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Original Article

Effect of transforming growth factor-β1 869C/T polymorphism and radiation pneumonitis

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Abstract: Background: The Transforming growth factor-β1 (*TGFβ1*) 869C/T polymorphism was associated with radiation pneumonitis (RP) susceptibility. However, the results remained controversial. Thus, a meta-analysis was conducted. Methods: Relevant studies were systematically searched by using the NCBI, Medline, Web of Science and Embase databases. Summary odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were estimated using random-effects models. Results: There was a significant association between *TGFβ1* 869C/T polymorphism and RP susceptibility (OR = 1.77; 95% CI, 1.27-2.47; *P* = 0.0007). Conclusion: This study suggested that *TGFβ1* 869C/T polymorphism was a risk factor of RP.

Keywords: Radiation pneumonitis, transforming growth factor, meta-analysis, polymorphism

Introduction

Radiation pneumonitis (RP) is the one of the most significant complications of acute treatment-related toxicities in lung cancer and other cancers. It occurs in 5-15% of people who go through radiation therapy for cancers. The occurrence is higher if chemotherapy is given at the same time [1]. Previous studies have demonstrated an association between RP risk and multiple therapeutic and patient-related factors, such as Karnofsky performance status (KPS), dosimetric parameters, smoking status and plasma inflammatory cytokine levels [2]. Recently, some genetic variants, such as single nucleotide polymorphisms (SNPs) of several genes, are also shown to be associated with an increased risk of severe RP in patients with NSCLC [3], suggesting that genetic factors may play an important role in RP development.

Transforming growth factor (TGF)-β1 is a multiplicity factor mediating cellular processes, including cell growth, cell differentiation, apoptosis, and cellular homeostasis. Plasma values of TGFβ1 are often elevated during radiotherapy in patients who developed RP [4]. Some researchers reported that the return of plasma TGF1 levels to normal after radiotherapy accurately predicted that patients would not develop RP [5].

The human *TGFβ1* gene is located on chromosome 19q13.1-13.39. Some studies have investigated the associations between the *TGFβ1* 869C/T polymorphism and susceptibility of RP [6-10]. However, the results were quite controversial and inconsistent. In this meta-analysis, we comprehensively evaluated the correlation between *TGFβ1* 869C/T polymorphism and RP risk.

Methods

Publication search

Relevant studies were systematically searched by using the NCBI, Medline, Web of Science and Embase databases (The last retrieval date was August 17, 2014, using the search terms: "Radiation pneumonitis" and "Transforming growth factor-β1" and "single nucleotide polymorphism"). All searched studies were retrieved and only published studies with full-text articles

