MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2014; 20: 2358-2362
DOI: 10.12659/MSM.891122

Received: 2014.06.03
Accepted: 2014.06.23
Published: 2014.11.20

# Transforming Growth Factor-β1 rs1800470 Polymorphism is Associated with Lung Cancer Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Source of support:** Self financing

**Background:** Transforming growth factor-β1 is a member of a large class of polypeptides that regulate the proliferation, differentiation, and carcinogenesis of epithelial cells. The rs1800470 polymorphism influences transforming growth factor-β1 expression and has been associated with lung cancer susceptibility. However, the association between the rs1800470 polymorphism and lung cancer risk remains controversial. Thus, a meta-analysis was conducted.

**Material/Methods:** We comprehensively searched PubMed and EMBASE databases. Summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using random-effects models or fixed-effects models.

**Results:** Overall, there was a significant association between rs1800470 polymorphism and lung cancer susceptibility (OR=1.23; 95%CI, 1.03–1.47; *P*=0.02). In the stratified analysis by ethnicity, we found that this polymorphism was significantly associated with lung cancer in Asians (OR=1.26; 95%CI, 1.01–1.57; *P*=0.04). However, we did not find any significant association between this polymorphism and lung cancer risk in Caucasians (OR=1.04; 95%CI, 0.60–1.82; *P*=0.88). In the NSCLC subgroup, we found that rs1800470 polymorphism could increase NSCLC risk (OR=1.36; 95%CI, 1.06–1.74; *P*=0.02).

**Conclusions:** This meta-analysis suggested that rs1800470 polymorphism was a risk factor of lung cancer.

**MeSH Keywords:** Lung Neoplasms • Meta-Analysis • Polymorphism, Genetic • Transforming Growth Factor beta

**Full-text PDF:** http://www.medscimonit.com/abstract/index/idArt/891122







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## Background

Lung cancer is the most commonly diagnosed cancer and is the leading cause of cancer death in males, as well as being the fourth most commonly diagnosed cancer and second leading cause of cancer death in females [1,2]. About 80% of newly diagnosed lung cancer cases are non-small cell lung cancer (NSCLC), and most of them are at advanced stage. Currently, the prognosis for NSCLC is still poor, with a 5-year survival rate of less than 15% [3]. Thus, identification of biomarkers for early detection of NSCLC is of great importance.

*Transforming growth factor-β1* is located on chromosome 19q13.1-13.39. Some studies have investigated the associations between the *transforming growth factor-β1* rs1800470 polymorphism and susceptibility to lung cancer [4–9]. However, the results were quite controversial and inconsistent. In this meta-analysis, we comprehensively evaluated the correlation between rs1800470 polymorphism and lung cancer risk.

## Material and Methods

### Publication search

Online databases of PubMed and EMBASE were searched to retrieve potentially relevant studies. Comprehensive searches were conducted using the combination of key words and medical subheadings: "Transforming growth factor-β1", "single nucleotide polymorphism" or "SNP" or "polymorphism", and "lung cancer" or "lung tumor" or "neoplasm, lung". There was no limitation of research and the latest research was performed on April 2013. References of related studies and reviews were manually searched for additional studies.

### Inclusion and exclusion criteria

The following inclusion criteria were used: (1) evaluate the association between rs1800470 polymorphism and lung cancer risk; (2) a case-control design; (3) sufficient data should have been provided to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied: (1) not for lung cancer study; (2) only case population; (3) studies were repeated or publications overlapped.

### Data extraction and qualitative assessment

The following data were recorded from each article: first author, year of publication, ethnicity of participants, histology, smoking, and numbers of cases and controls. The data were extracted by 2 of the authors independently. Discrepancies between these 2 authors were resolved by discussion.

### Statistical analysis

The strength of association between rs1800470 polymorphism and lung cancer risk was assessed by calculating OR with 95% CI. The pooled ORs were performed for the dominant model. Departure from Hardy-Weinberg equilibrium (HWE) in controls was tested by the chi-square test. A statistical test for heterogeneity was performed based on the Q statistic. The $P>0.10$ of the Q test indicated a lack of heterogeneity among studies. When heterogeneity was present, the random effects model was used to calculate the pooled ORs, otherwise the fixed effects model was used. The summary OR estimate of each study was calculated by the random-effects model. Stratified analysis was performed by ethnicity and histology. One-way sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled ORs. Potential publication bias was examined by Egger's test [10]. All statistical tests were performed with STATA version 11.0 software (Stata Corporation, College station, TX, USA). A $P$ value <0.05 was considered statistically significant.

