

**Review Article****A review of viruses related to prostatic cancer**Iman Ghasemzadeh<sup>1</sup>, Payam Sadeghi\*<sup>2</sup>, Rokhsareh Zare Shahri<sup>2</sup><sup>1</sup> Infectious & tropical diseases research center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.<sup>2</sup> Student Research Committee, Hormozgan University of Medical Sciences (HUMS), Bandar Abbas, Iran<sup>3</sup> Health Information Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.\*Corresponding Author: [payamsadeghi68@gmail.com](mailto:payamsadeghi68@gmail.com)

**Abstract:** Today malignancy causes many mortality around all of the world, primary or secondary malignancy imposed economic and emotional costs to patients, families and the community. Several etiology have been reported for malignancy, like genetics, microorganism (bacteria, viruses) and etc. Viruses are known as microorganisms causing various diseases, cancers and malignancies such as cervical cancer and liver cancer. Today, different investigations are conducted on the presence of viruses as an etiology of prostate cancer. In this review article, it will be indicated that viruses including HPV, HSV and XMRV are more recognized as involved in prostate cancer. Other viruses such as BKV, ADV, CMV, SD-MSV, JCV and EBV have also been investigated. Generally speaking, whether or not any of these viral factors are oncogenes for prostate cancer has not been proved. Research findings have been divergent. It seems that conducting studies through specific and similar procedures and consideration of factors differing between the two research groups such as epidemiologic conditions and background diseases is highly required.

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**Keywords:** Prostatic Neoplasms; Viruses; Risk Factors**1. Introduction**

Malignancy is a process duo to rapid growing in cell proliferation or stop apoptosis (1). It can be a primary malignancy like blood malignancy, breast cancer and some else, or can be secondary and metastatic from a primary malignancy (2). Another side it may be duo to underline disease, for example in HIV patient, we see Kaposi's sarcoma (caused by Human Herpesvirus 8) (3) or gastric malignancy can caused by H Pylori (4). Malignancy imposed economic and emotional costs to patients, families and the community (5). Malignancy of the urinary tract system (kidney, bladder, prostate) comprises part of mortalities in societies (6) One of these malignancies is prostate cancer, prostate is an organ in male genital system, its two common disease are benign prostatic hyperplasia and prostate cancer (PCa), and the most common type of prostate cancer is adenocarcinoma (7). Some research has witnessed the growing occurrence of prostate cancer in the last two decades. This disease is in fact the second widespread malignancy and the sixth cause of mortality among men in the world (8). In European countries, this cancer is considered as the most prevalent non-dermatologic malignancies among men. It led to 90 thousand mortalities in 2008 in Europe (9). The occurrence of prostate cancer differs from one country to another. Some statistics

show that in China 12.1 and in Japan 12.7 per 100 thousand people are afflicted with prostate cancer (10). Various factors are involved in the development of this cancer including age, smoking, hereditary factors, genetics as well as environmental factors such as bacteria and viruses (11-13). Inflammations, today, have a significant role in causing prostate cancer. They account for 17% of total malignancies (14). Infectious diseases such as sexually transmitted diseases, prostate inflammation, etc. are among them (15). Viruses can also act as an oncogene to develop the diseases through different pathologies (16). Such viruses are Human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), Human herpes virus (HHV), Human papillomavirus (HPV), Hepatitis B virus (HBV), Hepatitis C virus (HCV) and so on. Each can lead to a certain malignancy in some part of body. As an instance, HPV can produce cervical cancer in women, HBV could lead to some metabolic malignancies such as liver cancer (17-21). Generally speaking, affliction with a viral disease can cause personal, economic and other similar crises for both patients and their families. This attests to the importance of knowing about such diseases (18). The role of viruses in producing prostate cancer has been investigated in different experimental methods every time focusing on the effect of one particular virus.

Cancer is a situation which can lead to taking difficult situations (22). A higher level of education in students or nurses can diminish these situations. (22-24). However, due to the scarcity of review research with this concern (the role of viruses in developing prostate cancer or malignancy) and the role that is played by chronic medical diseases in every aspects of life (25-28), the present article intends to discuss the findings of different studies which investigated the viruses involved in developing prostate cancer.

