Association between Genetic Variants of Transforming Growth Factor-β1 and Susceptibility of Pneumoconiosis: A Meta-analysis

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Abstract

Background: Transforming growth factor-beta 1 (TGF-β1) and gene variants have been extensively studied in various human diseases. For example, *TGF-β1* polymorphisms were associated with fibrosis and pneumoconiosis, but the data remained controversial. The aim of this meta-analysis was to assess the association between *TGF-β1* −509 C>T [rs1800469], +869 T>C [rs1800470], and +915 G>C [rs1800471] polymorphisms and pneumoconiosis.

Methods: A comprehensive literature search was conducted through searching in PubMed, Embase, the Chinese Biomedical Database, and the Wei Pu (Chinese) Database by the end of April 2016. Eleven publications with 21 studies were included in this meta-analysis, covering a total of 4333 patients with pneumoconiosis and 3478 controls. Study quality was assessed, and heterogeneity and publication bias were measured. All statistical analyses were performed using STATA version 12.0 (StataCorp, College Station, TX, USA) software.

Results: The data showed significant associations between *TGF-β1* −509 C>T polymorphism and the risk of pneumoconiosis development (T vs. C, odds ratio [*OR*] = 1.35, 95% confidence interval [*CI*]: 1.00–1.81, *P* = 0.046); between *TGF-β1* +915 G>C polymorphism and the pneumoconiosis risk (C vs. G, *OR* = 1.69, 95% *CI*: 1.19–2.40, *P* = 0.004; CG vs. GG, *OR* = 1.79, 95% *CI*: 1.23–2.60, *P* = 0.002; CC+CG vs. GG, *OR* = 1.80, 95% *CI*: 1.24–2.61, *P* = 0.002). In addition, the subgroup analysis of ethnicity versus pneumoconiosis types indicated a significant association of silicosis among Asian populations but not that of coal workers' pneumoconiosis in Caucasian populations. In contrast, no significant association was exhibited between *TGF-β1* +869 T>C polymorphism and risk of pneumoconiosis.

Conclusion: The polymorphisms of both *TGF-β1* −509 C>T and +915 G>C are associated with increased risk of pneumoconiosis.

Key words: Meta analysis; Pneumoconiosis; Polymorphism; Transforming Growth Factor-beta1

Introduction

Pneumoconiosis is an occupational disease mainly caused by inhalation of microscopically respirable coal dust, crystalline silica particles, and other various dust particles. Clinically, pneumoconiosis is characterized by shortness of breath and chest X-ray patchy, subpleural or bibasilar interstitial infiltrates, or small cystic radiolucencies (honeycombing).[1-3] Pathologically, the inhaled dust induces chronic lung inflammation and pulmonary fibrosis.[1-3] Early pneumoconiosis may be asymptomatic, but advanced stages of pneumoconiosis result in airflow limitation, hypoxia, pulmonary hypertension, respiratory or heart failure, and premature death, even without further exposure to the dust.[1-3]

Pathogenesis of pneumoconiosis is multifactorial, and different dust particles can induce relatively different host

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immune responses, which are controlled by expression of various genes and gene pathways.[4-6] For example, it was reported that not all individuals exposed to similar levels of dust developed pulmonary fibrosis, which suggests that genetic predisposition plays a crucial role in individual pneumoconiosis susceptibility.[7,8] Therefore, a better understanding of the interaction between genetic mutations and dust exposure can help identify high-risk individuals and prevent pneumoconiosis development.

Transforming growth factor-β (TGF-β) is a multifunctional cytokine with various effects on cell proliferation, differentiation, apoptosis, migration, inflammation, tissue repair, and immune responses.[9] The subtype TGF-β1, cloned from human placenta, is the most abundant isoform in the human body. As a growth factor with important immunomodulatory and fibrogenic properties, TGF-β1 facilitates chemotaxis through stimulation of monocyte, lymphocyte, neutrophil, and myofibroblast migration. Thus, it may function as a candidate for pneumoconiosis.[10-13]

TGF-β1 gene includes seven exons and six introns and is located at chromosome 19q13.[14] Several polymorphic variants in *TGF-β1*, such as −509 C>T (rs1800469), +869 T>C (rs1800470), and +915 G>C (rs1800471), were assessed for association with pneumoconiosis risk, the data remain controversial currently.[15-25] In 2012, a meta-analysis published in Chinese reported that *TGF-β1* gene −509 C>T, +869 T>C polymorphisms were not associated with risk of developing pneumoconiosis.[26] However, only small sample size related to *TGF-β1* gene −509 C>T, +869 T>C was involved in this meta-analysis, and thus, it was unable to provide enough persuasiveness. It is unclear yet whether there are significant associations between −509 C>T (rs1800469), +869 T>C (rs1800470), and +915 G>C (rs1800471) polymorphisms and the risk of pneumoconiosis. To summarize and clarify the published data, we performed this meta-analysis.

