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Polymorphisms of TGFβ1T+869C and C-509T with Lung Cancer Risk: A Meta-analysis**

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Lung cancer is the most common malignancy worldwide. A better understanding of the mechanisms may contribute to early diagnosis and establishment of new therapeutic targets.
Objectives. A meta-analysis was performed to investigate the association of transforming growth factor-beta 1 (TGFβ1) T+869C and C-509T polymorphisms with lung cancer susceptibility.
Material and Methods. Relevant studies were identified through PubMed, Medline, Embase and CNKI databases. The pooled odds ratios (ORs) with its 95% confidence intervals (CIs) were employed to assess these associations in a fixed- or random-effects model.
Results. For the TGFβ1 T+869C polymorphism, 5 published case-control studies with 1167 cases and 1365 controls were included. Overall, no significant association was found between the TGFβ1 T+869C polymorphism and lung cancer susceptibility under any genetic models in the total population ($p > 0.05$). A subgroup analysis by ethnicity showed no significant association among the Asian population as well, while a significant association was observed in Caucasian descendants. For the TGFβ1 C-509T polymorphism, 4 studies were considered, including 1029 cases and 1133 controls. However, this polymorphism also did not increase the risk of lung cancer in all genetic comparison models.
Conclusions. This meta-analysis suggests that TGFβ1 T+869C and C-509T polymorphisms may not contribute to lung cancer risk in the total population, while the T+869C polymorphism may increase the risk of lung cancer in the Caucasian population. However, many studies are still required to evaluate these associations in large populations (**Adv Clin Exp Med 2016, 25, 6, 1165–1172**).

Key words: lung cancer, polymorphism, meta-analysis, transforming growth factor-beta 1.

Lung cancer is the most common type of cancer and the main cause of cancer-related mortality worldwide, leading to more than a million deaths annually [1]. Even though epidemiological research has revealed more than 80% of lung cancers are attributed to tobacco, few smokers develop lung cancer [2]. Recent evidence suggests that genetic susceptibility may play a central role in carcinogenesis [3–5]. Moreover, numerous reports have demonstrated that single nucleotide polymorphisms (SNPs) in cytokine genes are associated with susceptibility to cancer [6, 7]. Therefore, anti-inflammatory cytokine transforming growth factor β1 (TGFβ1) may have a complex role in carcinogenesis.

TGFβ1 is a polypeptide that regulates cell growth and differentiation, immune modulation, wound healing, and embryogenesis [8]. Researchers have proved that TGFβ1 plays a dual role in carcinogenesis, acting as a tumor suppressor in the early stages and as a tumor promoter in later stages, by enhancing tumor cell motility, immunosuppression and invasiveness [9, 10].

Several genetic variants in the TGFβ1 gene have previously been identified. Some of these

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variants are associated with TGFβ1 production [11, 12]. A functional polymorphism in the TGFβ1 gene, a T-to-C substitution at nucleotide 29 of codon 10, leading to a replacement of leucine to proline (TGFβ1 T+869C, rs1982073), was located in the hydrophobic core of the signal peptide. This transition was shown to be related to higher circulating levels of TGFβ1 [13, 14]. Another polymorphism, a C-to-T substitution at nucleotide 506 (TGFβ1 C-509T, rs1800469), is associated with increased susceptibility and severity of asthma, risk of developing breast cancer and Alzheimer's disease [15–17]. This variant is located in the negative regulatory region, leading differential genetic regulation of TGFβ1 plasma levels [13].

Genetic variants which influence TGFβ1 expression and protein serum levels may have an impact on lung cancer development and prognosis. Furthermore, several articles have investigated the role of the TGFβ1 T+869C and C-509T polymorphisms in the etiology of lung cancer. However, the data from these studies was inconsistent. Hence, we conducted this meta-analysis to evaluate the associations of these polymorphisms with lung cancer risk.

Material and Methods

Selection of Studies

Relevant studies were identified by a computerized literature search of the Embase, Medline, PubMed, Wanfang and CNKI (China National Knowledge Infrastructure) electronic databases (prior to March 2014) using the following words and terms: lung cancer, lung carcinoma, transforming growth factor beta 1, TGFβ1, polymorphism, variant and mutation as well as their combinations. We also manually screened the references of the retrieved articles to obtain more relevant articles.

