Research Article

The Association Study of rs10090154 and rs1691053 with Predisposition to Prostate Adenocarcinoma in the Iranian Population

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Abstract

Prostate cancer is the second most prevalent malignancy in men and the fifth leading cause of death worldwide. It is the second most common urinary tract cancer among Iranian men. The aim of this study was to investigate the association between rs10090154, located on the 8q24 locus, and rs1691053 on chromosome 5p15.31, with prostate adenocarcinoma and PSA levels. This study also aimed to identify the potential of these genetic markers as screening factors. This case-control study included 79 patients with prostate adenocarcinoma aged between 48 to 86 years, as well as 98 patients with benign prostatic hyperplasia aged between 47 to 81 years. The Tetra-primer ARMS-PCR method was applied to determine the genotype of each participant. In this study, no significant differences in genotypic distribution between the prostate adenocarcinoma and control groups were discovered for rs10090154 (P-value = 0.608) and rs1691053 (P-value = 0.102) polymorphisms. Moreover, for the study of the additive genetics model of the rs10090154 polymorphism, with the TT genotype as the reference, the CC genotype with P-value = 1 and OR {95%CI} = 0.750, {0.039-14.576} and CT genotype with P-value = 0.324 and OR {95%CI} = 0.577, {0.191-1.739}, were not associated. Correspondingly, for rs1691053, with the CC genotype as the reference, the CT genotype with P-value = 0.176 and OR {95%CI}= 0.196, {0.022-1.793}, and the TT genotype with P-value= 0.464, OR{95%CI}= 0.125, {0.005-3.225}, were not associated. These findings suggest that rs10090154 and rs1691053 may not be associated with prostate cancer among Iranians. However, further research with larger sample sizes and investigation of various Iranian subpopulations are needed to confirm these results.

***Keywords*:** Prostate adenocarcinoma, Association, Tetra-primer ARMS-PCR,8q24, 5p15.31

Introduction

Prostate cancer is the second most common type of cancer worldwide and the fifth leading cause of death among men, with nearly 1.2 million new cases diagnosed in 2018 (Casado et al., 2022). In 2022, prostate cancer was shown to account for 27% of all cancers diagnosed in male patients (Siegel et al., 2022). The prostate cancer incidence varies among different populations (Moradi et al., 2019). Studies have shown that African men of African Caribbean and South African descent have the highest rates of prostate cancer deaths worldwide (Rebbeck, 2017). African Americans also have an increased risk of developing this cancer, as well as an increased rate of advanced forms of the disease. Furthermore, studies have also shown that prostate cancer is the second leading cause of death among Americans (Daniyal et al., 2014). Another research showed that Northern Europe has the highest age-standardized rate of all-age incidence, while South-Central Asia has the lowest age-standardized rate (Gandaglia et al., 2021). The incidence and death of prostate cancer have increased across the continent, despite the fact that traditionally, Asia has been thought of as an area with a low incidence. Significant differences in prostate cancer incidence in different regions of Asia were also reported (Zhu et al., 2021). Iran, an Asian country, has seen an increase in the incidence of prostate cancer over the past decade from 11.46 cases per 100,000 men in 2005 to 25.67 cases per 100,000 men in 2020 (Shafiee et al., 2023).

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Differences in the incidence of prostate cancer across different populations may be related to factors such as age, genetic profile, lifestyle, screening practices, access to healthcare facilities, environmental factors such as constant exposure to pollutants, socioeconomic status, and cultural issues (Alvarez-Cubero et al., 2013; Baade et al., 2015; Culp et al., 2020). Current screening strategies for prostate cancer mainly rely on the prostate-specific antigen (PSA) test and digital rectal exam (DRE) (Roudgari et al., 2012). While these techniques can increase the number of diagnosed patients, they have several limitations, such as false-positive and false-negative results, overdiagnosis, limited specificity, and lack of precision (Bracarda et al., 2005). For instance, PSA screening for prostate cancer may result in high PSA levels in several other prostate disorders. One of the most well-known of these conditions is benign prostatic hyperplasia (BPH), a disorder in which the prostate enlarges and causes problems in older patients (McConnell et al., 1994). Although the exact cause of BPH is unknown, aging is a major risk factor (Kobayashi, 1990). Acute prostatitis and prostatic ischemia, amongst other conditions, can cause PSA levels to soar and produce inaccurate results when testing for prostate cancer (Bunting, 1995).

