Original Article

Effects of common polymorphisms in miR-146a and miR-196a2 on lung cancer susceptibility: a meta-analysis

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Background: MicroRNAs (miRNAs) may play an important role in organ development, cell differentiation, apoptosis, proliferation, cell growth regulation and act as tumor suppressor genes or proto-oncogenes. Single nucleotide polymorphisms (SNPs) in miRNAs are considered to be genetic factors to influence the susceptibility to lung cancer (LC). Rs2910164 in miR-146a and rs11614913 in miR-196a2 are shown to be associated with increased/decreased LC risk. The aim of this meta-analysis was to systematically summarize the possible association.

Methods: The relevant articles were retrieved from several important databases. Studies were selected using specific inclusion and exclusion criteria. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the strength of association between miRNA polymorphism and susceptibility to LC. All analyses were performed using the Stata software.

Results: Seven studies were included in this meta-analysis. There were 3,225 cases and 3,268 controls for SNP rs2910164 and 2,794 cases and 2,840 controls for SNP rs11614913. The significant associations between SNP rs2910164 and LC risk were observed (CC *vs.* GG: OR =1.30, 95% CI: 1.13–1.50; CC + GC *vs.* GG: OR =1.15, 95% CI: 1.02–1.29; CC *vs.* GC + GG: OR =1.27, 95% CI: 1.13–1.42; C *vs.* G: OR =1.15, 95% CI: 1.08–1.24). SNP rs11614913 was found to be associated with LC risk in most genetic models (TC *vs.* TT: OR =1.16, 95% CI: 1.02–1.32; CC *vs.* TT: OR =1.24, 95% CI: 1.06–1.44; CC + TC *vs.* TT: OR =1.19, 95% CI: 1.06–1.34; C *vs.* T: OR =1.11, 95% CI: 1.03–1.20). In the subgroup analysis by ethnicity, genotyping method and control characteristics, significantly affected LC risks were also suggested.

Conclusions: The rs2910164 in miR-146a and the rs11614913 in miR-196a2 are likely to be associated with LC risks.

Keywords: Lung cancer (LC); microRNA (miRNA); single nucleotide polymorphism (SNP); susceptibility; meta-analysis

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Introduction

An estimated 1.8 million new lung cancer (LC) cases occurred in 2012, accounting for about 13% of total cancer diagnoses and becoming the most frequently diagnosed cancer (1). LC is the leading cause of cancer death among males in both more and less developed countries, and has surpassed breast cancer as the leading cause of cancer death among females in more developed countries (1). Both environmental exposure factors and the genetic factors play

important roles in the development of LC. The researchers have identified a great number of genetic variants suggesting to be potentially associated with LC risk (2-5). However, the associations between many genetic alterations and LC susceptibility were inconclusive and the reliable markers are still lacking.

MicroRNAs (miRNAs) are a class of small non-coding, single-stranded RNA molecules that form base-pairs with target messenger RNA (mRNAs), leading to negatively regulate their translational stability and efficiency (6). MiRNAs are considered to be involved in crucial biological processes, including organ development, cell differentiation, apoptosis, proliferation, cell growth regulation and tumorigenesis (7). More than 50% of miRNA genes are located in cancer-associated genomic regions or in fragile sites, suggesting that miRNAs may play an important role in the pathogenesis of human cancers, including LC, by regulating the expression of tumor suppressor genes or proto-oncogenes (8-10). Single nucleotide polymorphisms (SNPs) occurring in the miRNA gene region may have effects on the property and function of miRNAs, consequently contributing to cancer susceptibility by altering miRNA expression and/or maturation (11,12). Two common SNPs rs11614913 and rs2910164 have attracted wide attention in recent years. Rs11614913 (Homo sapiens, cytosine to thymine, C>T), located in precursor of hsa-miR-196a2, was reported to be associated with the risks of multiple kind of cancers, including LC (13-17). Rs2910164 (Homo sapiens, guanine to cytosine, G>C) of miR-146a was suggested to be related with the susceptibility of LC in some studies (13,16-19).

