Original Article

# Effects of three common polymorphisms in microRNAs on lung cancer risk: a meta-analysis

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**Background:** Many studies demonstrated that miRNAs could affect the initiation and progression of malignant tumor. Recently, many studies on the association of these three common polymorphisms (*miR-146a*, *miR-196a2* and *miR-499*) with lung cancer risk found inconsistent results.

**Methods:** These studies were collected from PubMed, Wanfang, VIP and CNKI database. ORs (odds ratios) with 95% CIs (confidence intervals) were used to assess the association between three genetic polymorphisms and the risk of lung cancer. All results were performed by using the Stata 14 software.

**Results:** Eleven studies including 9,231 lung cancer cases and 9,280 case-free controls were analyzed in this meta-analysis. The analysis revealed that a significant association was found between *miR-146a* polymorphism and lung cancer (CG *vs.* CC, GG *vs.* CC, GG + CG *vs.* CC, G *vs.* C: OR =0.859, 95% CI: 0.781–0.945, P=0.002; OR =0.846, 95% CI: 0.751–0.953, P=0.006; OR =0.855, 95% CI: 0.782–0.935, P=0.001; OR= 0.910, 95% CI: 0.859–0.964, P=0.001, respectively). We also found that the significant association between *miR-146a* polymorphism and the risk of lung cancer was found among hospital-based population. We found that *miR-196a2* polymorphism was associated with an increased lung cancer risk (CC *vs.* TT: OR =1.200, 95% CI: 1.056–1.364, P=0.005; CC + CT *vs.* TT: OR =1.117, 95% CI: 1.011–1.235, P=0.029; CC *vs.* CT + TT: OR =1.123, 95% CI: 1.009–1.251, P=0.034; C *vs.* T: OR =1.089, 95% CI: 1.022–1.161, P=0.008, respectively). For the Asian samples alone, we achieved the same results. Subgroup analysis found that a statistically association between *miR-196a2* (rs11614913) and the lung cancer risk among hospital-based. There was significant association between *miR-499* and lung cancer (AG *vs.* AA: OR =1.131, 95% CI: 1.022–1.252, P=0.018; GG *vs.* AA: OR =1.702, 95% CI: 1.093–2.650, P=0.019; AG + GG *vs.* AA: OR =1.207, 95% CI: 1.042–1.398, P=0.012; GG *vs.* AG + AA: OR =1.640, 95% CI: 1.066–2.523, P=0.024; G *vs.* A: OR =1.226, 95% CI: 1.026–1.464, P=0.025, respectively).

**Conclusions:** All three common polymorphisms in microRNA are associated with the risk of lung cancer.

**Keywords:** Lung cancer; meta-analysis; miRNA; single nucleotide polymorphisms (SNPs); susceptibility

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## Introduction

Lung cancer is the most common malignant cancer, which causes approximately 1.59 million cases deaths, with less than 15% of the 5 years survival rate according to World Health Organization (WHO) (1,2). For Chinese, lung cancer is the second common malignant tumor in female and the most frequent malignant tumor in male. Tumorigenesis is a very complex process (3). And the etiology of lung cancer is also strongly affected by genetic or environmental factors and the interaction of gene-environment. Molecular epidemiological studies also indicated that a large number of genetic variants might be associated with the risk of lung cancer (4). The GWAS studies indicated that there were many disease-associated loci in non-coding RNAs (5,6). MicroRNAs played pivotal roles in non-coding RNAs and were associated with cancer cell proliferation, invasion and cell cycle regulation. Many studies shown that miRNAs could influence the initiation of cancer or the progression of malignant tumor (7). Thus, the abnormal expressions of miRNAs may be the cause of lung cancer (8). Single nucleotide polymorphisms (SNPs) in microRNAs could affect the cancer risk by changing the expressions of miRNAs (9). In the past, many studies shown that the three common polymorphisms [*miR-146a* (rs2910164), *miR-196a2* (rs11614913) and *miR-499* (rs3746444)] could influence the susceptibility of lung cancer, but the results were contradictory. The common variants [minor allele frequency (MAF) >0.05] were concerned in previous studies, such as rs2910164, rs11614913 and rs3746444 (10).

*MiR-146a* (rs2910164) is exits on chromosome fifth LOC285628, and the mature *miR-146a* is located in the second exon (11,12). *MiR-146a* played an important role in a majority of disease (13) and it also can influence the occurrence and development of tumor by disturbing cell invasion and migration (14,15). Many studies have conducted to estimate the potential association between *miR-146a* and lung cancer in humans. According to the search strategy, we found six studies to analysis the association between *miR-146a* and lung cancer (16-21).

*MiR-196a-2* (rs11614913) located the mature miRNA complementary region of pre-miR-196a-2, and a large number of studies have shown that the SNP was associated with the risk of lung cancer by influencing the expression and maturation of miRNAs (19-24).

*MiR-499* gene is also exiting in miRNA mature region. *MiR-499* plays an important role in the regulation of cell differentiation. Some studies have indicated that *miR-499* (rs3746444) polymorphism was associated with the risk of lung cancer (7,19,20) (Qiu F, 2012, unpublished data).