## 2. Material and Methods

In this review research, accessible databases in Iran including Google Scholar and PubMed were perused searching for the key words: virus, prostate, prostate cancer, risk factor, etiology. All papers published on this subject between 1976 and 2014 were used.

### Human Papillomavirus (HPV)

In their investigation of the correlation of HPV and prostate cancer, Pascale et al. concluded that 74.67% of cancerous patients were exposed to HPV E7 protein. Moreover, the survival rate of positive HPV patients was greatly worse than the negative HPV (29). In a meta-analysis of 25 studies, Lin et al. finally concluded that the risk of prostate malignancy is increased by HPV types 8 and 16 and, therefore, a potential correlation exists between these two (30). Gherdovich et al. studied 60 BPH patients along with 5 patients down with prostate carcinoma in terms of HPV. They found that HPV infections are not prevalent in human prostate (31). The correlation between prostate cancer and HPV was explored in Iran by Mokhtari et al. who observed that HPV was positive in 10% of patients with prostate adenocarcinoma. In the BPH group, however, only 1.1% was found to be positive. They concluded that HPV was a risk factor for the occurrence of prostate adenocarcinoma (32). In a study using PCR technology, Whitaker et al. investigated HPV and EBV in prostate (33). They concluded that HPV virus is observed in normal tissues and malignant and benign prostate. Its type 18 can act as an oncogene (34). Nicol et al, in their study, view HPV as an etiologic factor in producing prostate diseases such as prostate cancer (35). In another research, the same researchers confirmed the role of this virus as an oncogene (36). In her research, Nicoliny mentioned the discovery of the DNA of HPV in the tissue of prostate gland. This researcher concluded that HPV type 16 is more prevalently found in malignant and benign tissues than type 18. In sexually transmitted infections, type 16 can even act as a potential factor or an oncogene (37). The conclusion Hoffman et al.

made was that HHV-8 was found more than the other groups among male patients suffering from prostate cancer, and that this virus can develop the disease further (38). Serth et al. concluded about HPV-16 that this virus can help to further advance the sub-categories of prostate cancer (39). In their research, Al Moustafa concluded that HPV could play a key role in the advancement of prostate cancer (40). In Brazil, Silvestre et al. reported that HPV is correlated with prostate cancer (41). The correlation of HPV and prostate cancer was also investigated by Dillner et al. who found a significant correlation between the level of anti-body against HPV 18 and prostate cancer. HPV was found to have a tendency towards the consequences of cancer and HPV types 11 and 33 are considered to be no risk for developing prostate cancer (42). Adami et al. concluded that HPV-16 and 18 were not correlated with the occurrence of cancer. HPV 33 is correlated with this cancer and the level of anti-body against it is increased in patients with prostate cancer (43). Ghasemian et al. pointed out the key role of HPV in prostatic diseases among Iranians. However, demographic findings prove the role and correlation of prostate inflammation and this virus which could finally lead to prostatic malignancies (44). Chen et al., in their research on 51 patients with prostate adenocarcinoma and 11 patients with benign prostate hyperplasia (BPH) concluded that different types of HPV are not correlated with the occurrence of prostatic diseases including prostate cancer (45). Sutcliffe et al. conducted a research aiming to explore the correlation of Chlamydia trachomatis, Human Herpesvirus type 8, Human Papillomavirus and prostate cancer. In this case-control study no correlation was found between prostate cancer and HPV types 16, 18 and 33 (46). In another case-control study, Hrbacek et al. compared the levels of anti-body against the microbes in male urinary-reproductive system in two groups of patients one with prostate cancer and another with BPH. The level of HPV-18 and CMV was lower in the cancerous group. The level of HPV-6 was correlated with Gleason score in cancerous patients. They concluded in their research that the presence of antibody or in high levels cannot be an indicator of a risk of affliction with prostate cancer (47). Tachezy et al. also found no correlation between this virus and prostate cancer (48). In Sarkar's study, HPV-16 was observed in some patients with prostate carcinoma, but dissimilar to the other studies, it does not approve the interference of this virus in the prevalence of prostate cancer (49). The role of HPV in the occurrence of prostate carcinoma was also investigated by Aghakhani et al. In their case-control study, no statistically significant difference was observed between the two groups of prostate

