Chapter

Genetic Polymorphism and Prostate Cancer: An Update

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Abstract

Genetic polymorphism and prostate cancer (PC) are the most pernicious and recurrently malignancy worldwide. It is the most dominating cause of cancer related casualty among men in the US. Asian countries are inflicted with PC at an alarming rate though still the prevalence of PC is lower than European and American men. Some of the genetic and environmental factors that might play a role in PC risk include: age genetic predilection, family history, race/ethnicity, lifestyle, and dietary habits and non-dietary environmental risk factors such as smoking. Socio-economic factors including economic, scholastic and intellectual factors do not, intrinsically seem to straight away influence the risk of acquiring PC. Other genetic changes that may support an increased risk of developing PC include *HPC1*, *HPC2*, *HPCX*, *CAPB*, *ATM,s HOXB13* and mismatch repair genes. PC occurrence rates are highly variable. Almost all PC mortalities are due to metastatic disease, generally through tumors the progress to be hormone refractory or castrate resistant. PC, developing research has acknowledged a number of candidate genes and biological pathways associated with PC. Indirect pathways such as P13K/AKT signaling pathway is one of most well known alternate pathway in PC Vascular endothelial growth factor (VEGF) is widely known to be potent stimulator of angiogenesis. The over expression of EGFR in a very large majority of cases is accompanied by the succession of PC, implying that this may play a mechanistic role. Numerous occupational factors have been proposed to cause PC. Some of the risk factors include; farmers/agricultural workers, pesticides, shift work and flight personnel. PC treatment can be done through surgery, radical prostatectomy is the main type of surgery. Risks of injury are many – reactions to anesthesia, loss of blood, blood clumps in the legs/lungs, injury to surrounding organs, infection at the site of surgery and many more. The other treatments are hormone therapy, chemotherapy and radio therapy chemotherapy. Chemotherapeutic drugs are typically used one at a time for PC such as transurethral resection of prostate (TURP). Some of the chemotherapeutic drugs are Docetaxel, Cabazitaxel, Mitoxantrone and Estramustine. Among the score of biomarkers being studied, numerous markers and techniques deserve awareness and acceptability for both patients and urologists in clinical practice.

Keywords: prostate, *BRCA2*, *P13K/AKT* signaling pathway, single nucleotide polymorphisms (SNPs)

1. Introduction

Cancer is both genetically and phenotypically sophisticated. Among all the cancers known so far, prostate cancer (PC) is the most pernicious and recurrently diagnosed malignancy worldwide (after lung cancer), counting 1,414,259 new cases (7.3% of all cancer associated diseases) and causing 375,304 deaths (3.8% of all deaths caused by cancer in men) in 2020 [1]. It is the second most dominating cause of cancer related casualty among men in the United States. Prostate cancer is expected to cause 248,530 new cases and 34,130 deaths in the United States in 2021, making it the most common cancer among American men [2]. Prostate cancer is thought to contain a genetic makeup that includes somatic copy number changes, point modifications, structural rearrangements, and chromosomal number differences [3]. The somatic transformation rate of prostate cancer lies between $1x10^{-6}$ and $2x10^{-6}$ which is identical to breast, renal and ovarian cancer [4]. However, in addition to somatic genetic alterations, it has been discovered that prostate cancer is associated with the loss of tumor suppressor gene activity due to epigenetic changes in their expression. Prostatic adenocarcinoma is the most frequent type of prostate cancer, accounting for nearly all occurrences. It grows in the cells of the glands that produce prostatic fluid. A digital rectal exam (DRE), a prostate-specific antigen (PSA) blood test, a prostate biopsy, or a computed tomography (CT) scan are all common ways for a clinician to detect prostate cancer [5].

Prostate cancer is categorized as the third highest among cancers of the male urinary and reproductive system in China. In Chinese populations, this condition impairs the quality of life and longevity of men over the age of 50 [6]. India presently has a population of over a billion people, with an estimated 1.5 million cancer cases reported each year. Asian Indians were diagnosed at an average age of 65.9 years (range: 46–86 years). India has a low incidence of prostate cancer. However, due to a dearth of prostate cancer screening, the majority of individuals are detected at an advanced stage [7]. The percentage of individuals with late-stage prostate cancer who have both high-grade illness and bone metastases is 65 percent. African-American men had a greater occurrence rate and a more severe kind of prostate cancer than White men. Prostate cancer is currently afflicting Asian countries at an alarming rate. Still, the prevalence of prostate cancer in Asian men is comparatively lower than European and American men. One reason that is endorsed by epidemiologic studies of immigrant populations and by recent somatic genomic alteration analysis is due to distinct genetic backgrounds. The etiological factors correlated with prostate cancer are still unresolved and ambiguous [8]. Variations in social, environmental, and genetic factors are thought to be the cause of this disparity. Some of the factors that may influence the risk of prostate cancer include:

- Age, genetic predisposition,
- family history
- race/ethnicity
- lifestyle and food habits are all factors to consider.

Although hereditary factors have been suspected to have a role in prostate cancer etiology, only a few genetic markers linked to prostate cancer risk have been identified. The strongest risk factor is acknowledged to be a hereditary liability [9]. Variations in the usage of diagnostic tests are reflected in the incidence rates around

the world. The importance of family history in obtaining evidence for major genetic determinants in cancer prevalence cannot be overstated. Prostate cancer progression and progression are influenced by lifestyle and nutritional habits. Future research is needed to better understand the interaction of environmental and diaspora factors [10]. Prostate cancer is generally asymptomatic at the initial stage and may require minimal or no treatment at all. However, the most recurring grievance is complications with urination and nocturia. Prostatic hypertrophy causes all of the symptoms listed above. Because the axial skeleton is the most prevalent site of bone metastatic disease, more advanced stages of the disease may exist with urine retention and back pain [11].

Genetics has an important role in the initiation and progression of prostate cancer. Tumor biomarkers are used to detect, treat, and diagnose many tumors in their early stages. Understanding the genesis and causative risk factors for prostate cancer can help to provide some solutions. This can aid in the expansion of significant screening and precluding methods for prostate cancer. Currently, no evidence supports how to prevent this cancer [12]. A promising understanding of the etiology and causative risk components is crucial for understanding cancer prevention. This cancer has a complex, multiple etiology, with 42 percent genetic factors and 58 percent environmental/lifestyle factors estimated to be involved. Prostate cancer is a growing threat to Asian men's health. Although the rate of incidence of prostate cancer is far greater in Western cultures (120 per 100,000 in Northern America) than in East Asian cultures (less than 10 per 100,000 in Asia), when Asians migrate to Western countries, their rate of prostate cancer incidence increases [13]. Prostate cancer has all of the criteria of an excellent chemoprevention target illness, including a lengthy latency, high incidence, a huge proportion of tumor markers, and identifiable preneoplastic lesions.

The increased morbidity and mortality from prostate cancer necessitate the implementation of current and effective preventive measures in everyday life. In conclusion, no vital known lifestyle or infectious agent is recognized as a risk factor for prostate cancer, categorizing it as one of the limited widespread cancers with unidentified risk factor [14].

2. Occurrence rates

Prostate cancer occurrence rates are highly variable. Occurrence, stringency, and mortality rates vary with ethnicities, geological location, and age. Its risk increases with an increase in age with the youngest being least susceptible. Also, this cancer is more widespread and invasive in African-Americans [15]. Native Asians, on the other hand, have a remarkably low incidence of prostate cancer, which is likely due to a combination of environmental and hereditary factors. Prostate cancer has the highest occurrence of 83.4% per 1000,000 incidences in Northern Europe, notably Ireland, and the lowest occurrence rate in South Central Asia, at 6.3 per 100,000. In Asia, however, prostate cancer accounts for only 1–10% of cases, but the incidence of occurrence is rapidly increasing [16].

