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Association between TGF-β1 rs1982073/rs1800469 polymorphism and lung cancer susceptibility

An updated meta-analysis involving 7698 cases and controls

Guangyuan Chen, MBBS[a], Cong Hu, MBBS[a], Penghui Lai, MBBS[a], Yuxuan Song, MS[b], Mengxi Xiu, MBBS[a], Haifei Zhang, MBBS[a], Yiling Zhang, MBBS[a], Peng Huang, MD, PhD[c,d,*]

Abstract

Background: There have been several case–control studies to assess the relationship between the transforming growth factor-β1 (TGF-β1) T+869C (rs1982073)/C-509T (rs1800469) gene polymorphism and lung cancer in recent years; however, the results remain controversial. In this study, we investigated the potential correlation between the TGF-β1 T+869C/C-509T polymorphism and increased risk of lung cancer through meta-analysis.

Methods: We searched the Cochrane Library database, Embase, PubMed, Web of Science, China National Knowledge Infrastructure, and the Wanfang Data Information Service platform to identify relevant case–control studies in strict accordance with the inclusion and exclusion criteria. The odds ratio (OR) and its 95% confidence interval (95% CI) were used to evaluate the correlation between TGF-β1 gene polymorphism and lung tumor risk. Sensitivity analysis and Egger test were used to evaluate the stability of the results and possible publication bias.

Results: A total of 8 studies, with 3680 patients and 4018 controls, were included. The meta-analysis revealed that there was no conspicuous correlation between the TGF-β1 T+869C (rs1982073)/C-509T (rs1800469) variant and lung cancer in the overall population. For TGF-β1 C-509T, a significant decreased risk was identified in patients with nonsmall-cell lung cancer (NSCLC) in the analysis stratified by disease (TT vs CT+CC: $P=.02$, OR=0.49, 95% CI 0.27–0.90). However, for TGF-β1 T+869C, subgroup analysis showed no correlation between the T+869C polymorphism and lung cancer susceptibility in patients with NSCLC. In the subgroup analysis by ethnicity, no distinct association was observed between T+869C (rs1982073)/C-509T (rs1800469) polymorphism and lung cancer susceptibility in the Asian and Caucasian groups. Moreover, no significant association was found in the analysis of groups stratified by age, sex, and smoking history.

Conclusion: The TGF-β1 T+869C (rs1982073) and C-509T (rs1800469) polymorphisms are not implicated in lung cancer susceptibility in the overall population. However, our analysis indicated that the C-509T (rs1800469) polymorphism decreases the risk of lung cancer in patients with NSCLC.

Abbreviations: CI = confidence interval, HWE = Hardy–Weinberg equilibrium, NSCLC = nonsmall-cell lung cancer, OR = odds ratio, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SNP = single-nucleotide polymorphism, TGF-β1 = transforming growth factor-β1.

Keywords: lung cancer, meta-analysis, rs1800469, rs1982073, transforming growth factor-β1

1. Introduction

Based on the GLOBOCAN 2018 global cancer statistics report, the morbidity and mortality of lung cancer are the highest among all tumors.[1] The incidence of lung cancer has increased almost 4-fold in the past 30 years, and the World Health Organization (WHO) predicts that the lung cancer population in China will reach 1 million by 2025, representing a serious public health concern.[2] The causes of lung cancer have not been fully

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GC, CH, and PL contributed equally and should be considered as co-first authors.

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[a] The Second Clinical Medical School, Nanchang University, Nanchang, Jiangxi, [b] Department of Urology, Tianjin Medical University General Hospital, Tianjin, [c] Center for Evidence-based Medicine, [d] Jiangxi Province Key Laboratory of Preventive Medicine, School of Public Health, Nanchang University, Nanchang, China.

[*] Correspondence: Peng Huang, Center for Evidence-based Medicine, School of Public Health, Nanchang University, Nanchang 330006, China (e-mail: huangpengncu@163.com).

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elucidated. According to current consensus, smoking is the main cause of lung tumors, although not all patients with lung cancer have a history of smoking, suggesting that genetic variations are also involved in the development of this malignancy. Present research suggests that the occurrence of lung cancer is accounted for by the interaction between the environment and heredity.[3]

As a complex multifunctional cytokine, transforming growth factor-β1 (TGF-β1) regulates the processes of cell migration, differentiation and cell cycle progression, which have been extensively investigated.[4] The TGF-β1 gene is located at 19q13.1-q13.3 and contains multiple single-nucleotide polymorphisms (SNPs).[5] Studies have shown that TGF-β1 plays a very important role in many diseases. Among other functions, TGF-β1 and its signaling pathway regulate immune responses, control cell proliferation, and maintain mineral balance.[6] Therefore, abnormal TGF-β1 expression will affect the occurrence and development of some tumors. Some important studies have shown that TGF-β1 polymorphisms are closely related to the risk of lung cancer susceptibility.[6,7] Li et al[7] and Ren et al[8] reported that TGF-β1 rs1982073/rs1800469 polymorphisms were related to lung cancer susceptibility in a Chinese population, and also that TGF-β1 T + 869C and C-509T genes induced other lung diseases via TGF-β1 signaling pathways.[9] In recent years, several case–control studies have been conducted to clarify the relationship between the of lung cancer susceptibility and TGF-β1 polymorphisms; however, the results are controversial. Thus, in this study, we investigated the potential correlation between TGF-β1 polymorphisms and increased risk of lung cancer through systematic evaluation and meta-analysis.

2. Methods

2.1. Selection of studies

We performed a comprehensive search of the Cochrane Library database, PubMed, Embase, Web of Science, China National Knowledge Infrastructure, and the Wanfang Data Information Service platform as well as manual searches to identify relevant studies. The following English search strategy was used: (lung carcinoma or lung cancer) and (SNP or variant or genotype or polymorphism) and (transforming growth factor beta 1 or TGF-β1). We searched the studies published before February 1, 2019, as well as the retrospective publication of the references relevant to the studies. We also conducted a manual search for relevant articles and degree papers.

2.2. Inclusion and exclusion criteria

Inclusion criteria: Case–control studies about an association between TGF-β1 gene variants and susceptibility to lung cancer; The study included TGF-β1 gene (rs1982073) and (rs1800469) polymorphisms; Genotypes or alleles in control and case groups could be extracted from the articles; Genotypes of controls were in Hardy–Weinberg equilibrium (HWE).

Exclusion criteria: These studies of the gene distribution in the control group were not in HWE; The study was published repeatedly.

2.3. Literature quality evaluation and data extraction

The Newcastle–Ottawa scale (NOS) was used to assess the quality of the included articles. Articles assigned a NOS score ≥ 5 points were considered to be high quality. Two research evaluators independently extracted data from included articles based on the inclusion/exclusion criteria, and then they carefully cross-checked. Cases of dispute were resolved by evaluation and review by a 3rd researcher. The extracted data included the 1st author's name, date of the publication, the target country, ethnicity, the number of participants in the case and control groups and the genotype distribution, age, sex, smoking history, and genotyping methods. In total, 8 articles were included in this study. The NOS scores for all 8 articles >5 points, indicating the high quality of the included studies.

