Systematic Review

Gene Polymormisms and Prostate Cancer: A Systematic Review

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Abstract: **Introduction:** The prostate is a gland that surrounds men's urethra and helps to produce semen. In developed countries, prostate cancer (PCa.) is the second most common and lethal disease in men. Hereditary history of PCa. is a major contributor to this cancer? While a number of genetic and molecular changes have been reported in PCa, the general picture of the genetic aberrations is needed in Iranian population.

Methods: In this study, a literature search from Jan. 2000 to June 2018 was performed through the PubMed, Google Scholar, Scopus, Web of Science, IranMedex, MEDLIB, IranDoc and Scientific Information databases using the keywords "genetic polymorphisms", "prostate cancer", "Iranian, and compare with regional and international population".

Results: The results revealed that several genome-wide association studies (such as rs2070744 and rs1799983 in the eNOS, rs243865 in the MMP2, rs1902023 in the UGT2B15, rs266882 in the PSA, rs10625775443 in the GNB3, rs 1800682 in the FAS, rs12052398 and rs13393577 in the ERBB4, rs181133 in the MTHFR, rs 1805087 in the MTR, rs1805355 in the MSH3, (rs60271534 in the CYP19, rs2234693 and rs9340799 in the ER-a, rs4986938 and rs1256049 in the ER-b) and single-nucleotide polymorphisms in important pathways (such as angiogenesis, androgen receptor binding site, cell signaling, folate metabolism, DNA repair, hormone synthesis and metabolism polymorphisms) involved in prostate cancer occurrence and mechanism could serve as candidate biomarkers for the detection of PCa. The most important results of the all studied articles is summarized in Table 1 and 2.

Conclusion: Several studies have been conducted on the family history of PCa. The main reason for this gathering is to inherit the involved genes. Additional studies are required to decipher precisely the gene combinations and personalize the management of prostate cancer. This article is the first comprehensive overview of genetic investigations of gene polymorphisms on PCa. in Iran.

Keyword: Polymorphisms; Prostate Cancer; Pathways

1. Introduction

PCa. is the most common malignant cancer in men. Most of the prostate cancers will never develop symptoms and remain undiagnosed during life though epidemiologic studies about prostate cancer include those patients who are diagnosed either due to the rise of serum level of PSA or clinical symptoms which are called clinical prostate cancers. According to 2010 men's cancer statistics, PCa. is the most commonly diagnosed cancer, with the highest incidence (28%) and the second leading cause of death (11%) after lung cancer

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(29%)(16). In general, out of every six men, 1 person will develop PCa. during their life, and the risk of developing is increased by age. Epidemiologic publications showed that there is alteration in the geographic and racial distribution of PCa. The incidence of clinical PCa. around the world is close to 50 cases per 100,000 populations, which varies between 3.9 in India and 178.8 in 100,000 people in the American Blacks. According to the 2008 report, an average annual Age-Standardized incidence Rates (ASR) per 100,000 person-years, in developing countries, in advanced countries and, in the world is 11.9, 61.7,and 27.9, respectively(20). Despite the decline in the incidence and, the death of PCa. in the United States and some other Western countries, the incidence, and death rate of this cancer is increasing in less developed and developing countries(21). The rate of PCa. in Asian countries is much lower than that reported by the Western population, but it is still rising in Asian countries(20). In Iran, the prevalence of PCa. in five provinces of Iran between 1996 and 2000 was 5.1 per 100,000 people of a year, while the cancer registry system has not recorded all cases, which means that the reported amounts are less than statistics. Clinical PCa. in Iran as in other developing countries is increasing. PCa. is the eighth cause of cancer deaths in Iran(20). The main reason for this gathering is to inherit the involved genes. The main difference in the incidence of PCa. among men in developed countries and in Asian countries is the important differences in their lifestyle. Diet, sexual behavior patterns, alcohol consumption, ultraviolet radiation, are important factors in this regard (31, 32). Few investigations have been directed to the risk factors for PCa. in the Iranian men. The incidence of PCa. in Iran is low as compared to the Western countries. This can partly be clarified by absence nationwide screening program, quality of cancer registration system and younger age population in Iran (33, 34). Because of the significant role of genetic factors, there has been increasing focus on the role of single nucleotide DNA variation. The single nucleotide polymorphisms (SNPs) mark varieties in our susceptibility and used for cancer association studies. Several authors have published gene polymorphisms in association with sporadic, hereditary, and familial-based PCa.(36).This article is a comprehensive overview of genetic investigations of gene polymorphisms on PCa. in Iran. SNPs in the angiogenesis, DNA repair, cell cycle control, cell signaling, androgen receptor (AR), regulating gene expression, regulating Immune responses, hormone synthesis and metabolism, drug metabolizer, detoxification and resistance, folate metabolism, renin -angiotensin system studies are reviewed in the present article. Since genetic variations are inheritable factors, and their frequency differs in different populations with varied ethnicity and background, the purpose of this review article was investigated previous reports regarding the association between genetic polymorphisms in different pathways and PCa. risk in an Iranian population.

2. Method

2.1. Search strategy:

A rapid literature search strategy was conducted for all English and Farsi language papers published until July 2018. The search was conducted using the electronic databases PubMed, Google Scholar, Scopus, Web of Science, IranMedex, MEDLIB, IranDoc and Scientific Information databases. The search strategy included the keywords "genetic polymorphisms", "prostate cancer", "Iranian, regional and international population". Furthermore, the reference lists of the extracted articles were checked to find other sources.

2.2. Inclusion and exclusion criteria:

The inclusion criteria were: (1) case–control studies designed to investigate the relationship between SNPs and prostate cancer risk; (2) available information on the genotype or allele frequencies in case and control groups; (3) selection of articles with the largest number of samples for comparison between studies in Iran and other countries. Papers repeated in more than one database were counted just once. The excluded elements encompassed: studies based on non-human research; studies with insufficient data and with no allele frequencies for each polymorphism; non-original studies such as Letters to the Editor, and brief communication were excluded. Two authors (Amini Nik S. and Soleimani M.) independently assessed and selected studies for final analysis; discrepancies were resolved by consensus.