Several risk factors have been identified for prostate cancer, including higher age, black race, previous positive family history, obesity, consumption of a diet high in dairy and calcium, and low concentrations of selenium and plasma alpha-tocopherol (Hayes et al., 1999; Platz and Ggiovancini, 2006). Genetic variation is also considered a factor that could modify the risk of prostate cancer. The human genome contains a wide variety of genomic variations, one of the most studied being single nucleotide polymorphisms. In genome-wide association studies, a large number of SNPs have been investigated for potential association with the risk of prostate cancer. To date, GWASs have identified nearly 70 SNPs associated with prostate cancer risk (Eeles et al., 2013).

In this study, we investigated two single nucleotide polymorphisms (SNPs), rs10090154 and rs1691053, located at loci 8q24.21 and 5p15.31, respectively. The 8q24.21 locus is a hotspot for variations that strengthen the risk of various cancers, including breast, prostate, bladder, colon, and lung (Eeles et al., 2013; Hubbard et al., 2016; Kiltie, 2010; Ling et al., 2013; Zhang et al., 2012). One of the oncogenes investigated in this region is *MYC*, which is believed to have function in 20% of human cancers. *MYC* plays a role as a transcription factor and is involved in regulating the cell cycle, metabolism, ribosome biogenesis, and cell adhesion. A large number of genetic polymorphisms associated with cancer risk are located in non-coding regions surrounding *MYC*, which could affect the regulation of *MYC* expression. Additionally, other protein-coding genes in this region, including *FAM84B*, *GSDMC*, *FAM49B*, and *ASAP1*, have also been implicated in tumorigenesis (Wilson and Kanhere, 2021).

The other SNP (rs1691053) in 5p15.31 has been identified to be associated with PSA levels at the time of diagnosis (Henríquez-Hernández et al., 2015). *SRD5A1*, which is located in 5p15.31, is expressed in a wide variety of tissues, including renal, hepatic, skin, and nerve tissues. This gene is important for the catabolism of both testosterone and dihydrotestosterone (DHT), and loss of its function can lead to abnormalities in androgen levels. Clinical data have shown that the application of 5α-reductase inhibitors to reduce the level of DHT can reduce the incidence of prostate cancer (Liu et al., 2020). In three types of prostate cancer cell lines, it has been demonstrated that activation of the androgen receptor (*AR*), one of the major genes implicated in prostate cancer, increases the expression level of *SRD5A1* (Audet-Walsh et al., 2017).

The purpose of this study was to evaluate rs10090154 and rs1691053 as a screening method for the Iranian population. Additionally, we aimed to investigate the association of these SNPs with prostate cancer, taking into account age, Gleason score, and PSA levels.

Materials and Methods

Patients' Characteristics

This study was approved by the Ethics Committee of the North Tehran Branch of the Islamic Azad University, Tehran, Iran (code: IR.IAU.TNB.REC.1400.092). In this case-control study, 79 patients with prostate adenocarcinoma, aged between 48 to 86 years, participated as the case group, and 98 patients with BPH, aged between 47 to 81 years, participated as the control group from Hasheminejad and Labbafinejad hospitals. Their clinical information, such as age, serum PSA level, prostate volume, Gleason score, extra prostatic extension, and perineural invasion, were recorded. The diagnosis of prostate adenocarcinoma was confirmed by physicians

through PSA screening, DRE, and prostate biopsy. In this study, participants signed consent forms to inform them of their participation in the study and the confidentiality of their names and information was noticed. Both groups had the same characteristics, except for the type of prostate disorder, and there was no history of any other disorder. The Gleason score was determined from the biopsy results. The physicians found the two areas that had the most cancer cells and assigned a separate Gleason score to each of these areas. Each of them got a score between 1 and 5, and they were added together to arrive at a composite score, often known as the Gleason total.

Sample collection and DNA extraction

In this study, 3 mL of blood samples were collected in EDTA (Ethylenediaminetetraacetic Acid) anticoagulants and stored at -20°C. Genomic DNA was extracted from peripheral blood using the FAVORGENE-Taiwan extraction kit, according to the manufacturer's instructions. The quantity and quality of the extracted DNA were assessed using Nanodrop and 2% agarose gel, respectively.

Primer design

In this study, the primer design strategy requires two unspecific external primers and two specific internal primers. The Primer1 database was used to design the primers, and the Primer-BLAST-NCBI database was used to confirm the accuracy of the primers. The primer sequences for rs10090154 and rs1691053 are shown in Table 1.