carcinoma and benign prostate hyperplasia in terms of the presence of HPV-DNA and risky types of HPV (50). In Sweden, Korodi et al. found no correlation between HPV-8 and the development of prostate cancer (51). In another study, the same researchers concluded that no risk is caused by HPV 16, 18 and 33 in the development of prostate cancer (52). Strickler et al. realized that HPV was not correlated with the occurrence of prostate carcinoma (53). In their investigations on black and white subjects, Wideroff et al. concluded that HPV was not a threat to prostate cancer and did not indicate the intensity of disease in the black race (54). In another research, Balis et al. were encountered with no effect of HPV on the development of prostate cancer. Gazzaz also found no interrelationship of HPV 18 or 16 in the occurrence of this kind of cancer (55). What Leiros et al. achieved after a genetic study on prostate cancerous patients was that no difference exists between the 72<sup>nd</sup> codon of the gene p53 in patients with positive and negative HPV (56). Similarly, no correlation was observed between HPV and prostate cancer in Groom et al.'s study (57).

#### **Xenotropic Murine Leukemia Virus-Related Virus (XMRV)**

According to Schlaberg, XMRV can be found in the prostate malignant epithelium and is closely related to prostate cancer especially in its high grades (58). XMRV is referred to by Kim et al. as a virus related to prostate cancer which enacts its role through a paracrine (59). Arnold et al. firstly stated in their research that this virus is correlated to the development of prostate cancer in 27% of cases. Secondly they concluded that this virus is found in some of the patients with prostate cancer and that patients infected by this virus should be taken under great care since its exact way of transmission is not evident (60). In a study on patients afflicted with prostate tumor in Germany, Hohn et al. found little trace of XMRV among these patients. They argued that this could have been affected by geographical area and epidemiologic status (61). Dong et al., obsessed with this background that XMRV plays a role in developing prostate tumors, concluded that this virus can be controlled with the help of anti-viral interferon (62). They also mention the role of RNALS in removing all infections and also add that XMRV can be a factor of developing cancer (63). No significant correlation was found by Groom et al. between this virus and prostate cancer (57).

#### **Herpes Simplex Virus (HSV, HHV)**

Luleci et al. investigated the correlation between HSV and the occurrence of malignancies in the male urinary system including bladder and prostate. They

let cases with known cancers enter their research. In the control group, anti-body was positive in 62.86% of cases. In the treatment group among patients with bladder cancer this rate was 90.70%. Among patients with prostate adenocarcinoma it was 87.5% (64). In their research aiming to examine the relationship of sexually-transmitted infections and prostate cancer, Dennis et al. found a strong correlation between HSV-2 and the occurrence of prostate cancer (65). In a meta-analytic study aiming to delve into the correlation of HSV-2 and 8 and prostate cancer, Geet al. analyzed 11 articles and eventually found a significant correlation between HSV-2 and the occurrence of prostate cancer (66). Baker et al. mentioned herpes as an etiologic factor for developing prostate carcinoma and suggest other similar research to investigate it further (67). Jenkins et al. concluded that HHV-8 cannot be a main factor of developing prostate cancer (68). After including 40 patients with benign or malignant neoplasms in their research, Peker et al. observed that the amount of anti-body against HSV was increased in patients with benign prostate such as BPH compared to the malignant group (69). Similarly Herbert et al. studied two groups of patients one with benign and the other with malignant prostate and observed no difference in terms of the level of Anti-body against HSV type 2 (70). Haid et al. investigated HSV-2 among patients with prostate cancer and BPH. Eventually they observed no significant divergence between the two groups. Although this virus is prevalent in prostate cancer, it has nothing to do with its occurrence (71). Korodi et al.'s research as well did not approve the role of HSV-2 in developing prostate (72). Eizuru et al. found traces of this virus in premalignant and malignant cervical cancer but not in prostate cancer (73). In their meta-analytic study concerned with HHV-8, Gee et al. found no correlation between this virus and the occurrence of prostate cancer (66). The interrelationship of HHV-8 and prostate cancer was also investigated by Donald et al. in a case-control study resulting in no significant correlation (62). A negative correlation was found between positive HHV-8 and the severity of the occurrence of prostate cancer by Sutcliffe et al. (46). The interrelationship of sexually-transmitted infections and the risk of prostate cancer was explored by Huang et al. who found no certain correlation. Therefore, more extensive research is required to prove that sexual infections act as a background factor involved in the development of prostate cancer (74).

