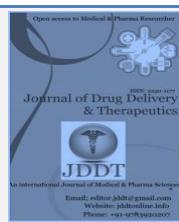


Available online on 15.03.2021 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

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Review Article

Risk Factors Associated with Prostate Cancer

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Article Info:



Article History:

Received 09 Jan 2021;
Review Completed 19 Feb 2021
Accepted 24 Feb 2021;
Available online 15 March 2021

Cite this article as:

Habib A, Jaffar G, Khalid MSZ, Hussain Z, Zainab SW, Ashraf Z, Haroon A, Javed R, Khalid B, Habib P, Risk Factors Associated with Prostate Cancer, Journal of Drug Delivery and Therapeutics. 2021; 11(2):188-193
DOI: <http://dx.doi.org/10.22270/jddt.v11i2.4758>

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Abstract

Globally prostate cancer is the second most familiar and fifth-most hostile neoplasm among male individuals. One of the emerging issues in men is prostate cancer. The Prostate is a ductal small walnut-shaped gland situated in men below the urinary bladder that produces the seminal fluid for sperms provision and transportation. The risk of emerging prostate cancer during the man's lifetime is one out of seven. According to the epidemiological studies, different environmental and genetic factors are associated with the progression of abnormal prostate cell growth which ultimately causes the development of cancerous cells. The chances of prostate cancer occurrence are more in those patients with familial member's history, and it can be more by two to three-folds associated with first-rank relatives to get prostate cancer. In the current review different risk factors which are associated with the development of prostate cancer, are discussed.

Keywords: Prostate cancer, Risk factors, Male, BRCA1, BRAC2.

Introduction

The Human body is made up of millions of cells. The growth of body cells in a normal mechanism takes place in a systematic and coordinated system. These organized cells in the early age of an individual multiply more swiftly so that the growth of the individual may be increased. Mostly cell division after the maturity proceeds the repairing of the dead tissues in the body to accomplish the repair mechanism. When the number of these dead or injured cells in the body increased inconsiderably then these cells ultimately change into cancerous conditions. There are different types of cancers, but the principal occurrence of all kinds of cancers is abnormal and unusual cell growth ¹. One of the emerging issues is prostate cancer occur in men because the prostate is a ductal small walnut-shaped gland situated in men below the urinary bladder that produces the seminal fluid for sperms provision and transportation ². During adult stages, the prostate gland has columnar epithelium that is covered with a layer of muscle and a fibrous capsule ³. Signaling interconnection between epithelium and mesenchyme plays a vital role in the divergence and normal growth of the prostate. But due to unbalanced interconnection between

epithelium and mesenchyme causes reactivation of cellular multiplication and divergence during aging ⁴. Prostate cancer is the second most emerging cancer and the fourth one in both sexes. Globally, during 2012 it was observed approximately 1.1 million men diagnosed with prostate cancer, and about 307,000, mortalities were reported. Due to the growth and aging of the global population, it was estimated the global epidemiology of prostate cancer is approximately increased 1.7 million new cases and about 499,000 mortalities up to 2030 ⁵. An American population is at a higher risk of prostate cancer and second most common cancer among them. In the United States during 2015, it was estimated that approximately 220,800 new individuals with prostate cancer diagnosed in which 26% males had malignancies and about 27,540 mortalities were reported. The risk of emerging prostate cancer during the man's lifetime is one out of seven ⁶⁻⁷. Naturally prostate enlarges with age causing a condition known as benign prostatic hyperplasia (BPH), in one-third of men over 60 and about half over 80 and symptoms with frequent urination ⁸. Due to common histopathology and molecular techniques, BPH has been specified by cancer tumor genesis, but their accurate connection remains vigorously contested ⁹. Those individuals

whose father or brother has prostate cancer have the chances of 2 to 3 times more as compared to those who have no record of familial prostate cancer. If any individual family has three members who developed prostate cancer at the same time, then this individual also has 10 times more chances to develop as compared to those who have no record of familial prostate cancer. A food supplement with an enhanced amount of fat is also a possible risk factor of prostate cancer¹⁰⁻¹¹.

Environmental Factors

Environmental factors associated with prostate cancer are studied in different countries among the different communities and it was concluded that different environmental factors may cause risk of prostate cancer such as smoking, a diet with an enhanced quantity of fat, workplace exposure such as stokers who have direct contact with different toxic ignition products, obesity, and diabetes, inflammation of the prostate, STDs and vasectomy, etc¹².

