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Prostate Cancer Review Article

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Abstract

Prostate cancer is somewhat unusual when compared with other types of cancer. This is because many prostate tumors do not spread quickly to other parts of the body. Some prostate cancers grow very slowly and may not cause symptoms or problems for years or ever. Even when prostate cancer has spread to other parts of the body, it can be managed for a long time, allowing men even with advanced prostate cancer to live with good health and quality of life for many years. Vitamin D is a steroid hormone that is thought to play a role in the etiology and progression of prostate cancer. Hormone activity requires binding to the vitamin D receptor (VDR), which contains several genetic polymorphisms that have been associated with risk of prostate cancer.

Introduction

The prostate cancer was first described by Venetian anatomist Niccolo Massa in 1536 and illustrated by Flemish anatomist Andreas Vesalius in 1538. J. Adams was a surgeon at The London Hospital who described the first case of prostate cancer in 1853. He discovered it by histological examination. He noted this was "a very rare disease" [1]. The estimation of new cases worldwide was about 1.1 million in 2012, and death rate of about 307,000. It is the second common cancer among American men [2]. Recent studies show that in Pakistani male's prostate cancer is a third common malignancy [3].

Prostate cancer is somewhat unusual when compared with other types of cancer. This is because many prostate tumors do not spread quickly to other parts of the body. Some prostate cancers grow very slowly and may not cause symptoms or problems for years or ever. Even when prostate cancer has spread to other parts of the body, it can be managed for a long time, allowing men even with advanced prostate cancer to live with good health and quality of life for many years. However, if cancer cannot be well controlled with existing treatments, it can cause symptoms like pain and fatigue and can sometimes lead to death. An important part of managing prostate cancer is monitoring it for growth over time, to determine whether it is growing slowly or quickly. Prostate tumors are usually slow growing, and symptoms may not occur for many years. In the early stages of prostate cancer, there are often no symptoms. However, due to its location surrounding the urethra, symptoms for the disease most affect urination. Prostate cancer symptoms include frequent urination, increased urination during the night (nocturia), difficulty in maintaining a steady stream of urine, blood in urine (hematuria) and painful urination (dysuria). It can also affect sexual function, for example, difficulty in achieving an erection or painful ejaculation. If the cancer is advanced, it can spread to other organs, causing bone pain in the pelvis or ribs. Many of the urinary symptoms also occur in other prostate diseases, such as benign prostate hyperplasia,

along with an enlargement of the prostate. Prostate tumors are only felt in a small percentage of cases during a digital rectal examination (DRE). Diagnosis of prostate cancer must be confirmed by a needle biopsy [4]. The prostate continues to enlarge over time, as men get older. This condition is called benign prostatic hypertrophy/hyperplasia (BPH). Prostate-specific antigen (PSA) is a glycoprotein and is unique to the prostate gland [5]. The function of PSA is to dissolve the seminal clot after ejaculation to facilitate the transport of spermatozoa along the female reproductive tract [6].

Prostate Gland

The prostate is the male sexual accessory gland. It is normally about the size of a walnut which is located behind the base of a

man's penis, in front of the rectum, and below the bladder. Its main function is to make seminal fluids, which protects, support and helps the sperm to transport to the penis. The section of the urethra which is running through the prostate is known as the prostatic urethra. In men, the urethra serves two purposes: urination and ejaculation. During ejaculation, the prostate muscles contract and expel the sperm into the prostatic urethra towards the penis. The average weight of a healthy prostate is approximately 11grams, ranging between 7 and 16grams [7]. It is encapsulated by a fibroelastic tissue layer, leading to septa extending inwards and dividing the prostate into different lobes [8]. The main male hormone is testosterone and is produced in the testicles. The prostate is regulated by Dihydrotestosterone. The slightly alkaline fluid produced by the prostate makes up 25% of seminal fluid and allows sperm motility and viability. The vaginal tract is acidic therefore the alkalinity of the semen neutralizes the environment to allow the sperm to stay viable. A major constituent of prostatic secretion is prostate-specific antigen (PSA), along with citrate, zinc, spermine, and cholesterol (https://www.livescience.com/32751-what-does-the-prostate-gland-do.html). The prostate can be classified by two different systems; zones or lobes. The zonal classification is used more in pathology, classifying the prostate into four different regions. The peripheral zone (PZ) forms about 70% of the prostate and surrounds the urethra. Nearly 80% of prostatic cancers develop in the PZ. The central zone (CZ) surrounds the ejaculatory ducts and forms 25% of the prostate. Only 2.5% of prostatic cancers arise in this region; however, the cancers that do develop here are more aggressive [9].

Incidence and mortality of prostate cancer

Prostate cancer is the sixth most common cancer in the world and second most common cancer in men [10]. The number of new cases estimated was 513,000 patients in 2000, while the number of new cases estimated was 1.1 million people in 2012. This suggests an increased incidence of prostate cancer in the past decade. It is expected that by 2030, 1.7 million new cases and 499,000 deaths will occur in the entire world [11]. The lowest incidence of the disease is seen in Asian countries, and included 14% of all cases in 2008, especially in Tian Jin, China (1.9/100,000 person-years). The highest incidence occurred in North America and Scandinavia, especially in African-American people (137/100,000 person-years) [12]. The incidence of prostate cancer is directly correlated with age. Almost 75% of new cancer cases occur in people older than 85 years. In other words, the incidence of this cancer increases with the increase in life expectancy [13]. However, the cause of this cancer is unknown [14]. Almost 90,000 deaths from prostate cancer were estimated to have occurred in 2008 in Europe, ranking it the third most common cause of cancer death amongst men, after lung and colorectal cancers [15].

