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ORIGINAL RESEARCH

miRNA-146a rs2910164 C>G polymorphism increased the risk of esophagogastric junction adenocarcinoma: a case–control study involving 2,740 participants

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Purpose: The miRNA-146a rs2910164 C>G polymorphism may contribute to the development of cancer. However, the association between this polymorphism and the risk of esophagogastric junction adenocarcinoma (EGJA) remains unclear. In the present study, we carried out a case–control study to explore the potential relationship between miRNA-146a rs2910164 C>G polymorphism and EGJA risk.

Patients and methods: In total, 1,063 EGJA patients and 1,677 cancer-free controls were enrolled. The SNPscan™ genotyping assay, a patented technology, was used to test the genotyping of miRNA-146a rs2910164 C>G polymorphism.

Results: We found that miRNA-146a rs2910164 C>G polymorphism was associated with a risk of developing EGJA (additive model: adjusted odds ratio (OR), 1.27; 95% CI, 1.07–1.51; P=0.006; homozygote model: adjusted OR, 1.31; 95% CI, 1.03–1.65; P=0.027 and dominant model: adjusted OR, 1.36; 95% CI, 1.15–1.60; P<0.001). After adjustment for the Bonferroni correction, these associations were also found in additive and dominant genetic models. In the subgroup analyses, after adjustment by sex, age, alcohol consumption, and smoking status, results of multiple logistic regression analysis indicated that miRNA-146a rs2910164 C>G polymorphism increased the risk of EGJA in males, females, <64 years old, ≥64 years old, never smoking, and never drinking subgroups.

Conclusion: The current study highlights that the miRNA-146a rs2910164 C>G polymorphism increased the risk of EGJA in eastern Chinese Han population.

Keywords: miRNA-146a, polymorphism, esophagogastric junction adenocarcinoma

Introduction

Gastric carcinoma (GC) is the second most commonly diagnosed cancer and the second leading cause of cancer-related death in China,[1] with an estimated 679,100 new GC cases and 498,000 related deaths in 2015.[1] The esophagogastric junction adenocarcinoma (EGJA) was proposed by Siewert in 1999 as a unique disease: EGJA is considered as a special clinical malignancy and its clinicopathologic characteristic and biologic behavior are quite different from that of GC. EGJA may be a multifactorial disease, which is caused by a number of potential susceptibility factors, involving genetic predisposition, overweight, obesity, and environmental factors (eg, foods preserved by salting, smoking, drinking, and so on). The incidence and prevalence of EGJA are increasing worldwide in recent decades,[2–4] most likely as a result of increases in the prevalence of overweight/obesity and of chronic gastroesophageal reflux disease.[5] The

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increase may also be related to the decreasing prevalence of *Helicobacter pylori* infection, which may be a protective factor for EGJA.[6] Although these mentioned factors may contribute to the etiology of EGJA, hereditary factors may also influence the incidence of EGJA. As malignancy-related deaths can be decreased by controlling susceptibility factors, early diagnosis, and more effective treatment, the identification of new biomarkers may be beneficial for early detection and prevention of EGJA.

MicroRNAs (miRNAs) are a series of single-stranded noncoding-RNA molecule (including about 22 nucleotides), which are found in plants, animals, and some viruses.[7] In general, miRNAs are similar to the small-interfering RNAs. The functions of miRNAs are RNA-silencing and suppression of translation.[8] Previous studies suggested that miRNAs were implicated in a number of complex biologic processes (eg, cell differentiation, development, apoptosis, proliferation, and so on).[9–12] Accumulating evidence demonstrates that the expression of many vital genes may be regulated by miRNAs.[13–15] It was reported that most of the miRNAs acted on cancer-related genomic areas, and this might contribute to oncogenesis.[16] Recently, Shin and Chu reported that miRNAs might act as important biomarkers and therapeutic targets of GC.[17]