Prostate cancer ranks second (37.5 per 100,000) in nations with a high Human Development Index (HDI), and vice versa in countries with a low HDI (11.3 per 100,000). The highest occurrence rates of prostate cancer are found among black men in the United States and the Caribbean, confirming the importance of Western African ancestry in controlling prostate cancer risk. The variation in prostate cancer incidence rates is mainly due to different prostate cancer diagnostic practices globally. In the early 1980s and late 1990s, there was a drastic increase in prostate cancer cases in the United States, Australia, and Canada due to which the detection

of pre-symptomatic cancer was feasible [17]. The adoption of prostate-specific antigen (PSA) testing was a major factor in this. One of the most striking features of prostate cancer is the wide range of occurrence rates caused by differences in race, geography, or age, as well as variations in environmental factors such as work environment, nutrition, and lifestyle, all of which can increase the risk of precocious prostate cancer. Environmental factors are one of the reasons for varied incidence rates of different cancers globally [18]. The cause of prostate cancer is unknown, even though it is more common in some populations. However, it is clear that prostate cancer is a multifaceted illness with various genetic and environmental variables contributing to its etiology.

3. Mortality rates

Almost all deaths from prostate cancer are caused by metastatic illness, which occurs when tumors become hormone-refractory or castrate-resistant. Prostate cancer mortality rates have dropped dramatically in Northern America, Northern, and Western Europe, indicating improved treatment and early detection through increased screening [19]. The highest mortality rate of prostate cancer is 27.9 per 100,000 in the Caribbean, with the lowest mortality rate being 3.1 per 100,000 in South Central Asia. The highest occurrence and mortality rates are found in African-American men. As a result, we can speculate that African-American males may maintain some genes that are more susceptible to mutations in prostate cancer and that these mutations are linked to a more aggressive type of cancer. African-American men, as well as men with a family history, should be screened at the age of 45. Undeniable death is the most important prostate cancer endpoint [20].

4. Genes associated with prostate cancer risk

Developing research has acknowledged a number of candidate genes and biological pathways associated with increased susceptibility to cancer. A significantly recent direction for scientists to identify genes involved in human disease is Genome-wide association studies (GWAS) [21]. This approach looks for tiny differences in the genome known as SNPs (single-nucleotide polymorphisms). Because genome-wide association studies examine SNPs across the genome, they promise a promising technique to research complex, prevalent diseases in which numerous genetic variations contribute to a person's risk. Genome-wide association studies provide an enormous approach for the identification of genetic markers correlated with prostate cancer risk. Hundreds of thousands of SNPs can be examined simultaneously in each analysis [22]. In genome-wide association studies (GWAS), case–control surveys, multiple linkage estimations, next-generation sequencing (NGS), and admixture mapping studies, several genes and chromosomal areas have been identified to be associated with prostate cancer. As more prostate cancer risk variations are identified, the cumulative effects of these variants may become increasingly important clinically. Unfortunately, attempts at specifying a reliable biomarker have thus far proved futile (**Table 1**) [15–17].

There is a significant role of genetics in prostate cancer that is indicated through epidemiological studies. In the advancement and succession of prostate cancer, there is an involvement of a heightening number of single nucleotide polymorphisms (SNPs). Individual SNPs show a moderate connection with prostate cancer risk, but when they are combined, they have a larger, dose-dependent association that presently accounts for 30% of prostate cancer family risk. An SNP is a

Genes	Population	N (Total Cases Studied)	Prostate cancer risk	Reference
BRCA1	UK and IRELAND	376	Weakly validated	Nyberg et al., 2020
BRCA2	UK and IRELAND	447	Validated	Nyberg et al., 2020
AR	NON-HISPANIC WHITE	226	Validated	Ingles et al., 1997
HOXB13	NORTHERN EUROPEAN	3508	Validated	Cooney et al., 2016
CYP17A1	TUNISIAN	250	Validated	Souiden et al., 2011
SRD5A2	CHINESE	495	Validated	Hsing et al., 2001
TLR4	NORTH INDIAN Asian	398	Validated	Singh et al., 2013
HNF1B	EUROPEAN AMERICANS, JAPANESE and AFRICAN AMERICANS	483	Validated	Grisanzio et al., 2012
MSMB	SOUTHERN CHINESE HAN	509	Validated	Xu et al., 2010
JAZF1	EUROPEAN	19421	Validated	Prokunina-Olsson et al., 2010
ESR1	CAUCASIAN	1859	Validated	Nicolaiew et al., 2009
(*RNase L*) *HPC1*	SWEDISH	2425	Not validated	Wiklund et al., 2004
ELAC2/*HPC2*	AUSTRALIAN	1557	Not validated	Severi et al., 2003
MSR1	CHINESE	410	Validated	Hsing et al., 2007
PSA	JAPANESE	782	Not validated	Wang et al., 2003
HPCX	ASHKENAZI JEWISH	2230	Validated	Agalliu et al., 2010

Table 1.
Genes associated with prostate cancer.

deviation from the predicted nucleotide in a DNA sequence that arises when a single nucleotide (A, T, C, or G) in the genome changes [20–24]. SNPs are thought to make a significant impact on disease vulnerability. SNPs are simple to find and only exist once, making them an ideal biomarker. Because of the growing interest in the role of SNPs in prostate cancer progression and succession, a large number of studies on SNPs in prostate cancer are being published [25].

Many case–control studies have recognized innumerable single nucleotide polymorphisms (SNPs) correlated with prostate cancer but the clinical role of these SNPs remains ambiguous. Some SNPs also affect levels of the prostate-secreted proteins, prostate-specific antigen (PSA), hexokinase (HK) 2, and β-microseminoprotein (β-MSP); prostate cancer risk was also related with some of these SNPs. Numerous SNPs associated with prostate cancer affect the role and/or generation of a prostate cancer marker. For example, rs198977 in *KLK2* may affect hK2 function and decrease hK2 levels in blood [26]. The SNP rs10993994 in *MSMB* reduces levels of β-MSP and is correlated with increased levels of PSA in the blood or semen of an active young man. The function of cell cycle dysregulation in prostate cancer vulnerability has been described via changing the cell's ability to respond effectively to DNA damage. Patients with advanced or metastatic prostate cancer have been reported to exhibit modifications in the *CDKN2* gene but not in primary tumors (**Table 2**) [27].

SNP	Chromosome	Population	N (Total Cases Studied)	Prostate Cancer Risk	Reference
rs6983267	8q24	Caucasians and Asians	50854	Identified	Li et al., 2015
rs1447295	8q24	Caucasians and Asians	50854	Identified	Li et al., 2015
rs16901979	8q24	Africans Americans	50854	Identified	Li et al., 2015
rs138213197	HOXB13	Europeans	9012	Identified	Beebe-Dimmer et al., 2015
rs4242382	8q24	Asian and Caucasian	3657	Identified	Zhao et al., 2014
rs4430796	17q12	Non-Hispanic White	421	Identified	Levin et al., 2008
rs7501939	17q12	Non-Hispanic white	421	Identified	Levin et al., 2008
rs10896449	11q13	European	19395	Identified	Chung et al., 2011
rs10486567	7p15.2	Finnish	947	Not identified	Chen et al., 2014
rs1938781	11q12	Japanese	5560	Identified	Akamatsu et al., 2012
rs2252004	10q26	Japanese	5560	Identified	Akamatsu et al., 2012
rs2055109	3p11.2	Japanese	5560	Identified	Akamatsu et al., 2012
rs1859962	17q24	Non-Hispanic white	421	Not Identified	Levin et al., 2008
rs12793759	11q13	European	19395	Identified	Chung et al., 2011
rs3737559	2p15	Icelander	23205	Identified	Gudmundsson et al., 2008
rs5945572	Xp11.22	Icelander	23205	Identified	Gudmundsson et al., 2008

Table 2.
SNPs associated with prostate cancer.

