Original Article
Association of transforming growth factor-β1 gene polymorphisms in pneumoconiosis susceptibility: a meta-analysis

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Abstract: Pneumoconiosis is an occupational, fibrotic lung disorder caused by the inhalation of dust, often in mines. Several articles have identified the role of transforming growth factor-β1 (TGF-β1) polymorphisms in development of pneumoconiosis, however, the results remain inconclusive. The objective of this meta-analysis was to systematically evaluate the effect of TGF-β1 polymorphisms in pneumoconiosis susceptibility. Eligible case-control studies published between January 2000 and 2016 were searched and retrieved in the electronic databases. The pooled odds ratio (ORs) with its 95% confidence interval (CI) was employed to calculate the effect. A total of 13 articles were screened out, including 2538 pneumoconiosis cases and 2435 controls. Overall, our result found a significant difference in the rate of allele mutation in TGF-β1 -509C/T and +915G/C polymorphisms between pneumoconiosis cases and controls (T versus C: OR=1.57, 95% CI=1.12-2.20, P=0.008; C vs. G: OR=1.59, 95% CI=1.06-2.39, P=0.03). This significant association was also detected in homologous model, dominant model and recessive effect for TGF-β1 -509C/T variant, AND heterogeneous model and dominant model for TGF-β1 +915G/C variant. TGF-β1 +869T/C polymorphism was not related with pneumoconiosis in any genetic models. Subgroup analysis by types of this disease showed that only TGF-β1 -509C/T polymorphism was significantly associated with coal workers' pneumoconiosis (CWP) risk, not with silicosis risk. In conclusion, our results suggested that there was a significant association between -590C/T and +915G/A variants and pneumoconiosis risk, especially in CWP patients. Future large-scale studies with more ethnicities are still needed to further evaluate the effect.

Keywords: Pneumoconiosis, TGF-β1, polymorphism, meta-analysis

Introduction

Pneumoconiosis, the parenchymal lung diseases, is the most serious occupational disease arising from inhalation and retention of inorganic dusts at work [1]. It generally evolves over decades of occupational exposure to mineral dusts depending on the exposure level of silica [2]. Asbestosis, silicosis and coal workers' pneumoconiosis (CWP) are the most common types. This disease remains an important public health issue, and is characterized by the formation of nodular, fibrotic changes to the lung parenchyma [3, 4]. The incidence of pneumoconiosis is still high, and its prevalence varies among different populations [5]: in China, a total of 122333 new cases of pneumoconiosis were reported from 1997 to 2009, accounting for nearly 80% of all occupational diseases [6];

in the United Kingdom General Population, a total of 1070 patients with an incident diagnosis of any type of pneumoconiosis were identified during the period 1997 to 2008 [7]. According to the Global Burden of Disease Study 2013 (GBD 2013), it was estimated 259700 all ages and both sexes combined deaths in 2013, up from 251200 deaths in 1990 from 188 countries [8]. Moreover, pneumoconiosis was shown to be associated with increased risk of a wide spectrum of complications, such as peripheral arterial disease [9], cerebrovascular events [10], and chronic obstructive pulmonary disease [11]. Diagnosis of pneumoconiosis is mainly based on clinical history and radiological findings, but plain radiography has limited role in the diagnosis of pulmonary complications of pneumoconiosis because of overlapping pneumoconiotic infiltra-

tion [12]. There are no specific and effective pharmacological treatments for pneumoconiosis [13]. Although therapeutic whole lung lavage has been used in patients with acute disease, the prognosis is poor [14]. Therefore, there is an urgent need to identify some vital biomarkers to predict this disease and guide the therapeutic strategies.

Although the pathophysiology of pneumoconiosis has not been fully understood, it is generally accepted that inflammatory responses may play an essential part in the pathogenesis of pneumoconiosis [15, 16]. Transforming growth factor-β1 (TGF-β1), one member of the TGF-β family, is located on human chromosome 19q 13.1-13.3 and consists of 7 exons [17]. It directs key developmental processes and regulates cellular proliferation, survival, differentiation, motility, adhesion and migration [18, 19]. TGF-β1 not only plays a central important role in wound healing [20], fibrosis [21], and in the negative regulation of inflammation [22], but also can act as a suppressor as well as a promoter of tumorigenesis [23, 24]. Increased TGF-β1 synthesis is seen in the majority of human diseases in which fibrosis is a dominant part of pathology. High serum level of TGF-β1 was shown to be associated with the progression of pneumoconiosis [25]. Qu et al. found that the expression level of TGF-β1 in serum maybe related to the occurrence and development of pneumoconiosis [26]. Feng et al. showed that serum expression of TGF-β1 correlates with dust-exposure, and abnormal expression can be one of the early diagnostic indexes for pneumoconiosis [27]. Yuan et al. suggested that serum TGF-β1 levels in CWP may be related to the severity degree of CWP [28]. However, the circulating concentration of TGF-β1 is predominantly under genetic control [29]. There were three known single nucleotide polymorphisms (SNP) in the highly polymorphic human TGF-β1 gene: -509C/T (rs1800469), +869T/C (rs1800470), and +915G/C (rs1800471). Studies have found the correlative relationship between the concentration of TGF-β1 in serum and its gene -509 site polymorphism [30].

Several studies have identified the role of TGF-β1 polymorphisms in pneumoconiosis susceptibility, but the results remain inconclusive. For example, Fan et al. found that there was no significant difference for frequency of TGF-β1 +869T/C genotypes and alleles between pneumoconiosis patients and controls [31]; while Qian et al. suggested that TGF-β1 +869-T/C polymorphism might contribute to susceptibility of CWP [32]. Therefore, we conducted this meta-analysis to summarize and clarify all eligible studies to obtain a relatively reliable result of the genetic risk of TGF-β1 genetic polymorphisms for pneumoconiosis.

## Materials and methods

Search strategy

We conducted a comprehensive literature search in the online databases of Medline, Web of Science, Embase, PubMed, CNKI (China National Knowledge Internet) and Wanfang to retrieve eligible studies published between January 2000 and 2016. The MeSH terms were: "pneumoconiosis or coal workers' pneumoconiosis or silicosis or asbestosis", "transforming growth factor-β1 or TGF-β1", and "polymorphism or mutation or variant" as well as their combinations. We manually searched the references of retrieved articles to obtain more potential data. Articles were only restricted in English and Chinese languages. When the same authors or laboratories reported the same issue on the same populations, only the recent full-text article was included.