#### **Epstein-Barr Virus (EBV)**

Grinstein et al. found evidence of EBV in different cancers such as breast, lungs, colon and prostate. This

virus can act as an oncogene (75). In an experimental research, Bergh et al. found no correlation between prostate cancer and EBV (76). Whitaker et al. pinpoint that EBV is found in normal tissues and benign and malignant prostate tumors. However, it cannot be considered as an oncogene for malignancy (34).

#### **John Cunningham virus (JCV)**

No significant correlation was found between the occurrence of prostate cancer and JCV as reported by J Bergh et al. (76).

#### **Soehner-Dmochowski Murine Sarcoma Virus (SD-MSV)**

With the help of an experimental method called 'Fixed immunofluorescence', Dmochowski et al. could show the reaction among 38% of patients with prostate cancer to this virus. In 11 patients signs of the type C virus were observed (77).

#### **Cytomegalovirus (CMV)**

The level of the anti-body against this virus was measured by Peker et al. who observed an increase in this level in patients with benign neoplasms (69). No significant correlation was reported between this virus and prostate cancer by Hrbacek et al. in their case-control study. They concluded that the risk of the occurrence of prostate cancer was not correlated with the level of the anti-body against this virus (47). Boldogh et al. concluded in their investigation that the presence of CMV is accompanied by degrees of prostatic abnormality such as prostate cancer and BPH (78).

#### **Adenovirus (ADV)**

Peker et al. found an increase in the amount of the anti-body against ADV among patients with prostate malignancy compared to the benign cases (69)

#### **BK virus (BKV)**

What Balis et al. found was that BKV could significantly affect the development of prostate cancer (73). No such correlation was found by Groom et al. between this virus and the occurrence and development of the above-mentioned cancer (57)

### **3. Discussions**

Today, viruses have become a great problem in societies. Such viruses as HIV, due to their diverse consequences, have actually concerned everyone (19). Some of the recent research report on the correlation of viral and bacterial infections as well as chronic inflammations in producing and developing cancers through metabolites and microbial factors such as cytokines (79). Prostate cancer is a major

problem that encounters human communities today and is caused by different factors including environmental factors along with others such as one's race (80).

A great body of research has been conducted to explore the role of viruses in developing prostate cancer. In the majority of studies, mention has been made of the correlation of HPV and HSV and this disease (30) (46) (47) (66). Considering the activity of prostate as a sexual gland and the existence of these two viruses as the factor of some sexually-transmitted diseases, they are expected to play a role in developing prostate cancer (65). What is evident from the perusal of the afore-mentioned literature is that considering HPV and HSV as an oncogene factor of prostate cancer is not proved yet. There are occasionally studies with similar methodologies and different results. The type of viruses discussed in these studies were types 11, 16, 18 and 33 for HPV and 2 and 8 for HSV (66) (42).

XMRV is a virus that has attracted the attention of many of the recent studies investigating its role in developing prostate cancer (81). Its role in causing prostate cancer is not proved yet and is more of a theory type. It needs to be reminded that the number of research on this virus is not as many as the other two. Nevertheless, the findings are considerable.

In the case of the other viruses (BKV, ADV, CMV, SD-MSV, JCV and EBV) the previous research neither proves nor rejects their role (47) (57) (69) (75) (76) (77).

One reason why there is a variety of research findings is the necessity of conducting more of the similar research abiding by more standardization techniques such as sample homogenization in terms of epidemiologic, demographic, health state and background disease conditions. For instance, in one study, the intervening factors might not have been omitted and this could be why findings different from reality were obtained (82).

Some of those studies made use of specific experimental methods. In some, for instance, the level of the anti-body against the virus was measured. In some others, they attempted to find the DNA of the virus using experimental methods such as PCR (34) (43) (47).

All in all, in order to approve the presence of viruses as an etiologic factor for producing and developing prostate cancer there is still a need for further research.

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