

RESEARCH ARTICLE

Association Between the Pre-mir-218 Polymorphism and Cancer Risk in the Chinese Population: a Meta-Analysis

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Abstract

Background: Several recent studies have explored associations between pre-mir-218 polymorphism (rs11134527) and cancer risk. However, published data are still inconclusive. To obtain a more precise estimation of the relationship in the Chinese population, we carried out a meta-analysis for the first time. **Materials and Methods:** Through retrieval from the PubMed, Medline, Embase, Web of Science databases, China National Knowledge Infrastructure and the Chinese BioMedical Literature Database, a total of four studies were analyzed with 3,561 cases and 3,628 controls for SNP pre-mir-218 rs11134527. We calculated odds ratios (ORs) and 95% confidence intervals (95% CIs) to explore the strength of associations. **Results:** The results showed that the rs11134527 polymorphism was associated with decreased cancer risk in GG versus AA and GG versus AA+AG models tested (GG vs AA: OR=0.82, 95% CI: 0.71-0.94; GG vs AA+AG: OR=0.84, 95% CI: 0.74-0.96), and significantly decreased cervical cancer risk was observed in GG versus AA and GG versus AA+AG models (GG vs AA: OR=0.79, 95% CI: 0.66-0.94; GG vs AA+AG: OR=0.80, 95% CI: 0.68-0.94). However, no significant association between the rs11134527 polymorphism and hepatocellular carcinoma risk was observed in all comparison models tested (AG vs AA: OR=0.94, 95% CI: 0.79-1.11; GG vs AA: OR=0.88, 95% CI: 0.70-1.10; GG+AG vs AA: OR=0.92, 95% CI: 0.79-1.08; GG vs AA+AG: OR=0.91, 95% CI: 0.75-1.11). **Conclusion:** The findings suggest that pre-miR-218 rs11134527 polymorphism may have some relation to cancer development in Chinese. However, well-designed studies with larger sample size and more detailed data are needed to confirm these conclusions.

Keywords: pre-miR-218 rs11134527 - meta-analysis - cervical cancer - hepatocellular carcinoma

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Introduction

MicroRNAs (miRNAs, miRs) are short non-coding, single-stranded RNAs of 18-25 nucleotides and were identified post transcriptional regulators of gene expression by base pairing with target mRNAs at the 3'-untranslated regions (3'UTR), leading to mRNA degradation or translational repression (Bartel, 2004; He et al., 2009). It has been showed that miRNAs are involved in many biological processes such as cell proliferation, differentiation, migration and apoptosis, etc (Anglicheau et al., 2010; Kutanzi et al., 2011). Most miRNA located at cancer associated genomic regions or fragile sites, aberrant expression of miRNAs play critical roles in carcinogenesis (Esquela-Kerscher et al., 2006). Single nucleotide polymorphism (SNP) which located in the pre-miRNA, may result in functional changes of miRNA by interfering interaction between miRNAs and their target mRNAs (Link et al., 2008; Chen et al., 2012), thus, leading to gene expression disorder and diseases.

However, the role of genetic variants in miRNAs on cancer susceptibility remains largely unclear. The link between genetic variants in miRNAs and cancer was highlighted by many researchers. Wang et al. (2012) found that hsa-mir-27a rs895819 may play an important role in breast cancer development. Zhang et al. (2013) reported the association of mir-499 rs3746444 polymorphism and mir-149 rs2292832 polymorphism with cancer risk in the Chinese population and found that rs3746444 GG genotype is associated with increased cancer risk, especially liver cancer, while the rs2292832 polymorphism showed no association with cancer risk in Chinese. An important SNP in the pre-miR-218 with a A to G change (rs11134527) was identified. Many studies have studied the role of this SNP in cancer risk (Zhou et al., 2010; Zhang et al., 2012; Han et al., 2013; Shi et al., 2013), but their results are conflicting rather than conclusive. Therefore, we conducted a meta-analysis of the studies to derive a more precise estimation of the association between pre-miR-218 rs11134527 polymorphism and cancer risk in the Chinese population.