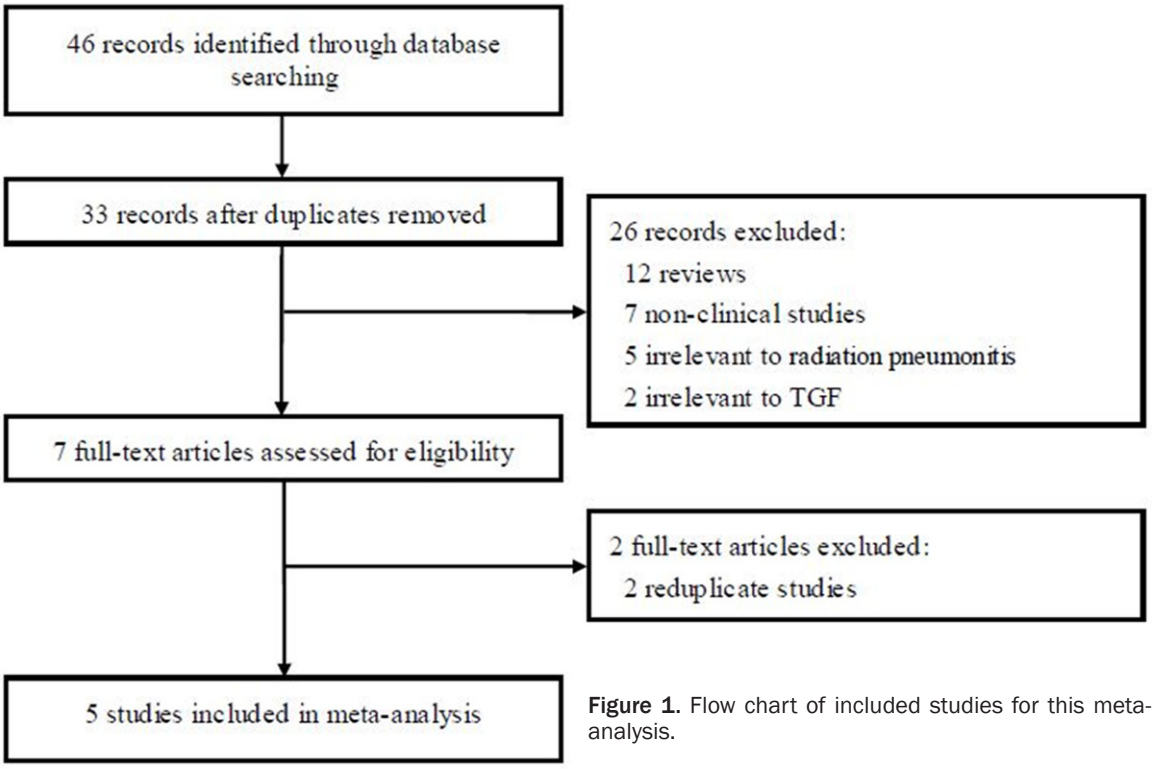

Figure 1. Flow chart of included studies for this meta-analysis.

Table 1. Characteristics of the included studies

First author	Year	Ethnicity	Gender	Age	No. of patients	Radiation dose	Site of cancer	HWE	NOS score
Yuan	2009	Caucasian	Mixed	63	164	63	Lung	Yes	6
Alsbeih	2010	Caucasian	Mixed	50	60	66	Nasopharyngeal	Yes	6
Niu	2012	Asian	Mixed	58	167	56	Lung	Yes	8
Tucker	2012	Caucasian	Mixed	62	141	63	Lung	Yes	7
Voets	2012	Caucasian	Mixed	66	209	60	Lung	Yes	6

were included. When more than publications with duplicate samples, only the newest study was used in this research.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) evaluate the association between *TGFβ1* 869C/T polymorphism and RP risk; (2) a case-control or cohort design; (3) sufficient data provided for calculating odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied: (1) not for RP study; (2) only case population; (3) studies were repeated or publications overlapped.

Data extraction

The following data were recorded from each article: first author, years of publication, ethnicity of participants, gender, age, radiation dose, numbers of patients, and site of cancer. The data were extracted by two of the authors independently. Discrepancies between these two authors were resolved by discussion.

Methodological assessment

Methodological quality was evaluated separately by two observers using the Newcastle-Ottawa Scale (NOS) criteria. The NOS criteria were based on 3 aspects: (1) subject selection: 0~4; (2) comparability of subject: 0~2; (3) clinical outcome: 0~3. Total NOS scores ranged from 0 to 9 with a score ≥ 7 meaning a good quality.

Statistical analysis

The strength of association between *TGFβ1* 869C/T polymorphism and RP risk was assessed by calculating OR with 95% CI. The pooled ORs were performed for recessive model. A statistical test for heterogeneity was

