

PROSTATE CANCER: FACTS AND INSIGHTS

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Abstract:

The occurrence of prostate cancer has shown significant variation all across the globe. In the late 1980s, the number of prostate cancer cases has significantly increased in the United States of America, surpassing the number of lung cancer cases in men. In the United States of America, prostate cancer is the most common cancer affecting men and has the highest mortality rate. Each year approximately 1.6 million prostate cancer cases are reported in men's out of which 366,000 lose their lives battling with this deadly disease. According to the data obtained from Nation cancer registries of India, prostate cancer incidence is increasing in India. It is one of the top ten leading cancer malignancy in India. It is the second most common type of cancer found in men in metropolitan Indian cities like Delhi, Pune, Kolkata, Mumbai, and Bangalore. It usually affects men of 65+ years. But in recent years, there has been a significant increase in cases reported in the age group of 35-45 years. Various factors such as old age, lack of proper nutrition, genetics, obesity, family history, African American ethnicity, etc., influence prostate cancer development. There is significant variation in the occurrence of prostate cancer and its diagnosis worldwide. The incidence and mortality rate of prostate cancer is highest in the age group of 65+ years, and its occurrence is most frequent in the African-American ethnic group. As far as now, there is no evidence on how to prevent prostate cancer, but by following a healthy lifestyle, the risk of cancer can be reduced. This review discusses treatment, diagnosis, and various facts that swing between the parable of myth and prostate cancer's scientific truth. A better understanding of etiology, epidemiology, and risk factors associated with prostate cancer will help prevent early detection and treatment.

Keywords — Prostate cancer, Mortality, Risk factors, Epidemiology, castration

I. INTRODUCTION

A. GLAND OF IMPORTANCE

Prostate cancer is a cancer of the prostate gland, one of the human male gonadal organs. To understand prostate cancer's mechanism, it is important to understand the structure and function of the gonadal organ. Its location is considered to be at the basal part of the urinary bladder and between the urinary bladder and penis [1]. This region is

prone to victimization from majorly three causes: prostate cancer, Benign Prostatic Hyperplasia, and Prostatitis [2]. Its first anatomical structure was first coined and observed by Andreas Vesalius in the year 1543 considered it to be an accessory gland. Its shape looked and looked likes like a walnut [3]. They are paced in front of the rectum, where the urethra allows the flow of urine out of the body where this gland comes in the way. The secretions of the prostate gland and their effect on the function

of testicles, i.e., the secretion of semen, are well known for generations where the ideal male conditions include soft and fluffy tissue.

In contrast, the affected structure has comparatively hard sometimes inflammation and pigmented conditions. In the affected case, secretion gradually decreases, which has the effect of seminal secretions. Generally, the secretion of the prostate gland is salty. The secretion of the prostate gland aids in the protection and nourishment of the sperm. Other function includes squeezing where it provides pressure for the expulsion of the sperm from the penis as semen. To understand the mechanism, working, and anatomy of the prostate gland, it is compared with mice and rat prostates' glands. Where four Wolffian ducts, urinogenital sinus, the development of prostate gland, start getting determined from the time of embryo formation itself Mullerian and fetal gonad interacts to form accessory sexual organs. Wolffian ducts after the embryo formation function as canals and the only duct that even stays preserved in females [4]. The duct later gets developed at later stages of embryonic development attaches to the hindgut with the aid of prerequisite tissue of renal function and gonad. One of the probable reasons for prostate cancer in males is supposed to be a tumor in this gland; however, the results are still under investigation [5]. Mullerian ducts develop later as well as UGS, where they later form into tubercule. Differentiation and specialization at a sexual level in males is a completely asymmetric process where the anti-Mullerian hormone is released to achieve the Mullerian duct [6]. Hormones play a major role in the differentiation of these glands, ducts, and organs.

It also includes the formation of the penis. By this, the onset of the prostate gland comes into the picture where the initial growth is rudimentary, where the growth is visible as buds of epithelial tissue at the lateral position on UGS walls adjacent to the mullerian duct. Branching cords of solid nature start developing as a result of forming a labyrinth of alveoli and tubules. Formation of lumen assures some of the secretory activity [7] stroma consists of muscles, whereas ducts have epithelium with columnar dimension having

secretory nature [8]. With the aid of various animal models, the molecular mechanism of prostate gland development is studied [9]. The prostate gland tissues have a major role in its functioning, yet it adds complexity to the system where the transition zone leads to benign prostatic hyperplasia [10]. It will lead to urination problems; however, these are benign and noncancerous changes. Cancerous changes occur in the peripheral zone of the tissues. The prostate fluid makes one of the components of the semen. The prostate gland is where the male sexual hormone enters as pro testosterone and converts into active form dihydrotestosterone, making the prostate gland of utmost importance. Antigen released by the gland is a prostate-specific antigen that offers consistency and fluidity to semen. The prostate secretions also contribute to the viability of the semen [11].