The t-allele of *MDM2* was found to be the most strongly linked to prostate cancer. The presence of at least one copy of the t allele of MDM2 tSNP309g increases the risk of advanced prostate cancer. The association of the rs1447295 A allele with prostate cancer was reported. However, no substantial relation of the rs6983267 G allele with prostate cancer patients was recorded. Seven single nucleotide polymorphisms (SNPs) on chromosome *17q*, 3 SNPs on *17q12*, and 4 SNPs on *17q24.3* are associated with the risk of prostate cancer was recognized in the European population by a genome-wide association study (GWAS) [25–28]. Research on susceptibility genes is one of the hottest subjects in prostate cancer risk factors. Even still, confirming the prostate cancer susceptibility genes has proven difficult. In 2007, in a GWAS conducted in the United States based on 3 known risk loci of

prostate cancer, SNPs rs4242382 and rs6983267 on 8q24 and SNP rs4430796 on 17q in the hepatocyte nuclear factor 1B (*HNF1B*) gene, 4 SNPs associated with prostate cancer, rs10993994 on chromosome 10 in the microseminoprotein-beta (*MSMB*) gene, rs4962416 on chromosome 10 in the C-terminal binding protein 2 (*CTBP2*) gene, rs10896449 on 11q13, and rs10486567 on chromosome 7 in the juxtaposed with another zinc finger protein 1 (*JAZF1*) gene was observed [29]. Two loci within the gene, SNPs rs1799950, and rs3737559, have been associated with early-onset prostate cancer and genealogical prostate cancer, respectively.

The steroid *SRD5A2* gene, located on chromosome 2p23 is a major gene that makes it prone to prostate cancer. Evidence supporting the linkage of this gene to prostate cancer is provided [30]. The transformation of testosterone (T) leads to dihydrotestosterone (DHT), the most powerful androgen receptor adversary in prostate cells by 5α-reductase (5-AR) enzymes (types 1 and 2). Under normal physiological conditions, a 5-AR enzyme that is encoded by *SRD5A2* is inevitably expressed over *SRD5A1* in the prostate. Attractive targets for preventing prostate cancer advancement are represented by 5-AR enzymes. The hypothetical basis for chemoprevention strategies is the inhibition of 5-AR enzymes and the reduction of prostate cancer succession in low-risk disease was also lately shown [30–33]. To potentially advance cancer growth and proliferation, *SRD5A* genetic variations alter sex-steroid exposure. Further studies are required to fully comprehend the influence of functional variations in *SRD5A* genes in both normal and prostate cancer cells.

Androgens are widely known to play a significant role in the progression of prostate cancer, even until it reaches advanced stages. In prostate cancer, especially castration-resistant prostate cancer, the androgen receptor (AR) plays a critical role (CRPC) [34]. Androgen deprivation therapy suppresses hormone-naive prostate cancer; however, AR is altered by prostate cancer and adapts for survival at castration levels of androgen. The AR gene can be found on chromosome X (Xq11–12). Shorter glutamine repeats have been linked to increased AR transcriptional activity [35]. The role of epithelial AR is to send secretory proteins to the prostate gland, such as prostate-specific antigen (PSA), whereas stromal AR is involved in prostate development. Most prostate cancers can be suppressed with androgen deprivation therapy, however, some high-risk prostate tumors progress to castration-resistant prostate cancer, which then thrives under castrated testosterone levels [36]. AR is the most frequent anomalous gene in metastatic CRPC. Several mechanisms play a fundamental role in the development of metastatic CRPC: Point mutations in the androgen receptor, Androgen receptor amplification, Variations of androgen biosynthesis, Variations in androgen receptor cofactor in the prostate cancer, and Androgen receptor variants [37].

The binding of anti-androgens such as bicalutamide and flutamide to the ligand-binding domain (LBD) of AR inhibits androgen binding to LBD. In the progression of prostate cancer to castration-resistant prostate cancer, prostate cancer survives and restarts its growth under castration levels of androgen. A second-generation non-steroidal anti-androgen with greater affinity for the LBD of AR is Enzalutamide [38]. Androgens play a critical role in the progression of both normal prostate epithelium and stromal prostate cancer, and activation of genes involved in androgen metabolism may be linked to an increased prostate cancer risk.

A fundamental regulatory enzyme in the steroidogenic pathway is Cytochrome P450 17α-hydroxylase/17,20-lyase (*CYP17A1*); Both 17α-hydroxylase and 17,20-lyase activities are catalyzed by *CYP17A1* and it is crucial for the production of both androgens and glucocorticoids [39]. *CYP17A* is a target for the hormonal treatment of prostate cancer. Many recent investigations have found that *CYP17A1* is

significantly expressed in more than 50% of human prostate carcinomas, indicating that cancer cells synthesize androgen intracellularly. The degree of expression was directly linked to nuclear expression of the phosphorylated active form of ARs. *CYP17A1* plays a crucial role in adrenal and intratumoral de novo biosynthesis of androgens. Abiraterone is a suppressor of *CYP17A1*. Current genes of interest that have been identified as genealogical tumor suppressor genes and act as biomarkers for prostate cancer include *RNase L* (*HPC1*, *1q22*), *MSR1* (8p), *ELAC2*/*HPC2* (17p11). Pathogenic variations in genes, such as *BRCA1*, *BRCA2*, the mismatch repair genes, and *HOXB13* exchange views on subtle to a mild lifetime risk of prostate cancer [40].

In the breast cancer predisposition gene 2 (*BRCA2*), germline mutations are the genetic events known to date that confer the highest risk of prostate cancer (8.6-fold in men ≤65 years). BRCA gene mutations, particularly in *BRCA2*, enhance the likelihood of developing PCa and have implications for disease prognosis and management [41]. *BRCA2* and *BRCA1*'s roles in prostate tumorigenesis are still unknown. The gene *BRCA1* has been linked to an increased risk of sporadic prostate cancer. The relevance of *BRCA1* and *BRCA2* to male cancer has been extensively researched since families with these mutations demonstrate clustering of cancer in men. Both *BRCA1* and *BRCA2* are tumor suppressor genes that are inherited in an autosomal dominant, incomplete penetrance manner [42]. Although some studies have begun to assess the involvement of these genes in prostate cancer, the precise role of *BRCA1* and *BRCA2* in prostate cancer progression and progression has yet to be determined. BRCA1 is one of the co-regulators of the androgen receptor (AR), which regulates a signaling pathway important for prostate cancer progression and progression. *BRCA2* was more common in castrate-resistant prostate cancer than primary prostate cancer, further inferring the invasive nature of prostate cancer in *BRCA2* mutation carriers [43]. Some, like *BRCA2*, are beginning to show clinical promise in the treatment and screening of prostate cancer. Numerous studies have shown that the common *BRCA1* and *BRCA2* mutations found in breast and ovarian cancer families also increase the risk of prostate cancer in Ashkenazi Jewish populations [41–44]. The odds ratios range from 2.1 to 4.8 and principally reach statistical significance for *BRCA2* but not *BRCA1*. Further, studies in various populations assist a role for *BRCA2*. *RNase L* (2′–5′ oligoadenylate-dependent ribonuclease L) (*HPC1*), located at chromosome 1q22; *MSR1*, with a linkage region on chromosome 8p; and *ELAC2* (*HPC2*), on chromosome 17p11 are the most pertinent candidate genes for prostate cancer [45]. In prostate cancer, these three genes have been identified as inherited tumor suppressor genes. The key changes in the *RNase L* gene linked to prostate cancer include D541E, R462Q, and I97L missense mutations. R462Q and D541E are antonymous variations of *RNase L* that exhibit a decrease in enzymatic activity [46]. In hereditary situations, the R462Q or Arg462G ln variation is linked to an increased prostate cancer risk in the Finnish population, American Caucasians, and Japanese men. I97L is a missense mutation in the ankyrin domain's third and seventh repeat sites. There is no clear link between this mutation and the risk of prostate cancer [47].

