

Quantitative assessment of pre-miR-218 rs11134527 polymorphism and cancer risk in Chinese population

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Background: Accumulated studies have evaluated the association of pre-miR-218 rs11134527 polymorphism with cancer risk in Chinese population. However, the results remain controversial.

Methods: To derive a more precise and more comprehensive estimation of the relationship, six studies focused on Chinese population were included for the pooled analysis for pre-miR-218 rs11134527 polymorphism using odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Pre-miR-218 rs11134527 polymorphism was associated with cancer risk (G versus A, OR = 0.93, 95% CI: 0.88–0.98; GG versus AG + AA, OR = 0.88, 95% CI: 0.79–0.97; GG versus AA, OR = 0.85, 95% CI: 0.76–0.96). In the stratified analysis by cancer type, the pre-miR-218 rs11134527 polymorphism was only associated with the risk of cervical cancer (G versus A, OR = 0.90, 95% CI: 0.83–0.98; GG versus AG + AA, OR = 0.80, 95% CI: 0.68–0.94; GG versus AA, OR = 0.79, 95% CI: 0.66–0.94).

Conclusion: These findings suggest that the pre-miR-218 rs11134527 genetic polymorphism may decrease the susceptibility to cervical cancer, which needs to be verified or linked with functional studies.

Keywords: single-nucleotide polymorphisms, meta-analysis, polymorphism, cancer, risk

Introduction

MicroRNAs (miRNAs) are a highly conserved family of small, noncoding RNA species. In mammals, mature miRNAs are generated from primary miRNAs (pri-miRNAs) and precursor miRNAs (pre-miRNAs) via sequential processing by Drosha and Dicer and negatively regulate the expression of tumor suppressor genes and oncogenes via RNA interference. Therefore, miRNAs play an important role in various biological processes, including cell differentiation, proliferation, apoptosis, and metastasis.^{1,2} Recently, several studies have shown that miR-218 is downregulated in various types of cancer, including glioma, bladder cancer, lung cancer, and oral cancer.^{3–6} The overexpression of miR-218 in cancer cells markedly suppresses invasion and proliferation and promotes apoptosis.^{6–8}

Single-nucleotide polymorphism (SNP) is the most abundant form of DNA variation in the human genome. Common polymorphisms in miRNA genes, including pri-miRNAs, pre-miRNAs, and mature miRNAs, may alter various biological processes by influencing the processing and/or target selection of miRNAs.⁹ A potential functional SNP (rs11134527, A > G) of the putative promoter region of pre-miR-218 has been identified, and many studies from People's Republic of China have explored the association between rs11134527 polymorphism and susceptibility

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to cancer, including esophageal squamous cell carcinoma, hepatocellular carcinoma, and cervical cancer.^{10–15} However, the results of these observations remain controversial and inconclusive. In the present study, we conducted a meta-analysis to derive a more precise and more comprehensive estimation of the associations.

Materials and methods

Publication search

We performed a publication search in the PubMed, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases (up to March 27, 2015) with the following search terms: “pre-miR-218” or “rs11134527”; “cancer” or “carcinoma”; “genetic variation” or “polymorphism”. Hand-searches were also performed to identify additional articles in the reference lists of included articles not retrieved by initial electronic search. All of the selected studies met the following criteria: 1) case-control study; 2) concerned the association between pre-miR-218 rs11134527 polymorphism and cancer risk in Chinese population; and 3) available genotype frequency.

Data extraction and quality assessment

Information was carefully reviewed and independently extracted from all the eligible articles by two investigators. The following items were collected: first author's name, year of publication, country of origin, genotyping method, source of the control groups (population- or hospital-based), total number of cases and controls, genotype distributions in the cases and controls, and *P*-value for Hardy–Weinberg equilibrium (HWE). If discrepancies and differences existed after data collection, discussion was carried out to get consensus.

Statistical analysis

HWE in the controls was measured via chi-square test. The recessive model (GG versus GA + AA), dominant model (GG + GA versus AA), codominant model (GG versus AA, GA versus AA), and allelic model (G versus A) were used to assess the association between pre-miR-218 rs11134527 polymorphism and cancer risk in Chinese population. The strength of the association between the pre-miR-218 rs11134527 polymorphism and cancer risk in Chinese population was assessed using odds ratios (ORs) and 95% confidence intervals (CIs). The significance of the pooled OR was determined using the *z*-test and $P_z < 0.05$ was considered statistically significant. Chi-square-based *Q* statistic and *I*² statistic were conducted to evaluate heterogeneity between studies. If $P_Q < 0.05$ or $I^2 > 50\%$, the random-effects model was used to calculate the pooled OR. Otherwise, the fixed-effects model was selected. In order to evaluate the influence of each study on the overall estimate, we carried out sensitivity analysis by sequentially removing individual studies. Finally, the potential publication bias was tested by funnel plot. All analyses were performed in RevMan 5.0 software. All the tests were two-sided, and the significance level was less than 0.05.

