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The role of herpes and human papillomavirus infection in prostate and bladder carcinogenesis

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ABSTRACT

Human papillomavirus (HPV) is a small epithelial, non-enveloped, double-stranded DNA virus that belongs to the Papillomaviridae family. HPV infection is one of the most common sexually transmitted infections, and certain types of HPV are known to be carcinogenic to humans. According to the scientific literature, there is reliable information about the role of highly oncogenic HPV types in the development of cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancer.

Currently, a relevant and promising research area is the study of the role of HPV infection in prostate cancer (PC) and bladder cancer (BC), but scientific data on the potential pathogenetic relationship between these phenomena remain contradictory. An in-depth study of the question how herpes and human papillomavirus affect the origin of malignant tumors of the prostate and bladder, as well as the course of these diseases, and the prognosis of their development can become a source of information for development of new approaches to their diagnosis, prevention, and monitoring of morbidity. This literature review analyzes the results of modern studies on the role of oncogenic HPV types in the carcinogenesis of PC and BC.

Key words: human papillomavirus, prostate cancer, bladder cancer, carcinogenesis.

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Роль инфекции, вызванной вирусами герпеса и папилломы человека, в канцерогенезе предстательной железы и мочевого пузыря

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РЕЗЮМЕ

Вирус папилломы человека (ВПЧ) – это небольшой эпителиотропный, безоболочечный, двухцепочечный ДНК-вирус, который относится к семейству Papillomaviridae. Инфекция, вызванная ВПЧ, является одной из наиболее распространенных инфекций, передаваемых половым путем. Известно, что определенные типы ВПЧ относятся к канцерогенам для человека. По данным научной литературы, имеется достоверная информация о роли высокоонкогенных типов ВПЧ в развитии рака шейки матки, анального канала, вульвы, влагалища, полового члена и ротоглотки.

Актуальным и перспективным направлением исследования в настоящее время является изучение роли ВПЧ-инфекции в раке предстательной железы (РПЖ) и раке мочевого пузыря (РМП). Однако научные данные о потенциальной патогенетической связи между этими явлениями остаются противоречивыми. Углубленное изучение вопроса о том, как вирусы герпеса и папилломы человека влияют на происхождение злокачественных опухолей предстательной железы и мочевого пузыря, течение данных заболеваний и прогноз их развития, может стать источником информации для разработки новых подходов к их диагностике, профилактике и мониторингу заболеваемости. В данном обзоре проанализированы результаты современных исследований по проблеме участия онкогенных типов ВПЧ в канцерогенезе ПЖ и МП.

Ключевые слова: вирус папилломы человека, рак предстательной железы, рак мочевого пузыря, канцерогенез.

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INTRODUCTION

The study of the etiological role of infectious agents (primarily viral) in carcinogenesis of various tumors is one of the most relevant problems in modern medicine. Currently, there is reliable information about the role of highly oncogenic types of human papillomavirus (HPV) in the development of cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancers.

In foreign and Russian literature, there is a growing number of publications that confirm the influence of HPV and herpes on the emergence of prostate and bladder cancer. This fact proves the need for a more profound and thorough study of the role of these viruses in the emergence, course, and prognosis of

these cancer types. This review analyzes the current research data on this topic.

THE ROLE OF HPV INFECTION IN THE CARCINOGENESIS OF PROSTATE CANCER

Prostate cancer (PC) is the second most common cancer and the fifth leading cause of cancer death in men [1]. According to the World Health Organization, 1.2 million new cases and 358.000 deaths were identified in 2018 [2]. More than 550 thousand new cases of PC are diagnosed in the world annually. USA, Canada, and some European countries have the highest rates of PC incidence, where it ranks first [3].

According to researchers' forecasts, in 2030, the number of PC cases in the world will be 1.7 million and the morbidity rate will reach about 500.000 [4]. In the Russian Federation, there has been a steady increase in the incidence of PC. In 2018, 42,518 new cases of PC were diagnosed, and the standardized incidence rate was 41.45 new cases per 100, 000 population. The increase in morbidity from 2008 to 2018 was 87.70%, with an average growth rate of 5.92% for 2018 [5].

RISK FACTORS

PC is traditionally considered a disease of the elderly. The disease is quite rare in men under 45 years of age. However, after that age, an increase in the incidence of PC is observed, with a maximum in the 65–74 age group [6]. Risk factors also include genetic predisposition, ethnicity (Black and Hispanic populations), obesity, alcohol consumption, and high testosterone levels [7].