Hereditary prostate cancer 1 gene (*HPC1*) (*1q24–25*), *CAPB* (*1p36*), *PCAP* (*1q42–43*), *HPC2* (*17p12*), *HPC20* (*20q13*), and *HPCX* (*Xq27–28*) are the genes responsible for the advancement of sporadic and, in particular, familial prostate cancer. Certain regions in the *MSR1* gene appear to play a role in prostate cancer. *rs12718376*, in the terminal 3= regions of gene *MSR1*, was characterized as linked to a heightened prostate cancer risk in the Caucasian population [48]. With *HOXB13* bearers, a subjective history of invasive cancer is strongly retained. The findings

of Beebe-Dimmer et al. show that the G84E mutation in the *HOXB13* gene affects about 0.5 percent of people of European heritage, confirming previous claims that the mutation is linked to prostate cancer [49].

5. Alternate pathways of PC risk

5.1 *PI3K/Akt* signaling pathway

PI3K/Akt signaling pathway is one of the most well-known alternate pathways in prostate cancer. This pathway's activation appears to be common in many aggressive prostate tumors. Additionally, as prostate cancer develops toward a resistant, metastatic condition, the *PI3K/Akt* pathway is more frequently activated [43–45]. Cellular metabolism, tumor genesis, growth, proliferation, metastasis, and cytoskeletal remodeling are all controlled by this signaling system. The activation of growth and survival pathways is one way that the PI3K pathway might cause cancer.

Further, there is an involvement of the *PI3k/Akt* pathway in prostate cancer with modulation of DNA damage repair pathway [46]. Furthermore, the *PI3K/Akt* pathway is involved in modifying a more invasive phenotype in prostate cancer cells through modulating cholesterol ester production. Phosphatases such as phosphatase and tensing homolog gene (PTEN), PH and leucine-rich repeat protein phosphatase (PHLPP), cellular prostatic acid phosphatase, PP2A, and INPP4B activate the *PI3K/Akt* pathway. The *PI3K/Akt* pathway has also been demonstrated to be important in the survival and proliferation of prostate cancer stem cells. The link between the *PI3K/Akt* and AR pathways has piqued researchers' curiosity as a potential co-targeting method in prostate cancer. In various preclinical studies, reciprocal connections between these pathways have been demonstrated. These preclinical discoveries have aided the advancement of clinical trials including the combined inhibition of both the AR and the PI3k/Akt/mTOR pathways. With the invasive oncogenic properties of the *PI3K/Akt* pathway, there has been a lot of interest in using it as a biomarker to discriminate more significantly [48].

Although present research suggests that this pathway gives predictive information, it is unclear whether it offers many significant advantages over currently employed clinical and pathologic indicators. However, there is continued interest in using this pathway as a predictive biomarker for newly targeted medicines of this pathway. Activation of the *PI3K/Akt* pathway is undoubtedly important in the invasive character of many prostate tumors. As more individuals develop non-AR-driven tumors, this non-androgen receptor pathway may become increasingly relevant with the use of contemporary AR pathway inhibitors and combination therapy.

5.2 Vascular endothelial growth factor (VEGF)

In both healthy and pathological settings, vascular endothelial growth factor (*VEGF*) is widely recognized as a potent activator of angiogenesis. Most solid tumors, including prostate cancer, have strong evidence of it. Prostate cancer is aided by vascular endothelial growth factor (*VEGF*) and pigment epithelium-derived factor (PEDF) [49]. Angiogenesis appears to play a significant role in prostate cancer, according to sufficient data. Secretion of protein factors such as the vascular endothelial growth factor (*VEGF*) is exuded by prostate cancer cells which are widely studied and known as the major angiogenic marker. Many variables control and regulate the *VEGF* pathway, including local environmental hypoxia and different hormones, growth factors, and cytokines.

5.3 Epidermal growth factor receptor (EGFR)

The overexpression of *EGFR* (epidermal growth factor receptor) is associated with the progression of prostate cancer in the vast majority of cases, showing that this may play a mechanistic role. The first known member of the HER receptor family was the Epidermal growth factor receptor (EGFR or HER-1). After total prostatectomy, the risk of recurrence and succession to hormone resistance is associated with the expression of *EGFR*. One hundred percentages of metastases of hormone-refractory prostate cancers express *EGFR*, implying that this receptor is a primary transduction pathway for tumor growth [50]. Only a few clinical trials using combos with anti-EGFR drugs have lately been conducted. Erlotinib is a reversible and orally active *EGFR* tyrosine kinase inhibitor that stops the cell cycle in the G1 phase. The preclinical results imply that combining additional targeted treatments with *EGFR*, particularly antiangiogenics, should be studied.

5.4 Single nucleotide polymorphisms (SNPs)

In addition, GWAS has identified more than 150 SNVs related to the advancement of prostate cancer, but the clinical advantage of these findings remains skeptical.

5.4.1 8q24

The *8q24* polymorphisms have been implicated in various cancers. Overall, each of the *8q24* polymorphisms was individually correlated with prostate cancer risk. Substantial relations were also observed in an analysis by ethnicity, source of control, and quality score. Interestingly, the effect of rs1447295 on prostate cancer risk was observed among Caucasians and Asians, but not Africa-Americans. The effect of rs16901979 was more eminent among Africa-Americans than Asians [37]. Similarly, rs6983267 conferred a higher prostate cancer risk among Caucasians than Asians. Collaboratively, these *8q24* variants (s) may regulate prostate cancer risk in an ethnic-specific manner. *8q24* rs4242382-A polymorphism was associated with prostate cancer risk in Chinese men.

5.4.2 17q12 and 17q24

Gudmundsson and colleagues identified two prostate cancer susceptibility loci on chromosome 17q in a recent genome-wide association study. Precisely, there was an association of two intronic SNPs in the *TCF2* gene (rs4430796 and rs7501939) at *17q12* and a third SNP (rs1859962) at *17q24* with the sporadic prostate cancer risk. The strongest evidence of prostate cancer association was observed in SNPs rs4430796 and rs7501939. Moreover, the results obtained by Levin et al., suggest that the increased risk associated with these SNPs is approximately doubled in individuals making them susceptible to develop the timely-onset disease. While the results for correlation of SNP rs1859962 at *17q24* were not statistically substantial, there was symbolic evidence that the "G" allele was over-transmitted to affected men [38–41].

5.4.3 HOXB13 gene

In the *HOXB13* gene, an exotic modification named as *G84E* (*rs138213197*) has been identified according to the studies conducted in 2012, which has been categorized as the first major genetic variation linked with familial prostate cancer.

The function of *HOXB13* in prostate cancer is not well recognized [43]. The *HOXB13* protein is known to be critical in the embryonic development of the prostate gland and is expressed in normal prostate tissue toward adulthood. There is an indication that *HOX* genes may act as both, an oncogene and a tumor suppressor gene in the prostate as well as other cancers. The carriers of the G84E mutation represent 0.5% of the total population and are found almost exclusively among patients of known European ancestry (**Figures 1** and **2**).