The aim of this meta-analysis was to achieve a combined risk estimate including most recently published studies before Apr 2017. And we were evaluated the relationship between these three polymorphisms (*miR-146a*, *miR-196a2*, and *miR-499*) with lung cancer risk.

## Methods

### *Data collection*

We conducted a comprehensive and systematic search to analyze the association between these three common polymorphisms and lung cancer in PubMed, Wanfang, VIP, CNKI database. Last search was conducted on April 2017. We used the subject headings and keywords such as, miRNAs, cancer, tumor, gene, polymorphism, variation, *miR-499* (rs3746444), *miR-146a* (rs2910164), *miR-196a2* (rs11614913) and supplemented by literature tracing methods to collect relevant studies.

### *Inclusion criteria*

The Inclusion criteria were: (I) published all over the world about *miR-146a* (rs2910164), *miR-196a2* (rs11614913) and *miR-499* (rs3746444) polymorphisms and lung cancer risk from case-control study; (II) providing the number of the case group and the control group; (III) obtaining the full text of the literature; (IV) providing enough data to calculate the statistical index of odds ratio (OR) 95% confidence interval (CI); (V) the similar method and assumption of each research; (VI) getting the consensus for each research from two inspectors.

### *Exclusion criteria*

The exclusion criteria were: (I) duplicated data; (II) meeting, case report and literature review; (III) involving gene expression, meta-analysis, cell lines; (IV) the Newcastle-Ottawa scale (NOS) quality assessment less than five stars (25).

### *Information extraction*

Two investigators independently extracted data. The following data were extracted: the first author's name, published time, country, race, control source, number of

 

**Table 1** The characteristics of the eligible studies (*MiR-146a*)

| Author | Year | Country | Ethnicity | Control | Lung cancer/control | Case | | | Control | | | Genotyping method | HWE | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | CC | CG | GG | CC | CG | GG | | | |
| Yin | 2017 | China | Asian | Hospital | 1,131/1,003 | 377 | 550 | 204 | 290 | 508 | 205 | PCR | 0.521 | 6 |
| Jia | 2014 | China | Asian | Hospital | 400/400 | 154 | 182 | 64 | 124 | 200 | 76 | PCR-RFLP | 0.77 | 7 |
| Jeon | 2013 | Korea | Asian | Hospital | 1,094/1,100 | 368 | 500 | 223 | 312 | 540 | 244 | RT-PCR | 0.721 | 6 |
| Tian | 2009 | China | Asian | Population | 1,058/1,035 | 188 | 510 | 360 | 169 | 502 | 364 | PCR-RFLP | 0.853 | 6 |
| Vinci | 2011 | Italy | Caucasian | Population | 101/129 | 9 | 48 | 44 | 11 | 45 | 73 | TaqMan | 0.292 | 6 |
| He | 2016 | China | Asian | Population | 1,053/1,058 | 413 | 476 | 140 | 420 | 502 | 125 | MALDI-TOFM-S | 0.878 | 7 |

HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa assessment scale; PCR, polymerase chain reaction; RT-PCR, reverse transcription-polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF-MS, matrix-assisted laser desorption/ionization time of flight mass spectrometry.

cases and controls, the number of cases and controls of each genotype, the detection method of miRNA, Hardy-Weinberg equilibrium (HWE), NOS (*Tables 1-3*). If difference was existed after data collection, the third author needs to ensure the data. HWE was used to evaluate the gene frequency and genotype frequency by the goodness of fit $\chi^2$ test or Chi-square test in each study control groups. The disequilibrium was exited, when P<0.05. We assessed the association between the three SNPs and lung cancer risk by using ORs with 95% CIs (P<0.05). We analyzed the pooled ORs using five different genetic models: dominant model, homozygote comparison, recessive model, allelic comparison and heterozygote comparison, respectively. Furthermore, subgroup analyses carried out by race and control source. Heterogeneity between the eligible studies was assessed using Chi-square-based *t*-test. When $I^2 \leq 50\%$, heterogeneity is not apparent. We can choose fixed effects model; whereas $I^2 > 50\%$, we think the heterogeneity exiting between studies, we should choose the random effect model (26,27). Further, to test the stability of the results, an accurate sensitivity analysis was needed by omitting one by one. We used quantitative method to determine publication bias in our meta-analysis (Egger's test) (28,29). All analyses results were performed by using Stata software.

## Results

### *The selection of eligible studies*

According to the search strategy, we got 519 articles from PubMed database, CNKI, Wanfang database and Chinese biomedical literature database. We removed 450 records by primary screening of titles. *Figure 1* shows the screening process of studies. We excluded 58 articles (17 studies were duplicate records, 8 studies were prognosis, 3 studies were involved in cells, 9 studies were gene expression, 14 studies were meta-analyses, 2 studies were review, 4 studies did not have the data which we needed, 1 study was cell line). Finally, there were 11 studies in our meta-analysis with 9,231 lung cancer cases and 9,280 controls. Six studies about *miR-146a* (rs2910164) polymorphism were included. Six studies about *miR-196a2* (rs11614913) polymorphism were analyzed. Four studies (5 data) about *miR-499* (rs3746444) were entered.

