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Review Article

Pharmacogenomics of Prostate Cancer: A Review of Recent Progress in Diagnosis, Personalized Medicine and Future Challenges

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Abstract

Prostate adenocarcinoma, in men, is the fifth leading cause of cancer casualties. Prostate cancer (PCa) is slow-growing with relatively low-grade aggressiveness. The prostate gland in the male reproductive system synthesizes and stores semen and seminal fluid. It sits inferior to the bladder, surrounds the superior part of the urethra and anterior to the rectum, and weighs approximately 20g in adult men. The prostate contains numerous small glands that produce 20% of the seminal fluid. In PCa, the cells of these glands undergo a malignant transformation and become cancerous. Single nucleotide polymorphisms (SNPs) are the most common type of gene variation, and many SNPs are associated with PCa risk. SNPs are small mutations in DNA sequences that can alter the structure and function of proteins. They are often inherited from parents and can vary frequently among different populations. SNPs in candidate genes, such as those involved in cell growth and differentiation, have been proven to increase susceptibility to prostate adenocarcinoma. Identifying SNPs linked with PCa risk can potentially upgrade early detection and disease prevention. The research on SNPs in PCa is still in its early stages. However, the findings to date suggest that SNPs have the potential to be valuable tools for the advancement of the diagnosis, prevention, and treatment of this devastating disease. For instance, rs6983267 and rs1447295 at the *8q24* gene in Caucasians and Asians have a strong association with prostate adenocarcinoma. In contrast, rs16901979 in the same gene in African Americans has shown a significant association with prostate malignancy. Meanwhile, in the European population, rs138213197 has a notable association with PCa. In addition to the association with the disease, SNPs may also be involved in treatment failure or toxicities in patients battling prostate carcinoma. For example, in the English population, rs4646487 *CYP4B1* and rs2227291 *ATP7A* are responsible for toxicities in the treatment of prostate gland carcinoma. In this review, we summarize our understanding of how common genetic variations, SNPs, contribute to the development of PCa and how they may be used to screen for and manage the disease. SNPs are linked with a greater risk of aggressive PCa and represent essential biomarkers. However, in addition to confirming the association of these SNPs in larger cohorts, there remains a need to identify additional clinically relevant genetic biomarkers for screening, detection, validation of diagnosis, prevention, and treatment of prostate cancer.

Keywords: Prostate cancer, genetic polymorphism, pharmacogenomics of prostate cancer, prostate specific antigen (PSA), next-generation sequencing.

1. Introduction

Acute The uncontrolled and hyperproliferative disorder involves uncontrolled cell division, extensive angiogenesis, cellular transformation, disruption in apoptotic pathways, invasion, and metastasis, and is known as cancer (Caruso et al. 2009). Cancers are complex diseases of various types, and they may originate in different tissues or organs in the body. It is worth knowing that each cancer has its characteristics, cellular signaling pathways, and treatment strategies. It is usually named based on the cell from which it originates, and the tissue or organ involved. Prostate adenocarcinoma/cancer (PCa) is the

fifth leading cause of casualties in men. PCa is slow-growing with relatively low-grade aggressiveness. In the male reproductive system, the prostate gland synthesizes and stores seminal fluid. It sits inferior to the urinary bladder, surrounds superior to the urethra and anterior to the rectum, and weighs approximately 20g in adult men. The prostate contains numerous small glands that produce one-fifth (20%) of the fluid that constitutes semen. In PCa, the cells of the prostate undergo a malignant transformation and become cancerous (Mustafa et al. 2016; Aumüller 2012). In most cases, PCa has early or initial symptoms. However, anemia leading to fatigue, bone pain, and renal failure is associated with bilateral urinary obstruction. PCa can be diagnosed with transrectal ultrasound-guided (TRUS) prostate tissue biopsy and prostate-specific-antigen (PSA test). Modern diagnostic techniques include Free-PSA level as well as total-PSA levels, genomic analysis, PCA3 urine testing, Prostate-health-index scoring (PHI), exosome testing, Prostate Imaging Reporting & Data System P.I.R.A.D.S scoring along with several other diagnostic techniques (Sivaraman and Bhat 2017; Leslie, Sajjad, and Villanueva).

According to the recent classification of PCa by the World Health Organization (W.H.O) 2016, PCa is classified into the following categories: epithelial tumors, nonendocrine tumors, mesenchymal tumors, hematological tumors, miscellaneous tumors, and metastatic tumors. (Humphrey et al. 2016).

