

IL-10 -1082A/G, -592C/A, and -819T/C polymorphisms in association with lung cancer susceptibility: a meta-analysis

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Abstract: Numerous studies have examined the association between interleukin-10 (*IL-10* -1082A/G, -592C/A, and -819T/C) gene polymorphisms and risk of lung cancer, but these have revealed inconsistent results. The aim of this study was to clarify the relationship between these polymorphisms and the risk of lung cancer by performing a meta-analysis. The published literature concerning *IL-10* polymorphisms and lung cancer risk were retrieved by systematically searching PubMed, Embase, Web of Science, China National Knowledge Infrastructure, Wan-Fang, and Database of Chinese Scientific and Technical Periodicals (VIP) database. Statistical analysis was conducted with Stata 12.0 software. A total of ten published articles comprising of 19 studies were selected, including seven studies (1,960 controls and 1,321 cases) for *IL-10* -1082A/G, seven studies (2,613 controls and 1,839 cases) for *IL-10* -592C/A, and five studies (1,558 controls and 926 cases) for *IL-10* -819T/C. This study found that the *IL-10* -1082A/G and -592C/A polymorphisms were significantly associated with the risk of lung cancer in the overall analysis. When stratified by ethnicity, significantly increased risks were observed for *IL-10* -1082A/G, -592C/A, and -819T/C polymorphisms in Asians (for -1082A/G, AA vs [AG + GG]: odds ratio [OR] = 1.20, confidence interval [CI] = 1.05–1.39, $P < 0.05$; for C-592A, C vs A, OR = 1.36, CI = 1.20–1.53, $P < 0.05$; CC vs AA, OR = 1.85, CI = 1.45–2.37, $P < 0.05$; CC vs [CA + AA], OR = 1.36, CI = 1.15–1.61, $P < 0.05$; for -819T/C, T vs C: OR = 1.21, CI = 1.06–1.38, $P < 0.05$; TT vs CC, OR = 1.54, CI = 1.18–2.01, $P < 0.05$; [TT + TC] vs CC, OR = 1.51, CI = 1.17–1.95, $P < 0.05$). Moreover, the data indicated that there was a significant association between *IL-10* -819T/C polymorphism and non-small-cell lung cancer risk. No significant publication bias was detected under the four genetic models (allele model, homozygous model, dominant model, and recessive model) in this meta-analysis. On the basis of these 19 studies, this study found that the *IL-10* -1082A/G and -819T/C polymorphisms might have a significant association with risk of lung cancer in Asian populations.

Keywords: interleukin-10, lung neoplasms, polymorphism, susceptibility, meta-analysis

Introduction

Lung cancer is one of the most commonly diagnosed tumors and continually leads to many deaths worldwide.¹ There were an estimated 1.8 million new cases of lung cancer in 2012, which occurred in the developing countries, accounting for 58% of the total cases. An estimated 1,987,909 new cases of lung cancer were diagnosed and 1,732,185 deaths were due to lung cancer in 2012. Moreover, lung cancer is the most common tumor in males.² The incidence of lung cancer is still obviously increasing.³ The 5-year survival rate for lung cancer patients was only 16% in the past four decades, and the main obstacle in improving lung cancer prognosis was delayed diagnosis.⁴

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There are many reasons for the occurrence of lung cancer, but the major external risk factor was easily identified – cigarette smoking. It has been reported that current smokers are approximately 20 times more likely than never smokers to develop lung cancer.^{5,6} Thus, smoking cessation is very important for public health. In addition, early detection and diagnosis play a crucial role in decreasing the mortality of lung cancer. Survival of lung cancer patients undergoing lung resection was more than 80%, which suggested that early detection and diagnosis helped immensely in the early treatment of lung cancer.^{7,8} Increasing evidence has indicated that polymorphisms of numerous susceptible genes play a significant association in the development of lung cancer. Thus, these polymorphisms could be useful as biomarkers for lung cancer detection.

Interleukin-10 (IL-10) cytokine, which is essential for T_H2 responses, plays a central role in anti-inflammation and is also capable of blocking tumor immune surveillance to inhibit T-cell immunity.⁹ A recent study has shown that the expression of IL-10 was associated with progression of tumors including lung cancer.¹⁰ Some genetic polymorphisms of IL-10 gene, especially in the promoter region, could affect the expression of gene-encoded proteins associated with lung cancer susceptibility and prognosis.¹¹ Three SNPs at positions -1082, -592, and -819 of IL-10 gene promoter have been reported to be associated with expression of IL-10 gene.¹² Moreover, many individual studies have investigated the role of *IL-10 -1082A/G*, *-592C/A*, and *-819T/C* polymorphisms in lung cancer risk. Nevertheless, the results of these studies remained ambiguous and inconclusive owing to the reduced power of single studies. In this study, an updated meta-analysis was performed to estimate the effect of *IL-10 -1082A/G*, *-592C/A*, and *-819T/C* polymorphisms on lung cancer risk.