Criteria for Inclusion

The inclusion criteria were as follows:

1. The paper should be a case-control study evaluating the association between lung cancer and TGFβ1 polymorphisms;
2. Each study involved T+869C and/or C-509T polymorphisms of the TGFβ1 gene;
3. The results were expressed as odds ratio (ORs) with its corresponding 95% confidence interval (CI);
4. Genotype distribution information of the control for each polymorphism must be in Hardy-Weinberg equilibrium (HWE).

Quality Assessment and Data Extraction

Two investigators evaluated the quality of the screened studies independently. Any disagreement was discussed with a third expert to reach a consensus. The following information was collected from each study included: the first author's name, published year, country where the study was conducted, ethnicity and sample size of the cases and controls, and genotype distribution of the TT, TC, and CC.

Statistical Analysis

OR with 95% CI was used to measure the strength of association of the T+869C and C-509T polymorphisms with lung cancer risk. The z-test was employed to determine the significance of the pooled OR ($p < 0.05$). For all the polymorphisms, the genetic models (allelic model, co-dominant effects, dominant effect and recessive effect) were examined. The Cochran's Q statistics test was used to assess the heterogeneity among the studies ($p \leq 0.1$ was considered significant) [18, 19]. The random-effect model (DerSimonian and Laird method) was used when the effects were heterogeneous [20], whereas the fixed-effect model (the inverse variance-weighted method) was used in its absence [21]. To evaluate whether our results were affected by each individual study, a sensitivity analysis was conducted by systematically removing each study one time and recalculating the pooled ORs. Publication bias was investigated by using a funnel plot, in which the standard error of log (OR) of each study was plotted against its OR [22]. Hardy-Weinberg equilibrium was tested using the χ^2-test for goodness of fit or Fisher's exact probability test, where appropriate. $P < 0.05$ was considered significant. All statistical tests for this meta-analysis were performed with Review Manager (v. 5.2; the Cochrane Collaboration, Oxford, UK). All p-values were two-sided.

Results

Study Characteristics

The search initially identified 103 articles. After applying the inclusion criteria, 6 articles were ultimately screened out in this meta-analysis, including 1377 lung cancer patients and 1573 healthy controls. The study selection process is shown in Fig. 1.

