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ORIGINAL ARTICLE

Association of MicroRNA-146a rs2910164 Polymorphism and Lung Cancer in Iranian Population: A Case-Control Study

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ABSTRACT

Background: Lung cancer is the first cause of cancer deaths worldwide. Polymorphisms in microRNAs genes affect their structure and their attachment to target genes. The purpose of the present study was to investigate the association of miR-146a rs2910164 polymorphism with the risk of non-small cell lung cancer (NSCLC) in Iranian patients.

Methods: This case-control study was performed among 103 patients with lung cancer and 100 healthy controls. The genotyping of miR-146a rs2910164 polymorphism was assayed by polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) and a number of samples were sequenced for final approval.

Results: A significant association was found between rs2910164 polymorphism CG genotype and risk of lung cancer progression in dominant models (CG vs. GG: OR=1.855, CI=1.09-3.33, P=0.03). There was no association between the C allele and frequency of rs2910164C>G polymorphism and risk of lung cancer (C vs. G: OR=1.54, CI=0.97-2.44, P=0.08).

Conclusion: There was a significant association between miR-146a rs2910164 polymorphism and lung cancer in Iranian population. This polymorphism can be considered as a risk factor of non-small cell lung cancer.

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Introduction

Lung cancer is among the five top causes of cancer and cancer-related mortality worldwide; In Iran, lung cancer is the fifth most common cancer and the fourth most common cause of cancer-related death.[1] Non-small cell lung cancer (NSCLC) comprises more than 80% of all lung cancers and includes two main subgroups; adenocarcinoma and squamous cell carcinoma (SCC).[2] Tobacco smoking is the major risk factor and causative agent of lung cancer, while other factors including age, sex, environmental factors, genetic and epigenetic factors can also influence the risk of lung cancer.[3]

MicroRNAs (miRNAs) are a class of small non-coding RNAs, which can regulate the expression of different genes by binding to the 3'-untranslated regions (3'-UTR) of its target messenger RNAs (mRNA); thus, they can change the translation of target genes.[4] MiRNAs can regulate different biological processes such as development, differentiation, cell proliferation and apoptosis of the cells.[5] Recent studies show that more than 50% of miRNA genes are in cancer-related genomic regions of the human genome and thus miRNAs have important functions in the pathogenesis of human cancers.[6]

There are specific genotypes that significantly increase the risk of developing lung cancer[7] and several miRNA mutations associated with different human cancers including lung cancer,[7, 8] specifically NSCLC.[9, 10]

Polymorphism in miRNAs genes have direct effects on mRNAs structure and result in different functional consequences. The single nucleotide polymorphism (SNP) can affect miRNA function and influence the individual susceptibility to the emergence of the cancers.[11, 12] Recent

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evidence emphasizes on the importance of identifying new biomarkers in diagnosis and management of cancers, especially miRNAs, which have been identified as important regulators of tumor formation, progression, and metastasis.[13] Oncogenic miRNAs can act as oncogenes by targeting tumor suppressive miRNA or tumor suppressor genes (TSGs) and are involved in signal transduction pathways. However, it has been suggested that the origin of the dysregulated miRNA is different in various cancer cells.[3, 4, 13] Some studies have shown the role of mutations and/or SNPs within miRNA genes that alter the expression or second structure of miRNAs or target genes of miRNA and consequently modify the cancer risk.[12, 14]

In our previous case-control study, we found a significant association between rs712 polymorphism within let-7 microRNA-Binding site and lung cancer in the Iranian population.[14] MiR-146a gene (rs2910164), located in the second exon of LOC285628 gene on chromosome 5,[15, 16] can contribute to the occurrence and development of different tumors by disturbing cell invasion and migration.[17, 18] It has been suggested that G/C substitution polymorphism (rs2910164) in miR-146a gene causes an alteration from G:U to C:U mismatch in the miR-146a precursor and it reduces production of mature miR-146a.[3] The miR-146a rs2910164 polymorphism is associated with the risk of various cancers including lung cancer.[19, 20] According to the role of this polymorphism in miR-146a function, we decided to investigate the association between the rs2910164 and NSCLC susceptibility in Iranian population.