Genotyping

The genotypes of the extracted DNA for rs10090154 and rs1691053 polymorphisms were determined using the Tetra-primer ARMS-PCR method. In Tetra-primer ARMS-PCR, three bands are observed, and the product size is used to identify the three wild alleles, mutated alleles, and positive control, which are two external primers. To ensure the experiment's success, half of the samples were genotyped again instead of sequenced, and the results were exactly similar. Additionally, three mismatches were designed through primer design to increase specificity.

Table 1. Sequence of rs10090154 and rs1691053 primers and their melting temperatures

rs1691053	Sequence	Length	TM
Forward inner	GATTTATTTAATACTATGGAAATTGGTGTGCC	32	64
Reverse inner	TATTTTTGTTACTGCAGCAACCCACTGCA	29	70
Forward outer	GAATTCTTTCTCCCAAGACAAGGATCAAG	29	67
Reverse outer	GCCTCTTGTTACCTTTGGTTTTCTGTTTTC	30	67
Product size for T allele	349		
Product size for C allele	524		
Product size of two outer primers	812		

rs10090154	Sequence	Length	TM
Forward inner	TAAAAATCTCTGCAAGATTTTTTTGTACAT	30	61
Reverse inner	TTTTTTTTCCAATATTGTTTTAGCTCTG	28	61
Forward outer	TAAATAAAAAGGCATATGTGTTGAAAGG	28	61
Reverse outer	AAGATCCATTTTTATGAGTGTTTCCTTT	28	61
Product size for T allele	344		
Product size for C allele	475		
Product size of two outer primers	761		

ARMS PCR

The PCR mixture was prepared in a volume of 25 µL, containing 12.5 µL of Master Mix Taq DNA Polymerase 2x (Master Mix RED-AMPLIQON-Denmark), 1 µL of extracted DNA (1-3 µg = final concentration), 8.5 µL of water, and 1 µL of each primer (10 picomoles = final concentration). For both polymorphisms, a temperature of 53°C was chosen for 40 seconds, based on the PCR gradient. The thermal cycle program consisted of 33 cycles, involving three stages: 1) 95°C for 30 seconds (denaturation), 2) 53°C for 40 seconds (annealing), and 3) 72°C for 35 seconds (extension), followed by 72°C for 10 minutes (final extension). Finally, 7 µL of PCR product was loaded on a 2% agarose gel along with 3 µL of DNA ladder and placed in an electrophoresis machine with a voltage of 90 for 45 minutes.

Statistical analysis

Finally, various statistical analyses were performed, including the comparison of age variable between the two groups, calculation of allele frequency, assessment of the Hardy-Weinberg equilibrium in both groups, investigation of the genotype-phenotype relationship, evaluation of the additive genetic model, and calculation of odds ratio and 95% confidence interval. These analyses were conducted using the SPSS software, with a significance level of $P < 0.05$.

Result

Study population

This study included 79 patients with prostate adenocarcinoma, with an age range of 48 to 86 years (mean age of 67.75 years, SD = 8.4211), and 98 BPH cases, with an age range of 47 to 81 years (mean age of 65.316 years, SD = 7.7000). The total mean age of the 177 participants was 66.418 years.

To determine the genotypes using the Tetra-primer ARMS-PCR method, the gel was placed in the gel dock device. The bands were visualized using a UV illuminator, and the sequences were photographed using a computer (Figures 1 and 2).

The significance of genotypic frequency differences between the prostate adenocarcinoma and BPH groups was evaluated using the chi-square test. Based on the Chi-square test (P-value < 0.05), there was no significant difference in the genotypic distribution between the case and control groups for both rs10090154 (P-value = 0.608) and rs1691053 (P-value = 0.102) polymorphisms. The genotypic frequencies for rs10090154 and rs1691053 are presented in Table 2. It is noteworthy that Hardy-Weinberg equilibrium was not established for both rs10090154 and rs1691053, in both the control group (P-value=0) and the adenocarcinoma group (P-value=0).