Material and methods

Literature search strategy

The databases of PubMed, Embase, Web of Science, China National Knowledge Infrastructure, WanFang, and Database of Chinese Scientific and Technical Periodicals (VIP) were searched up to July 2016 to identify relevant studies published concerning the correlation of *IL-10 -1082A/G*, *-592 C/A*, and *-819T/C* polymorphisms with lung cancer risk. The following MESH terms and their synonyms were used: (“Lung Neoplasms” [MESH] or “lung cancer” or “lung tumor” or “lung carcinoma”) and (“Interleukin-10” or “IL-10”). Language restriction was not applied in the

process of retrieval. The reference lists of retrieved article were hand searched.

Inclusion criteria and exclusion criteria

The following inclusion criteria were used: 1) studies investigating the association between *IL-10 -1082A/G*, *-592C/A*, and *-819T/C* polymorphisms and lung cancer risk; 2) studies with a case–control or cohort design; 3) studies with sufficient genotyping data available for calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs); and 4) studies performed in humans. The exclusion criteria were as follows: 1) not a case–control or cohort study, 2) studies without available genotype data, 3) studies with duplicate data, and 4) meta-analysis and reviews.

Quality score assessment

The Newcastle–Ottawa scale was used to assess the quality of studies included. Two investigators independently calculated the score of each study. The scores ranged from 0 to 9, and a score of ≥ 7 indicated a high quality study.

Data extraction

Two investigators independently searched articles and extracted the original data according to the inclusion criteria and exclusion criteria. The extracted information from each eligible study included the following: 1) the first author’s name, 2) year of publication, 3) ethnicity, 4) source of controls, 5) number of cases and controls, and 6) genotype frequencies. Disagreement in data extraction was settled by consulting with the third investigator.

Statistical analysis

The strength of association between *IL-10 -1082A/G*, *-592C/A*, and *-819T/C* polymorphisms and lung cancer risk was evaluated by calculating crude ORs and 95% CIs under an allele, a homozygous, a dominant, and a recessive model, respectively. Chi-square-based Q -test and I^2 statistic test were performed to evaluate the heterogeneity assumption. A random-effects model (the DerSimonian and Laird method) was used to calculate the crude ORs of each study in case of $P < 0.05$ or $I^2 > 50\%$, whereas a fixed-effects model (the Mantel–Haenszel method) was used if heterogeneity did not exist.^{13,14} Potential publication bias was evaluated using Begg’s funnel plots and Egger’s test. Sensitivity analysis was conducted to estimate the stability of the results by omitting each single study. The overall analysis and stratified analysis were performed using Stata 12.0 software (Stata Corp LP, College Station, TX, USA).

Results

Characteristics of published studies

Based on the inclusion criteria, a total of 372 publications were obtained on literature searching. After removing the articles that did not deal with the association of IL-10 polymorphism with lung cancer risk, reviews, and meta-analysis, 14 were left for further analysis. After further evaluation by reading full texts, four publications were excluded because of insufficient data on IL-10 genotype. Finally, 10 articles with 19 studies that investigated the correlation of *IL-10* -1082A/G, -592C/A, and -819T/C polymorphisms with lung cancer risk were used for the further statistical analysis. Of these, eleven studies were conducted in Asians and eight studies were performed in Caucasians. In addition, eight publications were in English and two publications were in Chinese. The characteristics of all the studies included are listed in Table 1 and shown in Figure 1.

Quantitative analysis

A total of 10 publications amounting to 19 case-control studies were included in this meta-analysis. In the overall analysis, the presence of *IL-10* -1082A/G polymorphisms was associated with increased lung cancer risk, while *IL-10* -592C/A polymorphisms were shown to decrease the lung cancer risk (for A-1082G, A vs G, OR = 1.17, CI = 1.04–1.30, $P < 0.05$; AA vs [AG + GG], OR = 1.21, CI = 1.05–1.40, $P < 0.05$; for C-592A, C vs A, OR = 0.84, CI = 0.77–0.91, $P < 0.05$; CC vs AA, OR = 0.74, CI = 0.64–0.87, $P < 0.05$; CC vs [CA + AA], OR = 0.83, CI = 0.74–0.94, $P < 0.05$; [CC + CA] vs AA, OR = 0.79, CI = 0.69–0.91, $P < 0.05$). When stratified by ethnicity, *IL-10* -1082A/G, C-592A, and T-819C polymorphisms were associated with increased lung cancer risk in Asians (for -1082A/G, AA vs [AG + GG]: OR = 1.20, CI = 1.05–1.39, $P < 0.05$; for C-592A, C vs A, OR = 1.36, CI = 1.20–1.53, $P < 0.05$; CC vs AA, OR = 1.85, CI = 1.45–2.37, $P < 0.05$; CC vs [CA + AA], OR = 1.36, CI = 1.15–1.61, $P < 0.05$; for -819T/C, T vs C: OR = 1.21, CI = 1.06–1.38, $P < 0.05$; TT vs CC, OR = 1.54, CI = 1.18–2.01, $P < 0.05$; [TT + TC] vs CC, OR = 1.51, CI = 1.17–1.95, $P < 0.05$). Furthermore, when stratified based on disease type, a significant correlation was detected between *IL-10* T-819C polymorphism and non-small-cell lung cancer (NSCLC; for -819T/C, T vs C: OR = 1.57, CI = 1.15–2.16, $P < 0.05$; TT vs CC, OR = 3.15, CI = 1.58–6.30, $P < 0.05$; [TT + TC] vs CC, OR = 3.07, CI = 1.58–5.93, $P < 0.05$). Interestingly, no significant association between *IL-10* -1082A/G, C-592A, and T-819C polymorphisms and lung cancer risk was found in Caucasians.