### *The results of quantitative analysis*

#### *MiR-146a*

In this study, we set five different genetic models of *miR-146a* (CG *vs.* CC, GG *vs.* CC, GG + CG *vs.* CC, GG

**Table 2** The characteristics of the eligible studies (*MiR-196a2*)

| Author | Year | Country | Ethnicity | Control | Lung cancer/ control | Case | | | Control | | | Genotyping method | HWE | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | TT | TC | CC | TT | TC | CC | | | |
| Yin | 2016 | China | Asian | Hospital | 575/608 | 149 | 298 | 128 | 178 | 297 | 133 | PCR | 0.664 | 6 |
| Tian | 2009 | China | Asian | Population | 1,058/1,035 | 293 | 512 | 253 | 307 | 519 | 209 | PCR-RFLP | 0.7 | 6 |
| Hong | 2011 | Korea | Asian | Hospital | 406/428 | 96 | 224 | 86 | 134 | 198 | 96 | TaqMan | 0.163 | 8 |
| Kim | 2010 | Korea | Asian | Hospital | 654/640 | 162 | 305 | 187 | 185 | 300 | 155 | Fluorescence | 0.126 | 7 |
| Vinci | 2011 | Italy | Caucasian | Population | 101/129 | 12 | 54 | 35 | 10 | 61 | 58 | PCR-HRMA | 0.267 | 6 |
| He | 2016 | China | Asian | Population | 1,053/1,058 | 316 | 487 | 206 | 316 | 535 | 187 | MALDI-TOF-S | 0.13 | 7 |

HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa assessment scale; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-HRMA, polymerase chain reaction-high-resolution melting analysis; MALDI-TOF-MS, matrix-assisted laser desorption/ionization time of flight mass spectrometry.

**Table 3** The characteristics of the eligible studies (*MiR-499*)

| Author | Year | Country | Ethnicity | Control | Lung cancer/ control | Case | | | Control | | | Genotyping method | HWE | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | AA | AG | GG | AA | AG | GG | | | |
| Tian | 2009 | China | Asian | Population | 1,058/1,035 | 781 | 253 | 24 | 755 | 254 | 26 | PCR-RFLP | 0.404 | 6 |
| Vinci | 2011 | Italy | Caucasian | Population | 101/129 | 53 | 41 | 7 | 70 | 48 | 11 | PCR-HRMA | 0.503 | 6 |
| Qiu* | 2012 | China | Asian | Population | 1,056/1,056 | 709 | 271 | 76 | 771 | 254 | 31 | PCR | 0.075 | 7 |
| Qiu** | 2012 | China | Asian | Population | 503/623 | 338 | 132 | 33 | 455 | 152 | 16 | PCR | 0.442 | 7 |
| Li | 2016 | China | Asian | Population | 1,200/1,200 | 777 | 344 | 79 | 850 | 302 | 48 | TaqMan | 0.002 | 6 |

*, the study population is Guangzhou, China; **, the study population is Suzhou, China. HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa assessment scale; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-HRMA, polymerase chain reaction-high-resolution melting analysis.

