Review

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The high-risk HPV infection and urinary system tumor

DOI: 10.2478/ii-2018-0004

Received January 28, 2018; accepted February 06, 2018; published online April 10, 2018

Abstract: HPV is classified into high-risk and low-risk types depending on its probability of leading to tumorigenesis. Many studies have shown that HPV infection, especially the infection caused by the high-risk type, is always related to prostate cancer, bladder cancer, penile cancer, testicular cancer, and other urinary system tumors. However, previous studies differed in sexual openness and racial genetic susceptibility of the study object, sample size, and experimental methods. Hence, the correlation between high-risk HPV infection and urinary system tumors remains controversial. The early open reading frame of the HPV genome is composed of E1–E7, among which E6 and E7 are the key transfer proteins. The combination of these proteins with onco-gene and anti-oncogene may be one of the mechanisms leading to tumorigenesis.

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

HPV has a simple structure composed of protein capsid and covered core without an envelope. The virus has a small double-linked ring DNA located in the core. The virus is epithelial and dermatotropic. HPV has many different subtypes because of the diverse gene sequences of encoding L1 capsule protein. Over 200 subtypes of HPV have been discovered. HPV can be classified into skin type and mucous membrane type according to the infection site. It can also be categorized into high-risk and low-risk types depending on its probability of leading to tumorigenesis. The high-risk type covers HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV68, HPV73, HPV82, etc. Previous studies have proved that high-risk HPV infection had a certain correlation with the occurrence and development of lung cancer, cervical cancer, and many other malignant tumors [1]. HPV infection plays a very crucial role in the occurrence and development of urinary system tumors [2]. However, the diversity of sexual openness and racial genetic susceptibility of the study object, sample size, and experimental methods among these studies has resulted in the ambiguity in the correlation between high-risk HPV infection and urinary system tumors. This article describes the progress in the study on the relationship between high-risk HPV infection and tumors of the urinary system.

1 Relationship between high-risk HPV infection and tumors of the urinary system

1.1 High-risk HPV infection and prostate cancer

Studies have suggested that HPV infection, especially the high-risk type, is highly detectable in prostate carcinoma tissue. This characteristic indicates that HPV infection has a correlation with the occurrence and development of prostate cancer [3]. Early foreign studies had shown that the detection rate of high-risk

HPV in prostate carcinoma tissue is higher than that in benign prostate hyperplasia [4]. Anwar *et al.* [5] demonstrated that high-risk HPV16/18 infection was correlated with clinical staging and pathological Gleason score of prostate cancer. This finding implied that high-risk HPV infection was correlated with the development of prostate cancer. Pascale *et al.* [6] showed positive HPV E7 expression in 112 (74.67%) of the 150 prostate cancer specimens they investigated. This phenomenon indicated that high-risk HPV infection is correlated with the occurrence and development of prostate cancer; this correlation was also found in subsequent studies [7]. The early open reading frame (ORF) (E) of the HPV genome is composed of E1–E7, among which E6 and E7 are the key transfer proteins. Araujo-Neto *et al.* [8] collected 104 prostate cancer specimens from northeastern Brazil, and their test results showed negative expression of HPV16 E6/E7. Thus, they believed that HPV infection was not the pathogenic factor of prostate cancer. Chen *et al.* [9] showed 14% (7/51) positive rate of HPV18 in prostate cancer and 27% (3/11) positive rate of HPV18 in prostate hyperplasia. This result confirmed that HPV18 infection was not related to prostate cancer, which is consistent with the finding of Aghakhani *et al.* [10]. The diversity in sexual openness and racial genetic susceptibility of the study object, sample size, and experimental research methods led to different conclusions on the correlation between high-risk HPV infection and urinary system tumors.

1.2 High-risk HPV infection and bladder cancer

Shaker *et al.* [11] showed that the positive rate of high-risk HPV16/18 in transitional cell carcinoma of the bladder was much higher than that in chronic cystitis and normal bladder tissues and had a certain correlation with the clinical staging of bladder cancer. This finding indicated that HPV16/18 infection probably participated in the occurrence of transitional cell carcinoma of the bladder and had a certain influence on the malignancy and progression of the disease. Berrada *et al.* [12] conducted a test over the high-risk HPV DNA in the tumor tissue of 45 bladder cancer patients from Morocco. The results implied that high-risk HPV infection, especially HPV16 infection, was related to the occurrence and development of bladder cancer.

Cai *et al.* [13] suggested that the positive rate of HPV in bladder cancer tissue specimens was 34.5%, and the ORF (E) of HPV genome in urine specimens of bladder cancer patients was composed of E1–E7, among which E6 and E7 were key transfer proteins. These proteins account for 46.1%, which is markedly higher than that of normal people. Meanwhile, Shigehara *et al.* [14] also confirmed the correlation between high-risk HPV infection and bladder cancer.

