A Likely Role for a Novel Cell Therapeutic Target of Transforming Growth Factor-β1 on Radiation Pneumonitis in Lung and Nasopharyngeal Cancer Patients

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Abstract

The association between the polymorphism of transforming growth factor (TGF)-β1 and risk of radiation pneumonitis has been extensively investigated; however, conclusive results were unavailable. Eligible studies were identified from the database of Medline, Web of Science, EMBASE, and CNKI (China Knowledge Resource Integrated Database) up to September 2019. The odds ratio (OR) and 95% confidence interval (95% CI) were used to assess the strength of the relationship. The results showed that there were associations between TGF 869 T/C (rs1982073) and risks of radiation pneumonitis. Subgroup analyses showed that TGF 869 T/C was associated with risk of radiation pneumonitis in Caucasians (OR [95% CI]: 0.45 [0.31 to 0.67] for C carriers vs. TT). In addition, subgroup analyses also suggested that the C allele was associated with decreased risks of radiation pneumonitis among hospital-based case–control studies (0.56 [0.39 to 0.82] for C carriers vs. TT). Meanwhile, C allele was also suggested to be associated with decreased risk of radiation pneumonitis among PCC (0.60 [0.38 to 0.96] for C carriers vs. TT). Especially, C allele was also found to be associated with decreased risk of radiation pneumonitis from the participants with lung cancer (0.57 [0.37 to 0.90] for C carriers vs. TT). Our meta-analysis shows that T allele in TGF 869 T/C is significantly associated with the increased risk of radiation pneumonitis, especially for Caucasians, and for the participants with lung cancer.

Keywords

transforming growth factor, radiation pneumonitis, polymorphism

Introduction

Radiation pneumonitis (RP) is the one of the most significant complications of acute treatment-related toxicities in lung cancer and other cancers[1]. It occurs in 5% to 15% of people who go through radiation therapy for cancers[2,3].

It is well known that the development of RP is a complex multistage and multifactorial course during which several pathogenic factors are involved[1,4–6]. The effects of inflammatory factors on predisposition to RP were investigated in recent years[7,8]. Several genetic mutations for inflammatory process were verified to be closely related to RP[9–12]. It has also been demonstrated that different genetic pathways lead to increases in the risk of RP, confirming the functional role of genetic factors on the risk of RP[13–15]. It is now commonly accepted that the pathogenesis of RP is a multifactorial interaction of environmental triggers and genetic susceptibility[16–18]. Meta-analyses confirmed that several gene polymorphisms are related to increased risk of RP.

Among the genetic factors, the transforming growth factor (TGF) gene, located on the chromosome 19q13.1-13.39, is one of the most important tumor suppressor genes[19,20].

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The TGF gene encodes a transmembrane glycoprotein that mediates intercellular adhesion and cellular polarity[21–23]. Cell adhesion plays an important role not only in regulating morphogenesis of both normal and neoplastic tissues, but also in tumor invasion and metastasis[14,24–26].

Identification of individuals at risk of RP will obtain the benefit from the prevention, early detection, and treatment of RP. Over the past decade, increasing studies were performed to assess the relationship between TGF-1 869 T/C polymorphism and the risk of RP in humans[27–31]. However, these findings reported conflicting results and conclusions. In our current study, therefore, we targeted to quantitatively analyze the relationship between TGF-1 869 T/C polymorphism and genetic predisposition to RP.

Research Design and Methods

Search Strategy and Selection Criteria

Our analyses were done in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for a meta-analysis of observational studies. The databases of Medline, Web of Science, EMBASE, and CNKI (China Knowledge Resource Integrated Database) without language restrictions were searched from inception to September 2019, targeting the studies investigating the association between TGF and the risk of RP. To perform a comprehensive literature search, the keywords used during searching were "TGF," "polymorphis," and "radiation pneumonitis." Reference lists of pertinent studies also were searched for identifying further eligible studies.

Study Selection and Data Extraction

The studies meeting the following criteria were only included: (1) case–control studies about the associations between TGF polymorphisms and RP; and (2) sufficient information for assessing an odds ratio (OR) and 95% confidence interval (95% CI). We excluded (a) duplicate data; (b) abstract, comment, case reports, review, and editorial; and (c) nonhuman studies and studies where no sufficient data were reported.