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Materials and Methods

Publication Search

To identify published studies on the association of pre-miR-218 rs11134527 polymorphism with cancer risk, using the searching terms with the following terms: (“rs11134527” or “pre-miR-218” or “miR-218” or “microRNA218”) and (“cancer” or “tumor” or “carcinoma”)AND (“SNP” or “mutation” or “variation” or “polymorphism”), we searched the PubMed, Medline, Embase, Web of Science databases, China National Knowledge Infrastructure and the Chinese BioMedical Literature Database without language, publication, or date restrictions. For overlapping papers, only the first published one was selected. A total of 4 published papers matching the eligible criteria listed below were included in this analysis. All the steps were operated shown in Figure 1.

Inclusion criteria

All studies in the current meta-analysis met the following criteria: (1) evaluation of the pre-miR-218 rs11134527 polymorphism and cancer risk; (2) case-control study; (3) the diagnosis of cancer patients was confirmed pathologically and controls were confirmed as free from cancer; (4) sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs); (5) published on the journal; (6) fulfilling Hardy-Weinberg equilibrium (HWE) in the control group ($P > 0.05$ was eligible).

Data extraction

Data was extracted independently by two reviewers (Gao Y and Ran LK) and consensus were reached on every item. If they could not come to an agreement, a third investigator (Zeng F) adjudicated the disagreements. The final eligible articles selected for further meta-analysis. Data collected from these articles included the first author’s name, publication time, study country origin, ethnicity, genotyping method, type of cancer, number of cases and controls, genotype frequencies for cases and controls, HWE of controls, Characteristics of the enrolled studies were assigned in the structured form (Table 1).

Statistical analysis

Based on the genotype frequencies in cases and controls, OR and 95%CI were calculated to assess the strength of association between the pre-miR-218 rs11134527 polymorphism and cancer risk. We investigated the associations of the SNP and cancer susceptibility with different genetic models: dominant model (GG/AG versus AA), recessive model (GG versus AG/AA), homozygote model (GG versus AA) and heterozygote

model (AG versus AA), respectively. Subgroup analyses were performed by cancer type.

The statistical significance of the pooled OR was checked with the Z test, and $p < 0.05$ being considered significant. The heterogeneity among studies was evaluated by the Chi-square based Q statistical test (Higgins et al., 2002). When the heterogeneity was absent ($p > 0.10$), the pooled OR was estimated by the fixed-effects model (the Mantel-Haenszel method) (Mantel et al., 1959). otherwise, the random-effects model (the DerSimonian and Laird method) was employed (DerSimonian et al., 1986). All statistical analyses were performed with Review Manager Software 5.0 (Cochrane Collaboration, Oxford, UK).

Results

Study characteristics

A total of 45 articles were retrieved in the PubMed, Medline, Embase and Web of Science databases, After screening abstract, 15 studies were excluded and 30 were selected and evaluated in detail. 20 of those 30 studies were excluded according to the inclusion criteria. Finally, 4 articles were included with 3, 561 cases and 3, 628 controls in the meta-analysis (Zhou et al., 2010; Zhang et al., 2012; Han et al., 2013; Shi et al., 2013). The main Characteristics of studies were presented in Table 1. All of the studies were from Chinese population. Several genotyping methods were employed, including fluorescent-probe real-time quantitative PCR (Han et al., 2013), Taqman assay (Shi et al., 2013) and polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) (Zhou et al., 2010; Zhang et al., 2012). Among these studies, there were two studies related to cervical cancer (Zhou et al., 2010; Shi et al., 2013),