Methods

Literature search strategy

We searched the electronic databases of PubMed, Embase, the Chinese Biomedical Database, and the Wei Pu (Chinese) Database to retrieve eligible studies for inclusion in this meta-analysis. The following terms were used in the search: "Pneumoconiosis" OR "silicosis" OR "asbestosis" AND "transforming growth factor β" OR "TGF-β" OR "TGF beta" AND "single nucleotide polymorphism" OR "polymorphisms," etc. These keywords were combined with Boolean logic words "OR/AND". Additional studies were identified by a manual search of the references of related articles, reviews, even citation tracking and so on, and the search included all published literature through April 30, 2016. In cases where publications used the same patient population, we only included the most recent or complete study in the meta-analysis.

Selection criteria

The inclusion criteria were as follows: (1) studies investigating the association between pneumoconiosis risk and *TGF-β1* polymorphisms −509 C>T (rs1800469), +869 T>C (rs1800470), and +915 G>C (rs1800471); Any study about TGF-β1 −509 C>T (rs1800469) or +869 T>C (rs1800470) or +915 G>C (rs1800471) was considered as an independent study. (2) case–control studies; (3) studies providing sufficient information for genotype and allele frequencies to estimate the odds ratio (*OR*) with its corresponding 95% confidence interval (*CI*) and *P* values; (4) studies written in English or Chinese; (5) human studies; and (6) studies including only cases with definitive diagnosis of pneumoconiosis. The exclusion criteria were as follows: (1) case reports, abstracts, reviews, and repeat studies; (2) genotype distribution did not reach Hardy–Weinberg equilibrium (HWE).

Data extraction

The following data were independently extracted from all eligible publications by two investigators (Chang-Wen Deng and Xing-Xing Zhang) according to the inclusion criteria, and any disagreement was discussed with coauthors until a consensus was reached. A standardized data form was used that included first author's name, year of publication, country origin, study ethnicity, genotyping methods, total number of cases and controls, genotype distributions in cases and controls, source of controls, and information on HWE test. These data were also tracked manually if missing. Population categories were divided into Caucasian, Asian, and mixed.

Statistical analysis

The pooled *OR*s with 95% *CI* were used to determine the association between risk of pneumoconiosis and *TGF-β1* polymorphisms −509 C>T, +869 T>C, and +915 G>C according to allele contrast, homozygote, heterozygote, dominant, and recessive models. The pooled *OR*s were calculated for additive, codominant, dominant, and recessive models, respectively. The significance of pooled *OR*s was analyzed using the *Z*-test in recessive models. $P < 0.05$ was considered statistically significant. The Chi-square-based Q statistic test, quantified by the I^2 metric value, was used to analyze heterogeneity assumption among the studies ($I^2 > 50\%$ or $P \leq 0.1$ was considered statistically significant. All *P* values were two-sided). When studies were homogenous, the fixed effects model (Mantel–Haenszel method) was performed. Otherwise, the random effects model was applied to estimate the *OR*s and 95% *CI* according to the previous studies.[27,28] The Chi-square test was used to test HWE. The statistical program STATA version 12.0 (StataCorp, College Station, TX, USA) was used to analyze all data in this study.

Results

Characteristics of studied subjects

Based on our search strategy, 11 articles involving 21 studies were included in this meta-analysis, covering a total of 4333 cases with pneumoconiosis and 3478 controls. The controls were matched with those cases for age, dust

exposure period and job type, etc. The study selection process is shown in Figure 1. Seven of these studies investigated association between *TGF-β1* −509 C>T polymorphism and pneumoconiosis,[15-21] nine involved +869 T>C polymorphism,[15,17-20,22-25] and five involved +915 G>C polymorphism.[15,17,19,20,24] The characteristics of each selected study are listed in Tables 1-3. Specifically, Table 1 shows characteristics of case and control for association of −509 C>T polymorphism with pneumoconiosis, six of which were performed in Asia.[15,17-21] One was performed in Caucasus,[16] originating from China and USA, respectively. Pneumoconiosis was induced by coal in two studies, and others were induced by silicosis. However, there were only two studies that did not follow the HWE.[18,21] The characteristics of case and control for association of +869 T>C polymorphism with pneumoconiosis are presented in Table 2. Seven studies were performed in Asia,[15,17-20,22,25] one in Caucasus,[24] and one in mixed[23] and originated from China, German, Turkish, and the USA, respectively. Two studies did not follow the HWE, and one study had insufficient data for HWE calculation.[18,23] Pneumoconiosis was present in coal workers in four studies, and in five studies, silicosis was the irritant. Table 3 illustrates the characteristics of case and control for association of +915 G>C polymorphism with pneumoconiosis. Four studies were performed in China[15,17,19,20] and one in Caucasus in Germany.[24] One study did not follow the HWE, and one study had insufficient data for HWE calculation.[15,17] Pneumoconiosis occurred in coal workers type reported in three studies and in silicosis in two studies.