B. Causes of Prostate Gland

Prostate cancer is one of the most prevalent cancers, yet it is not fatal in most cases for the affected. There are chances that during a lifetime, the person not even feels that he is affected. It usually occurs in the later ages of life, as mentioned, mostly due to the growth of cells in the prostate gland's peripheral zone. However, recently 307000 deaths are found, and it is the sixth major reason for death in the male sex [12]. It can be cured, and the person gets recovered at an initial stage as this cancer grows slowly. Due to the increasing medical concerns and development in detection strategies increasing number of affected cases are being reported. Most of the cases are found when it is present in old age, or the people with hormonal imbalance such as elevated testosterone levels, or people who have a history of prostate cancer in their family. The major reason prostate cancer is still known, but various reasons and molecular mechanisms of the uncontrolled cell division and multiplication are continuously under investigation [13]. The twenty-second century of modern biotechnology has manipulated the molecular mechanism behind disease through the aid of studies based on gene and protein levels, i.e., genomics and proteomics level. It has also

contributed to prostate cancer studies, which is one of the most complex diseases. Studies have identified various gene sequences with signature expression direct to specialized, customized, and individual-specific studies in the diseased cases. It can aid in understanding the genetic mechanism [14].

Contrary to genes associated with colon and breast cancer, genetic linkage in prostate cancer was not determined as such. Although, segregation and aggregation analysis associated with families reveals a different story. The odd ratio (positive numbers divided by negative numbers), when determined under various experiments, was 2.5 in the case of prostate cancer, showing some of the relation of family history as a risk factor for the affected. However, it can be an overestimated value. Later experiments suggested that with the increasing number of affected first-degree relatives, the odd ratio got increased. It is expected that the spread of the disease has some association with genes. The standardized incidence ratio (observed cases divided by expected cases) supported the odds ratio results to a higher extent. In the allele identification and frequency calculation process, the frequency was an average figure of 0.003 to 0.006. It was found to exhibit be autosomal dominant nature, and penetrance was in 88 to 97%, which is quite a high figure.

Various experiments at different periods showed variation among the penetrance and dominant/recessive data. Most of the earliest data supported autosomal dominance; however, limitations such as small pedigrees with localized studies and studies within specific age groups didn't give strong evidence. Certain experiments also proclaimed x linked inheritance but left it unjustified, yet the recessive gene or locus instead of dominant was much supported and acceptable. Another idea of two different loci in different locations was also dismissed. Another study on monozygotic and dizygotic twins, which gave a higher MZ ratio, proved that simple Mendel categorization was not sufficient and well explanatory. Studies including the association of prostate cancer with other types of cancers such as breast cancer and brain cancers showed positive results. Still, the significance was

found to be very low, and the studies are very inconsistent. Studying genes shows positive but strong evidence for concluding results is still not present.

Linkage is the best-used method for analyzing the genetic association. Certain parameters are used, such as HLOD scores, NPL scores, and various other investigation studies, to confirm its association with prostate cancer [15]. Linkage scans were not successful because of heterogeneity. Recent studies have found 8q24 regions having a strong association with the disease [16]. Although there is continued research that confers risk against cancer, many genes provide immunity against cancer itself, such as TCF2 [17]. Various gene fusions confer prostate cancer risks, such as TMPRESS2-ERG genetic fusion, which provides the tumor cells an invasive nature to ease spread across the gland. There are positive and negative expressions of the same gene itself, providing particular types to prostate cancers. ERG gene has proved to be most important in gene fusions [18].

GENE /CHROMOSOME	CHROMOSOMAL REGION	Substantial support present
HPC1 REGION	1q23-25	Yes
RNASEL GENE	Within HPC1 region	Yes, this gene has an association with the disease
PCAP REGION	1q42.2 -43	No association with the disease
HPCX REGION	Xq27-28	No gene was found proving the association. High scores It didn't support the association.
CAPB REGION		Yet to be confirmed
HPC 20 REGION	20q13	No linkage found and supported

MSR1 GENE	8p22-23	No. need for more reliable data for a conclusion.
ELAC 2 GENE		Yes. supports weak association
BRCA 1 AND BRCA 2		Found association but with minimal data

Table I: Genetic association of various genes with prostate cancer [19]