The Gleason score, a histopathological grading approach for PCa, was first designed by D. Gleason, in 1974 (Gleason and Mellinger 1974; Tzelepi 2023). It is a powerful prognostic indicator that assesses the tumor's aggressiveness (Gleason and Mellinger 1974). The Gleason grading approach continues to be the established method for histological grading of prostate adenocarcinoma. Following the 2004 WHO classification, adjustments were made to the Gleason grading approach, and in 2016, these changes were integrated into the WHO guidelines for grading PCa (Epstein et al. 2016; Moch et al. 2016b; Sehn 2018; Moch et al. 2016a). The Gleason score system, accurately predicts the pathological and oncological stage and outcomes for men with PC. The most recent amendment was done in 2014 by the International Society of Urological Pathology (ISUP), and it improved the alignment between the Gleason sum from biopsy and radical prostatectomy. These improvements are intended to strengthen patient categorization and clinical outcome prediction (Pierorazio et al. 2013; Montironi et al. 2021).

- Grade group (GG) 1: GS less than or equal to 6 (i.e., GS≤6)
- GG 2: GS equals to 7 (i.e., GS 3 + 4 = 7)
- GG 3: GS to 7 (i.e., GS 4 + 3 = 7)
- GG 4: GS equals to 8 (i.e., GS 4 + 4 = 8 or 3 + 5 = 8 or 5 + 3 = 8)
- GG 5: GS 9–10 (i.e., GS 9 and 10)

Globally, cancer is a leading health issue and the second major cause of death even in the United States. The extent of PCa expanded by 3% annually from 2014-19, translating to an additional 99,000 new cases. PCa affected 1,414,259 people globally in 2020 (Siegel et al. 2023). It is important to find out the survival rate (SR) of people with PCa. To the best of our knowledge, it is worth remembering that the SR is just an estimate of life years for an individual with PCa. The 5-year relative SR for PCa in the US is 97%. The 10-year relative SR is 98%. 83% of prostate cancers are found early, with a 5-year S.R of nearly 100%. For advanced prostate cancer, the 5-year SR is 32% (Siegel et al. 2023; Aliakbari et al. 2020). SR varies based on stage, grade, age, health, and treatment (Aliakbari et al. 2020).

The typical diagnosis age is 66 years. PCa is rarely diagnosed in people under the age of 40. Compared to white males, black men are more likely to receive a PCa diagnosis (Aliakbari et al. 2020; Bleyer, Spreafico, and Barr 2020). The exact etiology of PCa is still elusive however, male

gender, age, nutrients, alcohol, smoking, increased height, obesity, hypertension, family history, insufficient physical activity, consistently increased testosterone levels, exposure to carcinogens, and one's ethnic background have all been identified as significant risk factors for prostate cancer (Gann 2002; Mullins and Loeb 2012; Rhoden and Averbeck 2009; Kaiser et al. 2019; Ng 2021).

2. Search Methodology

To conduct the present review, our team started gathering data in 2023 and conducting a thorough search across several databases, including Google Scholar, PubMed, Springer, Elsevier ScienceDirect, and Web of Science, for studies published from 2005 to 2023. Some past research (1974 & 2002 etc.) was included in this paper due to their relevance. The research studies (original research+ review) were chosen because they were only written in English, and selection was done for the following keywords: "prostate cancer," "PCa genetics," "PCa diagnosis and treatment," "cancer statistics," "the prostate," "genetic polymorphism in PCa treatment," "pharmacogenomics of prostate cancer,", "next generation sequencing".

3. Pathophysiology of Prostate Cancer (PCa)

PCa is a multistep process disease, beginning with the conversion of benign epithelial cells into malignant cells. The most common precursor lesion of PCa is prostatic intra-epithelial neoplasia (PIN). The PIN is a multifocal condition that can be defined as malignant growth within the pre-existing benign epithelium of the acini or ducts. PIN can be classified into two grades: low-grade PIN (LGPIN) and high-grade PIN (HGPIN). HGPIN is a pre-cancerous cell growth that has a high predictive range for progression to adenocarcinoma. HGPIN can only be detected by taking a needle aspiration of the prostate gland. It does not cause serum Prostate-specific-antigen (PSA) levels to rise and cannot be seen on transrectal ultrasound TRUS (Murray 2021b).