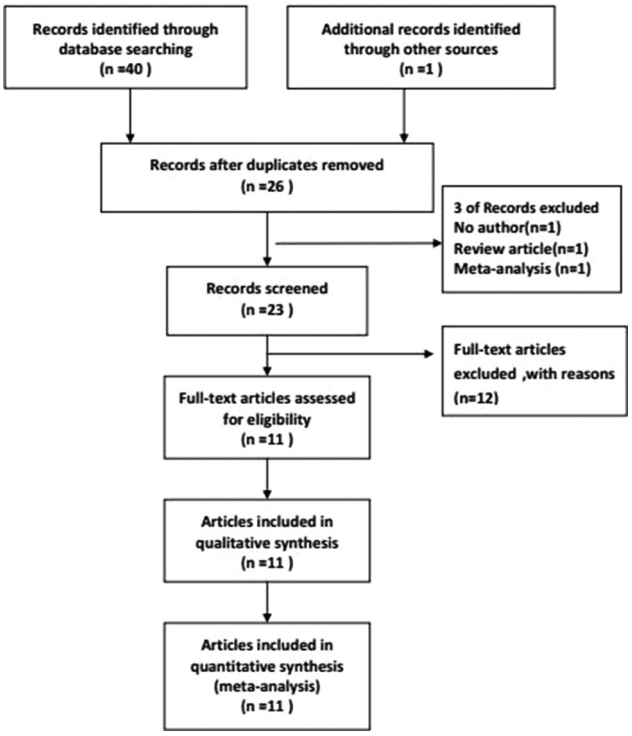

Figure 1: Illustration of study selection and inclusion process.

Quantitative data synthesis

For *TGF-β1* −509 C>T polymorphism, we conducted seven studies to evaluate the overall association between −509 C>T polymorphism and risk of pneumoconiosis. We found an overall association between −509 C>T polymorphism and the risk of pneumoconiosis in terms of allele frequency [T vs. C, *OR* = 1.35, 95% *CI*: 1.00–1.81, *P* = 0.046; Figure 2]. However, there was no significant association detected under homozygous, heterozygous, recessive, and dominant models [*P* > 0.05; Table 4]. The subgroup analysis showed that −509 C>T polymorphism was not significantly associated with pneumoconiosis risk based on pneumoconiosis type and ethnicity.

Moreover, *TGF-β1* +915 G>C polymorphism was significantly associated with risk of pneumoconiosis

Table 1: Characteristics of enrolled case–control studies for association of −509 C>T polymorphism with pneumoconiosis

References	Year	Ethnicity (country)	Subjects	Frequency of allele			Distribution of genotype				Pneumoconiosis type	Method of genotyping	HWE
				T	C	Total	TT	TC	CC	Total			
Fan *et al*.[15]	2007	Asian (China)	Case	131	103	234	40	51	26	117	Silicosis	PCR-RELP	0.08
			Control	100	134	234	26	48	43	117			
Yucesoy *et al*.[16]	2008	Caucasus (USA)	Case	171	395	566	31	109	143	283	CWP	PCR-SSP	0.08
			Control	189	461	650	34	121	170	325			
Wu *et al*.[17]	2008	Asian (China)	Case	175	191	366	46	83	54	183	Silicosis	PCR-RELP	0.42
			Control	119	103	222	34	51	26	111			
Qian *et al*.[18]	2010	Asian (China)	Case	515	501	1016	121	273	114	508	CWP	PCR-RELP	<0.05
			Control	546	506	1052	122	302	102	526			
Li *et al*.[19]	2009	Asian (China)	Case	92	62	154	28	36	13	77	Silicosis	PCR-RELP	0.06
			Control	70	84	154	20	30	27	77			
Li *et al*.[20]	2010	Asian (China)	Case	41	39	80	13	15	12	40	CWP	PCR-RELP	0.80
			Control	30	50	80	6	18	16	40			
Yao *et al*.[21]	2006	Asian (China)	Case	124	96	220	34	56	20	110	CWP	PCR-RELP	<0.05
			Control	76	144	220	18	40	52	110			

CWP: Coal workers' pneumoconiosis; HWE: Hardy–Weinberg equilibrium; PCR-SSP: Polymerase chain reaction-sequence-specific primer; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism.

