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Original Article

Association of Mir-149C/T (rs2292832) Polymorphism and Lung Carcinoma Occurrence in the Iranian Population: A Case-Control Study

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Abstract

Introduction: Lung carcinoma (LC) is a group of anomalies associated with abnormal respiratory cell divisions. Some studies reported the possible role of the miR-499 (rs3746444) polymorphism in LCs in various societies. In the current case-control study, we decided to investigate the role of miR-149C/T variant on LC occurrence in the Iranian population.

Materials and Methods: In this case-control study, a total of 172 subjects (72 LC patients and 100 control) were genotyped by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique, for this aim, 5 ml peripheral blood sample was obtained from each subject and the genomic DNA was extracted by the salting-out method. After genotyping and data collection, the frequency of alleles and genotypes were statistically analyzed (SPSS, v.20).

Results: Since the results showed, in the frequency of all types of genotypes (Dominant, Codominant, Over-dominant, and Recessive) and associated alleles (C and T) in miR149C/T no significant difference (p >0.05) was observed in comparison between the patient group and the control group.

Conclusions: According to the findings of this study there is no significant relation between the miR-499C/T (rs3746444) polymorphism and lung cancer occurrence and this polymorphism is not a significant risk factor for lung cancer in the Iranian population.

Keywords: Carcinoma, Lung, rs2292832, miR-149C/T, Polymorphism

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Introduction

Cancers are malignant masses which are occurred following gene mutations leading to uncontrollable cell proliferation. In this condition, the cell cycle repeats abnormally and the cellular checkpoints are completely inhibited. Malignant masses involve the associated tissue and, depending on the severity and metastasis ability, can potentially metastasize to nearby or even distant tissue.[1] Thus, clinical signs and symptoms appear. LC is reported as the second most common malignancy in humans.[2] Besides, it was reported that this type of cancer has a high rate of detection in Iranian population than other pathologies.[3] Globally, more than 18% of all cancer death are related to LC.[4] Pathologically, two types of LC are categorized; Non-small Cell Lung Carcinoma (NSCLC) and Small Cell Carcinoma (SCLC) with the prevalence of 85% and 15%, respectively.[5] The metastasis rate of SCLC is higher than NSCLC. Thus, evaluation of the genetic bases of this disease seems necessary for the treatment process. Single nucleotide polymorphisms (SNPs) are variable regions in DNA sequence with rare allele frequency (1%) in the population. According to the published papers, these regions have a considerable role in human diseases, especially in cancers.[6] miRNAs are small single-stranded RNA with a critical role in RNA silencing and post-transcriptional gene expression regulation. Almost half of the human miRNAs are detected in fragile DNA sites. Thus, the miRNAs deletion (with tumor-suppressing role) or increased level of miRNAs generation (with oncogenic property) can be detected genetically in many types of cancers. Articles have shown that insufficient regulation of miRNA expression is found in tumors.[7] Human miR-149 is located at the chromosomal region of 2q37.3, encoded by a single exon. Two isoforms of miR-149 are both predicted to target oncogene and tumor suppressor, leading to dual impacts of accelerator or suppressor. miR-149-5p participates mostly in ErbB pathway, insulin signaling pathway, MAPK signaling pathway, and chemokine signaling pathway, which are necessary for tumor growth, while miR-149-3p plays roles in the toll-like

receptor signaling pathway, T and B cell receptor signaling pathway, focal adhesion-pathway, vascular smooth muscle contraction-pathway and lysosome-pathway which also related closely to tumorigenesis and tumor progression.[8] According to the probable role of miR-149 in the occurrence of LC, and the lack of a case-control study in this regard, this study was designed to assess the association between miR-149C/T polymorphism and LC in Iranian society.