The prostate gland, for proper functioning, requires male hormones, androgens. Androgens in men include testosterone, which is synthesized in the male gonads, dehydroepiandrosterone (DHEA), which is synthesized by the adrenal glands, and dihydrotestosterone (DHT), which is converted from testosterone within the prostate itself. Androgens in males are also responsible for male secondary attributes such as low-pitched voice, height, increased muscle mass, and facial hair (Shi et al. 2019; Rey 2021). Adenocarcinomas of the prostate usually originate in the zone of the periphery of the gland. In the initial stages, small clumps of cancer cells remain confined to the otherwise normal prostate gland, a condition known as carcinoma in situ (CIS) or prostate intraepithelial neoplasia (PIN) (Tzelepi 2023). Although there is no definitive proof that PIN is a precursor, or it is closely associated with the PCa. Over time, the cancer cells proliferate and spread to the surrounding prostate tissue (stroma), causing the formation of a cancerous lump i.e., Tumor. The tumor may eventually grow large enough to invade nearby organs such as the seminal vesicles or rectum, or the cancer cells may develop the ability to metastasize through the bloodstream and lymphatic system. This spread of cancer cells to other organs is known as metastasis. PCa usually metastasizes to the organs like bones, rectum, and eventually lymph nodes (Figure 2). It may also invade the bladder and lower ureters after local progression. The PCa cancer cells are thought to be metastasized to bone through the bloodstream, specifically as the prostatic venous plexus that connects with the vertebral veins (Mustafa et al. 2016).

Since, for the normal development, differentiation, and survival of cells, androgen receptor signaling is necessary. The activity of the androgen receptor is activated by ligand attachment and heat shock proteins (HSPs). Ligand (testosterone) is transported into the cytoplasm from where it converts into DHT by the enzyme involved in steroid metabolism, 5-α-reductase. In

Table 1: Grading and Scoring of Prostate Cancer.

Gleason Score	Description
1	Small, uniform, and normal cells
2	More stroma between cells
3	Distinctly infiltrative margins
4	Sperate and well-differentiated cancer
5	Moderately differentiated cancer
6	Mixed moderately and poorly differentiated cancer
7	Poorly differentiated cancer
8	Mixed poorly and very poorly differentiated cancer
9	Very poorly differentiated cancer
10	Very poorly differentiated cancer

the cytoplasm of androgen-receptive cells, the AR is bound to HSPs, which maintain it in an inactive state. When testosterone (T) binds to the AR, it dissociates from HSPs and is phosphorylated by MAPK. This leads to the translocation of the dimerized AR into the nucleus, where it binds to the specific DNA sequence called androgen response elements (AREs), this binding turns on the gene expression involved in the growth of the cell, cellular differentiation, and cell survival (Murray 2021a).

4. Clinical Biomarkers and Current Treatment of Prostate Cancer

A number of biomarkers for prostate tumors are associated with the prognosis of PCa, some of which are Markers of apoptosis including B-cell lymphoma-2 *(Bcl-2)*, BCL-2 associated X protein *(Bax)*, Ephitilial-cadherin *(E-cadherin)*, Cyclin-dependent-kinase inhibitor 1B *(p27)*, Tumor Protein p53 *(TP53)*, Cyclin-dependent kinase inhibitor 2A *(p16)*, Marker of proliferation *(Ki67)*, Distal-less homeobox 1 messenger RNA *(DLX1 mrna)*, PCA3 Progensa PCa *Antigen 3*, *PSA*, *PHI*, transmembrane protease serine 2:v-ets erythroblastosis virus E26 oncogene homolog *(TMPRSS2-ERG Fusion)*, micro-vessel density, DNA-ploidy, Phosphatase and tensin homolog gene *(PTEN)* hypermethylation and allelic losses (Sekhoacha et al. 2022).

4.1. Conventional Therapy of Prostate Adenocarcinoma

Clinicians now have a better capacity to evaluate patient risk and prescribe therapy considering cancer prognosis and the patient's preferences because of advancements in diagnosis and treatment of PCa. The accepted standard therapy for males with stage 1-3 PCa is surveillance, prostatectomy, and radiation. All stage 4 and high-risk stage 3 patients can achieve a long-lasting remission after androgen ablation through surgical or Pharmacological/chemical castration. 1st generation antiandrogens like flutamide and bicalutamide can help in this situation. Stage 4, on the other hand, is defined by castration resistance, which is characterized by genetic alterations in the androgen receptor, and the prognosis is extremely poor (Sekhoacha et al. 2022).

A structured monitoring approach called active surveillance (AS) is used for patients with low-risk or indolent PCa. The rationale behind it is

that some prostate tumors grow slowly and might not need prompt treatment and require routine PSA tests, digital rectal exams (DREs), and biopsies to track the malignancy while scanning for any indications of progression. It can be shifted to a more active treatment strategy, including surgery or radiation therapy if cancer does advance (Choo et al. 2002).