Single-nucleotide polymorphisms (SNPs) are a common genetic variation that occurs at a certain position in the genome. SNPs occur more frequently in noncoding regions than in coding regions. Results of previous investigations indicated that SNPs may influence susceptibility to human diseases. SNPs in miRNAs could influence both their expression and function,[18] which might, therefore, alter the risk of cancer.[19,20] In addition, several case–control studies and functional investigations reported that miRNA SNPs could affect GC susceptibility and their influence was closely related to their role in miRNAs' expression.[21,22] Although there are some case–control studies indicating that the rs2910164 C>G polymorphism in miRNA-146a could influence the risk for gastric cancer,[23–25] the association between this polymorphism and the risk of EGJA remains unclear. To shed some light on this issue, we enrolled 2,740 participants to investigate the potential relationship between the miRNA-146a rs2910164 C>G polymorphism and EGJA susceptibility.

Materials and methods

Subjects

This hospital-based case–control study consisted of 280 EGJA patients who were consecutively recruited between January 2014 and May 2016 from the Affiliated Union Hospital and the Affiliated Cancer Hospital of Fujian Medical University. An additional 783 EGJA patients were consecutively recruited from the Affiliated People's Hospital of Jiangsu University from January 2008 to November 2016. The EGJA patients were enrolled without any restriction of age. We have defined EGJA as tumors that have their center within 5 cm proximal and distal of the anatomical cardia.[26] Siewert type I EGJA has its center within 1–5 cm proximal of the anatomical cardia. In addition, Siewert type II and III EGJA have their center within 1 cm proximal and 2 cm distal, and 2–5 cm distal of the anatomical cardia, respectively. In the present study, all Siewert type II EGJA cases were diagnosed by gastroscope and during surgery. All of the cases were recruited before their operation and pathologically confirmed. Those EGJA cases who received chemotherapy or radiotherapy or had a history of other malignancy were excluded. For comparison, 1,677 cancer-free subjects matched with the EGJA cases were recruited as controls. All subjects were unrelated. Each participant answered a questionnaire by face-to-face interview. Experienced doctors collected the useful information on demographic variables and risk factors. The related data are listed in Table 1. A written informed consent was signed by each participant. This study protocol was in accordance with the Declaration of Helsinki and approved by the ethics committee of Jiangsu University (Zhenjiang, China) and Fujian Medical University (Fuzhou, China). In this study, each participant donated a blood sample, which was anticoagulated with EDTA.

Selection of SNPs

To determine the potential relationship between miRNA SNPs and EGJA risk, we selected the miRNA-146a rs2910164 C>G polymorphism according to the literature, which was significantly associated with cancer,[27,28] type 2 diabetes,[29,30] autoimmune diseases,[31–33] and coronary artery disease[34,35] in some studies. The corresponding information about the miRNA-146a rs2910164 C>G polymorphism is presented in Table 2.

DNA extraction and genotyping

Genomic DNA was extracted from the peripheral blood samples collected in EDTA test tubes using a DNA Purification Kit (Promega, Madison, WI, USA). SNPscan™ genotyping assay (Genesky Biotechnologies Inc., Shanghai, China) was used to analyze the genotyping of miRNA-146a rs2910164

Table 1 Distribution of selected demographic variables and risk factors in esophagogastric junction adenocarcinoma cases and controls

Variable	Overall cases (n=1,063)		Overall controls (n=1,677)		*P*-value[a]
	n	%	n	%	
Age, mean (±SD)	64.19 (±8.63)		63.91 (±10.22)		0.451
Age (years)					
<64	494	46.47	825	49.19	0.165
≥64	569	53.53	852	50.81	
Sex					
Male	759	71.40	1194	71.20	0.909
Female	304	28.60	483	28.80	
Smoking status					
Never	773	72.72	1323	78.89	**<0.001**
Ever	290	27.28	354	21.11	
Alcohol use					
Never	908	85.42	1507	89.86	**<0.001**
Ever	155	14.58	170	10.14	
Lymph node status					
Positive	625	58.80			
Negative	438	41.20			
Tumor–node–metastasis stage					
I+II	305	28.69			
III+IV	758	71.31			

Notes: [a]Two-sided chi-square and Student's *t*-test. Bold values are statistically significant ($P<0.05$).

