al. 1999 [46]	**Germany**	**10/47 21%**	**1/37% 3%**	**16**	**0.027**
Carozzi et al. 2004 [47]	Italy	6/24 25%	3/25 12%	16, 18, 31	0.333 ns
Leiros et al. 2005 [48]	**Argentina**	**15/41 37%**	**0/30 0%**	**16**	**0.011**
Silvestre et al. 2009 [49]	Brazil	2/65 3%	0/6 0%	16	–
Martinez-Fierro et al. 2010 [50]	**Mexico**	**11/55 20%**	**4/75 5%**	**33, 45, 52, 58, 66**	**0.020**
Aghakhani et al. 2011 [51]	Iran	10/104 10%	5/104 5%	16, 18	0.213 ns
Chen et al. 2011 [52]	Australia	7/51 14%	3/11 27%	18	0.367 ns
Tachezy et al. 2012 [53]	Czech Republic	1/51 2%	2/95 2%	–	–
Whitaker et al. 2013 [38]	**Australia**	**29/50 58%**	**8/50 16%**	**18**	**0.003**
Ghasemian et al. 2013 [54]	**Iran**	**5/29 17%**	**8/167 5%**	**–**	**0.026**
Mokhtari et al. 2013 [55]	Iran	3/30 10%	1/90 1%	–	–
Michopoulou et al. 2014 [56]	Greece	8/50 16%	1/30 3%	16, 18, 31	0.127 ns
Singh et al. 2015 [57]	**India**	**36/95 38%**	**4/55 7%**	**16, 18**	**0.001**
Huang et al. 2016 [58]	**China**	**30/75 40%**	**9/73 12%**	**–**	**0.001**
Davila Rodriguez et al. 2016 [30]	Mexico	12/62	1/25 4%	18, 51, 52	0.104 ns
Atashafrooz et al. 2016 [31]	**Iran**	**16/100 16%**	**2/100 2%**	**16, 18, 31, 33, 54**	**0.002**
Medel-Flores et al. 2018 [32]	**Mexico**	**37/189 20%**	**16/167 10%**	**16, 18, 31, 33, 52, 58**	**0.014**

$p \leq 0.05$ – statistically significant (shown in bold); ns – not statistically significant

that men act as vectors for HPV transmission during sexual intercourse, passing the infection to women, in whom HPV constitutes a significant oncological risk.

Due to the lack of previous scientific data regarding the presence of HPV in this specific structure of the prostate, it was not possible to predict the diagnostic utility or direction of the findings. However, considering that chronic inflammation is a well-established risk factor in prostate carcinogenesis, and that HPV is the only sexually transmitted oncogenic virus for which effective vaccination is available, the authors considered it justified to analyze the presence of HPV in patients with prostate cancer.

Because of the small size and anatomical location of the prostatic utricle, it was only possible to collect material from surgically removed prostate specimens, which limited the study to patients undergoing radical prostatectomy. In 42 cases (84%), identification of the utricle on the seminal colliculus of the posterior urethral wall posed no technical difficulty. In the remaining cases, magnification tools were used to assist in its localization; nevertheless, the presence of this residual anatomical structure was ultimately confirmed in all patients.

Although the exact histological structure of the prostatic utricle was not evaluated as part of this study, the authors hypothesized – based on its shared embryological origin with the cervical canal – that the utricle may be lined with epithelium similar to that to which HPV shows the highest affinity. Therefore, the study was based on the hypothesis of morphological and functional similarity between these anatomical structures.

A primary limitation of the meta-analysis conducted by Lawson and Glenn was the heterogeneity of study designs, methodologies, and the quality and manner of tissue sampling. Two main techniques were employed for HPV identification: tissue-based polymerase chain reaction (PCR) and serological testing [36].

In eight studies included in the meta-analysis, the presence of various sexually transmitted pathogens was analyzed in histological samples from prostatectomy and TURP. The most recent of these studies was by Yow et al. [33] (2014). Among 115 samples, regardless of the prostate cancer stage, HPV DNA was not detected using the RT-PCR method. This finding suggests that HPV is unlikely to have a role in prostate carcinogenesis. Similar conclusions were drawn by the authors of the remaining seven studies, who also failed to detect HPV DNA in biopsy or histopathological samples of prostate cancer using modern RT-PCR genotyping methods. The results of these studies are summarized in Table 6.