The prostate gland is surgically removed during a Radical-Prostatectomy (RP). For local-advanced prostate carcinoma, it is a curative procedure. Numerous procedures, such as open surgery, laparoscopic surgery, and robotic surgery, can be used to treat RP (Mellman, Coukos, and Dranoff 2011). Cryotherapy is a minimally invasive process that employs extremely low temperatures to destroy cancer cells. It is not as frequently utilized as radiation therapy or RP to treat localized prostate cancer (Mouraviev and Polascik 2006). To eradicate malignant growth by damaging cancerous cells, radiation therapy (RT) uses high-energy radiation. A radioactive seed inserted in the prostate gland can transmit it internally or outside the body. For PCa that is localized, RT is a curative procedure (Baskar et al. 2012). A systemic treatment called hormone therapy (HT) prevents the production of testosterone, the male hormone that promotes the growth of PCa. Treatment for advanced PCa that has progressed outside of the prostate gland frequently involves HT (Heidenreich et al. 2008; Crawford et al. 2015). In the above discussion, all these treatment strategies possess several adverse effects which are shown in Figure 3.

5. Pharmacogenomics Exploration for Better Diagnosis and Precision Medicine

PCa is a complex genetic disease, with many genes involved in its pathogenesis. There is a need to identify novel genetic markers that can be used to predict susceptibility to PCa or to identify genes involved in its development (Khoury, Janssens, and Ransohoff 2013). Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation, and many SNPs have been associated with PCa risk. SNPs are small changes in the DNA sequence that can alter the structure and function of proteins. They are often inherited from parents and can vary in frequency among different populations. SNPs in candidate genes, such as those involved in cell growth and differentiation, have been shown to increase susceptibility to prostate cancer (Komar 2009). Genome-wide association studies (GWAS) have identified numerous SNPs associated with PCa risks (1 et al. 2001). These SNPs are typically located in non-coding regions of the genome, and their functional significance is not yet fully understood. However, some SNPs, such as those in the *8q24* region, have been shown to be associated with more aggressive forms of prostate cancer (Matejcic et al. 2018). The identification of SNPs associated with PCa risk has a significant consideration in upgrading early detection and prevention of the disease (Beuten et al. 2009). For instance, genetic testing could be used to detect the high risk of PCa individuals who have benefited from more aggressive screening or chemoprevention strategies. Additionally, SNPs could be used to develop new approaches for targeted therapies for prostate cancer. Overall, the research on SNPs in PCa is still in its early stages. However, the findings to date suggest that SNPs have the potential to be valuable tools for improving the diagnosis, prevention, and treatment of this devastating disease (Beuten et al. 2009).

This review covers the current understanding of the role of common SNPs in PCa development and their potential utility in screening and managing prostate disease. SNPs are associated with an increased risk of aggressive PCa and represent important genetic biomarkers. However, there remains a need to identify additional clinically relevant genetic biomarkers for screening, diagnosis, and mitigation and effective targeted treatment of prostate cancer.

Table 2: Single nucleotide polymorphism (SNPs) associated with prostate cancer diagnosis and progression.

SNPs/ Specific gene(s)	Ethnicity	Population size	Association to PCa	References
rs6983267, 8q24 gene	Caucasian and Asian	50854	Associated with PCa	(li et al. 2015)
rs1447295, 8q24 gene	Caucasian and Asian	50854	Associated with PCa	(li et al. 2015)
rs16901979, 8q24 gene	Africans' Americans	50854	Associated with PCa	(li et al. 2015)
rs138213197, HOXB13 gene	Europe	9012	Associated with PCa	(Beebe-Dimmer et al. 2015)
rs4242382, 8q-24 gene	Asian and Caucasian	3657	Associated with PCa	(Zhao et al. 2014)
rs4430796, 17q12 gene	White non-Hispanic	421	Associated with PCa	(Levin et al. 2008)
rs7501939, 17q12 gene	Non-Hispanic White	421	Associated with PCa	(Levin et al. 2008)
rs10896449, 11q13 CCND1	Europe	19395	Associated with PCa	(Chung et al. 2011) (Huang et al. 2002b)
TA repeats, SRD5A2	Lebanese	69	Associated with PCa	(El Ezzi, Boyko, Baker, Zaidan, Hraiki, El-Saidi, et al. 2017)
rs1938781, 11q12	Japan	5560	Associated with PCa	(Akamatsu et al. 2012)
rs2252004, 10q26	Japan	5560	Associated with PCa	(Akamatsu et al. 2012)
rs2055109, 3p11.2	Japan	5560	Associated with PCa	(Akamatsu et al. 2012)
rs1801320, RAD51	Polish	317	Increased risk of PCa	(El Ezzi, Boyko, Baker, Zaidan, Hraiki, El Saidi, et al. 2017)
rs12793759, 11q13	Europe	19395	Associated with PCa	(Chung et al. 2011)
rs3737559, 2p15	Iceland	23205	Associated with PCa	(Gudmundsson et al. 2008)
rs5945572, Xp11.22	Iceland	23205	Associated with PCa	(Gudmundsson et al. 2008)
rs10895304, MMP7	African American,	212	Reduce reoccurrence	(Jaboin et al. 2011b)
rs8844019, EGF, EGFR	Lisbon	275	Increased metastasis	(Teixeira et al. 2008; Perez et al. 2010)
rs3846716, CTNNB1, APC	Taiwan	307	Associated with prognosis	(Huang et al. 2010)
rs6434568, rs16834898, PCGEM1	Chinese	NA	Contribute the risk of PCa	(Xue et al. 2013a)
SRD5A2, V89L	Japanese	773	Association with PCa	(Li et al. 2003)
rs6434568, rs16834898, PCGEM1	Chinese	NA	Contribute the risk of PCa	(Xue et al. 2013a)
SRD5A2, V89L	Japanese	773	Association with PCa	(Li et al. 2003)
Fok l, VDR	Lebanese	69	Associated with PCa	(El Ezzi, Boyko, Baker, Zaidan, Hraiki, El-Saidi, et al. 2017)

