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Association of single nucleotide polymorphism in *hsa-miR-499* and *hsa-miR-196a2* with the risk of prostate cancer

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Abstract

Background Prostate cancer (PCa) is one the most common malignant cancers in men. Micro-RNAs are a group of a noncoding small molecule, which plays critical roles in signalling pathways, metabolism, apoptosis and cancer development. The purpose of this study was to examine the possible association between the *hsa-miR-499* (rs3746444) and *hsa-miR-196a2* (rs11614913) gene polymorphisms with the risk of PCa.

Methods The case–control investigation was performed on 300 peripheral blood samples, consisting of 150 patients with PCa and 150 healthy men without a family history of cancers. Genetic variations of *hsa-miR-499* and *hsa-miR-196a2* genes were assessed using the PCR–RFLP method.

Results The T/T + TC/CC genotype frequencies showed a significant association between *has-mir499* (rs3746444 T>C) gene polymorphism with the risk of PCa ($p = 0.027$; OR 1.780; 95% CI 1.030–3.113). The genotype frequencies of *hsa-miR-196a2* gene did not reveal a statistically significant difference between two groups ($p > 0.05$).

Conclusion Our findings supported that *hsa-miR-499* gene polymorphism significantly increased susceptibility to PCa and may be considered as a potential prognostic biomarker in PCa patients. The findings suggested that no correlation between *hsa-miR-196a2* gene polymorphism and PCa susceptibility in an Iranian population.

Keywords Prostate cancer · Prognostic biomarker · *Hsa-miR-499* · *Hsa-miR-196a*

Introduction

Prostate cancer (PCa) is one the most common malignancy and the second causes of cancer related-deaths in men [1]. The prevalence of PCa in middle-aged and elderly men is notable between other malignancies [2, 3]. The first reported PCa susceptibility gene was the hereditary prostate cancer locus-1 (*HPC1*) [4]. The androgen receptor gene plays an important role in initiation and progression of PCa. In addition, *HSD3B2, HSD3B1, SRD5A2, CYP17, AR* genes showed crucial roles in metabolism of androgens and cell proliferation in PCa progression. Some of polymorphisms in these genes are associated with an increased risk of the PCa [5]. Previously, the findings reported a group of small noncoding RNA with 21–24 nucleoside length, which play important roles in control of cellular and metabolic pathways [6]. The *hsa-miR-196a2* gene is located on chromosome 12q12.13 at the *HOX* C gene site with 110 bp length. The target gene is *HOXB8*, which was involved in the myeloid differentiation and organogenesis [7]. *HOXB8* prevents the differentiation of ancestral cells into the myeloid differentiated cells. Overexpression of *hsa-miR-196a2* could be led to a decrease in *HOXB8* gene expression and myeloid differentiation. The *hsa-miR-196a2* gene expressed in the dorsal organ and could be inhibiting the *HOXB8* gene expression [8]. A single nucleotide change rs11614913 C>T has been reported at position 78, which increased the risk of several cancers and disorders [9–11]. The *hsa-miR-499* rs3746444 gene polymorphism found at 20q11.11 chromosome [12]. A single nucleotide variation in *hsa-miR-499* rs3746444 T/C can be led to create a mismatch in the stem area of the *hsa-miR-499* precursor and changed the secondary construction of miRNA [13, 14]. In the previous investigations, rs3746444 and rs11614913 genetic variants have been assessed in the several types of cancers and disorders and showed conflicting results [15]. The findings disclosed that these genetic variants associated with the risk of several

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types of carcinoma [11, 14–16]. Notwithstanding, several investigations have been revealed the functional significant effects of nucleotide changes in genes encoding of *has-miR-196a2* and *hsa-miR-499*; a few studies evaluated the association between these SNPs with the risk of PCa [17–20]. However, in the present investigation, we aimed to evaluate the association between *has-miR-196a2* and *hsa-miR-499* gene polymorphisms with the risk of PCa patients in Iranian.