2.4. Statistical analysis

Using STATA 12.0 software for analysis, the odds ratio (OR) and its 95% confidence interval (95% CI) were used to assess the strength of correlation between the susceptibility to lung cancer and TGF-β1 gene polymorphisms. The Q-test and heterogeneity coefficient I^2 were used to assess the heterogeneity between the studies. $P > .1$ and $I^2 < 50\%$ were considered to indicate study homogeneity, and the fixed effect model was used to merge the indexes; otherwise the random-effect model was used. The ORs were calculated for the following models: allele model; homozygote model; dominant model; codominant model; and recessive model. Publication bias was evaluated using the Begg funnel chart and Egger test. Each document was removed successively for sensitivity analysis. Subgroup analysis was carried out as necessary.

3. Results

3.1. Characteristics of the selected studies

In total, 154 potentially relevant articles were selected according to the search strategy (Fig. 1). Eight case–control studies[7,8,10–15] with 7698 subjects (3680 cases with lung cancer and 4018 controls) were finally included in our meta-analysis. For the T + 869C polymorphism, 6 relevant articles with 1774 cases and 1967 controls were included in the meta-analysis.[10–15] Of these studies, 3 were conducted on Asian population, and 3 on Caucasian descendants. For the C-509T polymorphism, 6 articles were finally screened out of this meta-analysis, including 1906 cases and 2051 controls.[7,8,11,14,15] Of these studies, 5 were conducted on Asian population, and 1 on Caucasian descendants. The characteristics of the main studies are shown in Table 1. For genotyping, four studies adopted TaqMan techniques, 3 used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and 1 used single-strand conformational polymorphism-PCR. The distribution of genotypes in these 8 studies was all in HWE.

3.2. Meta-analysis results

The results of our meta-analysis of TGF-β1 gene rs1982073 and rs1800469 polymorphisms and the susceptibility to lung cancer as well as well as the main results of subgroup analysis are listed in Tables 2–4.

3.2.1. Association between lung cancer risk and TGF-β1 T + 869C (rs1982073) polymorphisms. For T + 869C (rs1982073), 6 studies were included, with a total of 1774 and 1967 individuals in the case and control groups, respectively. The pooled results suggested that the T + 869C polymorphism has no correlation with lung cancer risk ($P > .05$) (Table 2). As the

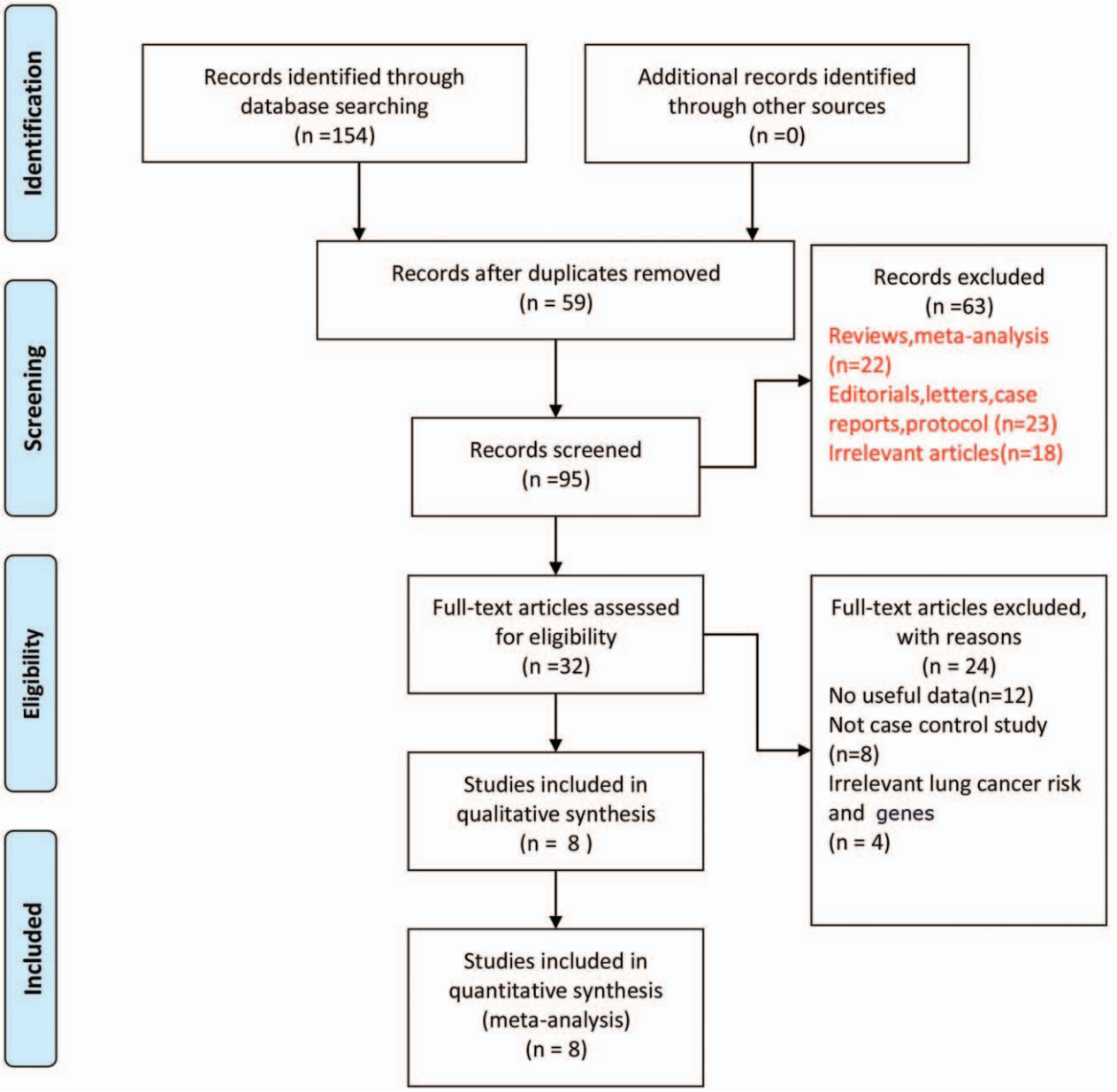


Figure 1. Flow chart illustrating the search strategy for articles reporting studies of transforming growth factor-β1 T + 869C (rs1982073) and C-509T (rs1800469) polymorphisms and susceptibility to lung cancer.

Table 1

Main characteristics of studies included in this meta-analysis.

SNPs	Author	Year	Country	Ethnicity	Methods	Age (years)	Sex	Smoking history	Disease	Case/n	Control/n	*P* for HWE
T869C												
	Keith	2018	USA	Caucasian	TaqMan	59.7 ± 5.3	Mixed	43.0 ± 18.0	Lung cancer	608	608	.675
	Bai	2013	China	Asian	TaqMan	58.0 ± 12.0	Male	NA	Lung cancer	193	210	.968
	Teixeira	2011	Portugal	Caucasian	TaqMan	63.1 ± 9.9	Mixed	NA	NSCLC	305	380	.719
	Colakogullari	2008	Turkey	Caucasian	SSP-PCR	60.0 ± 9.8	Male	45.8 ± 27.2	Lung cancer	43	59	.926
	Park	2006	Korea	Asian	PCR-RFLP	52.4 ± 11.9	Mixed	7.39 ± 12.57	Lung cancer	193	278	.586
	Kang	2006	Korea	Asian	PCR-RFLP	61.6 ± 9.0	Mixed	39.9 ± 17.9	Lung cancer	432	432	.847
C509T												
	Keith	2018	USA	Caucasian	TaqMan	59.7 ± 5.3	Mixed	43.0 ± 18.0	Lung cancer	605	605	.693
	Yang	2015	China	Asian	TaqMan	54.0 ± 12.1	Mixed	NA	Lung cancer	272	313	.528
	Bai	2013	China	Asian	TaqMan	58.0 ± 12.0	Male	NA	Lung cancer	193	210	.752
	Li	2012	China	Asian	PCR-RFLP	54.1 ± 11.2	Mixed	30.0 ± 17.0	NSCLC	210	208	.286
	Park	2006	Korea	Asian	PCR-RFLP	52.4 ± 11.9	Mixed	7.39 ± 12.57	Lung cancer	194	283	.663
	Kang	2006	Korea	Asian	PCR-RFLP	61.6 ± 9.0	Mixed	39.9 ± 17.9	Lung cancer	432	432	.501

HWE = Hardy–Weinberg equilibrium, NA = not available, NSCLC = nonsmall-cell lung cancer, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SNP = single-nucleotide polymorphism, SSP = single-strand conformational polymorphism.