Furthermore, significantly decreased risk of lung cancer risk was found in the overall analysis of C-592A polymorphism, whereas significantly increased risk was detected in the Asian population (Table 2).

Heterogeneity analysis

Under the homozygous genetic models, significant heterogeneity existed among the studies on *IL-10* -1082A/G and -819T/C polymorphisms (for 1082A/G, $I^2 = 71.8\%$, $P = 0.007$; for -819T/C, $I^2 = 88.0\%$, $P = 0.000$). The forest plots suggested that ethnicity and disease type might be one of the sources of heterogeneity for *IL-10* -1082A/G and -819T/C polymorphisms. However, heterogeneity was significantly lowered after the subgroup analyses based on ethnicity and disease type were conducted. This indicated that the ethnicity and disease type might lead to the heterogeneity. Furthermore, a meta-regression revealed that score, sample size, and genotyping method were not the sources of heterogeneity (for *IL-10* -1082A/G and -819T/C, $P > 0.05$; Figures 2–4).

Publication bias and sensitivity analysis

On the basis of the Begg's test and Egger's test, no publication bias was found for the association between *IL-10* -1082A/G, -592C/A, and -819T/C polymorphisms and lung cancer risk. Moreover, sensitivity analysis indicated that the results were stable after sequentially omitting each study (Figures 5–7).

Discussion

IL-10 was shown to have a significant effect on the tumorigenesis of different cancers and could even protect tumors by inhibiting the function of macrophages and dendritic cells, which present tumor cell antigens to the cytotoxic T lymphocytes.¹⁵ Previous studies have found an association between IL-10 polymorphism and oral cancer, breast cancer, gastric cancer, colorectal cancer, esophageal cancer, hepatocellular cancer, cervical cancer, thyroid cancer, and nasopharyngeal cancer.^{16–24} As for lung cancer, many studies have revealed that the loss of IL-10 expression could promote progression and poor clinical outcomes of lung cancer; however, the opposite effects were also found in some patients.²⁵ Interestingly, the absence of IL-10 had opposite effects on the early and late stages of NSCLC.²⁶ Hence, the expression or polymorphisms of IL-10 gene might serve as a good indicator of susceptibility and prognostic outcome for lung cancer in different stages of the disease.²⁷ These lung cancer biomarkers might be used for screening, early

