



# The rate of miR-146a rs2910164 mutations in patients with lung cancer: a meta-analytic review

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**Background:** Worldwide, lung cancer has become the most common cancer type and lung cancer gradually becomes the leading cause of cancer death. MiR-146a rs2910164 polymorphism might be associated with the susceptibility to lung cancer. This article will discuss the rate of miR-146 rs2910164 mutation in lung cancer and normal people.

**Methods:** We searched the relevant published literature from January 1, 2009, to December 31, 2019, in English or Chinese, using the PubMed, Medline, Embase, China Biology Medicine disc, China National Knowledge Infrastructure, and WanFang databases. Two reviewers extracted data from eligible studies in duplicate with a standard data collection form and reached a consensus on each item. All analyses were performed using the Review Manager.

**Results:** In conclusion, the frequency of miR-146a GC genotype mutation in normal people and patients with lung cancer is 44% and 47% respectively and the rate of miR-146a CC genotype mutation in the normal people and patients with lung cancer is 17% and 22% respectively. What's more, the frequency of miR-146a C allele mutation in normal people and patients with lung cancer is 40% and 46% respectively.

**Conclusions:** In conclusion, we can find that the mutation rate of the lung cancer group is higher than the normal people. In the lung cancer group, we can find that the rate of mutation is highest in Italians and lowest in Indians, both in genotypes and in allele C, in which there are significant differences. Chinese and Koreans have similar mutation rates.

**Keywords:** MiR-146a; polymorphism; cancer; rate; meta-analysis

Submitted May 24, 2020. Accepted for publication Oct 09, 2020.

doi: 10.21037/tcr-20-2171

**View this article at:** <http://dx.doi.org/10.21037/tcr-20-2171>

## Introduction

Cancer is a major public health problem, and its rapidly increasing risk has threatened human health throughout the country and around the world (1). The mortality rate of lung cancer is highest, which leads to approximately 1.6 million deaths annually, 19.4% of the total (2). A quantity of research has demonstrated that the occurrence and development of cancer is a complex multi-step, multi-

stage, and multi-factorial process (3). The formation of lung cancer is not only related to environmental factors but also depends on individual genetic susceptibility. For example, although more than 80% of lung cancer patients have smoked, only 15% of smokers will eventually be diagnosed with lung cancer, indicating that other factors such as genetic predisposition are considered to play a vital role in the development of lung cancer (4). At present, targeted therapy and immunotherapy play an important

role in advanced lung cancer, and the mechanism of action also depends on gene mutation. Therefore, it is of great significance to study the pathogenesis of lung cancer from the perspective of a gene mutation for the treatment and prevention of lung cancer. For example, because of the mutation of *rs2910164* G to C allele, the production and expression of mature mir-146a were affected, which could influence the process of tumor development. MicroRNAs (miRNAs) are an abundant category of endogenous small non-coding RNAs, which are associated with cancer development and have medical implications (5). Research suggests that miRNA regulates up to 30% of human genes (6) and accumulating evidence supports a significant association between miRNAs and the risk and prognosis of lung cancer (7,8). Takamizawa *et al.* reported that lower expression of the let-7 miRNAs aggravated lung cancer (9), while Hayashita *et al.* found that upregulation of the miRNA-17-92 may decrease lung cancer risk (10). Single-nucleotide polymorphisms (SNPs) can change the properties of miRNAs, thereby influencing an individual's susceptibility to cancers (11-13). The miRNA-146a *rs2910164* polymorphisms, in particular, have been found to be relevant to lung cancer susceptibility (14). Therefore, a great of published data was performed to further explore the correlation between SNPs of miRNA-146a *rs2910164* and lung cancer risk. For example, Jeon *et al.* (15) reported that individuals carrying CG/GG genotype had a significantly lower risk of lung cancer compared with the CC genotype in the Korean population. Xiao *et al.* (16) found that mir-146a *rs2910164* the CC genotype was associated with increased susceptibility to lung cancer compared with GG genotype in both the Chinese and Korean. Xia *et al.* (17) discovered that the individuals with the CC genotype were more likely to develop lung cancer than those with GG. However, there is no meta-analysis of previously and newly published research, which focuses on the different rates of miR-146a G/C mutation in normal people and patients with lung cancer. The purpose of our research is to solve the above problems that could tell us which country needed to test the gene mutation and whether all lung cancer patients needed to do the test.

We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2171>).