Table 2

Meta-analysis results.

SNPs	Contrast model		OR (95% CI)	P	Test for heterogeneity		Publication bias (Egger test)		Analysis model
					I^2, %	P	t	P	
T869C									
	C vs T	Overall	1.13 (0.93–1.38)	.22	75.20	.001	1.07	.346	R
	CC vs TT	Overall	1.26 (0.87–1.82)	.21	69.00	.006	1.38	.239	R
	CT vs. TT	Overall	1.23 (0.89–1.70)	.22	75.10	.001	−1.09	.336	R
	CC + CT vs TT	Overall	0.80 (0.57–1.12)	.20	79.20	<.001	−1.18	.303	R
	CT + TT vs CC	Overall	1.06 (0.90–1.25)	.46	7.30	.369	1.35	.248	F
C509T									
	T vs C	Overall	1.03 (0.88–1.20)	.75	64.70	.015	2.30	.083	R
	TT vs CC	Overall	1.04 (0.74–1.47)	.80	65.70	.012	3.01	.040	R
	CT vs CC	Overall	1.04 (0.82–1.33)	.74	57.50	.038	1.92	.127	R
	TT + CT vs CC	Overall	0.95 (0.73–1.23)	.68	65.60	.013	−1.62	.180	R
	TT vs CT + CC	Overall	1.00 (0.86–1.17)	.97	40.30	.137	0.03	.977	F

CI = confidence interval, F = fixed effect model, OR = odds ratio, R = random-effect model, SNPs = single-nucleotide polymorphisms.

heterogeneity of the codominant gene model, allele model, homozygous model, and dominant model was large, the random effect model was selected for analysis. In contrast, the heterogeneity of the recessive model is small, so the fixed effect model was selected for analysis (Fig. 2).

3.2.2. Subgroup analysis of the correlation between lung cancer risk and TGF-β1 T + 869C (rs1982073) polymorphism. For TGF-β1 T + 869C (rs1982073), we conducted subgroup analysis to identify the influence of the other factors in relation to lung cancer risk. Following stratification according to genotyping method, no significant association was identified between lung cancer risk and TGF-β1 T + 869C polymorphism in the TaqMan and PCR-RFLP groups. In addition, no significant correlation was observed in patients with non-small-cell lung cancer (NSCLC). Following stratification according to age, sex, and smoking history, the meta-analysis did not show any significant association between the TGF-β1 T + 869C polymorphism and lung cancer susceptibility in these subgroups (Table 3).

3.2.3. Association between lung cancer risk and TGF-β1 C-509T (rs1800469) polymorphism. For C-509T (rs1800469), 6 studies were included, with a total of 1906 and 2051 individuals in the case and control groups, respectively. The pooled results suggested that the C-509T polymorphism was not associated with susceptibility to lung cancer in the 5 genetic models ($P > .05$) (Table 2). As the heterogeneity of the recessive model was small, the fixed effect model was selected for our analysis (Fig. 3).

3.2.4. Subgroup analysis of the correlation between lung cancer risk and TGF-β1 rs1800469 (C-509T) polymorphism. Following stratification according to genotyping method, no significant associations between the TGF-β1 C-509T polymorphism and cancer risk were identified in the TaqMan and PCR-RFLP groups. Stratified analysis by disease showed a significant association in patients with NSCLC (TT vs CT + CC: $P = .02$, OR = 0.49, 95% CI 0.27–0.90). However, stratified analysis showed no obvious associations in the different age groups or in male patients. Furthermore, we found no significant association in people with a smoking history regardless of the duration (<10 years or > 10 years) (Table 4).

3.2.5. Subgroup analysis of the correlation between lung cancer risk and T + 869C (rs1982073)/C-509T (rs1800469) polymorphism in different population. For T + 869C (rs1982073), there was no evident correlation between the TGF-β1 T + 869C variant and lung cancer risk in the Asian (C vs T: $P = .83$; CC + CT vs TT: $P = .66$) and Caucasian descendants (C vs T: $P = .28$; CC + CT vs TT: $P = .25$) groups. In the Asian population, our results indicated that individuals with C or T alleles no significantly increased risk of lung cancer. In Caucasians, we found that patients with lung cancer with the TT variant did not have a significantly higher risk of lung cancer compared to those with the CC or CT genotype (Table 3). Furthermore, for C-509T (rs1800469), no significant correlation between the TGF-β1 C-509T variant and cancer risk was observed in the Asian (T vs C: $P = .56$; TT + CT vs CC: $P = .55$) and Caucasian descendants (T vs C: $P = .33$; TT + CT vs CC: $P = .69$) groups (Table 4).

3.3. Sensitivity analyses

Sensitivity analysis was performed by sequential removal of each individual study. Moreover, the results showed no marked changes for each analysis, which indicated the reliability of the results of our analyses.

3.4. Publication bias

The symmetry of Begg funnel graph and Egger test (the homozygote model: $P = .239$; Fig. 4), suggested that no significant publication bias existed for the relationship between TGF-β1 T + 869C polymorphisms and lung cancer risk in the included studies ($P > .05$). However, significant publication bias was identified in the homozygote model for TGF-β1 C-509T ($P < .05$). After excluding the study by Li, $P > .05$, which indicated that this study may be the cause of the bias (Table 2).

4. Discussion

Variations in the TGF-β1 gene can affect cytokine expression in patients with cancer and have an important influence on the development of tumors.[16–18] Several TGF-β1 polymorphisms have been identified to date, including T869C, C509T, G915C, A1572G, and G800A. Among them, the C-509T (rs1800469)