Inclusion and exclusion criteria

The retrieved articles must meet the following criteria: 1) case-control studies that focused on the association between TGF-β1 polymorphisms and pneumoconiosis risk; 2) the diagnosis of pneumoconiosis patients should be based on the 1980 International Labor Office Classification of Pneumoconioses in the judgment of opacity profusion [33]; 3) the controls should be age-, race-, dust exposure period- and job type-matched participants, or healthy subjects without any exposure to carcinogenic or fibrogenic agents at the work place; 4) the results were expressed as odds ratio (ORs) with its 95% confidence interval (CI), and 5) the frequencies of alleles and genotypes for a certain polymorphism in each included article were available to extract.

The exclusion criteria were: 1) without control group; 2) with duplicate data; 3) data not available; and 4) review reports or conference papers.
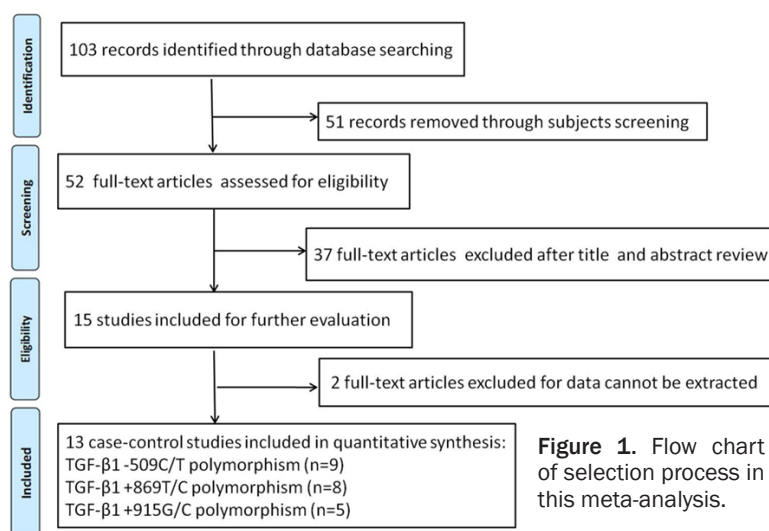
Figure 1. Flow chart of selection process in this meta-analysis.

Data extraction

Two of our authors independently estimated the quality of the included studies. Any disagreement was subsequently resolved by discussion with a third author to obtain a final consensus. The following information was extracted from each included article: the name of first author, published year, country, ethnicity, mean age, sample size, source of cases and controls, stages of cases, SNPs, genotyping method, frequencies of genotypes and alleles, and evidence of Hardy-Weinberg equilibrium (HWE) in controls.

Statistical analysis

Statistical analyses were conducted in Review Manager (version 5.3, The Cochrane Collaboration). The HWE of genotype distribution in controls for a certain polymorphism was calculated by HEW test [34]. The strength of the correlation between TGF-β1 polymorphisms and pneumoconiosis susceptibility was measured by ORs with 95% CI. The significance of the pooled ORs was determined by the Z test, with a *P* value less than 0.05 considered statistical significance. The allelic model (M vs. m), homologous model (MM vs. mm), heterogeneous model (Mm vs. mm), dominant model (MM + Mm vs. mm), and recessive effect (MM vs. Mm + mm) were examined to evaluate the TGF-β1 variants and the risk of pneumoconiosis. The I^2 test and the Q-statistic test were used to define the between-study heterogeneity. The fixed-effect model was used when the I^2 was less than 50% and the *p*-value for the Q-test was more than 0.10; otherwise, the random-effect model was used. The evidence of publication bias was assessed by visual funnel plot inspection.

Results

Study characteristics

We firstly identified 103 potentially eligible articles based on our search strategy. After applying the inclusion and exclusion criteria, only 13 articles were finally screened out, including 2538 pneumoconiosis cases and 2435 controls. **Figure 1** exhibited the flow diagram of the search process. The thirteen articles (five were written in English [32, 35-38] and eight were in Chinese [39-46]) were conducted in four countries (China, Turkey, USA and Germany). Ten articles were performed in Asian population and three were in Caucasian population. Three SNPs of the TGF-β1 gene were identified: -509C/T, +869T/C, and +915G/C. These polymorphic sites were measured by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Three studies did not follow the HWE and three studies have insufficient data for calculation of the HWE. Two articles contained two comparison groups respectively. **Table 1** listed the main characteristics of the studies identified. **Table 2** listed the distribution of alleles and genotypes of TGF-β1 polymorphisms in each study.

Association between TGF-β1 polymorphisms and pneumoconiosis susceptibility

Table 3 provided the meta-analysis findings of the associations between TGF-β1 variants and pneumoconiosis risk.

TGF-β1 -509C/T polymorphism

There were nine articles considering the effect of TGF-β1 -509C/T polymorphism in pneumoconiosis risk. Total 1452 pneumoconiosis cases and 1550 controls were included. Our result found that the frequency of the T allele

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

First author	Year	Country	Ethnicity	Mean age		Sample size		Stage of cases	Source of		SNPs	Genotyping methods
				Cases	Controls	Cases	Controls		Cases	Controls		
Yao W	2006	China	Asian	29-79	29-79	110	110	I, II, III	CWP	DEW	-590C/T	PCR-RFLP
Ates I	2008	Turkey	Caucasian	58.2 ± 4.2	48.8 ± 5.21	67	92	-	CWP	DEW	+869T/C	PCR-RFLP
Wu F	2008	China	Asian	69.3 ± 6.0	67.3 ± 7.3	183	111	I, II, III	Silicosis	DEW	-590C/T, +869T/C, +915G/C	PCR-RFLP
Yucesoy B	2008	USA	Caucasian	69.9 ± 8.9	69.9 ± 9.0	304	344	-	CWP	DEW	-590 C/T	PCR-RFLP
Helmig S	2009	Germany	Caucasian	68.06 (40-91)	44.8 (20-75)	591	83	-	Silicosis, Asbestosis	HP	+869T/C, +915G/C	PCR-RFLP
Yu C	2009	China	Asian	63.59 ± 7.72	62.25 ± 8.98	234	440	I, II, III	CWP	DEW	+869T/C	PCR-RFLP
Li J	2010	China	Asian	55.9 ± 9.4	55.6 ± 9.4	40	40	I	CWP	DEW	-590C/T, +869T/C, +915G/C	PCR-RFLP
Qian HY	2010	Chian	Asian	69.47 ± 9.70	65.95 ± 6.58	508	526	I, II, III	CWP	DEW	-590C/T, +869T/C,	PCR-RFLP
Yang WH	2010	China	Asian	48.30 ± 13.16	43.86 ± 4.20	110	110	I, II, III	CWP	DEW	-590C/T,	PCR-RFLP
					41.73 ± 5.45		110			HP		
Fan XY	2011	China	Asian	56.3 ± 6.4	55.8 ± 8.4	128	128	I	CWP	DEW	-590C/T, +869T/C, +915G/C	PCR-RFLP
Wang S	2011	China	Asian	62.91 ± 11.94	42.96 ± 7.25	112	138	I, II, III	Silicosis	DEW	-590C/T	PCR-RFLP
Zhou WW	2012	China	Asian	24-61	27-52	70	85	-	Silicosis	DEW	+869T/C, +915G/C	PCR-RFLP
							60			HP		
He XM	2013	China	Asian	33-50	26-45	81	58	-	Silicosis	DEW	-590C/T	PCR-RFLP

DEW, dust-exposed workers; HP, healthy participants; SNPs, single nucleotide polymorphisms; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; -, not available.