## Methods

### Literature retrieval method

We searched the relevant published literature from January 1, 2009, to December 31, 2019, in English or Chinese, using the PubMed, Medline, Embase, China Biology Medicine disc, China National Knowledge Infrastructure, and WanFang databases, with the following keywords: “lung cancer”, “miRNA-146a”, “polymorphism”, “*rs2910164*”. References of the retrieved articles were published in the primary literature and had no distinct overlap of the population with other studies. The inclusion criteria were as follows: (I) data on the miRNA-146a *rs2910164* polymorphisms. (II) The case group for the diagnosis of lung cancer patients and the control group for the non-lung cancer population. We excluded reports with the same data or overlapping data by the same authors. The researches with incomplete data or poor quality were also eliminated.

### Data extraction

Two reviewers extracted data from eligible studies in duplicate with a standard data collection form and reached a consensus on each item. The following information was extracted for each study: first author, publication date, country, genotype miRNA-146a *rs2910164* polymorphism.

### Statistical analysis

The Newcastle-ottawa Scale literature quality evaluation scale to assess the quality of collected literatures. Before the effect size was combined, heterogeneity of the included literature was tested by the Q test or  $I^2$  test. If  $P > 0.1$ ,  $I^2 < 50\%$ , heterogeneity was considered to be nonexistent. The fixed effect model was selected for combination analysis. If  $P < 0.1$ ,  $I^2 > 50\%$ , then heterogeneity is considered, and the random effect model is selected. Publication bias was assessed by visual inspection of the funnel plot. All of the above processes are done using the Review Manager.

## Results

### Study characteristics

We searched online databases using search criteria related to

**Table 1** Characteristics of miR-146a rs2910164 gene mutation and the included researches

Study	Country	N	Lung cancer						Healthy population						
			GC (%)	SE	CC (%)	SE	C (%)	SE	Number	GC (%)	SE	CC (%)	SE	C (%)	SE
Fang (18)	China	492	0.467	0.022	0.118	0.015	0.352	0.015	209	0.526	0.035	0.153	0.025	0.416	0.024
Jeon (15)	Korean	1,101	0.454	0.015	0.334	0.014	0.561	0.011	1,096	0.493	0.015	0.285	0.014	0.531	0.011
Jia (19)	China	400	0.455	0.025	0.385	0.024	0.613	0.017	400	0.500	0.025	0.310	0.023	0.560	0.018
Mohamed (20)	Egypt	120	0.500	0.046	0.133	0.031	0.383	0.031	120	0.392	0.045	0.050	0.020	0.246	0.028
Sodhi (21)	India	250	0.336	0.030	0.020	0.009	0.188	0.017	255	0.243	0.027	0.008	0.006	0.129	0.015
Tian (22)	China	1,058	0.482	0.015	0.178	0.012	0.419	0.011	1,035	0.485	0.016	0.163	0.011	0.406	0.011
Vinci (23)	Italy	101	0.475	0.050	0.089	0.028	0.327	0.033	129	0.349	0.042	0.085	0.025	0.260	0.027
Wei (24)	China	198	0.500	0.036	0.343	0.034	0.593	0.025	218	0.390	0.033	0.138	0.023	0.333	0.023
Yin (25)	China	575	0.487	0.021	0.344	0.020	0.588	0.015	608	0.515	0.020	0.276	0.018	0.534	0.014
Yin (26)	China	258	0.519	0.031	0.306	0.029	0.566	0.022	310	0.516	0.028	0.281	0.026	0.539	0.020

miRNA-146a rs2910164 SNPs and the risk of lung cancer. Ten published articles (15-23) were initially collected with 4,553 and 4,380 participants in the case and control groups, respectively (Table 1).

The frequency of miR-146a GC genotype mutation in normal people and patients with lung cancer is 44% and 47% respectively (Figure 1).

The frequency of miR-146a CC genotype mutation in normal people and patients with lung cancer is 17% and 22% respectively (Figure 2).

The frequency of miR-146a C allele mutation in normal people and patients with lung cancer is 40% and 46% respectively (Figure 3).

The funnel plot of miR-146a rs2910164 was constructed to evaluate the publication bias of the literature; the results indicated that no obvious publication bias affected this meta-analytic review (Figure 4).

Characteristics of miR-146a rs2910164 gene mutation in different countries are shown below. In the lung cancer group, we can find that the rate of mutation is highest in Italians and lowest in Indians, both in genotypes and in allele C, in which there are significant differences. Chinese and Koreans have similar mutation rates (Table 2).