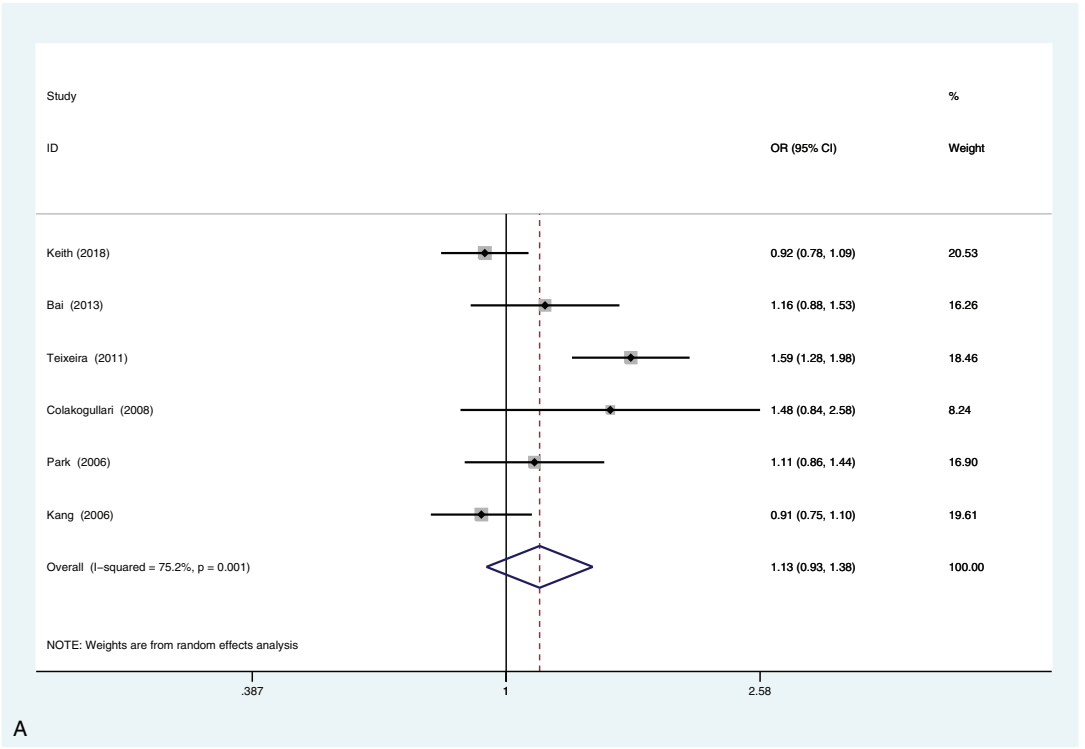
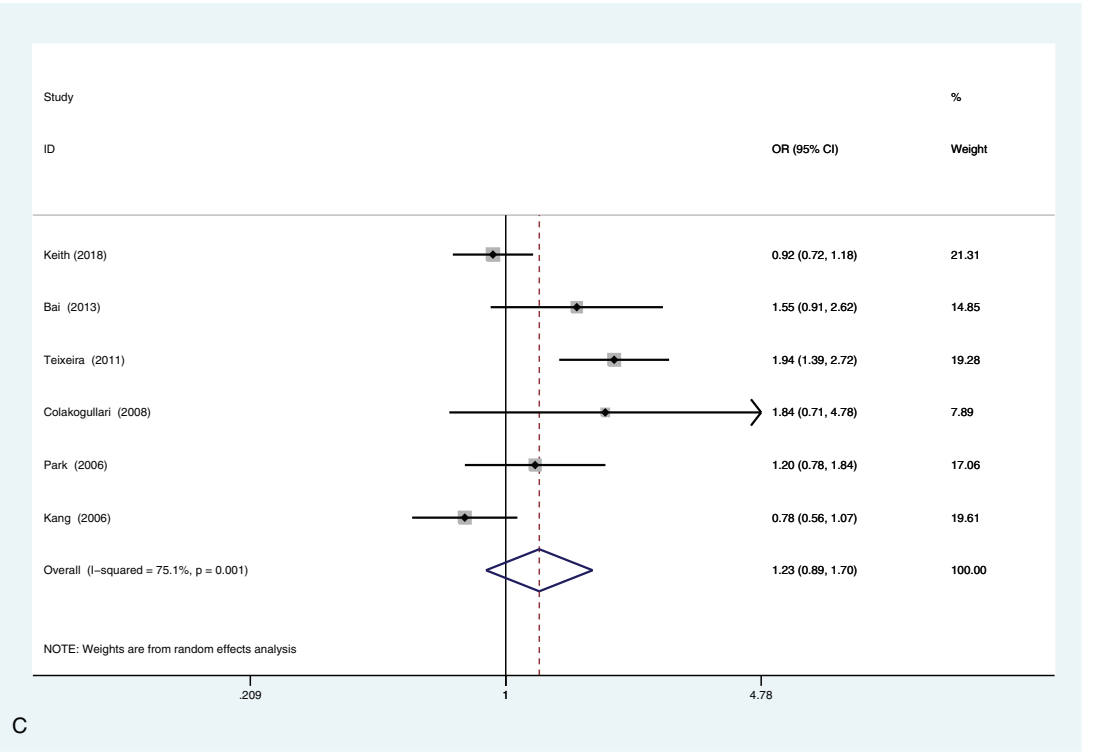


Figure 2. Forest plot of association between lung cancer and transforming growth factor-β1 T + 869C polymorphism. (A) C allele vs T allele. (B) CC vs TT. (C) CT vs TT. (D) CC + CT vs TT. (E) CC vs CT + TT.

and T + 869C (rs1982073) polymorphisms are the most intensively studied.[19,20] TGF-β1 gene polymorphisms are correlated with many human diseases. It has been reported that TGF-β1 polymorphisms are significantly related to the morbidity of patients with breast cancer in a large Asian population.[21] Other research showed that C-509T polymorphisms have a protective effect on the development of hepatocellular carcinoma.[22] The associations between TGF-β1 gene polymorphisms and lung cancer have been widely reported; however, the relationship between the TGF-β1