All necessary information were extracted and cross-checked independently by two reviewers. For included studies, the following information were extracted by two authors independently: the family name of first author, year of publication, statistical methods, ethnicity of the population, sample size (number of case and control/total participants), covariates adjusted in the multivariable analysis, and the OR (with the 95% CI) with the corresponding number of cases and person-years for each category.

Quality Assessment of Studies and Evidence

The Newcastle-Ottawa Scale (NOS) was used to test the quality of the included studies by no less than two reviewers[32] (QY and JZ were included). This scale ranged from nine stars (excellent) to zero (poor) and awards four stars for inclusion of study participants, three stars for the adequate ascertainment of outcomes, and two stars for comparability of studies. Scores of 7 to 9, 4 to 6, and 0 to 3 are regarded as high quality, moderate, and low, respectively. The quality of evidence was assessed applying the GRADE system (GRADE profiler 3.6.1) by two reviewers (QY and JZ). There are some reasons for downgrade of data, which are imprecision or publication bias, inconsistency, indirectness, and several reasons to upgrade the evidence: plausible confounders and large effect size that cannot be prone to decrease the apparent effect size. The categories for the different evidences are very low, low, moderate, and high.

Statistical Analysis

The ORs and 95% CIs were to test the associations between TGF polymorphisms and RP risk as the effect size for all studies, and we extracted the maximally adjusted OR (95% CI). The meta-analysis was performed with the fixed-effects model (Mantel–Haenszel method)[33] when there was no heterogeneity of the results. Otherwise, The random-effects model (DerSimonian Laird method)[34] was used. Stratified analyses were done according to study design, ethnicity, and NOS score.

The Galbraith plot was used to detect the potential sources of heterogeneity, and reanalyses were conducted when the studies possibly causing the heterogeneity were excluded. Heterogeneity across studies was assessed with the Q test and $I2$ statistics[35]. Heterogeneity across studies was assessed with the Q test and $I2$ statistics. The Egger's weighted regression method was used to statistically assess publication bias ($P < 0.05$ was considered representative of statistically significant publication bias).

All statistical analyses were performed with Stata version 13.1 (STATA Corp, College Station, TX, USA). In our study, $P < 0.05$ was considered statistically significant and all statistical tests were two-sided.

Results

Characteristics of Incorporated Studies

The flowchart of inclusion of studies and reasons for exclusion is presented in Fig. 1. A total of seven articles were included in our study based on the inclusion and exclusion criteria. The data extracted from each eligible study are described in Table 1. Four case–control studies were conducted in Caucasians, and three studies were conducted in Asians. Of the seven original studies, three were carried out in China, two each in USA, one in Belgium, and one in Netherlands. Among the included studies, different genotyping methods were reported in the studies, and DNA sequencing technology or polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) was mostly used.
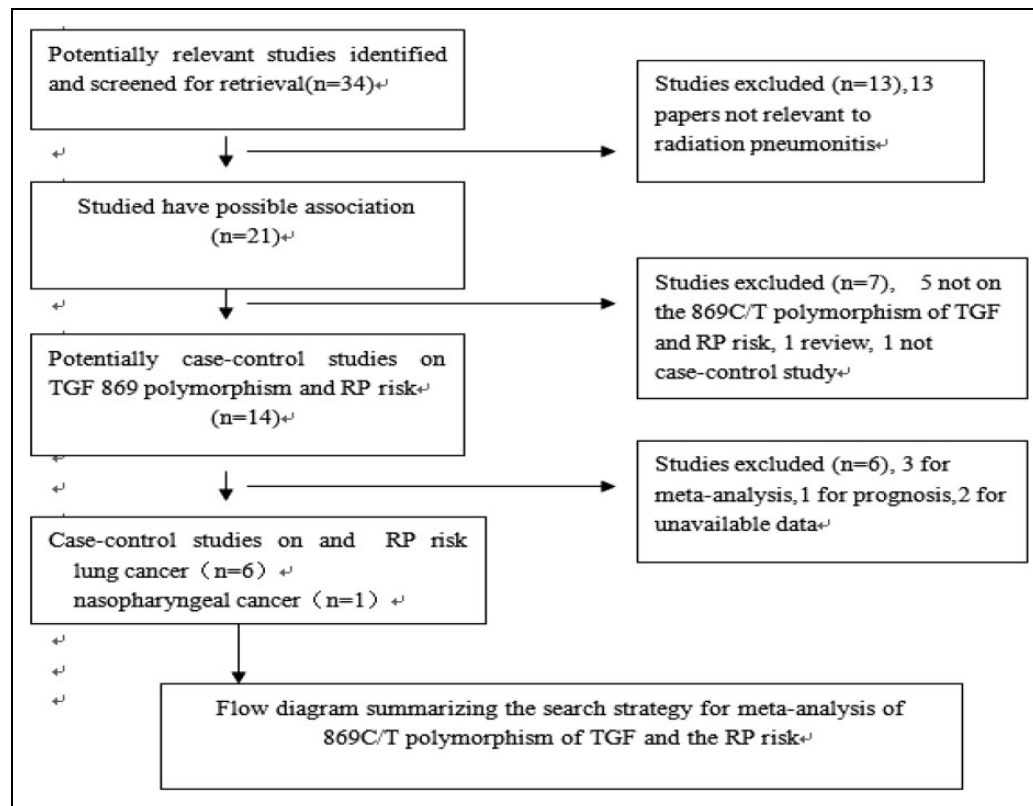
Fig. 1. Flow diagram summarizing the search strategy for meta-analysis of 869C/T polymorphism of TGF and the radiation pneumonitis risk. TGF: transforming growth factor; RP: radiation pneumonitis.