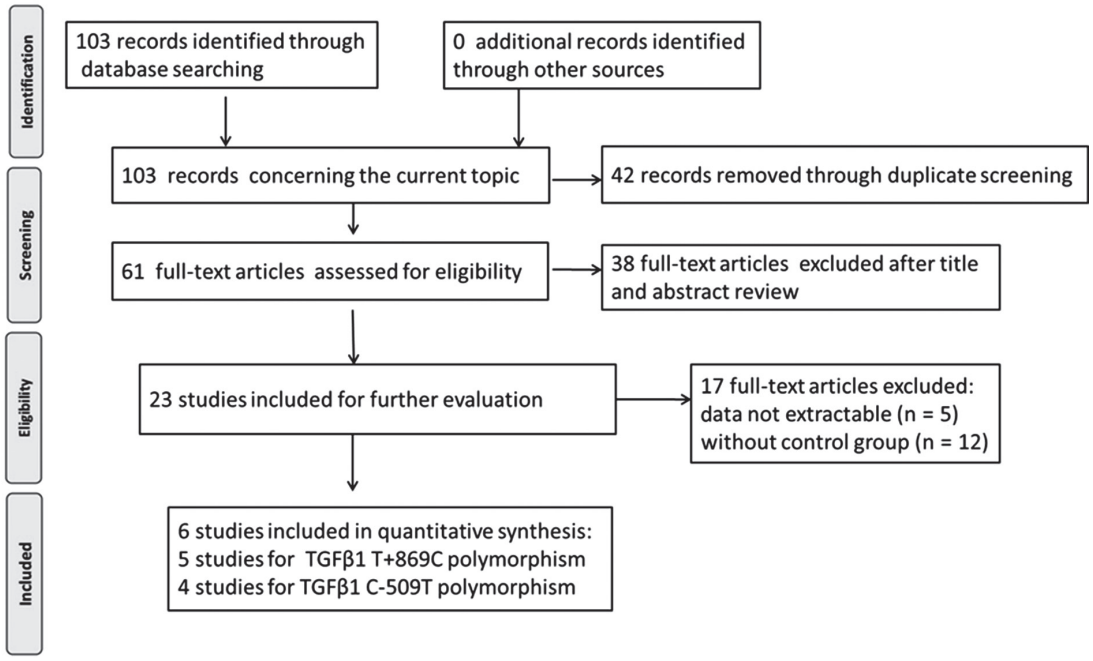

Fig. 1. Literature search and study selection procedures

For the T+869C polymorphism, 5 relevant studies with a total number of 1167 cases and 1365 controls were included in the meta-analysis [23–27]. Of these studies, 3 were conducted on Asian populations, and 2 on Caucasian descendants. For the C-509T polymorphism, 4 case-control studies met our inclusion criteria, including 1029 cases and 1133 controls [23, 25, 26, 28]. All these studies were conducted on Asian populations. The main study characteristics are summarized in Table 1.

Association Between TGFβ1 T+869C Polymorphism and Lung Cancer Risk

Table 2 lists the results of each comparison model in this meta-analysis. In the overall analysis, we found that the frequency of the C allele in the T+869C polymorphism is a little higher in lung cancer patients than in the healthy controls (48.4% vs. 44.4%). However, no significant association was found between the TGFβ1 T+869C polymor-

Table 1. Main characteristics of included studies in this meta-analysis

First author	Year	Country	Ethnicity	Total number		Cases			Controls		
				cases	controls	CC	CT	TT	CC	CT	TT
TGFβ1 T+869C											
Kang HG	2006	Korea	Asian	432	432	107	200	125	108	218	106
Park KH	2006	Korea	Asian	194	283	43	97	53	58	133	87
Colakogullari M	2008	Turkey	Caucasian	43	59	10	24	9	10	20	20
Teixeira AL	2011	Portugal	Caucasian	305	380	53	165	87	44	166	170
Bai L	2013	China	Asian	193	211	55	107	31	58	105	47
TGFβ1 C-509T											
Kang HG	2006	Korea	Asian	432	432	131	197	104	104	223	105
Park KH	2006	Korea	Asian	194	283	53	100	41	84	137	62
Li T	2012	China	Asian	210	208	18	87	105	36	92	80
Bai L	2013	China	Asian	193	211	31	108	54	46	107	57

Table 2. Stratified analysis of TGFß1 T+869C polymorphism with lung cancer risk

Genetic model	OR (95% CI)	P	$P_{heterogeneity}$	Analysis model
Total				
C vs. T	1.20 (0.95, 1.52)	0.12	0.004	R
CC vs. TT	1.42 (0.91, 2.17)	0.12	0.02	R
CT vs. TT	1.39 (0.91, 2.13)	0.13	0.001	R
CC + CT vs. TT	1.41 (0.92, 2.15)	0.12	0.005	R
CC vs. CT + TT	1.13 (0.93, 1.36)	0.22	0.49	F
Asian				
C vs. T	1.02 (0.89, 1.16)	0.83	0.28	F
CC vs. TT	1.04 (0.79, 1.36)	0.78	0.25	F
CT vs. TT	1.08 (0.72, 1.63)	0.69	0.06	R
CC + CT vs. TT	1.09 (0.74, 1.59)	0.66	0.06	R
CC vs. CT + TT	1.03 (0.82, 1.28)	0.82	0.94	F
Caucasian				
C vs. T	1.59 (1.29, 1.95)	< 0.00001	0.97	F
CC vs. TT	2.33 (1.50, 3.63)	0.0002	0.93	F
CT vs. TT	2.01 (1.46, 2.76)	< 0.0001	0.55	F
CC + CT vs. TT	2.08 (1.53, 2.81)	< 0.00001	0.67	F
CC vs. CT + TT	1.54 (1.03, 2.28)	0.03	0.61	F

F – fixed-effect model; R – random-effect model.

phism and lung cancer susceptibility under any genetic model (C vs. T: p = 0.12; CC vs. TT: p = 0.12; CT vs. TT: p = 0.13; CC + CT vs.TT: p = 0.12; CC vs. CT + TT: p = 0.22).