Results

Study selection and characteristics

Through the systematic literature search, six eligible studies containing 11,024 subjects (5,376 cancers cases and 5,648 controls) on the association between pre-miR-218 rs11134527 polymorphism and cancer risk in Chinese population are included in the present meta-analysis. The characteristics of each case-control study are summarized in Table 1. There were two case-control studies of esophageal

Table 1 General characteristics of studies included in the meta-analysis

Authors	Year	Country	Cancer type	Source of controls	Detection	Sample size (cases/controls)	Cases			Controls			HWE
							AA	AG	GG	AA	AG	GG	
Zhang et al ¹²	2014	People's Republic of China	ESCC	Population	SNaPshot	1,109/1,275	396	529	184	454	630	191	0.25
Jiang et al ¹⁰	2014	People's Republic of China	ESCC	Hospital	PCR-LDR	706/745	273	344	89	268	348	129	0.38
Han et al ¹¹	2014	People's Republic of China	HCC	Hospital	qPCR	1,009/1,011	372	470	167	336	493	182	0.96
Shi et al ¹³	2013	People's Republic of China	Cervical cancer	Hospital	TaqMan	1,565/1,391	588	752	225	512	638	241	0.08
Zhang et al ¹⁴	2012	People's Republic of China	HCC	Hospital	PCR-RFLP	302/513	88	170	44	165	269	79	0.07
Zhou et al ¹⁵	2010	People's Republic of China	Cervical cancer	Hospital	PCR-RFLP	685/713	268	316	101	247	339	127	0.57

Abbreviations: ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; HWE, Hardy–Weinberg equilibrium; PCR, polymerase chain reaction; PCR-LDR, PCR–ligase detection reaction; PCR-RFLP, PCR–restriction fragment length polymorphism; qPCR, quantitative PCR.

Table 2 Meta-analysis of the pre-miR-218 rs11134527 polymorphism and cancer risk among Chinese population

Variables	Allelic model (G versus A)				Dominant model (GG + GA versus AA)				Recessive model (GG versus AG + AA)			
	I^2	P_{het}	P_z	OR (95% CI)	I^2	P_{het}	P_z	OR (95% CI)	I^2	P_{het}	P_z	OR (95% CI)
All	29%	0.22	0.01	0.93 (0.88–0.98)	0%	0.42	0.08	0.93 (0.86–1.01)	45%	0.11	0.01	0.88 (0.79–0.97)
Cancer type												
ESCC	73%	0.05	0.55	0.95 (0.79–1.14)	0%	0.42	0.49	0.95 (0.84–1.09)	86%	<0.01	0.64	0.89 (0.55–1.44)
Cervical cancer	0%	0.39	0.02	0.90 (0.83–0.98)	29%	0.23	0.18	0.92 (0.81–1.04)	0%	0.98	<0.01	0.80 (0.68–0.94)
HCC	34%	0.22	0.24	0.94 (0.84–1.04)	63%	0.10	0.81	0.97 (0.72–1.29)	0%	0.88	0.36	0.91 (0.75–1.11)
	Codominant model (GG versus AA)				Codominant model (GA versus AA)							
All	39%	0.14	<0.01	0.85 (0.76–0.96)	0%	0.49	0.34	0.96 (0.88–1.04)				
Cancer type												
ESCC	83%	0.02	0.58	0.87 (0.54–1.41)	0%	0.96	0.62	0.97 (0.84–1.11)				
Cervical cancer	0%	0.59	<0.01	0.79 (0.66–0.94)	35%	0.21	0.64	0.97 (0.85–1.10)				
HCC	0%	0.38	0.25	0.88 (0.70–1.10)	64%	0.10	0.91	0.98 (0.72–1.34)				

Abbreviations: CI, confidence interval; ESCC, esophageal squamous cell carcinoma; HCC, hepatocellular carcinoma; OR, odds ratio; het, heterogeneity.

squamous cell carcinoma, two of hepatocellular carcinoma, and two of cervical cancer. The genotype frequencies for the control group were all consistent with HWE in the included studies.