Table 2 Primary information for hsa-mir-146a rs2910164 C>G polymorphism

Genotyped polymorphism	hsa-mir-146a rs2910164 C>G
Chr	5
Position_37	160485411
Region	nc transcript variant
MAF for Chinese in database	0.43
MAF in our controls (n=1,677)	0.38
P-value for HWE test in our controls	0.919
% Genotyping value	99.09

Abbreviations: Chr, chromosome; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; nc, noncoding.

C>G polymorphism. In brief, a 150 ng DNA sample was heated to 98°C and held for 5 minutes. The ligation reaction was carried out in an ABI 2720 thermal cycler. Then, a 48-plex fluorescence polymerase chain reaction (PCR) was conducted. In an ABI 3730XL sequencer, capillary electrophoresis was harnessed to analyze the PCR products. GeneMapper 4.1 software (Applied Biosystems, Foster City, CA, USA) was used to read the information of the genotype. For quality control, different technicians genotyped 4% of the genomic DNA samples that were randomly selected. And, the results were in full accord with the findings of the first assays.

Statistical analysis

The distribution of age was expressed as the mean ± SD. The age difference between EGJA patients and cancer-free controls was evaluated by using the Student's *t*-test. Differences in the distributions of age, sex, smoking and drinking status, and frequencies of miRNA-146a rs2910164 C>G genotype between EGJA cases and controls were assessed using the χ^2-test (for categorical variables). We used an online calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) to assess Hardy–Weinberg equilibrium (HWE) in controls. The relationship between the miRNA-146a rs2910164 C>G polymorphism and susceptibility to EGJA was estimated by calculating crude and adjusted odds ratios (ORs) and 95% CIs. Adjustments were performed by age, sex, and smoking and drinking status using a multiple logistic regression model. A *P*-value <0.05 (two sided) was accepted as statistically significant. All analyses were conducted with the software SAS 9.4 (SAS Institute, Cary, NC, USA). The Power and Sample Size Calculator (http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize)[36] was harnessed to obtain the power value (α=0.05). We used a Bonferroni correction to adjust for multiple testing.[37,38]

Results

Baseline characteristics

A total of 2,740 individuals were enrolled for the present case–control study; out of those, 1,677 subjects were healthy participants (controls), and their mean age was 63.91±10.22 years (Table 1). Similarly, for the 1,063 EGJA patients, the mean age at diagnosis was 64.19±8.63 (Table 1). This study was fully matched by age and sex (P=0.451 and 0.909, respectively). The minor allelic frequency distribution of miRNA-146a rs2910164 C>G is 0.38 (Table 2). The success rate of genotyping was 99.09%. Genotype distribution of the miRNA-146a rs2910164 C>G polymorphism is shown in Table 3. The frequencies of miRNA-146a rs2910164 CC, CG, and GG were 38.47%, 47.07%, and 14.52% in control subjects compared to 31.41%, 52.16%, and 16.43% in EGJA patients, respectively. We found that the frequencies of the miRNA-146a rs2910164 CG, GG, and G allele were slightly higher in the EGJA cases than in the control group (52.16% vs 47.07%, 16.43% vs 14.52%, and 42.51%

Table 3 The frequencies of miRNA-146a rs2910164 C>G polymorphisms in EGJA patients and controls

Genotype	Overall EGJA cases (n=1,063)		Overall controls (n=1,677)	
	n	%	n	%
CC	327	31.41	644	38.47
CG	543	52.16	787	47.07
GG	171	16.43	243	14.52
CG+GG	714	68.59	1,030	61.53
CC+CG	870	83.57	1,431	85.48
GG	171	16.43	243	14.52
G allele	885	42.51	1,273	38.02

Abbreviation: EGJA, esophagogastric junction adenocarcinoma.

vs 38.02%, respectively). The *P*-value of HWE in controls was 0.919 (Table 2).

