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*Original Article*

# Lack of association between risk of esophageal squamous cell carcinoma and polymorphisms of miR-146a and miR-423

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**Abstract:** Esophageal squamous cell carcinoma (ESCC) is one of the major causes of morbidity and mortality worldwide. Many microRNAs are associated with the development of ESCC. Previous studies showed that the polymorphisms of miR-146a rs2910164 and miR-423 rs6505162 are linked with susceptibility to ESCC. However, conclusions in published reports were inconsistent. Consequently, this meta-analysis was conducted to evaluate the association between ESCC risk and polymorphisms of miR-146a rs2910164 and miR-423 rs6505162. A systematic literature search was performed using the databases of PubMed, Embase, and Web of Science up to May 2017. Nine case-control studies were included in the final meta-analysis. Overall, our data indicate that neither miR-146a rs2910164 nor miR-423 rs6505162 is associated with the risk of ESCC in any genetic model. The sensitivity analysis showed that our result was robust in all genetic models and no publication bias was found in any model. In conclusion, the current meta-analysis demonstrated that polymorphisms of miR-146a rs2910164 and miR-423 rs6505162 are not associated with the susceptibility to ESCC. However, large-scale epidemiological studies including more detailed relevant information should be conducted to validate our findings.

**Keywords:** miR-146a, miR-423, ESCC, risk, polymorphism

## Introduction

Esophageal squamous cell carcinoma (ESCC) is one of the leading causes of cancer-related deaths all over the world. During the last two decades, the incidence rate of ESCC has been increasing. The disease brings about an enormous burden on society [1, 2].

MicroRNAs are tiny non-coding RNAs that regulate gene expression at the posttranscriptional level [3]. MicroRNAs could promote tumorigenesis by altering the cellular processes. It has been demonstrated that dysregulation of many microRNAs is associated with development of ESCC [4].

Carcinogenesis of ESCC is multi-factorial and always affected by genetic factors. Single nucleotide polymorphism (SNP) is the most common type of gene variation. SNPs in the DNA sequences of microRNAs could regulate the expression and function of the corresponding microRNAs and this process is always associated with tumor susceptibility [5]. Many published studies showed that some SNPs that affected microRNA expression could alter the risk of ESCC.

To date, an association between two SNPs (miR-146a rs2910164 and miR-423 rs6505162) and ESCC risk has been analyzed in several previous studies. However, their conclusions were inconsistent. Guo H et al. demonstrated that miR-146a rs2910164 contributed to the high risk of ESCC [6]. However, no association between miR-146a rs2910164 and ESCC risk was found in other studies [7-11]. For miR-423 rs6505162, three studies indicated that the SNP could alter individual susceptibility to ESCC [12-14]. In contrast, three other stud-

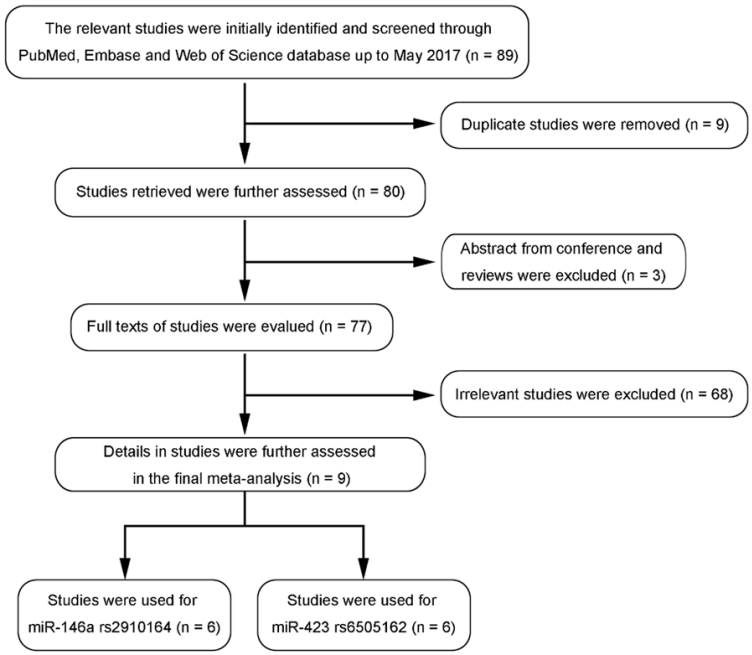


**Figure 1.** Flow diagram of study search and selection in this meta-analysis for the association between risk of esophageal squamous cell carcinoma and polymorphisms of miR-146a rs2910164 and miR-423 rs6505162.

ies showed that miR-423 rs6505162 was not associated with the risk of ESCC [7, 9, 10]. Considering the relationship of the susceptibility to ESCC and the polymorphisms of miR-146a rs2910164 and miR-423 rs6505162 remain controversial, meta-analysis was performed to assess the association between the two SNPs and ESCC risk.