Bsml, VDR	Lebanese	69	No association with PCa	(El Ezzi, Boyko, Baker, Zaidan, Hraiki, El-Saidi, et al. 2017)
Apa 1, VDR	Lebanese	69	No association with PCa	(El Ezzi, Boyko, Baker, Zaidan, Hraiki, El-Saidi, et al. 2017)
TaqαI, VDR	Lebanese	69	No association with PCa	(El Ezzi, Boyko, Baker, Zaidan, Hraiki, El-Saidi, et al. 2017)
MspA1I, CYP17	Lebanese	69	No association with PCa	(El Ezzi, Boyko, Baker, Zaidan, Hraiki, El-Saidi, et al. 2017)
rs10486567, 7p15.2	Finnish population	947	No association with PCs	(Chen et al. 2014)
rs1859962, 17q24	White non-Hispanic	421	No Association with PCa	(Levin et al. 2008)

Table 3: Association of single nucleotide polymorphism (SNPs) with the treatment of prostate cancer.

SNPs/ Specific gene(s)	Ethnicity	Population size	Association to PCa Treatment	References
rs6922548, rs2016520, rs1883322, rs3734254, rs7769719, PPAR-δ	UK	170	Potentially associated with response to therapy	(Deeken et al. 2010b)
rs4148943, rs4148947, rs12418, rs730720, rs4148950, rs1871450, rs4148945, CHST3	UK	170	Significantly associated with response to therapy	(Deeken et al. 2010b)
rs2292954, rs12960, SPG7	UK	170	Toxicities to treatment	(Deeken et al. 2010b)
*CYP2D6*19, CYP2D6*	UK	170	Toxicities to treatment	(Deeken et al. 2010b)
rs1799931, NAT2	UK	170	Toxicities to treatment	(Deeken et al. 2010b)
rs2238472, ABCC6	UK	170	Toxicities to treatment	(Deeken et al. 2010b)
rs2227291, ATP7A	UK	170	Toxicities to treatment	(Deeken et al. 2010b)
rs4646487, CYP4B1	UK	170	Toxicities to treatment	(Deeken et al. 2010b)
rs2301159, SLC10A2	UK	170	Toxicities to treatment	(Deeken et al. 2010b)
rs1799794, ERCC2, MLH1, ATM, XRCC3, LIG4	Spain	698	GIT toxicity during treatment	(Fachal et al. 2012)
2677TT-3435TT, ABCB1	N/A	73	Neutropenia, Neurotoxicity induced by docetaxel	(Sissung et al. 2008)
rs1982073, rs1800469, TGFB1	Caucasian	141 322	Rectal bleeding during treatment Nocturia during treatment	(Peters et al. 2008; De Langhe et al. 2013b)
rs1056836, CYP1B1	Italy	60	Predictive marker for treatment optimization	(Pastina et al. 2010)

6. Discussion

There are several treatment options available for patients with low or intermediate-risk localized PCa, including radical prostatectomy, active surveillance, radiotherapy, and brachytherapy (Huggins and Hodges 1941). The choice of treatment depends on the patient's preferences and individual circumstances, such as surgical risk and comorbidities. Patients with high-risk PCa are typically treated with radical prostatectomy or radiotherapy in combination with ADT, as these tumors are more likely to metastasize. For patients with metastatic PCa, palliative therapies such as chemotherapy (docetaxel), hormonal therapy (abiraterone), and radionucleotide therapy can be used to prolong disease-free survival (Sekhoacha et al. 2022). However, the leading cause of death in PCa patients is resistance to ADT and the development of CRPC. Recently, targeted therapy has been used in combination with radiotherapy to reduce pain in patients with CRPC. These new therapies require careful monitoring to ensure optimal drug delivery and minimize adverse events. However, there is still a need for predictive biomarkers to guide the use of current treatments in a more optimized manner. Prostate carcinoma thought to be a heterogeneous health condition, with a wide range of clinical outcomes observed in patients with similar Gleason scores, Tumor, nodes, metastasis, staging (TNM), and PSA levels. This heterogeneity is considered because of genetic, epigenetic, and environmental influences.