Published reports vary among regions. Schmid *et al.* [15] collected 109 bladder cancer tissue specimens, among which 14 were superficial tumors, 56 were infiltrating tumors, and 12 were high-level carcinoma *in situ*. They measured the expression of 14 types of high-risk HPV and 35 types of low-risk HPV by using the quantitative PCR method. The results showed negative HPV expression in all tissues. Pichler *et al.* [16] conducted a test over the cancer tissue specimens from 186 patients who were treated with radical cystectomy. Positive HPV16 expression was found in only two cases, and positive HPV6 expression was found in only one case. However, the majority of domestic reports concluded a correlation between high-risk HPV infection and bladder cancer. Fu *et al.* [17] showed that high-risk HPV infection was the pathogenic factor of bladder cancer and negatively correlated with bladder cancer staging. Wang *et al.* [18] conducted the test over urine specimens of 60 bladder transitional cell carcinoma patients by PCR technology and specific endonuclease technology. The results showed corresponding 80% and 75% positive rates of HPV18, as well as the correlation of this virus with the progression of the disease. This result indicated that HPV in urine could work as the biomarker for the early screening of bladder cancer.

1.3 High-risk HPV infection and penile cancer

Stratton and Culkin [19] collected a total of 1010 penile cancer tissue specimens from 25 countries during 1983–2011 and found 33.1% positive rate of HPV in penile cancer tissues. Thus, positive HPV16 expression

was found in 68.7% of all specimens and positive HPV6 expression in 6.7% of all specimens [20]. Djajadiningrat *et al.* [21] showed 25% positive rate of high-risk HPV in penile cancer tissue (HPV16 infection accounted for 79%), and high-risk HPV had a certain correlation with the clinical staging and pathological grading of penile cancer patients. The five-year survival rate of these patients with negative HPV expression was markedly higher than those with positive HPV expression. Zhai *et al.* [22] found high-risk HPV infection in 25.9% of the penile cancer tissues, and HPV16 accounted for the highest proportion. However, the high-risk HPV infection was irrelevant for the clinical staging and pathological grading of penile cancer patients.

1.4 High-risk HPV infection and testicular cancer

A few studies have investigated the relevance between high-risk HPV infection and testicular tumor, and conclusions remain controversial [23]. Kondoh *et al.* [24] found that the incidence of testicular germ cell tumor was very high in the transgenic mice that carried the HPV16 E6/E ORF. This result indicated that HPV16 infection had a certain correlation with the occurrence of testicular cancer. Strickler *et al.* [25] studied 905 epithelial cell-derived tumor patients, and the findings showed positive HPV16 immunoglobulin G antibody in the serum of 52% of cervical cancer patients and only 5% of testicular cancer patients. Thus, they concluded that serological test may not provide evidence for the relevance between HPV16 infection and testicular cancer.

2 Action mechanism of HPV in tumorigenesis

The action mechanism of HPV in tumorigenesis remains unclear. At present, HPV is believed to lead to changes in the expression of some oncogenes and anti-oncogenes and accordingly participate in or result in the occurrence of some tumors. E6 and E7 need oncogenes to be activated, whereas E6 oncoprotein could enhance the transfer of epithelial cells. E6 and E7 have been proved to be closely related to tumorigenesis, and their combined action with oncogenes and anti-oncogenes may lead to tumorigenesis [26]. Integration of DNA of viruses into the cellular gene is the key step for tumorigenesis. The HPV DNA integrated into the human cellular gene exhibits the following activities: leads to inhibiting effect on the vascular endothelial growth factor through E2 gene inactivation and E5 gene; leads to high expression of E6 and E7 proteins; inhibits the activity of P53, retinoblastoma (RB), and other anti-oncogenes; and results in abnormal cell differentiation and activated transcription of telomerase. These activities may be the mechanisms for tumorigenesis [27].

In summary, the occurrence of urinary system tumors is the result of combined actions of many factors. High-risk HPV infection is not only a carcinogenic factor but also a risky factor for tumorigenesis. The clinical and trial study of high-risk HPV provides another clue for exploring the causes and pathogenesis of tumors in the urinary system. Few domestic studies have determined the relevance between HPV infection and urinary system tumors or the relevant action mechanism. Thus, subsequent studies will be conducted on the following aspects: (1) elucidating the HPV infection of Chinese urinary system tumor patients and the distribution of different HPV subtypes, especially in the regions with high HPV prevalence; and (2) exploring the molecular mechanism of HPV infection in the occurrence of urinary system tumors and the relationship of HPV with oncogene and anti-oncogene.

Acknowledgments: None.

Conflict of interest: The author states no conflicts of interest.

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