## Materials and methods

### *Search strategy*

A systemic search was carried out to identify all potentially relevant studies, using the databases of PubMed, Embase, and Web of Science up to May 2017. The following search terms were used: "esophageal squamous cell carcinoma or ESCC" and "miR-146a or miRNA-146a or microRNA-146a or miR-423 or miRNA-423 or microRNA-423" and "polymorphism or SNP or rs2910164 or rs6505162 or mutation or variant or genotype". Additionally, manual searching was performed for scanning the references cited in retrieved articles. The full text was further assessed to determine whether they could be included in the final meta-analysis.

### *Inclusion criteria*

Studies included in this meta-analysis needed to meet the following inclusion criteria: (1) evaluating the association between the two SNPs (miR-146a rs2910164 and miR-423 rs6505162) and the risk of ESCC; (2) written in English; (3) a case-control study design; and (4) with sufficient detailed information including available phenotypes and allele frequencies of cases and controls to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Furthermore, abstracts from conferences and review articles were removed.

### *Data extraction*

The following elements were extracted from each eligible study: the first author's name, year of publication, country, ethnicity, the total number of cases and controls, the frequency distribution, and minor allele frequency (MAF). The Newcastle-Ottawa scale was used to assess the quality of the studies included in this meta-analysis.

### *Statistical analysis*

All of the statistical analyses were performed using STATA 11.0 software, (STATA Corp., College Station, TX, USA). Hardy-Weinberg equilibrium (HWE) was detected by Chi-square test among controls. To examine the strength of the association between the two SNPs and ESCC risk, the significance of the pooled ORs and their corresponding 95% CIs in four genetic models (including the allelic model, dominant model, recessive model, and additive model) were determined by the Z test. The between-study heterogeneity across all eligible comparisons was assessed using the Chi square-based Q-test and $I^2$ index was calculated. Heterogeneity was considered significant when $P < 0.10$ for the Q-test or $I^2 > 50\%$ and the random-effect model was performed to calculate the pooled OR. Otherwise, the fixed-effect model was used. Meta-regression analysis was conducted

**Table 1.** Characteristics of the studies included in this meta-analysis

| Author | Year | Region | Ethnicity | Sample size | | Score | Risk |
|---|---|---|---|---|---|---|---|
| | | | | Case | Control | | |
| miR-146a rs2910164 G > C | | | | | | | |
| Guo H | 2010 | China | Asian | 444 | 468 | 7 | Increased |
| Qu Y | 2014 | China | Asian | 381 | 426 | 6 | Unchanged |
| Shen F | 2015 | China | Asian | 1400 | 2185 | 5 | Unchanged |
| Umar M | 2012 | India | Asian | 289 | 309 | 5 | Unchanged |
| Wei J | 2013 | China | Asian | 368 | 370 | 6 | Unchanged |
| Zhu J | 2015 | China | Asian | 238 | 278 | 5 | Unchanged |
| Total | | | | 3120 | 4036 | | |
| miR-423 rs6505162 C > A | | | | | | | |
| Nariman | 2017 | Iran | Asian | 200 | 300 | 6 | Increased |
| Shen F | 2015 | China | Asian | 1400 | 2185 | 5 | Unchanged |
| Umar M | 2012 | India | Asian | 289 | 309 | 5 | Unchanged |
| Wang Y | 2013 | South Africa | African | 538 | 992 | 5 | Increased |
| Yin J | 2013 | China | Asian | 600 | 651 | 6 | Increased |
| Zhu J | 2015 | China | Asian | 242 | 280 | 5 | Unchanged |
| Total | | | | 3269 | 4717 | | |

to delineate the major sources of between-study heterogeneity. Moreover, sensitivity analysis was performed by omitting one study in turn to assess the stability of our results. Publication bias among literatures was analyzed using both Begg's test and Egger's test.

