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

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Received June 21, 2016; Accepted August 19, 2016; Epub November 15, 2016; Published November 30, 2016

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-
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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 correaltive 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 +869T/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.
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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), heterogenous 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 I² test and the Q-statistic test were used to define the between-study heterogeneity. The fixed-effect model was used when the I² 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-restriktion 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...
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<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Mean age</th>
<th>Sample size</th>
<th>Stage of cases</th>
<th>Source of cases</th>
<th>SNPs</th>
<th>Genotyping methods</th>
</tr>
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<tr>
<td>Yao W</td>
<td>2006</td>
<td>China</td>
<td>Asian</td>
<td>29-79</td>
<td>29-79</td>
<td>I, II, III</td>
<td>CWP</td>
<td>-590C/T</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Ates I</td>
<td>2008</td>
<td>Turkey</td>
<td>Caucasian</td>
<td>58.2 ± 4.2</td>
<td>48.8 ± 5.21</td>
<td>-</td>
<td>CWP</td>
<td>+869T/C</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Wu F</td>
<td>2008</td>
<td>China</td>
<td>Asian</td>
<td>69.3 ± 6.0</td>
<td>67.3 ± 7.3</td>
<td>I, II, III</td>
<td>Silicosis</td>
<td>-590C/T, +869T/C, +915G/C</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Yucesoy B</td>
<td>2008</td>
<td>USA</td>
<td>Caucasian</td>
<td>65.9 ± 8.9</td>
<td>69.0 ± 9.0</td>
<td>-</td>
<td>CWP</td>
<td>-590C/T</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Helmig S</td>
<td>2009</td>
<td>Germany</td>
<td>Caucasian</td>
<td>68.06 (40-91)</td>
<td>44.8 (20-75)</td>
<td>-</td>
<td>Silicosis, Asbestosis</td>
<td>+869T/C, +915G/C</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Yu C</td>
<td>2009</td>
<td>China</td>
<td>Asian</td>
<td>63.59 ± 7.72</td>
<td>62.25 ± 8.98</td>
<td>I, II, III</td>
<td>CWP</td>
<td>+869T/C</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Li J</td>
<td>2010</td>
<td>China</td>
<td>Asian</td>
<td>55.9 ± 9.4</td>
<td>55.6 ± 9.4</td>
<td>-</td>
<td>CWP</td>
<td>-590C/T, +869T/C, +915G/C</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Qian HY</td>
<td>2010</td>
<td>China</td>
<td>Asian</td>
<td>65.97 ± 9.70</td>
<td>65.95 ± 6.58</td>
<td>I, II, III</td>
<td>CWP</td>
<td>-590C/T, +869T/C, +915G/C</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Fan XY</td>
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<td>China</td>
<td>Asian</td>
<td>56.3 ± 6.4</td>
<td>55.8 ± 8.4</td>
<td>-</td>
<td>CWP</td>
<td>-590C/T, +869T/C, +915G/C</td>
<td>PCR-RFLP</td>
</tr>
<tr>
<td>Wang S</td>
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<td>China</td>
<td>Asian</td>
<td>62.91 ± 11.94</td>
<td>42.96 ± 7.25</td>
<td>I, II, III</td>
<td>CWP</td>
<td>-590C/T</td>
<td>PCR-RFLP</td>
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<tr>
<td>Zhou WW</td>
<td>2012</td>
<td>China</td>
<td>Asian</td>
<td>24-61</td>
<td>27-52</td>
<td>-</td>
<td>CWP</td>
<td>+869T/C, +915G/C</td>
<td>PCR-RFLP</td>
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<tr>
<td>He XM</td>
<td>2013</td>
<td>China</td>
<td>Asian</td>
<td>33-50</td>
<td>26-45</td>
<td>-</td>
<td>CWP</td>
<td>-590C/T</td>
<td>PCR-RFLP</td>
</tr>
</tbody>
</table>

DEW, dust-exposed workers; HP, healthy participants; SNPs, single nucleotide polymorphisms; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; -, not available.
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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
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Table 3. Meta-analysis results of TGF-β1 polymorphisms on pneumoconiosis risk in total and sub-group analysis