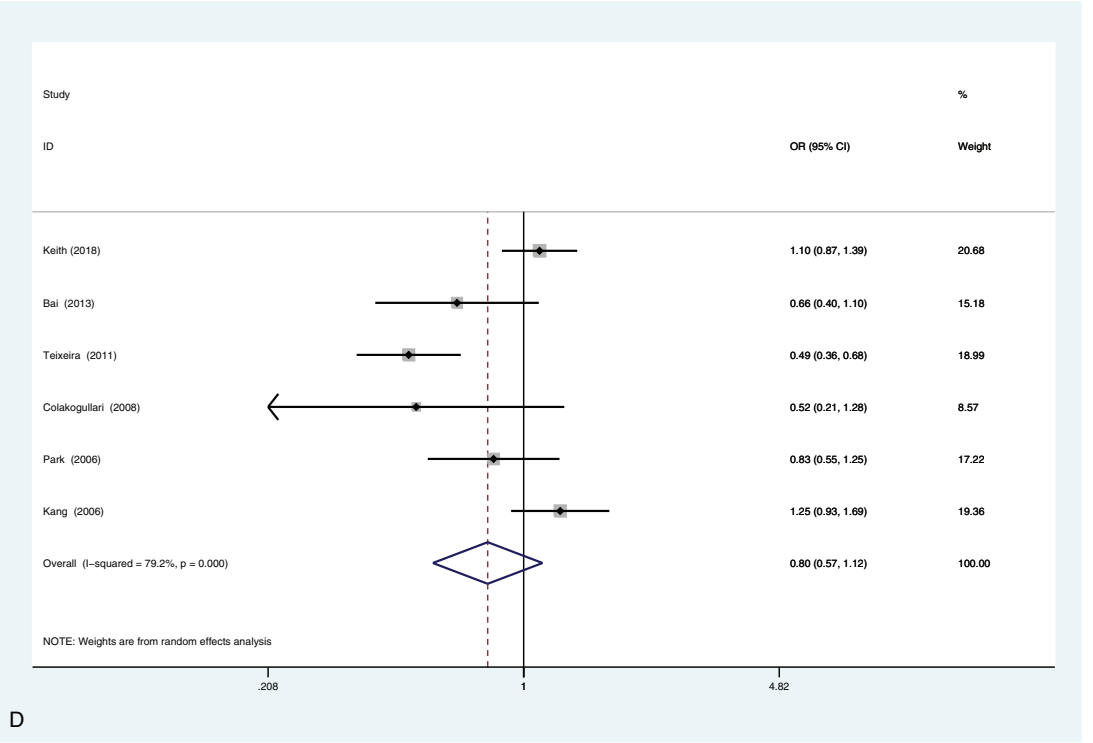
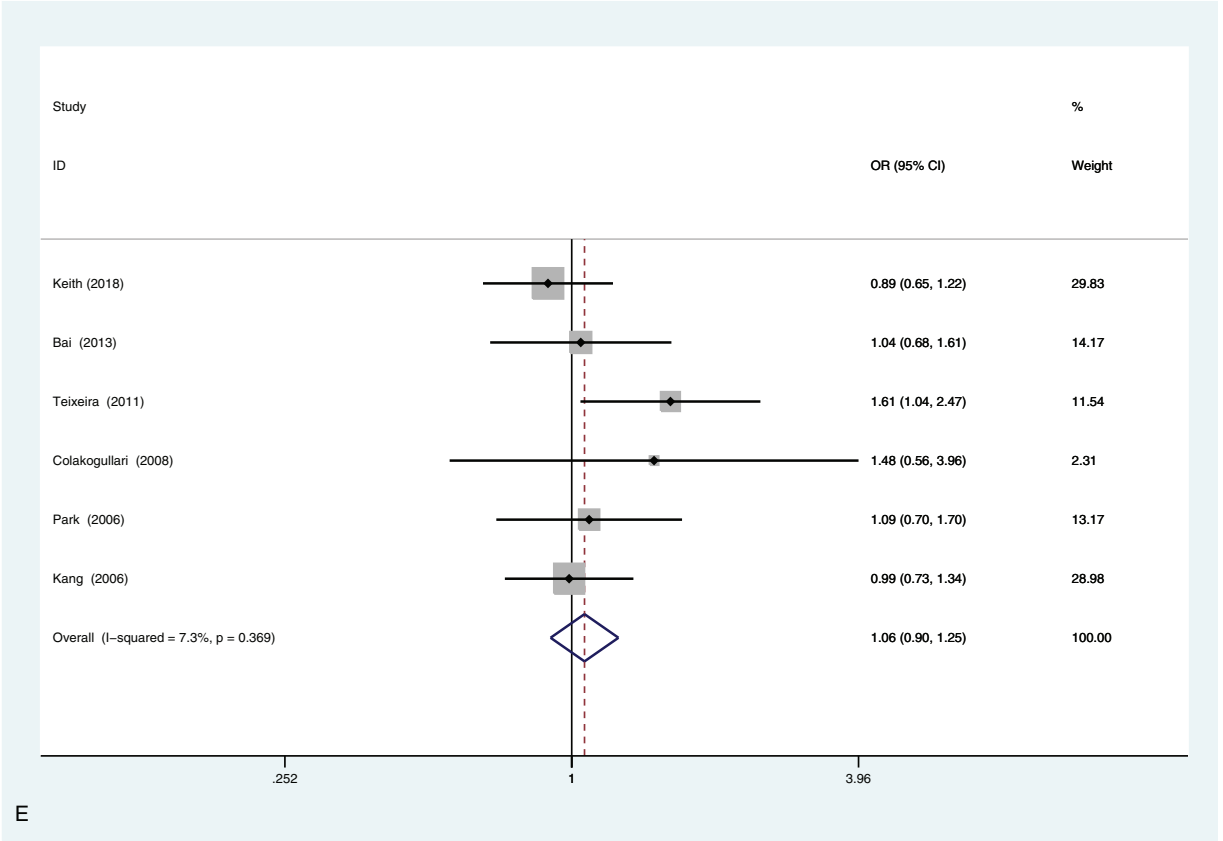


Figure 2. (Continued).

variants and susceptibility to lung tumor remains to be fully elucidated.[23,24]

In this study, we found no significant relationship between susceptibility to lung cancer and TGF-β1 C-509T and T + 869C variants. Stratified analysis by disease showed conspicuous associations between the C-509T variant and lung cancer risk in patients with NSCLC. In the stratified analysis by age, sex, and smoking history, we did not observe any significant associations between lung cancer risk and the TGF-β1 T + 869C polymorphism in these subgroups. Based on subgroup analysis of ethnicity, we found that the TGF-β1 T + 869C polymorphism had no correlation with the susceptibility to lung tumors in the



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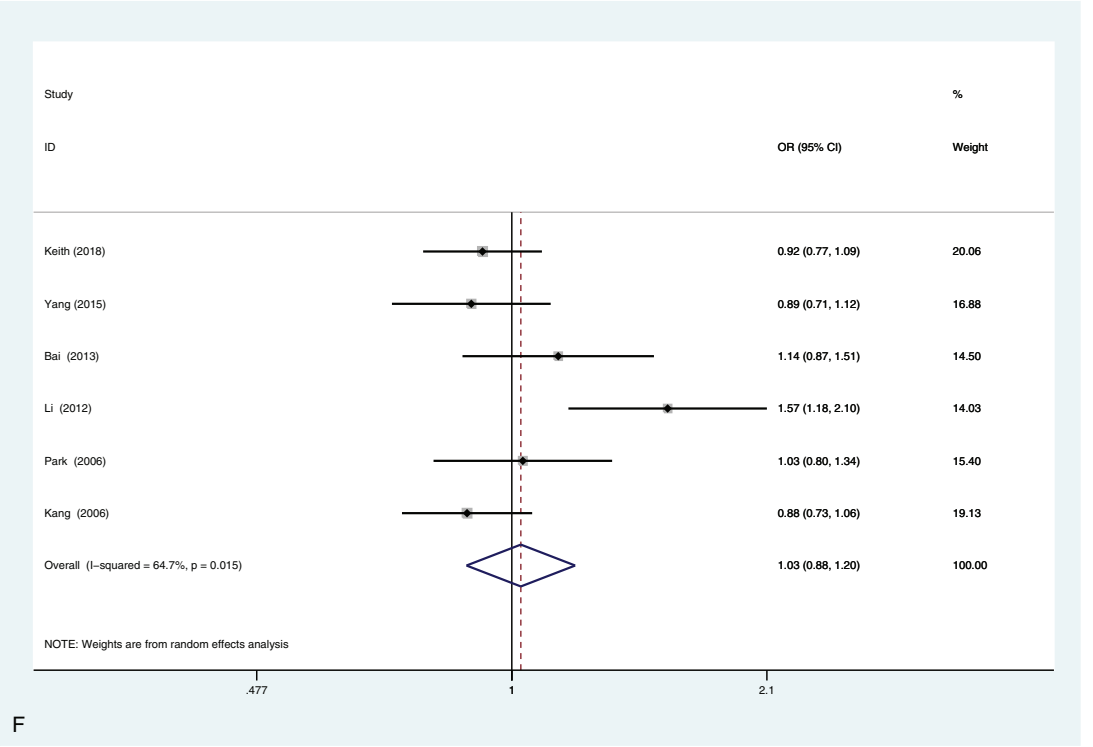
Caucasian descendant and Asian population, which is consistent with the study by Bai et al.[14] However, studies by Ren et al[8] and Kang et al[13] implicated that TGF-β1 T+869C and C-509T as protective factors against lung cancer. Furthermore, other studies revealed that the TGF-β1 T+869C and C-509T polymorphisms were risk factors for lung cancer. For example, Teixeira et al[10] demonstrated an increased risk of developing epidermoid and nonepidermoid NSCLC in C carriers. The study by Colakogullari et al[12] was the only one to show a correlation with lung tumor stage, with 11 patients at stages I and II 33

Table 3

Transforming growth factor-β1 T+869C (rs1982073) subgroup meta-analysis results.