The number of RP patients included in our studies varied from 28 to 64. Controls ranged from 30 to 150. Controls were drawn from the general population in four studies and hospital in three studies.

The NOS scores are presented in Table 2. The range of NOS scores was 6 from to 8. The mean score was 6.7. High-quality original studies were included in our meta-analysis.

Quantitative Synthesis

The results of quantitatively pooled analysis have been presented in Table 1. Since one study just presents the data for genotypes of TT and TC and CC, seven studies were included for analysis for the TC and CC vs. TT model, and six studies were combined for other three comparison models. There was relationship between TGF 869T/C and risk of radiation pneumonia, and ORs (95% CIs) were 0.82(0.69 to 0.97) for C carriers vs. TT (Fig. 2). Stratification analysis according to ethnicity and source of control was conducted. The results indicated that TGF 869T/C was associated with the risk of radiation pneumonia for Caucasians (0.45 [0.31 to 0.67] for C carriers vs. TT), while not associated for Asians (0.69 [0.35 to 1.37] for CC vs. TT, 0.31 [0.72 to 2.4] for CC vs. TC, 1.04 [0.60 to 1.80] for CC vs. T carrier, 0.79 [0.851

to 1.22] for C carriers vs. TT) and 0.94 (0.70 to 1.27) for C vs. T.

When subgroup analyzing for the sources of controls (hospital-based or people-based), there was relationship between TGF 869T/C and risk of radiation pneumonia in population-base studies (0.79 [0.45 to 1.40] for CC vs. TT [supplemental Figure S1], 0.56 [0.39 to 0.82] for C carriers vs. TT, 0.66 [0.23 to 1.90] for CC vs. TC, 0.60 [0.38 to 0.96] for C carriers vs. TT) and hospital-based studies (0.79 [0.45 to 1.40] for CC vs. TT, 1.42 [0.84 to 2.40] for C carriers vs. TT, 1.10 [0.68 to 1.77] for CC vs. TC, 0.56 [0.39 to 0.82] for C carriers vs. TT). In addition, in subgroup analyses according to genotyping methods, there was no significant different association between TGF 869T/C and risk of radiation pneumonia in population-base studies by PCR-RFLP methods (1.12 [0.99 to 1.27] for CC vs. TT, 1.07 [0.96 to 1.19] for C carriers vs. TT, 0.67 [0.32 to 1.43] for CC vs. TC [supplemental Figure S2], 1.08 [1.00 to 1.17] for C carriers vs. TT) and by DNA sequencing methods (1.15 [0.97 to 1.37] for CC vs. TT, 1.13 [0.97 to 1.29] for C carriers vs. TT, 1.14 [0.99 to 1.31] for CC vs. TC, 1.08 [0.95 to 1.19] for C carriers vs. TT). When analyzing the subgroups for NOS, there was significant association between TGF 869T/C and risk of radiation pneumonia in NOS score ≥7 (0.58 [0.31 to 1.07] for CC vs. TT, 1.27 [0.72 to 2.23] for C carriers vs. TT, 0.95

Table I. Distribution of Genotypes of the T 869C Polymorphism in Studies of the TGF Gene and Susceptibility to Radiation Pneumonitis.