In the stratified analysis by ethnicity, we did not find a significantly association between the TGFβ1 T+869C polymorphism and cancer risk in the Asian descendants groups as well. However, significant association was observed in Caucasian descendants (C vs. T: p < 0.00001; CC vs. TT: p = 0.0002; CT vs. TT: p < 0.0001; CC + CT vs. TT: p < 0.00001; CC vs. CT + TT: p = 0.03), as shown in Fig. 2. No significant heterogeneity was found between the included studies in Caucasian descendants (I^2 = 0%).

Association Between TGFβ1 C-509T Polymorphism and Lung Cancer Risk

Overall, there was no association between the TGFβ1 C-509T polymorphism and lung cancer risk in all genetic models (T vs. C: p = 0.39; TT vs. CC: p = 0.35; CT vs. CC: p = 0.49; CT + TT vs. CC: p = 0.40; TT vs. CT + CC: p = 0.26). Table 3

Table 3. Meta-analysis of the TGFβ1 C-509T polymorphism on lung cancer risk

Genetic model	OR (95% CI)	P	$P_{heterogeneity}$	Analysis model
T vs. C	1.11 (0.87, 1.42)	0.39	0.01	R
TT vs. CC	1.27 (0.77, 2.08)	0.35	0.01	R
CT vs. CC	1.17 (0.75, 1.83)	0.49	0.01	R
CT+TT vs. CC	1.22 (0.77, 1.94)	0.40	0.04	R
TT vs. CT+CC	1.12 (0.92, 1.35)	0.26	0.22	F

F – fixed-effect model; R – random-effect model.