SNP	Subgroups	Contrast model	Study	OR (95% CI)	*P*	Test for heterogeneity		Analysis model
						I^2, %	*P*	
T869C								
	Ethnicity 1	C vs T	Asian	1.02 (0.89–1.16)	.83	21.90	.278	F
		CC vs TT	Asian	1.04 (0.79–1.36)	.78	28.30	.248	F
		CT vs TT	Asian	0.92 (0.61–1.38)	.70	64.40	.060	R
		CC+CT vs TT	Asian	0.92 (0.63–1.34)	.66	63.40	.065	R
		CT+TT vs CC	Asian	1.03 (0.82–1.28)	.82	0.01	.937	F
	Ethnicity 2	C vs T	Caucasian	1.23 (0.82–1.95)	.28	87.60	<.001	R
		CC vs TT	Caucasian	1.55 (0.69–3.48)	.29	84.00	.002	R
		CT vs TT	Caucasian	0.70 (0.39–1.29)	.26	84.50	.002	R
		CC+CT vs TT	Caucasian	0.68 (0.36–1.31)	.25	88.20	<.001	R
		CT+TT vs CC	Caucasian	1.21 (0.77–1.91)	.41	60.20	.081	R
	Methods	CT+TT vs CC	PCR-RFLP	1.02 (0.79–1.29)	.91	0.00	.781	F
		CT+TT vs CC	TaqMan	1.07 (0.86–1.32)	.56	43.30	.172	F
	Age	CT+TT vs CC	<55	0.92 (0.59–1.44)	.71	7.30	.369	F
		CT+TT vs CC	>55	0.94 (0.79–1.12)	.52	25.70	.250	F
	Sex	CT+TT vs CC	Male	0.90 (0.61–1.35)	.62	0.00	.521	F
		CT+TT vs CC	Mixed	0.95 (0.79–1.13)	.56	39.20	.176	F
	Smoking history	CT+TT vs CC	<10	0.92 (0.59–1.45)	.71	NA	NA	F
		CT+TT vs CC	>10	1.04 (0.84–1.29)	.71	0.00	.606	F
	Disease	CT+TT vs CC	NSCLC	1.50 (0.98–2.30)	.06	NA	NA	F

CI=confidence interval, F=fixed effect model, NA=not available, NSCLC=nonsmall-cell lung cancer, OR=odds ratio, R=random-effect model, SNP=single-nucleotide polymorphism.



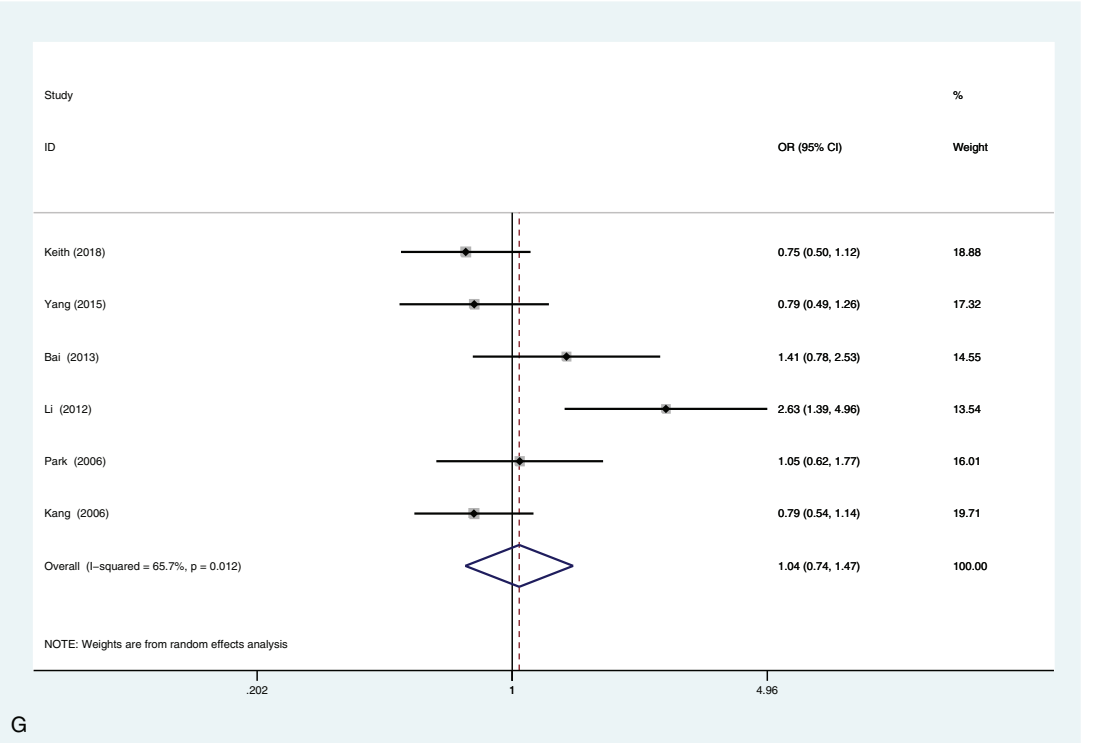
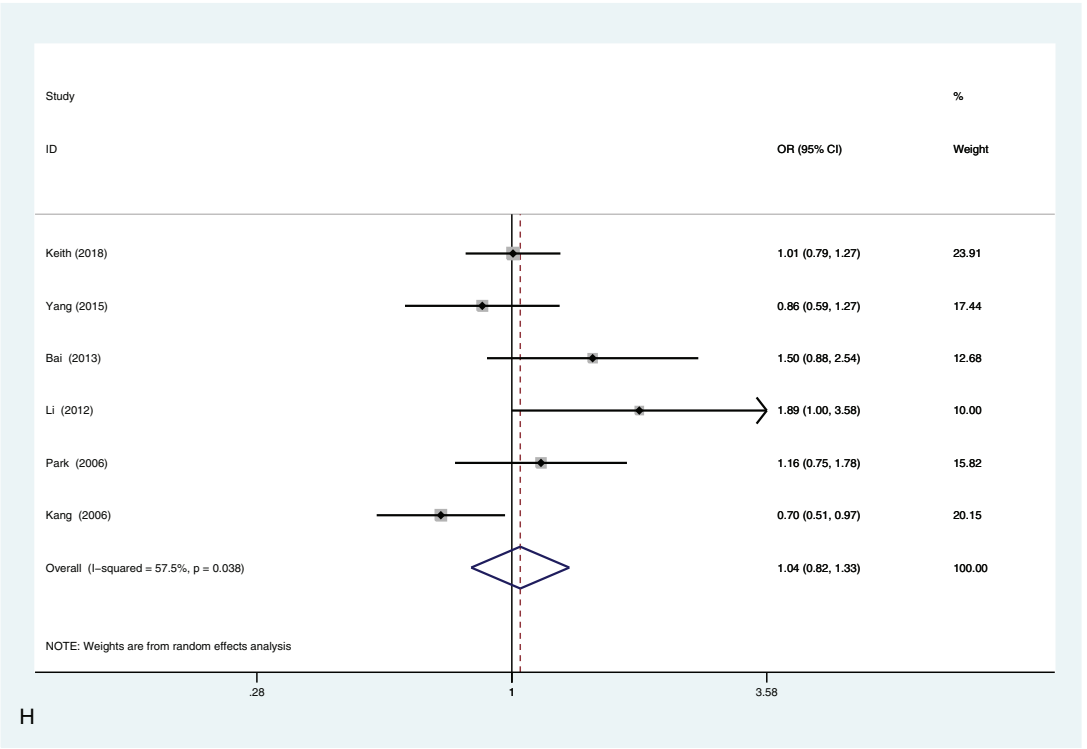