Current clinical risk stratification algorithms, such as those based on Gleason score, TNM staging, and PSA, cannot fully account for this heterogeneity. As a result, a significant proportion of patients are either overtreated or undertreated. For example, 20-60% of intermediate and high-risk PCa patients who are treated with radiotherapy or radical prostatectomy experience biochemical recurrence. This suggests that a significant proportion of these patients were overtreated, as their tumors were likely to have been indolent and would not have progressed to metastatic disease without treatment. On the other hand, a significant proportion of low-risk PCa patients are undertreated, as their tumors progress to metastatic disease despite being treated with conservative measures. This suggests that these patients may have benefited from more aggressive treatment. The development of personalized medicine approaches for PCa has the potential to address these challenges. By identifying the molecular and genetic characteristics of each patient's tumor, clinicians can develop individualized treatment plans that are more likely to be effective and minimize the risk of side effects.

Genotyping of SNPs can be used to predict the risk of developing prostate cancer, but SNPs are not considered to be definitive diagnostic markers for this disease. However, a recent study suggests that SNPs may be useful in clinical settings in other ways, such as in combination with PSA screening to identify high-risk individuals (Klein et al. 2012).

SNPs are genetic variants that can modulate the expression of novel biomarkers for PCa (Mottet et al. 2017). The analysis and interpretation of SNPs in conjunction with other risk factors is essential for accurate PCa diagnosis. SNPs can also have a causal association with the development of prostate cancer, and their interpretation can have a significant impact on diagnostics. SNPs have the potential to improve PCa diagnostics by increasing the accuracy and sensitivity of biomarker tests. This can lead to earlier detection and treatment of prostate cancer, which can improve the quality of life and reduce complications and costs (Vatandoost et al. 2016). For instance, rs6983267 and rs1447295 at the *8q24* gene in Caucasians and Asians have a strong association with prostate adenocarcinoma (li et al. 2015). In contrast, rs16901979 at the same gene in African Americans has shown a significant association

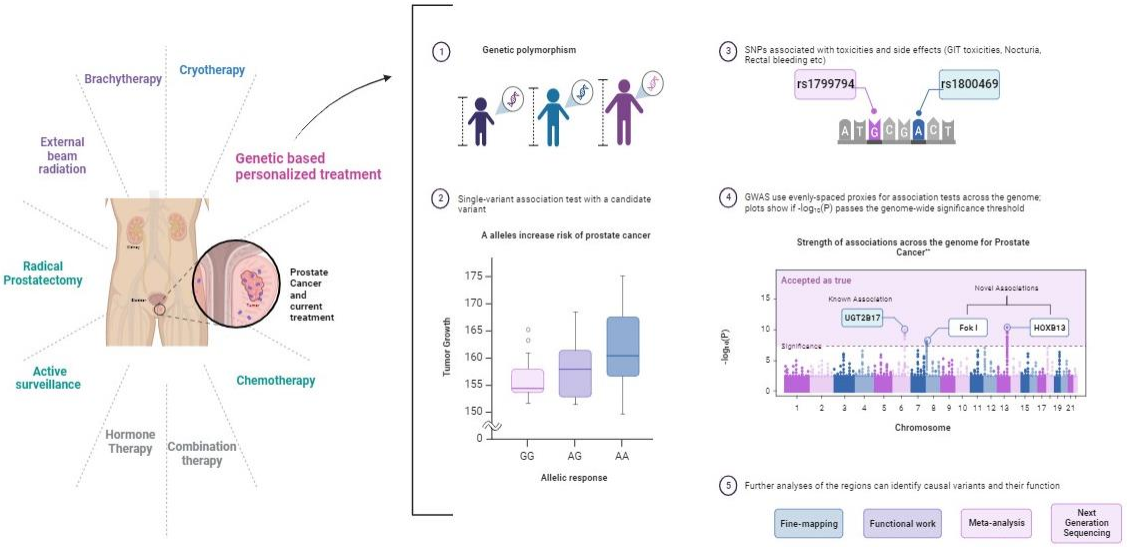

Figure 1: Pharmacogenomics of Prostate Cancer: A Review of Recent Progress in Personalized Medicine and Future Challenges.

