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AN UPDATE ON THE RISK FACTORS FOR PROSTATE CANCER

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Abstract – *Prostate cancer has a complex etiology, and multiple factors have been identified which increase the risk for developing this malignancy. In addition to the non-modifiable genetic component, various potentially modifiable environmental influences have also been linked with prostate cancer risk enhancement. Age, race, familial tendency and genetic aberrations are some of the established risk factors for prostate cancer while the complex interplay of environmental factors such as dietary content also appears to contribute to prostate cancer. The current state of knowledge on the risk factors for prostate cancer has been reviewed in this work.*

KEYWORDS: *Prostate cancer, Risk factor, Etiology.*

INTRODUCTION

Prostate cancer (PC) is a major international health problem at present. It is one of the commonest life-threatening malignancies afflicting men the world over[1]. In the year 2012, more than a million men were globally estimated to have been diagnosed with PC, with variable incidence rates across different geographical regions[2]. PC is a multifactorial disease, and exact etiology is not clear yet. It has been suggested that genetic causes as well as environmental and life style factors contribute to the development of PC. In addition to these genetic and life style factors, variation in PC incidence and mortality rates across the different parts of the world can be attributed to healthcare differences in cancer screening and registration[3]. This text reviews the longstanding risk factors for prostate cancer while also looking at some of the newer potential influences on PC development.

AGE

PC is a considered a disease of the elderly as ageing is associated with an increased risk[4,5]. PC is very rare in men below the age of 40 years, but more than two-thirds of all PC diagnoses are in men older than 65 years. Autopsy studies have revealed a 50% prevalence of PC in men between 70-80 years of age[3].

RACIAL PREDISPOSITION

The race is an important risk factor for PC. The risk of developing PC and its associated mortality is highest among African-Americans, Caucasians have an intermediate risk while Asian men carry the lowest risk. This racial predisposition has been attributed to common genetics and exposure to similar environmental and/or life-style influences[4,5].

FAMILY HISTORY

Increased incidence of PC has been observed in families suggesting hereditary tendency[4]. It has been reported that 10-15% of patients with PC have at least one family member who is also affected. First-degree relatives of patients have a

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two to three-fold increased relative risk for developing PC[6]. The clustering of PC in families can be due to shared gene pool, exposure to common environmental factors and/or diet or perhaps due to chance alone considering the high prevalence of PC.

GENETIC SUSCEPTIBILITY

Genetic factors have been estimated to account for half of the risk of PC. Genome-wide association studies (GWAS), which scan the genome for genetic polymorphisms occurring frequently in a particular disease than in the normal population, have identified almost one hundred such variants which have a multiplicative effect on increasing the risk of PC development. These genetic variations are suggested to be a major reason of familial aggregation of PC. Genetic mutations of the tumour suppressor genes breast cancer antigen 1 (BRCA1) and breast cancer antigen 2 (BRCA2) have also been linked with a 10% and 25% increased risk of PC respectively[6,7].

SERUM SEX HORMONES

Serum sex hormones have been suggested to influence the risk of PC. Androgens in particular, due to their essential role in growth and proliferation of normal and cancerous prostate cells via androgen receptor signalling, have been implicated in the pathogenesis of prostate cancer. A prospective, case-control study investigated the link between plasma sex hormone and sex hormone-binding globulin (SHBG) levels in healthy men to the subsequent development of PC. Results demonstrated elevated levels of circulating testosterone and reduced levels of sex hormone-binding globulin (both within normal endogenous ranges) to be associated with increased PC risk while lower circulating estradiol levels were shown to be another risk factor[8]. In another prospective cohort study of men who developed PC (n=114) and controls (n=680) included from the Baltimore Longitudinal Study of Aging, a higher concentration of serum free testosterone was associated with an elevated PC risk[9]. On the contrary, pooled analysis of worldwide data from 18 prospective studies of men with incident PC (n=3886) and controls (n=6438) by the Endogenous Hormones and Prostate Cancer Collaborative Group found no associations between PC risk and serum sex hormone levels[10].

ANDROGEN RECEPTOR POLYMORPHISM

Polymorphisms in CAG repeat length in the androgen receptor (AR) gene have been linked to PC risk. A study of PC patients (n=57) and healthy controls (n=169) showed higher risk of PC in individuals having CAG repeat length shorter than 20 repeats compared with men with a CAG repeat length of 20 or longer (Odds Ratio 2.10; 95% Confidence Interval 1.11-3.99)[11]. In another study of men with PC (n=190) and healthy control subjects (n=304), a CAG allele of fewer than 23 repeats was associated with a two-thirds increased risk of prostate cancer as compared to individuals with CAG allele of 23 or more repeats[12].

SERUM INSULIN AND INSULIN-LIKE GROWTH FACTOR-1

Findings from a nested case–control study within the Northern Sweden Health and Disease Cohort Study comparing plasma samples of men who developed PC over the 10 years follow-up (n=149) with controls (n=298) showed elevated plasma insulin-like growth factor-1 to be associated with a higher PC risk. The mechanism for this increased risk of development of PC involves insulin-like growth factor-1 (IGF-1) induced stimulation of cellular proliferation and inhibition of apoptosis[13]. Serum insulin has also been shown to influence the risk for development of PC. A study of Chinese men with incident prostate cancer (n=128) and healthy control subjects (n=306) showed elevated serum insulin levels to be associated with a high risk of prostate cancer ($p<0.001$)[14].