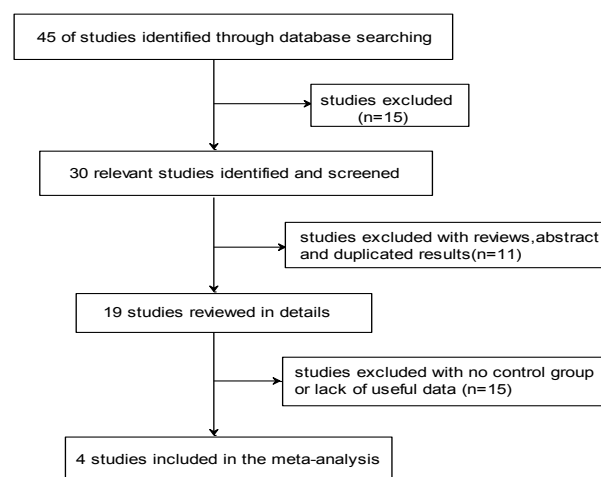


Figure 1. Flow Chart of Studies and Specific Reasons for Exclusion from the Meta-Analysis

Table 1. Characteristics of Studies in the Meta-analysis

Author (Year)	country	Ethnicity	Genotyping	Cancer type	Sample method		Cases (n)			controls (n)			HWE (p)
					Cases	Controls	AA	AG	GG	AA	AG	GG	
zhou Xiaoyi (2010)	china	Asian	PCR-RFLP	cervical cancer	685	713	268	316	101	247	339	127	$p=0.568$
Shi Tingyan (2013)	china	Asian	Taqman	cervical cancer	1565	1391	588	752	225	512	638	241	$p=0.083$
Zhang Lushun (2012)	china	Asian	PCR-RFLP	HCC	302	513	88	170	44	165	269	79	$p=0.07$
Han Yifang (2013)	china	Asian	qPCR	HCC	1009	1011	372	470	167	336	493	182	$p=0.96$

Table 2. Stratification Analyses of Genetic Susceptibility to Cancer Risk

		Test of association			Test of heterogeneity		I ² (%)
		OR (95%CI)	Z	p-value	χ^2	p value	
Total	AGvs.AA	0.96 (0.86, 1.06)	0.83	0.41	4.41	0.22	32
	GGvs.AA	0.82 (0.71, 0.94)	2.79	0.005	1.61	0.66	0
	GG/AGvs.AA	0.92 (0.84, 1.01)	1.68	0.09	4.12	0.25	27
	GGvs.AA/AG	0.84 (0.74, 0.96)	2.66	0.008	0.99	0.8	0
Cervical cancer	AGvs.AA	0.97 (0.85, 1.10)	0.46	0.64	1.55	0.21	35
	GGvs.AA	0.79 (0.66, 0.94)	2.65	0.008	0.28	0.59	0
	GG/AGvs.AA	0.92 (0.81, 1.04)	1.34	0.18	1.41	0.23	29
	GGvs.AA/AG	0.80 (0.68, 0.94)	2.69	0.007	0	0.98	0
HCC	AGvs.AA	0.94 (0.79, 1.11)	0.76	0.45	2.77	0.1	64
	GGvs.AA	0.88 (0.70, 1.10)	1.15	0.25	0.76	0.38	0
	GG/AGvs.AA	0.92 (0.79, 1.08)	1.01	0.31	2.71	0.1	63
	GGvs.AA/AG	0.91 (0.75, 1.11)	0.92	0.36	0.03	0.87	0

