Review Article
Single nucleotide polymorphisms (SNPs) in prostate cancer: its implications in diagnostics and therapeutics

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Abstract: Prostate cancer is one of the most frequently diagnosed malignancies in developed countries and approximately 248,530 new cases of prostate cancer are likely to be diagnosed in the United States in 2021. During the late 1990s and 2000s, the prostate cancer-related death rate has decreased by 4% per year on average because of advancements in prostate-specific antigen (PSA) testing. However, the non-specificity of PSA to distinguish between benign and malignant forms of cancer is a major concern in the management of prostate cancer. Despite other risk factors in the pathogenesis of prostate cancer, recent advancement in molecular genetics suggests that genetic heredity plays a crucial role in prostate carcinogenesis. Approximately, 60% of heritability and more than 100 well-recognized single-nucleotide-polymorphisms (SNPs) have been found to be associated with prostate cancer and constitute a major risk factor in the development of prostate cancer. Recent findings revealed that a low to moderate effect on the progression of prostate cancer of individual SNPs was observed compared to a strong progressive effect when SNPs were in combination. Here, in this review, we made an attempt to critically analyze the role of SNPs and associated genes in the development of prostate cancer and their implications in diagnostics and therapeutics. A better understanding of the role of SNPs in prostate cancer susceptibility may improve risk prediction, enhance fine-mapping, and furnish new insights into the underlying pathophysiology of prostate cancer.

Keywords: Prostate cancer, polymorphism, single nucleotide polymorphisms, prostate specific antigen, tumorigenesis

Introduction

Prostate cancer is one of the major non-skin malignancies because of its health-associated costs, high prevalence rate, and mortality [1]. The increasing trend of incidence is seen more often in developed countries probably due to more advanced medical care facilities and PSA screening at early stages of disease development [2]. However, the highest mortality rate has been observed in the males of the African race than the white race [3]. The lowest rate of prostate cancer mortality has been recorded in Asian men [4]. Prostate cancer is mostly diagnosed in elderly males over young males and is expected that its incidence could increase in

the coming future [5]. Owing to the presence of non-modifiable risk factors, such as ethnicity (race), age and genetic (*BRCA2, BRCA1, HOXB13, NBS1, CHEK2* mutations, and SNPs) factors [6], it is extremely hard to reduce prostate cancer incidence, and thus gives more importance to early diagnostics and therapeutics [7]. Despite having clinically confined and dormant tumors at the time of diagnosis of prostate cancer, yet the malignancy of the prostate holds among the major cause of mortality worldwide [8]. Owing to have high mortality rate, prevalence, and socioeconomic-related issues, the field of prostate carcinogenesis and affected patients have a major challenge in both diagnostics and therapeutics [9]. The

major reasons are the absence of specific cancer associated or prostate cancer patient-specific biomarkers, limitations, and non-specificity in existing diagnostics to distinguish between benign and aggressive tumors, and finally in the therapeutic modalities of prostate cancer due to over-treatment and development of drug resistance [10-12].

Prostate cancer is life threatening polygenetic disease, and many genes involved in the pathogenesis of this disease are imprecisely explored [13]. Therefore, there is a need to identify novel genetic markers which could be used as indicators to predict the most susceptible segments of the population to the disease or for the genes that are involved in prostate cancer pathogenesis. Single nucleotide polymorphisms (SNPs) are variations in a genome's base pair in a DNA sequence and occur in nearly 1 out of 800 base pairs [14]. Conventionally, for a single nucleotide variation to be described as polymorphism it must occurs in the DNA of at least 1% of the population [15]. SNPs cause variations in genes which alters the protein and enzymatic machinery of the cell [16]. The inheritance of genes within families is strongly influenced by SNPs [17] and reports suggest that susceptibility to prostate cancer is associated with SNPs and the susceptibility of developing prostate cancer in certain individuals is higher than others [18]. It has become clear from genome-wide association studies (GWAS) and fine-mapping efforts that more than 100 common SNPs are associated with prostate cancer susceptibility [19]. For example, polymorphisms in gene 8q24 have shown strong links with prostate cancer susceptibility, signifying that 8q24 polymorphisms could be good markers in prostate cancer diagnosis and therapy [20]. Many other studies have shown the association of SNPs in candidate genes with increased susceptibility to prostate cancer [21]. The type of candidates that show association with increased susceptibility to prostate cancer include genes involved in steroid metabolism, oxidative stress, cell adhesion, angiogenesis, cell cycle and DNA repair as well as variants of other genes [22]. A recently conducted association analyses of more than 140,000 men have identified 63 new prostate cancer susceptibility loci [23].

Therefore, the current review outlines the role of common SNPs in prostate cancer development and how these SNPs could be utilized for the screening and management of prostate cancer. SNPs are predictors of aggressive prostate cancer and in this review the research findings highlighted that SNPs represents an important genetic biomarker that has strong association with susceptibility to prostate cancer. However, there are indications that research focused on genetic biomarkers is not complete and there is a need to identify clinically more relevant genetic biomarkers that could be used for screening, diagnosis, and prognosis of prostate cancer.

Prostate cancer progression

With the advancement in age, the enlargement of the prostate gland is common. At the age of around 40 years, benign prostate hyperplasia (BPH) develops from the transition zone of the prostate and implicates in urination complications [24]. Although there is no report that BPH is causally associated with prostate cancer, however recent evidence suggests that BPH might have a possible casual association with prostate cancer inflammation which is believed to be a key event in the progression of prostate cancer [25, 26]. The other common complication in the prostate with age is prostatitis [27]. Prostate cancer is commonly adenocarcinoma and arises from epithelial tissue of the prostate gland [28]. Around 70%, 25% and 5% prostate cancer arise from peripheral, transition and central zone, respectively [29]. Prostate tumors are usually multifocal bearing multiple tumors and are believed to be advanced from the Prostatic Intraepithelial Neoplasia (PIN) [30] **Figure 1**. The advancement in disease progression affects neighboring organs such as the seminal vesicle, pelvis, urethra, urinary bladder via lymph nodes and finally spreads to bones through the pelvis [31]. A plethora of reports suggests that prostate cancer can also metastasis to lungs and other organs [32]. Recent reports suggest that prostate metastasis originates and spreads from a single independent clone present within the prostate gland [33, 34]. This suggests the heterogeneity and aggressiveness of tumors within the prostate and implicates that future prostate cancer diagnostics and therapeutics will be a challenging task. Therefore, these studies suggest that prostate cancer is an elderly cancer in men which mainly arise from peripheral epithelial tissue of prostate. Additionally, it is a heteroge-
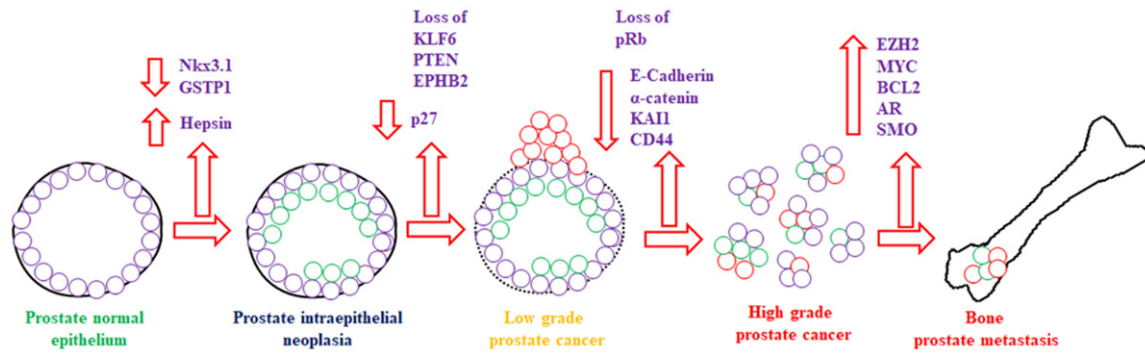
Figure 1. Prostate cancer initiation, progression, and metastasis to bone with upregulation and downregulation of tumor suppressor and proto-oncogenes involved in various signaling pathways.