Table 2: Characteristics of enrolled case–control studies for association of +869 T>C polymorphism with pneumoconiosis

References	Year	Ethnicity (country)	Subjects	Frequency of allele			Distribution of genotype				Pneumoconiosis type	Method of genotyping	HWE
				T	C	Total	TT	TC	CC	Total			
Fan *et al*.[15]	2007	Asian (China)	Case	106	128	234	28	50	39	117	Silicosis	PCR-RELP	0.17
			Control	125	109	234	37	51	29	117			
Wu *et al*.[17]	2008	Caucasus (USA)	Case	187	179	366	52	83	48	183	Silicosis	PCR-RELP	0.75
			Control	104	118	222	24	56	31	111			
Qian *et al*.[18]	2010	Asian (China)	Case	584	432	1016	123	338	47	508	CWP	PCR-RELP	<0.05
			Control	550	502	1052	109	332	85	526			
Li *et al*.[19]	2009	Asian (China)	Case	70	84	154	19	32	26	77	Silicosis	PCR-RELP	0.31
			Control	80	74	154	23	34	20	77			
Li *et al*.[20]	2009	Asian (China)	Case	36	44	80	9	18	13	40	Silicosis	PCR-RELP	0.38
			Control	45	35	80	14	17	9	40			
Yu *et al*.[22]	2009	Asian (China)	Case	249	219	468	74	101	59	234	CWP	PCR-RELP	0.20
			Control	464	416	880	129	206	105	440			
Ates *et al*.[23]	2008	Mixed (Turky)	Case	60	74	134	17	26	24	67	CWP	PCR-RELP	<0.05
			Control	94	90	184	22	50	20	92			
Helmig *et al*.[24]	2009	Caucasus (Germany)	Case	657	457	1114	189	279	89	557	CWP	PCR-SSP	0.38
			Control	100	66	166	32	36	15	83			
Yu *et al*.[25]	2009	Asian (China)	Case	264	254	518	56	–	–	56	Silicosis	PCR-RELP	
			Control	341	341	682	68	–	–	68			

CWP: Coal workers' pneumoconiosis; HWE: Hardy–Weinberg equilibrium; PCR-SSP: Polymerase chain reaction-sequence-specific primer; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism.

Table 3: Characteristics of enrolled case–control studies for association of +915 G>C polymorphism with pneumoconiosis

References	Year	Ethnicity (country)	Subjects	Frequency of allele			Distribution of genotype				Pneumoconiosis type	Method of genotyping	HWE
				G	C	Total	GG	GC	CC	Total			
Fan *et al*.[15]	2007	Asian (China)	Case	200	34	234	83	34	0	117	Silicosis	PCR-RELP	<0.05
			Control	214	20	234	97	20	40	117			
Wu *et al*.[17]	2008	Asian (China)	Case	364	2	294	181	2	0	183	Silicosis	PCR-RELP	<0.05
			Control	222	0	222	111	0	0	111			
Li *et al*.[19]	2009	Asian (China)	Case	128	26	154	51	26	0	77	Silicosis	PCR-RELP	0.38
			Control	140	14	154	63	14	0	77			
Li *et al*.[20]	2009	Asian (China)	Case	72	8	80	32	8	0	40	CWP	PCR-RELP	0.60
			Control	74	6	80	34	6	0	40			
Helmig *et al*.[24]	2009	Caucasus (Germany)	Case	1025	89	640	469	87	1	557	CWP	PCR-SSP	0.55
			Control	156	10	166	73	10	0	83			

CWP: Coal workers' pneumoconiosis; HWE: Hardy–Weinberg equilibrium; PCR-SSP: Polymerase chain reaction-sequence-specific primer; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism.

under allele contrast, heterozygous, and dominant models [C vs. G, *OR* = 1.69, 95% *CI*: 1.19–2.40, *P* = 0.004; CG vs. GG, *OR* = 1.79, 95% *CI*: 1.23–2.60, *P* = 0.002; CC+CG vs. GG, *OR* = 1.80, 95% *CI*: 1.24–2.61, *P* = 0.002; Figure 3]. Similarly, the subgroup study of ethnicity, allele contrast, heterozygous, and dominant models also indicated a significant association [C vs. G, *OR* = 1.84, 95% *CI*: 1.22–2.77, *P* = 0.003; CG vs. GG, *OR* = 2.01, 95% *CI*: 1.30–3.12, *P* = 0.002; CC + CG vs. GG, *OR* = 2.01, 95% *CI*: 1.30–3.12, *P* = 0.002; Table 4]. Furthermore, the subgroup analysis of pneumoconiosis types among silicosis, allele contrast, heterozygous, and dominant models also indicated a significant association [C vs. G, *OR* = 1.93, 95% *CI*: 1.24–2.40, *P* = 0.004; CG vs. GG, *OR* = 2.13, 95% *CI*: 1.33–3.42, *P* = 0.002; CC + CG vs. GG, *OR* = 2.13, 95% *CI*: 1.33–3.42, *P* = 0.002; Figure 4]. However, there was no association observed between *TGF-β1* +915 G>C polymorphism and risk of pneumoconiosis under other models between Caucasian and coal workers' pneumoconiosis (CWP) [*P* > 0.05; Table 4].