Table 2. Distribution information of alleles and genotypes of TGF-β1 polymorphisms in each included study in this meta-analysis

First author	Cases					Controls					
-590 C/T	CC	CT	TT	C	T	CC	CT	TT	C	T	HWE
Yao W	20	56	34	96	124	52	40	18	144	76	0.121
Wu F	54	83	46	191	175	26	51	34	103	119	0.724
Yucesoy B	143	109	31	395	171	170	121	34	461	189	0.215
Li J	12	15	13	39	41	16	18	6	50	30	0.968
Qian HY	114	273	121	501	515	102	302	122	506	546	0.003
Yang WH-1	20	57	33	97	123	59	34	17	152	68	0.015
Yang WH-2	20	57	33	97	123	68	28	14	164	56	0.003
Fan XY	26	51	40	103	131	43	48	26	134	100	0.216
Wang S	10	5	5	25	15	14	22	7	50	36	0.945
He XM	24	23	34	71	91	24	19	15	67	49	0.051
+869T/C	TT	TC	CC	T	C	TT	TC	CC	T	C	
Ates I	17	26	24	60	74	22	50	20	94	90	0.703
Wu F	52	83	48	187	179	24	56	31	104	118	0.991
Helmig S	197	302	92	696	486	32	36	15	100	66	0.690
Yu C	74	101	59	249	219	129	206	105	464	416	0.443
Li J	9	18	13	36	44	14	17	9	45	35	0.689
Qian HY	123	338	47	584	432	109	332	85	550	502	0.000
Fan XY	28	50	39	106	128	37	51	29	125	109	0.406
Zhou WW-1	34	32	4	100	40	36	34	15	106	64	0.394
Zhou WW-2	34	32	4	100	40	34	21	5	89	31	0.798
+915G/C	GG	GC	CC	G	C	GG	GC	CC	G	C	
Wu F	181	2	0	364	2	111	0	0	222	0	-
Helmig S	497	93	1	1087	95	73	10	0	156	10	0.843
Li J	32	8	0	72	8	34	6	0	74	6	0.876
Fan XY	83	34	0	200	34	97	20	0	214	20	0.599
Zhou WW-1	70	0	0	140	0	85	0	0	170	0	-
Zhou WW-2	70	0	0	140	0	60	0	0	120	0	-

HWE, Hardy-Weinberg equilibrium in controls; -, not applicable.

was higher in patients than that in controls (47.7% versus 40.9%), and the statistical analysis showed a significant difference in the rate of allele mutation between pneumoconiosis cases and controls (T versus C: OR=1.57, 95% CI=1.12-2.20, P=0.008) in the random-effect model as shown in **Figure 2**. This significant relationship was observed in homologous model (TT vs. CC: OR=2.14, 95% CI=1.22-3.77, P=0.008), dominant model (TT + CT vs. CC: OR=1.77, 95% CI=1.05-2.96, P=0.03), and recessive effect (TT vs. CT + CC: OR=1.59, 95% CI=1.17-2.17, P=0.003) as well as shown in **Figure 3**. While no association was detected between TGF-β1 -509C/T polymorphism and pneumoconiosis risk under the heterogeneous model (CT vs. CC: OR=1.58, 95% CI=0.95-2.62, P=0.08). Subgroup analysis by types of this

disease showed that TGF-β1 -509C/T polymorphism was significantly associated with CWP risk, not with silicosis risk (**Table 3**) under each genetic model.

TGF-β1 +869T/C polymorphism

Eight articles included 1810 cases and 1554 controls. Our result did not detect a significant correlation between TGF-β1 +869T/C polymorphism and pneumoconiosis susceptibility under any comparison models (C vs. T: OR=0.95, 95% CI=0.86-1.05, P=0.33; CC vs. TT: OR=0.91, 95% CI=0.63-1.33, P=0.63; TC vs. TT: OR=0.97, 95% CI=0.82-1.15, P=0.75; CC + TC vs. TT: OR=0.96, 95% CI=0.81-1.12, P=0.58; CC vs. TC + TT: OR=0.95, 95% CI=0.67-1.34, P=0.76). Subgroup analysis by types of

Table 3. Meta-analysis results of TGF-β1 polymorphisms on pneumoconiosis risk in total and subgroup analysis

SNPs	Groups	Comparisons	N	Test of association		Test of heterogeneity		
				OR (95% CI)	P	Ph	I²	Model
-590 C/T	Total	T vs. C	9	1.57 (1.12, 2.20)	0.008	<0.00001	89%	R
		TT vs. CC		2.14 (1.22, 3.77)	0.008	<0.00001	84%	R
		CT vs. CC		1.58 (0.95, 2.62)	0.08	<0.00001	87%	R
		TT + CT vs. CC		1.77 (1.05, 2.96)	0.03	<0.00001	89%	R
		TT vs. CT + CC		1.59 (1.17, 2.17)	0.003	<0.00001	61%	R
	Silicosis	T vs. C	3	1.06 (0.61, 1.84)	0.84	0.03	73%	R
		TT vs. CC		1.12 (0.47, 2.66)	0.79	0.07	63%	R
		CT vs. CC		0.79 (0.51, 1.23)	0.30	0.22	33%	F
		TT + CT vs. CC		0.89 (0.46, 1.73)	0.73	0.09	58%	R
		TT vs. CT + CC		1.17 (0.69, 1.97)	0.56	0.03	72%	R
	CWP	T vs. C	6	1.83 (1.21, 2.77)	0.004	<0.00001	91%	R
		TT vs. CC		2.75 (1.36, 5.58)	0.005	<0.00001	87%	R
		CT vs. CC		2.11 (1.13, 3.96)	0.02	<0.00001	90%	R
		TT + CT vs. CC		2.33 (1.23, 4.44)	0.010	<0.00001	92%	R
		TT vs. CT + CC		1.83 (1.41, 2.37)	<0.00001	0.29	18%	F
+869T/C	Total	C vs. T	8	0.95 (0.86, 1.05)	0.33	0.05	47%	F
		CC vs. TT		0.91 (0.63, 1.33)	0.63	0.01	58%.	R
		TC vs. TT		0.97 (0.82, 1.15)	0.75	0.45	0%	F
		CC + TC vs. TT		0.96 (0.81, 1.12)	0.58	0.33	12%	F
		CC vs. TC + TT		0.95 (0.67, 1.34)	0.76	0.004	64%	R
	Silicosis	C vs. T	3	0.91 (0.75, 1.11)	0.36	0.34	11%	F
		CC vs. TT		0.72 (0.48, 1.08)	0.12	0.35	9%	F
		TC vs. TT		1.08 (0.80, 1.46)	0.61	0.26	25%	F
		CC + TC vs. TT		0.99 (0.74, 1.31)	0.92	0.26	25%	F
		CC vs. TC + TT		0.75 (0.53, 1.08)	0.12	0.33	13%	F
	CWP	C vs. T	5	1.09 (0.85, 1.38)	0.50	0.02	66%	R
		CC vs. TT		1.12 (0.64, 1.95)	0.70	0.005	73%	R
		TC vs. TT		0.93 (0.75, 1.14)	0.47	0.55	0%	F
		CC + TC vs. TT		0.94 (0.77, 1.14)	0.54	0.28	21%	F
		CC vs. TC + TT		1.16 (0.70, 1.92)	0.58	0.001	77%	R
+915G/C	Total	C vs. G	5	1.59 (1.06, 2.39)	0.03	0.88	0%	F
		GC vs. GG		1.66 (1.08, 2.55)	0.02	0.84	0%	F
		CC + GC vs. GG		1.67 (1.08, 2.56)	0.02	0.85	0%	F