Genetic Basis of Prostate Cancer

Recently approximately 5000 somatic mutations in prostate growth have been reported, including PTEN-interacting protein MAGI2 or repeated translocations assuming the cell-adhesion molecule CADM2, besides the periodic mutations of the Speckle-type POZ Protein (SPOP)¹³. The 12 most seriously mutated genes are C14orf49, THSD7B, CDKN1B, TP53, NIPA2, SPOP, PTEN, ZNF595, SCN11A, PIK3CA, MED12 and FOXA1. SPOP with a ratio of 13% was the most regularly mutated gene in these tumors¹⁴. The individuals having BRCA mutations are at a 15-25% increased risk of prostate cancer. A study suggested that BRCA1, BRCA2 and HOXB13 might be possible of life alarming prostate cancer¹⁵. Many different gene integrations have been observed in prostate cancer until now. Following ESRP1-RAF1, SLC45A3-BRAF and TMPRSS2-ERG, gene integrations are the leading molecular subtype of PCa¹⁶. Due to hereditary factors, almost 10% of men get prostate cancer which causes the initial emergence of disease¹⁷. To the X chromosome on the position of chromosome 1q, two familial susceptibility loci have been mapped¹⁶. Different studies revealed the correlation of prostate cancer with breast cancer¹⁷. The allelic disappearance exhibit the failure of function or depletion of tumor suppressor genes in PCa. Disappearances of heterozygosity were commonly identified at 17p, 13q, 10q and 8p, whereas some research reported deprivation of 18q, 16q, 7q and 6q¹⁸. The initial investigators made it logical that hereditary prostate cancer (HPC) genes were located on chromosome 1; meanwhile, the second prostate cancer gene

was located on the X chromosome (Xq27-28) suggesting the X-linked pattern of HPC inheritance¹⁹. On the mapped region of chromosome 16 was observed that DNA sequence KIAA 0872 and 17-β hydroxyl steroid dehydrogenase present which showed that not any genes shift mutations in the protein-coding region, and this knowledge reported that these are limited to become the source of familial PCa¹⁸. On different chromosomes, prostate cancer risks have been reported particularly on chromosome 1. The selected possible gene *CAPB* on chromosome 1p36, *PCAP* on chromosome 1q42-43, *HPCX* on chromosome Xq27-28, *HPC2* on chromosome 17p, *HPC1* on chromosome 1q23-25, *HPC20* on chromosome 20q13 and correlation to chromosome 8p22-23. These correlation studies expressed the mutation detection and mapping of strong possible genes such as *MSR1*, *RNASEL* and *ELAC2*²⁰. The repeated and limited germline mutation G84E in HOXB13 has been linked with the higher threat of familial PCa⁴⁴. It has been observed that individuals holding both polymorphisms in the HPC2/ELAC2 gene encounter a significant increase in prostate cancer²¹.

Risk Factors of Prostate Cancer

Anything that determines the chances of getting an illness is known as a risk factor, for example, disease. Different diseases have different risk factors. Some kinds of risk factors can be replaced such as smoking, but others related to an individual's age or familial history cannot be replaced²². But it was observed risk factors don't express everything about the individual disease. Many individuals observed with one or more risk factors, but never get the disease while many individuals who have not identified with risk factor even though develop infections. It is still not identified the obvious possible risk reason for the development of prostate cancer, but professionals have found some of the risk factors associated with prostate cancer developed in men.

Age

Elder males are much more affected by prostate cancer²³. Elders are being diagnosed with prostate cancer due to an increase in the prostate-specific antigen (PSA) testing and life span²⁴. The risk of the prostate has been observed in African Americans, or those individuals with familial positive history after 40 years and after 50 years among those who have no positive familial history. After the age of 65, the risk of the prostate is 6 in 10²⁵. The men who have a different percentage of prostate cancer during the different periods are shown in Table 1. However, it is greatly suggested for older individuals to perform their digital rectal examination (DRE) and prostate-specific antigen (PSA) testing diagnosis²⁶.