In addition to these factors, infectious agents are of great importance in the pathogenesis of PC [8]. According to clinical and epidemiological studies, infections can lead to chronic inflammation, which induces an inflammatory microenvironment, promotes malignant cell proliferation, angiogenesis, and metastasis, disrupts adaptive immune responses, and alters the response to hormonal and chemotherapeutic agents [9, 10].

HPV infection is one of the most common sexually transmitted infections (STIs) worldwide [11]. HPV is a small, epitheliotropic, non-enveloped, double-stranded DNA virus that belongs to the Papillomaviridae family. According to numerous epidemiological studies, the International Agency for Research on Cancer (IARC) identified the types of HPV that are related to human carcinogens. These types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 [8]. Highly oncogenic types of HPV can cause cervical, anal, vulvar, vaginal, penile, and oropharyngeal cancer [12–15].

In the study of HPV-associated carcinogenesis, it was found that the most well-known studies are those on HPV-induced cervical cancer. Epithelial cells become malignant with prolonged exposure to oncogenic strains of HPV. Inactivation of tumor growth suppressors *p53* and *RB* (retinoblastoma gene) occurs under the influence of the expressed viral oncogenes *E6* and *E7*. Due to changes in the normal functions of these suppressor genes, the cell begins to divide uncontrollably, which leads to tumor formation. Suppression of the antitumor properties of these proteins depends on the viral activity: in viruses with high activity, the formed E6–p53 and E7–rRb complexes remain stable. On the contrary, infected cells become malignant [16].

HPV infection is one of the causes of intraprostatic inflammation, and there is evidence that chronic inflammation is involved in the regulation of cellular events in prostate carcinogenesis [17–20].

In 1990, P.J. McNicol and J.G. Dodd were the first to identify HPV DNA in the prostate tissue by polymerase chain reaction (PCR) [21]. Today, more studies are being conducted to investigate the association between HPV infection and PC.

In 2017, G. M. Volgareva et al. conducted a study of the surgical material from 17 patients with PC for the presence of the HPV 16 *E7* oncogene by PCR. The microscopic analysis of the surgical material confirmed PC in 16 of the 17 patients. In all these cases, except one, acinar adenocarcinoma was detected, and in 1 patient, moderately differentiated adenocarcinoma was observed. PCR revealed the presence of HPV 16 *E7* DNA in lysates obtained from 7 specimens of 17 examined patients. The result was positive in five cases of cancer and two cases of prostatic intraepithelial neoplasia (PIN) [22].

In 2019, G. M. Volgareva et al. analyzed the same group of patients to detect HPV 18. The *E7* oncogene was found in the tissues removed from patients with PC in 2 out of 17 cases. Together with the previously obtained data, this result suggested that HPV 16 and HPV 18 are the main types of HPV responsible for the development of cervical cancer and are often present in the prostate glands of patients with PC [16].

In 2016, F. Atashafrooz et al. conducted a study that evaluated the incidence of various types of HPV in PC and benign prostatic hyperplasia (BPH) in Kerman province (Iran) using the PCR method. The aim of the study was to identify the association of HPV infection with the occurrence of PC. PCR showed that HPV DNA was detected in 20% of 100 PC samples ($n = 20$), 80% (16 patients) of which had highly oncogenic HPV types, 40% (8 patients) had HPV 16 and 18, 30% (6 patients) had HPV 31 and 33, and 10% (2 patients) had HPV 54. The DNA of highly oncogenic HPV types was found in only 2% of prostate samples with benign hyperplasia.

This study confirmed the role of highly oncogenic HPV types in prostate diseases in Iranian patients and the correlation between the presence of HPV DNA and PC. In particular, HPV 16 and 18 may play an important role in the development of PC [23].

In the same year, L. Huang et al. examined prostate tissue samples from 75 patients with PC and 73 patients with BPH. The immunohistochemical study revealed positive staining for HPV 16 and 18 in 16 PC cases (21.3%) and in 7 benign hyperplasia samples (9.5%) with a statistically significant difference between the two groups ($p = 0.049$). PCR combined with western blotting showed the presence of HPV 16 in 17 (22.6%) cases and HPV 18 (17.8%) in 13 cases, including four positive episodes of HPV 16 and 18 in the PC group.

In the control group of BPH, six samples were infected with HPV 16 (8.2 %) and three samples – with HPV 18 (4.1%), while there were no patients with positive staining for HPV 16 / 18, which is significantly lower than in the group with PC. Additionally, no significant differences were found between the results of immunohistochemical testing and PCR in combination with western blotting ($p = 0.069$). The authors also found that HPV infection of types 16 and 18 correlated with the clinical stage and the Gleason score in PC ($p < 0.05$), but not with the patient's age, the level of prostate-specific antigen (PSA), and the presence of metastases in the lymph nodes ($p > 0.05$) [24].