Materials and Methods

Sample Collection

In the present study, all sample collections were applied under the supervision of the Ethics Committee of the University (IR.BMSU.REC.1399.460). Written consents were obtained from all subjects and also, they had the right to leave the research at any stage. Between February 2020 to February 2021, all patients with primary respiratory diseases referred to the Baqiyatallah Hospital (Tehran, Iran) were enrolled in this project. All indices for definite diagnosis of LC were considered for all patients including bronchoscopy procedure, biopsy collection and histopathological assessments, CT scan and x-ray and PET scan evaluations. Besides, all patients with primary respiratory-associated complications were no LC diagnosis were considered the control group.[9] Finally, 72 LC patients (among 350 cases) along with 100 healthy individuals (among 430 people) were considered for case and control groups, respectively. In order to precise identification of possible intervening variables, the tumor grading was applied based on histopathological evaluations in three categories including: I (more resemble to normal cells with the slow rate of cell proliferation and no metastasis), II (more resemble to abnormal cells with a moderate rate of metastasis), and III (abnormal cells with the high rate of cell proliferation and metastasis).[10] Also, alcohol consumption, smoking, LC of family history, and treatment response were recorded.

Genotyping

Blood samples (5 ml/individual) were aspirated in Imam Khomeini Hospital's cancer center (Tehran, Iran). High-quality DNA content was extracted (DNA Extraction Kit, Roje Co.) from the aspirated blood samples (2 ml in EDTA, Cat No: 60-00-4, Merck, Germany) using the modified Salting-Out protocol of Mohammad Shokrzadeh and coworkers.[11] The quality of purified DNA was assessed using electrophoresis (2% agarose gel, Cat No: 9012-36-6, Merck, Germany) and, NanoDrop Spectrophotometer (Thermo Fisher Scientific, Inc., Wilmington, DE, USA) was hired for assessment of DNA concentration and purity. Then, the PCR-RFLP assay (PCR master mix, Cat No: 201289, SinaClon Co) was used for the evaluation of miR-149 polymorphism. According to Table 1, the amplification of miR-149 promoter region was conducted using PCR cycles (n = 35); Denaturation (95 ºC, 10 min and 95 ºC, 30 s), Annealing (62 ºC, 30 s), and Extension (72 ºC, 25 s).[12] Also, the PCR product was found using the restriction enzyme of PVUII (37 ºC, overnight) and staining by Gel Red DNA stain. The PVUII restriction enzyme affects the cleavage sites of *CAG|CTG* and provide two fragments of 194 bp and 60 bp following C>T transformation. Also, a single fragment with a length of 254 bp can be detected in wild genotypes.[13]

Table 1. Forward and Reverse Primers of miR-149 Gene

	Primers	Sequences	PCR product	Tm (ºC)	GC (%)
miR-149	Forward	AGATACGTCTTTTGGGGGCAAC	254 bp	60.88	50
	Reverse	CGTTATTGTCTGCCATTGGTGC		60.73	50

Statistical Analysis

Chi-square test (X2 test) was used to assess the significant level of frequencies among the genotypes and alleles in case and control groups. Also, the Odds ratio (OR) was analyzed within the 95% confidence interval (CI 95%) to determine the risk of LC following LC occurrence. All statistical analysis was conducted using SPSS Software (v.23, IBM Corp., Armonk, NY, USA), and a p-value<0.05 was considered statistically significant.[14]

Results

The mean age of LC patients (n = 72) and control individuals (n = 100) were 62.82 ± 3.2 and 63.44 ± 2.1 years, respectively. Among these, 61.11% and 38.89% of patients and 69% and 31% of healthy controls were male and female, respectively. BMI was detected at 23.7 ± 2.1 and 22.8 ± 1.9 in control and case individuals, respectively. As represented in Table 2, no significant (p >0.05) differences were detected in gender, age, BMI, alcohol consumption, and smoking among healthy and control individuals. The frequency of CC, TT, and CT genotypes in case samples were 2.56, 82.05, and 15.38% and in control individuals were 7.79, 76.62 and 15.58%, respectively. Also, the frequency of C and T alleles were 10.52, and 89.74% in the case and 15.58 and 84.41% in control, respectively. Statistical analysis in genotypes (p = 0.4177 and p = 0.6257 in codominant, p = 0.4208 in dominant, p = 0.6344 in recessive and p = 0.9999 in over-dominant) and alleles (p = 0.3173) among case and control groups represented no significant (p >0.05) differences. Thus, the OR of LC was not correlated with the C/T mutant (Table 3).