Materials and methods

Study selection

The present case–control investigation was performed on 300 peripheral blood samples, consisting of 150 patients with histopathologically confirmed PCa and 150 healthy men ages matched without a family history of cancers, which referred to Imam Khomeini Hospital of Tehran, during May 2015 to April 2016. All PCa patients were evaluated and included in our investigation according to standard clinical protocol, such as digital rectal assessment, ultrasonography examination, abdominal and pelvic ultrasound, analysis level of serum prostate-specific antigen (PSA) and biopsy of the prostate that histopathologically confirmed. The control group consisting of healthy men age and racial (Fars) matched without a family history of cancers and was prepared in the same geographical region. The exclusion criteria for the control group were the subjects had an unusual PSA level, abnormal digital rectal assessment, and self-declared disorders and family history of PCa. Ethics Committee of the Tehran University of Medical Sciences approved our investigation, and written informed consent was obtained from all subjects.

Genotyping

In this survey, we have obtained 2 ml peripheral blood samples in tubes which containing anticoagulant EDTA. Genomic DNA was isolated using the salting-out method as described previously [21]. The sequence of the forward and reverse primers, which were used for *has-miR-196a2* (rs11614913) and *has-miR-499* (rs3746444) gene amplification, is mentioned in Table 1. The PCR condition for the *has-miR-196a2* (rs11614913) and *has-miR-499* (rs3746444) gene amplification was with the following protocol: the initial denaturation 5 min at 94 °C, then 35 cycles of 30 s at 94 °C, 30 s at 59.5 °C and 62.5 °C, respectively, and 72 °C in 30 s. For genotyping of rs3746444 and rs11614913 was performed using PCR–RFLP method. The PCR product for the *has-miR-196a2* (rs11614913) and *has-miR-499* (rs3746444) was digested (16 h at 37 °C) using Hpy1881 and BclI enzymes (Thermo Fisher Scientific company), respectively. The PCR products digested were separated on 4% agarose gel electrophoresis. In addition, in order to confirm the genotype frequencies obtained using PCR–RFLP method, we sequenced 20% of the samples through arbitrary selection.

Statistical analysis

In order to assess the allele and genotype frequencies of *has-miR-196a2* and *has-miR-499* in two groups, we were used the Chi-square tests. Statistical analysis was performed using SPSS 25.0 software (SPSS Inc. Chicago, IL). All the tests were two-sided, and a P value < 0.05 was considered as statistically significant.

Results

Sample characteristics

The mean age characteristics of the PCa patients studied were 58.81 ± 12.37 (range 40–86) years and 41.23 ± 5.39 (range 30–52) years for healthy men. To avoid the effects of other factors, all subjects matched in the age and racial (Fars). The genotype frequencies of *has-miR499* (rs3746444 T>C) polymorphism were shown (TT = 29, TC = 72 and CC = 49) and (TT = 35, TC = 83 and CC = 32) in case and control, respectively. Our data indicated lack of a significant difference between groups ($p = 0.086$). In addition, the genotype frequencies of *has-miR196a-2* (T>C rs11614913) polymorphism were shown (TT = 29, TC = 73, and CC = 48) and (TT = 22, TC = 80, and CC = 48) in case and control

Table 1 Primer sequences and enzyme digestion were used in PCR–RFLP method

Gene polymorphism	Primer sequences	PCR product (bp)	Enzyme digestion	Lengths fragments
Has-mir196a-2-F	5′-CCCTTCCCTTCTCCTCCAGATA-3′	149	Hpy188I	C allele: 125 bp, 24 bp
Has-mir196a-2-R	5′-CGAAAACCGACTGATGTAACTCAG-3′			T allele: 149 bp
Has-mir499-F	5′-CAAAGTCTTCACTTCCCTGCCA-3′	146	BclI	C allele: 146
Has-mir499-R	5′-GATGTTTAACTCCTCTCCACGTGATC-3′			T allele: 122, 24

groups, respectively. Similarly, the findings did not revealed a significant difference between both groups ($p = 0.527$).