However, for *TGF-β1* +869 T>C polymorphism, there were nine studies and our analyses showed no statistically significant association between *TGF-β1* +869 T>C polymorphism and the risk of pneumoconiosis under heterozygous, homozygous, allele contrast, recessive, and

dominant models [$P > 0.05$; Table 4]. Similarly, the subgroup study of ethnicity and pneumoconiosis types also showed no significant association between *TGF-β1* +869 T>C polymorphism and increased risk of pneumoconiosis under all models [$P > 0.05$; Table 4].

Sensitivity analysis and publication bias

Sensitivity analysis was performed to reflect the influence of the individual data set on the pooled *OR*s by sequentially excluding each case–control study. The data showed that the corresponding pooled *OR*s under all the genetic models were not materially altered.

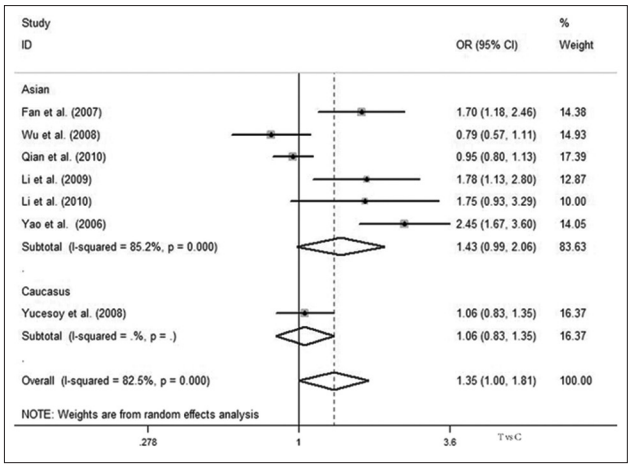

Figure 2: Forest plot that describes the meta-analysis under allele contrast model for association between transforming growth factor-β1 −509 C>T polymorphism and pneumoconiosis risk (T vs. C), test for overall effect ($z = 1.99$, $P = 0.046$).

Begg's funnel plot and Egger's regression test were used to check publication bias in our data. Begg's funnel plots did not reveal obvious asymmetry [Figures 5-7]. There were no statistically significant difference in the Egger's test, indicating that there was no significant publication bias for all genetic models (*TGF-β1* −509 C>T polymorphism, $P = 0.230$ for T vs. C, $P = 0.13$ for CT vs. CC; *TGF-β1* +869 T>C polymorphism, $P = 0.10$ for CC vs. TT; $P = 0.90$ for CT vs. TT; *TGF-β1* +915 G>C polymorphism, $P = 0.80$ for C vs. G; $P = 1.00$ for CG vs. GG).

Discussion

In this meta-analysis, we searched the literature and obtained 21 eligible case–control studies with a total of 4333 pneumoconiosis cases and 3478 controls. Our data provided evidence for statistically significant association between *TGF-β1* −509 C>T and +915 G>C polymorphisms with risk of pneumoconiosis development. However, we did not find an association between *TGF-β1* +869 T>C polymorphism and risk of pneumoconiosis. Further study will investigate the role of TGF-β1 on regulation of lung cell fibrosis and pneumoconiosis development.

Pneumoconiosis is a multifactorial disease, and the causes can be silicosis, coal, and other duct irritants. Pneumoconiosis workers develop progressive massive fibrosis in the lung

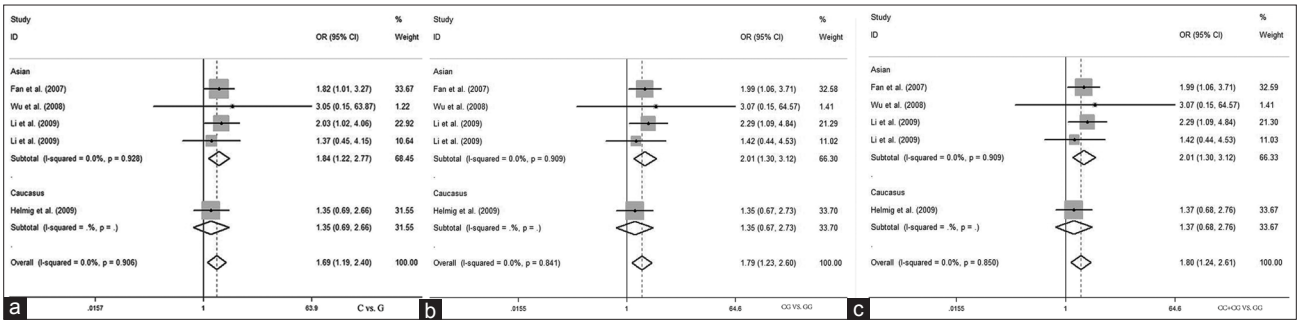

Figure 3: Forest plot that describes the meta-analysis under allele contrast model, homozygous model, and dominant model for the association between transforming growth factor-β1 +915 G>C polymorphism and ethnicities of pneumoconiosis risk. Test for overall effect ([a] C vs. G: $z = 2.91$, $P = 0.004$; [b] CG vs. GG: $z = 3.05$, $P = 0.002$; [c] CC+CG vs. GG: $z = 3.07$, $P = 0.002$).