Table 1 Characteristics of eligible studies included

Author	Year	Control type	Nationality	Ethnicity	Disease	Control	Case				P for HWE	Score	Genotyping method	
A-1082G														
Peddireddy et al ³¹	2016	HB	India	Asians	NSCLC	Total 250	AA 130	AG 84	GG 36	Total 246	AA 156	AG 69	GG 21	PCR-RFLP
Hsia et al ³²	2014	HB	People's Republic of China	Asians	Lung neoplasms	716	561	130	25	358	273	69	16	PCR-RFLP
Hart et al ³⁴	2011	HB	Norway	Caucasians	NSCLC	435	104	226	105	436	120	207	109	TaqMan
Hao et al ³⁷	2009	HB	People's Republic of China	Asians	Lung neoplasms	52	46	6		44	36	7		TaqMan
Colakogullari et al ³⁰	2007	HB	Turkey	Caucasians	Lung neoplasms	59	33	21	5	44	11	30	3	PCR-SSP
Shih et al ²⁸	2005	HB	People's Republic of China	Asians	NSCLC	205	194	11	0	154	115	39	0	PCR-RFLP
Seifart et al ²⁹	2005	HB	Germany	Caucasians	Lung neoplasms	243	86	115	42	39	6	21	12	PCR-RFLP
A-592C														
Zhang et al ³³	2015	HB	People's Republic of China	Asians	Lung neoplasms	336	75	176	85	330	110	156	64	PCR-RFLP
Hsia et al ³²	2014	HB	People's Republic of China	Asians	Lung neoplasms	716	71	277	368	358	40	145	173	PCR-RFLP
Hart et al ³⁴	2011	HB	Norway	Caucasians	NSCLC	433	243	175	15	434	264	144	26	TaqMan
Liang et al ³⁵	2011	HB	People's Republic of China	Asians	NSCLC	120	7	44	69	116	11	36	69	PCR-RFLP
Vogel et al ³⁶	2008	PB	Denmark	Caucasians	NSCLC	744	452	250	42	403	241	149	13	PCR-RFLP
Colakogullari et al ³⁰	2007	HB	Turkey	Caucasians	Lung neoplasms	59	27	25	7	44	19	23	2	PCR-SSP
Shih et al ²⁸	2005	HB	People's Republic of China	Asians	NSCLC	205	13	76	116	154	18	70	66	PCR-RFLP
T-819C														
Zhang et al ³³	2015	HB	People's Republic of China	Asians	Lung neoplasms	336	145	144	47	330	108	135	87	PCR-RFLP
Hsia et al ³²	2014	HB	People's Republic of China	Asians	Lung neoplasms	716	372	265	79	358	212	128	18	PCR-RFLP
Colakogullari et al ³⁰	2007	HB	Turkey	Caucasians	Lung neoplasms	59	7	26	26	44	2	23	19	PCR-SSP
Shih et al ²⁸	2005	HB	People's Republic of China	Asians	NSCLC	205	104	86	15	154	66	58	30	PCR-RFLP
Seifart et al ²⁹	2005	HB	Germany	Caucasians	Lung neoplasms	242	14	88	140	40	2	14	24	PCR-RFLP

Abbreviations: HB, control hospital based; PB, control population based; NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction; RFLP, restricted fragment length polymorphism; SSP, sequence specific primer.

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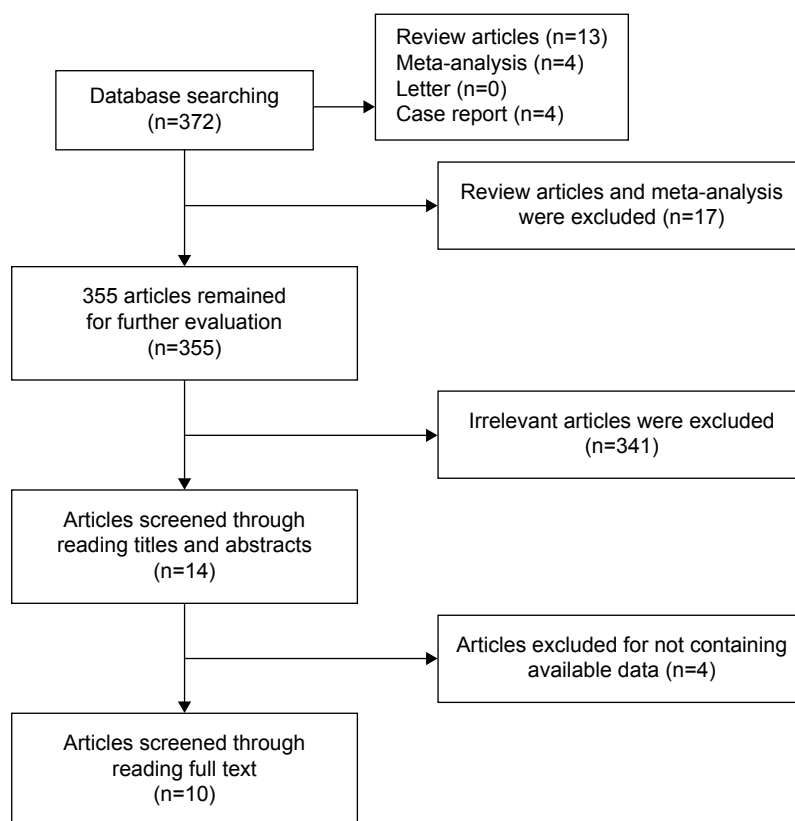


Figure 1 Flow diagram of the search literature.

detection, early diagnosis, prognosis, prediction, stratification, and therapy response monitoring.³ Although previous case-control studies showed that the IL-10 polymorphism might contribute to the risk of lung cancer, and the sample size of the studies was too small. Thus, this meta-analysis was performed.