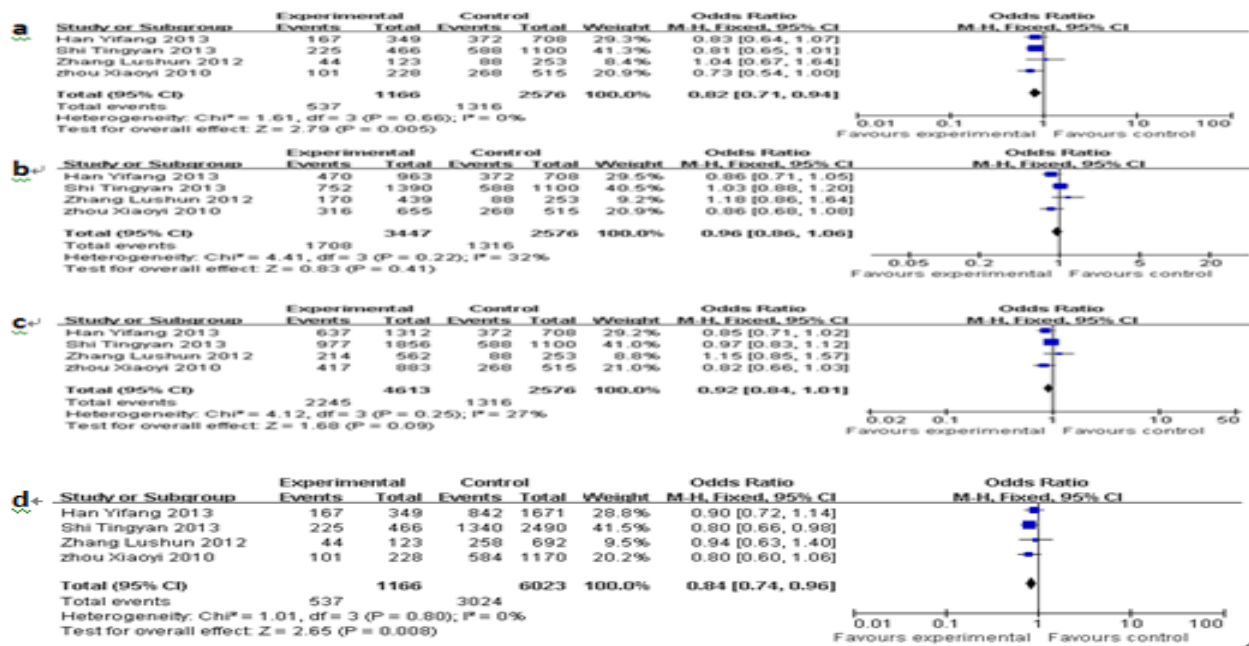


Figure 2. Overall Meta-analysis of pre-miR-218 rs11134527. A) AG versus AA; B) GG versus AA; C) GG/AG versus AA; D) GG versus AA/AG