5.4.4 11q13

The prostate cancer susceptibility alleles on chromosome *11q13* have been identified by genome-wide association studies. Chung et al. reported the results of fine-mapping the region surrounding the most notable SNP, rs10896449, originally associated with prostate cancer risk in *11q13*. Numerous locus models that included consequential SNPs consecutively identified that the second association of rs12793759 is independent of rs10896449 and remained significant [8].

5.4.5 JAZF1 gene

Chen et al. demonstrated that two loci (rs4242382 and rs10486567) are highly associated with familial multiple prostate cancer. A stronger effect of the risk allele

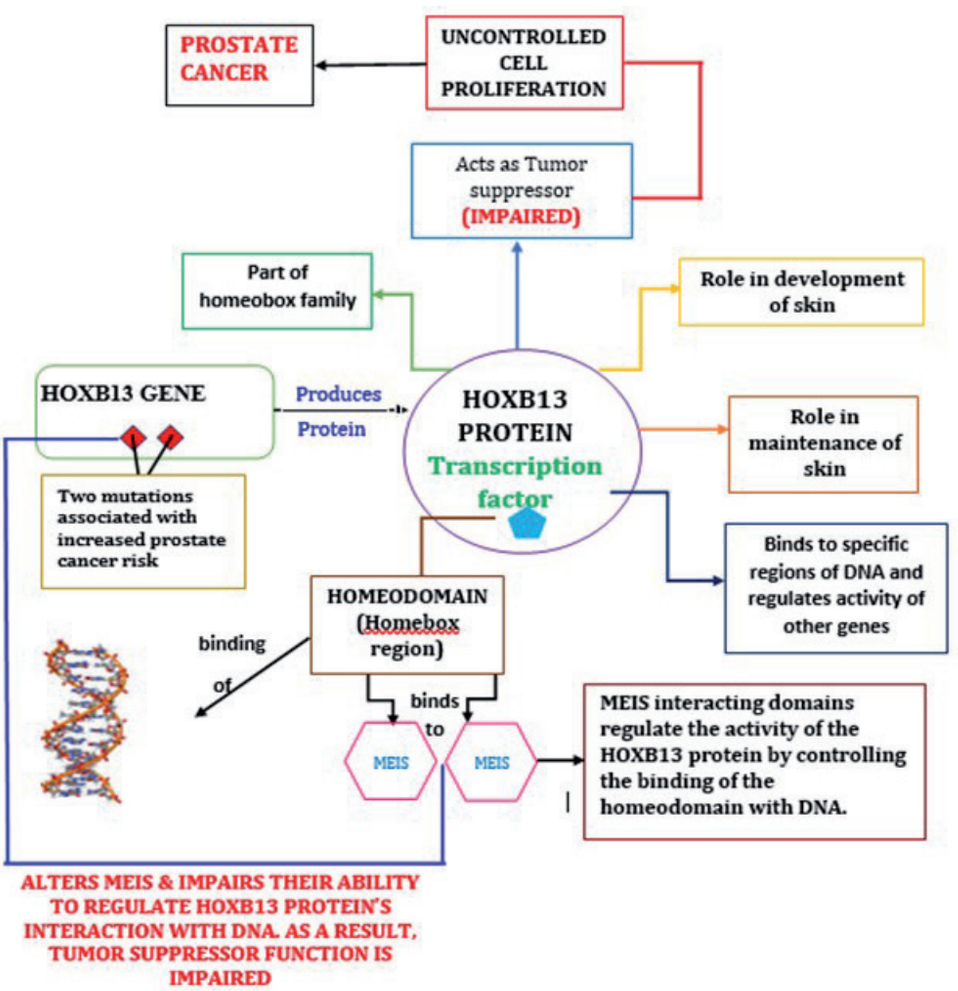

Figure 1.
Mechanism of action of HOXB13 gene.

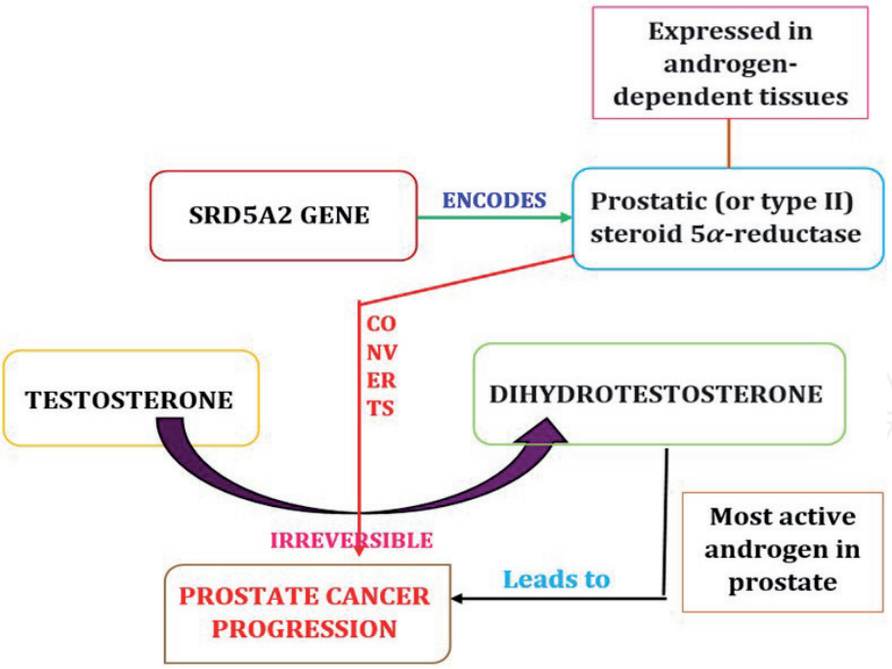

Figure 2.
Mechanism of action of SRD5A *gene.*

A at rs10486567 was observed in the presence of the risk allele A at rs4242382. The SNP rs10486567 at 7p15.2 was consistent with the genome-wide study. A three C2-H2-type zinc finger protein, which is a transcriptional repressor of *NR2C2*, a nuclear orphan receptor is encoded by the SNP rs10486567 located within intron 2 of the *JAZF*1 gene on chromosome 7p15.2. This protein is highly expressed in prostate tissue and interacts with the androgen receptor [9].

5.4.6 11q12*,* 10q26 *and* 3p11.2

We have identified three new loci, 11q12, 10q26, and 3p11.2, that are associated with prostate cancer susceptibility at a genome-wide significance level in the Japanese population. These findings provide additional support for conducting GWAS for prostate cancer in diverse populations to identify risk loci for this genetically heterogeneous cancer. Akamatsu et al. showed that there are three new loci, 11q12, 10q26, and 3p11.2 that are associated with prostate cancer vulnerability at a genome-wide significance level in the Japanese population. These findings provide additional assistance for conducting Genome-wide association studies for prostate cancer in diverse populations to recognize risk loci for this genetically heterogeneous cancer. Further functional studies are required to understand the biological consequences of the newly recognized vulnerable loci in prostate cancer carcinogenesis [10].