SNPs, single nucleotide polymorphisms; N, number of included studies; OR, odds ratio; 95% CI, 95% confidence interval; R, random-effect model; F, fixed-effect model; CWP, coal workers' pneumoconiosis.

pneumoconiosis showed that TGF-β1 +869T/C polymorphism was associated with neither CWP risk, nor silicosis risk under each genetic model.

TGF-β1 +915G/C polymorphism

Five articles contained 1001 patients and 496 controls. Our result found that this genetic variant was related with pneumoconiosis risk under the allelic model (C vs. G: OR=1.59, 95% CI=1.06-2.39, P=0.03), heterogeneous model (GC vs. GG: OR=1.66, 95% CI=1.08-2.55, P=0.02), dominant model (CC + GC vs. GG: OR=1.67, 95% CI=1.08-2.56, P=0.02) in the fixed-effect model as shown in **Figure 4**.
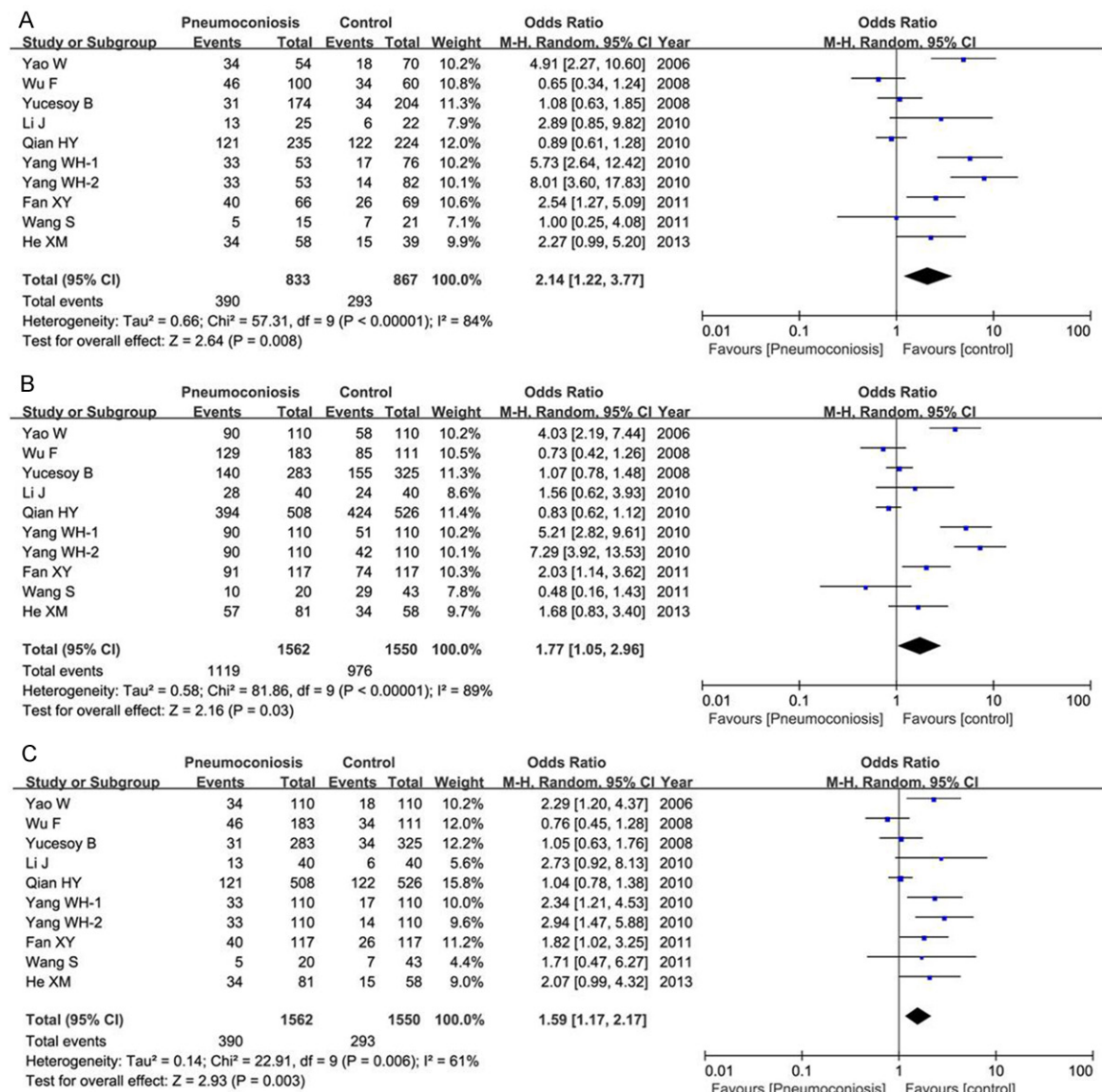
Sensitivity analysis and publication bias