Figure 3. Forest plot of association between transforming growth factor-β1 C-509T polymorphism and lung cancer. (A) T allele vs C allele. (B) TT vs CC. (C) CT vs CC. (D) TT + CT vs CC. (E) TT vs CT + CC.

patients at stages III and IV. In addition, this group found that patients with lung cancer with the TT variant of T + 869C had significantly longer survival compared to those with the CC genotype. Li et al[7] have found that compared with the CC genotype, the TT genotype of C-509T was an independent risk factor for the occurrence of NSCLC. Kang et al[13] reported that individuals with at least one C-509T allele were at decreased risk of small cell lung tumors. It can be speculated that the discrepancies between these studies can be accounted for by a number of explanations such as differences in the genetic



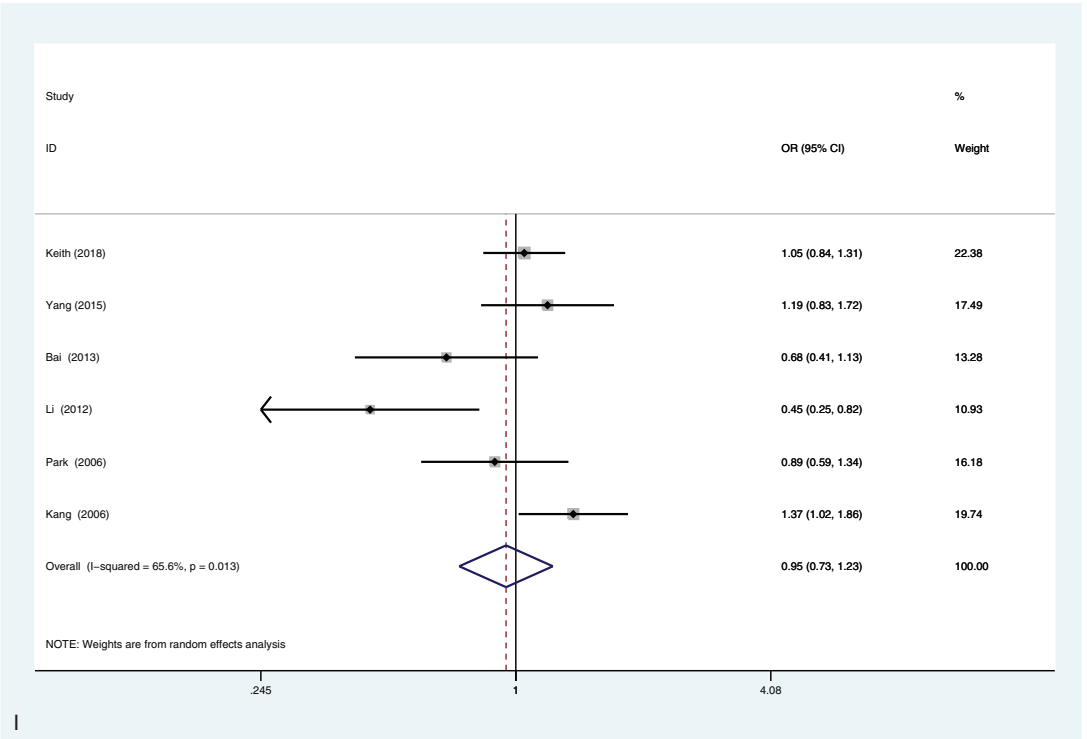


Figure 3. (Continued).

background of the study population, genotyping methods, and the type of lung cancer. Moreover, as a disease involving many complex factors, both environmental and genetic factors could influence susceptibility to lung tumors.

A previous meta-analysis conducted by Deng et al[25] showed that the T+869C polymorphism of TGF-β1 was related to lung cancer risk in Caucasians, which is in contrast to the findings of our study. There are several possible reasons for this difference such as the greater number of patients included in our study compared to that of the study by Deng et al. Second, it may have ethnic differences in the TGF-β1 gene allele frequencies. In addition, TGF-β1 T+869C and C-509T polymorphisms are

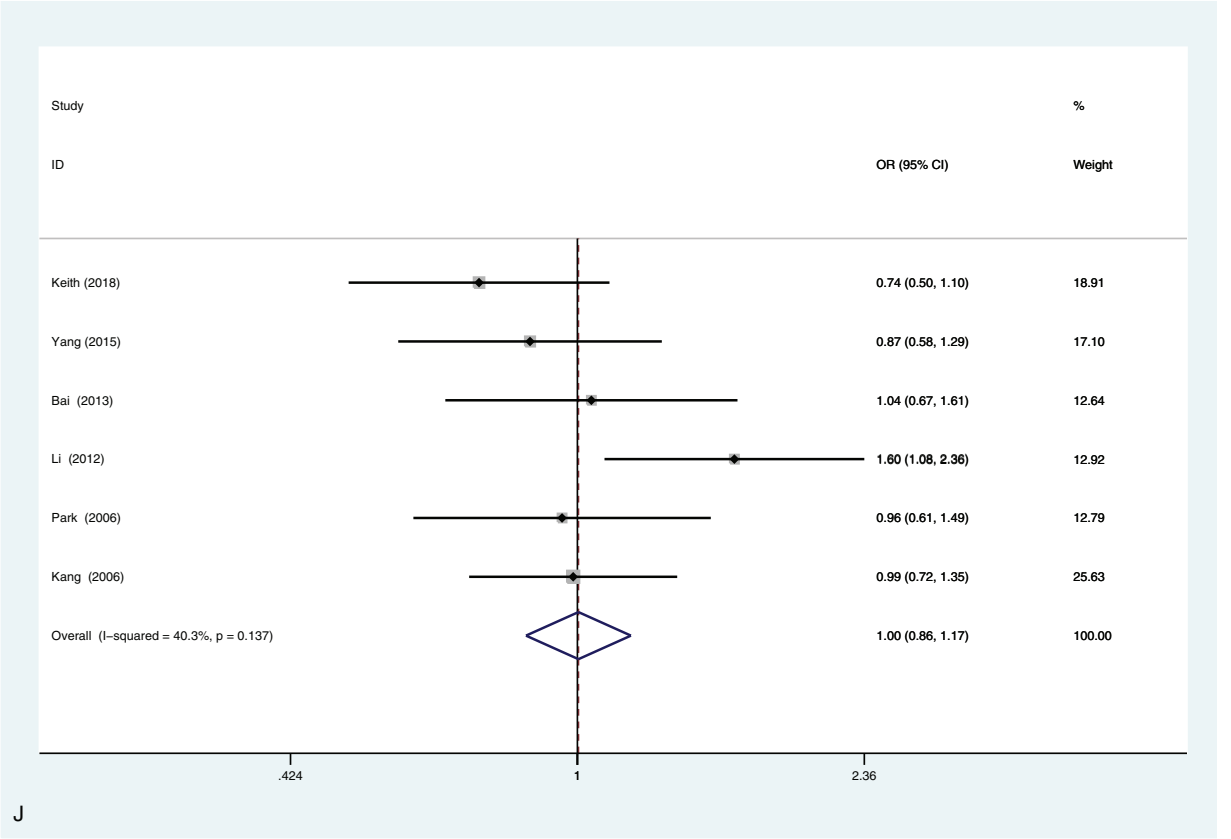


Figure 3. (Continued).