For SNP rs5945572 A on *Xp11* the findings were the same for cases with younger age at onset (≤65) or aggressive phenotype and the entire group. On the other hand, there was significantly higher frequency of rs721048 A, among individuals diagnosed with aggressive prostate cancer than among those with less aggressive disease. Both the *Xp11* and the 2p15 variants are familiar and confer a moderate risk, resulting in an estimated 7% of individuals of European descent to prostate cancer risk. However, the cardinal causative biological perturbation associated with these variants remains to be illuminated. Certainly, subsequent studies have not been able to confirm numerous considerable gene regions that are recognized by association

analysis and the strategies of identifying candidate genes have not worked effectively. Regardless of this, the advances in genomic technologies and techniques of detection have enhanced the proficiency to study the cardinal genetics of prostate cancer risk. Still, no other biomarkers are used at the moment for the identification of prostate cancer. Regardless, numerous studies for finding alternative biomarkers are in process, such as *PCA3* (prostate cancer antigen 3), *TMPRSS2: ETS* (transmembrane protease, serine 2: transcription factor ETS-related gene), *GSTP1* (glutathione-S-transferase enzyme), and *C-reactive protein*, but they still need to be examined in clinical trials [50–52].

A risk factor is anything that increases a person's chance of developing cancer. Although risk factors often influence the chance to develop cancer, most of them do not directly or by themselves cause cancer. Some people with several known risk factors never develop cancer, while others with no known risk factors do [53]. In prostate cancer, it is normal to distinguish between epidemiologic endogenic factors (e.g., race, hormonal factors, genealogical information, age, etc.) and exogenic factors (e.g., sustenance, ecological factors, and lifestyle) which also include smoking, excess body fat accumulation.

6. Genetic and environmental risk factors

6.1 Age

One of the most important risk factors for prostate cancer is age. Between the ages of 55 and 74, a person's risk of acquiring prostate cancer is estimated to be. The occurrence and mortality rates of prostate cancer are significantly linked to age, with the highest prevalence found in older men over 65 years of age [54].

6.2 Race/ethnicity

African-Americans have the highest prostate cancer risk, followed by whites, Hispanics, American Indians/Alaska Natives, and Asian/Pacific Islanders. According to the American Cancer Society, African-Americans have a death rate that is double that of white men. The risk of prostate cancer in Scandinavian males may also be higher. Historically, the occurrence rate in East Asia (Japan and China) has been low. However, when Chinese and Japanese men immigrate to the U.S., they have an elevated risk of developing prostate cancer when compared with their native populations [55].

6.3 Diet

The high intake of calories and fats in western diets is undoubtedly one of the primary causes of prostate cancer. Saturated fat, which is often ingested from animal sources, may be linked to the development of prostate cancer, however the link is small. Red meat is a key component of animal-fat consumption, and some research suggests red meat consumption has risk ratios. The biological causes for this link are still a mystery. Alpha-linolenic acid, an 18-carbon fatty acid found in meat and some vegetable oils, is significant because it is a necessary precursor for the creation of prostaglandins and leukotrienes. More research is needed to see if dietary substitution of fatty acids implicated in the prostaglandin production pathways affects prostate cancer development [56].

There are more than 20 epidemiological studies that have evaluated the role of dairy food intake in prostate cancer. These studies are compatible with a positive association, unrelated to the contribution of dairy foods to total and saturated fat intake. Although β-carotene intake has not been related with prostate cancer risk, another crucial dietary carotenoid compound—lycopene—has become the priority of considerable notoriety. Lycopene, which is mostly absorbed through the ingestion of tomato-based foods, is the most important carotenoid in most Americans' diets. Consuming either a lycopene-rich diet or a β-carotene additive is thought to reduce the incidence of prostate cancer by about 40% [57]. Legumes, which include but are not limited to soy, have also been researched concerning to prostate cancer risk. So far, nothing has been corroborated by the findings. Green tea, another plant product that includes several polyphenolic chemicals with possible anti-carcinogenic qualities, is also being investigated.

6.4 Obesity

Obesity has been found to not affect the overall risk of prostate cancer, according to numerous studies. Obese men, on the other hand, are more likely to develop more aggressive forms of prostate cancer.

6.5 Family history

Numerous investigations, including familial prostate cancer gatherings, twin studies, and illness incidence in young individuals, support the importance of genetic variables. Prostate cancer is classified into two types: familial and sporadic. Familial/genealogical prostatic disease is a malignancy that occurs in affected members of one family at an early age (55 years old). This type of cancer has at least one first-degree relative with prostate cancer [48–53]. However, in sporadic prostate cancer, the genetic material is damaged over time due to external environmental sensitivity. A family can be affected by this type of cancer if three generations are affected, three first-degree relatives are affected, or two relatives are affected before the age of 55. Both forms of cancer have different rates of occurrence. Familial/genetic cancer has a rate of 15%, while sporadic carcinoma has a rate of 80 to 90%. A meta-analysis of several studies found that the cancer risk is higher for men who have a brother who has been diagnosed with cancer rather than a father. The most and that the genealogical risk is higher for early-onset disease [52].

7. Non-dietary environmental risk factors

7.1 Smoking

Smoke from burning tobacco is considered a carcinogen for many human malignancies, both submissive and non-submissive. Regardless, determining its causal link with prostate cancer has been a lengthy procedure. Because tobacco smoke carcinogens work explicitly, producing DNA mutations, and indirectly, causing hormone metabolism alterations, the causal link with prostate cancer is biologically reasonable. Some researchers have discovered a link between smoking and specific genetic variants that are linked to an increased risk of prostate cancer [54].

7.2 Socio-economic factors

All social elements, including economic, lifestyle, scholastic, and intellectual aspects, do not appear to influence the risk of prostate cancer on their own. Despite

this, they are indirectly involved by influencing dietary factors, occupational exposure, and access to health systems, both for timely detection and appropriate treatment, and they are unquestionably involved by influencing dietary factors, occupational exposure, and acquisition to health systems [12–15].

7.3 Other genetic changes

Other genes that may support a heightened risk of developing prostate cancer include *HPC1*, *HPC2*, *HPCX*, *CAPB*, *ATM*, *FANCA*, *HOXB13*, and mismatch repair genes. None of these, however, has been proven to cause prostate cancer or to be specific to this illness. Researchers are working to find genes linked to an increased risk of prostate cancer, and they are always attempting to learn more about how specific genetic changes can influence the spread of prostate cancer [23].

7.4 Occupational risk factors

Prostate cancer is thought to be caused by a variety of occupational variables. Farmers/agricultural workers, chemicals (organochlorine insecticides), shift work, and flight personnel are also risk factors [45].

7.5 Insecticides/pesticides

The most often used pesticide/insecticide was lead arsenate. Its use was reduced, but not stopped, until 1988, due to later discoveries of its harmful health consequences. In the United States, however, the usage of lead arsenate has poisoned most of the farmed land. Many workers are expected to develop cancer as a result of its carcinogenic qualities. Most frequently used insecticides are organochlorine pesticides, organophosphorus pesticides, carbamates, concerning to and triazines [51–56]. Ancestry is also important in the interplay between pesticide susceptibility and ancestry. When exposed to pesticides, a person with a family history of prostate cancer has a significantly increased risk of prostate cancer, which has been confirmed for carbamates, fonofos, chlorpyrifos, and phorate. Evidence is also presented that pesticide exposure causes cancer to become more aggressive.

7.6 Organochlorine pesticides

In Swedish and American research, rational results demonstrated a link between organochlorine pesticides and a significantly elevated incidence of prostate cancer. In a Swedish study, chlordane was shown to be the most dangerous organochlorine pesticide, whereas heptachlor, 2,4-dichlorophenoxyacetic acid (2,4-D), and lindane were found to be the most dangerous. Certain review articles support a bit that pesticides may elevate the prostate cancer risk minimally. The specific pesticide that is responsible for the increased risk is not yet discovered [57].