In 2017, W.K. Glenn et al. carried out a study in which HPV was detected by PCR in prostate biopsy samples of 52 men with BPH who later developed PC after 1–10 years. HPV screening using the PCR method was performed among 28 of the 52 samples. HPV *L1* genes were detected in 13 patients with BPH and in 8 patients with PC. HPV *E7* genes were identified in 23 cases (82%) of BPH and in 19 (68%) cases of PC. The same types of HPV were present in patients with both BPH and PC, detected later in 9 episodes [25].

HPV 16 was detected in 15% and 3% of cases of BPH and PC, respectively. HPV 18 was detected in 26% of prostate samples with BPH and in 16% cases with PC. High reliability of the sequenced RNA data for HPV 16 and 18 was identified in 12 (2%) of the 502 transcriptomes of PC in The Cancer Genome Atlas (TCGA). The oncoprotein *E7* was positive in 23 (82%) of the 28 benign hyperplasia samples and only in 8 (29%) cases of the 28 PC samples. PSA expression was more prominent in 26 (50%) of the 52 PC samples compared with BPH samples in the same patients.

This study confirms that highly oncogenic HPV types are present in prostate tissues with BPH prior to the development of HPV-positive PC in the same patients. In addition, much more pronounced expression of the oncoprotein *E7* in BPH samples indicates that the oncogenic activity of HPV is an early phenomenon in prostate carcinogenesis [25].

In 2018, O. Medel-Flores et al. conducted a study aimed at identifying the relationship between the occurrence of PC and HPV in the Mexican population. 356 paraffin blocks from unrelated men with PC or BPH were studied, with the latter serving as a control group. HPV detection was performed by PCR using universal primers; viral genotypes were determined by sequencing or multiplex PCR [26].

The microscopic analysis revealed koilocytes in the material which was subsequently analyzed by *in situ* PCR for the presence of HPV, as well as by the immunohistochemical method for detecting the expression of p16-INK4A. *In situ* PCR is a modification of classical PCR, which has similar sensitivity, but at the same time allows to visualize infected cells and assess their relative number. The results showed that highly oncogenic HPV types were detected in 37 of the 189 (19.6%) PC samples, compared with 16 of the 167 (9.6%) BPH samples ($p = 0.01$).

These findings suggest that highly oncogenic HPV types may contribute to the development of PC. HPV 52 and 58 were the most common genotypes (33% and 17%, respectively) found in the studied population. Koilocytes, representing a pathognomonic sign of infection, were found in all *in situ* PCR HPV-positive samples. The researchers also observed increased expression of p16-INK4A

in HPV-positive samples compared with HPV-negative samples, indirectly confirming the presence of the oncoprotein E7.

These results demonstrate that HPV plays an important role in the development of PC. Detection of highly oncogenic HPV types amounted to 81.4% (83% in the BPH group and 79% in the PC group), and detection of low-risk HPV was four times lower – only 19% (17% in the BPH group and 21% in the PC group). The virus genotypes observed in the samples in order of decreasing prevalence were distributed as follows: HPV 52 (33.3%), HPV 58 (17.17%), HPV 11 (12.7%), HPV 18 (10.8%), HPV 16 (7.8%), HPV 33 (6.9%), HPV 6 (5.9%), and HPV 31 (4.0%) [26].

In 2020, G.I. Russo et al. conducted a meta-analysis of 30 studies examining the relationship between HPV 16 and 18 and an increase in PSA values in 6,321 individuals. All men with elevated PSA values ($p < 0.01$) tested positive for HPV 16. There were seven studies involving 2,391 patients with elevated PSA in the blood serum and 4,059 patients in the control group. All studies investigated the relationship between HPV 18 and an increase in the PSA value. The results of the studies did not reveal an increase in the PSA value ($p = 0.49$) in men with positive HPV 18. This meta-analysis suggests that HPV 16 may be a risk factor for an increase in the PSA value, whereas no similar association was found for HPV 18 [27].

In 2019, M. Moghoofei et al. analyzed the results of 24 studies conducted from January 1990 to December 2016, which included 5,546 patients with PC, to assess the heterogeneity of the main parameters, reflecting the study area, sample type, HPV DNA source, detection method, publication calendar period, and Gleason score. The odds ratio (OR) and the corresponding 95% confidence interval (CI) were calculated to identify the relationship between the prevalence of HPV and the risk of developing PC. A significant positive correlation was found between HPV infection and the risk of developing PC (OR = 1.281).