A sensitivity analysis was performed to estimate whether our results were substantially influenced by the presence of any individual
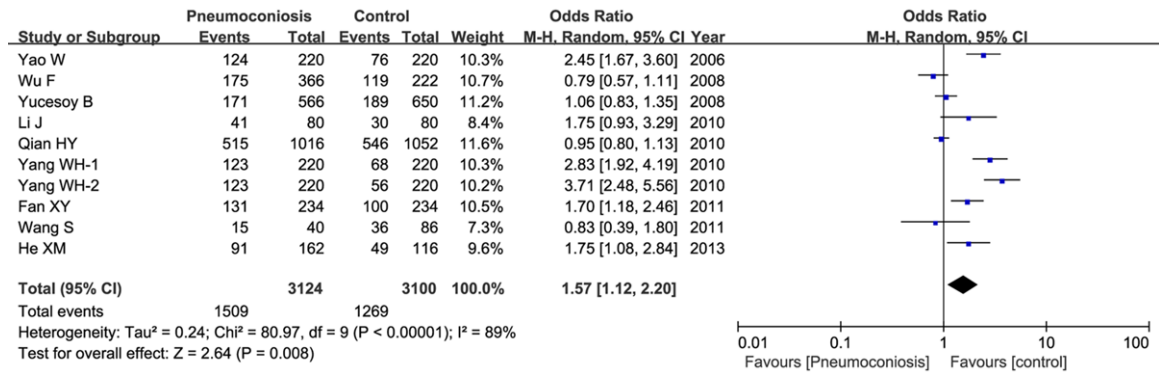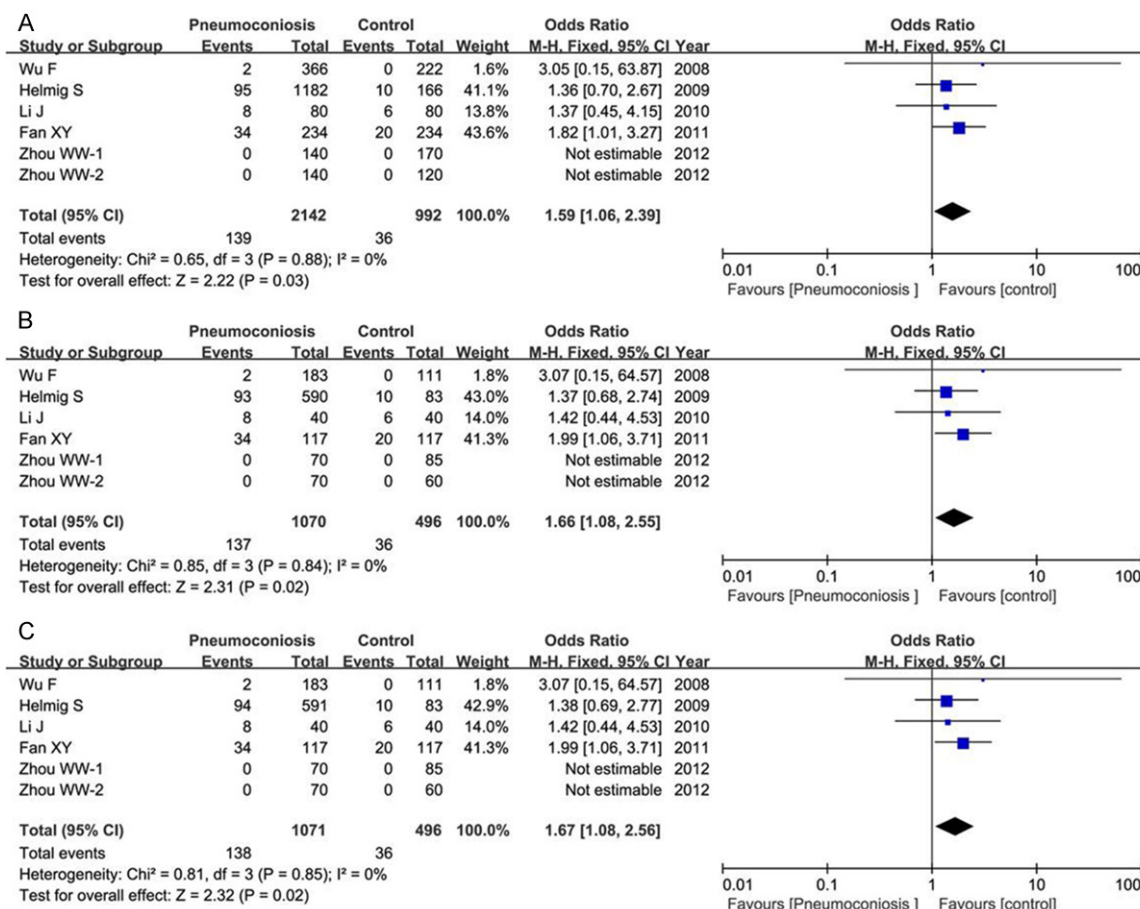
Figure 2. Meta-analysis of the correlation between theTGF-β1 -590 C/T polymorphism and pneumoconiosis susceptibility under the allelic model.
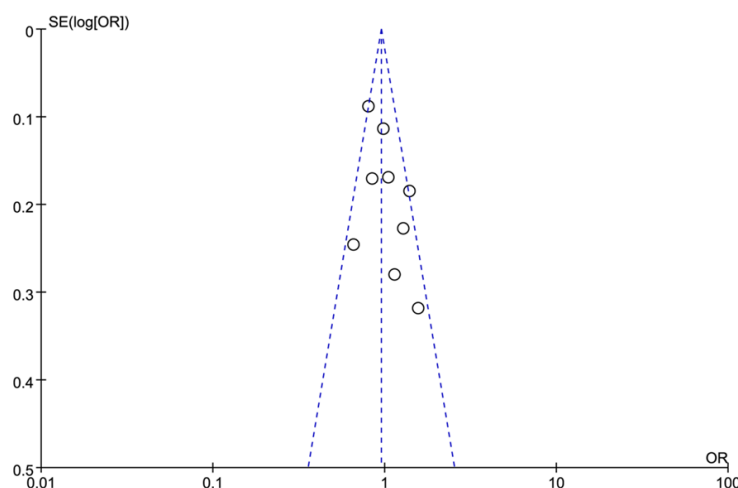

Figure 3. Forest plot of TGF-β1 -590 C/T polymorphism and pneumoconiosis risk under the homologous model (A: TT vs. CC), dominant model (B: TT + CT vs. CC), and recessive effect (C: TT vs. CT + CC).

Figure 4. Meta-analysis of the association of TGF-β1 +915G/C polymorphism in pneumoconiosis under the allelic model (A: C vs. G), heterogeneous model (B: GC vs. GG), and dominant model (C: CC + GC vs. GG).

Figure 5. Funnel plot of TGF-β1 +869T/C polymorphism in pneumoconiosis risk under the allelic model.

ORs, and our result showed that the ORs were not significantly changed. The funnel plots were used to assess the potential publication bias of included studies under each comparison model. The shape of the funnel plot did not reveal any obvious asymmetry as shown in **Figure 5**, indicating that there was no publication bias.