First author	Year	Country	Ethnic origin	Source of control	Radiation dose	Site of cancer	TT No. of Cases	TT No. of Controls	TC No. of Cases	TC No. of Controls	CC No. of Cases	CC No. of Controls	Genotyping methods	NOS score	HWE in controls
Niu	2012	China	Asian	HCC	58	Lung	8	20	22	67	16	34	Direct DNA sequencing	8	0.18
Tucker	2012	America	Caucasian	PCC	62	Lung	16	30	10	69	2	14	PCR-RFLP	7	0.009
Votes	2012	Belgium	Caucasian	HCC	66	Lung	36	77	16	59	7	14	PCR and Sanger sequencing	6	0.58
Jing Wan	2010	China	Asian	HCC		Lung	17	23	12	44	9	29	PCR-RFLP	8	0.43
Luhua Wang	2010	China	Asian	PCC		Lung	18	36	46	79			PCR-RFLP	6	NA
Alsbeih	2010	Netherland	Caucasian	PCC	50	Nasopharyngeal	15	8	10	11	5	11	Direct DNA sequencing	6	0.16
Yuan	2009	USA	Caucasian	HCC	63	Lung	17	35	18	93			PCR-RFLP	6	NA

HCC: hospital-based case–control studies; PCC: population-based case–control studies; PCR-RFLP: polymerase chain reaction restriction fragment-length polymorphism.

Table 2. Subgroups Analyses for the Associations Between TGF 869 T/C (rs1982073) and Risks of RP.

Indexes		No. of studies	CC vs. TT			CC vs. TC			CC vs. T carriers			C carriers vs. TT		
			OR (95% CI)	P_heterogeneity [a]	P_Begger [b]	OR (95%CI)	P_heterogeneity [a]	P_Begger [b]	OR (95% CI)	P_heterogeneity [a]	P_Begger [b]	OR (95%CI)	P_heterogeneity [a]	P_Begger [b]
Total		7	0.60 (0.37–0.98)	0.19	0.15	1.21 (0.76 –1.93)	0.65	0.28	0.89 (0.58 –1.35)	0.30	0.15	0.93 (0.77 –1.11)	0.97	0.90
Ethnicity	Caucasians	4	0.52 (0.26 –1.5)	0.28	1.11	1.007 (0.51–2.23)	0.81	0.29	0.71 (0.36 –1.39)	0.36	0.15	0.92 (0.73–1.15)	<0.01	0.11
	Asians	3	**0.69 (0.35–1.37)**	0.93	0.08	1.31 (0.72–1.24)	<0.01	0.13	1.4 (0.60–1.80)	0.65	0.11	0.79 (0.51–1.22)	0.02	0.91
Country	USA	2	**1.34 (0.95–1.71)**	**<0.01**	**0.17**	1.15 (0.95–1.40)	<0.01	0.29	**1.21 (0.80–1.47)**	<0.01	0.26	**1.23 (0.75–1.46)**	<0.01	0.94
	Others	5	0.88 (0.68–1.12)	0.11	**0.91**	0.91 (0.64–1.28)	0.06	0.71	0.91 (0.66–1.26)	0.06	1.00	0.95 (0.81–1.11)	0.84	0.88
Design[c]	HCC	4	0.79 (0.45–1.40)	0.15	0.04	1.42 (0.84–2.40)	0.72	0.17	1.10 (0.68–1.77)	0.26	0.10	0.56 (0.39–0.82)	0.11	0.11
	PCC	3	0.25 (0.09–0.72)	0.14	0.02	0.66 (0.23–1.90)	0.33	0.07	0.42 (0.16–1.10)	0.22	0.04	0.60 (0.38–0.96)	0.35	0.20
Methods	PCR-RFLP	4	1.12 (0.99–1.27)	<0.01	0.02	1.07 (0.96–1.19)	<0.01	0.07	1.09 (0.98–1.22)	<0.01	0.04	1.08 (0.98–1.17)	<0.01	0.20
	DNA sequencing	3	1.15 (0.97–1.37)	<0.01	0.04	1.13 (0.97–1.29)	<0.01	0.17	1.14 (0.99–1.31)	<0.01	0.10	1.08 (0.95–1.19)	<0.01	0.11
NOS	≥7	3	0.58 (0.31–1.07)	0.20	0.02	1.27 (0.72-2.23)	0.89	0.07	0.95 (0.57–1.57)	0.39	0.04	0.46 (0.28–0.73)	0.13	0.20
	<7	4	0.55 (0.13–2.34)	0.09	0.04	1.09 (0.48–2.50)	0.14	0.17	0.71 (0.19–2.61)	0.09	0.10	0.66 (0.46–0.95)	0.14	0.11
HWE	Yes	4	0.66 (0.40–1.12)	0.17	0.04	1.23 (0.76–2.01)	0.49	0.17	0.93 (0.60–1.45)	0.22	0.10	0.58 (0.39–0.86)	0.39	0.11
	No	3	NA	–	–	NA	–	–	NA	–	–	NA	–	–
Type of cancer	LC	6	0.68 (0.41–1.16)	0.19	0.11	1.07 (0.83–2.26)	<0.01	0.27	1.02 (0.65–1.60)	0.13	0.09	0.57 (0.37–0.90)	0.23	0.10
	NC	1	NA	–	–	NA	–	–	NA	–	–	NA	–	–