with prostate malignancy (li et al. 2015). Meanwhile, in the European population, rs138213197 has a notable association with PCa (Beebe-Dimmer et al. 2015). In addition to these, genetic variations such as SNPs are also involved in treatment failure or toxicities in patients battling prostate carcinoma. For example, in the English population, rs4646487 *CYP4B1* and rs2227291 *ATP7A* are responsible for toxicities in the treatment of prostate gland carcinoma (Deeken et al. 2010a). As per the study conducted by Chung et al. (2011*), in* the population of 19395 **in** Europe, SNPs rs12793759 *11q13* are Associated with PCa (Chung et al. 2011; Huang et al. 2002a). According to a study conducted in Japan in 2012, the Japanese population was rs1938781 11q12, rs2252004 *10q26*, and rs2055109 *3p11.2*. These SNPS are involved in the diagnosis and progression of PCa (Akamatsu et al. 2012). As reported in 2013, SNPs at *rs6434568 and rs16834898 PCGEM1gene* expression marker 1 contribute to the risk of prostate carcinoma in the Chinese population (Xue et al. 2013b).

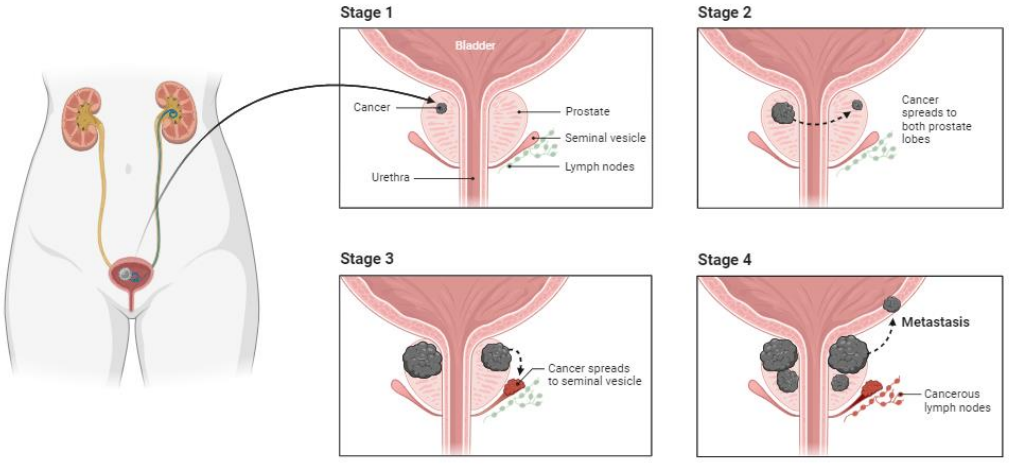

Figure 1: Stages of prostate cancer.

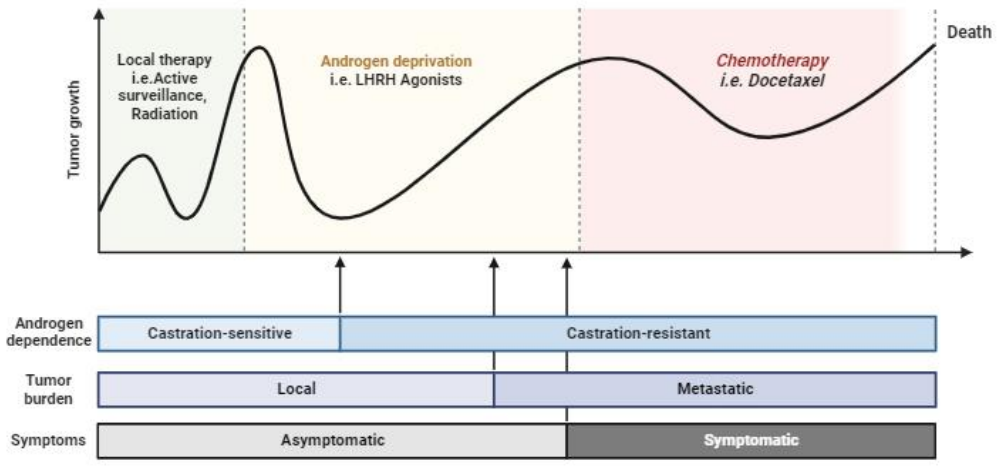

Figure 2: Tumor growth and metastasis with different therapy.

SNPs are not only promising candidates for the development of novel PCa biomarkers. However, they can also lead to minimizing treatment toxicities, and adverse effects and reduce the reoccurrence of prostate gland carcinoma, ultimately aiding in the patient's well-being. As per the study conducted in Spain, rs1799794 is associated with gastrointestinal tract toxicity (Fachal et al. 2012). In African American Caucasian ethnicity, rs10895304 is involved in the reoccurrence of PCa (Jaboin et al. 2011a). Modulation in the rs1982073, rs1800469 *TGFB1* rectal bleeding, and nocturia during treatment can be eradicated (De Langhe et al. 2013a).