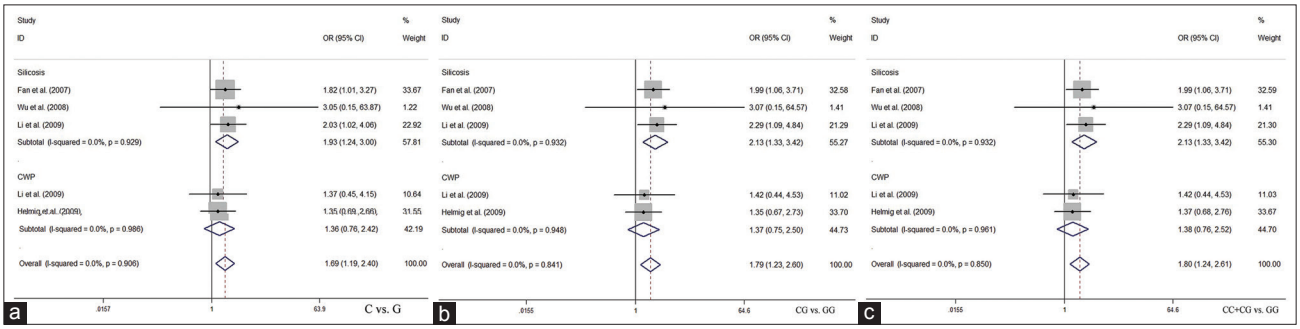

Figure 4: Forest plot that describes the meta-analysis under allele contrast model, homozygous model, and dominant model for association between transforming growth factor-β1 +915 G>C polymorphism and diseases types of pneumoconiosis diseases risk. Test for overall effect ([a] C vs. G: $z = 2.91$, $P = 0.004$; [b] CG vs. GG: $z = 3.05$, $P = 0.002$; [c] CC+CG vs. GG: $z = 3.07$, $P = 0.002$).

Table 4: Association of *TGF-β1* −509 C>T, +869 T>C, +915 G>C polymorphisms with risk of pneumoconiosis

TGF-β1 polymorphisms	Allele contrast model		Homozygous model		Heterozygous model		Dominant model		Recessive model	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
***TGF-β1* −509 C>T**	**T versus C**		**TT versus CC**		**CT versus CC**		**TT+TC versus CC**		**TT versus TC+CC**	
Overall	1.35 (1.00, 1.81)	0.046	1.69 (0.98, 2.92)	0.059	1.36 (0.90, 2.05)	0.14	1.48 (0.95, 2.31)	0.081	1.33 (0.98, 1.81)	0.071
Type of diseases										
Silicosis	1.32 (0.77, 2.28)	0.31	1.65 (0.62, 4.41)	0.32	1.45 (0.73, 2.86)	0.28	1.54 (0.70, 3.41)	0.28	1.28 (0.72, 2.28)	0.39
CWP	1.38 (0.92, 2.07)	0.12	1.75 (0.81, 3.78)	0.15	1.31 (0.74, 2.33)	0.34	1.46 (0.80, 2.68)	0.22	1.39 (0.90, 2.15)	0.13
Ethnicity										
Caucasian	1.06 (0.83, 1.35)	0.66	1.08 (0.63, 1.85)	0.76	1.07 (0.76, 1.51)	0.69	1.07 (0.78, 1.48)	0.66	1.05 (0.63, 1.76)	0.84
Asian	1.43 (0.99, 2.06)	0.060	1.87 (0.96, 3.66)	0.067	1.46 (0.85, 2.50)	0.17	1.61 (0.90, 2.87)	0.19	1.41 (0.98, 2.04)	0.067
***TGF-β1* +869 T>C**	**C versus T**		**CC versus TT**		**CT versus TT**		**CT+CC versus TT**		**CC versus TT+TC**	
Overall	0.97 (0.89, 1.07)	0.58	1.05 (0.73, 1.52)	0.79	0.95 (0.80, 1.13)	0.56	1.00 (0.86, 1.17)	0.96	1.09 (0.78, 1.51)	0.62
Type of diseases										
Silicosis	1.04 (0.89, 1.21)	0.64	1.23 (0.68, 2.23)	0.49	0.97 (0.67, 1.40)	0.86	1.15 (0.88, 1.49)	0.29	1.22 (0.87, 1.72)	0.24
CWP	0.94 (0.83, 1.06)	0.29	0.97 (0.60, 1.55)	0.88	0.94 (0.77, 1.15)	0.57	0.93 (0.77, 1.13)	0.47	1.02 (0.64, 1.64)	0.93
Ethnicity										
Caucasian	1.05 (0.76, 1.47)	0.75	1.00 (0.52, 1.95)	0.98	1.31 (0.79, 2.19)	0.29	1.22 (0.76, 1.97)	0.40	0.86 (0.47, 1.58)	0.63
Mixed	1.29 (0.82, 2.01)	0.26	1.55 (0.65, 3.70)	0.32	0.67 (0.31, 1.48)	0.32	0.92 (0.45, 1.92)	0.83	2.01 (0.99, 4.06)	0.052
Asian	0.95 (0.86, 1.05)	0.34	1.02 (0.64, 1.62)	0.92	0.92 (0.76, 1.12)	0.43	0.98 (0.83, 1.16)	0.84	1.04 (0.71, 1.51)	0.85
***TGF-β1* +915 G>C**	**C versus G**		**CC versus GG**		**CG versus GG**		**CC+CG versus GG**		**CC versus CG+GG**	
Overall	1.69 (1.19, 2.40)	0.004	0.47 (0.02, 11.64)	0.64	1.79 (1.23, 2.60)	0.002	1.80 (1.24, 2.61)	0.002	0.45 (0.02, 11.14)	0.62
Type of diseases										
Silicosis	1.93 (1.24, 3.00)	0.004			2.13 (1.33, 3.42)	0.002	2.13 (1.33, 3.42)	0.002		
CWP	1.36 (0.76, 2.42)	0.29	0.47 (0.02, 11.64)	0.64	1.37 (0.75, 2.50)	0.30	1.38 (0.76, 2.52)	0.29	0.45 (0.02, 11.14)	0.62
Ethnicity										
Caucasian	1.35 (0.69, 2.66)	0.37	0.47 (0.02, 11.64)	0.64	1.35 (0.67, 2.73)	0.39	1.37 (0.68, 2.76)	0.37	0.45 (0.02, 11.14)	0.62
Asian	1.84 (1.22, 2.77)	0.003			2.01 (1.30, 3.12)	0.002	2.01 (1.30, 3.12)	0.002		