Through this comprehensive meta-analysis, the association between *IL-10* -1082A/G, -592C/A, and -819T/C polymorphism and the risk of lung cancer was evaluated. To our knowledge, this is the first systematic meta-analysis to date that deals with the association between *IL-10* -1082A/G, -592C/A, and -819T/C polymorphisms

Table 2 Meta-analysis results of the association between *IL-10* -1082A/G, -592C/A, and -819T/C polymorphisms and lung cancer risk

IL-10	Allele model		Homozygous model		Dominant model		Recessive model	
	OR/95% CI	P-value	OR/95% CI	P-value	OR/95% CI	P-value	OR/95% CI	P-value
A-1082G	A vs G		AA vs GG		AA vs (AG + GG)		(AA + AG) vs GG	
Caucasians	1.37 (0.98–1.35)	0.08	1.33 (0.97–1.83)	0.08	1.21 (0.94–1.55)	0.14	1.21 (0.92–1.58)	0.17
Asians	1.14 (0.96–1.36)	0.14	0.99 (0.65–1.51)	0.95	1.20 (1.05–1.39)	<0.05	1.15 (0.92–1.43)	0.21
NSCLC	1.02 (0.89–1.18)	0.75	1.01 (0.77–1.33)	0.95	1.05 (0.87–1.27)	0.58	0.98 (0.76–1.27)	0.87
Total	1.17 (1.04–1.30)	<0.05	1.23 (0.98–1.54)	0.07	1.21 (1.05–1.40)	<0.05	1.15 (0.92–1.43)	0.21
C-592A	C vs A		CC vs AA		CC vs (CA + AA)		(CC + CA) vs AA	
Caucasians	0.96 (0.83–1.11)	0.55	0.88 (0.59–1.33)	0.55	0.96 (0.80–1.14)	0.62	0.89 (0.60–1.34)	0.58
Asians	1.36 (1.20–1.53)	<0.05	1.85 (1.45–2.37)	<0.05	1.36 (1.15–1.61)	<0.05	0.74 (0.62–0.87)	<0.05
NSCLC	0.98 (0.87–1.10)	0.70	0.96 (0.77–1.21)	0.74	0.98 (0.84–1.14)	0.75	0.97 (0.79–1.20)	0.79
Total	0.84 (0.77–0.91)	<0.05	0.74 (0.64–0.87)	<0.05	0.83 (0.74–0.94)	<0.05	0.79 (0.69–0.91)	<0.05
T-819C	T vs C		TT vs CC		TT vs (TC + CC)		(TT + TC) vs CC	
Caucasians	0.96 (0.65–1.41)	0.82	1.36 (0.44–4.17)	0.59	1.50 (0.50–4.50)	0.47	0.85 (0.53–1.38)	0.52
Asians	1.21 (1.06–1.38)	<0.05	1.54 (1.18–2.01)	<0.05	1.15 (0.97–1.37)	0.11	1.51 (1.17–1.95)	<0.05
NSCLC	1.57 (1.15–2.16)	<0.05	3.15 (1.58–6.30)	<0.05	1.37 (0.90–2.09)	0.14	3.07 (1.58–5.93)	<0.05
Total	0.97 (0.86–1.10)	0.63	0.95 (0.76–1.20)	0.68	0.96 (0.82–1.14)	0.66	0.97 (0.79–1.19)	0.77

Abbreviations: NSCLC, non-small-cell lung cancer; OR, odds ratio; 95% CI, 95% confidence interval.