In our study, HPV DNA was not detected in any of the 50 samples collected from the prostatic utricle or in the 24 washings from random prostate sites. These findings suggest that neither the prostatic utricle nor cancerous prostate tissue serves as a reservoir for the virus. Positive HPV DNA results (types 18, 39, 51) were identified only in two cases (7.69%) in swabs taken from under the foreskin and the external urethral meatus. Notably, both patients reported no current sexual activity, which may indicate the virus's ability to persist in the body for extended periods. In addition, both men were active smokers, diagnosed with high-risk prostate cancer according to the EAU classification, and presented with relatively small prostate volumes.

Although our findings and the current literature do not support a direct role of HPV infection in prostate cancer carcinogenesis, an indirect association cannot be ruled out. The virus may contribute to tumorigenesis through interactions with coexisting factors such as chronic inflammation. This potential relationship could be particularly relevant in younger individuals, in whom increased sexual

Table 6. *Results of studies showing no correlation between HPV infection and prostate cancer*

Study	Country	PCa	BPH	HPV subtype	p-value
Masood et al. 1991 [34]	USA	0/20	0/20	–	–
Effert et al. 1992 [56]	USA	0/30	–	– (16, 18*)	–
Serfling et al. 1992 [59]	USA	0/30	–	–	–
Anderson et al. 1997 [60]	UK	0/14	0/10	– (16, 18*)	–
Noda et al. 1998 [61]	Japan	0/38	3/71	16 (16, 18*)	p = 0.19 ns
Saad 1999 [62]	Canada	0/40	–	16, 18, 31	–
Gazzaz and Mosli 2009 [63]	Saudi Arabia	0/6	0/50	–	–
Yow et al. 2014 [33]	Australia	0/115	–	–	–

p ≤0.05 was considered statistically significant; ns – not statistically significant, (16,18*) – study focused exclusively on the two oncogenic HPV subtypes 16 and 18

activity raises the likelihood of HPV infection. Our results are partially consistent with previous studies (Anwar and Singh) that identified a correlation between HPV infection and more advanced stages of prostate cancer [38, 57].

The analysis of the relationship between smoking and the results revealed that non-smokers had lower PSA levels (median 5.59 ng/ml vs 9.16 ng/ml in smokers) and were more often diagnosed with less aggressive prostate cancer (ISUP 1). Smoking may therefore contribute to higher PSA levels and more aggressive forms of prostate cancer, as corroborated by existing literature on the detrimental effects of smoking on health [33, 36].

Our study stands out from existing research primarily due to its original premise and the unique site of biological material collection. Most previous studies – including the work by Yow et al. [33] – focused on detecting HPV DNA in routinely obtained samples such as prostate tumor tissue, semen, or urine. In contrast, our project is the first to investigate the prostatic utricle as a potential reservoir of the virus in men. This structure shares a common embryological origin with the cervical canal, to which HPV exhibits a strong affinity.

In addition, simultaneous analysis of samples collected from various anatomical locations (the prostatic utricle, random sites within the prostate, and the area under the foreskin) allowed for a more comprehensive assessment of the possible presence of the virus within the entire male genitourinary tract. Our study also employed a strictly controlled methodology for collecting operative material under aseptic conditions, thereby minimizing the risk of contamination.

In the present study, HPV DNA was detected in only 7.69% of cases (2/26) in swabs collected from under the foreskin, and no viral DNA was found in any of the samples from the prostatic utricle or prostate tissue. This detection rate is noticeably lower compared to several earlier studies, where HPV DNA was identified in approximately 15% to 58% of prostate cancer tissue samples [36, 37, 48, 57, 58].

Several factors may account for this discrepancy. First, many previous studies were based on the analysis of tissue obtained from biopsies, TURP, or post-prostatectomy samples, often without a clear specification of sampling sites and with varying degrees of contamination control [36, 37, 53]. In contrast, our study employed a highly controlled methodology and aseptic conditions during intraoperative material collection, which likely reduced the risk of false-positive results.

Second, our study population was relatively homogeneous (men undergoing radical prostatectomy for prostate cancer), and the sample size was limited (n = 50), which could have contributed to the lower HPV detection rate, and which limits direct comparison with large-scale, population-based studies [33].