Table 1: Percent of US. men who develop PCa over 10-, 20-, and 30-year intervals according to their current age, 2008-2010†

Current Age	10 Years	20 Years	30 Years
30	0.01	0.35	2.54
40	0.34	2.57	8.18
50	2.31	8.12	13.74
60	6.41	12.59	14.92
70	7.73	10.64	N/A

Adapted from SEER Cancers Statistics Review 1975-2012

Ethnicity

Different recently researches identified that ethnicity is the major risk factor associated with prostate cancer²⁷. Prostate cancer is observed to have strong ethnic relations. African ethnic male individuals have greater chances of this disease. African Americans are more probably identified with PCa in the United States and the death rate was observed 2.5 times more among them²⁸. According to the Surveillance, Epidemiology, and End Results (SEER) US population registry, the black ethnic population was related to a major risk of prostate cancer death rate²⁹. Individuals in Sub-Saharan Africa were probably died 5-fold more with PCa as compared to African Americans in the United States³⁰. Prostate cancer risks have been reported is correlated with chromosomal 8q24 variants and are much more familiar among the population of African American male individuals. A few studies have also suggested the increased rate of variations in cells programmed death-associated genes such as BCL2 and EphB2 tumor suppressor genes in the African American population³¹.

Family history

To the occurrence of prostate cancer both genetic and environmental factors are also associated with them. The

chances of prostate cancer occurrence are more in those patients with familial member's history and diagnosis at a young age and it can be more by two to three-folds with first-rank relatives get prostate cancer³². HPC1 found at chromosomal location 1q24-25 and HPCX at Xq27-28 are hereditary prostate cancer (HPC) genes associated with PCa³³. RNASEL gene mutation located at chromosomal position 1q25 is also related to the occurrence of prostate cancer³⁴. RNASE gene is associated with the functioning of the innate immune mechanisms, thus fighting against the upcoming viruses and regulation of apoptotic pathways³⁵. Hereditary prostate cancer (HPC) associated with mutations in BRCA1 and 2 have been seen as clinically more combative variants of PCa³⁶. For searching chromosomal regions, linkage studies using genetic markers that express immoderate sharing of inherited alleles in cancer-associated families have been supportive in the diagnosis of important cancer sensitive genes in other cancers. To facilitate the improvements in biogenetics have permitted the diagnosis of the many allelic low penetrance mutations denominated genetic polymorphisms, which are entangled in the rest of familial types of prostate cancer. In table 2 the greater risk caused by the hereditary factors is mentioned³⁷.

Table 2: Main genes associated with the hereditary formation of familial prostate

Chromosomal location	Genes	Characteristics
1q24-25	HPC1	Autosomal dominant inheritance, associated with brain tumors
1q42-43	PCaP	Autosomal dominant inheritance
Xp11		Sex-related inheritance
Xp27-28	HPCX	Sex-related inheritance
17p11	HPC2	
20q13	HPC20	
5q31-33		Very aggressive clinical evolutionary forms
7q32		
19q12-13		
1p36	CAPB	Associated with brain tumors
10q25	PRCA1	
8p22-23	PG1/MSR1	
17q24	ELAC2	
16q23		
8q24 (region 1)		Very aggressive clinical evolutionary forms association with colorectal, breast, ovary, and urinary bladder cancers
8q24 (region 2)		
8q24 (region 3)		
2p15; 3p12; 6q25		
7p21; 10q11; 10q26		
11q13; 17q12		
17q21; 13q12-13		

Adapted from Tortatiada and castell³⁷.

Genetic conditions

BRCA1 & BRCA2 mutations

Many hereditary mutations but most of the notable is the BRCA2 gene has been identified with a major risk factor of PCa. BRCA1 and BRCA2 are both homologous recombination proteins, Ashkenazi Jewish populations are much more affected with these proteins mutation and commonly related with more chances of ovarian and breast cancer. However,

the men with the age over 65 are at more risk by 8.6-fold with the BRCA2 mutation prostate cancer and 2.64-fold more among all the aged individuals. But the lower risk is associated with BRCA1³⁸. A cohort study illustrated that the men with BRCA2 transformation have a greater threat up to 5 times more with prostate cancer meanwhile, the risk of prostate cancer with BRCA2 change contrasted and the overall public among the individual under 65 years of age is more than 7 times higher³⁹. Prostate tumor threat might be

greater in men with BRCA1 variation, but still not confirmed⁴⁰. The individuals with BRCA2 carriers at the age of 40 are suggested for prostate cancer screening⁴¹. In BRCA mutant breast and ovarian cancers, Poly-ADP Ribose Polymerase (PARP) inhibitors are used due to synthetic lethality, are recently go through clinical experiments for BRCA mutant PCa proteins⁴². Prostate malignancy risk may be increased due to some other hereditary mutations which are under examination⁴³.