CI: confidence interval; HCC, hospital-based case–control study is defined as controls from hospitalized patients; LC: lung cancer; Mixed: the controls are from both patients and healthy people; NC: nasopharyngeal cancer; OR: odds ratio; PCC, population-based case–control study is defined as controls from healthy population; Unclear: the source of controls is not clearly stated in primary study.

Bold values have no significant association between TGF 869T/C and risk of radiation pneumonia (0.69 (0.35–1.37) for CC vs. TT in Asian.

[a] P-value for Heterogeneity, if P <0.10, random-effects model was used, otherwise fixed-effects model was used.

[b] P-value for Begger, P <0.05 indicated that publication bias might have existed.

[c] HWE, Hardy–Weinberg equilibrium, which was tested using the chi-square test, and P <0.05 was considered to be statistical significance for control group.
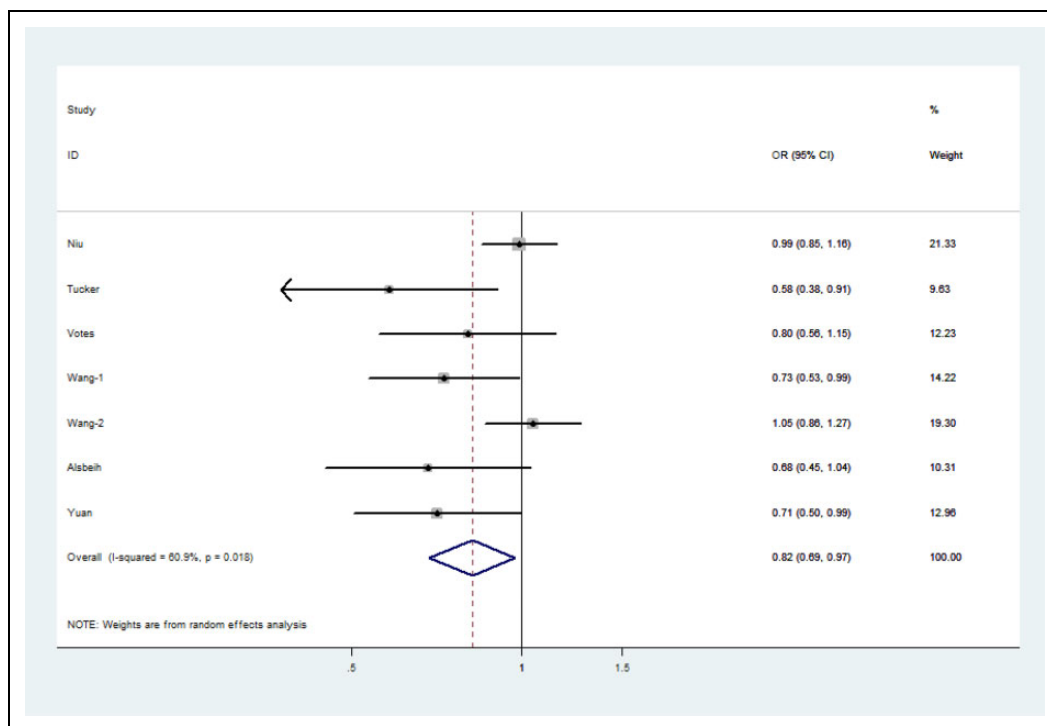
Fig. 2. Forest plot of radiation pneumonitis risk associated with transforming growth factor 869 T/C in the overall analysis (C carriers vs. TT).
CI: confidence interval.