Table 1. Threshold level of PSA and age group of patients with digital rectal examination

S. No	Digital Rectal Examination	PSA level	Age
01	Negative	≥ 2 μg/l	< 50 years
02	Negative	≥ 3 μg/l	50-70 years
03	Negative	≥ 5 μg/l	70-80 years
04	Negative	≥ 7 μg/l	> 80 years

nous malignancy that originate from PIN which further affects neighbouring organs and finally metastasis to various organs that includes bones and lungs.

Prostate cancer diagnosis and grading

The common mode of detection of prostate cancer is PSA testing or occasionally by clinical symptoms such as complications in urination to empty the urinary bladder [35]. At the initial stage of prostate malignancy when the tumor is confined to the prostate with no symptoms, the metastatic spread often emerges with pain in the hips, pelvis, and back portion of the skeleton [36]. The foremost step in the diagnostics of prostate malignancy is PSA testing, followed by digital rectal examination (DRE) [37]. The PSA testing was debatable for quite some time to fix the threshold level of PSA under various guidelines to limit the overdiagnosis of clinically invaluable malignancies associated with the prostate [38]. The **Table 1** shows the PSA threshold level for the age group when the DRE is negative to be recommended for further investigations for the diagnosis of prostate malignancy. The follow-up for the suspected prostate cancer patients includes an examination of transrectal ultrasonography-guided needle biopsy with at least 12 cores of prostate

samples followed by an examination of the specimens by histopathological means and the reporting should be performed as per the Gleason grading system [39]. The Gleason's score ranges from 1 for well-characterized prostate glandular cells to 5 for poorly characterized glandular cells [40]. Therefore, the common mode to diagnose prostate cancer is detection of PSA. However, due to its non-specificity and sensitivity, the suspected prostate cancer patients should perform DRE, followed by transrectal ultrasonography-guided needle biopsy to characterize the stage of malignancy based on Gleason's grading system.

Primary risk factors and their causal association with prostate cancer

The primary risk factor for the development of prostate cancer is familial history, age, and ethnicity [41]. Recent studies of epidemiology suggest that prostate cancer is one of the prominent heritable malignancy and suggests a strong causal association between genetic factors and the development of prostate cancer [42, 43]. A person having a heritable link with a person who had diagnosed with prostate cancer has a 2-3-fold higher risk of developing prostate malignancy as compared with the family without any familial history of prostate cancer [44]. A Nordic twin study revealed that around 60% of prostate cancer patients had familial history to develop prostate cancer [45].

With the advancement in technology, recent studies suggest that molecular genetics plays a crucial role in the development of prostate cancer [46]. The human genome contains nearly
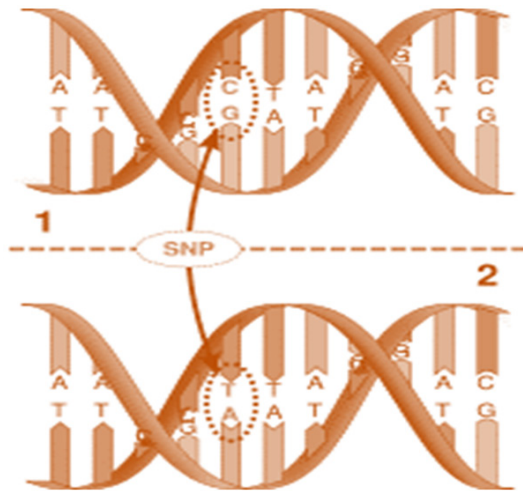
Figure 2. A small change in nucleotide sequence results in the formation of single nucleotide polymorphism.

30 million base-pairs of nucleotides, of which 99% of these nucleotide base pairs are in the same sequence in all human beings [47]. During the evolutionary process, the sequence sites where the mutations have happened and dispersed to more than 1% of the population are called polymorphic [48]. The human genome has various types of variation called polymorphisms and has been reported to be associated with the progression of cancer [49]. One of the common polymorphisms is SNPs. The SNP is a variation in the sequence of DNA at a single position of a nucleotide (A, T, C, or G) in the genome that varies from the regularly expected nucleotide as shown in **Figure 2** [15]. Various genetic sequence programs at the international level have revealed the identification of millions of SNPs in the human genome [15]. SNPs does not directly influence the protein-coding function because they are localized within the introns and intergeneric regions of the genome [50]. The SNPs act as an interesting genetic marker to differentiate the susceptibility of a person to disease [51]. The determination of SNPs is quite easy, simple, and performed only once, these features make them appealing biomarkers in the field of molecular genetics to analyze the disease status [52]. The growing demand for the reputation of SNPs in prostate cancer pathogenesis is verified by the numerous studies conducted recently and suggests a key role of SNPs in the field of prostate cancer diagnostics [42, 53].

Genome-wide association studies (GWAS) have demonstrated that more than 100 SNPs have been identified with low to moderate association with prostate cancer **Table 2** [54]. Interestingly, studies reveal that a moderate effect of prostate cancer risk was observed when SNPs were single. However, the effect of prostate cancer risk increases significantly when the SNPs were in combination [54]. This can be explained by approximately more than 39% of prostate cancer risk is associated with familial history. Further, analysis of GWAS in present and future, to add some more genetic variants which could help the scientific community to better explain the familial risk in prostate cancer. However, the interesting question raised here is, does the identification of more SNPs and their association with increased prostate cancer risk has the worth over the established SNPs.