2.3. Data extraction:

According to the strategy adopted initially, 672 manuscripts were found. After reviewing the titles, abstracts and manuscripts entirely cited, the total of 195 articles were obtained and selected according to the eligibility criteria. The following data were extracted from each included study: (1) first author's name and year of publication, (2) gene function, (3) ethnicity, (4) country, (5) number of cases and controls, (6) allele or genotype frequencies of cases and controls. Missing data were examined by contacting the first or corresponding author. At first, the importance of genetic review has been presented in the form of family history, followed by genes and polymorphisms in separate functional groups. Then, a summary of the performance of each pathway and the role of the studied genes mentioned and, finally, the association between polymorphisms and prostate cancer in Iran are presented and the comparison of the results with the regional and global countries has been carried out.

Table 1: List of gene polymorphisms in Iranian men with PCa.

Function	Gene	Number of Case/Control	Association	Ref.
Angiogenesis	MMP2	102/139	No	(4)
	MMP2	50/50	No	(5)
	eNOS	100/340	Yes	(10)
	eNOS	95/111	No	(14)
	VEGF	50/50	Yes	(17)
DNA repair	ApE1	100/100	Yes	(22)
	MSH3	18/60	Yes	(27)
	XPC	154/205	No	(30)
AR Pathway	CAG repeat length	110/100	Yes	(12)
	UGT	120/120	Yes	(35)
	PSA	95/111	No	(38)
Cell cycle regulators	MDM2	103/142	Yes	(39)
	TP53	103/142	Yes	(39)
	TP53	40/80	No	(44)
	TP53	68/85	No	(49)
	TP53	187/185	Yes	(51)
	TP53	45/45	Yes	(58)
	PRKCI	169/182	Yes	(59)
Cell Signalling	G protein	172/344	Yes	(63)
	ERBB4	169/182	No	(64)
	FAS	100/100	No	(66)
	TGF-β1	--/--	Yes	(69)
	LAPTM4B	168/176	Yes	(70)
Regulating Gene Expression	SETD8(miR-502)	169/182	Yes	(72)
	miR-499	169/182	Yes	(1)
	miR-196a2, miR-146a and miR-149	169/182	No	(1)
	ANRIL	125/220	No	(73)
	PRNCR1	178/180	Yes	(25)
	Pri-miR-34b/c	151/152	Yes	(85)
	Pre-microRNA-3131	177/170	Yes	(92)
Regulating Immune responses	RNASEL	61-101	No	(45)
	RNASEL	40/80	No	(47)
	IL1A	150/155	Yes	(55)
Hormone synthesis and metabolism	CYP17	74/128	Yes	(67)
	CYP17	150-150	Yes	(77)
	CYP19	59/95	No	(83)
	MSMB	169/182	Yes	(97)
	SHBG	120/120	Yes	(111)
	ER-a and ER-b	162/324	Yes/No	(113)
Drug metabolizer, detoxification and resistance	GST	60/60	No	(3)
	GST	110/100	No	(12)
	GST	168/336	Yes	(18)
	ABCC1	45/45	Yes	(58)
	NAT2	147/207	No	(54)
	COMT	41/193	Yes	(69)
Folate metabolism	MTHFR	10,832/ 11,993	No	(103)
	MTHFR	67/75	No	(93)
	FVL, PTH,MTHFR	30/40	No	(110)
	MTR	100/100	Yes	(120)
Renin -angiotensin system	ACE	95/111	No	(129)

3. Result

3.1. Family history, related polymorphisms and prostate cancer:

PCa. diagnosis in a family member is called family PCa. and the prevalence rate of it is estimated to be around 20%. The presence of similar genes, lifestyle, and environmental status are the reasons associated with it(50). Articles showed that PCa. risk is 2.3 times higher in the first-degree family members than in others(56). Inherited PCa. arises when a gene mutation is transmitted from one generation to the next and occurs in men who have one of the following features: at least 3 of their first-degree relatives are affected by PCa.; three generations of a family or two generations or more of close relatives are affected by PCa. (50, 65). In the following, in the table 1, the polymorphisms studied in Iran were compared on the basis of the relevant gene function and their association and in the table 2, the comparison was made on the basis of P-value with other countries.

3.2. Angiogenesis-Related Genes:

Angiogenesis refers to the process of the formation of new blood vessels, which is important for the natural development of the body and depends on the exact balance between natural stimulants and inhibitors. If this balance is collapsed from the normal state, conditions for diseases such as cancers occurred. In general, this process is affected by a variety of factors, including a series of cellular events such as migration, proliferation, and differentiation of endothelial cells, and ultimately vascular formation, puberty and ultimate restoration. For this reason, angiogenesis inhibition as a contributing factor in conventional cancer treatments such as chemo and radiation therapy has attracted the attention of researchers who are studying in this area. MMP, VEGF, and NOS are important genes in this process. The main angiogenic factor is vascular endothelial growth factor (VEGF). Hypoxia is one of the factors that induce angiogenesis. Several angiogenic compounds, such as VEGF, are induced by hypoxia. The presence of high-density vascular tumor regions in PCa. has a poor prognosis. Oncogenetic changes in tumor cells may contribute to angiogenesis by inducing angiogenic factors. The mutation in the oncogenic genes of ras-K, ras-H and src-V induces VEGF expression. Mehini et al. in 2015 revealed a significant difference of variants VEGF460 C / T in term of T polymorphism in prostate cancer patients compared with normal group(17). In another study, in 2008, researchers stated that polymorphisms and haplotypes of VEGF would not change the risk of PCa.(78). Also, in Taiwan the results showed that the polymorphism 460 C / T of VGEF gene would be a biological marker for PCa.(17). Moreover, Onen et al. did not find any significant association between 460C/T polymorphism and PCa. in the Turkish population(57) which agrees with Fukuda's results(94).On the other hand, Matrix metalloproteinase (MMPs) are the most important extracellular matrix degrading proteases whose key roles in invasion, metastasis, and angiogenesis have been proven. MMP2 has a collagenase activity, its over-expression causes base membrane ruptures and plays the main role in metastasis(103). Many several researches have evaluated the association between MMP2 -1306 CT polymorphism and PCa. in different populations. While some of these investigations have confirmed the role of MMP2-1306 CT polymorphism in PCa. development and metastasis, others have failed to establish any relationships between them. In 2015, a study by Adabi showed that there was not association between MMP2 -1306 C/T polymorphism and risk of PCa. (p = 0.08). They explained, in a population of Iranian men with PCa., the 1306 C/T MMP2 polymorphism showed no association with either serum PSA levels or with the risk of metastasis of PCa. and seems not to be a genetic susceptibility factor for the development of PCa. (4). Also, consistently with their results, Shajarehpoor et al in 2017 could not find any association too(5). In a meta-analysis, researcher reported that the frequency of T allele in MMP2 -1306 CT polymorphism to be much higher in in European populations than Asian populations (114). Another meta-analysis by Liu et al. showed that there is no statistical evidence between MMP2 1306 C/T polymorphism and risk of metastasis(116). In India, Srivastava et al. study showed that CT genotype was significantly associated with a 1.68-fold increased risk of PCa.(7). In a survey in Turkey, Yaykasli et al. reported the frequency of CT genotype in patients to be 2.17 times higher than that control group(122). The discrepancy between the results of different investigations may be associated with the race and the incidence of PCa. in an Iranian population(5).