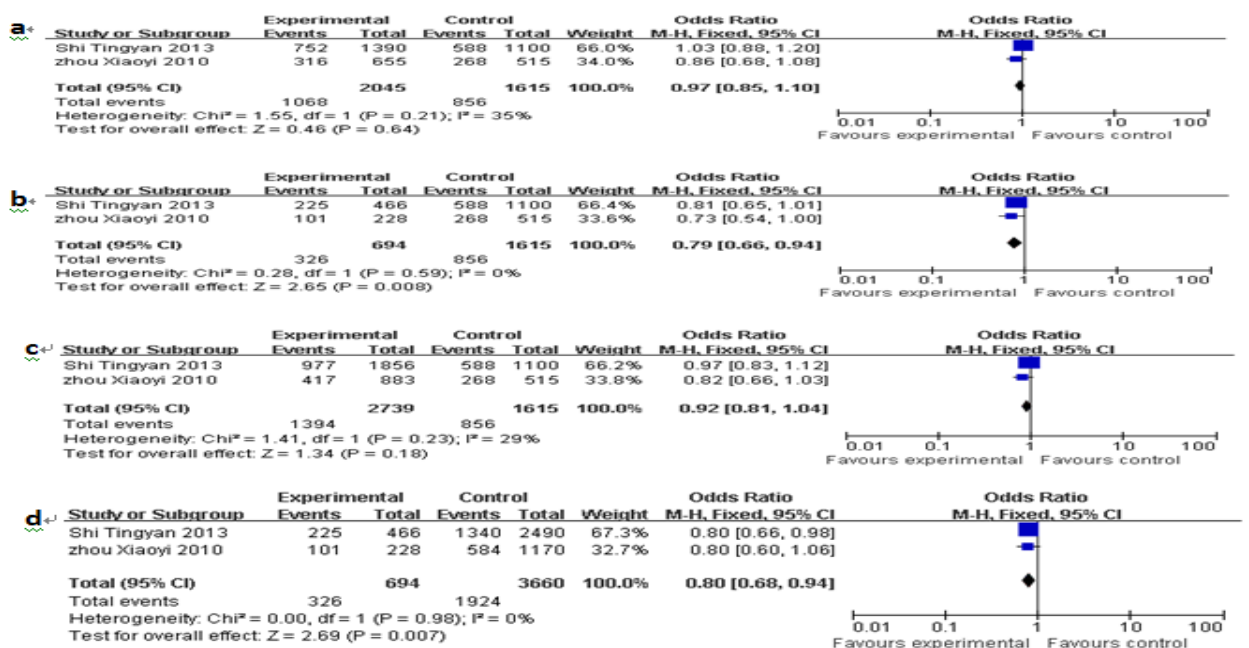


Figure 3. Subgroup Analysis of pre-miR-218 rs11134527 in Cervical Cancer. A) AG versus AA; B) GG versus AA; C) GG/AG versus AA; D) GG versus AA/AG

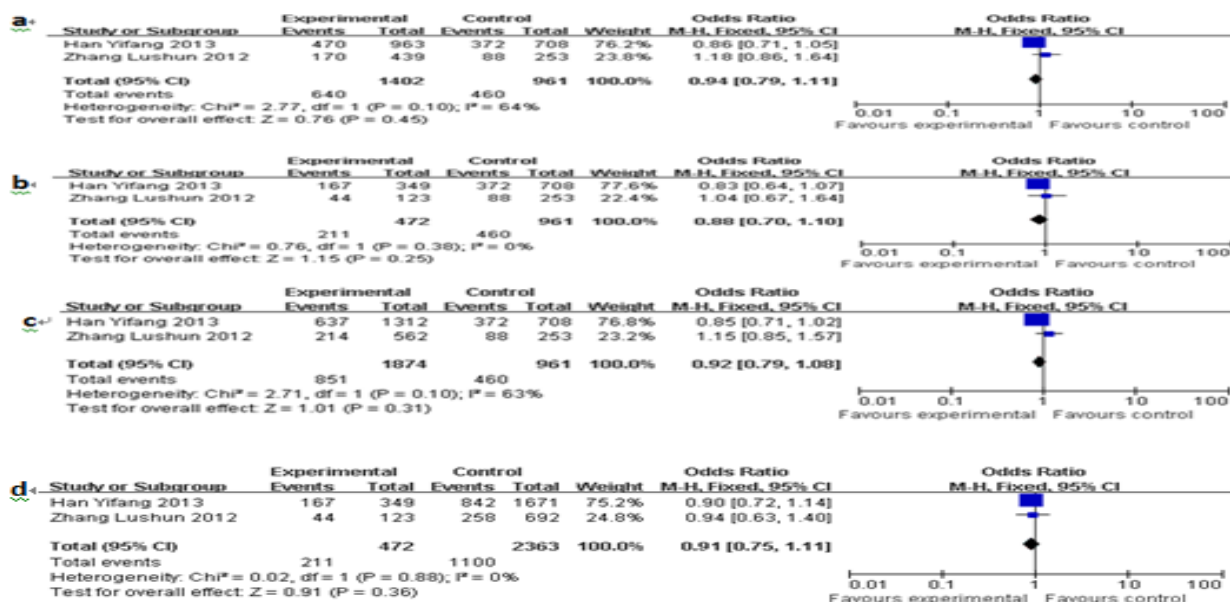


Figure 4. Subgroup Analysis of pre-miR-218 rs11134527 in HCC. A): AG versus AA; B): GG versus AA; C): GG/AG versus AA; D):GG versus AA/AG