Discussion

In this meta-analysis, we totally screened out 13 relevant articles concerning three TGF-β1 polymorphisms. Our results showed that there were significant association between -590C/T and +915-G/A variants and pneumoconiosis risk. How-

study. We systematically deleted each study and recalculated the significance of the pooled

ever, TGF-β1 +869T/C polymorphism was not related with pneumoconiosis susceptibility. Subgroup analysis by types of this disease showed that only TGF-β1 -509C/T polymorphism was significantly associated with CWP risk under each genetic model. Our results were not consistent with previous meta-analysis which did not found a significant association between TGF-β1 -590C/T gene polymorphism and pneumoconiosis [47].

Pneumoconiosis, a form of diffuse interstitial lung disease, is a social, economic, and public health issue [48]. Its major cause is occupational silica exposure [49]. Although the pathogenesis of pneumoconiosis is connected with the total dose and intensity of dust exposure, individual variation in the susceptibility to pneumoconiosis has been observed among the subjects with equally exposed to the dust [50]. In addition, trends in incidence of this disease are difficult to interpret due to varying definitions of disease states and changing eligibility criteria for compensation benefits over time. Therefore, identifying some genetic biomarkers on the host may play a vital role in exploring the development of pneumoconiosis.

Epidemiologic studies have shown that pneumoconiosis is mediated by macrophage-derived cytokines and growth factors. TGF-β1, a multifunctional cytokine with fibrogenic properties, is a master driver of fibrosis and is the most extensively studied pro-fibrotic mediator [51]. It regulates the proliferation and differentiation of a wide variety of cell types in vitro [52, 53]. Precise control of TGF-β1 expression is required for normal embryogenesis [54]. To be inactivated, TGF-β1 serves as a disulphide-bonded homodimer, non-covalently bound to latency-associated protein (LAP); To be activated, TGF-β1 must dissociate from LAP [55-57]. High levels of TGF-β1 have been reported in many fibrotic diseases and regions of fibrosis/remodeling in all tissues are often characterised by increased expression of active TGF-β1 [58]. Activated TGF-β1 signals modulate the transcription of important pro-fibrotic target genes primarily via heteromeric complexes of type II and type I serine/threonine kinase receptors and the SMAD signaling pathway [59]. Recently, pathological misregulation of the TGF-β pathway has been implicated in the development of several major disease groups, including cancer, atherosclerosis, fibrotic disease and auto-immune disease [60-63]. In addition, TGF-β1 is growth inhibitory and pro-apoptosis to benign cells, any herbal medication that can induce the production of TGF-β1 in the target cells will be beneficial to the patients [64, 65].

TGF-β1 polymorphism may play a significant role in the level of the mRNA expression of TGF-β1 [66]. It is likely that TGF-β1 has a role in a number of common important diseases, predisposition to these conditions may be associated with alleles at the TGF-β1 locus. The certain common polymorphisms influenced the circulating concentration of TGF-β1 [29]. TGF-β1 polymorphisms genetically determined TGF-β1 protein concentrations, thus play a role in blood pressure regulation in humans [67]. TGF-β1 genotypes might have a role in mediating pulmonary dysfunction in patients with cystic fibrosis [68]. Panek et al. demonstrates that the -509C/T SNP was a significant clinical risk factor for asthma and that the TGF-β1 cytokine contributes to the progression of the illness [69]. Son et al. suggests that the TGF-β1 gene +869T/C polymorphism might affect susceptibility to idiopathic pulmonary fibrosis in Koreans [70]. TGF-β1 can be a potential effect marker of monitoring early change of physical function among workers exposed to dust [71], and plays an important role in pulmonary fibrosis induced by silica dust [72].

Several limitations were presented in this meta-analysis. Firstly, there was significant between-study heterogeneity in some genetic models, which might influence our results. Secondly, most of the included studies were conducted in China, and very little articles were conducted in other countries. Further researches are still needed to confirm the current results on other ethnicities. Thirdly, some important effectors such as the amount of dust absorption in the patients and controls, exposure time, work types, and smoking habits could not be extracted from the original articles. Fourthly, the interaction of gene-gene and gene-environment should be considered because this disease is largely affected by the interaction between genotypes and environment.

In conclusions, our results found a significant association between -590C/T and +915G/A

variants and pneumoconiosis risk, especially in CWP patients. Future well-designed, large-scale studies with more ethnicities are still needed to further evaluate the effects.

Disclosure of conflict of interest

None.

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References

[1] Cullinan P and Reid P. Pneumoconiosis. Prim Care Respir J 2013; 22: 249-252.

[2] Lapp NL and Castranova V. How silicosis and coal workers' pneumoconiosis develop-A cellular assessment. Occup Med 1993; 8: 35-56.

[3] Leslie KO and Wick MR. Practical pulmonary pathology: a diagnostic approach. Elsevier Health Sciences; 2011.

[4] Blanc PD and Seaton A. Pneumoconiosis Redux. Coal Workers' Pneumoconiosis and Silicosis Are Still a Problem. Am J Respir Crit Care Med 2016; 193: 603-605.

[5] Joy G, Colinet J and Landen D. Coal workers' pneumoconiosi prevalence disparity between Australia and the United States. Mining Engineering 2012; 64.

[6] Zhang M, Wang D, Zheng YD, Du XY and Chen SY. [Analyses on the characteristics and the trends of pneumoconiosis notified between 1997 and 2009, in China]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2013; 31: 321-334.

[7] Amar RK, Jick SS, Rosenberg D, Maher TM and Meier CR. Incidence of the pneumoconioses in the United Kingdom general population between 1997 and 2008. Respiration 2012; 84: 200-206.

[8] Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, Vollset SE, Ozgoren AA, Abdalla S and Abd-Allah F. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 385: 117-171.

[9] Shen CH, Lin TY, Huang WY, Chen HJ and Kao CH. Pneumoconiosis increases the risk of peripheral arterial disease: a nationwide population-based study. Medicine 2015; 94: e911.

[10] Chuang CS, Ho SC, Lin CL, Lin MC and Kao CH. Risk of Cerebrovascular Events in Pneumoconiosis Patients: A Population-based Study, 1996-2011. Medicine 2016; 95: e2944.

[11] Ornek T, Atalay F, Erboy F, Altinsoy B, Tanriverdi H, Uygur F and Tor M. Is pneumoconiosis a factor of severity in acute exacerbation of chronic obstructive pulmonary disease? Clin Ter 2013; 164: e473-477.

[12] Jun JS, Im Jung J, Kim HR, Im Ahn M, Han DH, Ko JM, Park SH, Lee HG, Arakawa H and Koo JW. Complications of pneumoconiosis: Radiologic overview. Eur J Radiol 2013; 82: 1819-1830.

[13] Karkhanis VS and Joshi J. Pneumoconioses. Indian J Chest Dis Allied Sci 2012; 55: 25-34.