Various investigations have demonstrated that nitric oxide (NO) and nitric oxide synthase (NOS) system plays a key role in carcinogenesis. Gene polymorphisms of endothelial nitric oxide synthase (eNOS) remarkably affect serum NO concentrations(130). Publications addressing the relationship between eNOS gene polymorphisms and PCa. are rare. In Safarinejad association study for three polymorphisms (T-786C, G894T, and 4a/b) of eNOS gene, detected significant differences in allelic frequencies between PCa. cases and controls for the T-786C, and 4a/b polymorphisms(10). A study in Brazil showed that, the GG and GT G894T genotypes present a 3.32-fold higher risk of PCa. occurrence(40). Alternatively, 161 PCa. patients were analyzed by Medeiros et al. but ascertained no association between eNOS G894T polymorphism and PCa. Regarding 4a/b polymorphism, they reported that the combination of the eNOS 4a/b "a"

with the 'T' allele from the G894T polymorphism increases the risk of PCa. occurrence(23).

3.3. Cell Signaling Genes:

Cells communicate with each other by sending and receiving signals. Signals come from the environment or from another cell. To start a reaction, these signals must be transmitted across the membrane. Sometimes, the signal alone can pass through the membrane. In other cases, it acts by reacting with receptor proteins that communicate with both sides of the inside and outside of the cell. In this case, only cells that have the correct receptors at their levels can respond to the signal. The last way to escape cancerous cells is apoptosis. Cell membrane and organelles degradations lead to quickly swallowed by phagocytes(137). G proteins transmit signals between the cell surface receptor and intracellular signaling pathways, thereby controlling a wide range of biological processes such as cell growth, transcription, and secretion. The GNB3 825T allele is associated with signal transduction and alternative splicing(139). Safarinejad et al. results indicated that PCa. is significantly associated with the T allele of the GNB3 C825T polymorphism and individuals homozygous for 825T had 6.24-fold increased risk for advanced PCa. compared with those homozygous for the C825 allele(63). According to Dong et al. investigation that examined the C825T polymorphism in a black African population, the frequency of T allele in Africans was 80% vs less than 25% Europeans(142), so researchers, hypothesized that this genetic variant may be a factor predisposing to PCa. in the black population(63).

ERBB4 is a member of the epidermal growth factor receptor subfamily of receptor tyrosine kinases. Amass evidence displays that ErbB4 plays key roles in the development and prognosis of different tumors(144). Hashemi et al. survived the association of rs12052398 T>C, rs13393577 A>G, rs13424871 A>T, rs16847082 A>G and rs6147150 (12-bp I/D) polymorphisms on risk of PCa. Although, no significant association was detected among ERBB4 polymorphisms and PCa. risk(64). In China, a genome-wide association study (GWAS) identified the ERBB4 gene as a PCa. susceptibility gene(146).

Fas is a cell surface receptor expressed in different types of tissues. Fas Ligand is one of the members of the large tumor necrosomal factor that interacts with Fas to send a cell death message to the death cell, leading to the death of the cell expressing Fas(147). Studies have shown that reducing the expression of Fas or increasing the expression of Fas ligand is associated with many types of human tumors. Polymorphism rs 2234767, which leads to the replacement of A instead of G and may reduce stimulatory protein 1 transcription factor

binding site. These changes in the sequence of the promoter region of the Fas gene can affect the expression of it and lead to an imbalance in cellular apoptosis and contribute to carcinogenesis(66, 111). According to, Sabor et al. in 2018 no significant relationship was observed between this polymorphism and PCa. in Iranian men(66) and in Indian origin too(149). But, Chinese researchers found an association between fas 1377 G/A polymorphism and PCa. on 602 patients and 703 healthy men (140).

The cytokine transforming growth factor-beta 1 (TGF-b1) plays a key role in regulating the proliferation and apoptosis of prostate cells. Many investigations related to the association between TGFβ1 Leu10Pro polymorphism and PCa. risk, but get conflicting consequences. An Iranian survey showed that T allele of the TGFB1 gene has a dominant effect on the development of PCa. (p = 0.009) and BPH (p = 0.005)(69). Results of a meta-analysis with 2,604 cases and 3,129 controls appeared to be consistent with that (150).

Lysosome-associated protein transmembrane-4 b (LAPTM4B) is an oncoprotein that is localized mostly to the late endosome and lysosome and is involved in cancer cell proliferation by upregulating the PI3K/ATK signaling pathway. Based on the findings of Hashemi et al. LAPTM4B*2 polymorphism significantly decreased the risk of PCa. in Iranian population (70). A meta-analysis in the Chinese Han population showed that LAPTM4B polymorphism is associated with an increased risk of cancer (151).

3.4. Cell Cycle Control Genes:

The aberrant cell cycle is due to deregulation of the cell cycle and loss of cell cycle checkpoint control. Tumor protein 53 (TP53), is a fundamental cellular cancer suppressor in multicellular organisms. The inhibitor of TP53 activity in the cells is Murine double minute-2 (MDM2) oncoprotein. The results of Hashemi et al. research on polymorphisms of a 40-bp insertion/deletion (I/D) polymorphism (rs3730485) in the MDM2 promoter region and a 16-bp I/D polymorphism (rs17878362) in TP53 demonstrated that the MDM2 polymorphism increased the risk of PCa. but no significant association was seen between the TP53 16-bp I/D polymorphism and PCa. In agreement with them, Mittal et al. reported no association between the TP53 16-bp I/D polymorphism and PCa. in an Indian population. It has been suggested that the TP53 intron 3 16-bp I polymorphism is associated with lower levels of TP53 transcripts, which offers that this duplication variant causes an alteration in mRNA processing and developing cancer. In PCa., studies of p53 codon 72 polymorphism have indicated different results in several populations. It has been suggested that the TP53 codon 72 variant may be