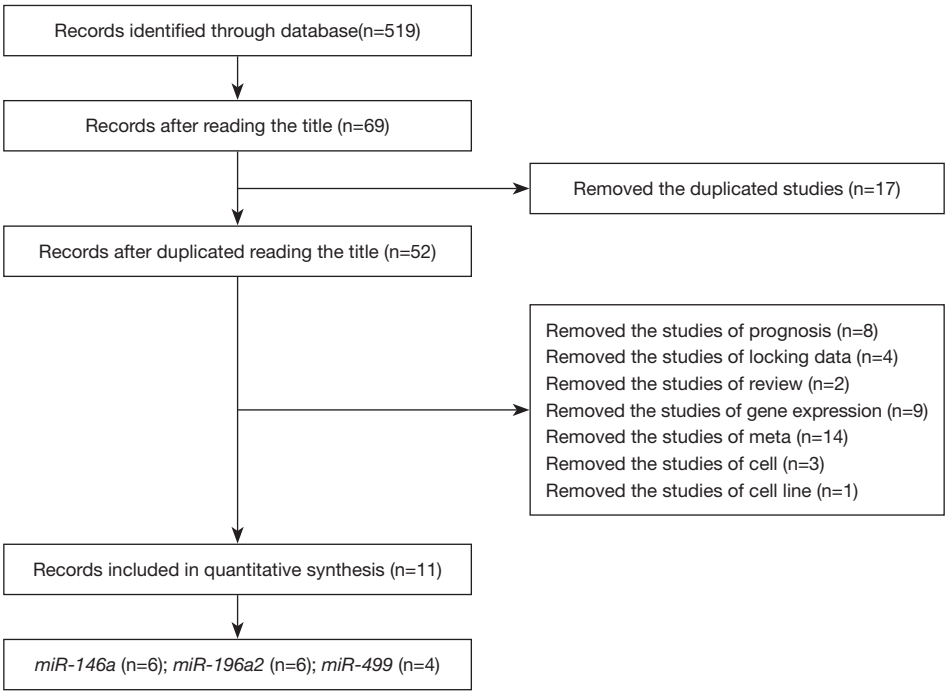


**Figure 1** The concrete selection process of the studies was shown.

*vs.* CG + CC, G *vs.* C). *Table 4* showed all the detailed results. The analysis revealed that *miR-146a* polymorphism was significantly associated with the risk of lung cancer (CG *vs.* CC: OR =0.859, 95% CI: 0.781–0.945, P=0.002; GG *vs.* CC: OR =0.846, 95% CI: 0.751–0.953, P=0.006; GG + CG *vs.* CC: OR =0.855, 95% CI: 0.782–0.935, P=0.001; G *vs.* C: OR =0.910, 95% CI: 0.859–0.964, P=0.001). In the subgroup analysis by source of controls, statistically decreased lung cancer risk was found in hospital-based groups (*Table 4*). No significant association between *miR-146a* and lung cancer risk was found in the population-based groups. Stratified analysis by ethnicity, the *miR-146* a polymorphism was significantly associated with lung cancer risk among Asians (*Table 4*). *Figure 2* shows the forest plot of *miR-146a* (CG *vs.* CC).

### *MiR-196a2*

In this study, we set the heterozygote comparison of *miR-196a2* (CT *vs.* TT), homozygote comparison (CC *vs.* TT), dominant model (CC + CT *vs.* TT), recessive model (CC *vs.* CT + TT), and allelic comparison (C *vs.* T). The analysis revealed that *miR-196a2* polymorphism was significantly associated with increased lung cancer risk (CC *vs.* TT: OR =1.200, 95% CI: 1.056–1.364, P=0.005; CC + CT *vs.* TT: OR =1.117, 95% CI: 1.011–1.235, P=0.029; CC *vs.* CT + TT: OR =1.123, 95% CI: 1.009–1.251, P=0.034; C *vs.* T: OR =1.089, 95% CI: 1.022–1.161, P=0.008). In the stratified analysis by ethnicity, the *miR-196a2* polymorphism was significantly associated with lung cancer risk in Asians (*Table 5*). In the subgroup analysis by source of controls, we found a statistically association between *miR-196a2* and the lung cancer risk among hospital-based groups (*Table 5*). The forest plot of *miR-196a2* (CC *vs.* TT) was shown in *Figure 3*.

### *MiR-499*

*Table 6* listed the results of each genetic model. The analysis showed that *miR-499* polymorphism might have association with lung cancer risk in the five different genetic models (AG *vs.* AA: OR =1.131, 95% CI: 1.022–1.252, P=0.018; GG *vs.* AA: OR =1.702, 95% CI: 1.093–2.650, P=0.019; AG + GG *vs.* AA: OR =1.207, 95% CI: 1.042–1.398, P=0.012; GG *vs.* AG + AA: OR =1.640, 95% CI: 1.066–2.523, P=0.024; G *vs.* A: OR =1.226, 95% CI: 1.026–1.464, P=0.025). Results of the stratified analysis by ethnicity suggested that the significant effect for *miR-499* polymorphism was observed in the risk of lung cancer in among Asian (*Table 6*). *Figure 4* shows the forest plot of *miR-499* (AG *vs.* AA).

 