Association of miRNA-146a rs2910164 C>G polymorphism with EGJA

When compared to the frequency of the miRNA-146a rs2910164 CC genotype, the miRNA-146a rs2910164 CG genotype was associated with the risk of EGJA (crude OR=1.28; 95% CI, 1.08–1.52; *P*=0.005). When the miRNA-146a rs2910164 CC genotype was used as reference, there was a significant difference in the frequency of the miRNA-146a rs2910164 GG genotype between EGJA cases and cancer-free controls (*P*=0.027). When compared to the miRNA-146a rs2910164 CC genotype, the frequency of the miRNA-146a rs2910164 CG/GG genotype also associated with a significantly increased risk of EGJA (*P*<0.001). After adjustments for age, sex, smoking, and drinking, an increased risk of EGJA was also found in these genetic models (CG vs CC: *P*=0.006; GG vs CC: *P*=0.027; and GG/CG vs CC: *P*<0.001, Table 4). After adjustments for multiple comparisons (Bonferroni correction), the association of the miRNA-146a rs2910164 C>G polymorphism with EGJA risk was also found in additive and dominant genetic models.

For the miRNA-146a rs2910164 C>G polymorphism, the power value was 0.808 in the additive model, 0.604 in the homozygote model, and 0.960 in the dominant model.

Association of miRNA-146a rs2910164 C>G polymorphism with EGJA in different subgroups

In the subgroup analyses, the genotype frequencies of the miRNA-146a rs2910164 C>G polymorphism in different sex, age, alcohol consumption, and smoking subgroups are summarized in Table 5. After adjustment by sex, age, alcohol consumption, and smoking status, results of multiple logistic regression analysis indicated that the miRNA-146a rs2910164 C>G polymorphism increased risk of EGJA in several subgroups (male group: CG vs CC: *P*=0.012 and CG/GG vs CC: *P*=0.002; female group: CG/GG vs CC: *P*=0.040; <64 years subgroup: CG vs CC: *P*=0.009 and CG/GG vs CC: *P*=0.001; ≥64 years subgroup: CG/GG vs CC: *P*=0.042; never smoking group: CG vs CC: *P*=0.004 and CG/GG vs CC: *P*<0.001 and never drinking group: CG vs CC: *P*=0.009 and CG/GG vs CC: *P*<0.001 [Table 5]).

Association of miRNA-146a rs2910164 C>G polymorphism with lymph node status in EGJA patients

We found no statistically significant difference in genotype distribution of the miRNA-146a rs2910164 C>G polymorphism with different lymph node status (Table 6).

Discussion

As the miRNA SNPs potentially affect the miRNA biogenesis and change the target selection,[39] people have paid more attention to the relationship of miRNA polymorphisms with risk of cancer. To the best of our knowledge, this case–control study is the largest sample size used to determine the association between the miRNA-146a rs2910164 C>G polymorphism and risk of EGJA.

Table 4 miRNA-146a rs2910164 C>G polymorphism with esophagogastric junction adenocarcinoma

Genotype	Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value
Additive model	**1.28 (1.08–1.52)**	**0.005**	**1.27 (1.07–1.51)**	**0.006**
Homozygote model	**1.31 (1.03–1.65)**	**0.027**	**1.31 (1.03–1.65)**	**0.027**
Dominant model	**1.37 (1.16–1.61)**	**<0.001**	**1.36 (1.15–1.60)**	**<0.001**
Recessive model	1.16 (0.94–1.43)	0.178	1.16 (0.94–1.44)	0.166

Notes: [a]Adjusted for age, sex, smoking status, and alcohol use in a logistic regression model. Bold values are statistically significant (*P*<0.05).
Abbreviation: OR, odds ratio.