## Results

### *Study selection and characteristics*

As shown in **Figure 1**, a total of 89 potentially eligible articles were initially identified through the literature search (PubMed: 9, Embase: 68, and Web of Science: 12). Among them, 9 studies were duplicated and removed. Thus, 80 articles correlated with the search terms were retrieved. After full text assessment, one abstract from conference, two reviews, and 68 obvious irrelevant studies were excluded. The remaining 9 studies met the inclusion criteria and the data from them were extracted for further assessment [6-14]. All the distributions of the control genotypes in the studies included in this meta-analysis were in HWE. Finally, six case-control studies with 3120 cases and 4036 controls were used to evaluate the possible relationship of miR-146a rs2910164 and ESCC risk [6-11]. Additionally, six case-control studies with 3269 cases and 4717 controls were included to evaluate the possible relationship of miR-423 rs6505162 and ESCC risk [7, 9, 10, 12-14]. The main characteristics of these selected studies are listed in **Table 1**. The genotype frequency distributions of miR-146a rs2910164 and miR-423 rs6505162 in these studies are shown in **Tables 2** and **3**, respectively.

### *Meta-analysis results*

The results on the association between ESCC risk and the polymorphisms of miR-146a rs2910164 and miR-423 rs6505162 are shown in Supplementary Table 1; Supplementary Figures 1, 2. For miR-146a rs2910164, the clear heterogeneity was observed in allele model and additive model. Therefore, the ORs and 95% CIs were calculated in random-effect model (Supplementary Figure 1A and 1D). Simultaneously, the fixed-effect model was used in dominant model and recessive model (Supplementary Figure 1B and 1C). For miR-423 rs6505162, no obvious heterogeneity was found in recessive model. Therefore, the ORs and 95% CIs were calculated in fixed-effect model (Supplementary Figure 2C) and the random-effect model was used in allele model, dominant model, and additive model (Supplementary Figure 2A, 2B and 2D). These data indicate that neither miR-146a rs2910164 nor miR-423 rs6505162 was

**Table 2.** Genotype and allele frequency distribution of miR-146a rs2910164 in the studies included in this meta-analysis

| Author | Case | | | Control | | | MAF | | HWE |
|---|---|---|---|---|---|---|---|---|---|
| | GG | CG | CC | GG | CG | CC | Case | Control | |
| Guo H | 234 | 190 | 20 | 206 | 220 | 42 | 0.259 | 0.325 | 0.120 |
| Qu Y | 62 | 203 | 116 | 75 | 228 | 123 | 0.571 | 0.556 | 0.082 |
| Shen F | 220 | 685 | 495 | 345 | 1060 | 780 | 0.598 | 0.600 | 0.630 |
| Umar M | 163 | 102 | 24 | 155 | 127 | 27 | 0.260 | 0.293 | 0.892 |
| Wei J | 67 | 184 | 117 | 67 | 181 | 122 | 0.568 | 0.574 | 0.993 |
| Zhu J | 82 | 120 | 36 | 99 | 139 | 40 | 0.403 | 0.394 | 0.432 |

**Table 3.** Genotype and allele frequency distribution of miR-423 rs6505162 in the studies included in this meta-analysis

| Author | Case | | | Control | | | MAF | | HWE |
|---|---|---|---|---|---|---|---|---|---|
| | CC | CA | AA | CC | CA | AA | Case | Control | |
| Nariman | 110 | 81 | 9 | 141 | 123 | 36 | 0.248 | 0.325 | 0.256 |
| Shen F | 920 | 421 | 59 | 1421 | 680 | 84 | 0.193 | 0.194 | 0.814 |
| Umar M | 90 | 132 | 67 | 96 | 143 | 70 | 0.460 | 0.458 | 0.233 |
| Wang Y | 30 | 212 | 296 | 46 | 372 | 574 | 0.747 | 0.766 | 0.143 |
| Yin J | 374 | 197 | 29 | 425 | 207 | 19 | 0.213 | 0.188 | 0.299 |
| Zhu J | 99 | 122 | 21 | 109 | 140 | 31 | 0.339 | 0.361 | 0.159 |

remarkably associated with the increased risk of ESCC in the four genetic models (Supplementary Table 1; Supplementary Figures 1, 2).

Stratification analysis was carried out by considering MAF (MAF < 0.5). In this subgroup, miR-146a rs2910164 was significantly associated with ESCC risk only in recessive model, but not in the other models. However, miR-423 rs6505162 remained unassociated with ESCC risk (**Table 4**).

*Heterogeneity and sensitivity analyses*

There was significant heterogeneity in some genetic models. Thus, meta-regression was performed for miR-146a rs2910164 and miR-423 rs6505162 to explore the source of heterogeneity.