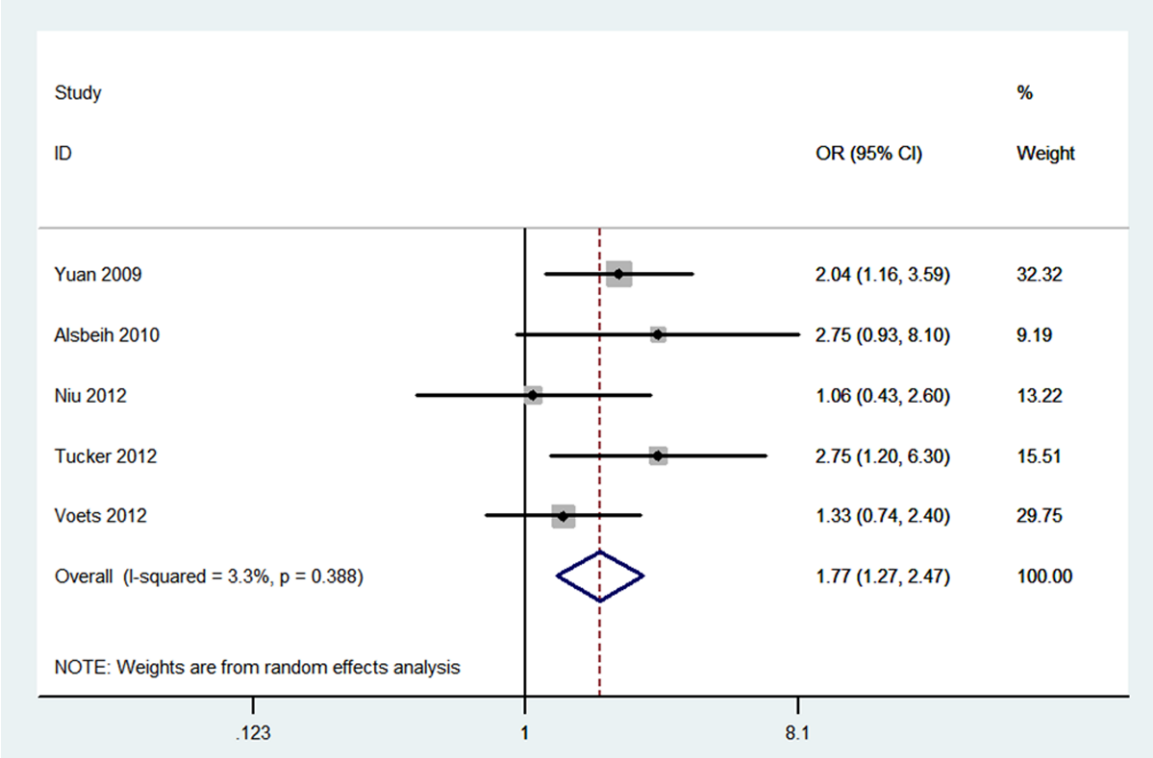

Figure 2. Meta-analyses of the *TGFβ1* 869C/T polymorphism and RP risk.

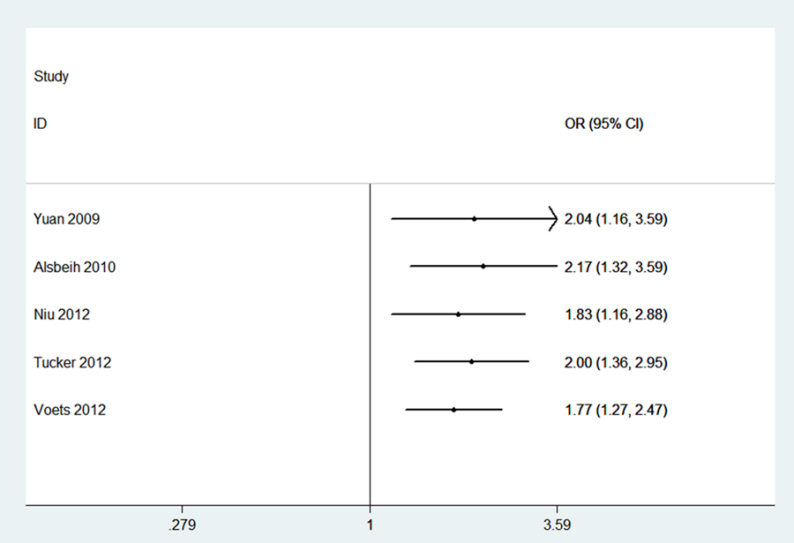

Figure 3. Cumulative meta-analysis of associations between the *TGFβ1* 869C/T polymorphism and RP risk.

performed based on the Q statistic. The $P > 0.10$ of the Q-test indicated a lack of heterogeneity among studies. The random effects model was used to calculate the pooled ORs. Cumulative meta-analysis was conducted. The 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 to the pooled ORs. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value < 0.05 was considered statistically significant.

