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Review Article

# FACTORS INFLUENCING PROSTATE CANCER

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**ABSTRACT**

Prostate Cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males. It accounts for 14% of the total new cancer cases and 6% of the total cancer deaths in males in 2008 [1]. The incidence and mortality rates were different in diverse geographic regions and racial ethnic population. But lack of consistency between studies additionally indicates that prostate cancer is a genetically heterogeneous disorder, with multiple genetic and environmental factors involved in its etiology.

The cause for prostate cancer remains unknown but age and family history have some vital role in its genesis. Diagnosis of this cancer in men less than 40 years is extremely difficult but the possibility for detection rises effectively after middle age. Inflammation also may play a role in the formation of prostate cancer [2, 3]. Several proxy measures of inflammatory status, such as history of prostatitis [4], history of sexually transmitted infections [5] and genetic variation in immune response genes [6] have been associated with prostate cancer risk. Common polymorphisms in pro-inflammatory and anti-inflammatory cytokine genes can influence cytokine production and may play a role in prostate cancer. This review will discuss the factors influencing prostate cancer.

**Keywords:** Prostate cancer, Risk factors, Cytokines, Single-nucleotide polymorphism.

**Prostate cancer**

Prostate cancer is generally regarded as a primary tumor due to their multiple independent histological foci which are often genetically distinct [7]. At initial stage it will not evince any clinical manifestation but in some cases symptoms often similar to that of BPH (Bovine Prostatic Hyperplasia). The common clinical signs include frequent urination, nocturia, dysuria and hematuria. Vas deferens deposits seminal fluid into the prostatic urethra and secretions from the prostate gland itself included in semen content. So, prostate cancer may also affect sexual function and performance [8].

In advanced stage it will spread to other parts of the body possibly causing additional symptoms. The most common symptom is bone pain often in the vertebrae, pelvis or ribs. Spread of cancer into other bones such as the femur also possible. Even though lung, liver and pleura are the common sites of secondary metastasis of prostate cancer, it can also affect the bone with characteristic osteoblastic lesions [9].

**Risk factors of prostate cancer**

Pathology of the prostate is a frequent cause of morbidity and mortality in male. Prostatitis affects around 15% of men at some point in their lives [10] and clinical benign prostate hyperplasia accounts for 20-40% but the histological prevalence is much higher [11]. Studies done in the past have pointed out that dietary carcinogen, hormonal imbalance; inflammation, host immune response and obesity are highly correlated with prostate cancer [2].

**Non-genetic factors:**

**Age**

The cause for prostate cancer remains unknown but age and family history being the main factors. Age is considered to be the most significant prostate cancer risk factor as the diagnosis of this cancer in men less than 40 years is extremely rare but the rate rises effectively after middle age. Autopsy studies of prostate cancer prevalence showed high prevalence of latent prostate carcinoma in men over 50 years of age when compared to incidence rates.

**Family history**

Depending upon the family history, prostate cancer can be classified as hereditary, familial and sporadic. Hereditary prostate cancer accounts for 5% to 10% of total prostate cancer [12]. Familial prostate cancer is estimated to accounts for 10% to 20% of all cases of prostate cancer but does not need strict criteria because it represents families in which there are two first-degree or one first-degree and two or more second-degree relatives with prostate cancer [12,13]. Sporadic prostate cancer signifies that only one man in a family has been diagnosed with prostate cancer. A meta analysis of 11 case-control studies and two cohort studies reported the risk of prostate cancer according to family history among first degree relatives estimated a pooled relative risk of 2.5 (95% confidence interval [CI] 2.2-2.8 [14].

**Ethnicity**

There exists noticeable ethnic variation in the incidence of clinically detected prostate cancer. In US and the UK black men are 2-3 times more likely to develop prostate cancer than white men [15]. The highest rates are in the USA, Canada, Sweden, Australia and France (48.1-137.0 cases per 1,00,000 person-years 1988-1992); European countries (Spain, Italy, England and Denmark) have intermediate rates (27.2-31.0cases per 1,00,000 person-years) and Asian countries the lowest rates (2.3-9.8cases per 1,00,000 person-years [16]. Risk factor for prostate cancer in different ethnicity groups involves three factors namely differences in diet, differences in detection (including clinical practice patterns and screening methods) and difference in the genetic makeup. There was an increase in prostate cancer risk when Japanese immigrated to Hawaii [17] and Los Angeles [18] and it revealed that diet and environmental differences play an immense role.

**Obesity**

The relationship between obesity and prostate cancer appears more complex. Obesity seems to contribute a greater risk for aggressive or fatal prostate cancer but perhaps to a lower risk for nonaggressive prostate cancer. Moreover, men with type 2 diabetes mellitus are at lower risk of developing prostate cancer [19].

**Genetic factors**

In fact, men who have a first-degree relative (father or brother) with prostate cancer have twice the risk of developing the disease and those with two first-degree relatives affected have a fivefold greater risk compared to men with no family history [20].

Carcinogenic factors can be endogenous (i.e. reactive radical species) or exogenous (i.e. ultraviolet A rays, oncogenic viruses) alter the oncogenes and/or tumor suppressor genes in the cells. Several genome-wide association studies have shown that the 8q24 region contains several risk loci that are linked to an increased risk of prostate cancer [21]. Using immunohistochemistry in combination with mutation verification, abnormal nuclear p53 accumulation and p53 mutation have been observed in prostate cancer and the association of mutated alleles with metastasis has been repeatedly detected [22].