C. Circumcision and Prostate Cancer

Circumcision is one of the controversial practices started as an ethnic practice in Africa and a certain group of Australian and pacific islanders [20]. Later it became the religious practice of Jewish and Muslim customs. Worldwide none of the medical claims are strongly in favor or against the practice, but socialists' social rights and freedom level is questioned by socialists [21]. Yet, this is the only method for treating two diseases: phimosis and balanoposthitis [22]. World health organization has considered circumcision to prevent the risk of HIV Aids [23]. Certain studies also have hypothesized that sexually transmitted diseases can be reduced by circumcision. It is known that STD can increase the rate of prostate cancer as well. There is an indirect relationship that is visible in the relationship itself. [24] found a 15% reduction in the chances of prostate cancer in the patients who were circumcised. The people showed reduced risk that came under the category of circumcised before the first intimation compared to people who were circumcised after their first sexual experience. Circumcision is believed to reduce the chances of direct exposure of the gonadal organ's internal structure to microbial agents and reduces the chances of inflammation. It is also believed that keratinization of the penis after the procedure protects from infectious agents' attack [25]. Certain other investigations prove this practice to have no role in reducing prostate cancer incidences but are not significant [26]. It is also reported that 12 % reduced risk of non-aggressive prostate cancer and

18% reduced risk of aggressive prostate cancer among the circumcised. Almost half of the penile cancers are due to the prostate gland, and it can be reduced if the prostate gland is protected from the risks. The fact that circumcision after sexual intercourse is not much significant against cancer can protect from bacteria and microbes responsible for urinary tract infections [27]. Almost 60 % of the risk is increased due to lack of circumcision, and 0.3 million prostate cancer cases are prevented and treated in the USA [28]. The carcinogenic mortality rate related to the prostate gland was found to be reduced in a similar study. The reduced chances of prostate cancer have reduced the chances of penile cancers [29] [30].

D. Masturbation, Sex and Prostate Cancer

Studies describe that prostate cancer has less or nothing to do with multiple sexual partners. However, this is mostly for heterogeneous intimation; inhomogeneous numbers are positive, but mostly due to less control, the number is not concluding. A maximum number of masturbations do not affect cancer probability in a particular period, but frequency does affect. Masturbation at the sexually active age, either of adolescence or adult, reduces prostate cancer chances. However, at old age, increasing masturbation can increase the carcinoma cells' risk to proliferate [31].

II. DIAGNOSIS OF PROSTATE CANCER

Detection of prostate cancer is usually difficult and sometimes insignificant as, most of the time, it does not affect the individual. Here are specific techniques to diagnose the disease. Rectal examination and blood test determine the concentration of the prostate-specific antigen, but it gives the positive value for the non-diseased as well. As a result, modern techniques are identified to diagnose the disease at the initial stage. Transrectal ultrasound prostate biopsy is the common method to act as a boon [32].

SUB PARAMETERS OF PRUS	RELATIVE FUNCTION
Prostate-specific antigen level	Same as rectal examination. It is the first step of biopsy. Lacks specificity and detection at minute quantities leads to a lack of effectiveness.
Antigenic density	It can be calculated as a ratio of total antigen to the volume of the same antigen. The value of 0.05ng/ml to 0.2 ng/ml is considered to be control value.
Antigenic velocity	A value greater than 075ng/ml is considered to be a chance of prostate cancer.
Free prostate-specific antigen	The ratio of free antigen to a bound antigen. The value of 4.0 to 9.0 nanogram is considered to be an effective parameter in detection.
Phi test	Value depending upon all the three parameters of density, velocity and requires the specific calculation.

TABLE II: various numerical sub-parameters of the PRUS technique

PRUS is now used along with fusion with magnetic resonance imaging due to the advancements in the technique. Imaging systems and data analysis are used. Radiological methods are also used to check various other factors such as lymph nodes, bone metastasis, which one way or the other is the determinant factor of prostate cancer. Nuclear evaluation is the new strategy to detect disease [33] [34].

III. PREVENTION AND TREATMENT STRATEGIES OF PROSTATE CANCER

Most of the cases of prostate cancer happen in old age after the age of greater than 60. It carries across different regions, and prevention strategies won't work in the longer future [35]. There are various treatment strategies where either they are used as a combination or in an individual manner. Conventional methods are well known, such as surgery, radiation, and proton beam therapy, but the modern methods are overpowering due to their long-term effects. Hormones are chemotherapy, and

the application of high-intensity ultrasound, where they are focused on the region affected, are now getting popular. The selection of the treatment strategies depends on various factors that are complex and need medical expertise. Other factors include the patient's age, overall health condition, and his/her suitability for the treatment (regarding comfortability and beliefs). One also has to think about the possible side effects. It is well known that prevention is better than cure and modification, and lifestyle and health practices may positively influence the disease. Control of diet patterns is the significant alterations in lifestyle which the physicians suggest. It is also suggested by the medical professionals to be in continuous treatment until it is not completely cured. However, the irony of prostate cancer is that its specific treatment has still not been determined in the medical world [36] [37].