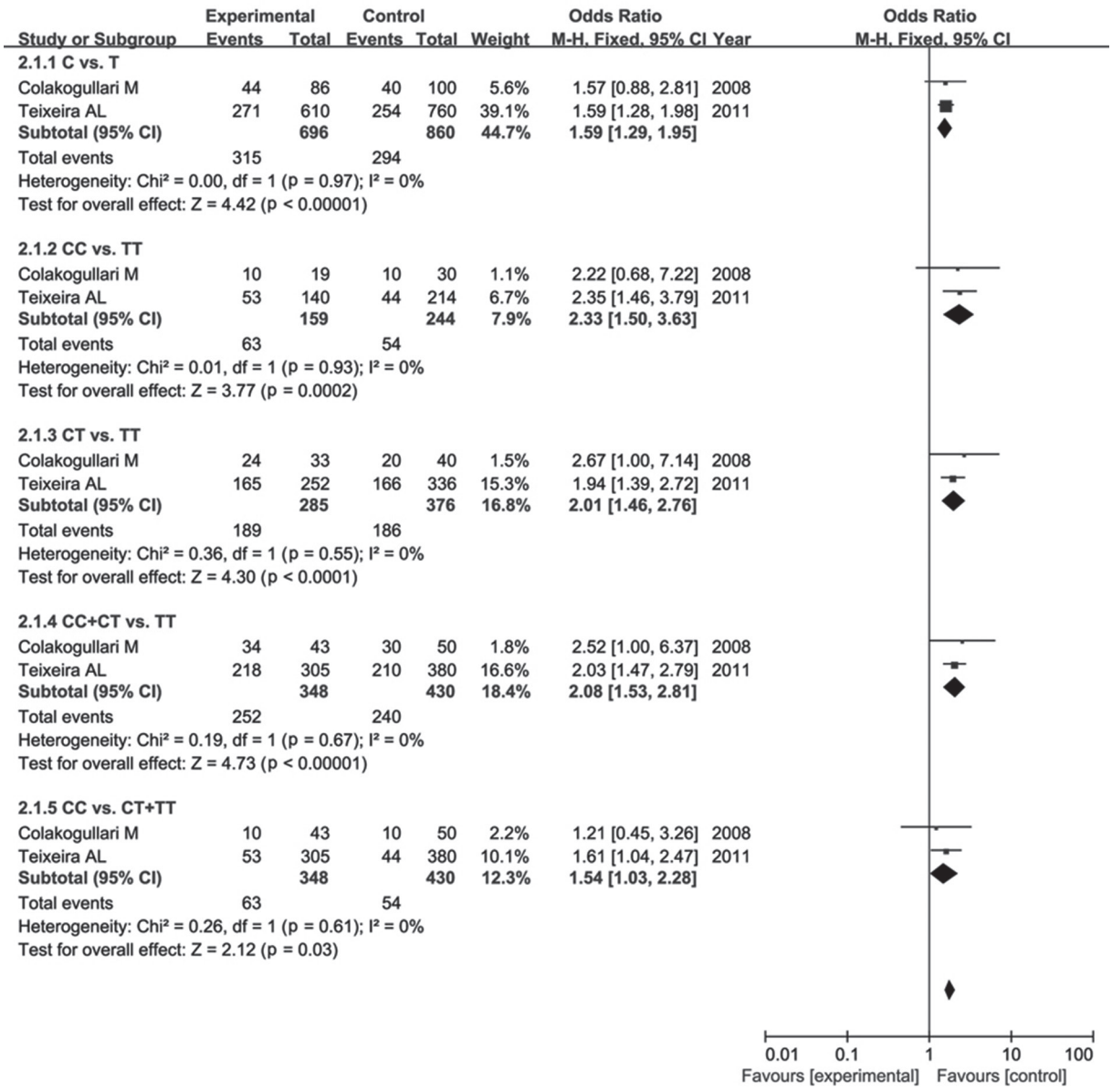

Fig. 2. Forest plot of lung cancer risk associated with TGFβ1 T+869C polymorphism under all genetic models among Caucasian population

shows the TGFβ1 C-509T polymorphism on lung cancer risk.

Sensitivity Analyses and Publication Bias

The corresponding pooled ORs were not materially changed when a single included study was deleted each time. This procedure confirms the stability of our overall result.

The shape of the funnel plots does not reveal any evidence of funnel plot asymmetry as shown in Fig. 3 and Fig. 4, indicating no publication bias was present.

Discussion

Genetic susceptibility to cancers has led to growing attention to the studies of the polymorphism genes involved in carcinogenesis [29–31]. TGFβ1 is a multifunctional cytokine that is essential for maintaining homeostasis involving bone and muscle differentiation, immune response, and tumor suppression [32, 33]. This cytokine, which induces cell proliferation and apoptosis, plays a key role in various types of cancers [34–36]. There is evidence that TGFβ1 functions as a tumor initiation suppressor, but as a tumor progression promoter when the proliferative inhibition effect of the TGFβ1 signaling pathway has been overridden by other oncogenic mutations [37, 38].

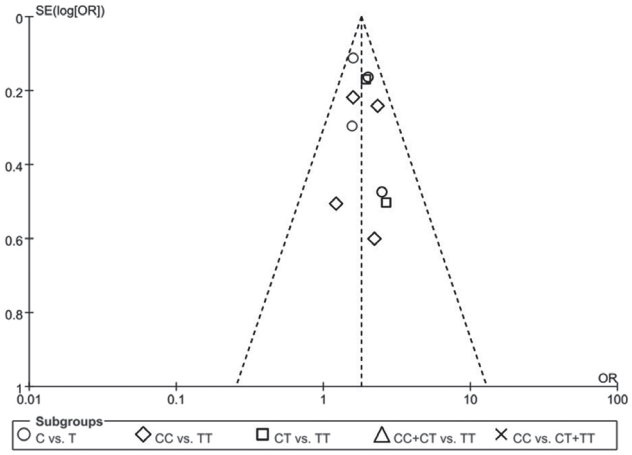

Fig. 3. Funnel plot of T+869C polymorphism and cancer risk for publication bias among Caucasian population

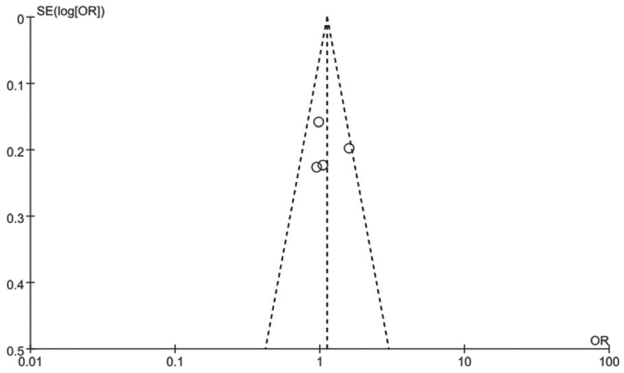

Fig. 4. Funnel plot of TGFβ1 C-509T polymorphism and cancer risk for publication bias in recessive genetic model (TT vs. CT + CC)