## Discussion

Lung cancer is the highest morbidity and mortality of malignant tumors in both developed and developing countries (27). Both environmental exposure and SNPs

can make an individual more susceptible to lung cancer. MiRNAs are an abundant category of endogenous small non-coding RNAs of about 18–25 nucleotides in length, which negatively regulate their target mRNAs via posttranscriptional gene silencing to participate in multiple biological processes (including immunity, inflammation, tumor and so on (28-30)). In the process of tumor development, because of the mutation of rs2910164 G to C allele, the production, and expression of mature mir-146a were affected. The transcriptional activity of the precursor containing the C allele of mir-146a was low, which ultimately affected the binding of mir-146a to the target mRNA, thereby affecting the risk of tumor development in individuals (31,32). Many studies have explored the common SNPs of miRNAs and their associations with the risk of various cancers, including lung cancer (33-38). Identifying SNPs is important in predicting the risks of individuals and understanding the pathogenesis of cancer.

Up to now, there are many studies about mir-146a rs2910164 gene polymorphism in the risk of tumor occurrence with many inconsistencies. For example, heterozygote GC can increase the risk of thyroid papillary cancer in the population (39). Xu *et al.* (40) found that CC genotype can reduce the risk of prostate cancer. Shen *et al.* (41) found that the C allele can increase the risk of familial breast cancer in the population. Jeon *et al.* (15) reported that individuals carrying CG/GG genotype had a significantly lower risk of lung cancer compared with the CC genotype in the Korean population. Xiao