Until now, the role of SNPs in miRNAs on LC susceptibility remains unknown. There are some meta-analysis reports on the association between miRNA SNPs and risks of combined multiple kind of cancers (20-25). Some studies have implied that polymorphisms in miRNAs may have different effect on carcinogenesis in different organs, reflecting the diversities of the susceptible factors for different tumor types (25). Although there are subgroup analyses in different types of cancer, but LC is not included. In addition few meta-analyses were conducted among specific type of cancer, especially in LC. The published results of original studies on the association between miR-196a2 rs11614913 and miR-146a rs2910164 with LC risks were contradictory and inconclusive. So we perform this updated meta-analysis on all available studies to assess the LC risk with both rs2910164 in miR-146a and rs11614913 in miR-196a2.

Methods

Data sources

We conducted a systematic search using PubMed, EMBASE, ISI Web of Science, Cochrane library, ScienceDirect, Wiley Online Library, Chinese Biomedical Literature Database (CBM) and Chinese National Knowledge Infrastructure (CNKI) databases with the last search updated on April 1, 2016. The following searching terms were used: "microRNA OR miRNA OR miR-146a OR miR-196a2", "lung cancer OR lung carcinoma OR lung tumor OR lung neoplasm" and "polymorphism OR SNP OR variation". Searching was carried on without restriction on publication date and language. We evaluated potentially relevant publications by examining their titles and abstracts and all of the studies matching the eligible criteria were retrieved.

Study selection and data extraction

Eligible studies were selected according to the following inclusion criteria: evaluation of the rs11614913 and/or rs2910164 and LC risks; using an independent case-control or cohort study; offering the size of the samples in cases and controls; presenting useful allele and genotype frequencies for computing the odds ratios (ORs) with 95% confidence intervals (95% CIs). The major exclusion criteria were as follows: duplication of the published results; review and meta-analysis; studies on cell lines and gene expression.

The PRISMA checklist was conducted as the guideline and protocol of the meta-analysis (*Figure 1*) (26). Duplicate and obviously unrelated articles were eliminated by two investigators (YG Ren, XM Zhou). Three investigators (YG Ren, ZG Cui, G Hou) evaluated the abstracts of the remaining articles independently to determine whether the full-text article should be obtained and then extracted the data of included studies. The following information was sought from each publication: the name of the first author, year of publication, country origin, ethnicity, control characteristics, total number of cases and controls, allele and genotype frequencies for cases and controls, and genotyping method.

Statistical methods

Hardy-Weinberg equilibrium was firstly assessed for each study using Chi-square test in control groups and a P value <0.05 was considered significant disequilibrium. The