The pooled analysis

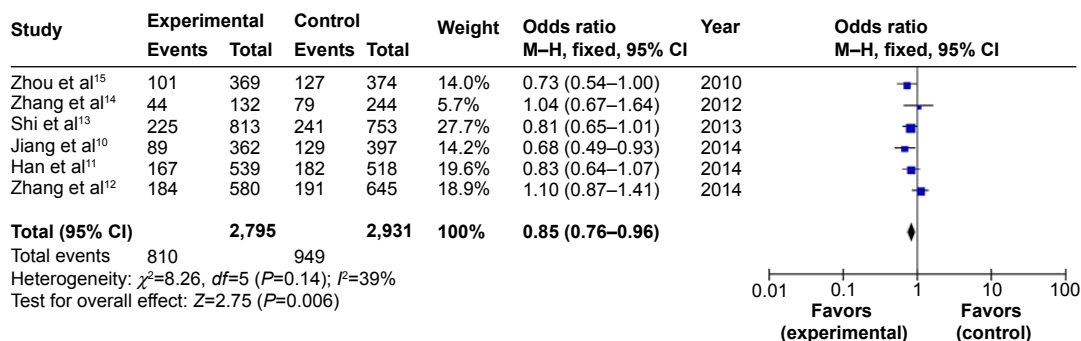
The main results of pooled ORs for pre-miR-218 rs11134527 polymorphism and cancer risk in Chinese population are listed in Table 2. Overall, the pooled OR showed significant associations under the allelic model (G versus A, OR=0.93, 95% CI: 0.88–0.98), recessive model (GG versus AG + AA, OR=0.88, 95% CI: 0.79–0.97), and codominant model (GG versus AA, OR=0.85, 95% CI: 0.76–0.96) (Figure 1). In the stratified analysis by cancer type, the pre-miR-218 rs11134527 polymorphism was only associated with the risk of cervical cancer (G versus A, OR=0.90, 95% CI: 0.83–0.98; GG versus AG + AA, OR=0.80, 95% CI: 0.68–0.94; GG versus AA, OR=0.79, 95% CI: 0.66–0.94).

Sensitivity analysis and publication bias

Sensitivity analysis was performed to evaluate the stability of the results by removing one study at a time. We found that the estimated pooled ORs changed quite little, indicating that our results were statistically robust. Funnel plots were used to assess publication bias. As shown in Figure 2, the shapes of the funnel plots seemed symmetrical, suggesting the absence of publication bias.

Discussion

Genetic testing for cancer susceptibility has become a standard component of clinical practice over the last few years. Increasing evidence suggests that some SNPs play vital roles in the development of cancer.^{16,17} Some studies indicated that a potential functional SNP (rs11134527) in tumor-suppressive miR-218 was associated with the risk of cancer in Chinese population.^{10,11,13,15} In contrast, others showed that miR-218 rs11134527 polymorphism was not associated with cancer risk in Chinese population.^{12,14} Considering that

**Figure 1** Forest plot of the association between pre-miR-218 rs11134527 polymorphism and cancer risk under GG versus AA.

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel test.

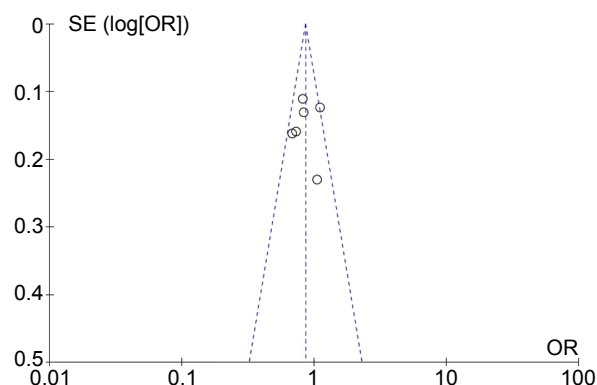


Figure 2 Funnel plot of the association between pre-miR-218 rs11134527 polymorphism and cancer risk under GG versus AA.

Abbreviations: OR, odds ratio; SE, standard error.

previous studies from single centers and with small sample sizes may lack enough statistical power to assess the associations, we performed the meta-analysis with larger sample sizes. Results showed miR-218 rs11134527 polymorphism was associated with cancer risk in Chinese population. Furthermore, the stratified analysis based on cancer type suggested that pre-miR-218 rs11134527 polymorphism was only associated with the risk of cervical cancer.

There were some limitations in the current meta-analysis. First, these results are based on unadjusted estimates due to lack of original data from the eligible studies. In addition, only six studies were included in this meta-analysis. Thus, more studies are needed to identify this association more comprehensively.

Conclusion

A significant association was found between the miR-218 rs11134527 polymorphism and cervical cancer risk in Chinese population. However, large-scale case-control and population-based studies involving potential gene–gene and gene–environment interactions are warranted to confirm our findings.

Disclosure

The authors report no conflicts of interest in this work.

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