In our survey, we have analysed the genotype frequencies in the tree genetically inheritance models such as co-dominant, dominant and recessive in case and control groups. In dominant model, the T/T + TC/CC genotype frequencies showed a significant association between *has-miR-499* (rs3746444 T>C) gene polymorphism with the risk of PCa ($p = 0.027$; OR 1.780; 95% CI 1.030–3.113). In addition, our findings disclosed a borderline association between the allele frequencies in *has-miR-499* (rs3746444 T>C) across two groups ($p = 0.060$; OR 1.631; 95% CI 0.987–1.877). The genotype frequencies of *has-miR-499* (rs3746444 T>C) gene polymorphism C/C + CT/TT did not show a statistically significant association with the risk of PCa ($p = 0.356$; OR 1.260; 95% CI 0.732–2.307). Of note, in homozygous co-dominant (CC vs. TT) genotype frequencies showed a borderline association between *has-miR-499* (rs3746444 T>C) gene polymorphism with the risk of PCa ($p = 0.069$; OR 1.848; 95% CI 0.952–3.589) (Table 2).

Regarding the genotype and allele frequencies of *has-miR196a-2* (rs11614913 T>C), the findings did not reveal a statistically significant difference between both groups in three heredity models ($p > 0.05$) (Table 3). We have also analysed the correlation between the genotype frequencies for each polymorphism in case and control groups with demographic characteristics such as age, stage, Gleason score, the rate of cell growth and prostatic specific antigen (PSA). Our findings showed that *has-miR-499* (rs3746444 T>C) gene polymorphism was correlated with the stage

Table 2 Allele and genotype frequencies of *has-miR499* (rs3746444 T>C) in case and control subjects in three heredity models

Gene polymorphism	Case	Control	Total	OR[a]	CI 95%[b]		*p* Value[c]
	n = 150 (%)	*n* = 150 (%)	*n* = 300		Down	Up	
has-miR499 (rs3746444 T>C)							
Co-dominant							
T/T	29 (45%)	35 (55%)	64				
T/C	72 (46%)	83 (54%)	155	1.047	0.583	1.879	0.878
C/C	49 (60%)	32 (40%)	81	1.848	0.952	3.589	0.069
Recessive							
C/C	49 (51%)	32 (49%)	96	1.260	0.732	2.307	0.356
T/C + T/T	101 (44%)	118 (56%)	228				
Dominant				1.780	1.03	3.113	0.027
T/T	29 (45%)	35 (55%)	64				
T/C + C/C	121 (51%)	115 (49%)	236				
Allele frequency				1.361	0.987	1.877	0.060
T	130 (51%)	153 (49%)	283				
C	170 (49%)	147 (51%)	317				

Table 3 Allele and genotype frequencies of *has-miR196a-2* (rs11614913 T>C) in case and control subjects in three heredity models

Gene polymorphism	Case	Control	Total	OR[a]	CI 95%[b]		*p* Value[c]
	n = 150 (%)	*n* = 150 (%)	*n* = 300		Down	Up	
has-miR196a-2 (T>C rs11614913)							
Co-dominant							
T/T	29 (57%)	22 (43%)	51				
T/C	73 (48%)	80 (52%)	153	1.445	0.763	2.736	0.258
C/C	48 (50%)	48 (50%)	96	1.318	0.665	2.611	0.428
Recessive				1.000	0.616	1.624	1.000
C/C	48 (50%)	48 (50%)	96				
T/C + T/T	102 (50%)	102 (50%)	204				
Dominant				0.717	0.391	1.316	0.282
T/T	29 (57%)	22 (43%)	51				
T/C + C/C	121 (49%)	128 (51%)	249				
Allele frequency				0.909	0.657	1.256	0.563
T	131 (51%)	124 (49%)	255				
C	169 (49%)	176 (51%)	345				

($p=0.0001$), Gleason score ($p=0.0001$), the rate of cell growth ($p=0.016$) and PSA ($p=0.0001$). In addition, the results showed a significant association between *has-miR-196a-2* (rs11614913 T>C) gene polymorphism with the stage, Gleason score, and PSA ($p=0.0001$) of PCa patients (Table 4).