Various SNPs are associated with each other via "linkage disequilibrium". It is an association (non-random) of alleles at two loci or more than two loci projected from a distinct inherited chromosome [55]. Nevertheless, the identification of SNPs through GWAS studies are mainly "index SNPs" that are different from SNPs connected through linkage disequilibrium [56]. Reports suggest that index SNPs are not associated with the increase in prostate cancer risk [57]. Therefore, the identification of causative linkage-type SNPs and their underlying molecular analysis is warranted. Some SNPs that are located within an open reading frame of an exon can modify the stability of messenger RNA (mRNA) or efficiency of translation of proteins as well as modulations in the activity or structure of translated proteins [58]. However, most SNPs lie outside the exonic region of the functional gene and could modulate both transcriptions as well as the level of genome organization [59] **Figure 3**. Therefore, the recent findings revealed that genetic factors have a major contribution in prostate malignancy. Among them SNPs which acts as an appealing genetic marker to differentiate the susceptibility of a person to prostate cancer progression. Thus, the need to identify and investigate the role of different SNPs in the progression of prostate cancer as biomarkers is deeply needed for early prostate cancer diagnosis.

Clinical utility of single nucleotide polymorphisms (SNPs) in prostate cancer

Table 2. List of SNPs along with their endpoint conclusion discussed in table with the appropriate references

High risk SNPs involved in prostate cancer	Investigated gene(s)/loci	Number of cases in the study	Endpoint Conclusion	References
rs17021918, rs7679673, rs1447295, rs721048, rs9364554, rs16901979, rs2928679, rs4430796, rs1512268, rs6983267, rs16902094, rs12621278, rs920861, rs1855962, rs4962416, rs2660753, rs10934853, rs7127900, rs10486567, rs12418451, rs10993994, rs8102476, rs10896449, rs2735839, rs5945619, rs5759167, rs1465618	-	4621	Risk prediction models at genetic level lead the identification of a subset of high-risk suspected prostate cancer patients at early curable stage	Sun et al. 2011 [74]
rs7841060, rs620861, rs6983267, rs1447295, rs721048, rs4242382, rs12621278, rs7837688, rs4857841, rs16902094, rs12500426, rs1571801, rs9364554, rs10993994, rs6465657, rs4962416, rs1512268, rs7127900, rs1016343, rs12418451, rs16901979, rs7931342, rs1465618, rs10896449, rs2660753, rs11649743, rs4430796, rs7501939, rs1859962, rs17021918, rs266849, rs7679673, rs2735839, rs10486567, rs5759167, rs6465657, rs5945572, rs2928679, rs5945619, rs4961199	SLC25A37, CPNE3, EHBP1, MSMB, BIK, SLC22A3, ITGA6, TCF2, PDLIM5, EEFSEC, CTBP2, KLK3, TET2, THADA, CNGB3, JAZF1, LMTK2, NUDT11, NKX3-1	15161	Addition of familial history and genetic information apart from PSA screening in predictive risk models of prostate cancer could be beneficial for young suspected prostate cancer patients	Lindstrom et al. 2012 [75]
rs721048, rs1465618, rs12621278, rs2660753, rs17021918, rs12500426, rs7679673, rs9364554, rs10486567, rs6465657, rs10505483, rs6983267, rs1447295, rs2928679, rs1512268, rs10086908, rs620861, rs10993994, rs4962416, rs7931342, rs7127900, rs4430796, rs1859962, rs2735839, rs5759167, rs5945619	-	2885	Development of algorithm to predict prostate cancer using familial history and genotypes of more than 25 SNPs. This can be used to assess the pedigrees of an arbitrary population size or structure.	Macinnis et al. 2011 [76]
rs2736098, rs11067228, rs10788160, rs17632542	-	964	Combination of genotyping and PSA detection more specifically detect suspected prostate cancer and delay or prevent needless prostate biopsies	Helfand et al. 2013 [88]
rs10486567, rs17632542, rs11228565, rs5759167	JAZF1, IGF2, TPCN2, HNF1B, DPF1, MYC, PPP1R14A, NCOA4, SPINT2, TH, KLK3, INS, TTLL1, MYEOV, BIK, MSMB, NUDT11	3772	Using SNPs for assessing prostate cancer risk is less accurate than PSA detection and there is no advancement in prostate cancer diagnostics using both SNPs and PSA.	Klein et al. 2012 [80]
rs721048, rs10993994, rs12621278, rs7127900, rs10086908, rs10896449, rs13252298, rs11649743, rs16901979, rs4430796, rs6983267, rs1859962, rs1016343, rs8102476, rs6983561, rs2735839, rs7679673, rs5759167, rs16902094, rs5945619, rs1447295	EEFSEC, CTBP2, THADA, HNF1B, ITGA6, PPP1R14A, PDLIM5, KLK3, FLJ20032, TNRC6B, JAZF1, BIK, LMTK2, NUDT11, MSMB, 8q24.21, EHBP1, 11q15.5, SLC22A3, 11q13.2, NKX3-1, 17q24.3	5241	Implementation of risk-prediction and genetic risk score decreases biopsies by 22.7% and missing diagnosis cost of prostate cancer by 3%	Aly et al. 2011 [131]
rs8844019	EGFR	212	After radical prostatectomy, the authors observed a strong association between prostate biochemical recurrence and the SNPs	Perez et al. 2010 [132]
rs9282861, rs198977, rs11536889	SULT1A1, KLK2, TLR4	703	After radical prostatectomy predicting biochemical recurrence in prostate cancer were significantly improved by the inclusion of patient genetic information and clinicopathological data interpretation.	Morote et al. 2010 [133]
rs2208532, rs4952197, rs12470143, rs518673, rs523349, rs12470143	SRD5A2, SRD5A1	846	Multiple variations in SRD5A2 and SRD5A1 are associated with either decreased or increased rates of BCR after radical prostatectomy.	Audet-Walsh et al. 2011 [134]