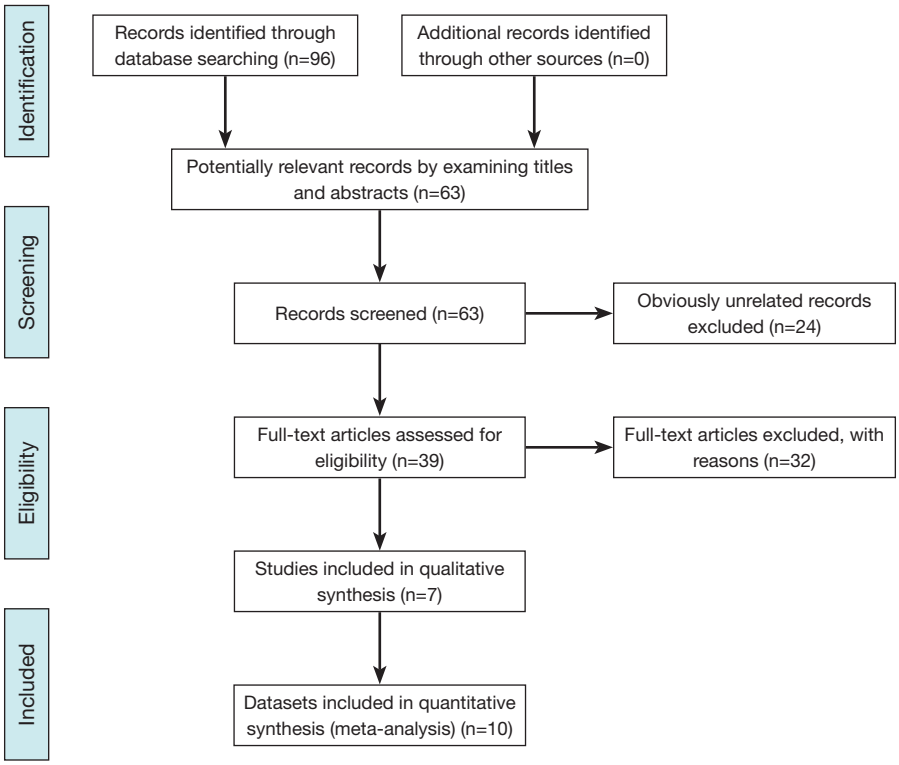

Figure 1 Flow chart of the study selection process.

strength of association between miRNA polymorphisms and susceptibility to LC was determined by calculating ORs with 95% CIs. The significance of the pooled ORs was assessed by the Z-test, and the results with P value <0.05 were considered statistically significant. Pooled ORs were obtained from combination of single study by heterozygote comparison [GC versus (*vs.*) GG for rs2910164; TC *vs.* TT for rs11614913], homozygote comparison (CC *vs.* GG for rs2910164; CC *vs.* TT for rs11614913), dominant model (CC/GC *vs.* GG for rs2910164; CC/CT *vs.* TT for rs11614913), recessive model (CC *vs.* GC + GG for rs2910164; CC *vs.* CT/TT for rs11614913) and allelic model (C *vs.* G for rs2910164; C *vs.* T for rs11614913) respectively. Subgroup analyses were investigated according to ethnicity, genotyping method and control characteristics for each genetic comparison model.

The heterogeneity among different studies were assessed by the Cochran's Q test and quantified by I^2 index and the results with P value <0.10 and/or $I^2 \geq 50\%$ indicated the existence of significant heterogeneity among the studies. To obtain summary statistics for ORs of miRNA polymorphism and cancer risk, we performed initial analyses with a fixed-effect model and confirmatory analyses with a random-effect model if there was significant heterogeneity. If the heterogeneity was significant, the result of the random-effect model was used, otherwise the result of the fixed-effect model was adopted.

The effect of publication bias was examined by Begg's inverted funnel plots and Egger's test. The significance of the intercept was determined by the t-test as suggested by Egger's test. A P value <0.05 was considered representative of statistically significant publication bias.

All of P values were two-sided and all analyses were performed using the STATA software version 11.0 (STATA Corporation, College Station, TX, USA).

Results

Characteristics of eligible studies

A total of 95 articles were retrieved by literature search using different combinations of key terms. Flow chart of the study selection process was shown in *Figure 1*. Eight studies about cancer survival were excluded. Four cell line

Table 1 Characteristics of all studies in meta-analysis

Author, year	Country	Ethnicity	Cancer type	SNP	Genotyping method	Study design	No. (case/control)	Case			Control			
								GG/TT	GC/TC	CC/CC	GG/TT	GC/TC	CC/CC	HWE (P)
Tian [2009] (13)	China	Asian	LC	rs2910164	PCR-RFLP	PB	1,058/1,035	360	510	188	364	502	169	0.853
Vinci [2011] (16)	Italy	Caucasian	NSCLC	rs2910164	PCR-HRMA	HB	101/129	44	48	9	73	45	11	0.292
Jeon [2014] (18)	Korea	Asian	LC	rs2910164	PCR-RFLP	PB	1,094/1,100	223	500	368	244	540	312	0.721
Jia [2014] (19)	China	Asian	NSCLC	rs2910164	PCR-RFLP	HB	400/400	64	182	154	76	200	124	0.770
Yin [2016] (17)	China	Asian	LC	rs2910164	TaqMan	HB	575/608	97	280	198	127	313	168	0.398
Tian [2009] (13)	China	Asian	LC	rs11614913	PCR-RFLP	PB	1,058/1,035	293	512	253	307	519	209	0.700
Kim [2010] (14)	Korea	Asian	LC	rs11614913	Fluorescence	HB	654/640	162	305	187	185	300	155	0.126
Hong [2011] (15)	Korea	Asian	NSCLC	rs11614913	TaqMan	PB	406/428	96	224	86	134	198	96	0.163
Vinci [2011] (16)	Italy	Caucasian	NSCLC	rs11614913	PCR-HRMA	HB	101/129	12	54	35	10	61	58	0.267
Yin [2016] (17)	China	Asian	LC	rs11614913	TaqMan	HB	575/608	149	298	128	178	297	133	0.664