Table 4

Transforming growth factor-β1- C-509T (rs1800469) subgroup meta-analysis results.

SNP	Subgroups	Contrast model	Study	OR (95% CI)	*P*	Test for heterogeneity		Analysis model
						I^2, %	*P*	
C509T								
	Ethnicity 1	T vs C	Asian	1.06 (0.87–1.29)	.56	64.70	.011	R
		TT vs CC	Asian	1.14 (0.76–1.70)	.53	68.40	.013	R
		CT vs CC	Asian	1.08 (0.77–1.52)	.66	65.90	.019	R
		TT + CT vs CC	Asian	1.11 (0.78–1.59)	.55	72.30	.006	R
		TT vs CT + CC	Asian	1.06 (0.89–1.26)	.48	29.90	.222	F
	Ethnicity 2	T vs C	Caucasian	0.92 (0.77–1.09)	.33	NA	NA	F
		TT vs CC	Caucasian	0.75 (0.49–1.12)	.16	NA	NA	F
		CT vs CC	Caucasian	1.01 (0.79–1.28)	.96	NA	NA	F
		TT + CT vs CC	Caucasian	0.96 (0.76–1.19)	.69	NA	NA	F
		TT vs CT + CC	Caucasian	0.75 (0.50–1.10)	.14	NA	NA	F
	Methods	TT vs CT + CC	PCR-RFLP	0.88 (0.55–1.41)	.61	74.70	.019	R
		TT vs CT + CC	TaqMan	1.01 (0.86–1.18)	.91	2.50	.358	F
	Age	TT vs CT + CC	<55	1.11 (0.75–1.62)	.61	62.50	.070	R
		TT vs CT + CC	>55	0.92 (0.74–1.14)	.44	0.00	.441	F
	Sex	TT vs CT + CC	Male	1.04 (0.67–1.62)	.85	NA	NA	R
		TT vs CT + CC	Mixed	0.99 (0.78–1.28)	.98	52.00	.080	R
	Smoking history	TT vs CT + CC	<10	0.96 (0.61–1.49)	.84	NA	NA	R
		TT vs CT + CC	>10	1.05 (0.70–1.59)	.80	73.80	.022	R
	Disease	TT vs CT + CC	NSCLC	0.49 (0.27–0.90)	.02	NA	NA	F

CI = confidence interval, F = fixed effect model, NA = not available, NSCLC = nonsmall-cell lung cancer, OR = odds ratio, R = random-effect model, SNP = single-nucleotide polymorphism.

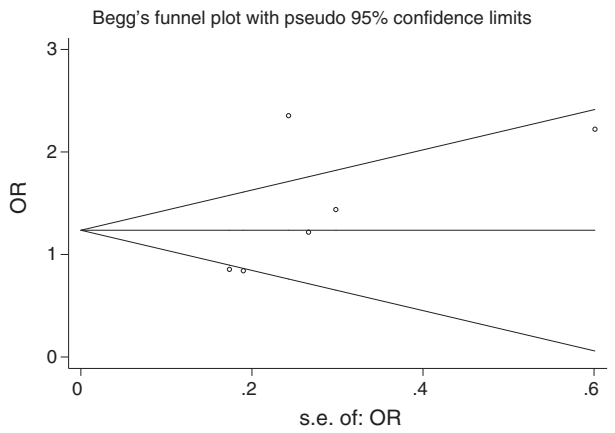


Figure 4. Begg funnel plot of studies of the association between transforming growth factor-β1 T+869C (CC vs TT) polymorphism and lung cancer susceptibility. OR = odds ratio.

involved in the metabolism of a variety of tumors, not only lung cancer.

Compared with the previous meta-analysis by Deng et al,[25] the advantage of our study is that we included more than 7698 subjects consisting of 3680 cases with lung cancer and 4018 controls. Therefore, the sample size was large enough to confirm the results of our analysis. Moreover, sensitivity analysis and Egger test showed the results were stable.

Data heterogeneity has an important influence on the accuracy of the results of a meta-analysis. We found the heterogeneity was significant in a lot of models. Therefore, we divided the included studies into different subgroups according to ethnicity, disease, and genotyping methods. The heterogeneity was drastically decreased in the ethnicity subgroups, suggesting that this factor had a significant influence on heterogeneity in our meta-analysis.

There were some limitations of this study that were impossible to avoid. First, some studies with negative results tend not to be published, which could skew the results of our analysis. Second, the included studies were available only in English and Chinese, which might cause language bias. Third, the correlation with lung tumor stage was not evaluated because only 1 study[12] included data for the stage of the lung tumors. Fourth, only 8 studies were included in our analysis, which might limit the statistical power of our results. Therefore, more multicentric studies with large samples are required to clarify the correlation between TGF-β1 polymorphisms and lung cancer risk.

5. Conclusion

Our study indicates that TGF-β1 polymorphisms are not correlated with lung cancer susceptibility in the total population, while the C-509T polymorphism may be related to susceptibility to lung tumors in patients with NSCLC. In addition, TT genotype carriers have a slightly lower incidence of lung cancer compared to that of CT or CC carriers and the TT variant is a protective factor for lung cancer susceptibility in patients with NSCLC. That is, the incidence of lung cancer varies among individuals with different C-509T genotypes or forms of the disease. More prospective cohort studies are needed before to support a comprehensive conclusion on the correlation between TGF-β1 polymorphisms and lung cancer susceptibility, especially in NSCLC.

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Author contributions

Conceptualization: Guangyuan Chen, Cong Hu, Haifei Zhang, Peng Huang.
Data curation: Guangyuan Chen, Cong Hu, Haifei Zhang, Penghui Lai, Peng Huang.
Formal analysis: Guangyuan Chen, Cong Hu, Haifei Zhang, Penghui Lai.
Funding acquisition: Guangyuan Chen, Cong Hu.
Investigation: Guangyuan Chen, Cong Hu, Penghui Lai, Peng Huang.
Methodology: Guangyuan Chen, Cong Hu, Haifei Zhang, Peng Huang.
Project administration: Guangyuan Chen, Cong Hu, Haifei Zhang, Mengxi Xiu, Peng Huang.
Resources: Guangyuan Chen, Cong Hu, Yuxuan Song, Penghui Lai.
Software: Guangyuan Chen, Cong Hu, Mengxi Xiu, Penghui Lai.
Supervision: Guangyuan Chen, Cong Hu, Yiling Zhang, Penghui Lai, Yuxuan Song.
Validation: Guangyuan Chen, Cong Hu, Yiling Zhang, Mengxi Xiu, Peng Huang.
Visualization: Guangyuan Chen, Cong Hu, Yiling Zhang, Yuxuan Song, Penghui Lai.
Writing – original draft: Guangyuan Chen, Cong Hu, Yiling Zhang, Mengxi Xiu, Yuxuan Song.
Writing – review & editing: Guangyuan Chen, Cong Hu, Yiling Zhang, Peng Huang, Yuxuan Song, Penghui Lai.

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