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SNP	Genes	N	Findings	Reference
rs10895304	MMP7	212	Predictive analysis of A/G genotype in clinically localized prostate cancer patients reduces recurrence	Jaboin et al. 2011 [135]
rs2279115	bcl2	290	Biochemical recurrence frequency was more observed in -938 A/A genotype carriers than -938 CC + C/A carriers	Bachmann et al. 2011 [136]
rs3846716	APC, CTNNB1	307	After radical prostatectomy, the SNP genotype of AA/GA has promising prognostic role	Huang et al. 2010 [137]
rs2016347, rs2946834	IGF1R, IGF1	320	Post radical prostatectomy associated with biochemical recurrence has a strong genetic association between IGF1R rs2016347 and IGF1 rs2946834	Chang et al. 2013 [138]
rs2569733, rs9282861, rs198977, rs1800247	KLK3, SULT1A1, KLK2, BGLAP	670	In post radical prostatectomy Genetic testing such as SNPs and clinicopathological data allows improvement of preoperative prediction of early biochemical recurrence	Borque et al. 2013 [139]
rs25489	XRCC1	603	In post radiotherapy polymorphism of XRCC1 Arg280His could be protective against the high-grade late toxicity	Langsenlehner et al. 2011 [140]
rs1982073, rs1800469	TGF β1	322	After radical prostatectomy followed by radiotherapy with IMRT, the genetic variants of TGF β1 in codon 10 T > C and codon -509 C > T are involved in nocturia induced by radiations	De langhe et al. 2013 [141]
rs1799794	ERCC2, MLH1, ATM, XRCC3, LIG4	698	Development of gastrointestinal toxicity by the mean dose and SNP in post 3D-CRT	Fachal et al. 2012 [142]
None	TGF β1	413	No association was observed between the risk of late toxicity and haplotypes or investigated SNPs	Fachal et al. 2012 [143]
None	XRCC6, ABCA1, MRE11A, ALAD, MSH2, APEX1, NEIL3, BAX, NFE2L2, ATM, NOS3, CDKN1A, PAH, DCLRE1C, PRKDC, EPDR1, PTTG1, ERCC2, RAD17, ERCC4, RAD21, GSTA1, RAD9A, LIG4, REV3L, HIF1A, SART1, LIG3, SH3GL1, MED2L2, SOD2, TGFB1, MLH1, TGFB3, MAP3K7, TP53, MAT1A, XPC, CD44, XRCC1, IL12RB2, XRCC3, GSTP1, XRCC5, MPO	637	No association was confirmed in the current study after evaluating previous reports. The study further evaluates the SNPs *P* value distribution against the toxicity score.	Barnett et al. 2012 [144]
rs12422149, rs1077858, rs1789693,	SLCO1B3, SLCO2B1	538	Patients on ADT possess three SNPs in SLCO2B1 and have a strong associated with time to progression. However, SLCO1B3 and SLCO2B1genotype patients on ADT translocate androgens efficiently and displayed median 2-year shorter TTP	Yang et al. 2011 [99]
-	TGFBR2	1765	The post ADT patients have more risk of early relapse when TGFBR2-875GG are in homozygous condition. Combination of genetic interpretation and clinicopathological data revealed high ability to envisage the risk of failure of ADT	Teixeira et al. 2009 [145]

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rs6900796, rs1268121	TRMT11, WBSCR22, PRMT2, SRD5A1, PRMT7, SRD5A2, HSD17B1, UGT2B10, PRMT6, HSD17B12, HSD11B1, PRMT3, THBS1, UGT2B7, SULT2A1, CYP3A4, UGT2B4, SULT2B1, PRMT5, CYP11B2, PRMT8, METTL6, HSD3B2, CARM1, UGT1A4, HEMK1, ARSE, METTL2B, UGT1A8, UGT2B11, UGT1A5, UGT1A10, CYP19A1, ESR2, ESR1, LCMT2, UGT2A3, UGT1A9, SERPINE1, AR, UGT1A6, UGT1A7 AKR1D1, AKR1C4, UGT2A1, STS, SULT1E, HSD17B8, UGT2B28, ARSD, HSD17B3, HSD17B2, LCMT1, HSD17B7 CYP11B1, UGT1A1, HSD3B1, UGT1A3	304	The study demonstrated that a strong association was observed between TRMT11 and time to ADT failure. Further, the study revealed that two out of 4 TRMT11 tag SNPs are strongly associated with time to ADT failure.	Kohli et al. 2012 [101]
rs6728684, rs1071738, rs3737336, rs998754, rs1045747, rs4351800	KIF3C, PALLD, ACSL1, CDON, GABRA1, IFI30, SYT9, ETS1, ZDHHC7, has-mir-423, MTRR	601	In multivariate models that includes clinico-pathological predictors, the genotypes IFI30 RS1045747, CDON rs3737336 and KIF3C rs6728684 emerge significant predictors for the progression of disease. More number of unfavourable type of genotypes was found to be associated with quick disease progression and lessens the prostate cancer-specific survival time after ADT	Bao et al. 2011 [102]
rs2051778, rs16934641, rs3763763, rs3763763	SKAP2, GNPDA2, TACC2, BNC2, SKAP1, ZNF507, KLHL14, ZNF521, NR4A2, SPRED2, FBXO32, ALPK1, AATF	601	In post ADT, the clinical outcome is associated with genetic variant in TACC2, BNC2 and ALPK1. Further, the effect is cumulative when combination of ACM and genotypes of ADT of two loci of interest were investigated	Huang et al. 2012 [103]
rs9508016, rs2939244, rs7830622, rs9508016, rs6504145	FLT1, ACTN2, PSMD7, ARRDC3, SKAP1, XRCC6BP1, FBXO32, FLRT3, NR2F1	601	For PCSM the genetic variants in FLT1, ARRDC3, and SKAP1 are significant predictors. However, for ACM the genetic variants that are significant predictors are in FLT1 and FBXO32. Together, there was a strong combined effect on ACM and PCSM.	Huang et al. 2012 [104]
rs4862396, rs7986346, rs3734444	BMP5, RXRA, NCOR2, ERG, IRS2, BMPR1A, MAP2K6	601	The study suggests a strong association of genetic variants in BMP5, CASP3 and IRS2 with ACM. However, a significant association was observed in genetic variants in IRS2 and BMP5 with PCSM. In ADT patients, the greater number of unfavourable genotypes at interested loci have less time to PCSM and ACM.	Huang et al. 2012 [146]
-	IGF-1	251	The study suggests that considering sum of all the genetic risk factors in each LD block, there is reduction in cancer-specific survival significantly when compared to 0-2 risk factors.	Tsuchiya et al. 2013 [105]
rs1056836	CYP1B1	60	The clinical outcome in CPRC patients to docetaxel and predictive marker is polymorphism.	Pastina et al. 2010 [120]
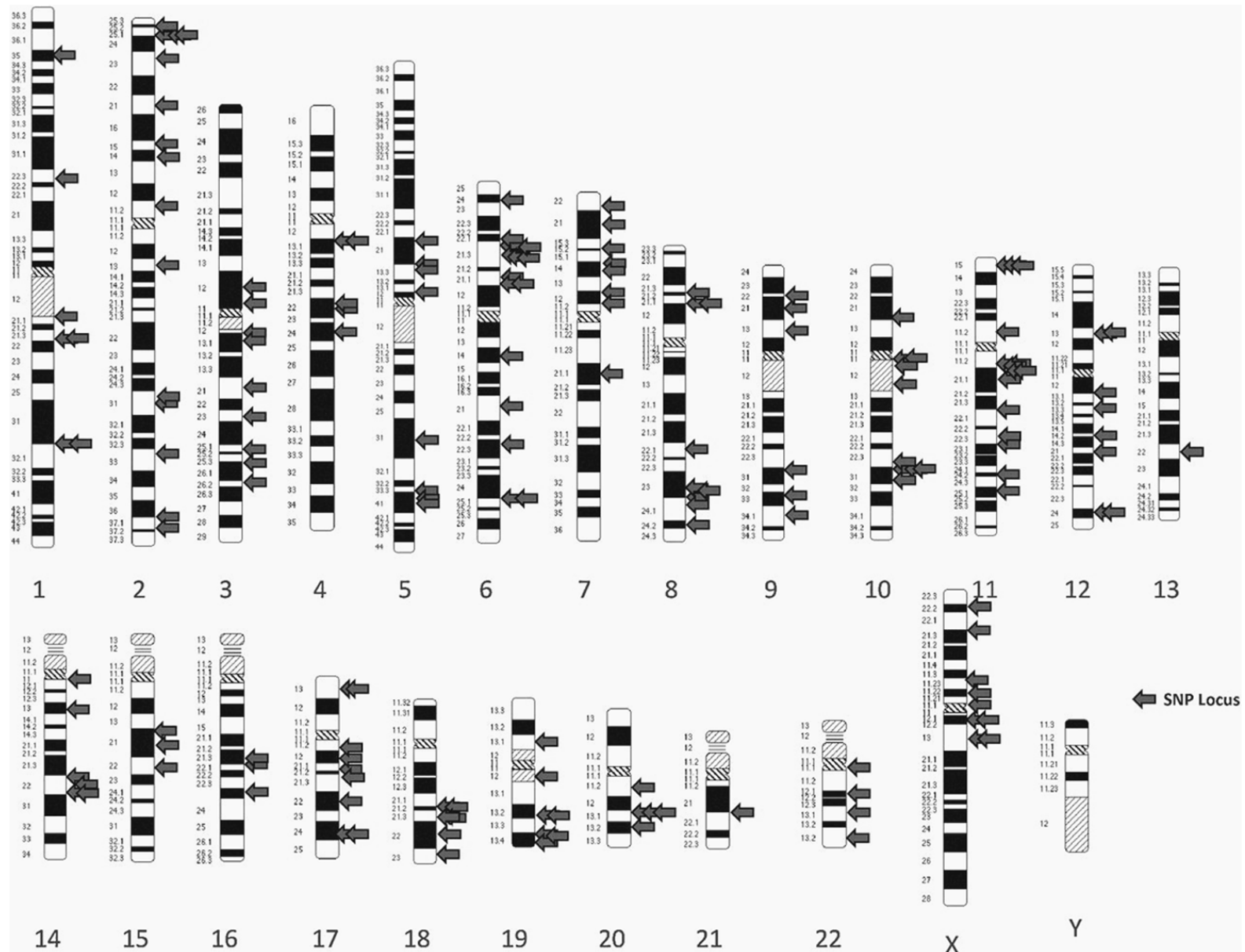
Figure 3. Idiogram showing SNPs locus associated with prostate cancer risk by GWAS studies.