The MAF was regarded as the potential confounding factor. However, MAF did not significantly contribute to the source of heterogeneity in any genetic model for miR-146a rs2910164 or miR-423 rs6505162 (Supplementary Table 2).Afteromittinganystudyincludedinthismeta-analysis, neither miR-146a rs2910164 nor miR-423 rs6505162 was associated with risk of ESCC in the four genetic models (Supplementary Tables 3 and 4). These data of sensitivity analysis implies that our meta-analysis results of the two SNPs remained robust in all genetic models.

*Publication bias*

For miR-146a rs2910164 and miR-423 rs6505162, no publication bias was found in any genetic model (**Table 5**).

## Discussion

Around the world, ESCC significantly contributes to the cause of cancer associated death [15]. As an aggressive malignancy, ESCC is always companied with very poor prognosis. The 5 year survival rate for ESCC is approximately 10% [16]. Moreover, the incidence rate of ESCC keeps increasing year after year [17]. Therefore, clinical doctors have realized that the early detection of ESCC is very important for the patients.

MicroRNAs have been well-known for their important roles in regulation of gene expression by targeting mRNAs. It has been demonstrated that microRNAs could affect amounts of biological processes, such as differentiation, cell proliferation and apoptosis [18]. Furthermore, microRNAs are closely linked to the development of tumors. Recent years, many studies indicated that certain microRNAs influenced the ESCC carcinogenesis.

Tumorgenesis is multifactorial, involving activities such as tobacco smoking, alcohol consumption, and genetic factors [19]. Emerging evidence indicates that genetic predisposition may play an important role in the etiology of ESCC [20, 21]. In recent, the SNPs in miRNAs or their binding sites have been demonstrated to be the new variants that are associated with susceptibility to disease [22]. More than that, several prior reports indicated that the SNPs in miRNA genes always affected microRNA maturing, microRNA binding, and post-transcriptional regulation. Therefore, the SNPs related to

**Table 4.** Meta-analysis for the association between risk of esophageal squamous cell carcinoma and polymorphisms of miR-146a rs2910164 and miR-423 rs6505162 (including the studies in which MAF is less than 0.5)

| Genetic comparison | $P_Q$ | $I^2$ | Random model 95% CI | $P_Z$ | Fixed model 95% CI | $P_Z$ |
|---|---|---|---|---|---|---|
| miR-146a rs2910164 G > C | | | | | | |
| G vs. C | 0.092 | 58.10% | 0.85 (0.69-1.05) | 0.138 | | |
| GG + CG vs. CC | 0.083 | 59.80% | 0.79 (0.48-1.29) | 0.340 | | |
| GG vs. CG + CC | 0.211 | 35.70% | | | 0.80 (0.67-0.95) | 0.013 |
| GG vs. CC | 0.048 | 67.00% | 0.73 (0.41-1.29) | 0.275 | | |
| miR-423 rs6505162 C > A | | | | | | |
| C vs. A | 0.048 | 58.30% | 0.96 (0.83-1.11) | 0.573 | | |
| CC + CA vs. AA | 0.018 | 66.30% | 0.93 (0.63-1.36) | 0.704 | | |
| CC vs. CA + AA | 0.353 | 9.30% | | | 0.98 (0.88-1.08) | 0.640 |
| CC vs. AA | 0.013 | 68.60% | 0.91 (0.60-1.38) | 0.657 | | |

**Table 5.** Publication bias analysis of the meta-analysis

| Genetic comparison | Test | t | *P* value | 95% CI |
|---|---|---|---|---|
| miR-146a rs2910164 G > C | | | | |
| G vs. C | Begg's Test | | 0.260 | |
| | Egger's Test | -0.71 | 0.519 | -5.75, 3.41 |
| GG + CG vs. CC | Begg's Test | | 0.260 | |
| | Egger's Test | -0.90 | 0.418 | -3.62, 1.84 |
| GG vs. CG + CC | Begg's Test | | 1.000 | |
| | Egger's Test | 0.02 | 0.987 | -5.57, 5.64 |
| GG vs. CC | Begg's Test | | 0.133 | |
| | Egger's Test | -0.89 | 0.424 | -5.13, 2.64 |
| miR-423 rs6505162 C > A | | | | |
| C vs. A | Begg's Test | | 0.260 | |
| | Egger's Test | -0.90 | 0.419 | -7.47, 3.81 |
| CC + CA vs. AA | Begg's Test | | 0.707 | |
| | Egger's Test | -0.31 | 0.775 | -5.27, 4.23 |
| CC vs. CA + AA | Begg's Test | | 0.133 | |
| | Egger's Test | -0.96 | 0.390 | -3.69, 1.79 |
| CC vs. AA | Begg's Test | | 0.260 | |
| | Egger's Test | -1.17 | 0.306 | -9.91, 4.02 |

microRNAs could eventually influence cancer development and susceptibility [5, 23]. On the basis of the biological and pathologic significance of miRNAs, the functional genetic variations (for instance, SNPs) in miRNAs may promote the development of ESCC.