Table 5 Stratified analyses between miRNA-146a rs2910164 C>G polymorphism and EGJA risk by sex, age, smoking status, and alcohol consumption

Variable	miRNA-146a rs2910164 C>G (case/control)[a]			Adjusted OR[b] (95% CI); *P*-value				
	CC	CG	GG	CC	CG	GG	CG/GG	GG vs (CG/CC)
Sex								
Male	235/458	396/566	115/167	1.00	**1.30 (1.06–1.59); *P*: 0.012**	1.29 (0.97–1.71); *P*: 0.082	**1.36 (1.12–1.65); *P*: 0.002**	1.13 (0.87–1.46); *P*: 0.363
Female	92/186	147/221	56/76	1.00	1.23 (0.89–1.69); *P*: 0.215	1.35 (0.88–2.06); *P*: 0.171	**1.39 (1.02–1.89); *P*: 0.040**	1.25 (0.85–1.83); *P*: 0.263
Age								
<64	153/335	256/374	73/114	1.00	**1.39 (1.09–1.79); *P*: 0.009**	1.32 (0.93–1.88); *P*: 0.121	**1.48 (1.16–1.88); *P*: 0.001**	1.12 (0.81–1.55); *P*: 0.481
≥64	174/309	287/413	98/129	1.00	1.18 (0.93–1.49); *P*: 0.176	1.28 (0.93–1.76); *P*: 0.136	**1.27 (1.01–1.59); *P*: 0.042**	1.18 (0.89–1.58); *P*: 0.250
Smoking status								
Never	228/506	398/614	128/201	1.00	**1.33 (1.09–1.63); *P*: 0.004**	1.30 (0.99–1.70); *P*: 0.058	**1.43 (1.18–1.73); *P*<0.001**	1.13 (0.89–1.44); *P*: 0.325
Ever	99/138	145/173	43/42	1.00	1.09 (0.77–1.53); *P*: 0.638	1.37 (0.83–2.27); *P*: 0.221	1.16 (0.83–1.62); *P*: 0.376	1.32 (0.83–2.10); *P*: 0.247
Alcohol consumption								
Never	282/585	461/697	144/223	1.00	**1.28 (1.06–1.53); *P*: 0.009**	1.24 (0.96–1.59); *P*: 0.097	**1.36 (1.14–1.62); *P*<0.001**	1.11 (0.88–1.39); *P*: 0.392
Ever	45/59	82/90	27/20	1.00	1.11 (0.67–1.85); *P*: 0.680	1.72 (0.84–3.54); *P*: 0.142	1.22 (0.75–1.99); *P*: 0.425	1.61 (0.84–3.08); *P*: 0.151

Notes: [a]For miRNA-146a rs2910164 C>G, the genotyping was successful in 1,063 (97.93%) EGJA cases and 1,677 (99.82%) controls; [b]Adjusted for multiple comparisons (age, sex, smoking status, and alcohol consumption [besides stratified factors accordingly]) in a logistic regression model. Bold values are statistically significant (*P*<0.05).
Abbreviations: EGJA, esophagogastric junction adenocarcinoma; OR, odds ratio.

Table 6 Logistic regression analyses of association between miRNA-146a rs2910164 C>G polymorphism and lymph node status in EGJA patients

Genotype	Positive (n=625)		Negative (n=438)		Crude OR (95% CI)	*P*-value	Adjusted OR[a] (95% CI)	*P*-value
	n	%	n	%				
miRNA-146a rs2910164 C>G								
CC	185	30.18	142	33.18	1.00		1.00	
CG	327	53.34	216	50.47	1.17 (0.89–1.53)	0.264	1.16 (0.88–1.52)	0.299
GG	101	16.48	70	16.36	1.11 (0.77–1.61)	0.571	1.10 (0.76–1.60)	0.613
CG+GG	428	69.82	286	66.82	1.15 (0.88–1.50)	0.305	1.14 (0.87–1.48)	0.352
CC+CG	512	83.52	358	83.64	1.00		1.00	
GG	101	16.48	70	16.36	1.01 (0.72–1.41)	0.959	1.01 (0.72–1.41)	0.975
G allele	529	43.15	356	41.59				

Notes: [a]Adjusted for age, sex, alcohol use, and smoking status.
Abbreviations: EGJA, esophagogastric junction adenocarcinoma; OR, odds ratio.

