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Review

Viral etiology of prostate cancer: Genetic alterations and immune response. A literature review

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ABSTRACT

Prostate cancer is one of the most common cancers in men. Recent estimates suggest that over a million men are diagnosed with the disease annually. Prostate cancer pathogenesis involves both heritable and environmental factors. The molecular events involved in the development or progression of prostate cancer are still unclear. Recent body of literature highlights the role of viral infections in initiation or progression of prostate cancer. In this regard, certain viruses have been reported to interact with host proteins and bring about changes in genetic, immunological and inflammatory events that lead to initiation or progression of prostate cancer.

We conducted a comprehensive PubMed database search to identify publications relevant to viruses associated with prostate cancer. In this review, we discuss the possible viral etiology of prostate cancer and evidence of viral-mediated genetic changes, and immune dysregulation involved in initiation or progression of prostate cancer.

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men. According to recent estimates, over a million men are diagnosed with the disease annually, with the greatest incidence in more developed regions such as Australia, New Zealand, North America, and Western and Northern Europe. Incidence rates are also relatively high in the Caribbean and sub-Saharan Africa, which also has the highest prostate cancer mortality rates [1].

PCa pathogenesis involves both heritable and environmental factors. The latter have been implicated from studies in immigrant Asian populations to the West that exhibits a higher incidence of PCa than their counterparts still living in Asia. As in cancers of the stomach, intestine, and liver, chronic inflammation secondary to infection and other environmental factors such as diet, may also play a role in the development of prostate cancer [2].

Mechanisms of prostate carcinogenesis and role of inflammation have been reviewed in detail previously [2,3]. Here we focus specifically on possible viral etiology of prostate cancer and evidence of viral-mediated genetic changes and associated immune dysregulation.

2. Methods

The PubMed, Medline, Google Scholars, and Cochrane databases were searched for publications relevant to viruses associated with PCa (Fig. 1). An initial broad search was conducted using the terms “Prostate cancer”, “prostate cancer, virus and immune system”, “prostate cancer, virus and genetic changes” and “virus-mediated genetic changes in prostate cancer”. The 1176 articles identified were further limited to 561 after only selecting studies on humans and those published in English. After additionally excluding unrelated publications, such as those involving bacterial etiology, infectious diseases, cancer therapy, case reports, methodology papers, etc., 48 full-text articles were reviewed. This includes four articles identified by reference hand-searches.

3. Viruses associated with prostate cancer

A number of pathogens can infect the prostate, including viruses. Several studies have documented the presence of viruses such as human papillomavirus (HPV), herpesviruses including cytomegalovirus (CMV), human herpes simplex virus type 2 (HSV2), human herpesvirus type 8 (HHV8) and Epstein-Barr virus (EBV), polyomavirus BKV and xenotropic murine leukemia virus-related virus (XMRV), in the prostate.

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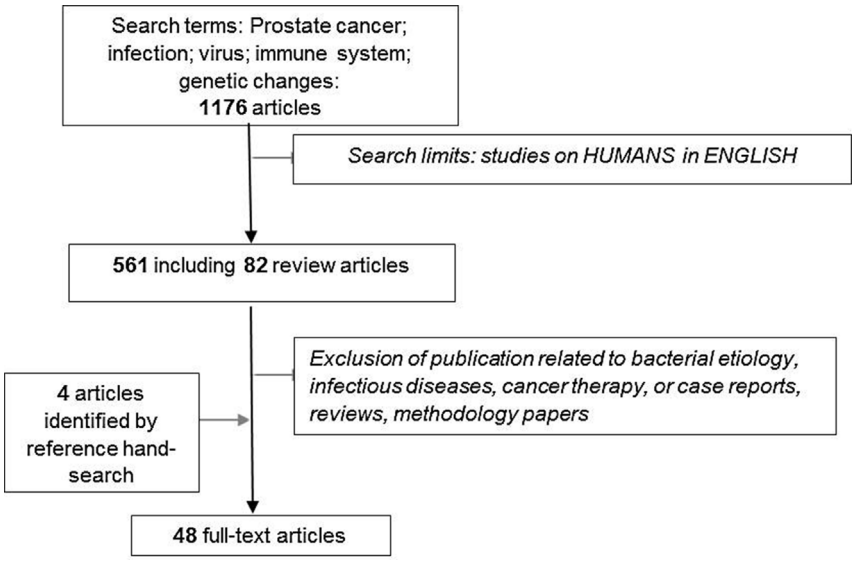

Fig. 1. Flowchart outlining the search strategy employed to identify the relevant studies.