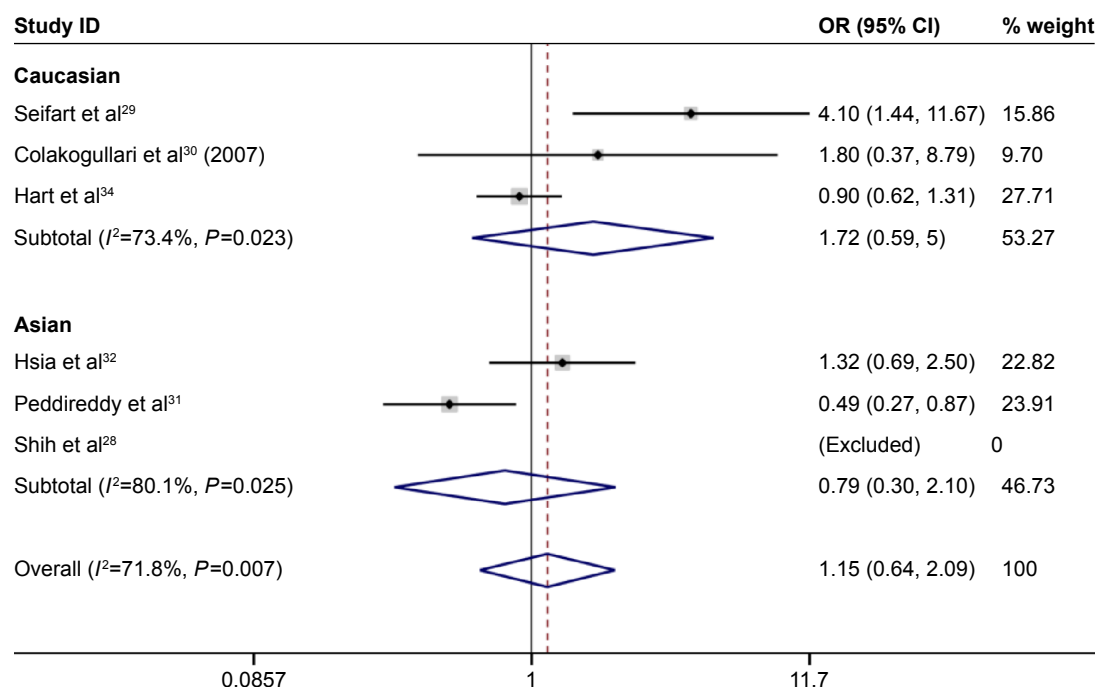


Figure 2 Forest plot of lung cancer risk associated with *IL-10 -1082A/G* (AA vs GG) polymorphism stratified by ethnicity.
Note: Weights are from random effects analysis.

and lung cancer risk. In the overall analysis, we found that *IL-10 -1082A/G*, *-592C/A*, and *-819T/C* polymorphisms were significantly associated with lung cancer risk. Interestingly, *IL-10 -1082A/G*, *-592C/A*, and *-819T/C* polymorphisms were significantly associated with lung cancer risk in

Asians, but not in the Caucasians. Furthermore, the results indicated that individuals who carried the *IL-10 -1082G* allele had an increased risk of lung cancer, and those with the *IL-10 -819T* allele were shown to have a decreased risk of lung cancer compared to those with the *-819C* allele.

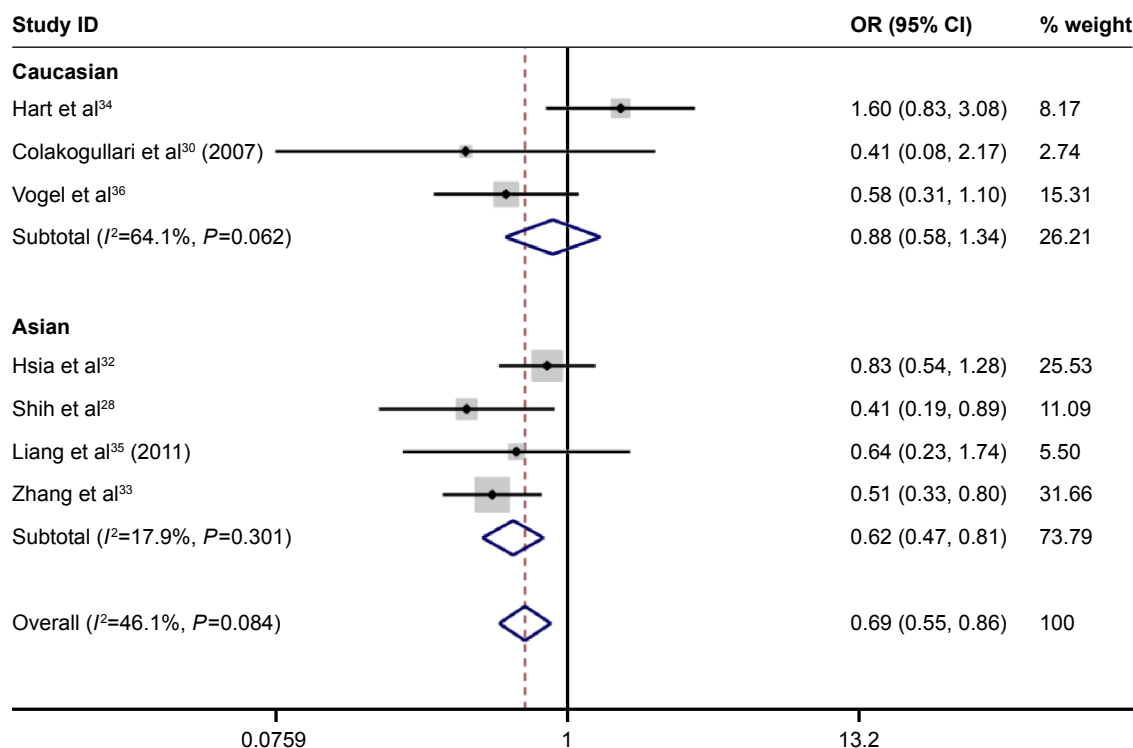


Figure 3 Forest plot of lung cancer risk associated with *IL-10 C-592A* (CC vs AA) polymorphism stratified by ethnicity.