**Table 4** The results of *miR-146a* subgroup analysis were shown

| Population | OR (95% CI) | Test of association | | Test of heterogeneity | | Model |
|---|---|---|---|---|---|---|
| | | Z | P | P | $I^2$ (%) | |
| Overall (N=6) | | | | | | |
| CG *vs.* CC | 0.859 (0.781–0.945) | 3.14 | 0.002 | 0.494 | 0 | F |
| GG *vs.* CC | 0.846 (0.751–0.953) | 2.75 | 0.006 | 0.224 | 28.1 | F |
| GG + CG *vs.* CC | 0.855 (0.782–0.935) | 3.43 | 0.001 | 0.317 | 15.1 | F |
| GG *vs.* CG + CC | 0.919 (0.832–1.014) | 1.68 | 0.092 | 0.229 | 27.4 | F |
| G *vs.* C | 0.910 (0.859–0.964) | 3.21 | 0.001 | 0.139 | 39.9 | F |
| Asian (N=5) | | | | | | |
| CG *vs.* CC | 0.856 (0.778–0.941) | 3.20 | 0.001 | 0.451 | 0 | F |
| GG *vs.* CC | 0.848 (0.752–0.956) | 2.70 | 0.007 | 0.143 | 41.8 | F |
| GG + CG *vs.* CC | 0.854 (0.781–0.935) | 3.43 | 0.001 | 0.212 | 31.5 | F |
| GG *vs.* CG + CC | 0.934 (0.844–1.032) | 1.34 | 0.181 | 0.392 | 2.6 | F |
| G *vs.* C | 0.914 (0.862–0.969) | 3.01 | 0.003 | 0.133 | 43.3 | F |
| Caucasian (N=1) | | | | | | |
| CG *vs.* CC | 1.304 (0.494–3.440) | 0.54 | 0.592 | – | – | – |
| GG *vs.* CC | 0.737 (0.283–1.918) | 0.63 | 0.531 | – | – | – |
| GG + CG *vs.* CC | 0.953 (0.379–2.396) | 0.10 | 0.918 | – | – | – |
| GG *vs.* CG + CC | 0.592 (0.350–1.001) | 1.96 | 0.051 | – | – | – |
| G *vs.* C | 0.723 (0.482–1.084) | 1.57 | 0.116 | – | – | – |
| Hospital (N=3) | | | | | | |
| CG *vs.* CC | 0.796 (0.702–0.902) | 3.57 | 0.000 | 0.779 | 0 | F |
| GG *vs.* CC | 0.756 (0.646–0.885) | 3.49 | 0.000 | 0.850 | 0 | F |
| GG + CG *vs.* CC | 0.784 (0.696–0.882) | 4.04 | 0.000 | 0.776 | 0 | F |
| GG *vs.* CG + CC | 0.868 (0.757–0.996) | 2.02 | 0.044 | 0.886 | 0 | F |
| G *vs.* C | 0.859 (0.794–0.928) | 3.82 | 0.000 | 0.789 | 0 | F |
| Population (N=3) | | | | | | |
| CG *vs.* CC | 0.964 (0.802–1.160) | 0.66 | 0.506 | 0.765 | 0 | F |
| GG *vs.* CC | 0.985 (0.820–1.183) | 0.16 | 0.870 | 0.361 | 1.9 | F |
| GG + CG *vs.* CC | 0.962 (0.838–1.104) | 0.55 | 0.581 | 0.789 | 0 | F |
| GG *vs.* CG + CC | 0.941 (0.718–1.232) | 0.44 | 0.656 | 0.071 | 62.3 | R |
| G *vs.* C | 0.976 (0.895–1.064) | 0.55 | 0.580 | 0.203 | 37.2 | F |

CI, confidence interval; OR, odds ratio; F, fixed effect; R, random effect.

### *The analysis of sensitivity*

We analyzed the sensitivity analysis by excluding study one by one. The analysis of sensitivity was suggesting that no obviously effects were exited from each article. That was say, our results were stable.

### *Publication bias analysis*

We performed quantitative analysis by Egger's test. We

 

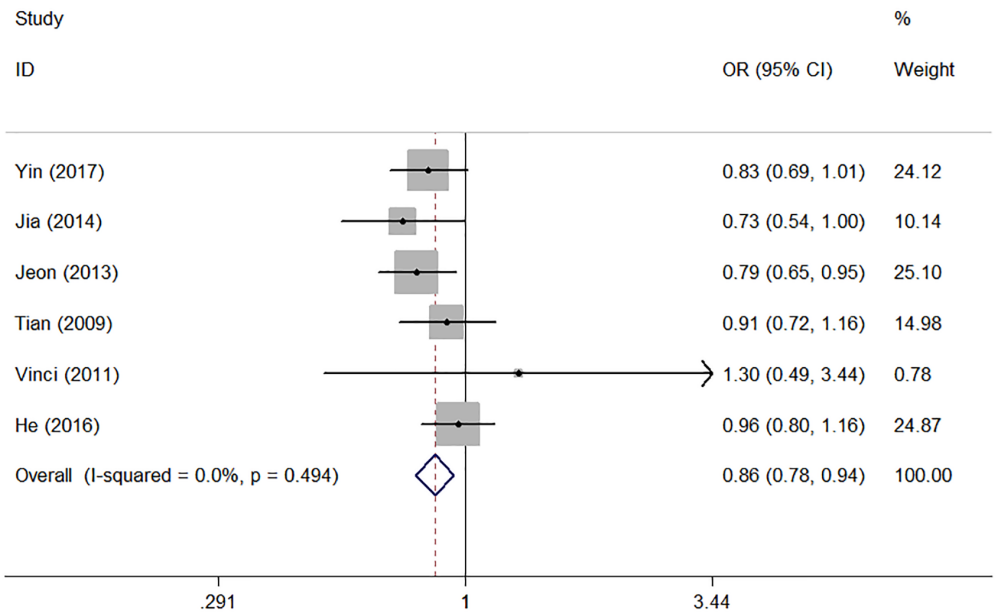


**Figure 2** The forest plot of *miR-146a* (CG *vs.* CC) was shown. OR, odd ratio; CI, confidence interval.

found P>0.05 and 95% CI including 1 in this study, suggesting no meaningful bias in this meta-analysis.