Early diagnostics in prostate cancer

The only diagnostic test for the suspected prostate cancer patients at the early stage of the disease is the detection of serum PSA level which acts as a marker for prostate cancer [60]. Owing to its low specificity and sensitivity issues, PSA screening at the mass level has been immensely debated [61]. Two primary screening trail studies: The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and The European Randomized Study of Screening for Prostate Cancer (ERSPC) has discussed and concluded that there is no significant difference in prostate cancer patient mortality who are screened or not [62]. Based on the data from the ERSPC study which concludes that detection of prostate cancer by PSA-over diagnosis prevents one prostate cancer-associated death, while screening as many as 1410 suspected men to treat additional 48 prostate cancer cases [63]. Based on these studies, the US Preventive Services Task Force has reduced the mass detection of PSA and ignored approximately 50% of prostate cancer-associated mortality since the introduction of PSA [64]. However, without PSA screening in most cases, diagnosis of prostate cancer was detected late with prominent symptoms and often disease has been progressed to advanced stages with limited therapeutic response. Therefore, the currently followed European association of urology (EAU) guidelines urge for opportunistic screening for suspected prostate cancer patients. This includes PSA screening, genetic analysis for the detection of SNPs, and searching for novel biomarkers which is the need of an hour for prostate cancer diagnostics [65]. To conclude, recent findings suggest that in addition to PSA screening detection of SNPs and other associated markers are extremely important for early diagnosis of prostate cancer.

Using opportunistic screening strategy to improve prostate cancer diagnostics

Although overdiagnosis of PSA screening remains a concern for both clinicians and suspected patients of prostate cancer [66]. However, as per new EAU guidelines, opportunistic PSA testing would be performed in high-risk suspected patients apart from genetic screening [67]. Recent studies suggest that molecular

genetics play a crucial role in the development of prostate cancer. Therefore, apart from performing opportunistic screening of PSA, analysis of genetic modifications could be a deciding factor to predict the high-risk patient groups which could be susceptible to develop prostate cancer [68]. Interestingly, this could have a great advantage in determining which suspected patients would be benefited from PSA testing that in turn will decide the suspected patient's group go for prostate biopsies. The present genetic variations were analyzed by GWAS studies to correlate the risk associations. However, the only limitation in clinics is the characterization and prediction of risk in suspected patients is based on establishing the categorizing people into various groups. This categorization of suspected patients allows the stratification of the high-risk group which has greater chances of developing prostate cancer than other groups in the population. This stratification provides a platform for clinicians to better understand and calculate the absolute prostate cancer risk for patients after assessing an individual's medical information.

Numerous epidemiological models developed by clinicians and scientists reveal that using various risk factors such as age, history and genetic modification could have a great impact on predicting the risk and analyzing the development of prostate cancer [69] **Figure 4**. Zheng et al. demonstrate that good efficiency was achieved in prostate cancer detection when a comparison of risk factors was combined with a level of PSA cut-off of 4.1 ng/mL [70]. Owing to the low sensitivity and specificity of PSA screening, initially, the analysis looks like irrelevant, but the efficiency of detection was good. The genetic analysis reveals that it is economically cost-effective as well as determined once in a lifetime, however, determination of PSA level in serum varies and needs to fix by performing many times. Unfortunately, once the PSA level, age and familial history were well recorded, the cumulative predictive analysis of genetic screening and PSA screening for the diagnosis of prostate cancer did not have improved the prostate cancer diagnostics [70, 71].