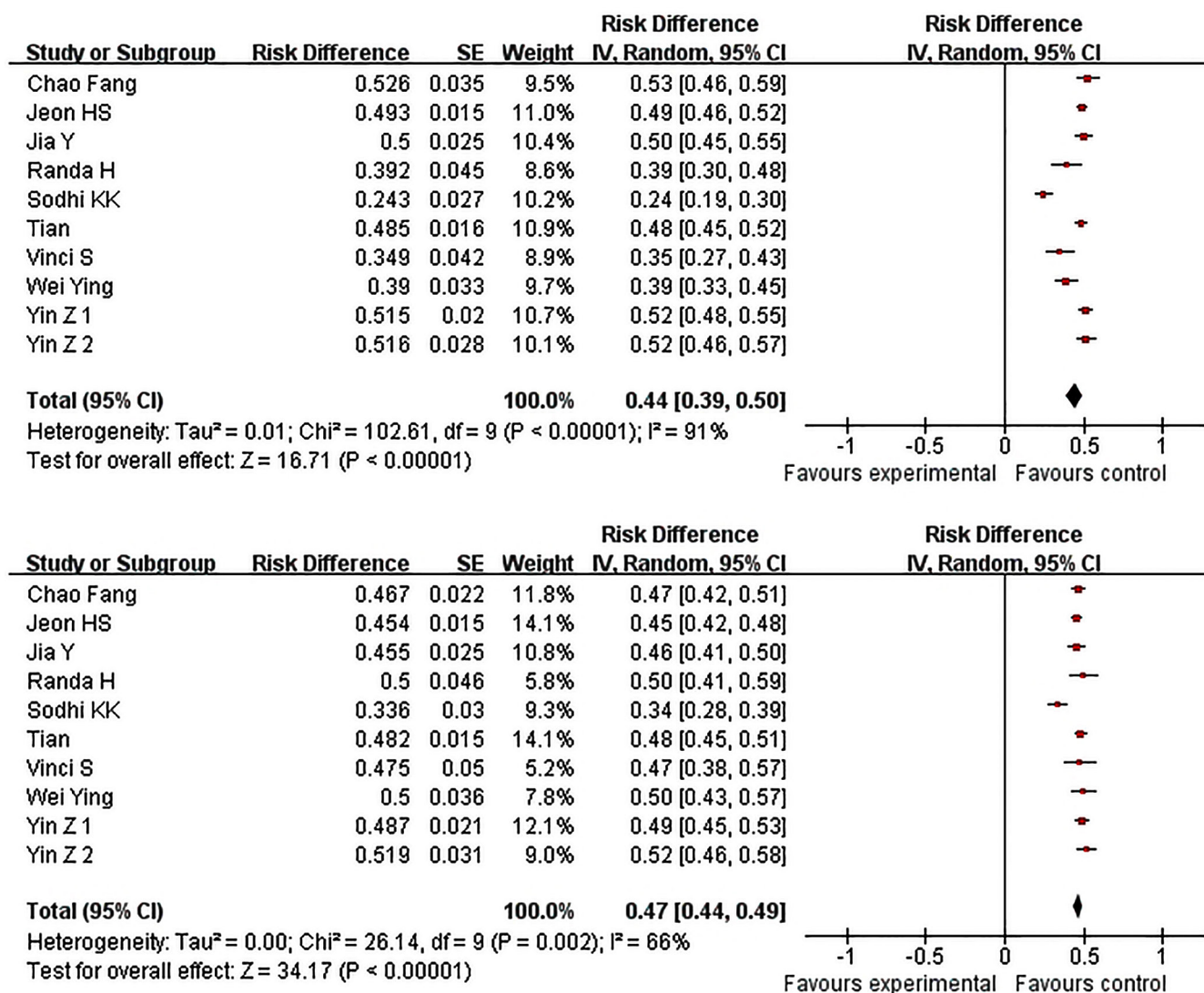
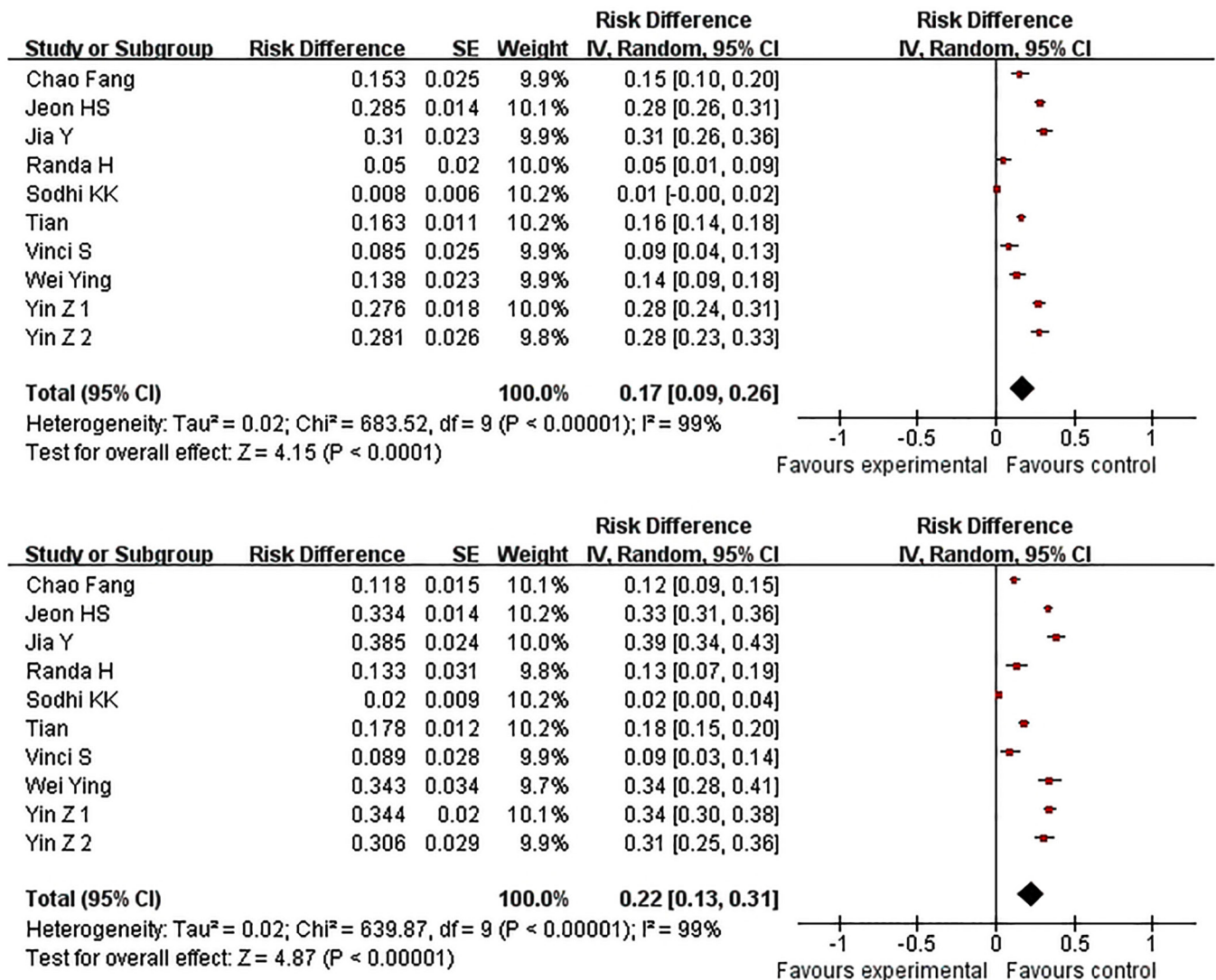


Figure 1 The frequency of miR-146a GC genotype mutation in normal people and patients with lung cancer.