The HPV16 genotype was more common in patients with PC, which significantly increased the risk of developing cancer (OR= 1.60). The risk of developing PC increased significantly at the age of 65 years and older (OR = 3.564). The results of this meta-analysis support a potential pathogenetic association between HPV infection and an increased risk of developing PC, confirming that HPV infection may contribute to the risk of developing PC [28].

THE ROLE OF HPV INFECTION IN THE CARCINOGENESIS OF BLADDER CANCER

Bladder cancer (BC) is the seventh most common type of cancer in the world. The prevalence of BC is the highest among men, where it is the fourth most common cancer type [29]. In the Russian Federation, the incidence of BC increases every year. In 2018, 13,479 new cases of BC were diagnosed, and the standardized incidence rate was 13.20 new cases per 100, 000 population. The increase in morbidity from 2008 to 2018 was 28.12%, with an average growth rate of 2.44 % in 2018 [5].

Histologically, 94% of BC cases are urothelial carcinomas. The remaining cases include squamous cell carcinoma (2%), adenocarcinoma (2%), and mesenchymal and other tumors (2%) [30]. Squamous cell carcinoma and urothelial carcinoma with squamous cell differentiation are often high-grade tumors associated with poor prognosis and worse outcomes after surgery, radiation, and chemotherapy, compared with urothelial carcinomas [31].

Well-known risk factors for BC are chronic urologic diseases, the presence of co-morbidities that reduce immune response (COPD, asthma, autoimmune thyroiditis, etc.), occupational hazards, cigarette smoking, alcohol consumption, radiation exposure, as well as a family history of cancer. Risk factors specifically associated with squamous cell BC encompass chronic bladder irritation caused by prolonged use of catheters and previous schistosomiasis [32]. Recently, HPV has been considered as a causative agent of squamous cell BC [33]. In this regard, more research has been conducted in this area lately.

In 2019, B. Javanmard et al. studied HPV DNA in the tumor tissue and urine at various stages of BC. The average age of 110 patients was 61.6 ± 10 years, 14 patients were female (12.7%). The authors believe that the selection of urine samples for HPV detection is as reliable as the selection of tumor tissue, which can be considered as a prognostic marker. PCR for the common HPV primer in the bladder tumor tissue was positive in 3 (9.4%), 22 (38.6%), and 15 (71.4%) Ta, T1, and T2 stage bladder tumors, respectively ($p < 0.001$).

PCR for HPV 16 in the bladder tumor tissue was positive in 2 (6.3%), 10 (17.5%), and 13 (61.9%)

cases, and PCR for HPV 18 in the bladder tumor tissue was positive in 1 (3.1%), 14 (24.6%), and 12 (57.1%) Ta, T1, and T2 stage tumors, respectively ($p < 0.001$, $p < 0.001$). 37 (33.6%) urine samples were positive for HPV using PCR, and HPV 16, 18 subtypes were positive in 17 (15.5%) and 14 (12.7%) urine samples, respectively. This study suggests that HPV infection may be associated with the development of late-stage BC [34].

In 2018, K.R. Børgensen et al. conducted a study in which the relationship between HPV, oncoprotein p16INK4a, and squamous cell BC was evaluated. The patients were divided into three groups based on the histological evaluation. A study included 100 patients: 50 patients with squamous cell BC, 25 patients with urothelial carcinomas, and 25 patients with urothelial carcinoma with squamous cell differentiation. Overall, HPV was found in 12 of 100 (12%) patients and in 9 of 50 (18%) patients with squamous cell carcinoma.

Overall, overexpression of p16INK4a was observed in 52/100 (52%) patients. However, concomitant HPV and p16INK4a overexpression were observed in only 4/100 (4%) patients. The study demonstrated the presence of HPV in one-fifth of the patients with squamous cell carcinoma, which may significantly contribute to the carcinogenesis of squamous cell carcinoma [35].

In 2018, U.K. Mete et al. (India) studied material from 50 patients with urothelial BC. The control group included ten people who were hospitalized for transurethral resection of the prostate for BPH and/or ureterorenoscopy for urolithiasis. The average age of patients was 54.1 years. Tissue samples were analyzed for the presence of HPV 16 and 18 with PCR. Histological examination of the tumor tissue was performed to assess the degree of differentiation of the tumor.

A total of 28 (56%) patients were diagnosed with low-grade tumors and 22 (44%) patients – with high-grade tumors. 18 (36%) patients had T2 or higher stage of the disease. All tumor biopsies and control samples were HPV-negative. The prevalence of HPV in the urothelium was very low, regardless of the stage and degree of the disease, and, therefore, it is unlikely that HPV is the causative agent of urothelial BC in the Indian population. However, the role of other types of HPV in the etiology of BC requires clarification and further research on this topic [36].