a low-penetrant risk factor for developing PCa. in Caucasians, but not in Asians, and polymorphisms within the TP53 binding sites may be valuable biomarkers for the prognosis of patients with PCa.(39). Babaei findings revealed that TP53 codon 72 polymorphism may have a great impact in the development of PCa. especially Pro/Pro with a 6.8-fold in comparison to those with Arg/Arg. The results study of the Behfarjam et al. were similar to the findings of them(58). Although, in another study, it is revealed that the Pro/Pro allele was correlated with a strikingly less risk of PCa. (44, 152). Also, the findings of Doosti et al. showed that p53 Arg/Arg genotype could be a risk factor for the development of PCa. among patients in southwest Iran (51). The last gene in this part is atypical protein kinase C iota (aPKCι) oncoprotein that is encoded by the PRKCI gene. The results of Hashemi's study on two polymorphisms rs546950 C>T and rs4955720 C>A confirmed the association of rs546950 in reducing PCa. in Iranian population (59).

3.5. DNA Repair Pathways Genes:

Products of the DNA repair genes help to maintain the genetic information of the cell and contribute to the repair of the damaged DNA. In other words, it prevents rapid growth and proliferation with uncontrolled cells. Mutations in these genes disrupt the ability of cells to repair damaged DNA and lead to the survival of potentially harmful mutations. A lot of genes has been detected to be involved in the progress of the PCa. Human apurinic/apyrimidinic endonuclease 1 (APE1) is a multifunctional protein that has a substantial role in the base excision repair (BER) pathway. In 2015, Pournourali et al. demonstrated that the association between 1349T>G polymorphism of ApE1 gene is significant and it could increase the risk of PCa.(22). MSH3 gene is a member of a mismatch repair system (MMR) is a post-replicative DNA repair mechanism whose defects can lead to cancer. Jafary et al. investigated two polymorphisms in codon 222 and codon 1036 of MSH3 gene. There was significantly association between G/A genotype of MSH3 codon 222 and G/G genotype of MSH3 codon 1036 with an increased PCa. risk (P=0.012 and P=0.02 respectively). In a study, performed on PCa. by Hirata et al. indicated that the MSH3 codon 222 and MSH3 codon 1036 polymorphism might be a risk factor for PCa. in Japanese men (27). Another important DNA repair pathway is nucleotide exchange repair (NER). XPC is one of the important gene in this pathway. Hence, Kahnamouei et al. studied two Lys939Gln and PAT polymorphisms in 145 PCa patients and 205 Benign Prostate Hyperplasia. Their results indicated the significant association between XPC PAT and reduction of PCa. risk and no association with XPC Lys939Gln gene polymorphism (30).

3.6. Regulating Gene Expression and noncoding RNA:

Non-coding RNAs that play an important role in controlling the transcription, splicing, translation, epigenetic gene expression and cell cycle, recent studies have shown that some of them are abnormally expressed in PCa. They bind to the 3′untranslated regions (3′-UTRs) of target mRNAs and regulate gene expression. According to recent studies, miRNAs have a potential diagnostic value in PCa.(153). Narouie et al. investigated the impact of rs16917496 polymorphism at the 3′UTR of SETD8 on PCa. risk. This gene is involved in a different of biological processes, such as transcriptional regulation, and genomic stability. Results have shown that the C allele significantly increased the risk of PCa. (p < 0.001) compared to T allele. The findings suggested that the CC genotype of SETD8 is associated with low expression, which demonstrated the general mechanism of miR-502 mediated SETD8 expression in modifying cancer development (72).In another study, Hashemi et al. studied association between miR-499, miR-196a2, miR-146a and miR-149 with PCa.. The findings indicated that CC genotype of miR-499 rs3746444 polymorphism increased the risk of PCa. (P = 0.019) compared to TT genotype. No statistically association was detected between miR-196a2 rs11614913, miR-149 rs2292832, and miR-146a rs2910164 polymorphisms and PCa. risk. Results of George et al. survey presented that heterozygous genotype in miR196a2 and miR-499, heterozygotes confers the increased risk of developing PCa. in North Indian population. In another investigation, Nikolic et al. have found no statistically significant association between miR-499 rs3746444 and miR-196a2 rs11614913 polymorphisms and PCa. risk in the Serbian population (1). Taheri et al. investigated the association between rs1333045, rs4977574, rs1333048 and rs10757278 polymorphisms of ANRIL gene with PCa. Only the rs1333045 showed no significant (73). In 2017, Sattarifard et al. analysis the association between rs13252298, rs1456315, rs7841060 and rs7007694 polymorphisms of PRNCR1 and the risk of PCa. in Iranian population. Except for rs7007694, the other polymorphisms are significantly associated with increased risk of PCa.(25). In another by Hashemi et al. 2017 a significant association had been found between miR-34b/c rs4938723 polymorphism and PCa. risk(85). Moreover, their findings manifested that the 3-bp indel polymorphism could affect the expression level of miR-3131 by influencing the binding of splicing factor SRp20 with pre-miR-3131 (92). The primary method for diagnosis of PCa. is the prognostic antigen test (PSA), but this serum marker is associated with limitations such as low sensitivity and specificity? In order to overcome these limitations, it is necessary to replace or at least improve

the performance of the PSA test with new biomarkers. Although more studies are needed to clarify the functions and regulations them during tumorigenic processes (153-155).

3.7. Folate Metabolism Genes:

On the pathway of folate, there are three basic genes that are: Methylenetetrahydrofolate Reductase (MTHFR), Methionine Synthase (MS), and Methionine Synthase Reductase (MTR). These three enzymes play a major role in the processes of methylation and DNA synthesis. Folate maintains the balance of nucleotides within the cell. Disrupting the amount of folate can replace U instead of T in the body of DNA, which can cause point mutations in DNA. Two functional polymorphisms in the MTHFR gene have been identified C677T andA1298C, which have been associated with reduced enzyme activity. In a meta- analysis by Abedinzadeh et al. is stated that no find association between MTHFR C677T polymorphism and risk of PCa. in the subgroup analyses of Caucasians (103). Their results were consistent with two previously published meta-analyses (156, 157). Also, the result of a study in Iran was no association between this polymorphism and PCa.(93). In another research by Ghasemi et al. no significant association had been found between three polymorphisms of FVL(G1691A), PTH (G20210A) and MTHFR (C677T)(110). A Case-Control Study of Methionine Synthase-A2756G Transition with PCa. showed a significant association between G allele and PCa. Iranian men(120) similar to Marchal et al. investigation results (158). However, there is a study in China that showed no association between MTR A2756G polymorphism and risk of PCa.(159).