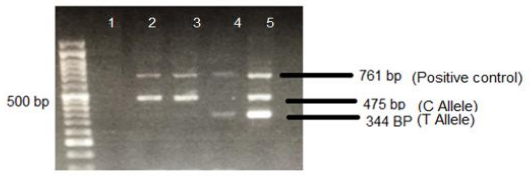

Figure 1. PCR products for rs10090154 on agarose gel (1: Negative control; 2 and 3: Homozygous CC; 4: Homozygous TT; 5: Heterozygous CT)

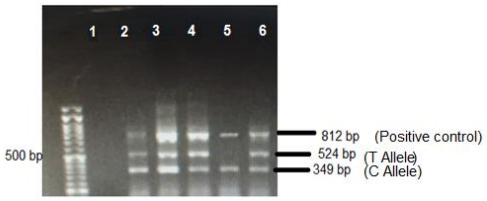

Figure 2. PCR products for rs1691053 on agarose gel (1: Negative control; 2, 3, 4 and 5: Heterozygous CT; 5: Homozygous CC)

Table 2: Genotypic frequencies of rs10090154 and rs1691053

rs10090154	**Adenocarcinoma**	**Control**	**p-value**
CC	1 (1.3%)	1 (1.0%)	
CT	70 (88.6%)	91(92.9%)	
TT	8 (10.1%)	6 (6.1%)	0.608
rs1691053	**Adenocarcinoma**	**Control**	**p-value**
CC	3(3.8%)	0(0.0%)	
CT	76 (96.2%)	97 (99%)	0.102
TT	0 (0.0%)	1 (1.1%)	

Since Hardy-Weinberg equilibrium was not established in both study groups, an additive genetic model was studied for both polymorphisms. In this model, based on considering the TT genotype as the reference, the CC genotype and CT genotype were not associated with the additive model for rs10090154. Similarly, for rs1691053, considering the CC genotype as the reference, the CT genotype and TT genotype were not associated

with the additive model. The results are presented in Table 3.

In this study, Fisher's exact test, odds ratio, odds confidence interval, and P-value were used to evaluate the relationship between alleles and calculate clinical features. Tables 4 and 5 show that there was no significant difference between the two groups in terms of the three levels of PSA score, three levels of Gleason score, and perineural invasion score.

Discussion

Prostate cancer is the second most prevalent form of malignancy worldwide, and numerous factors are thought to contribute to its high rate of occurrence, including but not limited to genetic and environmental components (Alvarez-Cubero et al., 2013). Genetic variations are among the genetic factors that could affect the risk of prostate cancer. In our study, we investigated two SNPs for their possible association with prostate cancer risk. Our data demonstrated that there was no association between rs10090154 and rs1691053 and prostate cancer. Additionally, no SNPs were associated with any clinical measures, such as PSA or Gleason score.

Table 3. rs10090154 and rs1691053 in additive genetics model

rs10090154	**control**	**Case**	**OR confidence) (95%interval**	**P-Value**
TT	6 6.2%	8 10.3%	Reference)1 (genotype	-
CC	1 14.3%	1 11.1%	0.750 {0 .039- 14.576}	1
CT	91 93.8%	70 89.7%	0.577 {0 .191- 1.739}	0.324
rs1691053	**control**	**Case**	**OR confidence) (95%interval**	**P-Value**
CC	1	4	Reference) 1 (genotype	-
TT	2	1	0.125 {0 .005- 3.225}	0.464
CT	98	77	0.196 {0.022-1.793}	0.176

The first locus (8q24) is flanked by two cancer susceptibility genes, *MYC* at the centromeric end and FAM84B at the telomeric end (Li et al., 2017). FAM84B is a membrane-bound protein that is expressed by malignant tumor cells, and its exact function is not well understood, but overexpression of this gene has been associated with poor prognosis among prostate cancer patients (Gu et al., 2020). Furthermore, adenocarcinoma cells of the prostate, similar to most malignant cells, show high expression and amplification of *MYC* (Fleming et al., 1986; Freedman et al., 2006). In our study of the Iranian population, no significant difference in the genotypic distribution between the prostate adenocarcinoma and the control groups was observed for the rs10090154 polymorphism (P-value = 0.608). Moreover, in the study of the additive genetics model of the rs10090154 polymorphism, based on considering the TT genotype as the reference genotype, genotype CC with a P-value of 1 and OR {95% CI} = 0.750 {0.039-14.576}, and CT genotype with a P-value of 0.324 and OR {95% CI} = 0.577 {0.191-1,739} were not associated with the additive genetics model. In a study of the Russian population, the T allele in the rs10090154 polymorphism was found to be associated with prostate cancer (Oskina et al., 2014). Similarly, a significant difference was observed between the case and control groups in rs10090154 in a study by Ming et al. in China (Liu et al., 2012). Li et al. also found that the T allele at rs10090154 was significantly associated with prostate cancer in a study in Northern China (Li et al., 2015). The differences observed in studies related to prostate cancer risk and polymorphisms in the 8q24 region may be attributed to heterogeneity among ethnic groups. In our study, no significant difference in the genotypic distribution was observed between the prostate adenocarcinoma group and control group in rs1691053 (P-value = 0.102). Moreover, based on CC as the reference, CT genotype with a P-value of 0.176 and OR {95% CI} = 0.196 {0.022-1.793} and TT genotype with a P-value of 0.464 and OR {95% CI} = 0.125 {0.005-3.225} were not associated with the additive genetics model. According to Setlur et al., rs1691053 is one of the probable SNPs that could affect DHT metabolism via *SRD5A1* alterations (Setlur et al., 2010). Genes linked to serum DHT levels have a role in prostate cancer. It is also hypothesized that germinal polymorphisms in those genes may affect the clinical outcomes of cancer by affecting the