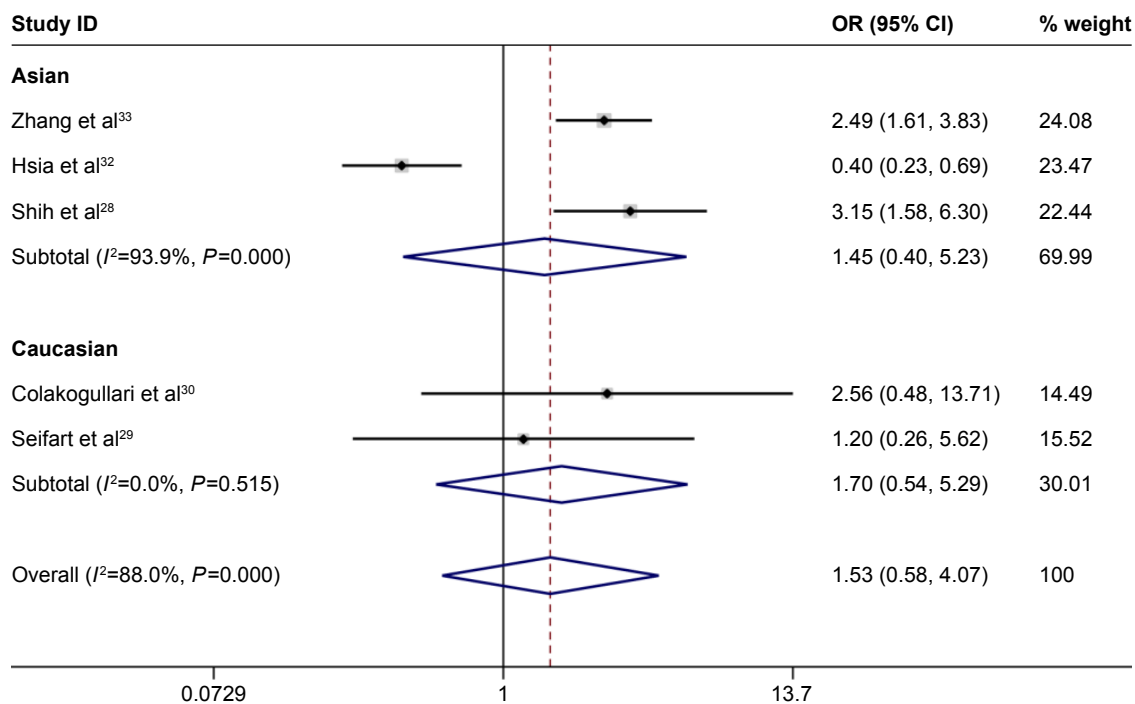


Figure 4 Forest plot of lung cancer risk associated with *IL-10* -819T/C (TT vs CC) polymorphism stratified by ethnicity. **Note:** Weights are from random effects analysis.

The results of previous case-control studies by Shih et al,²⁸ Seifart et al,²⁹ Colakogullari et al,³⁰ and Peddireddy et al³¹ for *IL-10* -1082A/G polymorphism were consistent with this meta-analysis and indicated that the *IL-10* -1082A/G polymorphism could increase the risk of lung cancer. The results of Hsia et al,³² Shih et al,²⁸ and Zhang et al³³ for *IL-10* -819T/C polymorphism showed that *IL-10* -819T/C polymorphism was significantly associated with an increased risk of lung cancer. Nevertheless, different results were also found in the studies of Hsia et al³² and Hart et al³⁴ concerning the *IL-10* -1082A/G polymorphism. However, several of

the included studies showed no significant correlation of *IL-10* A-592C and -819T/C polymorphisms with lung cancer risk.^{29,30,32,34–36} In addition, there was adequate evidence indicating the different frequency distribution of *IL-10* -592C/A and -819T/C allele between Asians and Caucasians in the meta-analysis. And this result was consistent with the data given in the HapMap database. Thus, a decreased risk of lung cancer in Caucasians and an increased risk of lung cancer in Asians was associated with the *IL-10* -592C/A and -819T/C polymorphisms, although no significant association of *IL-10* -592C/A and -819T/C polymorphisms

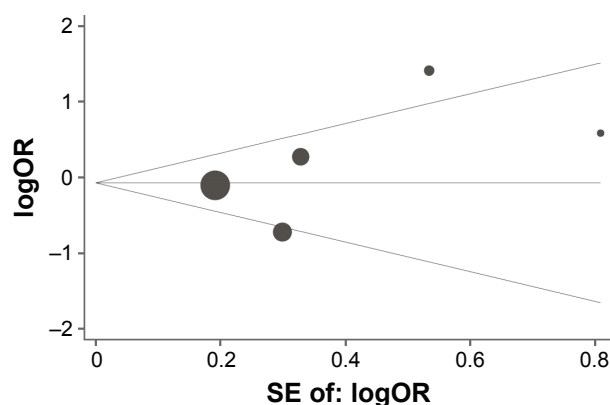


Figure 5 Begg's funnel plot with pseudo 95% confidence limits for studies of the association between lung cancer risk and *IL-10* -1082A/G (AA vs GG) polymorphism. **Abbreviation:** SE, standard error.