Materials and Methods

A total of 203 blood samples were used in this study, including 100 healthy as control and 103 as lung cancer group. The patients were referred to Baqiyatallah Hospital, Tehran during 2017-2018. The Controls group were selected from healthy individuals. Lung cancer of all patients was confirmed by two oncology experts in the hospital. The clinical data form, such as the individual's age, gender, and status of smoking and drinking and familial history of cancer was filled and signed by each participant and then about 5 mL peripheral blood was obtained from each individual and stored at -70°C until DNA extraction.

DNA Extraction and Genotyping

Genomic DNA was extracted from all blood samples using standard salting out method. The purity of the extracted DNA was determined by spectrophotometry (DU-640; Beckman) and the DNA was stored at -20 °C. PCR was performed using the following primers: forward 5′-GAGGGGTCTTTGCACCATCTC-3′ and reverse 5′-GTCTCCAGTCTTCCAAGCTCT-3′.

PCR reaction was performed with a mixture containing 50 ng genomic DNA, with 10 µM of both primers, 10 µl 2x PCR master mix and 5 µl deionized water. The PCR conditions were 95°C for 5 min, followed by 40 cycles of 30 sec at 95°C, 40 sec at 53° C, 5 min at 72°C and a final elongation step at 72°C for 10 min. Subsequently, a total 10 µl PCR product was digested using 0.2 µl (10U/µl) *sacI* restriction enzymes (Thermo Fisher, USA) for 16h at 37°C. The digested fragments were analyzed by electrophoresis on a 1% Agarose gel. The CC genotype showed two DNA bands at the positions of 122 bp and 25 bp, whereas the GG genotype showed a single band (144 bp), and the heterozygote samples showed four bands (144 bp, 122 bp and 25 bp). Finally ten random samples were directly sequenced by Sanger sequencing (Macrogen Inc. Korea) (Figure 1).

Statistical Analysis

The statistical analysis was carried out using SPSS software, version 20.0. In order to verify the Hardy–Weinberg equilibrium for microRNA-146a SNP, Chi-square and degree of Freedom tests were used. The genotype distribution and the genotype frequencies were analyzed by the chi square test. In this study, 3 statistical parameters including odd ratio (OR), confidence interval and P-value were calculated before and after adjustment.

Results

The mean age of the patients and control group was 61.79±10.22 and 63.93±9.88 years old, respectively.

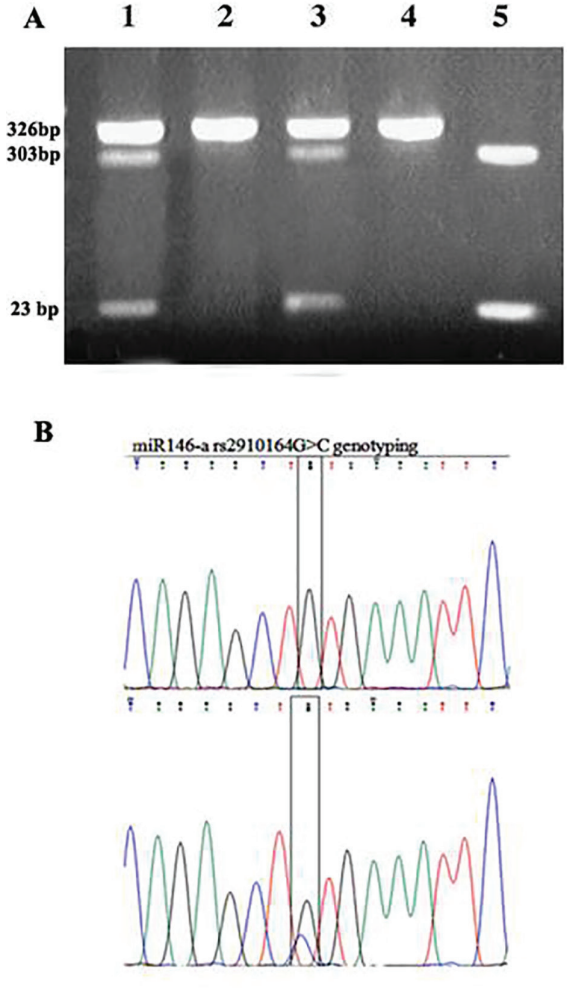


Figure 1: miR146-a rs2910164G>C polymorphism genotyping. A: gel electrophoresis of PCR-RFLP products. B: direct sequencing results. PCR-RFLP was used for rs11614913T>C genotyping and direct sequencing was used for validation of RFLP results.