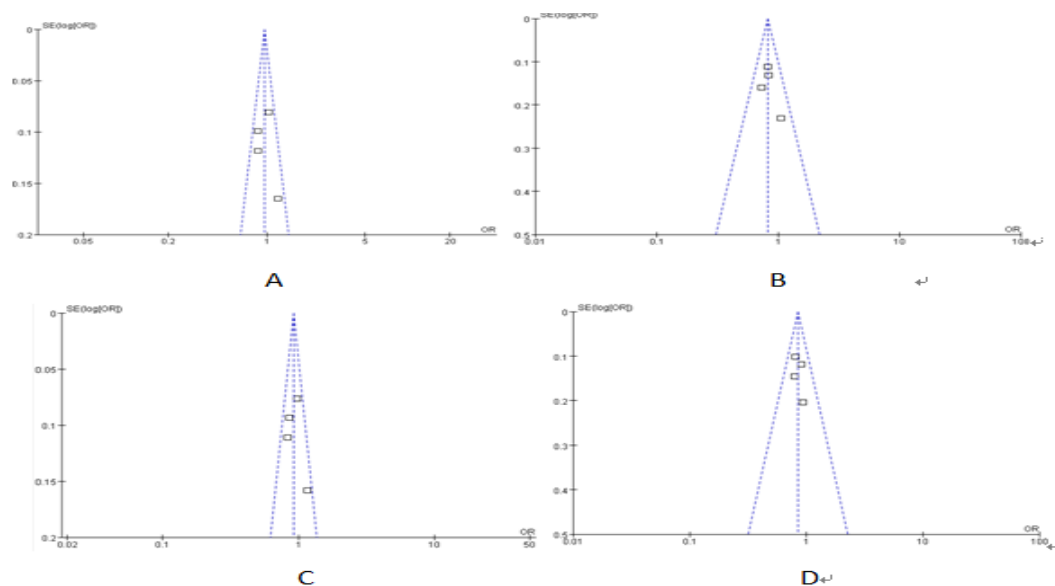


Figure 5. Funnel Plot for Publication Bias Test. Each circle denotes an independent study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line stands for mean effect size. **A)**: AG versus AA; **B)**: GG versus AA; **C)**: GG/AG versus AA; **D)**:GG versus AA/AG

two studies related to hepatocellular carcinoma (HCC) (Zhang et al., 2012; Han et al., 2013). The distribution of genotypes in the controls of all studies was in agreement with the HWE .

Main results

The association between pre-miR-218 rs11134527 polymorphism and cancer risk was analyzed in 4 studies with 3, 561 cases and 3, 628 controls. The main results of this meta-analysis are shown in table 2. Q-test was carried out in all of the genetic models and showed no significant heterogeneity. Therefore, fixed-effects model was applied to analyze the association.

When all the eligible articles were pooled into this meta-analysis. we observed that pre-miR-218 rs11134527 polymorphism had some relationship with decreased cancer risk in GG versus AG/AA and GG versus AA models tested (GG vs AG/AA: OR=0.84, 95%CI: 0.74-

0.96; GG vs AA: OR=0.82, 95%CI: 0.71-0.94; AG vs AA: OR=0.96, 95%CI: 0.86-1.06; GG/AG vs AA: OR=0.92, 95%CI: 0.84-1.01) (Table 2, Figure 2).

In the subgroup analyses, significantly decreased risk was also found in cervical cancer in GG versus AG/AA and GG versus AA model tested (AG vs AA: OR=0.97, 95%CI: 0.85-1.10; GG vs AA: OR=0.79, 95%CI: 0.66-0.94; GG/AG vs AA: OR=0.92, 95%CI: 0.81-1.04; GG vs AG/AA: OR=0.80, 95%CI: 0.68-0.94). (Table 2, Figure 3). However, no significant association between pre-miR-218 rs11134527 polymorphism and HCC risk was observed in all genetic models. (AG vs AA: OR=0.94, 95%CI: 0.79-1.11; GG vs AA: OR=0.88, 95%CI: 0.70-1.10; GG/AG vs AA: OR=0.92, 95%CI: 0.79-1.08; GG vs AG/AA: OR=0.91, 95%CI: 0.75-1.11) (Table 2, Figure 4).