interpersonal levels of testosterone and DHT (Henríquez-Hernández et al., 2014). Serum DHT levels may act as a potential diagnostic marker of 5α-reductase activity in the prostate during treatment of patients with 5α-reductase inhibitors, and the effect of 5α-reductase inhibitors on PSA and DHT levels could be influenced by genetic variations in *SRD5A1* (Stanczyk et al., 2013). A study in Spain examined 32 polymorphisms and found that only two of them (rs3822430 and rs1691053, both located in *SRD5A1*) were significantly associated with prostate cancer among patients (Henríquez-Hernández et al., 2015). Taken together, our findings suggest that rs10090154 and rs1691053 may not be associated with prostate cancer among Iranians. However, further research with larger sample sizes and investigation of various Iranian subpopulations are needed to confirm these results.

Table 4. Clinical features of rs10090154

PSA	**Adenocarcinoma**		**Control**		**OR (95%Confidence interval)**	**P-Value**
	T	C	T	C		
>10	42 (58.3%)	30 (41.7%)	27 (54.0%)	23 (46.0%)	0.839 {0 .405- 1.735}	0.711
4.1-10	36 (51.4%)	34 (48.6%)	57 (50.9%)	55 (49.1%)	0.979 {0 .539- 1.779}	0.944
≤4	8 (50.0%)	8 (50.0%)	19 (55.9%)	15 (44.1%)	1.267 {0 .385- 4.168}	0.767
Gleason score						
Control	**C**		**T**		**OR (95%Confidence interval)**	**P-Value**
	93(47.4%)		103(52.6%)			
≥8	23(41.1%)		33(58.9%)		0.772 {0 .439- 1.409}	0.398
=7	3(45.7%)		38(54.3%)		0.933 {0 .539- 1.612}	0.803
<7	17(53.1%)		15(46.9%)		1.255 {0 .594- 2.654}	0.551
Perineural invasion						
	CC		**CT**	**TT**	**P-Value**	
Total	1(1.3%)		70(88.6%)	8(10.1%)		
Negative	0(0.0%)		25(92.6%)	2(7.4%)	0.640	
Positive	1(1.9%)		45(86.5%)	6(11.5%)		

Table 5. Clinical features of rs1691053

PSA	**Adenocarcinoma**		**Control**		**OR (95%Confidence interval)**	**P-Value**
	T	C	T	C		
>10	34 (45.9%)	40 (54.1%)	24 (50.0%)	24 (50.0%)	0.850 {0 .411- 1.759}	0.661
4.1-10	34 (50.0%)	34 (50.0%)	57 (50.0%)	57 (50.0%)	1 {0 .548- 1.823}	1
≤4	8 (50.0%)	8 (50.0%)	18 (52.9%)	16 (47.1%)	0.889 {0 .271- 2.919}	1
Gleason score						
	C	**T**			**OR(95%Confidence interval)**	**P-Value**
Control	97(49.5%)	99(50.5%)				
≥8	28(51.9%)	26(48.1%)			0.910 {0 .498- 1.662}	0.878
=7	35(51.5%)	33(45.8%)			0.924 {0 .532- 1.604}	0.888
<7	17(50.0%)	17(50.0%)			0.980 {0 .473- 2.030}	1
Perineural invasion						
	CC	**CT**	**TT**		**P-Value**	
Total	3(3.8%)	76(96.2%)	0		0.203	
Negative	0(0.0%)	27(100%)	0			
Positive	3(5.8%)	49(94.2%)	0			

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