DIET AND NUTRITION

The role of dietary factors in the development of PC has been studied since long but results are conflicting and no clear evidence has become available as yet[15]. Excessive consumption of red meat, fats, dairy products and alcohol have been associated with an increased risk of PC. Fresh fruits and vegetables are thought to decrease the risk[3,5,15,16]. High intake or elevated blood levels of the ω-3 essential fatty acid α-linolenic acid have been associated with an increased risk of PC[17].

LYCOPENE AND TOMATO INTAKE

Lycopene, a natural carotenoid present in high amounts in tomatoes, has a strong antioxidant ac-

tion and it has been linked with a reduced risk of PC. A nested case-control study within the Physician's Health Study using plasma samples of men who went on to develop prostate cancer (n=578) over the 13 years follow-up and age-matched controls (n=1294) showed the mean plasma lycopene to be significantly lower in the study group as compared to controls (p=0.04)[18]. In another large study of men from the Health Professionals Follow-up Study (n=47365) of whom 2481 developed PC, frequent tomato or lycopene intake was associated with a reduced PC risk[19].

ALLIUM VEGETABLES

Allium vegetables (garlic, scallions, onions, chives, leeks) and garlic constituents have been shown to have antitumor effects. In a population-based study of Chinese men with PC (n=238) and healthy controls (n=471), a high intake of allium vegetables was associated with a reduced risk of PC which was independent of body weight and caloric intake[20].

MINERALS AND TRACE ELEMENTS

Several dietary minerals and trace elements have been implicated in the etiogenesis of PC. Increased dietary intake and/or serum levels of copper, cadmium, iron and calcium have been linked to increased risk of PC but the data is inconsistent with inadequate study designs so that no clear associations can be determined (reviewed by Shah et al. 2015)[21].

VASECTOMY

Vasectomy, a common and effective contraceptive procedure, has been linked to an increased risk for PC. However, some previous studies did not report such association[22]. A recent study investigated this association in a large cohort of men enrolled in the Health Professionals Follow-Up (n=49405) of which a quarter had vasectomies and 12% were diagnosed with prostate cancer over the 24 years follow-up period. Vasectomy was shown to be associated with a modestly elevated PC risk overall (Relative Risk 1.10; 95% Confidence Interval 1.04-1.17). Risk was higher for high-grade and advanced disease while no association was observed between vasectomy and the risk of low-grade or organ-confined PC[23].

BODY WEIGHT AND PHYSICAL ACTIVITY

Obesity is linked to PC development and aggressive disease while regular exercise is associated with a reduced risk. A strong correlation between body mass index (BMI) at the time of PC diagnosis and PC-specific mortality has been shown recently and this is more marked in overweight or obese patients with aggressive disease[24]. A recent study showed BMI greater than 30 kg/m^2 to be associated with a higher grade disease in men with localized prostate cancer. BMI at the time of surgery was also found to be a predictor of biochemical recurrence in men undergoing radical prostatectomy[25].

TABLE 1. Major risk factors for prostate cancer.

Factors	*Influence on prostate cancer risk*
Advanced age	Increased risk; >66% of all PC diagnoses in men over 65 years
Positive family history	Increased risk; 1 in 7 patients diagnosed with PC has a relative with the disease
Genetic associations	Mutations in several genes increase risk; BRCA2 mutations increase PC risk by 25%
Serum androgens	Increased risk, clear evidence lacking
AR gene polymorphism	Increased risk; short CAG repeat length in AR gene is linked to an increased PC risk
Dietary factors	Red meat, alcohol and dairy products increase PC risk, fresh fruits and vegetables reduce PC risk
Lycopene intake	Decreased risk; high intake of tomatoes (rich source lycopene) and overall lycopene intake are linked to a reduced PC risk
Allium vegetables	Decreased risk; high intake of allium vegetables (e.g. garlic, onion) Is linked to reduced PC risk
Vasectomy	Increased risk,
Body weight	Increased risk
Minerals	Increased risk seen with high intakes and/or elevated serum concentrations of copper, calcium, iron and cadmium

OTHER INFLUENCES

Results from a recent study have shown male pattern baldness to be associated with an increased risk of aggressive PC[26]. It has been indicated that childhood height is associated with increased risk of PC and PC-specific mortality[27]. Sexually transmitted diseases have also been implicated as risk factors for PC[5]. Medications including aspirin, statins and anti-diabetics were previously suggested to reduce the risk of PC but a recent study did not find any such protective effect[28].

CONCLUSIONS

PC is a multifactorial disease and several risk factors have been identified which seem to contribute to its development. Table 1 summarizes the various factors that are recognized to influence the development of PC. Some of these risk factors are well established and may have a cumulative effect in predisposing an individual to a greater risk of PC. Genetically determined influences are increasingly implicated in the pathogenesis of PC but the impact of environmental factors, though complex, has also been highlighted in recent times. Exploration of these risk associations further in future research studies may help us better understand the pathogenesis of PC and also inform us of potential preventative measures in minimising the risk of PC.

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Conflict of Interests:

The Authors declare that they have no conflict of interests.

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