[14] Fishwick D. Pneumoconiosis. Medicine 2008; 36: 258-260.

[15] Yucesoy B, Vallyathan V, Landsittel DP, Simeonova P and Luster MI. Cytokine polymorphisms in silicosis and other pneumoconioses. Mol Cell Biochem 2002; 234: 219-224.

[16] Borm P and Schins R. Genotype and phenotype in susceptibility to coal workers' pneumoconiosis. The use of cytokines in perspective. Eur Respir J Suppl 2001; 18: 127s-133s.

[17] Kim SJ, Glick A, Sporn M and Roberts A. Characterization of the promoter region of the human transforming growth factor-beta 1 gene. J Biol Chem 1989; 264: 402-408.

[18] Horbelt D, Denkis A and Knaus P. A portrait of Transforming Growth Factor β superfamily signalling: Background matters. Int J Biochem Cell Biol 2012; 44: 469-474.

[19] Massague J. The transforming growth factor-beta family. Annu Rev Cell Biol 1990; 6: 597-641.

[20] Penn JW, Grobbelaar AO and Rolfe KJ. The role of the TGF-β family in wound healing, burns and scarring: a review. Int J Burns Trauma 2012; 2: 18-28.

[21] Hinz B and McCulloch C. Integrin function in heart fibrosis: mechanical strain, TGF-β1 activation and collagen glycation. Extracellular Matrix: Pathobiology and Signalling. DeGruyter Berlin, Germany; 2012. pp. 407-431.

[22] Graciarena M, Roca V, Mathieu P, Depino AM and Pitossi FJ. Differential vulnerability of adult neurogenesis by adult and prenatal inflammation: Role of TGF-β1. Brain Behav Immun 2013; 34: 17-28.

[23] Zhang Y, Li L, Yu J, Zhu D, Zhang Y, Li X, Gu H, Zhang CY and Zen K. Microvesicle-mediated delivery of transforming growth factor β1 siRNA for the suppression of tumor growth in mice. Biomaterials 2014; 35: 4390-4400.

[24] Su HT, Weng CC, Hsiao PJ, Chen LH, Kuo TL, Chen YW, Kuo KK and Cheng KH. Stem cell marker nestin is critical for TGF-β1-mediated tumor progression in pancreatic cancer. Mol Cancer Res 2013; 11: 768-779.

[25] Lee JS, Shin JH, Lee KM, Hwang JH, Baek JE, Kim JH and Choi BS. Serum Levels of TGF-β1 and MCP-1 as Biomarkers for Progressive Coal Workers' Pneumoconiosis in Retired Coal Workers: A Three-year Follow-up Study. Ind Health 2014; 52: 129-136.

[26] Qu L, Wang HY and Tao L. Analysis on Contents of TGF-β and PDGF in Serum of Patients with Pneumoconiosis. Journal of Beihua University (Natural Science) 2013; 2: 12.

[27] Feng ZH and Li XZ. Detection of TGF-β_1 and PIIINP Levels in Dust-exposed workers. Occupation and Health 2009; 6: 013.

[28] Yuan BJ, Li C, Zou JM, Wang DM, Ma YH and Zhu XP. Changes of peripheral blood CD4~+CD25~(high) regulatory T cells and serum TGF-β1 levels in stage I coal worker's pneumoconiosis. Chinese Journal of Industrial Medicine 2013; 1: 6.

[29] Grainger DJ, Heathcote K, Chiano M, Snieder H, Kemp PR, Metcalfe JC, Carter ND and Specter TD. Genetic control of the circulating concentration of transforming growth factor type β1. Hum Mol Genet 1999; 8: 93-97.

[30] Yao W, Wang Z, Wang M, Hao C and Wang N. [The relationship between the concentration of TGF-beta1 in serum and its gene polymorphisms in CWP]. Sichuan Da Xue Xue Bao Yi Xue Ban 2005; 36: 827-829.

[31] Fan X, Li J, Wang X, Wang L, Bai Y, Yao S and Zhang S. [Relationship between gene polymorphism of transforming growth factor-beta and pneumoconiosis]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2007; 25: 1-4.

[32] Qian H, Song Z, Wang M, Jia X, Li A, Yang Y, Shen L, Wang S, Ni C and Zhou J. Association of transforming growth factor-β1 gene variants with risk of coal workers' pneumoconiosis. J Biomed Res 2010; 24: 270-276.

[33] ILO/UC. International Classification of radiographs of pneumoconiosis 1980, N° 22 revised. Occupational Safety and Health Series 1980.

[34] Elston R and Forthofer R. Testing for Hardy-Weinberg equilibrium in small samples. Biometrics 1977; 536-542.

[35] Yucesoy B, Johnson VJ, Kissling GE, Fluharty K, Kashon ML, Slaven J, Germolec D, Vallyathan V and Luster MI. Genetic susceptibility to progressive massive fibrosis in coal miners. Eur Respir J 2008; 31: 1177-1182.

[36] Ates I, Suzen HS, Yucesoy B, Tekin IO and Karakaya A. Association of cytokine gene polymorphisms in CWP and its severity in Turkish coal workers. Am J Ind Med 2008; 51: 741-747.

[37] Helmig S, Belwe A and Schneider J. Association of Transforming Growth Factor β1 Gene Polymorphisms and Asbestos-Induced Fibrosis and Tumors. J Investig Med 2009; 57: 655-661.

[38] Wu F, Qu Y, Tang Y, Cao D, Sun P and Xia Z. Lack of association between cytokine gene polymorphisms and silicosis and pulmonary tuberculosis in Chinese iron miners. J Occup Health 2008; 50: 445-454.

[39] WenHai Y, Jin Y, FaXuan W, YaNa W, Ling W, LiLi C and QiRu S. The distribution of TGF-β1 gene -509C/T polymorphism in coal worker's pneumoconiosis patients in Ningxia area. Journal of Environmental Occupational Medicine 2010; 27: 670-672.

[40] Fan XY, Ma QK, Yao SQ, Bai YP, Wang YH and Li J. Study on the relationship of genetic polymorphism of pulmonary fibrosis and sensibility of pneumoconiosis. China Occupational Medicine 2011; 5: 12.

[41] Yao W, Hao CF and Wu YM. The relationship between concentration, gene polymorphisms of TGF-β_1 and the risk of CWP. China Occupational Medicine 2006; 4: 009.

[42] Li J, Fan XY and Hao XH. Relationship between genetic polymorphism of transforming growth factor-β and susceptibility of coal worker's pneumoconiosis. Chinese Journal of Industrial Medicine 2010; 5: 5.

[43] He XM, Chen J, Zhou WW and Huang XQ. Analysis on polymorphism of gene transforming growth factor-β1 C-509T for silicosis patients in Zhuang and Han nationalities people of Guangxi. China Occupational Medicine 2013; 4: 023.