The role of herpesviruses in the carcinogenesis of prostate and bladder cancer

The role of viruses of the Herpesviridae family in the etiology of bladder and prostate cancer is currently being discussed. Herpesviridae is a large group of big viruses with linear genomic DNA up to 20 thousand nucleotide pairs in size. With more than 25 groups, only 6 can reliably cause diseases in humans: herpes simplex virus I and II, herpesvirus type 3 (chickenpox virus), herpesvirus type 4 (Epstein-Barr virus), herpesvirus type 5 (Cytomegalovirus), and herpesvirus type 6. Data on the carcinogenic effect of cytomegalovirus infection (CMV), herpes simplex virus (HSV), and Epstein-Barr virus (EBV) are increasingly appearing in the literature.

In recent years, more research has been conducted on the role of various viruses in the carcinogenesis of PC. According to the study by T.T. Andabekov et al. (2010), low-grade PC was observed in patients with a positive test for CMV ($p < 0.05$). Moreover, in this category of patients, the five-year survival rate after radical prostatectomy without relapse was lower (38.1%) compared with CMV-negative men (96.3%) ($p < 0.05$). The average life expectancy of deceased patients with CMV who underwent combination treatment was less than in uninfected patients: 27.71 and 76.6 months, respectively ($p < 0.05$). The data of the conducted study show that CMV is an important risk factor for the relapse of the disease, which should be taken into account when choosing surgical treatment for patients with PC [37].

In the study by O.B. Laurent et al. (2015), 54 patients (44 men and 10 women) with BC and one patient with urothelial papilloma were examined. The histological evaluation revealed high-grade urothelial cancer in 72.2% of cases (39 patients), low-grade cancer in 25.9% (14 patients), and urothelial papilloma in 1 case (1.8%). Fifteen patients (27.8%) had a relapse of the disease. All patients participating in the study also underwent blood tests for IgG and IgM antibodies to herpes simplex virus (HSV) type I and II, CMV, and Epstein–Barr virus (EBV). The results of the study revealed high titers of anti-CMV IgG in patients with BC. Moreover, the level of these antibodies in patients with recurrent tumors, a high degree of anaplasia, and high grade of the disease was much higher. There was a statistically significant correlation between the presence of CMV DNA in the tumor and the level of anti-CMV IgG, as well as the stage of the disease, the level of early EBV

antibodies, and antibodies to the nuclear antigen of EBV. In addition, the relationship between the level of anti-CMV IgG and the stage of the disease, tumor recurrence, the level of early antibodies to EBV, as well as a significant change in the level of anti-HSV I and II IgG was revealed [38].

In 2018, I. V. Kosova et al. examined and analyzed 100 patients (72 men and 28 women) aged 38 to 90 years with BC. This study was performed using molecular and genetic and ELISA methods for diagnosing the presence of viral infections (HSV I and II, CMV, EBV, and human papillomavirus). Additionally, histological (evaluation of lymphocytic infiltrate, inflammatory activity, cytopathic changes) and immunohistochemical (CD31, EGFR, Ki67, p63, p53, CD44, Bcl-2) methods were used.

In the course of this study, a relationship was revealed between the studied viral infection parameters in patients with BC. EGFR expression and the level of anti-EBV Ig-VCA ($p = 0.032$), proliferative activity ($p = 0.05$), and p53 ($p = 0.025$) correlated in patients with the presence of viral DNA in the tumor tissue, and the presence of CMV was associated with focal hyperplasia ($p = 0.012$), koilocytosis ($p = 0.028$), the presence of leukocytes ($p = 0.012$) and eosinophils ($p = 0.012$). Infection of tumor tissues with highly oncogenic HPV strains affected proliferative activity ($p = 0.05$), koilocytosis, and neoangiogenesis ($p = 0.008$). Increased proliferative activity, expression of apoptotic factors, growth factors, and neoangiogenetic factors in patients with the presence of viral DNA in the tumor tissue indicates an unfavorable course of the tumor process [39].

CONCLUSION

An in-depth study of how human herpes and papillomaviruses affect the origin of malignant tumors of the prostate and bladder, as well as the course and prognosis of these diseases, can become a source of information for the development of new approaches to their diagnosis, prevention, and monitoring of morbidity. In addition, the data obtained can be used in practical medicine, which can significantly improve the five-year survival rate in patients.

The analysis of available literature has shown the importance of viral infection testing for herpes and human papillomaviruses in the male population for timely treatment. It will definitely become one of the links in the prevention of prostate and bladder cancer development.

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