3.8. Regulating Immune Responses:

The ability of tumor cells to escape from host immune responses and their compatibility with different conditions, and on the other hand, the use of these cells from peripheral biomolecules to provide materials and signals for their growth, has posed cancer as one of the complex and old challenges of human health (160). RNase L is a cytoplasmic enzyme of the innate immune system that destroys RNA viruses and also has a main role in the apoptosis of different cells. Rezaee et al. analysis of the association between RNASEL R462Q polymorphism and PCa. They found that AA genotype polymorphism was associated with increased susceptibility to PCa. (p= 0.02) (45). Contradictory to mentioned study, Babaei et al. could not find any association between RNASEL R462Q polymorphism and PCa. in Iranian men (47). In a meta-analysis performed on 3009 patients with PCa. and 703 familial prostate subjects, no significant association was found between RNase L R462Q variants and risk of PCa.(161). The results of the Hashemi et al. investigations showed that an association

between 4-bp insertion/deletion (rs3783553) polymorphism within the 3′UTR of IL1A and PCa.(55). Although, Liao et al.' study stated that allele I is associated with the reduced PCA. risk (P=0. 001)(60).

3.9. Renin–Angiotensin System:

The renin–angiotensin system (RAS) involved in regulating blood pressure and cardiovascular homeostasis. An enhanced RAS activity has been proposed to play a role in neoplastic cell proliferation and metastasis. Angiotensin I-converting enzyme (ACE) is the key enzyme of RAS and to be expressed differentially in several carcinomas and may be signify in migration of tumor cells and tumor angiogenesis. The Alu repetitive sequence insertion/deletion (I/D, rs4646994) polymorphism in the ACE gene has been implicated in cancer susceptibility (162). A case-control study on 95 patients with PCa. and 111 patients with benign prostatic hyperplasia by Hasanzad et al. showed no association between the ACE gene insertion/deletion (I/D) polymorphism and cancer risk(129). The results of a meta-analysis found that a significant association between ACE I/D polymorphism and PCa. (163).

3.10. Hormone Synthesis and Metabolism:

Reviews have shown that changes in steroid hormone metabolism, specifically involving testosterone, influence the risk of PCa. CYP17 and CYP19 genes are involved in metabolism pathways of testosterone and estrogen, respectively (67, 83). Similar to Iranian study more studies have shown a significant association between an A2 allele of CYP17 gene and risk of PCa. (67, 164). A study had conducted by Souiden et al. manifested that genotypes containing the A2 allele is associated with increased risk of PCa. (P value=0.029) (165). Some investigations have illustrated a significant difference between case and control groups in genotype groups of TTTA variant in CYP19 gene (83). For example, Latil et al. showed 171 and 187 alleles are associated with PCa. risk (P-value=0.05 and 0.045, respectively) (166). A study was conducted by Farzaneh et al. found no association between various length of tetranucleotide repeats and PCa., risk (with P-value=0.4)(83).

Microseminoprotein-beta (MSMB) is one of the most plentiful proteins in human seminal plasma. GWASs recognized rs10993994 polymorphism in the promoter region of MSMB gene, which was significantly associated with PCa. susceptibility. In a meta-analysis disclosed that this SNP was associated with an increased risk of PCa. among Caucasians, while no association was discovered among Asians. As for other populations, a weak association among African-Americans and mixed populations had been found (167). Also, the result of Shahkar et al. investigation showed that MSMB rs10993994 polymorphism increased the risk of PCa. in an Iranian population(97).

Sex hormones have been signified in prostate carcinogenesis and are thought to adjust cell proliferation and growth (119). In 2016 Tahmasebi Fard et al. studied the association between the Asp327Asn Polymorphism of SHBG gene and PCa. They demonstrated that homozygous mutant genotype AA (p value= 0.007) and heterozygous AG (p-value =0.51) increase risk of getting PCa. in carriers(168). In Berndt's review, stated that SHBG D356N polymorphism, heterozygotes were found to have an increased risk of PCa. among whites (P = 0.0007) (119).

Estrogen impacts are mediated by two estrogen receptors ER-α and ER-β. The association between ER-α and ER-β genes variants and PCa. have been addressed in very few reviews. Safarinejad et al. found that the ER-a Pvull C, ER-a XbaI G,and ER-b AluI G alleles were significantly associated with an increased risk of PCa.(113). A study of 170 PCa. patients in Indian population found a significant difference in Pvull polymorphism of ER-a gene distribution between patients and controls(169). In a large population-based case-control investigation (1,415 cases and 801 controls) 28 SNPs spanning the entire ER-β gene were checked out. Only for one of the typed htSNPs (rs2987983) found a significant difference in allele frequency between cases and controls (170).

3.11. Androgen Receptor (AR):

The prostate is an androgen-dependent organ and genes that are involved in the signaling pathways and metabolism of these hormones have been implicated as factors involved in the initiation or progression of prostate adenocarcinoma. The N-terminal domain of the AR gene has polymorphic trinucleotide repeats CAG, encoding polyglutamine. Studies have illustrated that the number of CAG repeats is associated with a risk of PCa. In the same way, Ashtiani et al. studied the CAG repeat length of AR gene in Iranian patients and stated that CAG repeat polymorphism in AR gene may act as a risk modifier (12). Also, in 2016 researcher found that patients with ≤21 CAG repeats have an increased risk of developing PCa. (P<0.001) and the combination of ≤21CAG and ≥17 GGC repeats was associated with the risk of developing PCa.(171).