It is important to note that if SNPs are not taken into consideration when developing new PCa biomarkers, we may face similar challenges to those we currently face with PSA screening (Vatandoost et al. 2016). PSA screening is not specific enough to distinguish between benign and malignant prostate cancer, which can lead to overdiagnosis and unnecessary treatment (Seibert et al. 2018). Overall, SNPs play a vital role in PCa diagnostics, developing novel biomarkers for interpreting existing biomarker tests and regulating treatment to minimize the side effects of PCa therapy. By taking SNPs into account, we can improve the accuracy and sensitivity of PCa diagnostics, leading to earlier detection and treatment and better patient outcomes. There are several promising personalized medicine approaches for PCa in development. For example, Next Generation Sequencing (NGS) can identify genetic mutations and other genomic alterations in PCa tumors. These could be approaches to select targeted therapies designed to target the patient's tumor more specifically. Another promising approach is the use of liquid biopsies, such as blood tests, to monitor the response of PCa tumors to treatment and to detect the early signs of recurrence. This information can then adjust the patient's treatment plan as needed. Personalized medicine for PCa is still in its early stages of development, but it can potentially revolutionize treating this disease. By tailoring treatments to each patient's individual needs, personalized medicine can help improve outcomes and reduce the risk of side effects.

7. Future Directions

Despite the advancement achieved in understanding the significance of SNPs in prostate carcinoma, there are still hurdles to be faced when attempting to translate this

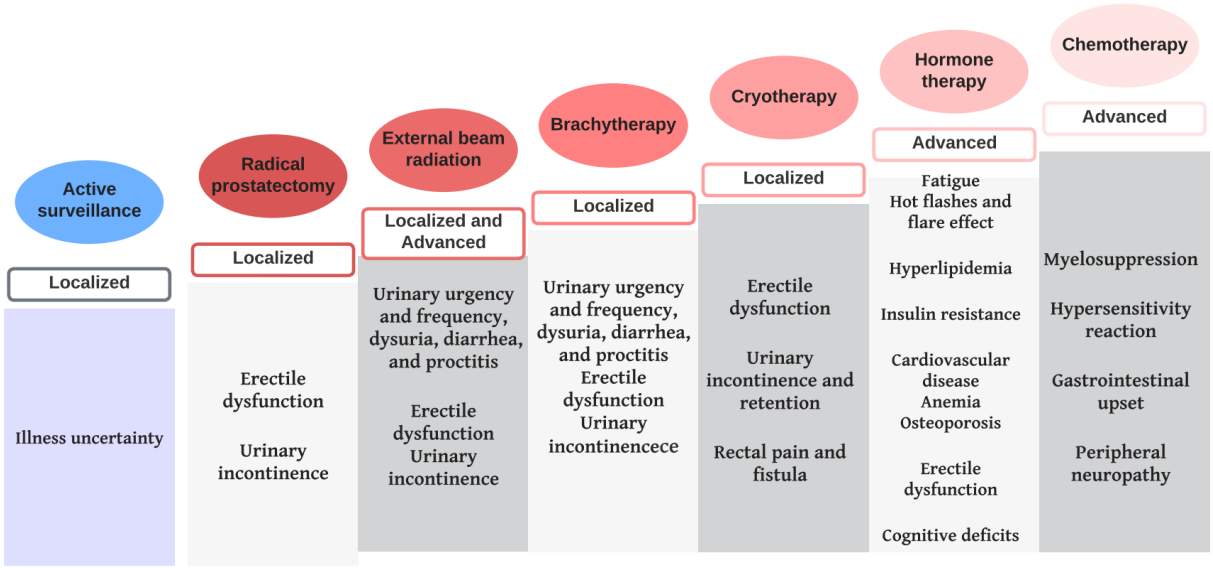

Figure 3: Side effects of different treatment regimens.

knowledge into clinical practice. Future studies should concentrate on well-powered clinical trials to validate the role of SNPs in PCa progression, identify new biomarkers, and minimize the treatment toxicities. Additionally, fundamental research is needed to elucidate the causal association between SNPs and signaling pathways in PCa, which could lead to the discovery of novel therapeutic targets. Precision medicine, which tailors treatment to an individual's genetic makeup, is still in its early stages of development for PCa. The heterogeneous and multigenic nature of PCa is a significant challenge in developing effective precision therapies. However, worldwide research studies suggest that precision medicine for PCa is promising. With further research, fine mapping, functional work, and next-generation sequencing analysis, precision treatment and SNPs-based diagnosis for PCa could become a reality soon.

Conflict of Interest

The authors declare that they have no competing interests.

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Study Approval

NA

Consent Forms

NA

Data Availability

NA

Authors Contribution

Fawad Bashir conceptualized the study and wrote the manuscript, Kinza Farooq collected the data from web sources and proofread the manuscript. Ayesha Irfan performed graphical work and compilation of data.

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