7.7 Shift work

Shift work is usually classified as work that is not done during the day. As a result, continual night shift work is classified as shift work. There is a strong link between shift work exposure and prostate cancer. Because of the various exposure conditions, the degree of variability is fairly significant. A meta-analysis conducted by Krstev et al. and prior meta-analyses provided evidence that shift employment, including night work, can raise the risk of prostate cancer [48].

7.8 Flight personnel

A great number of researchers have looked into the risk of cancer in-flight crew members. Because flight crews frequently travel across multiple time zones, they are sometimes thought to be representatives for circadian rhythm disturbance. They are, nonetheless, subjected to carcinogenic ionizing cosmic radiation [57]. They are, nonetheless, subjected to carcinogenic ionizing cosmic radiation. Cancer risk might be increased as a result of several exposures. According to a meta-analysis undertaken by Krstev et al., pilots had a considerably increased risk of prostate cancer. It is difficult to explain the variation between the pilots and cabin crew by circadian rhythm disorder or cosmic radiation and could be due to unrestricted distraction [58]. The evidence implies that there may be a link between pilots and prostate cancer.

7.9 Farming

A farmer's job entails a variety of responsibilities, including animal care, dealing with feed, seed, and animal waste, salvaging hay and other grains, driving tractors and other vehicles, operating various machines, and performing maintenance and repairs. As a result, they are exposed to organic and inorganic dust, pesticides, fungus, germs, viruses, lubricants, diesel exhaust, and welding fumes, and ultraviolet light [49–53]. Due to a variety of exposures, numerous studies have suggested an increased prostate cancer risk in farmers compared to other occupations.

7.10 Screening

PSA (prostate-specific antigen) is a substance produced by the prostate gland. High PSA readings can indicate prostate cancer, prostatitis (a noncancerous illness), or an enlarged prostate gland. The prostate-specific antigen (PSA) test is the most widely used prostate cancer screening method. This is a straightforward blood test that determines the amount of PSA in your circulation. This test is usually the first step in any prostate cancer diagnosis. Nonetheless, PSA screening alone cannot determine whether cancer is present. The PSA test is also used to monitor the effects of treatment for prostate cancer, such as surgery, radiation, hormone therapy, and chemotherapy [55]. When a man undergoes treatment for prostate cancer, his PSA level will plunge significantly. Conventional screening with PSA is one of the tools the physician will use to measure if cancer has recurred. Biochemical recurrence occurs when PSA levels rise to a certain threshold following prostate cancer treatment. This means that some cancer cells have managed to survive and are now releasing PSA. If this occurs, the doctor will schedule additional testing and suggest additional treatment options.

8. Prostate cancer treatment

8.1 Surgery for prostate cancer

A radical prostatectomy is the main type of surgery for prostate cancer. In this operation, the surgeon removes the complete prostate gland and additionally some of the tissue around it, including the seminal vesicles [56]. This includes:

- Open/radical prostatectomy
- Laparoscopic prostatectomy

In the more conventional approach to prostatectomy, called an open prostatectomy, the surgeon operates through a single long skin incision (cut) to eliminate the prostate and surrounding tissues whereas, in a laparoscopic prostatectomy, the surgeon makes numerous minor incisions and uses extraordinary long surgical tools to eliminate the prostate. The surgeon either holds the equipment straight away or uses a control panel to specifically move robotic arms that clasp the equipment [57]. This technique of prostatectomy has become more common in recent times. If done by experienced surgeons, the laparoscopic radical prostatectomy can provide outcomes analogous to the open approach.

8.1.1 Open prostatectomy

Open prostatectomy comprises Radical retropubic prostatectomy and Radical perineal prostatectomy.

8.1.1.1 Radical retropubic prostatectomy

For this open operation, the surgeon creates an incision in the lower abdomen, from the umbilicus down to the pubic bone. Either general anesthesia (asleep) or spinal or epidural anesthesia (drugging the lower half of the body) is given together with sedation during the surgery. If there is a plausible chance that cancer might have spread to surrounding lymph nodes (based on your PSA level, prostate biopsy results, and other conditions), the surgeon may also eliminate some of these lymph nodes at this time which is known as a pelvic lymph node dissection. The nodes are then dispatched to the laboratory to identify if they have cancer cells in them. If the cancer cells are found in any of the nodes, the surgeon might not proceed with the surgery [59]. This is because it is doubtful if cancer can be cured with surgery and eliminating the prostate could assist with severe side effects. After the prostate is eliminated, still under anesthesia, a catheter which is a thin, flexible tube will be put in the penis to help exude the bladder. The catheter will usually stay in place for 1 to 2 weeks until healed. After the catheter is removed, patients can urinate on their own [60].

8.1.1.2 Radical perineal prostatectomy

In this open operation, the surgeon makes an incision in the skin between the anus and scrotum (the perineum). This strategy is used less often because it is more plausible to lead to erection problems and because the surrounding lymph nodes cannot be eliminated. But it is usually a shorter operation and might be an alternative if erections are not concerned and there is no need for the lymph nodes to be removed. It also might be used if any other medical conditions make retropubic surgery dangerous. It can be just as remedial as the retro public approach if done accurately [57]. The perineal operation may cause less pain and an easier recuperation than the retropubic prostatectomy. After the surgery, still under anesthesia, a catheter will be put in the penis to assist exude the bladder. The catheter usually stays in place for 1 to 2 weeks until healed. After the catheter is removed, patients can urinate on their own.

8.1.2 Laparoscopic prostatectomy

If treatment with laparoscopic surgery is taken under consideration, it is crucial to comprehend what is familiar and what is not yet familiar about this approach. The most significant factors are likely to be the aptitude and experience of the

surgeon. If it is decided that laparoscopic surgery is the right treatment, be sure to look for a surgeon with a lot of experience. Laparoscopic prostatectomy comprises Laparoscopic radical prostatectomy and Robotic-assisted laparoscopic radical prostatectomy [59].

8.1.2.1 Laparoscopic radical prostatectomy

For a laparoscopic radical prostatectomy (LRP), the surgeon inserts special long equipment through numerous small incisions in the abdominal wall to eliminate the prostate. One of the pieces of equipment has a small video camera on the end, which lets the surgeon see the interior of the body. Laparoscopic prostatectomy has some advantages over open radical prostatectomy, encompassing limited blood loss and pain, shorter hospital stays (usually no more than a day), rapid recovery times, and the catheter will need to remain in the bladder for less time [60]. The rates of major side effects from LRP, such as erection difficulties and discomfort holding urine (incontinence) seem to be about as identical as for open prostatectomies. Recovery of bladder control may be hindered slightly with this approach. However, more long-term studies are required to compare side effects and risks of recurrence. Between open prostatectomy and laparoscopic radical prostatectomy, the success of either technique seems to be determined primarily by the experience and aptitude of the surgeon [55].

8.1.2.2 Robotic-assisted laparoscopic radical prostatectomy

This technique is also known as robotic prostatectomy. In this technique, laparoscopic surgery is done using a robotic system. The surgeon settles down at a control panel in the operating room and robotic arms are moved to operate through numerous small incisions in the patient's abdomen. Robotic prostatectomy has superiority over the open approach in terms of less pain, blood loss, and healing time. But with regards to the side effects, men are most concerned about urinary and/or erection difficulties [53]. There does not seem to be a discrepancy between robotic prostatectomy and other techniques. For the surgeon, the robotic system may provide more maneuverability and more accuracy when moving the equipment than a conventional laparoscopic radical prostatectomy. Regardless, the most important factor in the accomplishment of either type of laparoscopic surgery is the surgeon's experience and aptitude.