A catalog of 106 single-nucleotide polymorphisms (SNPs) and 11 other types of variations in the TGFβ1 gene and its signaling pathway have been identified, and a few of these have been associated with human diseases [39]. Among the different polymorphisms of TGFβ1, the polymorphisms of C-509T and T+869C have been most intensively studied. Researchers have reported that C-509T and T+869C are significantly related to the disease-free survival of breast cancer patients in a large Chinese population [40]. Furthermore, the C-509T polymorphism of promoter region in the TGFβ1 has been shown to be associated with increased transcriptional activity with a gene dose effect [16]; the T+869C gives rise to a Leu to Pro substitution at amino acid residue 10 in the signal peptide sequence and to increased formation of TGFβ1 [41]. Both of those SNPs have been shown to have a protective effect on hepatocellular carcinoma in Korean patients with chronic hepatitis B virus infection [42]. However, few reports have been conducted on the association between the SNPs of TGFβ1 and lung cancer risk.

To systematically explore the association between TGFβ1 C-509T and T+869C polymorphisms and lung cancer risk, we conducted a meta-analysis of relevant studies. This meta-analysis, including 1166 cases and 1359 controls from 5 studies, explored the association between the TGFβ1 T+869C polymorphism and cancer risk. We found that the TGFβ1 T+869C polymorphism was not significantly associated with cancer risk in overall comparisons, compared to wild homozygotes. Using stratified analysis for ethnicity, the T+869C polymorphism showed a significantly increased lung cancer risk in the Caucasian group. However, this association was not found among the Asian group.

For the TGFβ1 C-509T polymorphism, our meta-analysis analyzed 4 studies, including 1029 cases and 1133 controls. All of these 4 studies were conducted in the Asian population. We found that variant homozygotes or heterozygotes of the C-509T polymorphism were not associated with cancer risk in overall comparisons; the insignificance of this relationship holds up under various genetic models. Our results are consistent with all the studies on lung cancer. While 1 study demonstrated that the TGFβ1 C-509T polymorphism was associated with higher lung cancer risk [25], this association is not significant according to our present meta-analysis.

TGFβ1 polymorphisms are associated with many human diseases. Wei et al. have suggested that TGFβ1 T+869C was a low-penetrant risk factor for prostate cancer and cancer in Asians [43]. Liu et al. have proved that that the TGFβ1 C-509T polymorphism might contribute to a decreased risk of colorectal cancer susceptibility, especially for Caucasians [44]. Hou et al. have demonstrated that serum TGFβ1 levels were significantly higher in patients with lung cancer compared to healthy volunteers [45]. Polymorphisms in TGFβ1 may influence its levels. A previous meta-analysis conducted by He et al. suggested that the T+869C polymorphism of TGFβ1 is associated with radiation pneumonia risk only in Caucasians, while there may be no association between the C509T polymorphism and radiation pneumonia risk [46].

Several limitations of this meta-analysis should be addressed. Firstly, the original information was insufficient and the assessment of potential interactions is limited. Secondly, the number of published studies was small and insufficient for comprehensive analyses, particularly for lung cancer. Thirdly, a more precise analysis should be conducted if individual information, including other covariates such as age, sex and smoking condition, becomes available.

In conclusion, research on the relationship between TGFβ1 polymorphisms and lung cancer is of

intense interest but is in conflict at present. Our meta-analysis suggests that the TGFβ1 T+869C allele is not significantly associated with lung cancer risk, especially in the Asian group, while a significant association was observed in the Caucasian group. TGFβ1 C-509T polymorphism was also not associated with lung cancer risk. However, large trials, containing large numbers of cases and controls, and gene-environment interactions, should be considered to evaluate the association in further analyses.

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