Risk factors of prostate cancer

Risk factors can be classified as endogenous or exogenous, although some factors are not exclusively one or the other (e.g., race, aging, oxidative stress). Some factors may reflect both endogenous and exogenous influences.

Endogenous Risk Factors

Endogenous risk factors for prostate cancer include the following.

- Family history
- Hormones
- Race
- Aging and oxidative stress

Exogenous Risk Factors

Exogenous risk factors for prostate cancer include the following.

- Diet
- Environmental agents
- Occupation and other factors

Progression of prostate cancer

As development and progression of cancer are driven by molecular alterations, the analysis of molecular features may enable a better prediction of the behavior of individual cancers. Since tissues are heterogeneous, alterations on the serum level would be especially suited as diagnostic and prognostic markers in prostate cancer [16]. Increasing evidence from epidemiological and laboratory studies suggests that diet and lifestyle may have a role in the development of prostate cancer [17]. The intake of specific vegetables, tomato products (lycopene), vitamin E, selenium, vitamin C and soy products has been inversely associated with prostate cancer risk. In addition, epidemiological evidence and migrant studies indicate that the incidence of clinically significant prostate cancer is much lower in parts of the world where people eat predominantly low fat, plant-based diet [18].

Genetic epidemiology of prostate cancer

Most of the human genome is non-coding DNA; therefore, most genetic changes are harmless. Only mutations in the exon regions of the genome are subject to harmful changes which may affect protein composition [19]. Although the genetics of prostate cancer is poorly understood, we know cancers almost always arise from a single somatic cell that undergoes several genetic

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changes which cause a change in gene activity and therefore phenotype [20]. Cancer-causing mutations usually arise in genes involved in the regulation of cellular growth or death [21]. Most cancer cells have six different capabilities; self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, infinite replication ability, sustained angiogenesis and ability to invade tissue and metastasise [22]. A mutation-specific for prostate cancer is yet to be identified. Also, common mutations in oncogenes and tumor suppression genes for various other cancers are surprisingly rare in primary prostate cancer [23].

Genome-wide association studies

Genome-wide association studies (GWAS) has been highly successful in discovering susceptibility loci for prostate cancer. Currently, more than twenty GWAS have identified more than fifty common variants associated with susceptibility with PCa [24]. The first prostate cancer GWAS in 2005, more than 1300 studies have been added to the Catalogue of Published Genome-Wide Association Studies [25].

Vitamin D receptor gene

The vitamin D is a steroid hormone which is involved in a wide variety of biological processes including bone metabolism, modulation of the immune response, and regulation of cell proliferation and differentiation. It has specifically been shown to play a regulatory role in the growth of normal and malignant human prostate cells [26]. The VDR gene provides instructions for making a protein called vitamin D receptor (VDR), which allows the body to respond to vitamin D. VDR is present on chromosome no12q13.11 and having 100 kb size [27]. Recent studies have indicated many polymorphisms to exist in the vitamin D receptor (VDR) gene, but the influence of VDR gene polymorphisms on VDR protein function and signaling is largely unknown [26]. Vitamin D receptors are present in bone, intestine, kidney, and the parathyroid gland, but more importantly, high levels of VDR are taken as a positive indicator of prostate cancer regression. The vitamin D receptor (VDR) is a ligand-activated transcription factor that mediates the genomic actions of vitamin D. These actions involve regulation of calcium homeostasis, cell growth and differentiation, detoxification of xenobiotics, and modulation of adaptive and innate immunity; the latter including activation of monocyte-macrophages [28].

VDR gene polymorphisms

Vitamin D has an anticancer effect, so VDR gene polymorphisms have much attention. Polymorphisms of the vitamin D receptor gene (VDR) have been associated inconsistently with various diseases [29]. Several studies have shown a correlation between prostate cancer and VDR polymorphisms. However, there are other studies that could not find any significant association [30]. A series of common polymorphisms in the vitamin D receptor gene were recently reported to be associated with bone density and risk of osteoporosis. Four most studied VDR polymorphisms are FokI, TaqI, ApaI, and BsmI. The BsmI, ApaI and TaqI polymorphisms are strongly associated with one another and the presence of one polymorphism can predict the presence of the others, as they almost always occur together.

ApaI

This polymorphism lies at codon 352 in exon 9 of the VDR gene. The Apa1 A allele has been noticed at a higher frequency in the Asian population which is 74% [31].

FokI

The FokI polymorphism lies in the exonic region and is associated with a change in the reading frame of the VDR gene. The Fok1 polymorphism is the only known *VDR* gene polymorphism that results in the generation of an altered protein [32].

TaqI

TaqI polymorphisms are in the 3'-UTR region and have no direct effect on the protein sequence. T allele of TaqI is associated with a higher incidence of prostate cancer [33].

BsmI

Bsm1 is located in intron 8 and at the 3′ end of the gene. The Bsm1 restriction enzyme has a linkage disequilibrium with several other polymorphisms, including Apa1, Taq1, and the variable-length poly(A) [34].

VDR polymorphism studies in Pakistan

Various studies were carried out in Pakistani population to check the association of VDR and diseases. Results showed that VDR gene polymorphism is a significant risk factor of Rheumatoid arthritis as well as Osteoarthritis onset in Pakistani population [35]. Also, the GG genotype of VDR-Cdx2 polymorphism may increase the risk of breast cancer in females [36]. Some studies identified VDR polymorphisms as susceptible regions for T1D development [35-43].

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