## Results

### Study characteristics

Six studies met the inclusion criteria and were included in the final analysis of lung cancer [4–9]. Three case-control studies included Asian populations and 3 studies were performed in Caucasians. The final dataset for our meta-analysis on rs1800470 polymorphism and lung cancer included 2763 participants with a total of 1315 lung cancer cases. The characteristics of included studies and distribution of rs1800470 genotype in lung cancer are summarized in Table 1 and Table 2, respectively.

### Results of meta-analysis

Overall, there was a significant association between rs1800470 polymorphism and lung cancer susceptibility (OR=1.23; 95% CI, 1.03–1.47; $P$=0.02; Figure 1). In the stratified analysis by ethnicity, we found that this polymorphism was significantly associated with lung cancer in Asians (OR=1.26; 95% CI, 1.01–1.57; $P$=0.04). However, we did not find any significant association between this polymorphism and lung cancer risk in Caucasians (OR=1.04; 95% CI, 0.60–1.82; $P$=0.88). In the NSCLC subgroup, we found that the rs1800470 polymorphism could increase NSCLC risk (OR=1.36; 95% CI, 1.06–1.74; $P$=0.02). Table 3 lists the results of the association between rs1800470 polymorphism and lung cancer risk.

Sensitivity analysis was performed through sequentially excluding individual studies. Statistically similar results were





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**Table 1.** Characteristics of the case-control studies included in this meta-analysis.

| First author | Year | Ethnicity | Age | Male (%) | Tumor histology | Smoking status | Case number (n) | Control number (n) |
|---|---|---|---|---|---|---|---|---|
| Kang [4] | 2006 | Asian | 61.6 | 81.5 | Mixed* | Mixed | 432 | 432 |
| Park [5] | 2006 | Asian | 62.0 | 71.6 | Mixed | Mixed* | 194 | 283 |
| Colakogullari [6] | 2008 | Caucasian | 60.0 | 91.0 | Mixed | Mixed | 44 | 59 |
| Helmig [7] | 2009 | Caucasian | 67.3 | 100.0 | Mixed | Mixed | 147 | 83 |
| Teixeira [8] | 2011 | Caucasian | 63.1 | 71.0 | NSCLC | Mixed | 305 | 380 |
| Bai [9] | 2013 | Asian | 58.0 | 78.2 | Mixed | Mixed | 193 | 211 |

* Different data could be extracted separately. NSCLC – non-small cell lung cancer.

**Table 2.** Distribution of rs1800470 genotype among patients and controls.

| Study | Patient | | | Control | | | HWE |
|---|---|---|---|---|---|---|---|
| | CC | CT | TT | CC | CT | TT | |
| Kang | 106 | 218 | 108 | 125 | 200 | 107 | Yes |
| Park | 53 | 100 | 41 | 84 | 137 | 62 | Yes |
| Colakogullari | 10 | 24 | 9 | 10 | 29 | 20 | Yes |
| Helmig | 62 | 62 | 23 | 32 | 36 | 15 | Yes |
| Teixeira | 53 | 165 | 87 | 44 | 166 | 170 | Yes |
| Bai | 31 | 107 | 55 | 47 | 105 | 58 | Yes |

HWE – Hardy-Weinberg equilibrium.

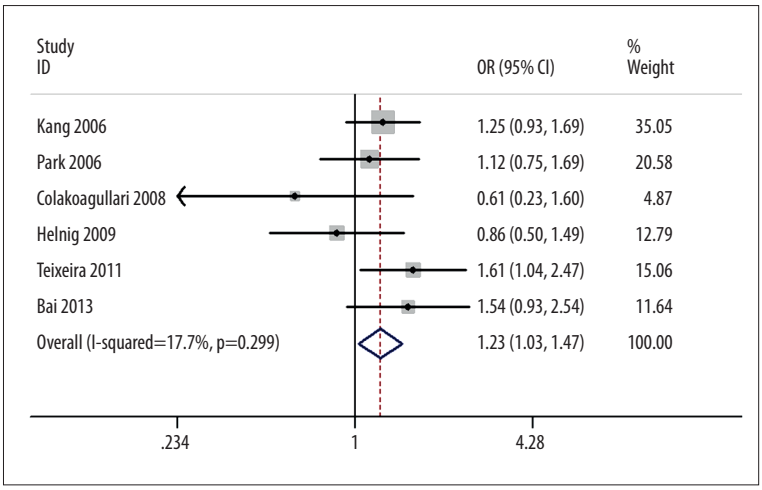


**Figure 1.** Meta-analyses of rs1800470 polymorphism association with lung cancer risk.

obtained after sequentially excluding each study, and the corresponding pooled ORs in the other genetic models were not materially altered (data not shown), suggesting stability and reliability of this meta-analysis.