## Discussion

In the past years, majority studies have shown that miRNAs play vital roles in cancer risks (30-32). And the newly miRNAs have enjoyed a high level of concern in medical science. *MiR-219-1* (rs213210 and rs107822) might be associated with lung cancer risk (33). A significant association between the *miR-608* (rs4919510) polymorphism and lung cancer risk was also observed (34). Rs12740674 in *miR-1262* was significantly related with increased risk of lung cancer (35). Many studies have proved that *miR-146a* (rs2910164), *miR-196a2* (rs11614913) and *miR-499* (rs3746444) were related to the incidence of lung cancer. Compared with other SNPs, these three common polymorphisms in microRNAs were more popular and hot. *MiR-146a* (2910164), *miR-196a2* (rs11614913) and *miR-499* (rs3746444) polymorphism may have different function in the variety of tumors (36-38).The down-regulation of *miR-146a* contributed to *COX-2* expression levels in lung cancer cells, including A549 cells (39). By influencing the expression and maturation of miRNAs, *miR-196a2* was associated with the risk of lung cancer (19). *MiR-196a2* was related with a wide variety of malignancies, including non-small-cell lung cancer (40). *MiR-499* might play an important role for early detection non-small cell lung cancer (NSCLC) (41). For lung cancer, previous meta-analysis did not get the same results about *miR-146a* and *miR-196a2* in some aspects. There was a meta-analysis found that *miR-146a* was not associated with lung cancer by Xu *et al.* (42). Xu *et al.* found that *miR-196a2* was associated with lung cancer risk. Ren *et al.* (43) indicated that *miR-146a* might have significant association with lung cancer risk, particularly in Asians and the control from hospital-base. For lung cancer, *miR-196a2* was a dangerous factor in Asians and the control from population-base.

It was worth noting that there were several problems in the above meta-analyses. As we can see, the association of *miR-146a*, *miR-196a2* and *miR-499* with lung cancer susceptibility could not be clear observed by previous meta-analysis. They got the different results might be limited the number of articles. Recently, we found more new researches in these fields and the sample size was large. Also, our own laboratory has been engaged in this research. Therefore, an update meta-analysis was needed to show the clear association between three common polymorphisms and lung cancer risk. Comparing with the previous meta-analysis, this meta-analysis including 9,231 cases and 9,280 controls combined previously published articles and an academic dissertation was conducted for the aim of estimating the real relation between three common polymorphisms and the risk of lung cancer. For all we know, this is the largest

 

**Table 5** The results of *miR-196a2* subgroup analysis were shown

| Population | OR (95% CI) | Test of association | | Test of heterogeneity | | Model |
|---|---|---|---|---|---|---|
| | | Z | P | P | $I^2$ (%) | |
| Overall (N=6) | | | | | | |
| CT *vs.* TT | 1.083 (0.974–1.204) | 1.47 | 0.142 | 0.080 | 49.1 | F |
| CC *vs.* TT | 1.200 (1.056–1.364 ) | 2.79 | 0.005 | 0.432 | 0 | F |
| CC + CT *vs.* TT | 1.117 (1.011–1.235) | 2.18 | 0.029 | 0.148 | 38.6 | F |
| CC *vs.* CT + TT | 1.123 (1.009–1.251) | 2.12 | 0.034 | 0.186 | 33.3 | F |
| C *vs.* T | 1.089 (1.022–1.161) | 2.64 | 0.008 | 0.258 | 23.4 | F |
| Asian (N=5) | | | | | | |
| CT *vs.* TT | 1.123 (0.952–1.326) | 1.38 | 0.169 | 0.058 | 56.2 | R |
| CC *vs.* TT | 1.220 (1.072–1.389) | 3.01 | 0.003 | 0.826 | 0 | F |
| CC + CT *vs.* TT | 1.126 (1.018–1.245) | 2.31 | 0.021 | 0.168 | 38.0 | F |
| CC *vs.* CT + TT | 1.150 (1.030–1.283) | 2.49 | 0.013 | 0.506 | 0 | F |
| C *vs.* T | 1.102 (1.033–1.175) | 2.94 | 0.003 | 0.695 | 0 | F |
| Caucasian (N=1) | | | | | | |
| CT *vs.* TT | 0.738 (0.295–1.843) | 0.65 | 0.515 | – | – | – |
| CC *vs.* TT | 0.503 (0.197–1.285) | 1.44 | 1.151 | – | – | – |
| CC + CT *vs.* TT | 0.623 (0.258–1.507) | 1.05 | 0.294 | – | – | – |
| CC *vs.* CT + TT | 0.649 (0.379–1.111) | 1.58 | 0.115 | – | – | – |
| C *vs.* T | 0.728 (0.494–1.071) | 1.61 | 0.107 | – | – | – |
| Hospital (N=3) | | | | | | |
| CT *vs.* TT | 1.270 (1.079–1.495) | 2.87 | 0.04 | 0.309 | 14.9 | F |
| CC *vs.* TT | 1.264 (1.043–1.532) | 2.39 | 0.017 | 0.724 | 0 | F |
| CC + CT *vs.* TT | 1.271 (1.090–1.482) | 3.06 | 0.002 | 0.541 | 0 | F |
| CC *vs.* CT + TT | 1.089 (0.927–1.278) | 1.04 | 0.299 | 0.313 | 13.8 | F |
| C *vs.* T | 1.134 (1.030–1.249) | 2.56 | 0.011 | 0.706 | 0 | F |
| Population (N=3) | | | | | | |
| CT *vs.* TT | 0.963 (0.974–1.204) | 0.53 | 0.596 | 0.574 | 0 | F |
| CC *vs.* TT | 1.151 (0.969–1.367) | 1.60 | 0.109 | 0.156 | 46.2 | F |
| CC + CT *vs.* TT | 1.016 (0.890–1.159) | 0.23 | 0.815 | 0.329 | 9.9 | F |
| CC *vs.* CT + TT | 1.089 (0.845–1.405) | 0.66 | 0.509 | 0.086 | 59.2 | R |
| C *vs.* T | 1.027 (0.886–1.190) | 0.35 | 0.727 | 0.098 | 56.9 | R |