[44] Zhou W, Huang X, Chen Z and Li R. Distribution of TGF-β1 T869C and +915C polymorphism in silicosis patients of Zhuang Nationality. Guangxi Medical Journal 2012; 34: 1441-1443.

[45] Wang S. Investigation on silicon levels in vivo and relationship between silicon level and genetic polymorphisms of TGF-β in workers exposed to silica [Master's thesis]. Hebei United University 2011.

[46] Yu C, Li L and Qi F. Relationship of genetic polymorphism of transforming growth factor-β and tumor necrosis factor in susceptibility of coal worker's pneumoconiosis. Chinese Journal of Industrial Hygiene and Occupational Diseases 2009; 27: 240-242.

[47] Liu Q, Su W, Shan Y, Zhang Z, Xu G, Zhang W, Zhang H and Wang R. [Meta-analysis of association of tumor necrosis factor alpha and transforming growth factor beta gene polymorphisms with pneumoconiosis]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 2012; 30: 587-592.

[48] Chan CC, Tsang EW, Siu A, Kwok H and Cheng A. Using WHO's ICF Model on Service Needs of Patients with Pneumoconiosis. In: editors. Handbook of Vocational Rehabilitation and Disability Evaluation. Springer; 2015. pp. 355-369.

[49] Fishwick D and Barber C. Pneumoconiosis. Medicine 2012; 40: 310-313.

[50] Yucesoy B and Luster MI. Genetic susceptibility in pneumoconiosis. Toxicol Lett 2007; 168: 249-254.

[51] Borthwick LA and Wynn TA. IL-13 and TGF-β1: Core Mediators of Fibrosis. Current Pathobiology Reports 2015; 3: 273-282.

[52] Van Meeteren LA and Ten Dijke P. Regulation of endothelial cell plasticity by TGF-β. Cell Tissue Res 2012; 347: 177-186.

[53] Oh SA and Li MO. TGF-β: guardian of T cell function. J Immunol 2013; 191: 3973-3979.

[54] Bowen T, Jenkins RH and Fraser DJ. MicroR-NAs, transforming growth factor beta-1, and tissue fibrosis. J Pathol 2013; 229: 274-285.

[55] Henderson NC and Sheppard D. Integrin-mediated regulation of TGFβ in fibrosis. Biochim Biophys Acta 2013; 1832: 891-896.

[56] De Crescenzo G, Grothe S, Zwaagstra J, Tsang M and O'Connor-McCourt MD. Real-time monitoring of the interactions of transforming growth factor-β (TGF-β) isoforms with latency-associated protein and the ectodomains of the TGF-β type II and III receptors reveals different kinetic models and stoichiometries of binding. J Biol Chem 2001; 276: 29632-29643.

[57] Van Laethem JL, Deviere J, Resibois A, Rickaert F, Vertongen P, Ohtani H, Cremer M, Miyazono K and Robberecht P. Localization of transforming growth factor β1 and its latent binding protein in human chronic pancreatitis. Gastroenterology 1995; 108: 1873-1881.

[58] Verrecchia F and Mauviel A. Transforming growth factor-beta and fibrosis. World J Gastroenterol 2007; 13: 3056-3062.

[59] Valcourt U, Kowanetz M, Niimi H, Heldin CH and Moustakas A. TGF-β and the Smad signaling pathway support transcriptomic reprogramming during epithelial-mesenchymal cell transition. Mol Biol Cell 2005; 16: 1987-2002.

[60] Principe DR, Doll JA, Bauer J, Jung B, Munshi HG, Bartholin L, Pasche B, Lee C and Grippo PJ. TGF-β: duality of function between tumor prevention and carcinogenesis. J Natl Cancer Inst 2014; 106: djt369.

[61] McCaffrey TA. TGF-betas and TGF-beta receptors in atherosclerosis. Cytokine Growth Factor Rev 2000; 11: 103-114.

[62] Epstein FH, Blobe GC, Schiemann WP and Lodish HF. Role of transforming growth factor β in human disease. N Engl J Med 2000; 342: 1350-1358.

[63] Bowen T, Jenkins RH and Fraser DJ. MicroR-NAs, transforming growth factor beta-1, and tissue fibrosis. J Pathol 2013; 229: 274-285.

[64] Lee CM, Park JW, Cho WK, Zhou Y, Han B, Yoon PO, Chae J, Elias JA and Lee CG. Modifiers of TGF-β1 effector function as novel therapeutic targets of pulmonary fibrosis. Korean J Intern Med 2014; 29: 281-290.

[65] Torres Lde S, Okumura JV, da Silva DG, Belini Júnior É, de Oliveira RG, Mimura KK, Lobo CL, Oliani SM, Bonini Domingos CR. Plasma levels of TGF-β1 in homeostasis of the inflammation in sickle cell disease. Cytokine 2016; 80: 18-25.

[66] Shah R, Hurley CK and Posch PE. A molecular mechanism for the differential regulation of TGF-β1 expression due to the common SNP−509C-T (c. −1347 C>T). Hum Genet 2006; 120: 461-469.

[67] Li B, Khanna A, Sharma V, Singh T, Suthanthiran M and August P. TGF-β1 DNA polymorphisms, protein levels, and blood pressure. Hypertension 1999; 33: 271-275.

[68] Arkwright PD, Laurie S, Super M, Pravica V, Schwarz MJ, Webb AK and Hutchinson IV. TGF-β1 genotype and accelerated decline in lung function of patients with cystic fibrosis. Thorax 2000; 55: 459-462.

[69] Panek M, Pietras T, Fabijan A, Zioło J, Wieteska Ł, Małachowska B, Fendler W, Szemraj J and Kuna P. Identification and association of the single nucleotide polymorphisms, C-509T, C+466T and T+ 869C, of the TGF-β1 gene in patients with asthma and their influence on the mRNA expression level of TGF-β1. Int J Mol Med 2014; 34: 975-986.

[70] Son JY, Kim SY, Cho SH, Shim HS, Jung JY, Kim EY, Lim JE, Park BH, Kang YA and Kim YS. TGF-β1 T869C polymorphism may affect susceptibility to idiopathic pulmonary fibrosis and disease severity. Lung 2013; 191: 199-205.

[71] He DD, Zhang ZD, Liu LF and Chen XM. Observation of early change of expression level of serum transforming growth factor-β1 among workers exposed to dust. Occupation and Health 2014; 18: 15.

[72] Li J, Zheng QH, Hao XH, Zhu LH, Si DW, Li C and Liu YN. Expression of TGF-β1 and its receptor TβRI, TβRII in pulmonary fibrosis induced by silica dust in rats. China Occupational Medicine 2013; 4: 7.