It is also worth noting that several studies reporting similarly negative findings employed modern RT-PCR techniques and likewise failed to detect HPV DNA in prostate tissues, highlighting the importance of detection method sensitivity and the quality of the biological material analyzed [33–35, 61].

These results, along with the literature review, suggest no direct role for HPV in prostate carcinogenesis. The virus may play an indirect role, potentially activating chronic inflammation or interacting with other pathogens, particularly in younger age groups where higher sexual activity may facilitate infections.

Currently, Poland has implemented a free HPV vaccination program for girls and boys aged 11–13 years. Similar programs are operational in many countries, with promising outcomes. In the UK, where HPV vaccination for girls was introduced in 2008, an 87% reduction in cervical cancer incidence has been reported, preventing thousands of precancerous cases. Including boys in such programs could further reduce virus transmission, decrease infections in women, and lower the incidence of HPV-related cancers in men, such as penile, anal, and oropharyngeal cancers [64].

In the long term, these vaccination programs may also provide data on the impact of HPV on prostate cancer, allowing an assessment of incidence rates in vaccinated male populations. Promoting HPV vaccination is a crucial step toward effective prevention, which could significantly improve public health outcomes and reduce the burden of HPV-related cancers.

The limitations of our study encompass several important aspects that may influence the interpretation of the results. First, the study was conducted on a relatively small patient population, which, given the low frequency of HPV DNA detection in the prostate – reported in some earlier studies to be below 5% – increases the risk that the number of virus-positive cases may be too small for reliable comparative analysis. Second, the study population was partially selected, as the material was obtained exclusively from patients with prostate cancer who were undergoing radical prostatectomy. Due to the eligibility criteria for this type of treatment, the majority of these patients had organ-confined disease, which may limit the generalizability of the findings. Another limitation stems from the study

design itself, which did not allow for the inclusion of a control group consisting of patients with a healthy prostate or benign prostatic hyperplasia, since collecting material from the prostatic utricle in vivo in such cases is technically unfeasible from a urological standpoint. Finally, the absence of HPV DNA in the analyzed material may represent a false-negative result. Prostate cancer typically develops slowly – there may be a period of 3 to 5 years between the onset of carcinogenesis and diagnosis. Therefore, if HPV persists in the body for only 2–3 years after infection, it is unlikely to still be present in the tissue obtained during prostatectomy. This is a significant limitation that must be taken into account when evaluating our study.

Future research directions should consider several aspects to address the limitations of this study and further explore the potential link between HPV infection and prostate cancer. First, increasing the size of the study population could improve statistical power and facilitate the identification of a subpopulation with detectable HPV presence. Second, inclusion of a control group comprising patients without prostate cancer (e.g., those undergoing TURP or biopsy) may offer valuable comparative data, although sampling the prostatic utricle in vivo remains technically and ethically challenging. Third, employing more sensitive viral detection techniques, such as next-generation sequencing (NGS) or digital PCR, might allow identification of HPV DNA in very low concentrations. Additional analyses focusing on the expression of viral oncogenic proteins (e.g., E6 and E7) and inflammatory or oncogenic signaling pathways in the tumor microenvironment and the prostatic utricle may offer mechanistic insight. Histological and immunohistochemical evaluation of the prostatic utricle is also warranted to confirm the epithelial phenotype and its susceptibility to HPV colonization. Finally, long-term prospective and population-based studies assessing the impact of male HPV vaccination on prostate cancer incidence would be valuable, although they require extended follow-up periods.

CONCLUSIONS

1. HPV DNA was not detected in the prostatic utricle or in randomly sampled areas of the prostate, which suggests no direct association between HPV and malignant prostate tissue. However, it should be noted that the study was conducted on a relatively small group of patients (n = 50), which limits the generalizability of the findings.
2. HPV DNA was found in only 7.69% of cases (2/26) in swabs from the foreskin and external urethral meatus, which may indicate limited colonization of the virus to superficial epithelial structures of the male genital tract. This result should also be interpreted with caution due to the small size of the analyzed subgroup.
3. Although HPV was not detected in prostate tissue, its indirect involvement in prostate carcinogenesis cannot be excluded – particularly through the induction of chronic inflammation, which is a recognized risk factor for prostate cancer. However, further population-based studies are needed to verify this hypothesis.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

The study was approved by the Ethics Committee of Pomeranian Medical University in Szczecin (No. Approval: KB-0012/13/19).

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