Publication bias

We used Funnel plot and to access the publication bias

of the literature. Symmetrical funnel plots were obtained in the SNP tested in all of the models. (Figure 5).

Discussion

Mounting evidences showed that miRNAs was involved in the initiation and development of various types of cancers (Esquela-Kerscher et al., 2006; Tran et al., 2010). MiRNAs, which can function either as tumor suppressors or oncogenes play an important role in human cancers. Previous studies demonstrated that MiR-218 functions as a tumor suppressor in some cancers. For example, miR-218 expression was reduced significantly in gastric cancer, colon, prostate, and pancreatic cancer (Volinia et al., 2006; Petrocca et al., 2008). Wu et al reported that miR-218 was decreased in glioma, lung cancer, bladder cancer and oral cancer (Wu et al., 2010). In gastric cancer, the low expression level of miR-218 was also correlated with tumor stage, LN metastasis and poor prognosis (Tie et al., 2010). Recent studies showed that miR-218, exhibited its tumor suppressing activity through regulating target genes such as ROBO1 (Tie et al., 2010), BIRC5 (Alajez et al., 2011), LAMB3 (Martinez et al., 2011) and RICTOR (Uesugi et al., 2008). These genes were reported to participate in many cancer signaling pathways, such as the ERK/MAPK, Wnt/ β -catenin and Notch pathways (Davidson et al., 2010). It means that up-regulation of miR-218 may contribute to decreased cancer risk through down-regulating these targets.

MiRNAs include primary, precursor and mature miRNA, in which single nucleotide polymorphisms (SNPs) of these miRNAs may improve miRNA binding affinity and change mRNA expression levels of the target genes, thus leading to cancer susceptibility (Liu et al., 2011; Chen et al., 2011). Zhou (2010) and Shi (Shi et al., 2013) found that the pri-miR-218 rs11134527 SNP was significantly associated with the risk of cervical carcinoma in Chinese women. Han et al. (2013) also reported that rs11134527 variant genotypes in dominant model was associated with HCC risk compared with all HCC-free subjects. However, Zhang et al. (2012) indicated that the pri-miR-218 rs11134527 was no significant association between the HCC patients and the control group. To better understanding of the association between rs11134527 polymorphism and cancer risk, we performed a meta-analysis with a larger sample and subgroup analysis and to our knowledge, this is the first meta-analysis on their association.

In this meta-analysis, we found that pri-miR-218 rs11134527 was associated with a significantly decreased cancer risk in the GG homozygote as opposed to the AA homozygote or AG/AA genotype in Chinese. When stratified by cancer type, we found a similar result in cervical cancer but not in HCC. This reason may be that different cancer types have different mechanisms of pathogenesis or this polymorphism may exert varying effects in different cancer types. These findings suggested, for the first time, that the GG homozygote of rs11134527 polymorphism may have the potentially protective role in Chinese population of cancer, especially, in cervical carcinoma.

This meta-analysis should be considered some limitations. First, no sufficient data about age, sex, smoking status, alcohol consumption and residence area could be extracted from the included studies. Second, potential gene-gene interaction and gene-environment interaction were not evaluated in this meta-analysis. Third, only published studies were enrolled in this meta-analysis, unpublished data and ongoing studies were not sought, which may have biased our results. Last, there was not enough study on Chinese and no study on other population in the meta-analysis, limitation of the ethnic population enrolled makes the interpretation of the association between the SNP and susceptibility to cancer should be more cautious.

In conclusion, the meta-analysis suggested that pri-miR-218 rs11134527 was associated with a significantly decreased cancer risk in the GG homozygote compared with the AA homozygote or AG/AA genotype in Chinese, notably cervical cancer. However, our results should be considered with caution due to limitations listed above. To further confirm the results, larger sample size are needed.

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