CWP: Coal workers' pneumoconiosis; *OR*: Odds ratio; *CI*: Confidence interval; TGF-β1: Transforming growth factor-beta 1.

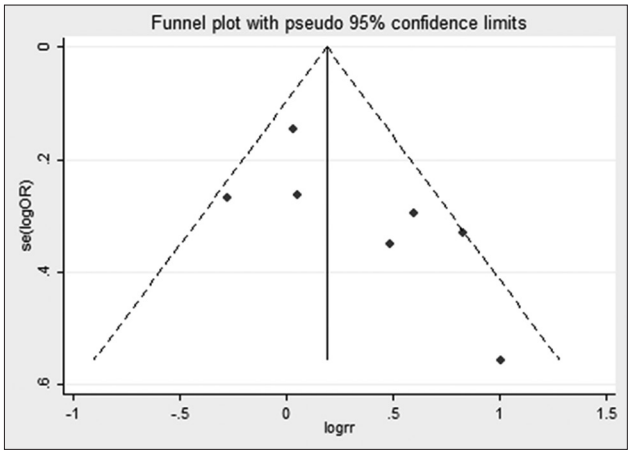

Figure 5: Publication bias analyzed by the funnel plot for association between transforming growth factor-β1 −509 C>T polymorphisms and the risk of pneumoconiosis under the recessive model.

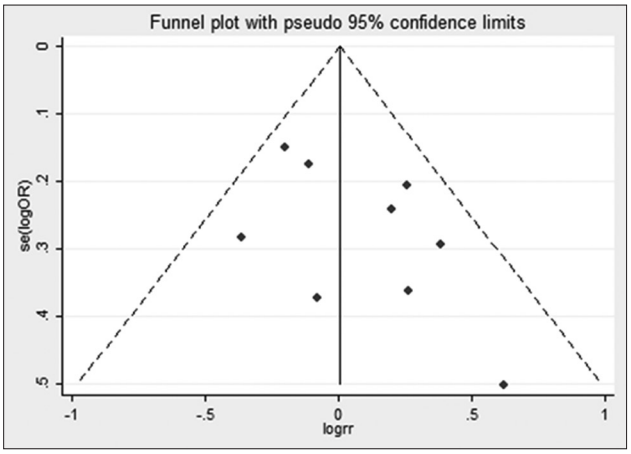

Figure 6: Publication bias analyzed by the funnel plot for association between transforming growth factor-β1 +869 T>C polymorphisms and the risk of pneumoconiosis under the dominant model.

after chronic dust inhalation, which involves complex gene–gene and gene–environment interactions. However, not all individuals who are exposed to the similar levels of dust develop pulmonary fibrosis. It is suggested that there is a genetic association for the development of pneumoconiotic diseases. Indeed, lung fibrosis generally results from dust-induced inflammation, wound healing, and scar formation that lead to serious breathing problems. TGF-β1 plays an important role by affecting wound healing and immunoresponses.[9,29] Furthermore, many candidate