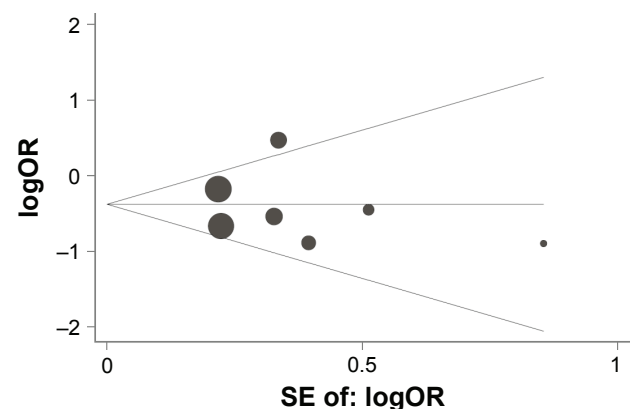


Figure 6 Begg's funnel plot with pseudo 95% confidence limits for studies of the association between lung cancer risk and *IL-10* C-592A (CC vs AA) polymorphism. **Abbreviation:** SE, standard error.

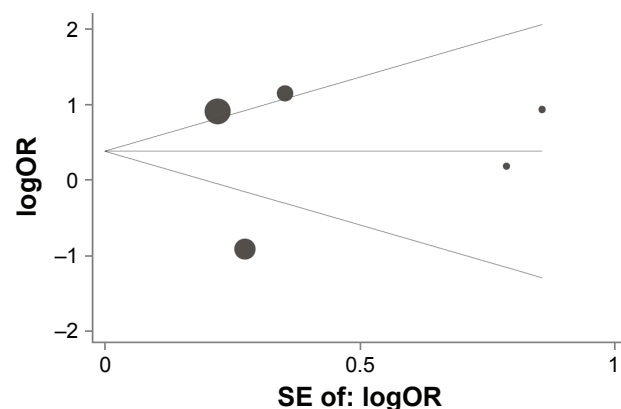


Figure 7 Begg's funnel plot with pseudo 95% confidence limits for studies of the association between lung cancer risk and *IL-10 -819T/C* (TT vs CC) polymorphism. **Abbreviation:** SE, standard error.

with lung cancer risk in Caucasians was found. In addition, based on the results of the subgroup analysis, we found that *IL-10 -819T/C* polymorphism was associated with susceptibility to NSCLC. A previous study reported that IL-10 might be involved in the process of tumor escape from the immune response, and increased production of IL-10 has been shown to correlate with the survival of NSCLC patients.²⁸ However, only one study was included in the subgroup analysis, and this lowered the statistical power. For the *IL-10 -1082A/G* and *-592C/A* polymorphism, no significant correlation with NSCLC risk was detected. The analysis of small-cell lung cancer was not performed because the sample of small-cell lung cancer was too small and the classification of small-cell lung cancer was not clear. On the basis of the meta-analysis, to a large extent, there was no significant association between *IL-10 -1082A/G*, *-592C/A* polymorphism and NSCLC risk. To confirm this conclusion, studies with larger sample number must be conducted. The study results showed that subgroup analysis is very important for a systematic review and meta-analysis. From the studies included, there is evidence that the association between IL-10 polymorphism and lung cancer risk is still not clear. Therefore, performing a meta-analysis and systematic review was necessary to clarify this relevance. These results are shown in Figure 3.

Limitations

Several limitations of this meta-analysis should be acknowledged. First, the small number of eligible studies might limit the meta-analysis. There were only five or seven studies available for three SNPs of IL-10 gene in the stratification analysis in particular, which might have attenuated the statistical power of the meta-analysis. Second, the missing individual data, for example, cancer stage and cancer subtype

might also have an impact on the interpretation. Third, this meta-analysis could not address the gene–environmental interactions in the correlation of IL-10 polymorphism with lung cancer risk. The conclusions only depend on the ORs, which might lead to confounding bias. Finally, the inclusion of data that was inconsistent with HWE might affect the accuracy of the results. However, the large sample size could weaken the impact of the association of IL-10 polymorphism with lung cancer risk.

In conclusion, this meta-analysis of ten case–control studies suggested that the *IL-10 -1082A/G*, *-592C/A*, and *-819T/C* polymorphisms were associated with the increased risk of lung cancer in Asians. Nevertheless, considering the limitations of the study, further large-scale, well-designed, and population-based studies are still needed to assess the correlation between IL-10 polymorphism and lung cancer risk.

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Disclosure

The authors report no conflicts of interest in this work.

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