Egger's test was used to provide statistical evidence of funnel plot symmetry (Figure 2) and did not detect evidence of publication bias ($P$=0.29)

## Discussion

This meta-analysis of 6 case-control studies systematically evaluated the association between rs1800470 polymorphism and lung cancer risk. The results indicated that rs1800470 polymorphism was a risk factor for lung cancer. In the stratified analysis by ethnicity, this polymorphism was significantly associated with lung cancer in Asians. However, no significant association





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**Table 3.** Results of meta-analysis.

| Polymorphism | Comparison | Association | | | Heterogeneity | | |
|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | *Z* | *P* Value | $\chi^2$ | *P* Value | $I^2$ (%) |
| TT+CT *vs.* CC | Overall | 1.23 (1.03–1.47) | 2.27 | 0.02 | 6.08 | 0.30 | 18.0 |
| TT+CT *vs.* CC | Asian | 1.26 (1.01–1.57) | 2.09 | 0.04 | 0.92 | 0.63 | 0.0 |
| TT+CT *vs.* CC | Caucasian | 1.04 (0.60–1.82) | 0.15 | 0.88 | 5.00 | 0.08 | 60.0 |
| TT+CT *vs.* CC | NSCLC | 1.36 (1.06–1.74) | 2.43 | 0.02 | 0.86 | 0.35 | 0.0 |

NSCLC – non-small cell lung cancer.

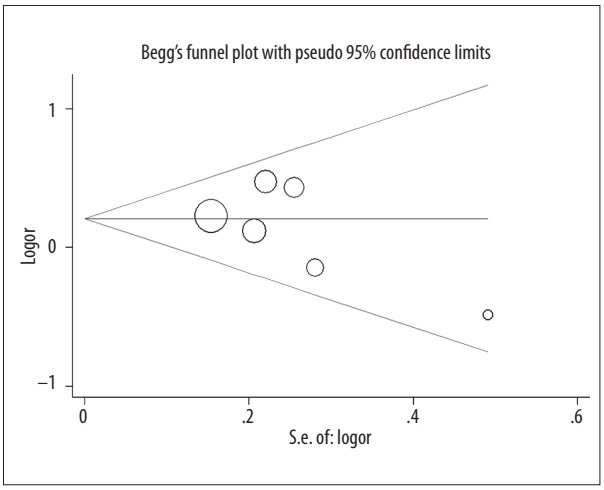


**Figure 2.** Begg's funnel plot showing the association of rs1800470 polymorphism with lung cancer risk.

between this polymorphism and lung cancer risk was detected. Only 3 studies with Caucasians were included. Thus, the positive associations between rs1800470 polymorphism and lung cancer risk could not be ruled out in Caucasians. In the NSCLC subgroup, we found that rs1800470 polymorphism could increase NSCLC risk. This result suggests that rs1800470 might play an important role in the development of NSCLC.

Transforming growth factor-β1 is a multifunctional regulatory polypeptide that controls many aspects of cellular function, such as cellular proliferation, differentiation, migration, apoptosis, adhesion, angiogenesis, immune surveillance, and survival [11]. In patients with lung cancer, transforming growth factor-β1 is frequently elevated and correlates with long-term outcomes [12–14]. The rs1800470 polymorphism has been identified in this gene. The rs1800470 polymorphism resulted in significant difference with regard to transforming growth factor-β1 expression and plasma concentration [15]. Therefore, it is possible that the rs1800470 polymorphism may increase lung cancer risk in the study population [16,17].

In this meta-analysis, we identified 6 eligible studies and 2763 subjects and provided a systematic overview of current studies. No significant heterogeneity was observed in the process of quantitative synthesis. Additionally, results of sensitivity analysis and Egger's test also support the reliability and stability of our results. However, limitation to this meta-analysis should be noted. First, the number of studies was relatively small because sub-group analyses were not available to explore the effect of smoking. Second, our results were based on raw data and were not adjusted for certain confounding factors, such as sex, age, and lifestyle.

## Conclusions

Our meta-analysis suggests that the rs1800470 polymorphism may be a risk factor for lung cancer.

### Conflicts of interest

None.

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