[0.57 to 1.57] for CC vs. TC, 0.48 [0.22 to 0.92] for C carriers vs. TT [supplemental Figure S3]) and NOS score <7 (0.55 [0.13–2.34] for CC vs. TT, 1.09 [0.48 to 2.50] for C carriers vs. TT–0.71 [0.19–2.61] for CC vs. TC, 0.66 [0.46 to 0.95] for C carriers vs. TT). Especially, when subgroup analyzing for type of cancer, there was significant association between TGF 869T/C and risk of radiation pneumonia among lung cancer patients (0.68 [0.41 to 1.16] for CC vs. TT, 1.07 [0.83 to 2.26] for C carriers vs. TT, 1.02 [0.65 to 1.60] for CC vs. TC, 0.57 [0.37 to 0.90] for C carriers vs. TT [supplemental Figure S4]).

Evaluation of Heterogeneity

There was not a significant heterogeneity for CC vs. TT ($P_{heterogeneity} = 0.19$) and CC vs. TC ($P_{heterogeneity} = 0.65$), CC vs. T carriers ($P_{heterogeneity} = 0.30$), and C carriers vs. TT ($P_{heterogeneity} = 0.97$) in total analysis among the lung and nasopharyngeal cancer patients. We did not find the heterogeneity for CC vs. TT ($P_{heterogeneity} = 0.28$) and CC vs. TC ($P_{heterogeneity} = 0.81$), CC vs. T carriers ($P_{heterogeneity} = 0.36$), but not for C carriers vs. TT ($P_{heterogeneity} < 0.01$) in Caucasians and for CC vs. TT ($P_{heterogeneity} = 0.93$) and CC vs. T carriers ($P_{heterogeneity} = 0.65$), but CC vs. TC ($P_{heterogeneity} < 0.01$), for C carriers vs. TT ($P_{heterogeneity} = 0.02$) in Asians.

We did not find the heterogeneity for CC vs. TT ($P_{heterogeneity} = 0.15$) and CC vs. TC ($P_{heterogeneity} = 0.72$), CC vs. T carriers ($P_{heterogeneity} = 0.26$), and for C carriers vs. TT ($P_{heterogeneity} = 0.11$) in hospital-based case-control study, and for CC vs. TT ($P_{heterogeneity} = 0.14$) and CC vs. T carriers ($P_{heterogeneity} = 0.33$), for CC vs. TC ($P_{heterogeneity} = 0.22$), and for C carriers vs. TT ($P_{heterogeneity} = 0.35$) in population-based case–control study. We did not find the heterogeneity for CC vs. TT ($P_{heterogeneity} = 0.19$), CC vs. T carriers ($P_{heterogeneity} = 0.13$), and for C carriers vs. TT ($P_{heterogeneity} = 0.23$), but not for CC vs. TC ($P_{heterogeneity} < 0.01$) among lung cancer patients.

Sensitivity Analyses and Publication Bias

Sensitivity analyses were conducted by omitting one study at a time, and then reanalysis was conducted. The results were robust, which revealed that our results and conclusions were credible. Through visual inspection of asymmetry of funnel plots and the Begg rank correlation method, publication bias may not exist for the overall analyses of CC vs. TT ($P = 0.06$) and CC vs. T carriers ($P = 0.07$).