<table>
<thead>
<tr>
<th>SNPs</th>
<th>Groups</th>
<th>Comparisons</th>
<th>N</th>
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<th>Test of heterogeneity</th>
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<td></td>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>-590 C/T</td>
<td>Total</td>
<td>T vs. C</td>
<td>9</td>
<td>1.57 (1.12, 2.20)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT vs. CC</td>
<td>2.14 (1.22, 3.77)</td>
<td>0.008</td>
<td>&lt;0.00001</td>
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<tr>
<td></td>
<td></td>
<td>CT vs. CC</td>
<td>1.58 (0.95, 2.62)</td>
<td>0.08</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT + CT vs. CC</td>
<td>1.77 (1.05, 2.96)</td>
<td>0.03</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TT vs. CT + CC</td>
<td>1.59 (1.17, 2.17)</td>
<td>0.003</td>
<td>&lt;0.00001</td>
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<tr>
<td></td>
<td>Silicosis</td>
<td>T vs. C</td>
<td>3</td>
<td>1.06 (0.61, 1.84)</td>
<td>0.84</td>
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<tr>
<td></td>
<td></td>
<td>TT vs. CC</td>
<td>1.12 (0.47, 2.66)</td>
<td>0.79</td>
<td>0.07</td>
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<td>CT vs. CC</td>
<td>0.79 (0.51, 1.23)</td>
<td>0.30</td>
<td>0.22</td>
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<tr>
<td></td>
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<td>TT + CT vs. CC</td>
<td>0.89 (0.46, 1.73)</td>
<td>0.73</td>
<td>0.09</td>
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<tr>
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<td>TT vs. CT + CC</td>
<td>1.17 (0.69, 1.97)</td>
<td>0.56</td>
<td>0.03</td>
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<td></td>
<td>CWP</td>
<td>T vs. C</td>
<td>6</td>
<td>1.83 (1.21, 2.77)</td>
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<td>TT vs. CC</td>
<td>2.75 (1.36, 5.58)</td>
<td>0.005</td>
<td>&lt;0.00001</td>
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<tr>
<td></td>
<td></td>
<td>CT vs. CC</td>
<td>2.11 (1.13, 3.96)</td>
<td>0.02</td>
<td>&lt;0.00001</td>
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<tr>
<td></td>
<td></td>
<td>TT + CT vs. CC</td>
<td>2.33 (1.23, 4.44)</td>
<td>0.010</td>
<td>&lt;0.00001</td>
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<td></td>
<td></td>
<td>TT vs. CT + CC</td>
<td>1.83 (1.41, 2.37)</td>
<td>&lt;0.00001</td>
<td>0.29</td>
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<tr>
<td>+869T/C</td>
<td>Total</td>
<td>C vs. T</td>
<td>8</td>
<td>0.95 (0.86, 1.05)</td>
<td>0.33</td>
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<tr>
<td></td>
<td></td>
<td>CC vs. TT</td>
<td>0.91 (0.63, 1.33)</td>
<td>0.63</td>
<td>0.01</td>
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<td>TC vs. TT</td>
<td>0.97 (0.82, 1.15)</td>
<td>0.75</td>
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<td>CC + TC vs. TT</td>
<td>0.96 (0.81, 1.12)</td>
<td>0.58</td>
<td>0.33</td>
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<td></td>
<td></td>
<td>CC vs. TC + TT</td>
<td>0.95 (0.67, 1.34)</td>
<td>0.76</td>
<td>0.004</td>
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<tr>
<td></td>
<td>Silicosis</td>
<td>C vs. T</td>
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<td>0.91 (0.75, 1.11)</td>
<td>0.36</td>
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<td></td>
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<td>CC vs. TT</td>
<td>0.72 (0.48, 1.08)</td>
<td>0.12</td>
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<td></td>
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<td>TC vs. TT</td>
<td>1.08 (0.80, 1.46)</td>
<td>0.61</td>
<td>0.26</td>
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<tr>
<td></td>
<td></td>
<td>CC + TC vs. TT</td>
<td>0.99 (0.74, 1.31)</td>
<td>0.92</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC vs. TC + TT</td>
<td>0.75 (0.53, 1.08)</td>
<td>0.12</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>CWP</td>
<td>C vs. T</td>
<td>5</td>
<td>1.09 (0.85, 1.38)</td>
<td>0.50</td>
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<tr>
<td></td>
<td></td>
<td>CC vs. TT</td>
<td>1.12 (0.64, 1.95)</td>
<td>0.70</td>
<td>0.005</td>
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<tr>
<td></td>
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<td>TC vs. TT</td>
<td>0.93 (0.75, 1.14)</td>
<td>0.47</td>
<td>0.55</td>
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<td>CC + TC vs. TT</td>
<td>0.94 (0.77, 1.14)</td>
<td>0.54</td>
<td>0.28</td>
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<td></td>
<td></td>
<td>CC vs. TC + TT</td>
<td>1.16 (0.70, 1.92)</td>
<td>0.58</td>
<td>0.001</td>
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<tr>
<td>+915G/C</td>
<td>Total</td>
<td>C vs. G</td>
<td>5</td>
<td>1.59 (1.06, 2.39)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GC vs. GG</td>
<td>1.66 (1.08, 2.55)</td>
<td>0.02</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CC + GC vs. GG</td>
<td>1.67 (1.08, 2.56)</td>
<td>0.02</td>
<td>0.85</td>
</tr>
</tbody>
</table>

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...
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Figure 2. Meta-analysis of the correlation between the TGF-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).
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We systematically deleted each study and recalculated the significance of the pooled 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-
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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
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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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