The debate is still going on whether SNPs are good enough to use them to predict prostate
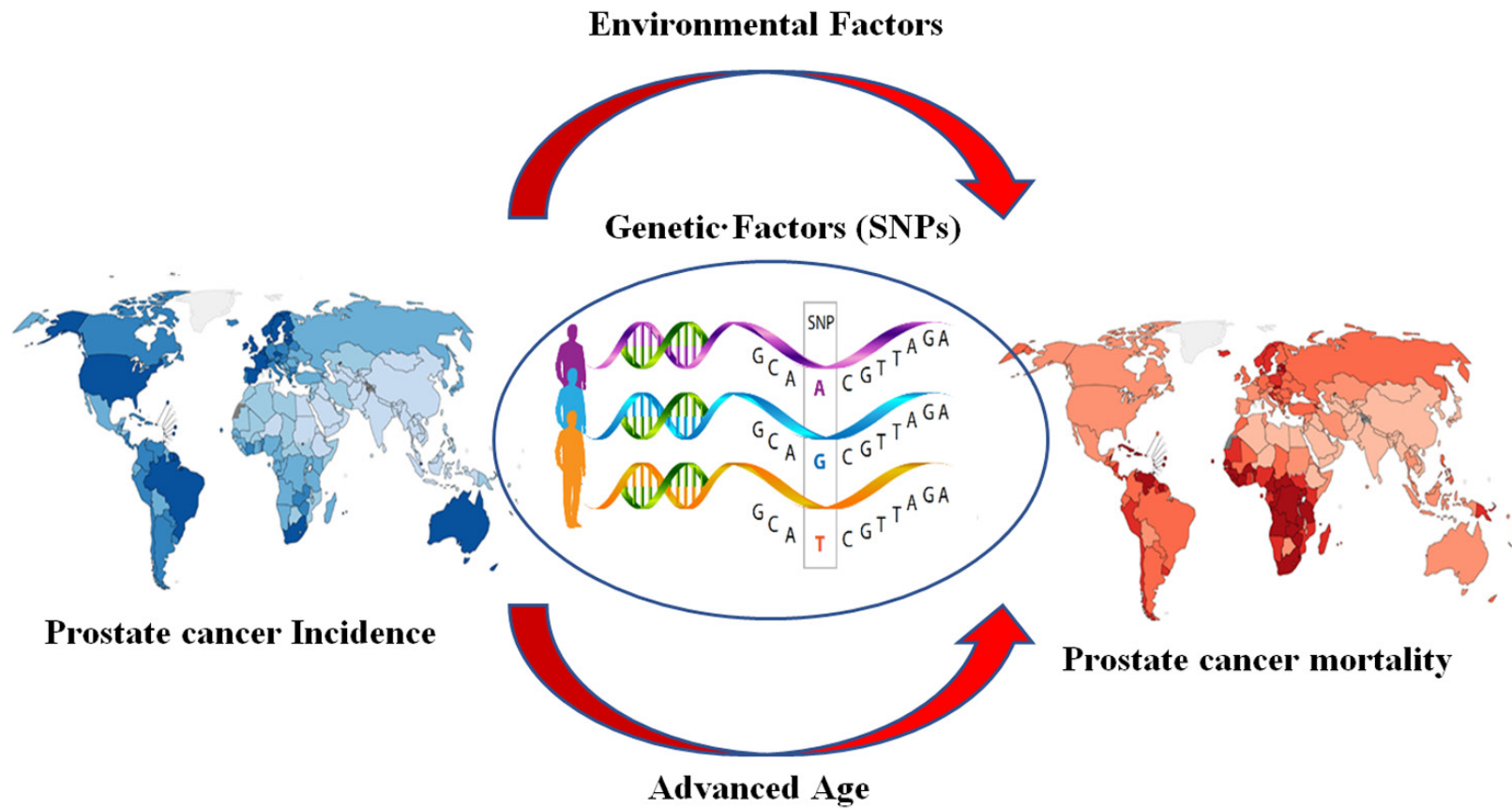
Figure 4. Various risk factors involved in prostate cancer progression.

cancer risk. A recent report suggests that SNPs are not able to differentiate cases within the control groups but could be especially useful in the analysis of determining the suspected prostate cancer patients [72]. To predict the absolute risk for the development of prostate cancer risk, Xu et al. predict an absolute model based on the cumulation of 14 SNPs, familial history, and a specific age group [73]. This model was used in the Swedish and USA population to detect a small subset of suspected patients (0.5-1%) who are at extremely high risk (52% and 41%) for developing prostate cancer between the age of 55-74 years. A similar study by Sun et al. demonstrated the absolute risk of three sets of SNPs in predicting and developing prostate cancer. The model efficiently differentiates the suspected patients who are significantly at higher risk (2-3-fold increased risk) of developing prostate cancer than the median population [74]. The significant impact of these risk factors predicted from various models is with the younger suspected patients with a familial history of developing prostate cancer. The logic behind this is that a suspected person with familial history has some inherent, specific subset of SNPs from parents and remain throughout one's life without any modification. Thus, the outcome of these inheritable SNPs could be from the initial stages of one's life [75]. A model developed by Macinnis et al. predicts prostate cancer risk algorithm using 26 common variants for familial risk of prostate cancer. The model predicts collective prostate cancer risk based on familial history (incidental prostate cancer to exceedingly burdened prostate cancer) and the number of inheritable SNPs (expressed in percentage) [76].

In general, the diagnostic role of SNP genotyping in prostate cancer is to analyze the suspected patients who are at high risk. The genotyping of SNPs for high-risk prostate cancer should be performed frequently at an early stage of life. Additionally, the high-risk group with familial history should also take preventive measures in lifestyle, diet, and chemoprevention [77, 78]. With respect to age-specific SNPs screening, the personal screening results in a 16% reduction in suspected patients to categorize them to be eligible for screening and a 3% reduction in cost for eligible cases [78]. The determination of SNPs can be performed at any age with low cost and makes them appealing

candidates for predicting high risk suspected patients to develop prostate cancer [79]. Therefore, these findings suggest that SNPs underlie differences in the susceptibilities of subsections of population to diseases, signifying the role of SNPs in diagnosis and therapeutic intervention of different diseases.