Discussion

The most common methods applied to cancer screening cannot reveal in the early stage, whereas identification of tumour miRNA released during the progressive of the disease in the bloodstream is an important marker in cancer diagnosis. miRNA by binding to the 3′-UTR of mRNA target leads to inhibit initiation translation or mRNA degradation [6]. Recently, miRNAs have proposed as therapeutic targets, diagnostic or prognostic biomarkers and screening tools in several disorders and malignancies [22, 23]. The effect of miRNA gene variations in cancerogenesis remains a controversial area. This study is an observational study that could open to new questions regarding the effect of miRNA variant on PCa development. In the present investigation, we analysed the possible effects of two SNPs *has-miR196a-2* and *has-miR-499* on PCa risk in patients of Iranian. Our findings revealed that *has-miR-499* (rs3746444 T>C) polymorphism significantly associated with the risk of PCa. Nevertheless, the findings did not show a positive association between *has-miR196a-2* (rs11614913 T>C) variant and PCa susceptibility. To date, a few investigations evaluated the roles of miRNA genes variants with the risk of PCa, which reported contradictory findings. Firstly, George et al. in the case–control investigation assessed the effects of SNPs at miRNA-binding sites in *has-miR196a-2* (rs11614913 T>C) and *has-miR-499* (rs3746444 T>C) genes, which may play important roles in PCa susceptibility in the population of North India [24]. The results revealed that the PCa patients with heterozygous genotype significantly increased the risk of progression PCa. Similar to our findings, the results supported that rs3746444 heterozygotes increased the risk of PCa.

In addition, Hashemi et al. evaluated the impact of rs3746444 and rs11614913 genetic variants on PCa risk in the Iranian population. The result showed that homozygous co-dominant (CC vs. TT) of rs3746444 increased the risk of PCa [25].

In a case–control investigation, Nikolic et al. evaluated the association between *has-miR-499* (rs3746444 T>C) gene polymorphism with the risk of PCa in the Caucasian population. The finding was adverse with our study and previously reported. They did not show a significant association between rs3746444 with the risk of PCa. On the other hand, findings supported that the presence of rs3746444 G allele confers reduced susceptibility to PCa developing [17]. The explanations for discrepancy findings [17, 24, 25] may be due to the differences in genetic backgrounds, sample size, geographical location, different ethnicity, and race and criteria sample selection.

In a meta-analysis study, Yan et al. analysed the association between *has-miR-499* (rs3746444) and *has-miR196a-2* (rs11614913) and the risk of cancer

Table 4 Correlation between the *has-miR499* T>C and *has-miR196a2* C>T gene polymorphisms with the demographic and clinicopathological characteristics of PCa