Lynch syndrome

A cohort study illustrated that the risk of prostate cancer in men with Lynch syndrome is 2.1-4.9 times higher⁴⁴.

Endogenous hormones

Insulin-like Growth Factor-1 (GF-1)

Mitotic and anti-apoptotic effects are associated with a polypeptide known as the Insulin-like growth factor (IGF-1). It is involved in both anti-apoptotic and mitogenic processes in prostate cancer cell lines and also plays a major role in its biology⁴⁵. Meta and pooled analysis have indicated prostate tumor risk is 38-83% much more in men with the increased abnormal level of insulin-like development element 1 (IGF-1)⁴⁶. Meta and pooled analysis have also indicated that prostate tumor risk is not associated with insulin-like development element 2 (IGF-2) levels⁴⁷. Furthermore, Meta and pooled analysis have also indicated prostate disease risk is by and large not associated with insulin-like development variable typing protein (IGFBP) levels, but this may fluctuate in between IGFBPs⁴⁸. It was observed that increased circulating IGF-I accumulation is positively connected with the danger of PCa over the short and long period in the European population, therefore circulating IGF-I accumulation is connected with a higher risk for prostate cancer⁴⁹.

Testosterone

International Agency for Research on Cancer (IARC) reported the appropriate explanation of the prostate tumor that androgenic steroids have significant impacts on testosterone production in the body, taking into description limited proof. As prostate tumors depend on testosterone to develop, the Prostate growth treatment can involve manipulation of solutions or surgery to reduce the testosterone production levels⁵⁰.

Ionizing Radiations

Thorium-232 and its decay items, X radiation, and gamma radiation are arranged by the International Agency for Research on Cancer (IARC) as likely explanations of prostate cancer, in light of restricted proof. The prostate malignancy danger is higher in nuclear bomb survivors contrasted and the all-inclusive community, an accomplished study has demonstrated⁵⁰.

Obesity

During the epidemiological evaluation, body mass index is used to measure the overall obesity and abdominal obesity is measured by the ratio of waist to the buttocks edge. Among some of the recognized adoptable risk factors, obesity is well characterized for prostate cancer. Obesity has been involved in the deregulation of the insulin level, oxidative stress of DNA impair and inflammatory cytokine signaling, enlarging the threat of different neoplasm, including colorectal, breast and prostate cancer⁵¹. Moreover, the elevated serum concentration of insulin is also associated with the risk of prostate cancer⁵². Therefore, a higher concentration of serum leptin which is the product of the obesity gene *Ob* has

been connected to immense tumor volume (>5 cm³)⁵³. Male individuals with type I obesity was identified with a 20% increased risk of PCa death ratio, while type II obese individuals with 34% of higher risk⁵⁴. One of the important particular metabolic results of obesity is the combination of physical lethargy, which ultimately causing lower tissue feedback to insulin, particularly in the term of lower absorption of glucose. This insulin resistance gives on to a chronically higher concentration of blood insulin, which is a growth-stimulating hormone and therefore it's a possible risk factor to developing progression and cancers⁵⁵.

Smoking

Different types of mutagens present in cigarettes increased the production of tumorigenesis of prostatic epithelial cells, which is the possible risk factor to causing tobacco smoking injurious for health by developing prostate cancer disease. According to the International Agency for Research on Cancer (IARC), tobacco and cigarette smoke consist of more than 4,000 chemicals in which more than 60 are recognized as class 1 or class 2 carcinogens⁵⁶. Therefore, different ingredients of cigarette smoke such as polycyclic aromatic hydrocarbons (PAH), requisite metabolic stimulation, evasion of detoxification mechanism and successive attachment with DNA to apply their carcinogenic action. However, functional polymorphisms in genes that take part in PAH metabolism and detoxification may alter the consequence of smoking on prostate cancer⁵⁷. The correlation with smoking may also have a hormonal background, it was diagnosed male smokers have a higher level of testosterone, roster one and circulating, which may cause an increased risk of prostate cancer or cancer advancement⁵⁸. The recent studies described that young age men smokers diagnosed with prostate cancer have an OR of 1.4, while an OR of 1.6 was observed in smokers with the age of above 40 years⁵⁹. One more study suggested that the risk of mortality among smokers was 1.6× more associated with prostate cancer. Smoking termination was observed to have an appropriate impact on prostate cancer extent and mortality, with a higher impact as time since termination increased⁶⁰.