SNPs and their interpretation for possible Novel Biomarkers

Determination of SNPs by genotyping indicates its role in predicting the risk for the development of prostate cancer. Despite recent reports suggest that SNPs are not to be considered as true diagnostic markers for prostate cancer. However, Klein et al. demonstrated in a recent study that SNPs could be useful in clinics in other ways but hypothetically, SNPs in combination with PSA screening could have critical importance in predicting the risk of developing prostate cancer in high-risk groups [80]. In addition, SNPs could be of much importance in modulating some novel biomarkers [81]. Their analysis and interpretation with reference to other risk factors are of great importance in prostate cancer diagnostics [82]. Previous studies revealed that numerous SNPs play an important role in modulating the expression and functions of a plethora of genes including transmembrane serine protease 2 (TMPRSS2) [83], hexokinase-2 (hK2) [84], and beta microseminoprotein (β-MSP) [85]. This modulation of genes by SNPs could have a promising causal association and its interpretation could have a great impact on the diagnostics of prostate cancer. Recent reports of epidemiological studies suggest that genetic modulations could occur in PSA as well. This can be explained by a recent report which suggests that around 40-45% PSA level could be modulated by genetic variations in the general population [86]. Owing to this genetic variation the specificity and sensitivity of PSA screening are low. This explains why in general there is no PSA threshold level of suspected patients to undergo prostate biopsies. To explain the variability of PSA level Gudmundson et al. demonstrated the deletion of six loci that modulates the PSA levels. Among them, four loci had a cumulative effect on the variation of PSA level. The PSA variability was supported by different groups which suggest that genetic modification has a great impact on the risk of developing

prostate cancer by changing the abnormal PSA level in men, thus prevents approximately 20% of biopsies that were supposed to undergo prostate biopsies [87, 88]. This helps in improving diagnostics, quality of life, and more importantly decreases the complications and cost which remains one of the important factors in developing nations for prostate cancer diagnostics. Therefore, with greater interest in the development of novel biomarkers in the diagnostics of prostate cancer, SNPs are the potential candidates that could modify the novel biomarkers and plays a critical role in the correct interpretation and analysis for the proper diagnosis of prostate cancer. It is believed that if SNPs are not taken into consideration for the identification of novel biomarkers, we might expect comparable hindrances as we are facing in PSA screening for prostate cancer diagnostics.

Predictive analysis of genetic polymorphism and androgen deprivation therapy (ADT) in metastatic prostate cancer

Hormonal therapy such as ADT showed a significant effect with promising efficacy in metastatic prostate cancer patients [89]. However, the main debacle of ADT to metastatic prostate cancer is an elevated relapse rate that initiates the development of castration-resistant prostate cancer (CRPC) [90]. To evaluate the patient response to ADT, the clinicopathological parameter monitored by clinicians such as the Gleason score, the kinetics of PSA screening are the crucial factors in predicting the patient's response to ADT and prognosis [91]. Despite providing information with respect to ADT response and improving prognosis in metastatic prostate cancer patients, the clinical parameters evaluated by clinicians are still insufficient to predict the complete picture of patients who develop CRPC [92]. Thus, as per EAU guidelines, the agonists of luteinizing hormone-releasing hormone (LHRH) have been recommended for those patients which are in state or have developed CRPC [93]. Considering, to improve risk stratification and predict the metastatic prostate cancer patient response to ADT and the outcome of prognosis, the identification of genetic markers might play a significant role in determining the response to hormonal therapy and prognosis outcome in CRPC. A recent study by Ross et al. revealed that phar-

macogenomics plays a crucial role in determining the patient's response to hormonal therapy such as ADT [94]. The study further demonstrated that three SNPs which are strongly associated with genes involved in prostate cancer progression such as hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 (HSD3B1) (prostate cancer susceptibility), cytochrome P450 family 19 subfamilies A member 1 (CYP19A1) (encodes aromatase enzyme which synthesizes estrogen from testosterone), and hydroxysteroid 17-beta dehydrogenase (HSD17B4) (associated with Gleason score) [95, 96]. Additionally, these three SNPs not only help in the progression of prostate cancer individually, but they have a profound cumulative effect on the progression of prostate cancer.

Besides the involvement of SNPs which are close to genes and play an important role in cancer progression, SNPs from various other loci have been documented to play a significant role in prostate cancer patients relapse that are on hormonal therapy such as ADT [97]. The SNPs of various loci are located within the genes such as epidermal growth factor (EGF) which plays a critical role in the activation of many prooncogenic signaling cascades [98]. The other SNPs loci are within genes are solute carrier organic anion transport family member 2B1 (SLCO2B1) and solute carrier organic anion transport family member 2B3 (SCCO2B3) which encodes for androgen transporter proteins and tumor-growth factor beta receptor 2 (TGFβR2) gene which encodes for receptor protein of TGFβ signaling cascade [99, 100]. These signaling pathways play a crucial role in the development of tumorigenesis. Apart from these, other SNPs have a key role in the relapse of prostate cancer hormonal therapy ADT and their location is still debatable and unknown [101].

A recent study from Taiwan has established a DNA library of 601 advanced prostate cancer patients treated with hormonal therapy ADT. The study further revealed that 5 SNPs detected from the established DNA library had a causal association with prostate cancer progression, whereas 14 other SNPs have a strong causal association with prostate cancer-specific mortality who undergo ADT hormonal therapy. A similar study by Bao et al. demonstrated

that 4 SNPs that were detected within the nucleotide sequence of mRNA and miRNAs were observed to have a causal association with disease progression in prostate cancer [102]. Additionally, 49 and 55 SNPs of estrogen and androgen-receptor binding sites were thoroughly evaluated by Huang et al. 5 SNPs which were localized on arrestin domain-containing protein 3 (ARRDC3), transforming acidic coiled-coil-containing protein 2 (TACC2), Src-kinase associated phosphoprotein 1 (SKAP1), Fms related receptor tyrosine kinase 1 (FLT1), and basonuclin 2 (BNC2) were observed to have a strong correlation with prostate cancer mortality specifically [103]. Interestingly, a single SNP was found to be associated with insulin receptor substrate 2 (IRS2) and bone morphogenetic protein 5 (BMP5) genes and are observed to have a role in prostate cancer metastatic survival [104]. The IRS2 is an especially important gene that encodes for various proteins which act as adaptor proteins for intracellular signaling of various key physiological processes within the cell such as IGF1 [105, 106]. This example nicely explains the intricacy and interwoven of genetic modulations and their outcome in the form of clinical effects.

Besides the interesting findings revealed from the genetic variations in the form of SNPs, it is worth to mentioning that majority of evaluated prostate cancer cases are heterogeneous [107]. The tumor characterization of advanced prostate cancer cases has 33% Gleason score varies from score 2 to 6, around 32% of prostate cancer cases are in T1/T2 stage [108]. Additionally, the proper protocol which was followed while giving ADT hormonal therapy was also in a heterogeneous state, which varies from ADT for biochemical failure to ADT in neo-adjuvant setting after post-radical prostatectomy [101]. This heterogeneity makes things more complex and as the result gives a poor interpretation of genetic variation in these types of clinical settings.