Discussion

This current meta-analysis, including 300 cases and 753 controls from 7 articles, tested the relationship between

TGF-β polymorphism and the risk of RP. Through our quantitative meta-analysis, it suggests that T869C polymorphism of TGF-β1 is significantly associated with increased risk of RP, especially for Caucasians. Previous meta-analyses have explored the association between T869C polymorphism of TGF-β1 and RP. Increasing interest has been shown so as to obtain more evidence for pooled analysis in a meta-analysis[36].

We found that rare C carriers significantly increased the risk of RP, when comparing with common homozygous TT, also CC vs. TT. In the subgroup analysis by source of controls, the positive association was also observed in population-based design studies and hospital-based design studies. The results indicated that a significant association was observed between the T869C polymorphism of TGF-β1 and RP in Caucasians. It is in line with the results of Wang and Shen et al. with our meta-analysis, which suggests that T869C polymorphism of TGF-β1 may be associated with RP risk only in Caucasians, but not in Asians. In addition, two new original articles by Jing Wang and Luhua Wang published in March and October 2010 were also included in our meta-study.

However, a previous meta-analysis conducted by He suggested that T869C polymorphism of TGF-β1 was associated with the risk of RP for Caucasians. Several reasons might contribute to the potential differences. First, two new articles published on March and October 2010 by Jing Wang and Luhua Wang were pooled in our updated meta-study. Second, the definition for the ethnicity of patients and participants might be varying. In the study by Shen and Wang, the participants from the study of Tucker, Wang, and Yuan were defined as out of HWE; in contrast, we categorized the participants to be in HWE when they were in the state in which the genetic structure of the population conformed to the prediction of the Hardy–Weinberg law. Furthermore, the data from the original study conducted by Alsbeih should have been from nasopharyngeal instead of lung cancer, which led to the wrong results and conclusion of the two meta-analyses by He and Shen.

The rapid growth in the detection of TGF-β1 polymorphism to illustrate the possible etiology of RP provides countless chances to study its associations with RP. However, the currently available results regarding the role of T869C polymorphism of TGF-β1 in risks of RP are often inconsistent. The first studied results often show a strong effect on subsequent studies, which may bring about a distorted understanding of inherited pathogenic factor and make it difficult to justify the reliability and accuracy of the published reported results. Meta-analysis as an important tool widely used in evidence-based medicine that provides a quantitative synthesis for pooling the results focusing on the same topic with congeneric study design and for assessing and exploring their variety.

The T869C (rs1982073) polymorphisms of TGF-β1 lead to amino acid substitutions in TGF-β1, which may change the TGF-β1 bioactivity and function. This alteration in protein biochemistry results in the supposition that variant alleles may diminish repair kinetics, thereby influencing the susceptibility to adverse health effects. TGF-β plays a key role in tumor progression allowing cancer cells to escape immune surveillance, proliferate, invade, and metastasize. A further understanding of the paradoxical nature of TGF-β in cancer is still warranted. This will aid in developing therapeutics specifically targeting TGF-β and its role in tumor progression and immunosuppression. Novel therapeutics that target TGF-β production or block its action are either in preclinical trials or early clinical trials and have shown promise. Further clinical trials will help define drugs that target TGF-β activity in cancer treatment[37].

Although several meta-analyses of TGF and RP have been published, there were some obvious deficits as addressed above. Our study had the following strengths. Our previous meta-analysis was based on case–control studies with large sample sizes. In addition, stratified analysis, sensitivity analysis, and publication bias showed the stability and reliability of our results and conclusion.

Several limitations have also been acknowledged in our study. First, residual confounding may exist due to unknown confounders although we applied the model adjusting for most of the potential risk factors. Second, the number of subjects including cases and controls in the eligible studies was limited. Third, meta-analysis is a pooled analysis from retrospective reports that are prone to the methodological limitations. Thus, we established a detailed protocol before initiating our study, and conducted a meticulous literature search for published articles by using explicit methods for paper selection, data extraction, and data quantitative synthesis so as to minimize the bias.

Conclusions

In conclusion, this meta-analysis suggests that T869C polymorphism of TGF-β1 is significantly associated with decreased risks of RP, especially for Caucasians. More large-scale and well-designed studies are required to obtain more precise evidences on the relationships between T869C polymorphism of TGF-β1 and the risk of RP.

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