SNP, single nucleotide polymorphism; LC, lung cancer; NSCLC, non-small cell lung cancer; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-HRMA, polymerase chain reaction-high resolution melting analysis; HWE, Hardy-Weinberg equilibrium; PB, population-based; HB, hospital-based.

studies and nine gene expression studies were excluded. Ten studies of review and meta-analysis were excluded. One study was excluded because of data missing. Finally seven articles were included and used in quantitative synthesis for systematic review (13-19). All studies were published in English. These studies included ten data sets of two SNPs. Five data sets were about miR-146a (rs2910164) SNP, including 3,225 cases and 3,268 controls. There were 2,794 cases and 2,840 controls in five data sets for miR-196a2 (rs11614913) SNP. Of the seven studies, sample sizes ranged from 230 to 2,093. Almost all of the cases were histologically confirmed. Controls were mainly frequency matched by gender and age. The distribution of genotypes in the controls was all in Hardy-Weinberg equilibrium (HWE). The main characteristics of the included studies were presented in *Table 1*.

Meta-analysis of the association between SNP rs2910164 and susceptibility to lung cancer

The association between SNP rs2910464 in miR-146a and susceptibility to LC was evaluated in five independent studies. The results of the meta-analysis and heterogeneity are shown in *Table 2*. Q-tests in all of the five genetic models did not suggest notable heterogeneity. Therefore, the results of the fixed-effect models were used. The overall ORs with their 95% CIs showed the statistically significant association between SNP rs2910164 and LC risk in all of the genetic models except for heterozygote comparison (GC *vs.* GG: OR =1.08, 95% CI: 0.95–1.21, P=0.417 for heterogeneity, I^2=0%; CC *vs.* GG: OR =1.30, 95% CI: 1.13–1.50, P=0.621 for heterogeneity, I^2 = 0%; CC+GC *vs.* GG: OR =1.15, 95% CI: 1.02–1.29, P=0.419 for heterogeneity, I^2=0%; CC *vs.* GC + GG: OR =1.27, 95% CI: 1.13–1.42, P=0.673 for heterogeneity, I^2=0%; C *vs.* G: OR =1.15, 95% CI: 1.08–1.24, P=0.380 for heterogeneity, I^2=0%). *Figure 2* showed the meta-analysis result of the association between rs2910164 polymorphism and LC risk under the allele model (C *vs.* G).

Table 3 showed the results of stratified analyses by ethnicity, genotyping method and control characteristics. The Asian carriers with CC genotype had 1.30-fold (OR =1.30, 95% CI: 1.13–1.50) increased risk of LC compared with the GG genotype carriers. Other comparisons also showed significantly increased LC risks (dominant model: OR =1.13, 95% CI: 1.00–1.27; recessive model: OR =1.27, 95% CI: 1.13–1.42; allele contrast: OR =1.15, 95% CI: 1.07–1.24). In the subgroup analyses based on genotyping method, the four studies using sequence-tagged techniques

Table 2 Association between polymorphisms in miRNAs and susceptibility to lung cancer