*et al.* (16) found that mir-146a rs2910164 the CC genotype was associated with increased susceptibility to lung cancer compared with GG genotype in both the Chinese and Korean. Xia *et al.* (17) discovered that the individuals with the CC genotype were more likely to develop lung cancer than those with GG. The C allele of rs2910164 was considered to be the risk allele for lung cancer. Vinci *et al.* (23) found that the rs2910164 GC genotype can significantly increase the risk of non-small cell lung cancer. Wei *et al.* (24) showed that the C allele of mir-146a rs2910164 gene polymorphism in Guang'an of China could increase the risk of non-small cell lung cancer in the population, and the risk of lung cancer in individuals with

GC/CC genotype increases by 5.04 times. In our study, we demonstrate that the frequency of miR-146a GC genotype mutation in normal people and patients with lung cancer is 44% and 47% respectively and the rate of miR-146a CC genotype mutation in the normal people and patients with lung cancer is 17% and 22% respectively. What's more, the frequency of miR-146a C allele mutation in normal people and patients with lung cancer is 40% and 46% respectively. We can find that the mutation rate of the lung cancer group is higher than the normal people. Characteristics of miR-146a rs2910164 gene mutation in different countries are shown below. In the lung cancer group, we can find that the rate of mutation is highest in Italians and lowest in Indians,



**Figure 2** The frequency of miR-146a CC genotype mutation in normal people and patients with lung cancer.

both in genotypes and in allele C, in which there are significant differences. Chinese and Koreans have similar mutation rates. Does this mean that different countries and races have different mutation frequencies? The sample size of this study was relatively small, further research is needed before any firm conclusions can be drawn regarding this population.

Although we conducted our meta-analysis carefully and rigorously, there were still some limitations. First, and most importantly, the results of the meta-analysis were limited by the available literature, such as the number of documents, quality, and sample size, which could influence the results

of the analysis. Secondly, the literature we collected did not completely exclude publication bias and selection bias. Last but not least, the rate of genetic mutation in gender, race, and other factors is not explored.

## Conclusions

In conclusion, we can find that the mutation rate of the lung cancer group is higher than the normal people. In the lung cancer group, we can find that the rate of mutation is highest in Italians and lowest in Indians, both in genotypes and in allele C, in which there are significant differences.