In our study, it was established that the miRNA-146a rs2910164 C>G polymorphism significantly increased the risk of EGJA in overall comparison. Furthermore, in the subgroup analyses, results of multiple logistic regression analysis suggested that the miRNA-146a rs2910164 C>G polymorphism increased the risk of EGJA in male, female, <64 years, ≥64 years, never smoking, and never drinking subgroups. With the promoting application of gene-related studies,[40–42] it is highly encouraged to assess the association between the miRNA-146a rs2910164 C>G polymorphism and cancer risk to obtain robust and replicable results. Considering the fact that most of the genetic variants usually have a low or moderate influence on future cancer susceptibility, this case–control study emphasizes the necessity of related large sample sizes to obtain a sufficiently precise estimate between the miRNA-146a rs2910164 C>G variants and the

development of EGJA. Recently, a number of case–control investigations focused on the relationship of the rs2910164 C>G variants with cancer risk. Subsequently, several quantitative assessment studies have reported positive signals of the miRNA-146a rs2910164 C>G polymorphism with cancer risk.[43,44] In addition, several meta-analyses indicated that the miRNA-146a rs2910164 C>G polymorphism also increased the risk of GC.[45–48] However, the association between this polymorphism and the risk of EGJA remains controversial. Xia et al reported that the miRNA-146a rs2910164 C>G polymorphism was not correlated with the development of gastric cardia adenocarcinoma,[49] while Okubo et al found it associated with increased risk of upper third anatomic locations GC.[50] Considering that only two case–control studies with related small sample sizes focusing on the relationship of this SNP with risk of EGJA, the results are still obscure. We recruited 2,740 participants to determine the potential relationship between the miRNA-146a rs2910164 C>G polymorphism and EGJA susceptibility. And we found that the C>G polymorphism increased the risk of overall EGJA susceptibility, which was very similar to the previous studies in Asians.[23,51,52] However, the observed results should be interpreted with caution. An evident variation in allele frequency of the miRNA-146a rs2910164 G has been identified across different populations, ranging from 0.362 in Asians to 0.774 in Caucasians.[53] In the future, more case–control studies with larger sample sizes and detailed gene–environment factors should be performed to confirm or refute these associations.

Some limitations in our study must be acknowledged. Firstly, in this study, only the miRNA-146a rs2910164 C>G polymorphism was included for exploring the association between this SNP and EGJA risk, and other SNP loci in the miRNA gene were not considered. Secondly, because of lack of sufficient EGJA samples, a replication study was not conducted. Thirdly, the relationship of the miRNA-146a rs2910164 C>G polymorphism with cancer subtypes or tumor stages was not analyzed. These limitations might decrease the validity of results because some potential susceptibility factors were not well considered. Finally, for the controls enrolled in local hospitals, they might not fully represent the whole Chinese population, and these possible biases may result in spurious findings.

In summary, the current study identifies the association between the miRNA-146a rs2910164 C>G polymorphism and EGJA risk in the eastern Chinese Han population. We have provided evidence for a potential cancer biomarker for EGJA early detection in the Chinese Han population and potentially for other countries. Well-designed case–control studies are needed to validate these primary findings and explore the potential interaction of gene–gene and gene–environment factors involved in miRNA-146a rs2910164 C>G polymorphism and EGJA.

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Disclosure

The authors report no conflicts of interest in this work.

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