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Demographic and clinical characteristics of the subjects are shown in Table 1. A total of 77.7 % of the patients were men. SCC and adenocarcinoma comprised 46.0% and 36.0% of the patients, respectively (Table 1).

Association between the rs2910164 and Lung Cancer

The results of the rs2910164 C>G genotype by PCR-RFLP and sequencing are shown in figure 1. The genotypes of miR196-a2 rs2910164 C>G for all patients and control are shown in Table 2. We did not find any sample with CC genotypes in the patients. There was a significant association between CG genotype of rs2910164 polymorphism and risk of lung cancer in codominant models (CG vs. GG: OR=1.855, CI=1.09-3.33, P=0.03). In addition, there was no significant association between the allelic frequencies of rs2910164C>G polymorphism and risk of lung cancer (C vs. G: OR=1.54, CI=0.97-2.44, P=0.08) (Table 2).

Discussion

In this case-control study, we evaluated the association between rs2910164 in miR-146a and lung cancer. Our findings suggested that the rs2910164 CG genotype was associated with increased risk of lung cancer. Previous studies have also focused on the role of this polymorphisms in cancers; review of 38 case-control studies in this regard showed that miR-146a rs2910164 polymorphism is associated with susceptibility to lung cancer and nasopharyngeal carcinoma.[21] The results of this review confirms that of the present study and emphasizes on the role of miR-146a rs2910164 polymorphism in lung cancer. Other studies have also confirmed the role of this polymorphism in lung cancer;[22, 23] however, some have suggested no association between miR-146a rs2910164 polymorphism and lung cancer.[24] This difference could be due to the difference in the distribution of C and G alleles of miR-146a rs2910164 in different races/ethnicities.[25]

Studying the role of C and G alleles of miR-146a rs2910164 polymorphism in different studies have proposed diverse results for the role of alleles in lung cancer.[22, 23] In our study, there were no patients with CC genotype in the case group and CG vs. GG resulted in 1.855-fold increase in the risk of lung cancer, but the allelic frequencies of rs2910164C>G polymorphism was not associated with the risk of lung cancer. These results confirm the important role of CG genotype in the risk of lung cancer. Similar to the results of our study, Jia and colleagues suggested that the miR-146a expression of CC subgroup was lower than CG/GG subgroup in patients with NSCLC in a sample of Chinese population.[22] Other studies have shown different roles for the C and G alleles in lung cancer. In the meta-analysis by Hao et al., CC vs. GG resulted in 1.275-fold increase, CC + CG vs. GG resulted in 1.166-fold increase, CC vs. CG + GG resulted in 1.239-fold increase, and C vs. G resulted in 1.151-fold increase in the chance of lung cancer.[21] In the study by Jeon et al., the authors compared the genotype of 1094 Korean patients with lung cancer with 1100 healthy subjects and showed that CC genotype of miR-

Table 1: Demographic characteristics of NSCLC patients and controls

Characteristic	Patient (n=103)	Control (n=100)	P value
Age (mean±SD)	61.79±10.22	63.93±9.88	0.13
Male* (%)	80(77.7)	52(52.0)	0.01
Female (%)	23 (??)	48 (??)	
NSCLC cancer-type (%)			
Adenocarcinoma	36(34.0)	-	
Squamous cells carcinoma	46(44.7)	-	
Large cells carcinoma	3(2.9)	-	
Other and unclassified carcinoma	18(17.5)	-	

Table 2: Frequency distributions of miR- 146-a alleles and genotypes among the groups