Results

Study characteristics

Five studies met the inclusion criteria and were included in the final analysis (**Figure 1**) [6-10]. One case-control study included Asian population; while four studies were performed in Caucasians. One study included nasopharyngeal cancer patients, while four studies were performed in lung cancer patients. The final dataset for our meta-

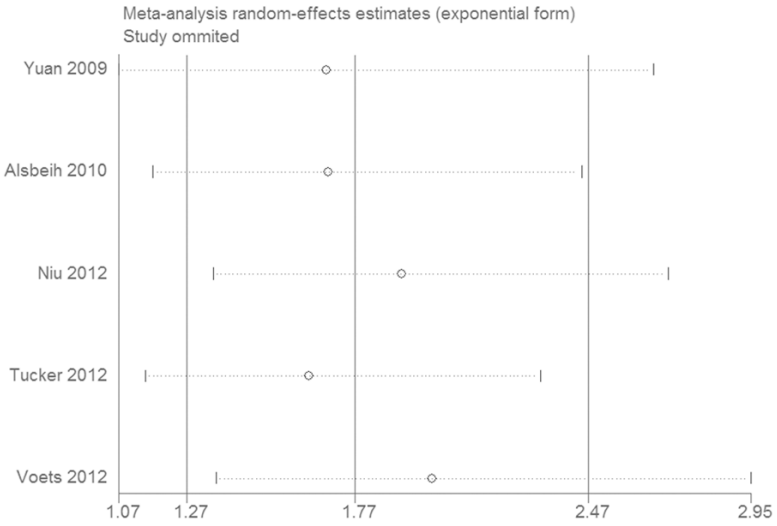

Figure 4. Sensitivity analysis for the *TGFβ1* 869C/T polymorphism and RP risk.

analysis on *TGFβ1* 869C/T polymorphism and RP risk included 741 participants. The characteristics of included studies summarized in **Table 1**.

Results of meta-analysis

There was a significant association between *TGFβ1* 869C/T polymorphism and RP susceptibility (OR = 1.77; 95% CI, 1.27-2.47; *P* = 0.0007; **Figure 2**).

As shown in **Figure 3**, significant associations were evident with each addition of more data over time. The results showed that the pooled ORs tended to be stable. Sensitivity analysis was performed through sequentially excluding individual studies. Statistically similar results were obtained after sequentially excluding each study and the corresponding pooled ORs were not materially altered (**Figure 4**), suggesting stability and liability of this meta-analysis.

Discussion

This meta-analysis of five studies systematically evaluated the association between *TGFβ1* 869C/T polymorphism and RP risk. The results indicated that *TGFβ1* 869C/T polymorphism was a risk factor for RP.

TGFβ1 is one of the most extensively studied cytokines in the development of tissue fibrosis in response to irradiation [11], and TGFβ1 signaling is an important modulator of the inflammatory response. Animal and human studies have demonstrated that TGFβ1 is a major regulator of radiation induced lung injury as a master switch for development and persistence of fibrosis [12]. Administration of anti-TGFβ antibodies can decrease the inflammatory response and reduce TGFβ activation several weeks after irradiation, further suggesting that targeting the TGFβ pathway may be a useful strategy to prevent irradiation-induced lung injury [13]. *TGFβ1* 869C/T polymorphism resulted in significant differences with regard to TGFβ1 expression and plasma concentration [14].

Our meta-analysis had some limitations that might affect the interpretation of the results. First, the numbers of published studies were not sufficient for a comprehensive analysis, particularly for Asians and Africans. Second, other than 869C/T polymorphism, there are other variants in the *TGF* gene. We did not carry out meta-analysis on these polymorphisms due to limited data. Third, lacking of the original data of the eligible studies limited the evaluation of the effects of the gene-gene interactions in RP.

In conclusion, this meta-analysis suggested that *TGFβ1* 869C/T polymorphism may be associated with the risk of RP. Well-designed studies with larger sample size and more ethnic groups should be considered to further confirm this association.

Disclosure of conflict of interest

None.

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