To date, several studies have been carried out to investigate the relationship between two SNPs (miR-146a rs2910164 and miR-423 rs6505162) and ESCC risk [6-14]. However, their results have been inconsistent. Therein, this meta-analysis was performed to explore the association between the two SNPs and the susceptibility to ESCC. Compared with European and American nations, Africa and Asia (especially China) have the higher incidence of ESCC in the world. Furthermore, some polymorphisms in miRNA genes have been found to be linked with the risk of ESCC in Chinese. Therefore, Asians are the main ethnicity included in this meta-analysis [24].

The observations from our study revealed that neither miR-146a rs2910164 nor miR-423 rs6505162 was associated with the risk of ESCC in any genetic model. Our results in all genetic models were robust. Furthermore, no publish bias was existed in any genetic model in this study.

Nevertheless, the interpretation of our observations should be viewed in light of several limitations. First, the sample size was relative small. Second, only studies published in English were included in this meta-analysis. Third, other populations were not fully considered. Fourth, meta-regression was performed considering only the MAF. Last, this meta-analysis was conducted without considering some valuable information involved in ESCC, such as environmental factors and lifestyle. Thus, the conclusions may be underpowered owing to all of limitations above.

Despite these limitations, the meta-analysis demonstrated no association between susceptibility to ESCC and polymorphisms of miR-146a rs2910164 and miR-423 rs6505162. The results also confirmed the conclusions in certain studies included in the current meta-analysis. However, for practical reasons, it is essential to validate these preliminary findings in the populations with larger sample sizes in the future research. Moreover, it is also necessary to carry out similar association studies across more different ethnicities to clarify the potential impact of miR-146a rs2910164 and miR-423 rs6505162.

To our knowledge, this is the first meta-analysis investigating the relationship between the two SNPs and ESCC risk. The results suggest that these polymorphisms may not have the potential to be the biomarker for ESCC risk. However, to better understand human susceptibility to ESCC and risk factors associated with this pathology, much more large-scale epidemiological studies including more detailed relevant information are needed to validate the conclusion.

## Acknowledgements

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## Disclosure of conflict of interest

None.