Inflammation may play a role in the etiology of prostate cancer [2, 3]. Several proxy measures of inflammatory status, such as history of prostatitis [4**]**, history of sexually transmitted infections (5) and genetic variation in immune response genes [6**]** have been associated with cancer risk.

**Cytokines**

Cytokines are low molecular weight glycoprotein that regulates intensity and duration of immune response. Cytokines such as IFN-γ, TNF-α, IL-6 and IL-12 play a pivotal role in the development of an acute or chronic inflammatory response. Primary immune cells like macrophages and T cells are the main producers of cytokines in the body. The balance between different cytokines is important for proper functioning of the host immune system.

Cytokines are divided into two types like pro-inflammatory and anti-inflammatory cytokines. Pro-inflammatory cytokines are produced predominantly by activated immune cells like macrophages and are involved in the amplification of inflammatory reactions. These include IL-1, IL-6, TNF-a and TGF-ß. Anti-inflammatory cytokines such as IL-10, IL-4 and IL-12 are involved in the reduction of inflammatory reactions.

Cytokines may play essential role in prostate cancer initiation and progression. Cytokine production by the cells of the immune system may occur through antigen-specific and non-antigen specific stimuli. For example, monocytes when exposed to bacterial cell wall products such as lipopolysaccharide produce IL-12 and other cytokines which have multiple functions including influencing the expression of cytokines by other cells. Antigen-specific responses are generated by B and T cells through immunoglobulin and T cell receptors respectively. B cell activation may result in the production of IL-6 and other cytokines. T cells are the central players in linking non-antigen specific B cell and T cell responses together [23].

The adipokines, including leptin, adiponectin and interleukin (IL)-6 can act both locally through autocrine and paracrine signal transduction and systemically through endocrine pathways. Several properties of adipokines could influence prostate carcinogenesis in particular progression. Leptin, the first adipokine to be discovered has been shown by several studies to induce proliferation, cell migration and invasion and/or prevent apoptosis when administered to the androgen independent prostate cancer cell lines PC3 or DU145 [24]. IL-6 has been proved to be responsible for activating a variety of signal transduction cascades, some of which have the ability to stimulate gene expression in prostate cancer cells.

Hereditary plays an important role in prostatic carcinogenesis with an estimated one-quarter of all prostate cancer occurring in family clusters. Several of the genes associated with prostate cancer risk play a critical role in inflammatory pathways. Pedigree analysis revealed that genes such as RNASEL, PDF and MSR1 are linked to prostate cancer [25, 26, and 27]. Variants in genes encoding other components of the immune response including interleukins (IL-6, IL-8, IL-10) and toll-like receptors (TLRs) have also been evaluated for their associations with prostate cancer in case control studies [6].

**Single-Nucleotide Polymorphism**

Single-nucleotide polymorphism (SNP) is a DNA sequence variation, which occurs when a single nucleotide A, T, C or G in the genome alters between members of a biological species or paired chromosomes in an individual. It can be understood as the two sequenced DNA fragments from different individuals (GAACTTA and GAAGTTA) have a difference in single nucleotide. The genomic distribution of SNPs is not homogenous. Most of the single nucleotide polymorphism has only two alleles. It occurs more often in non-coding regions than the coding regions [28]. It is the most common human genomic sequence variation. It is the stable substitution of a single base and has a minor allele frequency of greater than 1% in at least one population [29]. Being silent in nature, they do not alter the function or expression of a gene.

Single-nucleotide polymorphism frequencies are usually determined by following ways:

- The amount of time since the mutation occurred
- Evolutionary pressure on biologically significant variants and those linked to the functional variant
- Random genetic drift
- Bottleneck events

Genome-wide linkage and association studies have been used to identify genomic loci contributing to prostate cancer susceptibility. Recently, the results of a genome-wide scan in Icelandic families suggested a vivid testimony for association between microsatellite marker at 8q24 (DG8S737) and prostate cancer risk [30].

Several studies that carried on the involvement of SNPs in cancer growth implicated on the fact that SNPs in or near CRP and interleukin-6 associates with circulating concentrations of their respective protein products [31, 32,33,34,35] showed functionality in vitro [36,37] If there is a chance of involvement in prostate carcinogenesis, then variation in the genetic makeup within the CRP and IL-6 gene regions have the ability to influence prostate cancer risk and progression by altering gene regulation and protein expression. Also, such regulatory SNPs may be more reliable indicators of long-term blood concentrations than circulating biomarkers measured at a single time due to temporal variation in blood concentrations. CRP or IL-6 SNPs could also have the capability to alter protein structure and function thereby increasing prostate cancer risk. Few studies have assessed the relationships between IL-6 or CRP SNPs and cancer risk. A large Swedish case-control study found no association between any of six IL-6 tag SNPs and cancer risk [38].

**Future aspect**

It is clearly evident that prostate cancer is influenced by genetic and several non-genetic factors and detailed investigation about these factors in future will be useful in the prompt diagnosis and treatment.

**CONFLICT OF INTEREST**

SS, RR and RK have contributed equally in collecting details as well as writing the manuscript.

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