Glucuronidation is the main pathway for removal of exogenous and endogenous compounds such as environmental carcinogens and androgens from the body. This biochemical pathway is mediated by enzymes called uridine diphospho glucuronosyl transferases (UGTs). Three UGT2B classes of enzymes (UGT2B15, UGT2B17, and UGT2B28) inhibit the agglomeration of androgens in the prostate. In 2017 Iranian investigators reported D85Y polymorphism of UGT2B15 and CNVs in UGT2B28 and UGT2B17 genes is not associated with PCa. risk. There are many conflicting data about the association between the two UGT2B17, UGT2B28 polymorphisms and the risk of the disease (35). Karypidis et al. reported an association betweenUGT2B17 variation and the risk of PCa. in Caucasian population (172). To date, investigations have displayed UGT2B17 gene deletion is more prevalent among populations than whole gene deletion of UGT2B28. The association between del/del genotype of UGT2B28 and the risk of cancers was shown in various survives (35). Null genotype of UG-T2B28 has been linked to a higher risk of biochemical PCa. relapse (173). Gsur et al. presented no significant association between D85Y polymorphism of UG-T2B15 and the risk of PCa. (174).

Prostate-specific antigen (PSA) is a serine protease that is part of the kallikrein superfamily, usually produced by prostate cells. It has widely been used as a diagnostic marker of the PCa. since the early 1990s. The main regulators of PSA expression at the gene level are androgens. Production of PSA is mediated through binding of the androgen receptor (AR) to androgen response elements (ARE) in the promoter region of the PSA gene (38). There are two different reports on the association of this SNP with serum PSA level in the Japanese population. One showed an association between higher PSA level and GG genotypes and the other showed no association between PSA-158 G/A polymorphism and the serum PSA level (175, 176). In a study conducted on 95cases and 111contol in Iran, no significant association was found between rs266882 and PSA plasma levels (38). A case-control study on patients with Turkish origin reported that ARE-1 PSA polymorphism has a significant influence on PCa. risk (177).

3.12. Drug Metabolizer, Detoxification and Resistance:

Glutathione S-transferase (GST) is super family genes that encode enzymes which plays a key role to protect from DNA damage and detoxification of the cell. GSTM1, GSTP1, and GSTT1 are most widely studied in molecular epidemiology of cancer. Large genomic deletions of GSTM1 and GSTT1 (null genotype) result in a complete lack of enzyme activities. GSTP1 polymorphism (Ile105Val) produces an enzyme with decreased activity. A large number of studies related to the association between GST variations and PCa. risk, but get conflicting results. For example in Iran, Ansari et al. found no association between GSTT1 and GSTM1 gene polymorphisms and PCa.(3) but Safarinejad study detected a significant association between the null genotypes of GSTM1, GSTT1 and the Val allele of GSTP1 with a higher risk for PCa.(18). They stated that the frequency of the GSTM1 null genotype is ~50% of the Caucasian population in Europe. In this study, the frequency of the GSTM1 null genotype in the Iranian population was 43%, a rate compatible with that reported by Lai et al (18, 178). In

another survey, the association between GSTM1 null genotypes and PCa. risk was confirmed (12). Similar to the Indian (179) and German population, a positive association have been found between the increased risk of PCa. with the GSTT1 null genotype but not in the American population (18). Study of the articles about the impact of the GSTP1 gene on PCa., disclosed a significant association between heterozygous GSTP1 genotype (Ile/Val) and PCa.(18). However, two further case-control studies reported no association between GSTP1 and PCa. risk (18, 180).

ABCC1 (MRP1) is a member of the ATP-binding cassette superfamily of cell-surface transport proteins and is involved in drug resistance and cellular antioxidative defense system. SNPs in the coding region of the ABCC1 gene have been revealed to affect its function(181). Results showed that the AA genotype in ABCC1 in patients is higher than controls and are correlated with the risk of PCa. in Iranian population(58). On the other hand, a report by Zhao et al., indicated that promoter polymorphism of the ABCC1 gene too, is associated with cancer development(58). Evidence indicated that SNPs within the ABCC1 (MRP1) are important in predicting the response to chemotherapy in different cancers(182). SNPs in the promoter region of a gene can potentially alter the affinity of interactions between DNA and nuclear proteins and, so that, affect the efficiency of transcription(58).

NAT2 enzyme participates in bioconversion of heterocyclic arylamines and aromatic amines to electrophilic ions that can be critical initiators of the tumorigenesis process(183). NAT2 is most frequently expressed in the liver and implicates a variant which results in the expression of four mutant alleles. In 2017, Hasanzad et al. study demonstrated that carrying G857A, G590A and T481C polymorphisms of NAT2 may not affect developing PCa., but heterozygote genotype of T481C polymorphism can be associated with more advanced stages of cancer earlier in life(54). Steivastava et al. in a study of 130 patients and 140 controls of an Indian population found no significant association between NAT2 genotype and PCa. risk(184) that was in agreement with the findings of Wadelius et al. in Swedish and Danish populations(43).

It has been shown that activated estrogens are associated with several tumors in various tissues and the within catechol-o-methyltransferase (COMT) enzyme is responsible for this defense. It has been shown in some studies that single nucleotide polymorphisms COMT genes have been associated with benign prostatic hyperplasia and PCa.. The COMT gene has three polymorphic sites at codons 62, 72 and 158. The results of Omrani et al. did not show any association between the Met158 polymorphism and PCa.(80) but in Japan, researchers stated that G/A genotype of the COMT gene is

associated with a weak tendency toward increased prostate carcinoma risk(185).

To unravel any possible specific genetic aberration in Iranian population in compare with the rest of the world, we compared the results of the association between polymorphisms and the risk of prostate cancer between Iran and other countries. The result highlighted 11 genes which were different (Table 2, red numbers). For example, rs1256049 polymorphism in ER-β gene was significant in Iranian patients, while in other countries with a high sample size, such as America and China, no significant difference was found.

4. Discussion

Cancer is the third cause of death in Iran (186) and based on Globocan 2012, among Iranian men, PCa. is one of the most common cancers (187). One of the reasons for the inconsistency between the Globocan's and Iran's reported incidence rate could be due to different estimates and sources of information in Iran (188). The lowest ASR was belonged to Kerman province (3.2 per 100,000), in Iran(189). Globally, it is estimated that the highest Standardized Incidence Ratio (SIR) is related to countries in the Oceania region, such as Australia (111.6 per 100,000), and North America (97.2 per 100,000). The result of Hassanipour's review showed that the incidence of PCa. in Iran is low (ASR = 9.11 per 100,000), whereas the Asian countries such as Turkey (40.6 per 100,000) and Lebanon (37.2 per 100,000) have a high SIR. However, the lowest incidence rate was reported for South-Central Asian countries (4.5 per 100,000), and South East Asia (5.5 per 10 0,000)(190-192) In spite of numerous investigation attempts throughout the world, and the publication of various articles each year, the presumed association between specific genetic variations and cancer risk remains unknown. This controversy is raised from a small sample size and has been intensified currently by the development of high-throughput technology to precisely recognize SNPs (193). The etiology of PCa. is improbable to be clarified by allelic variability. Instead, the prevalence of PCa. in the population likely follow by complex interactions among many genetic and environmental factors over time. The most of PCa. cases are improbable to be due to significant susceptibility genes and genetic polymorphisms are presumably to be more valuable from a public health perspective. Its incidence rates are constantly rising because of increases in longevity and it is expected that in the future, the numbers of cancer cases will be growth in Iran (194). The results of associations of polymorphism with the incidence and severity of prostate cancer between Iran and other countries require more research. It is quite clear-cut that in order to