Considering all the facts associated with metastatic prostate cancer, SNPs, and ADT, it is necessary to perform SNP genotyping that might be useful in multi-ways for patients who are supposed to undergo ADT hormonal therapy. Firstly, it could identify the patient group which is at elevated risk of treatment failure to the current regiment of ADT hormonal therapy, thus

might have a prognostic role [101]. Therefore, predictive analysis of genetic polymorphism assists in the identification of a sub-group of patients who need more aggressive combinatorial treatment initially with novel drugs. Secondly, the implications of these SNPs on the functional analysis of enzymes could be targeted with the new therapeutic regiment to improve the efficacy of ADT hormonal therapy.

Role of genetic polymorphism in castration-resistant prostate cancer (CRPC)

To date, the only therapeutic option for CRPC is docetaxel which is derived from taxane a well-known anticancer agent [109]. Based on randomized phase III clinical trials from the two multicentre, there is a moderate increased effect in overall survival time of CRPC patients after docetaxel treatment [110]. Over the last decade, various novel small molecules and their derivatives for prostate cancer therapeutics have been developed [111-116]. However, there are equally many questions to be addressed regarding their optimization and long-term side effects. Although clinical evidence suggests that significant effects on CRPC were observed with one therapeutic regimen, the same regimen has deleterious effects from other side, this makes the job tough for clinicians to optimize the therapeutic regimen which has less long-term adverse effects [117]. Docetaxel treatment showed extreme variability in the clinical settings. Thus, to predict this clinical response before the docetaxel treatment would be of great interest [118]. Based on these observations, clinicians have a second line thought whether to continue with docetaxel as a first-line therapeutic regimen or to choose another therapeutic option [119].

The predicted outcome of docetaxel treatment in CRPC patients depends upon the genetic variability of cytochrome P450 family 1 sub-family B member 1 (CYP1B1) gene. A recent study by Pastina et al. demonstrated that the CRPC patients who carry the GG genotype of CYP1B1 gene at 4326 positions had significantly decreased in overall survival period than those CRPC patients who had CC genotype of CYP1B1 gene at 4326 positions. Further, the study reveals that after normalizing every other risk factor such as pathological, demographic, or biochemical parameters, the genotypic fac-

tor remains unchanged independent of the strong predictive parameter with an elevated risk of death in CRPC patients. This explains the genotypic parameter such as the GG at 4326 positions in CYP1B1 might act as an appealing pharmacogenetic marker for the CRPC patient's prevalent response to docetaxel treatment. Reports suggest that GG genotype of CYP1B1 at 4326 positions plays a crucial role in modulating the therapeutic effect of docetaxel via its major metabolite called 4-hydroxyestradiol. Mechanistically, the presence of GG genotype of CYP1B1 at 4326 position has elevated levels of 4-hydroxyestradiol, that induces structural modulation in docetaxel thereby interfere with the docetaxel functions by negatively regulates the stabilization of microtubules [120, 121]. Another interesting example is the ATP binding cassette subfamily B member 1 (ABCB1) gene. The important function of the ABCB1 gene is the efflux of docetaxel. The presence of three different types of genotypes 2677, 1236, and 3435 within the ABCB1 gene has a strong causal association with CRPC patient's survival who receive docetaxel chemotherapy [122]. Docetaxel in combination with thalidomide to CRPC patients who had these three types of genotypes has a strong cumulative effect to developed long-term neuropathy in patients receiving this combination therapy. With the advancement in developing novel therapeutic modalities, the outcome of these chemotherapeutics is of great interest in the future particularly in clinical settings [123]. Based on the patient's genotype and role of SNPs, clinicians have an option to use these novel therapeutics to predict the treatment response in advance. The therapeutic efficacy outcome of these novel modalities like enzalutamide and abiraterone could be assessed in the future using the same strategy to predict the outcome [124]. Therefore, the genetic variability of patients could play a crucial role in modifying drug metabolism, and associated genes to predict the outcome of chemotherapy in advance.

Limitations of SNPs in clinic

Besides, utilization of SNPs for population-based risk stratification to carry prostate cancer screening in susceptible men [125]. However, there are certain limitations associated with SNPs that needs great attention. Albeit several SNPs have been well documented with prostate cancer development, the single gene SNPs are known to provide little contribution to prostate cancer risk, therefore the utilization of multiple gene SNPs panels is often recommended [126, 127]. Moreover, many SNPs are located outside of the genes and are suspected to influence gene expression and genome organization, thus, warranting the need to determine the role of these SNPs in prostate cancer development [123, 128]. Public database of SNPs is often used to choose SNPs to study their association with complex disorders [129]. However, due to incomplete and uneven representation of the candidate SNPs in the public databases of different ethnic population groups, SNPs fail to explain the pathogenesis of complex disorders [130]. Therefore, there is an imperative need to accurately characterize SNPs in different ethnic groups at large-scale.

Conclusion

Genetic variability apparently plays an important role in assessing the susceptibility of individuals to various diseases. GWAS studies suggest that SNPs (single or multiple) groups could predict the elevated risk for prostate cancer. Besides, useful in identification and understanding the novel targets for therapeutic intervention, SNPs in combination with somatic tumor profile of patient could make personalized treatment strategy and work towards developing true precision medicine for managing prostate cancer.

However, there are limitations using SNPs in clinics for diagnosis and prognosis. First a small insignificant heterogeneous population of subjects might have false negative and positive results. Secondly, the causal association of SNPs and risk to develop prostate cancer are mostly conducted through GWAS. The genetic variability analysis to evaluate the phenotypic prostate cancer that varies from low penetrance to high has chances to be independent on GWAS and SNPs studies. These studies might not be sufficient to explain the underlying mechanism of these variations within response to the progression of prostate cancer. Additionally, Some SNPs are suspected to regulate transcriptional activity and genome organization, therefore necessitating to evaluate their involvement in prostate cancer development.

Furthermore, due to incomplete and uneven representation of the candidate SNPs in the public databases of different ethnic population groups, SNPs fail to explain the pathogenesis of complex disorders. Therefore, there is an imperative need to accurately characterize SNPs in different ethnic groups at large-scale.

Future perspectives

It becomes clear throughout the review that there are still major challenges to evaluate the translational role of SNPs in clinics for prostate cancer. The future studies should thrust on the following approaches, firstly, there is a need to perform well-powered clinical analysis of prostate cancer on SNPs that should explain all underlying queries in present as well as in the future with conclusive results. Secondly, more thrust should be given to basic research to validate the role of SNPs in the progression of prostate cancer. Hopefully, in near the future we could reveal the comprehensive role of SNPs not only as predictive markers for prostate cancer but could also help in finding the other novel biomarkers. Their causal association with signaling pathways in the development of prostate cancer could possibly be the new therapeutic targets in prostate cancer.

Acknowledgements

Disclosure of conflict of interest

None.

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