CI, confidence interval; OR, odds ratio; R, random effect; F, fixed effect.

meta-analysis to evaluate the relationship between the three common polymorphisms in miRNAs and lung cancer risk.

In the overall analysis, results implied that *miR-146a* (rs2910164) had a significant correlation with the risk of lung cancer. And compared with homozygous CC, homozygous GG might be a protective factor for lung cancer. Compared with allele C, allele G was found to be associated with decreased lung cancer risk. Subgroup analyses based on ethnicity, results

 

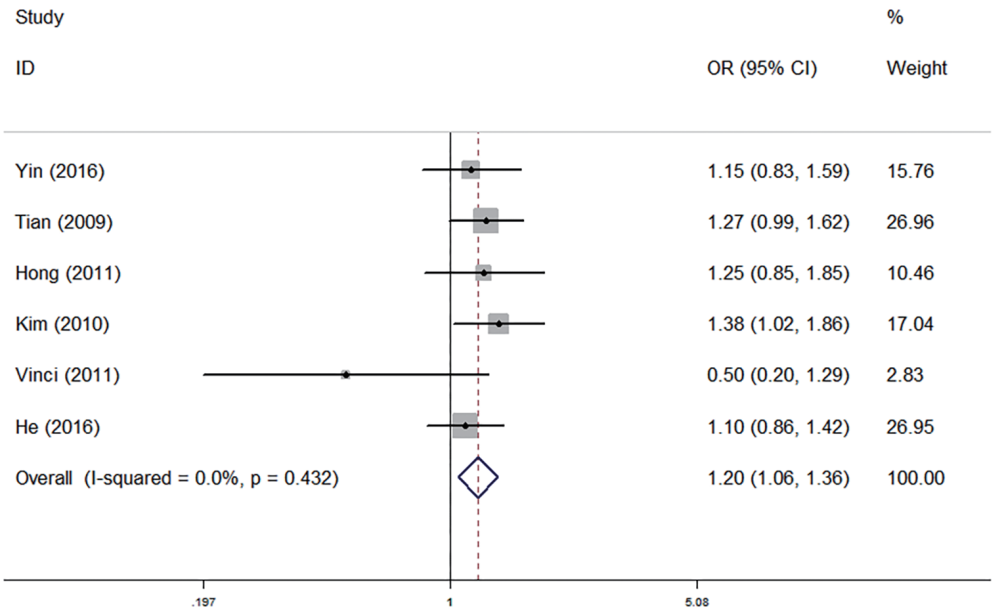


**Figure 3** The forest plot of *miR-196a2* (CC *vs.* TT) was shown. OR, odd ratio; CI, confidence interval.

**Table 6** The results of *miR-499* subgroup analysis were shown

| Population | OR (95% CI) | Test of association | | Test of heterogeneity | | Model |
|---|---|---|---|---|---|---|
| | | Z | P | P | $I^2$ (%) | |
| Overall (N=5) | | | | | | |
| AG *vs.* AA | 1.131 (1.022–1.252) | 2.37 | 0.018 | 0.453 | 0 | F |
| GG *vs.* AA | 1.702 (1.093–2.650) | 2.35 | 0.019 | 0.010 | 69.8 | R |
| AG + GG *vs.* AA | 1.207 (1.042–1.398) | 2.51 | 0.012 | 0.084 | 51.4 | R |
| GG *vs.* AG + AA | 1.640 (1.066–2.523) | 2.25 | 0.024 | 0.013 | 68.6 | R |
| G *vs.* A | 1.226 (1.026–1.464) | 2.24 | 0.025 | 0.003 | 75.4 | R |
| Asian (N=4) | | | | | | |
| AG *vs.* AA | 1.131 (1.020–1.254) | 2.33 | 0.020 | 0.300 | 18.2 | F |
| GG *vs.* AA | 1.870 (1.182–2.958) | 2.67 | 0.007 | 0.013 | 72.3 | R |
| AG + GG *vs.* AA | 1.217 (1.034–1.432) | 2.37 | 0.018 | 0.046 | 62.5 | R |
| GG *vs.* AG + AA | 1.807 (1.162–2.808) | 2.63 | 0.009 | 0.017 | 70.5 | R |
| G *vs.* A | 1.257 (1.036–1.524) | 2.32 | 0.020 | 0.002 | 80.2 | R |
| Caucasian (N=1) | | | | | | |
| AG *vs.* AA | 1.128 (0.652–1.953) | 0.43 | 0.667 | – | – | – |
| GG *vs.* AA | 0.840 (0.305–2.314) | 0.34 | 0.737 | – | – | – |
| AG + GG *vs.* AA | 1.075 (0.638–1.811) | 0.27 | 0.787 | – | – | – |
| GG *vs.* AG + AA | 0.799 (0.298–2.140) | 0.45 | 0.655 | – | – | – |
| G *vs.* A | 1.005 (0.664–1.520) | 0.02 | 0.982 | – | – | – |

CI, confidence interval; OR, odds ratio; R, random effect; F, fixed effect.