Table 2: Specific genetic aberration in Iranian population in compare with the rest of the world

IRAN				Other Countries				
Gene Name	Sample size (case -control)	P-VALUE	Ref.	Ethnicity	Country	Sample size (case-control)	P-VALUE	Ref.
MMP2-1306C/T	102/139	P= 0.1	(4)	Asian	India	190-200	p = 0.026	(7)
	50/54	P = 0.72	(5)	Latin	Brazil	100-100	P <0.00	(13)
eNOS- G894T	352/356	P = 0.001	(10)	Caucasians	Serbia	150-100	P > 0.05	(19)
	95/111	P =0.2	(14)	Caucasians	Portugal	125-153	p=0.037	(23)
				Eurasians	Turkey	193-85	p>0.05	(24)
				Eurasians	Turkey	84/116	P=.0001	(29)
eNOS-4a/b	352/356	P = 0.004	(10)	Eurasians	Turkey	84/116	P =.003	(29)
eNOS- T-786C	352/356	P = 0.001	(10)	Latin	Brazil	83-94	P=1.0	(40)
				Eurasians	Turkey	84/116	P = .026	(29)
VEGF-C460 T	50/50	P=0.031	(17)	Eurasians	Turkey	133-157	P > 0.05	(57)
				Asian	Taiwan	96-119	P<0.001	(61)
ApE1-1349T>G	100/100	P= 0.045	(22)	Caucasians	USA	228-335	P=0.03	(71)
				Asians	China	198-156	p = 0.02	(76)
MSH3 Pro222Pro	18/60	P=0.012	(27)	Asians	Japan	110-110	P>0.05	(82)
XPC T>G	154/205	P>0.05	(30)	Asians	China	1,004- 1,055	P>0.05	(86)
				Caucasians	USA	1457- 1351	0.97	(88)
				Caucasians	Poland	720 -1121	0.68	(89)
CAG repeat length	110/100	P< 0.0001	(12)	European	Europe	1744 cases	P < 0.0005	(99)
				Caucasians and Black	USA	1159 -1353	P>0.05	(104)
				Sweden	Sweden	1,461-796	P = 0.03	(106)
UGTB15,17,28	120/120	P>0.05	(35)	-	USA	233-342	p < 0.05 UGTB15	(108)
				Caucasian and Afri-can Ameri-can	USA	331-426	P=0.004 UGT2B17	(109)
				Caucasian	USA	411-397	P>0.05 UGT2B17	(112)
PSA	95/111	P =0.7	(38)	-----------	Australia	821-734	P =.001	(121)
				-----------	Portugal	151-127	P = .009	(123)
MDM2	103/142	P=0.023	(39)	Mixed	Norway	5002-7498	P>0.05	(124)
TP53 (In-tron3)	103/142	P>0.05	(39)	Asia	India	177-265	P>0.05	(125)
TP53 (co-don72)	40/80	P = 0.005	(44)	Caucasians	Slovakia	300-446	P<0.05	(133)
	68-85	P = 0.98	(49)	Caucasians	Germany	510-490	P>0.05	(134)
	187/185	P>0.001	(51)					
	45/45	p<0.05	(58)					
PRKCI rs546950 C>T and rs4955720 C>A	169/182	P<0.001 P>0.05	(59)	Asian	China	1015-1044	P = .045	(136)
GNB3 C825T	172/344	p = 0.003	(63)	Caucasians	Germany	235-111	p= 0.82	(138)
FAS- G1377A	100/100	P>0.05	(66)	Asian	China	602-703	P= 0.03	(140)
				northern India	India	192-224	P = 0.02	(143)

Table 2 continue: Specific genetic aberration in Iranian population in compare with the rest of the world

IRAN				Other Countries				
miR-499	169/182	*P = 0.019*	(1)	Caucasian	Serbia	355-312	*P<0.05*	(2)
				Asian	India	159-230	*P ≤ 0.001*	(8)
miR-146a	169/182	*P>0.05*	(1)	Caucasian	Serbia	286-199	*p =.006*	(9)
				Asian	China	251-280	*P = 0.01*	(15)
miR-196a2	169/182	*P>0.05*	(1)	Caucasian	Serbia	355-312	*P>0.05*	(2)
				Asian	India	159-230	*P = 0.01*	(8)
PRNCR1 rs13252298	178/180	*P=0.231*	(25)	Asian	China	286-288	*P>0.05*	(26)
				Caucasian	USA	943-2829	*0.093*	(28)
PRNCR1 rs1456315	178/180	*P<0.0001*	(25)	Caucasian	USA	40-40	*P=.002*	(37)
				Asian	China	495-640	*P=2.81× 10^{-4}*	
PRNCR1 rs7841060	178/180	*P<0.0001*	(25)	Mix	USA	10501-10831	*P<0.05*	(42)
RNASEL	181-19	*P<0.05*	(45)	European	Sweden	1,622-796	*P=0.627*	(46)
	40/80	*P=0.3*	(47)	European	USA	1,116-1,344	*P=0.237*	(52)
				Mix	Canada	996-1,092	*0.463*	(53)
IL1A rs3783553	150/155	*P<0.05*	(55)	Asian	China	131-229	*P=. 001*	(60)
CYP17 rs743572	74/128	*P<0.05*	(67)	Caucasian	USA	804-1357	*P = .014*	(74)
	150-150	*P=0.041*	(77)	Mix	USA	8,138-9,033	*P>0.05*	(79)
CYP19	59/95	*P =0.4*	(83)	Caucasian	France	1,101-882	*P =.003*	(87)
				Asian	Taiwan	244-261	*P= 0.15*	(91)
				-------	Bulgaria	246-261	*P<0.05*	(95)
MSMB rs10993994	169/182	*P = 0.03*	(97)	Caucasian	USA	10 487- 11 024	*p<0.05*	(98)
				African-American	USA	4,040- 3,748	*P=.005*	(100)
				Caucasian	Sweden	2899- 1722	*P =.001*	(101)
MSMB rs12770171	169/182	*P>0.05*	(97)	Asian -Indian	India	33-60	*P>0.05*	(107)
SHBG rs6259	120/120	*P<0.05*	(111)	Caucasian	USA	937-493	*P>0.05*	(115)
				Caucasian	USA	1,320-1842	*p<0.05*	(119)
ER-a rs2234693	162/324	*P = 0.002*	(113)	Mixed	USA	598-1,098	*P=0.03 black men*	(126)
				Caucasian	USA	1,320-1842	*P>0.05*	(119)
				Asian	Japan	750-870	*P>0.05*	(135)
ER-a rs9340799	162/324	*P = 0.002*	(113)	Mixed	USA	598-1,098	*p<0.05*	(126)
				Mixed	USA	609-843	*P>0.05*	(74)
				Caucasians Asian African	China	Meta- analysis	*P=0.016 P = 0.665 P=0.006*	(141)
ER-β rs4986938	162/324	*P = 0.003*	(113)	Asian	Japan	750-870	*P < 0.05*	(135)
				Caucasian	France	1045-814	*P>0.05*	(145)
ER-β rs1256049	162/324	*P = 0.003*	(113)	Caucasian	France	1045-814	*P>0.05*	(145)
				Caucasians Asian African	China	Meta- analysis	*P =.005 P =.703 P =.707*	(141)
				Caucasian	USA	5,946-6,576	*P>0.05*	(148)
				African	USA	778/966	*P>0.05*	(148)