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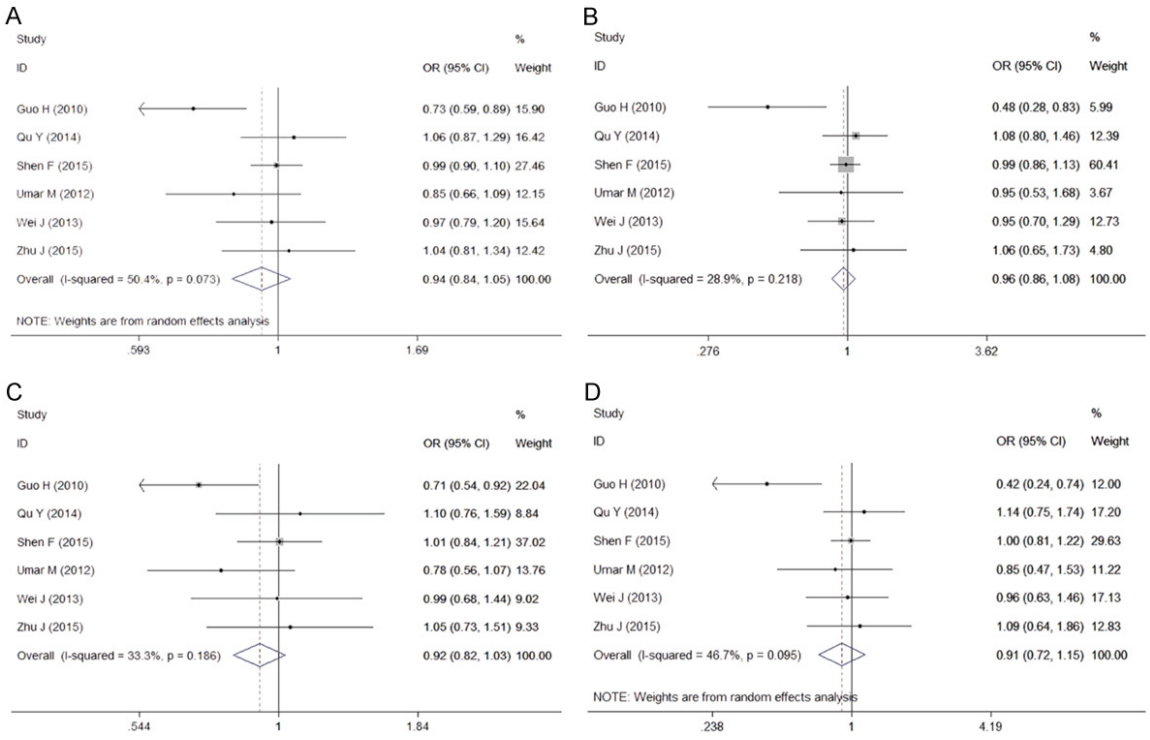
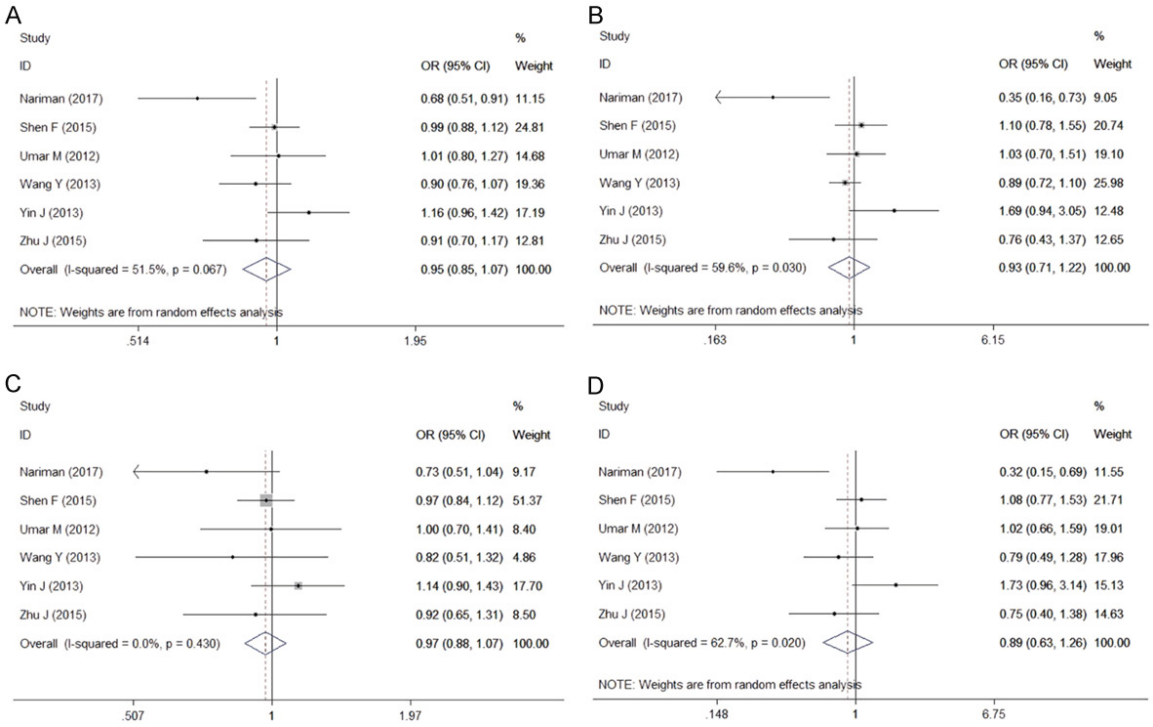
**Supplementary Table 1.** The meta-analysis for the association between the risk of esophageal squamous cell carcinoma and the polymorphisms of miR-146a rs2910164 and miR-423 rs6505162 (including all studies)