A. Surgery

The most common method yet most discouraged due to side effects associated with it. Physicians never encourage surgery as the sole method of treatment. In most cases, prostate surface antigen reoccurs after the treatment by surgery. But the method has immediate applicability and can prevent mortality. There are two types of surgery which are pelvic lymphadenectomy and radical prostatectomy. The basic lymphadenectomy includes removing lymph nodes for examination purposes, but prostate cancer, which includes local inflammation, can be treated by attacking at the peritoneal region. In contrast, there are certain cases where it was found that prostatectomy was not efficient as a treatment strategy [38] [39]. On the whole, surgery can be applied in cases where prostate antigen concentration is less than 20ng/ml, i.e., the lower amount of action in treatment.

B. Cryosurgery

Another kind of surgery was cold; an extremely cold solution contains a liquid such as liquid nitrogen applied to affected tissue or region. In various treatment analyses, this technique was less painful for the patient but had a short come of the

time-consuming process. As it can be used to treat small degrees of cancers, this treatment needs various exposure levels, such as 1st, 2nd, 3rd exposures, where later exposures become less complicated as the patient becomes used to the process [40].

C. Radiation Therapy

This technique includes two parts: external exposure of radiation on the affected tissue and inside insertion of radioactive seed, which will continuously secrete its components in the affected tissue. However, it has a half-life of just 60 days. The first component is called External beam radiotherapy and the second part further differentiates based on dose concentration that is high dose radiation therapy and high dose radiation therapy (EBRT, HDRT, and LDRT). This technique is effective as compared to surgery, but the treatment intensity is still not appropriately determined. This technique has also been useful in later stages of disease [41].

D. Hormonal therapy

Androgen is the primary hormone that can stimulate prostate cancer as it binds to the androgen receptor. In abnormal conditions, this AR leads to other secondary pathways rather than the primary pathway, stimulating Testosterone and dihydrotestosterone. In the tumor conditions, testosterone concentration goes beyond the normal. Androgen deprivation is one of the methods to treat prostate cancer. In hormonal therapy, most of the time-specific activity of the hormone or enzyme is inhibited; in some cases, certain enzymes are enhanced. Those enzymes would be responsible for controlling the development of tumors. ADT (androgen deprivation therapy) has many shortcomings as well, such as the treated can suffer rashes, boils, erectile dysfunction. It also can reduce insulin sensitivity and increase weight [42].

E. Vitamins and other compounds

Specific vitamins are now a day's being identified and used to prevent disease, but the process is under investigation.

VITAMINS AND OTHER COMPOUNDS	FUNCTIONS /PRESENT USE
Vitamin E and Vitamin C	Didn't found useful to treat a disease
Selenium	It may be sufficient. need for more studies
Tomatoes	Large quantities required. It cannot prove useful in case of low quantities.
Lycopene	Insufficient research available
Soy	Genistein is one of the components that significantly affect cell lines of prostate and breast cancer.
Polyphenols (from tea and herbal samples)	Act as a chemopreventive agent
Vitamin D and vitamin B6	Substantial support in treatment effectiveness

Table III: vitamins as treatment [43] [44] [45]

F. CHEMOTHERAPY

Earlier, this method was not considered to be useful, but in later times it was found that it reduces prostate antigen. Certain drugs that are used are in the table below.

DRUGS	FUNCTION
Doxorubicin	Controversial function
Docetaxel	Even life protective. Used as a combinatorial method with another drug, prednisone. It also reduces the rate of cell division (mitosis) of cancerous cells
Vinblastine	Controversial function
Mitoxantrone	Anticancer agent (Antineoplastic nature). It reduces pain response. Its action is fast, but it doesn't solve the mortality issue.

Table IV: Chemotherapy treatment [46]

G. Effect of diet on Prostate Cancer Prevention

Changes in diet patterns are expected to reduce the chances of prostate cancer, such as reducing oil-rich, fat-rich diets. Cholesterol reduction is a major way to reduce the chances of disease. This can either reduce the chances of tumor formation or either promotes antineoplastic activity. Certain reports suggested that carbohydrate diets do not reduce disease chances [47]. As prostate cancer chances are proportional to age, it is believed that the various food products' antioxidant activity can have a positive effect on prostate cancer. For food such as lycopene, different scientists have different views and have different facts to support it. A high level of zinc mineral-rich foods can be avoided to reduce the chances as zinc can increase testosterone levels, and increased levels of this hormone can increase the chances. Food must not be boiled at high temperatures, and substantial proof is needed for the fruit's role in disease prevention of prostate cancer. However, certain vegetables such as tomatoes have been useful. Red meat is also suggested to be avoided in the diet [48].

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