Genotype	Case (%) n=103	Control (%) n=100	OR	P value
Codominant				
GG	45 (56.3)	59 (56.0)	1.00	
GC	58 (43.7)	41 (44.0)	1.85 (1.09-3.33)	0.03
CC	0	---	---	
Dominant				
GG	45 (56.3)	59 (56.0)	1.00	
GC + CC	58 (43.7)	41 (44.0)	1.85 (1.09-3.33)	0.03
Recessive				
GG + GC	103 (100)	100 (100)	---	
CC	0	---	---	
Allele				
G	148 (71.5)	159 (79.5)	1.00	
C	58 (28.5)	41 (20.5)	1.54 (0.97-2.44)	0.08

*adjusted for gender and age

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146a rs2910164 polymorphism may contribute to genetic susceptibility to lung cancer, compared with CG and GG subtypes, which decreased the risk of lung cancer and the effect of rs2910164C>G genotype on lung cancer was more significant in nonsmokers.[23] The results of these studies show the wild nature of the homozygous subtype, CC,[22, 23] in line with the results of the studies by Yin et al., which showed that the CC subtype had a higher risk of lung cancer, compared to the heterozygous type, CG, and GG subtype, particularly in patients with adenocarcinoma type of lung cancer.[24, 25] In a recent meta-analysis on 3483 patients with lung cancer compared to 3578 healthy subjects, it has been shown that patients carrying CC genotype of miR-146a rs2910164 are at a 1.30-fold increased risk of lung cancer in comparison to those carrying GG genotype; therefore, they considered miR-146a rs2910164 C allele as a risk allele for lung cancer in Chinese population.[26] In our study, the association of C allele vs. G allele was not statistically significant, which can be due to the fact that we had no case of CC in our patients.

MiR-146a expression patterns are supposed to be correlated with the biological and clinical behavior of the tumor. In an Egyptian study by Mohamed et al., which showed the increased risk of lung cancer in patients carrying miR-146a rs2910164 CG and CC genotype, it has been suggested that the expression of miR-146a was lower in miR-146a CG and CC carriers than GG subtype.[27] The lower levels of miR-146a expression in CC genotype, compared to CG and GG genotypes, has been confirmed by other researchers, as well.[22] Similarly, Wu et al. suggested that the serum levels of miR-146a were significantly lower in patients with NSCLC than those in control group.[28] Nevertheless, in another study, miR-146a was overexpressed in patients with NSCLC compared with healthy subjects.[29] In terms of molecular function of miR-146a, numerous studies have reported that miR-146a acts as a tumor suppressor gene in NSCLC cell lines and inhibits cell growth and migration, induces cell apoptosis and inhibits epidermal growth factor receptor downstream signaling in NSCLC cell lines[30] Xu et al. reported that G allele of miR-146a increased the production of this miRNA in comparison with C allele in a cell model and thus suggested that miR-146a can cause cell proliferation and induce tumor formation.[31] Also, Jazdzewski and colleagues showed that rs2910164 Polymorphism can affect mRNA binding of the targets.[32] Accordingly, the different expression of miR-146a in different tumor types can be the underlying reason for the effect of C and G alleles in lung cancer. As in our study, the association between rs2910164 CG genotype and lung cancer,discovered in Iranian population, may be explained by the reduced expression of miR-2 in individuals with CG genotype, which suggests the role of miR-146a as a tumor suppressor microRNA. Therefore, we suppose that the reduced expression of miR-2 in individuals with CG genotype can intensify growth of tumoral cells and consequently increases the risk of cancer.

Conclusion

In conclusion, the current study showed a significant association between the miR-146a rs2910164 CG genotype and NSCLC in the Iranian population. According to the findings of this study, rs2910164 can functionally affect the miR-146a expression levels and can be considered as a risk factor of NSCLC. To the best of our knowledge, this is the first study to investigate the polymorphism of miR-2 and its association with lung cancer in Iranian population, which is of great significance, due to the role of ethnicity on this association. Future studies are suggested to confirm the findings of this study in different ethnical subgroups of patients with different tumor types.

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Conflict of Interest: None declared.

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