Diet

Ecologic observations have expressed a strong association between the occurrence of prostate cancer and dietary fat uptake. A western diet, particularly excessive in fat, has been connected to increase the risk of prostate cancer by enhancing the production and accessibility of both estrogen and androgens, while Asian and vegetarian diets have low-fat content which is connected with less circulating concentration of hormones⁶¹. The most intentional nutritional risk factor for prostate cancer is the excessive uptake of fat content. The role of the total, saturated, and animal fat has been observed in most epidemiological studies. The results of these studies suggested that monounsaturated, saturated and animal fat have a positive correlation and omega-3 fat has a negative correlation with prostate cancer. The findings for polyunsaturated fat are less reconcilable⁶². The dietary products high in dairy items and calcium with low in selenium and alpha-tocopherol have been observed to raise the chances of PCa. One of the meta-analyses about the Prostate Cancer SLR, in which 4 of 15 observations were revealed a significant positive correlation between dairy and PCa risk, while 5 of 15 observations were, reported a 7% higher risk per 400 g of dairy products per day. They also reported a significantly higher risk with calcium intake about 13 of 15 studies, with 5% higher risk per 400 mg per day about 15 of 16 studies. Calcium is identified to deregulate the effective form of vitamin D3

which ultimately causing the excessive growth of prostatic cells. Meanwhile, in the same studies, it was also observed low uptake of selenium and alpha-tocopherol was significantly associated with increased risk of PCa among 2/10 and 2/11 observations, respectively. According to the meta-analysis, Beta-carotene a precursor of vitamin A was observed to have no reasonable impact on prostate cancer risk⁶³.

Sexually transmitted diseases

Prostate cancer also has an association with sexually transmitted diseases (STDs). Prostate cancer risk about 2-3-fold correlated with STDs specifically with gonorrhea and syphilis infections recently suggested one large population-based study⁶⁴. Human papillomavirus-16, -18, and -33 diagnoses have been also shown a higher risk of PCa suggested some other studies⁶⁵. Meanwhile, the duration of HIV infection was connected with a higher risk of prostate cancer, reported a study based on human immunodeficiency virus (HIV) infected population⁶⁶. A current meta-analysis of 17 observations expressed that an increased ratio of sexual partners is correlated with higher PCa risk, especially through the more activities of sexually transmitted infections⁶⁷. However, the contraption is not clear, bacterial or viral pathogens through sexual activities have been involved in the initiation of chronic inflammation of the prostate which possibly becomes the source of prostate cancer.

Vasectomy

In the United States, vasectomy is the most frequently adapted procedure with approximately 500,000 achieved⁶⁸. But there is not an exact biological procedure that might illustrate the correlation between vasectomy and prostate cancer has been recognized. Different researches indicating low relative danger, data were negligible by methodological limitations and potential intolerance, including diagnosis and miscategorization bias annually. In some studies, it has been related to a higher risk of PCa⁶⁹.

Other factors

Many other kinds of risk factors are associated with prostate cancer such as diabetes, physical activity, alcohol consumption, profession and hepatic cirrhosis have been observed, but their role is less or indefinite in prostate cancer which depends on the scientific knowledge in the present literature⁷⁰.

Conclusion

Globally prostate cancer is the second most familiar and fifth-most hostile neoplasm among male individuals. It is the disease of the male genital system and particularly the abnormal growth of the prostate gland. According to the epidemiological studies different environmental and genetic factors are associated with the progression of abnormal prostate cell growth which ultimately causes the development of cancerous cells. Prostate cancer is specified by vast fluctuations in prevalence and mortality in the world. Epidemiological surveillance provides crucial indications to the etiology of PCa. In the advancement of molecular techniques, identification of the individual as well as the combined consequences of these factors has been initiated by a new generation of a wide range of population-based studies. Such studies may provide significant outcomes for risk factors which may be effective in recognizing the more adoptable subcategory of the population to observing prostate cancer.

Authors Contribution

All the authors contributed equally to the collection of data and to help in the formatting of the manuscript. All the authors support technically and responsible for manuscript reviewing, data analysis.

Conflict of Interest

All the authors declare no conflict of interest.

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