| Genetic comparison | $P_Q$ | $I^2$ | Random model 95% CI | $P_Z$ | Fixed model 95% CI | $P_Z$ |
|---|---|---|---|---|---|---|
| miR-146a rs2910164 G > C | | | | | | |
| G vs. C | 0.073 | 50.40% | 0.94 (0.84-1.05) | 0.268 | | |
| GG + CG vs. CC | 0.218 | 28.90% | | | 0.96 (0.86-1.08) | 0.509 |
| GG vs. CG + CC | 0.186 | 33.30% | | | 0.92 (0.82-1.03) | 0.152 |
| GG vs. CC | 0.095 | 46.70% | 0.91 (0.72-1.15) | 0.415 | | |
| miR-423 rs6505162 C > A | | | | | | |
| C vs. A | 0.067 | 51.50% | 0.95 (0.85-1.07) | 0.401 | | |
| CC + CA vs. AA | 0.030 | 59.60% | 0.93 (0.71-1.22) | 0.614 | | |
| CC vs. CA + AA | 0.430 | 0.00% | | | 0.97 (0.88-1.07) | 0.531 |
| CC vs. AA | 0.020 | 62.70% | 0.89 (0.63-1.26) | 0.524 | | |




**Supplementary Figure 1.** The forest plots for the meta-analysis of miR-146a rs2910164 and the risk of esophageal squamous cell carcinoma. A. Allelic model (G vs. C). B. Dominant genetic model (GG + CG vs. CC). C. Recessive genetic model (GG vs. CG + CC). D. Addictive genetic model (GG vs. CC).




**Supplementary Figure 2.** The forest plots for the meta-analysis of miR-423 rs6505162 and the risk of esophageal squamous cell carcinoma. A. Allelic model (C vs. A). B. Dominant genetic model (CC + CA vs. AA). C. Recessive genetic model (CC vs. CA + AA). D. Addictive genetic model (CC vs. AA).

**Supplementary Table 2.** The meta-regression for the association between the risk of esophageal squamous cell carcinoma and the polymorphisms of miR-146a rs2910164 and miR-423 rs6505162

| Genetic comparison | Heterogeneity | t | P > \|t\| | 95% CI |
|---|---|---|---|---|
| miR-146a rs2910164 G > C | | | | |
| G vs. C | + | 1.94 | 0.124 | -0.08, 0.43 |
| GG + CG vs. CC | - | 1.12 | 0.327 | -0.32, 0.76 |
| GG vs. CG + CC | - | 2.05 | 0.110 | -0.09, 0.57 |
| GG vs. CC | + | 1.35 | 0.249 | -0.33, 0.98 |
| miR-423 rs6505162 C > A | | | | |
| C vs. A | + | -0.32 | 0.767 | -0.58, 0.46 |
| CC + CA vs. AA | + | -0.06 | 0.957 | -1.49, 1.43 |
| CC vs. CA + AA | - | -0.65 | 0.548 | -0.89, 0.55 |
| CC vs. AA | + | -0.21 | 0.846 | -1.84, 1.59 |

**Supplementary Table 3.** The sensitivity analysis of the meta-analysis on miR-146a rs2910164

| Author | Genetic comparison | $P_Q$ | $I^2$ | Random model 95% CI | $P_Z$ | Fixed model 95% CI | $P_Z$ |
|---|---|---|---|---|---|---|---|
| Guo H | G vs. C | 0.714 | 0.00% | | | 0.99 (0.92-1.07) | 0.814 |
| | GG + CG vs. CC | 0.975 | 0.00% | | | 0.99 (0.89-1.11) | 0.926 |
| | GG vs. CG + CC | 0.632 | 0.00% | | | 0.98 (0.86-1.11) | 0.760 |
| | GG vs. CC | 0.937 | 0.00% | | | 1.00 (0.86-1.17) | 0.952 |
| Qu Y | G vs. C | 0.064 | 54.90% | 0.92 (0.81-1.04) | 0.177 | | |
| | GG + CG vs. CC | 0.168 | 38.00% | | | 0.95 (0.84-1.07) | 0.370 |
| | GG vs. CG + CC | 0.165 | 38.50% | | | 0.90 (0.80-1.02) | 0.094 |
| | GG vs. CC | 0.075 | 53.00% | 0.86 (0.65-1.14) | 0.283 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Shen F | G vs. C | 0.065 | 54.70% | 0.92 (0.79-1.06) | 0.264 | | |
| | GG + CG vs. CC | 0.145 | 41.50% | | | 0.93 (0.78-1.11) | 0.426 |
| | GG vs. CG + CC | 0.198 | 33.60% | | | 0.87 (0.75-1.01) | 0.061 |
| | GG vs. CC | 0.065 | 54.80% | 0.86 (0.62-1.20) | 0.384 | | |
| Umar M | G vs. C | 0.059 | 56.10% | 0.95 (0.84-1.08) | 0.441 | | |
| | GG + CG vs. CC | 0.134 | 43.10% | | | 0.96 (0.86-1.08) | 0.525 |
| | GG vs. CG + CC | 0.177 | 36.60% | | | 0.94 (0.83-1.07) | 0.342 |
| | GG vs. CC | 0.055 | 56.70% | 0.91 (0.69-1.19) | 0.491 | | |
| Wei J | G vs. C | 0.040 | 60.20% | 0.93 (0.81-1.06) | 0.296 | | |
| | GG + CG vs. CC | 0.135 | 43.00% | | | 0.97 (0.86-1.09) | 0.565 |
| | GG vs. CG + CC | 0.120 | 45.30% | | | 0.91 (0.81-1.03) | 0.135 |
| | GG vs. CC | 0.052 | 57.40% | 0.89 (0.66-1.19) | 0.419 | | |
| Zhu J | G vs. C | 0.048 | 58.40% | 0.92 (0.82-1.05) | 0.221 | | |
| | GG + CG vs. CC | 0.142 | 41.90% | | | 0.96 (0.86-1.07) | 0.465 |
| | GG vs. CG + CC | 0.141 | 42.10% | | | 0.91 (0.80-1.02) | 0.109 |
| | GG vs. CC | 0.058 | 56.10% | 0.87 (0.66-1.15) | 0.341 | | |