8.2 Risks of prostate surgery

The risks with any type of radical prostatectomy are much like those of any major surgery. Difficulties throughout or momentarily after the operation can encompass:

- Reactions to anesthesia
- Loss of blood from the surgery
- Blood clumps in the legs or lungs
- Injury to surrounding organs
- Infections at the site of surgery.

8.3 Side effects of prostate surgery

The major possible side effects of radical prostatectomy include incontinence of urine i.e., being unable to control urine and erectile dysfunction i.e., impotence; problems getting or keeping erections. These side effects can also occur with other forms of prostate cancer treatment [57–59].

Incontinence of urine: not being able to control urine or having leakage or dribbling. Being incontinent can influence not only physically but emotionally and socially as well. Some of the major types of incontinence include:

1. Men who lack self-restraint of stress might leak urine when they cough, laugh, sneeze, or exercise. Lacking self-restraint of stress is the most popular after prostate surgery. It's usually induced by trouble with the bladder sphincter valve. Prostate cancer treatments can damage this valve that keeps urine in the bladder or the nerves that keep the valve functioning.

2. Men who lack self-restraint of overflow have trouble emptying their bladder. They take a long time to urinate and have a dribbling stream with little force. This is usually inflicted by blockage or narrowing of the bladder opening by scar tissue.

3. Men who lack self-restraint of urge have an instant need to urinate. This happens when the bladder becomes too susceptible to stretching as it fills with urine.

4. Barely after surgery, men lost all proficiency to control their urine. This is called continuous incontinence.

9. Chemotherapy

Chemotherapy (chemo) utilizes anti-cancer drugs injected into a vein or given orally. These drugs travel through the bloodstream to reach cancer cells throughout the body. Chemo is periodically used if prostate cancer has spread outside the prostate gland and hormone therapy has been proven futile. Contemporary research has also indicated that chemo might be beneficial if provided along with hormone therapy. Chemo is still not a conventional treatment for timely prostate cancer [54].

9.1 Chemo drugs in treatment of prostate cancer

Chemo drugs are typically used one at a time for prostate cancer. Some of the chemo drugs used to treat prostate cancer comprise of:

- Docetaxel (Taxotere)
- Cabazitaxel (Jevtana)
- Mitoxantrone (Novantrone)
- Estramustine (Emcyt)

Extensively, the first chemo drug given is docetaxel, in combination with the steroid drug prednisone. If this does not function or stops functioning, cabazitaxel is usually the following chemo drug attempted (Although there may be additional treatment options as well).

Docetaxel and cabazitaxel have been indicated to help men live longer, on average than former chemo drugs. They may slow cancer's development and also decrease its symptoms, resulting in a better quality of life. However, chemo is very improbable to remedy prostate cancer. Other chemo drugs being researched for utilization in prostate cancer include carboplatin, oxaliplatin, and cisplatin [56–58].

Chemo drugs for prostate cancer are typically given intravenously (IV), as an infusion over a certain period and some drugs, such as estramustine, are given as a pill orally. Usually, a slightly larger and sturdier IV is required in the vein system to dispense chemo. They are known as central venous catheters (CVCs), central venous access devices (CVADs), or central lines. They are used to provide medicines, blood products, nutrients, or fluids right into the blood and can also be used to take out blood for testing. Many different kinds of CVCs are available. The most common types are the port and the PICC line [55].

Doctors usually give chemo in cycles, with each period of treatment followed by a relaxation period to give some time to recuperate from the impact of the drugs. Cycles are more frequently 2 or 3 weeks long. The schedule differs depending on the drugs used. For example, with certain drugs, the chemo is provided only on the first day of the cycle. With other drugs, it is provided for a few days in succession or once a week. Then, at the verge of the cycle, there are repetitions of the chemo scheduled to begin the next cycle. The duration of medication for progressive prostate cancer is based on how well it is functioning and what side effects it causes [56–58].

9.2 Apparent side effects of chemotherapy

Chemo drugs invade cells that are dividing instantly, which is why they function against cancer cells. But various cells in the body, such as those in the bone marrow (where new blood cells are made), the lining of the mouth and intestines, and the hair follicles, also divide rapidly. These cells can also be influenced by chemo, which can lead to side effects. The side effects of chemo are determined by the kind and dose of drugs provided and for how long they are consumed [59]. Various common side effects can include:

- Loss of hair
- Mouth sores
- Anorexia
- Nausea and vomiting
- Diarrhea
- Heightened chance of infections (from experiencing inadequate white blood cells)
- Manageable bruising or bleeding (from experiencing inadequate blood platelets)
- Exhaustion (from experiencing inadequate red blood cells)

These side effects are temporary and normally disappear once the treatment is finished. There are usually ways to reduce these side effects. For example, drugs can be provided to help intercept or decrease nausea and vomiting. Together with these risks, various side effects are observed more usual with particular chemo drugs. For example:

- Docetaxel and cabazitaxel occasionally cause drastic allergic reactions. Medicines are provided before each treatment to help preclude this. These drugs can also destruct nerves leading to a phenomenon known as peripheral neuropathy, which can cause numbness, tingling, or burning sensations in the hands or feet.
- Mitoxantrone can, very unusually, cause leukemia after several years.
- Estramustine conveys an intensified risk of blood clots.

If any side effects are noticed while getting chemo, report them to the cancer care team so that they can be treated quickly. In certain cases, the doses of the chemo drugs may need to be decreased or medication may need to be impeded or ceased to obstruct the effects from getting worse.

10. Chemoprevention

Chemoprevention, a prophylactic strategy that utilizes non-poisonous natural or artificial compounds to alter, impede, or avert cancer by targeting certain steps in the carcinogenic pathway, is gaining adhesion among health care practitioners. Soy isoflavones and curcumin, staples of the Asian diet, have demonstrated convincing results as practical factors for the chemoprevention of prostate cancer [60]. This is because of their proficiency to regulate various intracellular signaling pathways which comprise cellular proliferation, apoptosis, inflammation, and androgen receptor signaling. Contemporary information has disclosed that the DNA damage response (DDR) is one of the timeliest incidents in the multistep advancement of human skin cancers to aggressive malignancy. Soy isoflavones and curcumin stimulate the DDR, providing an alternative and justification for their clinical application in prostate cancer chemoprevention.

The prostate cancer risk can be ameliorated by approximately 30% by soy food consumption. Elevated soy consumption is correlated with localized prostate cancer reduction even among Japanese men with a significantly high soy intake concerning Caucasians. Moreover, a lower mortality rate from prostate cancer was correlated with soy consumption. The level of PSA decreases in prostate cancer patients simply because of the customary consumption of soy. Lately, it has been reported that the widespread presence of equal production, a potential risk factor for prostate cancer, is decreasing in the young generations of Korea and Japan [53–58].

Some of the important points to take into consideration are that chemoprevention must be safe, sustain the quality of life, reduce the occurrence, consequence, and harshness of the disease and be economically feasible. Of all the drugs that have demonstrated greater scientific evidence in clinical trials, worth mentioning are inhibitors of the enzyme 5-α reductase, which converts testosterone into dihydrotestosterone and two isoforms exist, type 1 and type 2 exist for this.

Dutasteride is an influential inhibitor of 5-α reductase and is 45 times stronger than finasteride in hindering type 1 isoform and twice as strong on isoform 2. Undoubtedly, this is a guaranteeing drug in the prevention of prostate cancer in

the risk population [59]. Among the scores of biomarkers being studied, numerous markers and techniques deserve awareness because of the promising published data indicating that better prostate cancer screening methods will be available in the coming times that will maintain non-aggressiveness and acceptability for both patients and urologists in clinical practice.

Conflict of interest

The authors declare a conflict of interest as none.

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