Table 2 continue: Specific genetic aberration in Iranian population in compare with the rest of the world

IRAN				Other Countries				
GSTM1	60/60	P>0.05	(3)	Asians Europeans Americans Africans Eurasians	Pakistan	7,281-9,082 Meta-analysis	P= 0.03 P=0.42 P= 0.05 P=0.40 P<.001	(6)
				Caucasian	USA	590-538	p<0.05	(11)
	110/100	P <.0001	(12)					
	168/336	P=0.005	(18)					
GSTT1	60/60	P>0.05	(3)	Asians Europeans Americans Africans Eurasians	Pakistan	7,281-9,082 Meta-analysis	P= 0.90 P= 0.89 P= 0.50 P<0.001 P= 1.0	(6)
	110/100	P>0.05	(12)	Caucasian	USA	590-538	P>0.05	(11)
	168/336	P=0.005	(18)					
GSTP1	168/336	P=0.002	(18)	Mixed	USA	2,528- 3,076 Meta-analysis	P < 0.01	(41)
				Caucasian	Sweden	850	P>0.05	(43)
				Caucasian	Austria	166-166	p<0.05	(48)
NAT2	147/207	P = 0.1	(54)	Mixed	China	14,469-10,689 Meta-analysis	P>0.05	(62)
				African Americans	USA	254-301	P>0.05	(68)
				Asian Caucasian	China	1,253 -1722 Meta- analysis	p<0.05 P>0.05	(75)
COMT rs4680	41/193	P=0.021	(80)	African	France	660-709	p<0.05	(81)
				Caucasian	British	89-178	P = 0.15	(84)
				Mixed	China	2292 – 2158 Meta- analysis	P>0.05	(90)
MTHFR rs1801133	67/75	P=0.20	(93)	Caucasian	Norway	3000-3000	P>0.05	(96)
	174/ 348	P=1.0	(102)	Caucasian	Sweden	2777- 1639	P=0.46	(105)
	30/40	P>0.05	(110)					
MTHFR rs1801131	174/ 348	P=0.08	(102)	Caucasian	USA	439 - 479	P = 0.08	(117)
				Caucasian	USA	1,144 - 1,144	p<0.05	(118)
MTR rs1805087	100/100	P=0.99	(120)	Asian	China	1871-2026	P=0.9	(127)
				Caucasian	Russia	370-285	P=0.5	(128)
ACE	95/111	P>0.05	(129)	Caucasian	Netherlands	209-6,015	P>0.05	(131)
				Asian	China	189-290	P <.001	(132)

achieve certainty, the need for further studies with high numbers of samples in Iranian men with prostate cancer is required, as well as the writing of meta-analytic articles related to the target polymorphism. Harmonizing the methods of studies may minimize the confounding factors to achieve a better study outcome. The purpose of these kinds of researches and writing of systematic and meta-analytic articles is that, in the future, using the results of them, it would be possible to predict the incidence of prostate cancer in susceptible individuals. For many of the genetic polymorphisms reviewed in this article, association with PCa. have been contradictory across investigations, which perhaps due to methodologic or sample size limitations or dissimilar in the basic frequencies of alleles. Many studies recognized in this review used available samples of cases and controls and were not really population-based. In some researches, there may have been insufficient control of confounding

factors. The prevalence of environmental risk factors, and the unknown etiologic factors may also differ across populations. This manuscript discussed molecular studies of polymorphisms and PCa. risk that have cases and controls from different racial and ethnic groups in Iran. The results from mention study can be used as evidence for gene-gene interactions. Although, social-environmental factors and gene-environment interactions, may also give a reason for discrepancies in PCa. incidence and mortality. Some authors have mentioned that, genetic polymorphism within racial and ethnic groups is higher than the genetic variation that exists across racial, ethnic, or cultural groups. There has been still ongoing controversy over the association between the gene polymorphisms and PCa. susceptibility. Further studies that assay associations among various genetic polymorphisms should take into account risk factors for PCa., such as diet and environmental exposures, possible biological pathways and gene-gene-environment interactions(36). Despite the existing clinical parameters, new biomarkers are needed to improve the prognosis. Some molecules and DNA-based genetic biomarkers are under survey as potential prognostic factors (195).

5. Conclusion:

In conclusion, performing more investigations are needed to map out the precise incidence rate and trend of PCa. in Iran. Albeit several studies had been done in this area, most of them were local or performed in the past years and must be updated. It would be essential to fulfill well-powered researches on SNPs to obtain definite results regarding their predictive role and in regard to their function in the PCa. development pathway, which could be considered as therapeutic targets.

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The authors have no conflicts of interest.

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