**Supplementary Table 4.** The sensitivity analysis of the meta-analysis on miR-423 rs6505162

| Author | Genetic comparison | $P_Q$ | $I^2$ | Random model 95% CI | $P_Z$ | Fixed model 95% CI | $P_Z$ |
|---|---|---|---|---|---|---|---|
| Nariman | C vs. A | 0.380 | 4.80% | | | 0.99 (0.92-1.07) | 0.822 |
| | CC + CA vs. AA | 0.260 | 24.30% | | | 0.98 (0.84-1.14) | 0.811 |
| | CC vs. CA + AA | 0.700 | 0.00% | | | 0.99 (0.89-1.10) | 0.891 |
| | CC vs. AA | 0.263 | 23.80% | | | 1.03 (0.84-1.26) | 0.800 |
| Shen F | C vs. A | 0.040 | 60.20% | 0.93 (0.80-1.09) | 0.399 | | |
| | CC + CA vs. AA | 0.023 | 64.80% | 0.89 (0.63-1.25) | 0.488 | | |
| | CC vs. CA + AA | 0.300 | 18.10% | | | 0.97 (0.84-1.12) | 0.639 |
| | CC vs. AA | 0.014 | 68.00% | 0.84 (0.54-1.31) | 0.440 | | |
| Umar M | C vs. A | 0.038 | 60.60% | 0.94 (0.82-1.08) | 0.367 | | |
| | CC + CA vs. AA | 0.016 | 67.00% | 0.90 (0.64-1.27) | 0.556 | | |
| | CC vs. CA + AA | 0.302 | 17.60% | | | 0.97 (0.87-1.07) | 0.516 |
| | CC vs. AA | 0.010 | 69.80% | 0.86 (0.55-1.32) | 0.485 | | |
| Wang Y | C vs. A | 0.048 | 58.30% | 0.96 (0.83-1.11) | 0.573 | | |
| | CC + CA vs. AA | 0.018 | 66.30% | 0.93 (0.63-1.36) | 0.704 | | |
| | CC vs. CA + AA | 0.353 | 9.30% | | | 0.98 (0.88-1.08) | 0.640 |
| | CC vs. AA | 0.013 | 68.60% | 0.91 (0.60-1.38) | 0.657 | | |
| Yin J | C vs. A | 0.184 | 35.50% | | | 0.93 (0.86-1.01) | 0.101 |
| | CC + CA vs. AA | 0.080 | 52.10% | 0.87 (0.67-1.12) | 0.286 | | |
| | CC vs. CA + AA | 0.628 | 0.00% | | | 0.93 (0.83-1.04) | 0.220 |
| | CC vs. AA | 0.063 | 55.20% | 0.81 (0.58-1.13) | 0.210 | | |
| Zhu J | C vs. A | 0.039 | 60.30% | 0.96 (0.84-1.09) | 0.509 | | |
| | CC + CA vs. AA | 0.019 | 66.20% | 0.96 (0.70-1.30) | 0.783 | | |
| | CC vs. CA + AA | 0.309 | 16.70% | | | 0.97 (0.88-1.08) | 0.606 |
| | CC vs. AA | 0.013 | 68.60% | 0.92 (0.62-1.37) | 0.671 | | |