SNP	Data set number	Fixed effect	Random effect	Phet	I-squared (%)
rs2910164					
GC *vs.* GG	5	1.08 (0.95, 1.21)	1.08 (0.95, 1.21)	0.417	0.0
CC *vs.* GG	5	1.30 (1.13, 1.50)	1.30 (1.13, 1.50)	0.621	0.0
CC + GC *vs.* GG	5	1.15 (1.02, 1.29)	1.15 (1.02, 1.29)	0.419	0.0
CC *vs.* GC + GG	5	1.27 (1.13, 1.42)	1.27 (1.13, 1.42)	0.673	0.0
C *vs.* G	5	1.15 (1.08, 1.24)	1.16 (1.07, 1.24)	0.380	0.0
rs11614913					
TC *vs.* TT	5	1.16 (1.02, 1.32)	1.17 (1.00, 1.38)	0.220	30.2
CC *vs.* TT	5	1.24 (1.06, 1.44)	1.23 (1.06, 1.44)	0.371	6.3
CC + TC *vs.* TT	5	1.19 (1.06, 1.34)	1.19 (1.04, 1.36)	0.327	13.7
CC *vs.* TC + TT	5	1.10 (0.98, 1.35)	1.07 (0.90, 1.28)	0.119	45.5
C *vs.* T	5	1.11 (1.03, 1.20)	1.10 (1.01, 1.20)	0.239	27.3

SNP, single nucleotide polymorphism; Phet, P value for heterogeneity.

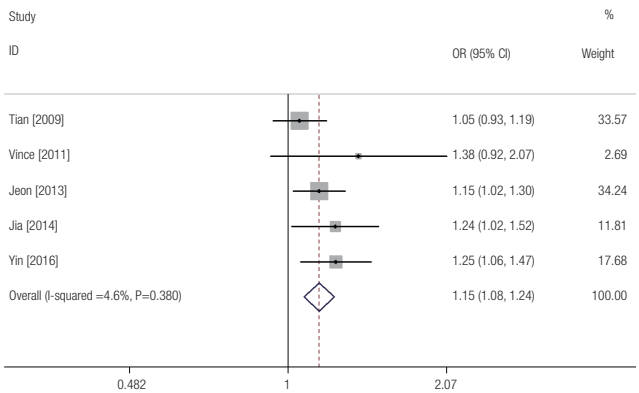

Figure 2 The meta-analysis result of the association between rs2910164 polymorphism and lung cancer risk under the allele model (C *vs.* G).

(PCR-restriction fragment length polymorphism and PCR-high resolution melting analysis) were combined and the statistically significant ORs were showed in three comparison (CC *vs.* GG: OR =1.25, 95% CI: 1.06–1.46; CC *vs.* GC + GG: OR =1.24, 95% CI: 1.09–1.41; C *vs.* G: OR =1.14, 95% CI: 1.05–1.23). In the subgroup analysis by control characteristics, the similar results were presented for the two studies using population-based control and three papers using hospital-based control, that is the significant associations in the four models except for the heterozygote comparison.

Meta-analysis of the association between rs11614913 and susceptibility to lung cancer

Overall, we found the significant associations of SNP rs11614913 with LC risk in all genetic models except recessive comparison (TC *vs.* TT: OR =1.16, 95% CI: 1.02–1.32, P=0.220 for heterogeneity, I^2 =30.2%; CC *vs.* TT: OR =1.24, 95% CI: 1.06–1.44, P=0.371 for heterogeneity, I^2 =6.3%; CC + TC *vs.* TT: OR = 1.19, 95% CI: 1.06–1.34, P=0.327 for heterogeneity, I^2=13.7%; CC *vs.* TC + TT: OR =1.10, 95% CI: 0.98–1.35, P=0.119 for heterogeneity, I^2=45.5%; C *vs.* T: OR =1.11, 95% CI: 1.03–1.20, P=0.239 for heterogeneity, I^2=27.3%) (*Table 2*). *Figure 3* showed the meta-analysis result of the association between rs11614913 polymorphism and LC risk under the allele model (C *vs.* T).