Table 2. Clinical Features of Individuals

Variables		Individuals		*p*-value
		Control Healthy (n = 100)	LC Patients (n = 72)	
Gender	Male	69 (69%)	44 (61.11%)	0.12
	Female	31 (31%)	28 (38.88%)	0.21
Age (year)		63.44 ± 2.1	62.82 ± 3.2	0.39
BMI		23.7 ± 2.1	22.8 ± 1.9	0.41
Histopathological grades	I	-	12	N/A
	II	-	32	N/A
	III	-	26	N/A
Metastasis	Yes	-	40	N/A
	No	-	32	N/A
Alcohol	Yes	23	19	0.52
	No	77	53	0.19
Smoking	Yes	43	52	0.43
	No	57	20	0.56
Family History	Yes	-	5	N/A
	No	-	67	N/A
Treatment Response	Yes	-	47	N/A
	No	-	26	N/A

N/A: Not Applicable; LC: Lung Carcinoma; BMI: Body Mass Index.

Table 3. Frequency of miR-149C/T Genotypes and Alleles along with OR in Healthy and LC Individuals

			Case N (%)	Control N (%)	OR (CI 95%)	*p*-value
miR-149C/T Genotypes	Codominant	CC	1 (2.56)	6 (7.79)	1	-
		TT	32 (82.05)	59 (76.62)	0.3073 (0.02604~2.068)	0.3912
		CT	6 (15.38)	12 (15.58)	0.3333 (0.02531~2.522)	0.7165
	Dominant	CC	1 (2.56)	6 (7.79)	1	-
		CT+TT	38 (97.43)	71 (92.20)	0.3114 (0.02650~2.057)	0.5132
	Recessive	CC+CT	7 (17.94)	18 (23.37)	1	-
		TT	32 (82.05)	59 (76.62)	0.717 (0.2828~1.953)	0.8124
	Over Dominant	TT+CC	33 (84.61)	65 (84.41)	1	-
		CT	6 (15.38)	12 (15.58)	1.015 (0.3380~3.003)	>0.9999
miR-149C/T Alleles		C	8 (10.25)	24 (15.58)	1	1
		T	70 (89.74)	130 (84.41)	0.619 (0.2796~1.415)	0.4168

OR: Odds Ratio; CI: Confidence Interval; LC: Lung Cancer

Discussion

LC is the consequence of the uncontrolled proliferation of cells derived from lung tissue. Checkpoints involved in the control of cell division are severely damaged in LC and as a result, the cell proliferation accelerates.[15] One of the causes of LC is gene mutations, especially in nucleotides. Thus, determination of the chromosomal location of mutation or detection of the type of nucleotide transformation can increase the genetic knowledge of cancers. The SNPs are single nucleotide polymorphisms which are resulted from nucleotide transformation. Various studies have approved the critical roles of these types of mutations in human diseases such as cancer. Since the direct relationship between SNPs and cancers are associated to the genetic basis, population, and country, thus SNP assessments can be conducted for each population with special geographic characteristics. miR-149C/T is a type of mutation involved in various kinds of cancers like prostate cancer, gastric cancer, thyroid carcinoma, and LC.[8] Thus, in this case-control study, the authors assessed the possible role of miR-149C/T mutant on LC occurrence in the Iranian population. RFLP assessments revealed a non-significant association between miR-149C/T mutation and LC in the Iranian population. The frequency of C allele in case and control individuals were 10.25% and 15.58%. Also, this factor was 89.74% and 84.41% in T alleles in case and control groups, respectively, which detected non-significant differences.