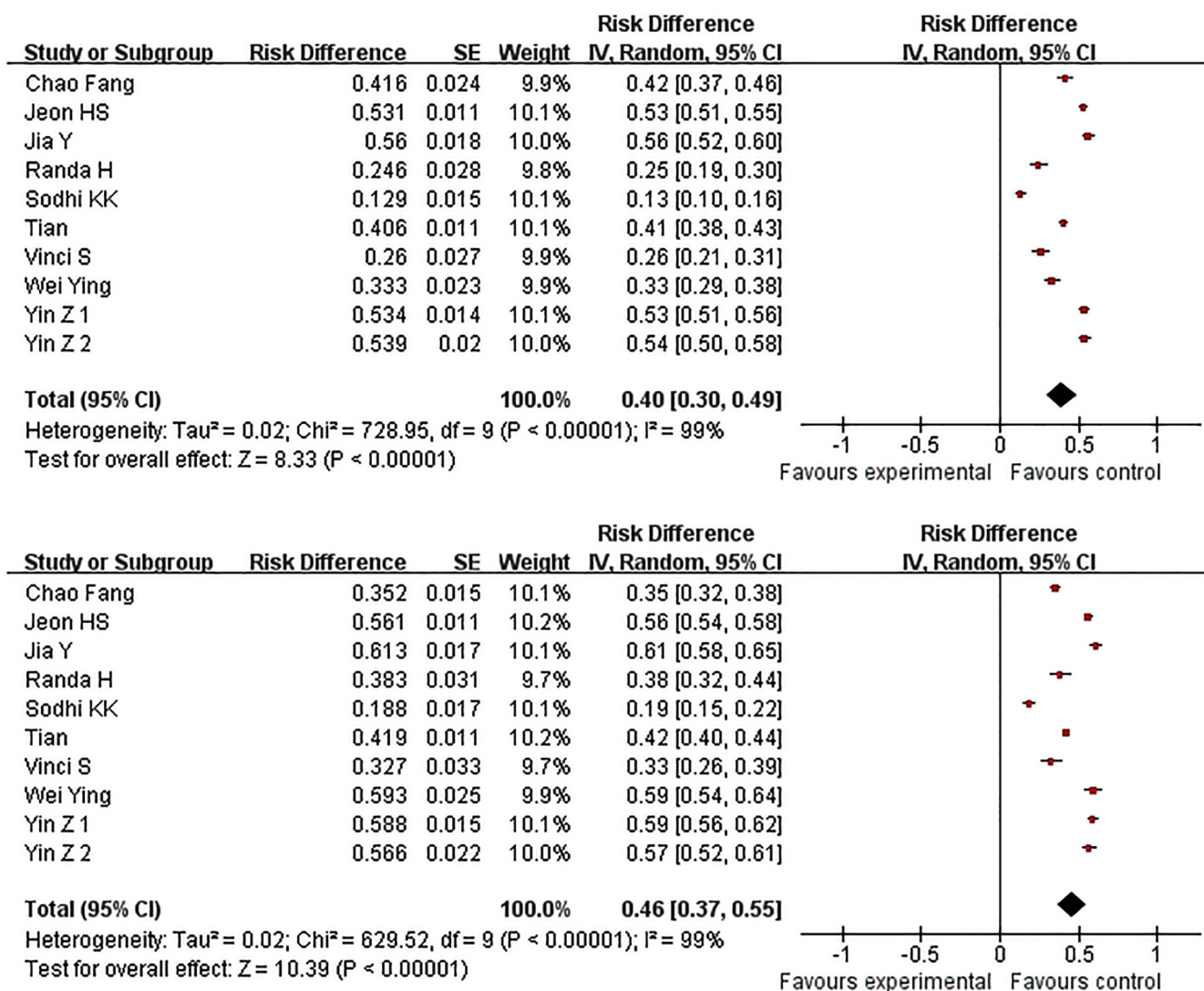


Figure 3 The frequency of miR-146a C allele mutation in normal people and patients with lung cancer.

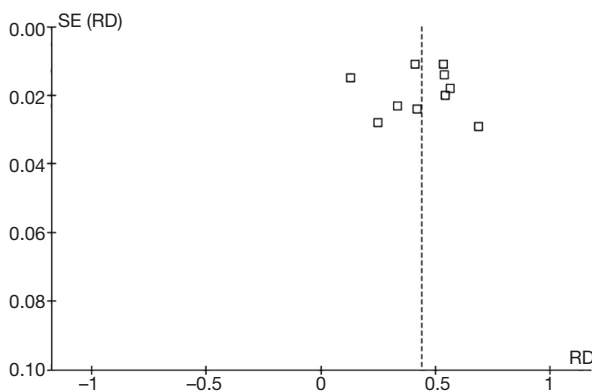


Figure 4 The funnel plot of miR-146a rs2910164.

**Table 2** Characteristics of miR-146a rs2910164 gene mutation in different countries

Country	Lung cancer			Healthy population		
	GC (%)	CC (%)	C (%)	GC (%)	CC (%)	C (%)
China	48.0%	28.0%	52.0%	49.0%	22.0%	47.0%
Korean	45.4%	33.4%	56.1%	49.3%	28.5%	53.1%
Egypt	50.0%	13.3%	38.3%	39.2%	5.0%	24.6%
India	33.6%	2.0%	18.8%	24.3%	0.8%	12.9%
Italy	53.5%	34.7%	61.4%	47.3%	45.0%	68.6%

Chinese and Koreans have similar mutation rates.

### Acknowledgments

*Funding:* None.

### Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tcr-20-2171>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-2171>). 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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**Cite this article as:** Zhang J, Shao W, Zhang Z, Liu D. The rate of miR-146a rs2910164 mutations in patients with lung cancer: a meta-analytic review. *Transl Cancer Res* 2020;9(11):6792-6800. doi: 10.21037/tcr-20-2171