In the subgroup analysis by ethnicity, the results in all genetic models were statistically significant in Asians (*Table 4*). The subgroup analyses results were completely different between two types of genotyping methods. There were no significant associations between rs11614913 and LC risks combining the studies using sequence-tagged techniques to detect polymorphism. However, meta-analyses of the studies with fluorescence-based techniques presented the significant results in most of the comparisons. As for the subgroup analyses of control characteristics, the individual with CC genotype were more likely to develop LC than those carrying TT genotype (OR =1.26, 95% CI: 1.03–1.55) and C

Table 3 Stratified analyses of SNP rs2910164 and susceptibility to lung cancer

Subgroup	SNP	Data set number	Association results			Heterogeneity	
			OR (95% CI)	P value	Model	P value	I^2 (%)
Asians	GC *vs.* GG	4	1.05 (0.93, 1.19)	0.441	F	0.884	0.0
	CC *vs.* GG	4	1.30 (1.13, 1.50)	0.000	F	0.531	0.0
	CC + GC *vs.* GG	4	1.13 (1.00, 1.27)	0.045	F	0.632	0.0
	CC *vs.* GC + GG	4	1.27 (1.13, 1.42)	0.000	F	0.536	0.0
	C *vs.* G	4	1.15 (1.07, 1.24)	0.000	F	0.334	11.7
Sequence-tagged	GC *vs.* GG	4	1.06 (0.93, 1.21)	0.381	F	0.310	16.3
	CC *vs.* GG	4	1.25 (1.06, 1.46)	0.005	F	0.707	0.0
	CC + GC *vs.* GG	4	1.12 (0.99, 1.27)	0.066	F	0.380	2.4
	CC *vs.* GC + GG	4	1.24 (1.09, 1.41)	0.001	F	0.616	0.0
	C *vs.* G	4	1.14 (1.05, 1.23)	0.001	F	0.371	4.4
Population-based	GC *vs.* GG	2	1.02 (0.88, 1.18)	0.776	F	0.926	0.0
	CC *vs.* GG	2	1.21 (1.02, 1.44)	0.030	F	0.437	0.0
	CC + GC *vs.* GG	2	1.08 (1.02, 1.44)	0.030	F	0.676	0.0
	CC *vs.* GC + GG	2	1.21 (1.05, 1.39)	0.009	F	0.332	0.1
	C *vs.* G	2	1.10 (1.01, 1.20)	0.022	F	0.304	5.3
Hospital-based	GC *vs.* GG	3	1.22 (0.98, 1.52)	0.079	F	0.336	8.3
	CC *vs.* GG	3	1.50 (1.17, 1.93)	0.000	F	0.963	0.0
	CC + GC *vs.* GG	3	1.33 (1.08, 1.64)	0.007	F	0.611	0.0
	CC *vs.* GC + GG	3	1.37 (1.14, 1.65)	0.001	F	0.846	0.0
	C *vs.* G	3	1.26 (1.11, 1.42)	0.001	F	0.887	0.0

SNP, single nucleotide polymorphism; F, fixed effect; R, random effect; OR, odds ratio; CI, confidence interval; I^2, I-squared.

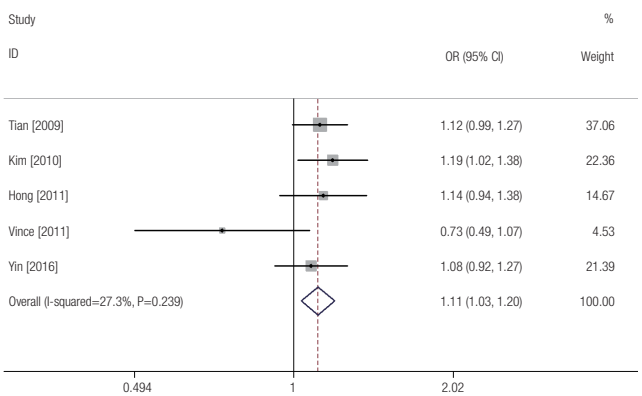

Figure 3 The meta-analysis result of the association between rs11614913 polymorphism and lung cancer risk under the allele model (C *vs.* T).

allele was suggested to be risk allele of LC (OR =1.13, 95% CI: 1.02–1.25) when the controls of the study were population-based. There were no significant results in the meta-analyses of the studies using hospital-based controls.