Parameters	*N*	*has-miR499* T>C			*p* Value	*has-miR196a2* C>T			*p* Value
		TT (%)	TC (%)	CC (%)		CC (%)	CT (%)	TT (%)	
Age at diagnosis (years)					0.113				0.459
≤65	119	20 (17%)	62 (52%)	37 (31%)		22 (18%)	61 (52%)	36 (30)	
>65	31	9 (29%)	10 (32%)	12 (39%)		7 (22%)	12 (39%)	12 (39%)	
Gleason score					0.0001				0.0001
≤7	135	24 (18%)	68 (50%)	43 (32%)		26 (19%)	65 (50%)	44 (31%)	
>7	15	5 (33%)	4 (27%)	6 (40%)		3 (20%)	8 (53%)	4 (27%)	
Stage					0.0001				0.0001
PT1 + PT2	130	26 (20%)	62 (48%)	42 (32%)		25 (19%)	63 (49%)	42 (32%)	
PT3 + PT4	20	3 (15%)	10 (50%)	7 (35%)		4 (20%)	10 (50%)	6 (30%)	
Rate of cell growth					0.016				0.123
Ki-67	102	18 (18%)	43 (42%)	41 (40%)		24 (24%)	49 (48%)	29 (28%)	
S—shape	48	11 (23%)	29 (60%)	8 (17%)		5 (10%)	24 (50%)	19 (40%)	
PSA (ng/ml)					0.0001				0.0001
≤10	130	24 (18%)	64 (50%)	42 (32%)		26 (19%)	62 (47%)	42 (34%)	
>10	20	5 (25%)	8 (40%)	7 (35%)		3 (15%)	11 (55%)	6 (30%)	

development. The results revealed a significant association between rs3746444 variation and the risk of cancers such as breast cancer [26].

In addition, we decided to evaluate the association between *has-miR196a-2* (rs11614913) gene polymorphism with the risk of PCa. Our findings showed no association between rs11614913 variants and PCa risk in Iranian. Discrepancy findings have reported in the several investigations performed in North Indian [24], Iranian [25], Caucasian [17] and Japanese [27] populations.

George et al. revealed that the heterozygous genotype in *has-miR196a-2* (rs11614913) gene polymorphism confers increased risk of PCa progression [24]. Our findings and others, did not support a genetic association between rs11614913 variant and the risk of PCa progression [25].

In addition, similar to our findings, Nikolic et al. did not reveal a significant association between rs11614913 nucleotide change and PCa risk in the Caucasian population [17]. Nevertheless, the results of meta-analysis performed by Yan et al. indicated that the *has-miR196a-2* (rs11614913) gene polymorphism is significantly associated with a decreased risk of cancers including, colorectal, lung and gastric cancer, especially [26].

The presence of nucleotide variations in *the has-miR-196a2* gene leads to the effects on the maturation procedure. In addition, a point mutation in miRNA gene may play critical roles in cancerogenesis pathway including, cell proliferation, differentiation, apoptosis, migration and invasion.

Previous findings revealed that the single nucleotide polymorphism in *has-miR196a-2* (rs11614913) gene correlated with the susceptibility of several types of cancers such as, lung and breast cancer [28].

Regarding the *has-miR-499* (rs3746444 T>C) gene variants, the findings showed that this polymorphism was associated with the risks of several malignancies. According to the previous investigation, numerous miRNAs genes abnormally expressed in multiple carcinomas could be a significant impact on the cancerogenesis [29]. Investigations have been revealed that the *has-miR-499* (rs3746444 T>C) gene polymorphism can control the expression level of *SOX* gene. Due to the up-regulation of *SOX6* gene, the anti-apoptosis function of *has-miR-499* (rs3746444 T>C) can be reversed [30]. Deregulation of *SOX* gene leads to activation Wnt/β-catenin signalling pathway, which correlated with cancerogenesis. The rs3746444 variants may play a critical role in the tumour formation by *SOX* gene expression changes. In addition, the mate-analysis findings showed that the *has-miR-499* (rs3746444 T>C) gene polymorphism could be considered as a risk factor for malignancies, in breast cancer, especially [26].

Conclusion

Our findings supported that *hsa-miR-499* gene polymorphism significantly increases susceptibility to PCa and may be considered as a potential prognostic biomarker in PCa patients. In addition, the findings showed no correlation between *hsa-miR-196a2* gene polymorphism with susceptibility to PCa Iranian. However, more investigations with the large sample size needed to reveal the association between these polymorphisms and PCa risk in further.

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Compliance with ethical standards

Conflict of interest Ramin Nouri and Saeid Ghorbian declare that no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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