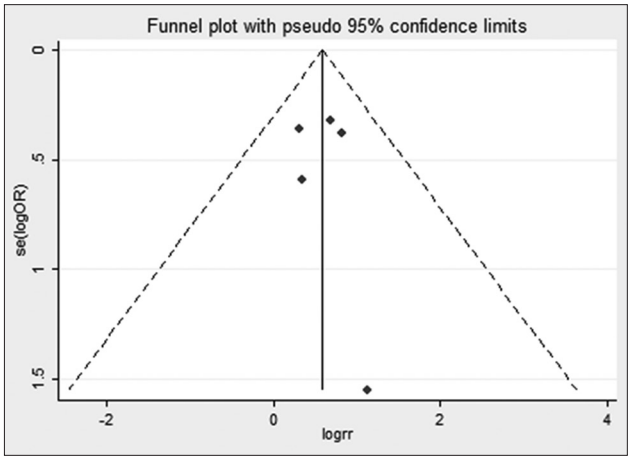

Figure 7: Publication bias analyzed by the funnel plot for association between transforming growth factor-β1 +915 G>C polymorphisms and the risk of pneumoconiosis under the dominant model.

genes have been evaluated for associations between genetic variability and pneumoconiosis susceptibility. To some extent, validation studies of most genetic polymorphisms and pneumoconiosis have been performed with diverse populations for identifying high-risk individuals for prevention and treatment, such as interleukin-1 and tumor necrosis factor gene families.[7,30-32]

TGF-β1 variants are of great importance in genetic modification of lung disease.[33,34] For example, overexpression of TGF-β1 occurs in lung tissue in animal models and patients with pulmonary fibrosis,[35-38] and the association between pulmonary fibrosis susceptibility and *TGF-β1* gene polymorphisms has been investigated.[39-41] Yao *et al.*[42] showed that *TGF-β1* −509 polymorphism influenced serum level of TGF-β1 in CWP. A previous study reported by Yucesoy *et al.*[16] indicated that *TGF-β1* +869 variants were associated with susceptibility to CWP development while Qian *et al.*[18] demonstrated that some representative genetic variants in *TGF-β1* may exert a role in CWP risk. In contrast, Wu *et al.*[17] found that there were no associations between *TGF-β1* polymorphisms at positions −509, +869, and +915 with silicosis risk in Chinese iron miners, even an analysis did by Liu *et al.*[26] showed that there were no associations between *TGF-β1* polymorphisms at positions −509 and +869 with pneumoconiosis. These inconsistent results prompted us to perform this meta-analysis due to larger sample size.

Meta-analyses can utilize different studies to enlarge the sample size and subsequently enhance the statistical power.[43] In the current meta-analysis, we obtained 21 case–control studies with a total of 4,333 pneumoconiosis and 3478 controls. Our data showed an association between *TGF-β1* −509 C>T and +915 G>C polymorphism and the risk of pneumoconiosis in terms of the frequency of allele comparison. Furthermore, the subgroup study of ethnicity Asian and pneumoconiosis types among silicosis indicated a significant association with *TGF* +915 G>C polymorphism. However, there was no significant association detected under homozygous, heterozygous, recessive, and dominant models as well as the subgroup analysis of pneumoconiosis type and ethnicity with *TGF-β1* −509 C>T polymorphism. There was also no significant association between *TGF-β1* +869 T>C polymorphism and the risk of pneumoconiosis, consistent with the subgroup analysis by the type of pneumoconiosis.

However, there are several limitations and potential bias which need further considering about how to interpret our meta-analysis. First, although we employed a thorough literature search strategy to identify qualified studies, a few studies may not get involved in the meta-analysis. Second, individuals in most studies were Chinese patients and the sample size of each study was relatively small in the ethnic standardized analysis, especially among Caucasian and the mixed. Third, there were no enough data included in the meta-analysis, especially some environmental factors, such as asbestos, biomass fuels, and wood chips associated with pneumoconiosis. Finally, due to limited data extraction from original studies, our current meta-analysis was mainly based on an unadjusted assessment and all genetic meta-analyses.

In conclusion, this study demonstrated that *TGF-β1* +869 T>C polymorphism was not associated with risk of pneumoconiosis, whereas *TGF-β1* −509 C>T and +915 G>C were associated with risk of pneumoconiosis. It will be necessary to perform a prospective study via using standardized and unbiased genotyping methods in further study. Such a study will eventually lead to a comprehensive understanding of association of *TGF-β1* gene polymorphisms with pneumoconiosis risk and therefore identifying high-risk individuals for prevention and treatment of this disease.

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Conflicts of interest

There are no conflicts of interest.

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