Above results of stratified analyses by ethnicity, genotyping method and control characteristics were showed in *Table 4*.

Sensitivity analysis

Every one single study included in our meta-analysis was sequentially deleted to detect the influence on the pooled ORs. The sensitivity analysis suggested no obvious effects from each study, which supported the robustness and reliability of our results.

Publication bias

No publication bias was detected by either the Begg's inverted funnel plot or Begg's test. The inverted funnel plot for the comparison of the two alleles of both rs2910164 and rs11614913 all seemed approximately symmetrical. The results were further identified by Egger's test, which did not show significantly statistical evidence of publication bias (all P>0.05).

Table 4 Stratified analyses of SNP rs11614913 and susceptibility to lung cancer

Subgroup	SNP	Data set number	Association results			Heterogeneity	
			OR (95% CI)	P value	Model	P value	I^2 (%)
Asians	TC *vs.* TT	4	1.17 (1.03, 1.33)	0.015	F	0.189	37.1
	CC *vs.* TT	4	1.27 (1.09, 1.47)	0.002	F	0.886	0.0
	CC + TC *vs.* TT	4	1.20 (1.07, 1.35)	0.003	F	0.465	0.0
	CC *vs.* TC + TT	4	1.14 (1.01, 1.30)	0.038	F	0.349	8.9
	C *vs.* T	4	1.11 (1.03, 1.20)	0.002	F	0.869	0.0
Sequence-tagged	TC *vs.* TT	2	1.02 (0.84, 1.24)	0.862	F	0.481	0.0
	CC *vs.* TT	2	0.90 (0.37, 2.16)	0.807	R	0.061	71.4
	CC + TC *vs.* TT	2	1.07 (0.89, 1.29)	0.452	F	0.217	34.4
	CC *vs.* TC + TT	2	0.94 (0.50, 1.77)	0.855	R	0.027	79.5
	C *vs.* T	2	0.94 (0.62, 1.43)	0.772	R	0.036	77.2
Fluorescence-based	TC *vs.* TT	3	1.27 (1.08, 1.50)	0.004	F	0.309	14.9
	CC *vs.* TT	3	1.26 (1.04, 1.53)	0.017	F	0.724	0.0
	CC + TC *vs.* TT	3	1.19 (1.05, 1.34)	0.002	F	0.541	0.0
	CC *vs.* TC + TT	3	1.09 (0.93, 1.27)	0.299	F	0.313	13.8
	C *vs.* T	3	1.13 (1.03, 1.25)	0.011	F	0.901	0.0
Population-based	TC *vs.* TT	2	1.25 (0.83, 1.89)	0.286	R	0.030	78.9
	CC *vs.* TT	2	1.26 (1.03, 1.55)	0.027	F	0.952	0.0
	CC + TC *vs.* TT	2	1.24 (0.94, 1.84)	0.132	R	0.115	59.8
	CC *vs.* TC + TT	2	1.11 (0.83, 1.46)	0.476	R	0.144	53.2
	C *vs.* T	2	1.13 (1.02, 1.25)	0.024	F	0.901	0.0
Hospital-based	TC *vs.* TT	3	1.13 (0.80, 1.61)	0.488	R	0.124	52.1
	CC *vs.* TT	3	1.15 (0.96, 1.39)	0.123	F	0.608	0.0
	CC + TC *vs.* TT	3	1.18 (0.99, 1.40)	0.064	F	0.343	6.5
	CC *vs.* TC + TT	3	1.02 (0.75, 1.36)	0.923	R	0.083	59.9
	C *vs.* T	3	1.05 (0.86, 1.27)	0.648	R	0.069	62.7

SNP, single nucleotide polymorphism; F, fixed effect; R, random effect; OR, odds ratio; CI, confidence interval; I^2, I-squared.