However, the frequency of infection and whether an inflammatory response is elicited or has a direct association with prostate carcinogenesis has not yet been established [2]. A systematic review of three decades of research on infection and prostate cancer published in 2013 also found no conclusive evidence of the role of infection in the etiology of PCa [4]. This may be because many reported studies investigating viral infections in PCa have been limited by small sample size, inability to test previous or non-persistent infections, and inadequate tissue sampling or viral detection methods [2]. In the past 5 years (January 2012–January 2017), further studies have continued to explore the viral etiology of PCa, which are summarized below.

3.1. HPV

HPV infection is an established etiologic factor for cancers of the cervix, uterus, vulva, vagina, penis, and anus [5]. Given its anatomic proximity to anogenital and urinary sites, the prostate has been extensively investigated for HPV infection. Studies reported in the literature, mostly in Western populations, have varied considerably in terms of study design and methodology. Consequently, conclusions have also not been homogenous, with only some studies showing statistically significant differences in HPV infection between prostate cancer patients and controls [4]. More recently, studies from Mediterranean and Asian populations have suggested a link between HPV, particularly high-risk sub-types 16 and 18, and prostate cancer [6–9]. The strength of association varies with geographic distribution [10–13]. Moreover, studies have found significant positive associations of PCa with sexual activities and sexually transmitted diseases [14–16], including HPV, suggesting further that an infectious etiology may be involved in prostate carcinogenesis. HPV warrants a more rigorous investigation, particularly to reconcile the diversity in reported results within the same populations [17–20].

3.2. Herpesviruses

Herpesviruses can be transmitted through both sexual and non-sexual routes, and are highly prevalent in some populations [21]. Herpesviruses, such as EBV and HHV-8, have been associated with human malignancies [22]. In prostate cancer, CMV, HSV-1, HSV-2, HHV-8 and EBV infections have been investigated [4]. A recent study in men from Tobago, a region with one of the highest incidence and mortality rates from PCa, showed that HHV-8 establishes a latent infection in the prostate that is associated with macrophage infiltration and inflammation [23]. However, a meta-analysis to explore the association between infections caused by several sexually transmitted pathogens, including HSV-1, HSV-2, HHV-8, and CMV, revealed no significant association with increased risk of PCa [24].

3.3. BKV

Polyomavirus BK is usually acquired in early childhood, has a long latency period with the urinary tract as the primary site of latency and possibly oncogenic potential as demonstrated in animal models. Theoretically, it is an attractive candidate for viral etiology of PCa and has been detected in PCa [4]. In a recent study from Iran, some of the highest BK infection rates were reported, with 28% in PCa, mainly in patients with lower Gleason scores, and 15% in benign prostatic hyperplasia samples [25]. Further research is needed to identify how BK may exert oncogenic activity over the clinical course of the disease, particularly in early stages of PCa development [26].

3.4. XMRV

Since its discovery in 2006, the role of the gammaretrovirus XMRV in PCa has been highly debated. XMRV has been detected in PCa, but high false positive rates in most published studies due to contamination of samples and/or laboratory reagents have brought its role as a human pathogen in prostate carcinogenesis into question [4,27]. Recent studies have not found any conclusive biologic evidence of XMRV infection in PCa in different populations [28–32]. Work in human cell lines has also shown XMRV is not a human pathogen [33], although it infects prostate cancer cell lines preferentially [34]. Further studies are required to determine whether XMRV has any clinical association with the onset or progression of PCa.

4. Prostate carcinogenesis: interplay of host genetics and viral infection

The molecular events involved in the development of PCa are still unclear. As discussed earlier, in addition to heredity causes, prostate cancer can be initiated or progressed by viral infections (Fig. 2). Many viruses are known to interact with host proteins and bring about changes in genetic, immunological and inflammatory events that lead to initiation or progression of tumors [35]. Viral products, for example, large T antigen of polyomaviruses, or E6/E7 proteins of HPV, can transform prostate cells and interfere with the interferon (IFN)