The physiological functions of microorganisms completely depend on the levels of gene expression. Besides, the studies showed that gene mutations are the considerable factor in human diseases and cancers. miRs are completely conserved gene which translates to single-stranded of non-coding RNA containing 19-24 nucleotides. miRs can potentially regulate gene expression through pairing with cellular content of mRNA in which these structures attach to the 30-UTR of mRNAs to inhibit the mRNA translation.[16] Thus, manipulation or induction of mutation in miRs can lead to various pathologies like progressive hearing loss (miR-96 mutation),[17] cataract (miR-184 mutation),[18] and skeletal-associated growth defects (miR-17~92).[19] miR mutation can damage the cellular arrest checkpoints,[20] increase the proliferation rate,[21] and induce cellular anti-apoptotic features.[22] In these situations, the formation of cancer is possible. miR-149 is known as a tumor suppressor and carcinogenesis in cells. The miR-149 hairpin produces miR-149-5p and miR-149-3p. Besides, both oncogenic and tumor suppressive roles have been reported for miR-149-5p.[23] In a study, it was stated that the miR-149 regulates metabolic pathways

through the AKT1/mTOR axis.[24] Ye and coworkers concluded that the miR-149 can inhibit the proliferation rate of medullary thyroid carcinoma cells.[25] Thus, following inhibition of miR-149 activity of mutation, the rate of cell growth can be accelerated. This finding was apposite to the results of the current study. Following assessment of the role of miR-149 in ovarian cancer, two studies with different findings were conducted. Manman Xu with emphasis on the chemotherapy resistance in the treatment of ovarian cancers, reported the role of miR-149 in this era. They reported that the miR-149 expression is markedly elevated in chemo-resistant ovarian cancer than a chemosensitive ovarian cancer and silencing of miR-149 can potentially enhance the chemosensitivity feature in ovarian cancer cells.[26] Conversely, Li et al. have shown a tumor suppressor role for miR-149-5p in ovarian cancer cells through targeting FOXM1.[27] Sun et al., reported the role of B3GNT3 in lung cancer, as the direct target of miR-149. Thus, it could be concluded that the down-regulation of miR-149 can be seen in LC.[28] This finding was not found parallel to the present study which reported no significant alteration of miR-149 in LC. Moreover, Hang Li and coworkers reported that the over-expression of HOTAIR can directly causes the miR-149 over-expression in LC patients. This over-expressed level of miR-149 can lead to the inhibition of LC proliferation through arrest in the G0/G1 cell cycle.[29] Lu Liu also approved the significant role of miR-149 in the HNF1A-AS1/miR-149-5p/Cdk6 pathway in NSCLC progression.[30] In the study of Zhi Zhou, the MIAT was detected as an oncogene in NSCLC pathology involved in the MIAT/miR-149/FOXM1 axis. They concluded that the miR-149 can be considered a biomarker or even therapeutic target for NSCLC remedy.[31] In contrast to our findings, Choupani and coworkers concluded that the miR-149 can modulate the risk of cancer.[32] In contrast to our findings, Fakhrezare et al. reported that miR-149 suppresses tumor cell proliferation, and the pre-mir-149 polymorphism affects the processing of miR-149, causing an alteration in the abundance of the miRNA mature form, which can regulate tumor progression and metastasis in breast cancer.[33] Kübra Yılmaz following assessment of 144 eligible subjects in a case-control study analyzing the miR-149C/T variant reported that the miR-149C/T has no considerable effects on the risk of oral squamous cell carcinoma in Turkish people.[34] This comprehensive finding was also approved by our investigation. The authors believed that according to the different findings of the role of miR-149 on the occurrence of LC, the vast investigation is strictly needed in other countries all over the world.

Conclusion

As the findings of this study showed, the miR-499C/T polymorphism was not associated with the occurrence of LC in the Iranian population. Thus, more comprehensive studies are needed to reveal the exact role of miR-149C/T in LC.

Authors' Contributions

MS designed the study, supervised the data collection, interpreted the results, and revised the manuscript. MT and MM conducted the data analysis, prepared the tables, and wrote the statistical analysis method and the results. MT and EK conducted the study, collected the data, and organized the data set. MT and MM assisted in protocol development and drafted the manuscript. All authors read and approved the final manuscript.

Ethical Approval

All assessments were conducted in accordance with ethical principles and under the supervision of the University's Ethics Committee (Ethic NO: IR.BMSU.REC.1399.460).

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

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