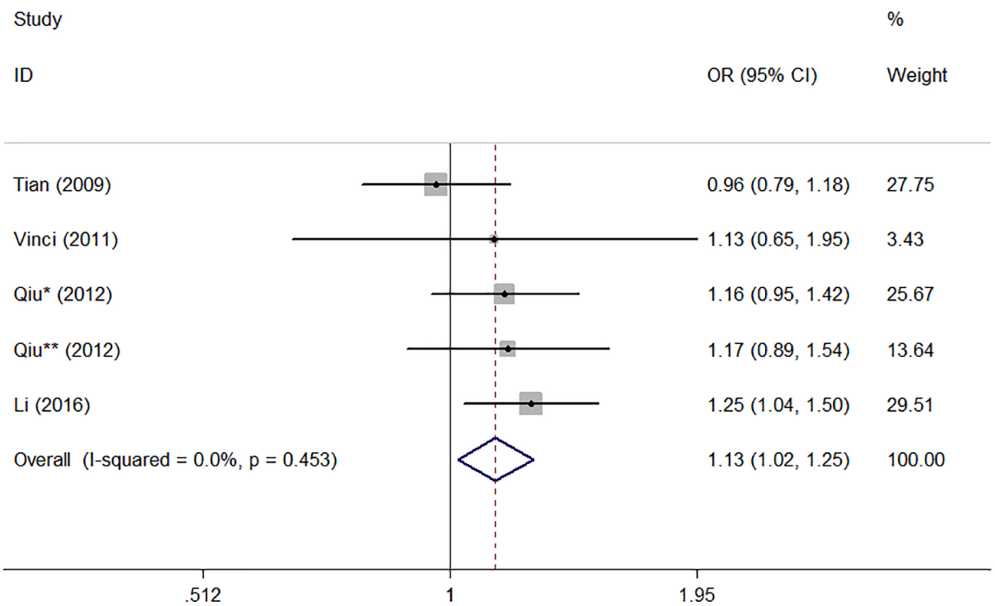


**Figure 4** The forest plot of *miR-499* (AG *vs.* AA) was shown. OR, odd ratio; CI, confidence interval. *, the study population is Guangzhou, China; **, the study population is Suzhou, China.

indicated that significantly affected lung cancer risk was found for *miR-146a* in Asians when subgroup analysis by sources of controls, it performed that *miR-146a* (rs2910164) had obvious correlation with lung cancer risk in the hospital-based study but not in population-based study. And compared with homozygous CC, homozygous GG might be associated with decreased the risk of lung cancer. Compared with allele C, allele G could decrease the risk of lung cancer. In the overall analysis, results presented that *miR-196a2* (rs11614913) had obvious correlation with the risk of lung cancer. Homozygous CC might be the risk factor for lung cancer compared with homozygous TT. By observing recessive model, we could find the homozygous CC increased the risk of lung cancer. The subgroup analysis by race, individuals with homozygous CC had the higher risk of lung cancer in Asian population compared with homozygous TT. When subgroup analyzed by sources of controls, homozygous CC/heterozygous CT could be associated with increased lung cancer risk compared with homozygous TT in the hospital-based study. In the overall analysis, results presented that *miR-499* had correlation with the risk of lung cancer. *MiR-499* might be related with increased lung cancer risk in five genetic models. The subgroup analyzed by race, the results of five genetic models showed the significant association between *miR-499* and the risk of lung cancer.

Although our research efforts are sufficient to implement a comprehensive analysis, there are still some limitations. Firstly, the different genetic backgrounds and living environments were exited in these conducted studies (44,45). Then, these case control studies only included Asian (Chinese and Korean populations) and Caucasian (Italy population). So the results could not be used as a model for other countries. Due to the limited number of Caucasians study, the results could not be used as a model for Caucasians. Secondly, publication bias might be existed, but the results of publication bias did not have statistical significance. Third, since the original studies did not have the smoking status, it was not possible to conduct subgroup analysis on smoking. Finally, we only analysis the published studies but not include unpublished articles.

## Conclusions

In conclusion, this meta-analysis provides evidence that *miR-146a* (rs2910164), *miR-499* (rs3746444) and *miR-196a2* (rs11614913) polymorphisms might contribute to associating with lung cancer risk. As we know, this is the first time to get the significant relationship between *miR-499* and lung cancer risk. Also, the result needs to be confirmed by a series of further experiments.

In this meta-analysis, *miR-146a* (rs2910164), *miR-196a2* (rs11614913) and *miR-499* (rs3746444) may be associated with the risk of lung cancer.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.03.32). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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