Discussion

Both environmental risk factors and individual susceptibility plays important role in the development of LC. Polymorphisms or mutations of genes involved in carcinogenesis may have accounted for the individual genetic susceptibility. Therefore, the association between SNP of genes and risks of LC has become a research focus in scientific community for a long time. However, the key gene is poorly understood after these years' research. Recently miRNA has drawn increasing attention of scientists and some studies have been done to figure out the role of SNPs in precursor and mature miRNA as well as their influences on susceptibility of LC. The most common and widely studied SNPs in miRNAs were rs2910164 in miR-146a and rs11614913 in miR-196a2. Growing number of studies have been adopted to discuss the relationship between these two SNPs and the risks of LC. However, the results are contradictive and inconclusive. In order to better understand the association between these polymorphisms and LC risk, a meta-analysis with larger sample size and subgroup analysis is necessary. The present study is the largest meta-analysis of the association between miR-146a rs2910164 and miR-196a2 rs11614913 polymorphisms with the risk of LC.

There are some meta-analysis reports on the association between these two SNPs and risks of overall cancer without the analyses among LC (20-23,25). For LC, three meta-analyses were conducted to investigate miR-196a2

rs11614913 and only one to study miR-146a rs2910164 (27-29). However, the most recent update time of these three meta-analyses was September 2012 and there were not subgroup analyses in their results. So we perform an updated meta-analysis on all available studies to assess the LC risk with both rs2910164 in miR-146a and rs11614913 in miR-196a2 as well as the subgroup analyses by ethnicity, genotyping method and control characteristics. This study found the statistical evidence for the associations between these two SNPs (rs2910164 in miR-146a and rs11614913 in miR-196a2) and susceptibility to LC in both overall analysis and subgroup analyses. The three advantages of our meta-analysis, which are including new publications, undergoing subgroup analyses and without significant heterogeneity in our results, have enhanced the credibility of our study.

In the stratified analysis by ethnicity, the similar results were found for the two SNPs in Asians compared those in all population. The results in Caucasians have not presented because there is only one study in Caucasian (16). It is widely accepted that a sufficient sample is essential for genetic association studies so more and larger sample size studies in Caucasians are required in future. Similarly, for rs2910164 subgroup analysis was only done in studies using sequence-tagged techniques to detect SNPs but not done in studies using fluorescence-based techniques. Conversely, for rs11614913 subgroup analysis was adopted for both SNP techniques and the results were greatly different. We did not find any risk in sequence-tagged studies but the significant results were found in most of the results among Fluorescence-based studies. The reason may be that there is difference in the accuracy of these two techniques in SNP detecting or included studies are too few to conclude the stable results. As for stratified analyses by control source, the significant results were found both in in population-based studies and in hospital-based studies for rs2910164, however for rs11614913 the significant results were suggested in population-based studies but not in hospital-based studies. All studies included in this meta-analysis were retrospective and were significantly different in their study designs (population-based or hospital-based cases and control selection), which would have caused between-study heterogeneity and affected the conclusions. In addition, the observed different effects could be likely due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate. So studies with larger sample size and different study designs are necessary to fully understand the relationship between the polymorphism and the risk of LC.

Despite our efforts in performing a comprehensive analysis, weakness of current meta-analysis was identified. First, our analysis used published international studies, which might arise publication bias, although the results for publication bias in our study were not statistically significant. Second, two SNPs were identified by case-control studies and no further validation was available. Third, lacking the original data of included studies limited our further evaluation of potential interactions, such as age, gender, family history, environmental factors and lifestyle. Fourth, there was only one study in Caucasian population and no study in African population.

In conclusion, our meta-analysis supports that the rs2910164 in miR-146a and the rs11614913 in miR-196a2 more likely contribute to LC risk. Future well-designed and larger sample size studies are of great value to confirm the findings. Moreover, interaction of genetic factors with environmental exposures should also be examined. The rs2910164 in miR-146a and the rs11614913 in miR-196a2 might be associated with susceptibility to LC.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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