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Review Article

Association between the TERT rs2736100 polymorphism and lung cancer risk: evidence from a case-control study and a meta-analysis

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Abstract: Background: The association between the *TERT* (telomerase reverse transcriptase) rs2736100 single nucleotide polymorphism and lung cancer risk has been studied by many researchers, but the results remain inconclusive. To further explore this association, we performed a meta-analysis to further studies. Material and methods: We performed a case-control study in 554 lung cancer cases and 693 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression. Afterwards a computerized search of PubMed and Google Scholar for publications on rs2736100 and lung cancer risk was performed. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association between rs2736100 and lung cancer risk in 21 selected case-control studies. A sensitivity analysis, a test of heterogeneity, a cumulative meta-analysis, and an assessment of bias were also performed. Results: In our study, we found that rs2736100 GT-GG increased the risk of lung in the dominant model (OR = 1.48, 95% CI: 1.13-1.94). In the meta-analysis, a significant association between the rs273610 polymorphism and lung risk was observed (OR = 1.225, 95% CI: 1.170-1.283 C vs. A; OR = 1.325, 95% CI: 1.285-1.365 for AC+CC vs. AA; OR = 1.324, 95% CI: 1.225-1.431 for CC vs. AA+AC), and further stratifications demonstrated a moderately increased risk for lung in Asian ethnicity studies. Conclusions: Our results and the meta-analysis suggest that the rs2736100 polymorphism may contribute to the risk of lung cancer in the Chinese population and Asian population.

Keywords: Lung cancer, single nucleotide polymorphism (SNP), case-control studies, meta-analysis

Introduction

Lung cancer is one of the most prevalent and deadliest cancers in the world. It is the most common cancer in men and the main cause of male cancer deaths worldwide, and it is the second leading cause of cancer deaths in women worldwide [1-3]. The major socio-environmental risk factor involved in the development of lung cancer is cigarette smoking. Additionally, recent genome-wide association studies (GWAS) have identified a number of chromosomal regions, which may also play a role in lung cancer risk. Of these regions, single-nucleotide polymorphisms (SNPs), especially many investigators have explored *TERT* rs2736100 contributing to inherited susceptibility to lung cancer [4-8].

Since the discovery of rs2736100, several research groups have reported associations between rs2736100 and cancer risk, lung cancer consists of four major histological types: adenocarcinoma (AD), squamous cell carcinoma (SQC), large cell carcinoma (LCC), and small cell carcinoma (SCC) [9, 10]. These observations suggest that inherited risk variants of different lung cancer subtypes may vary. The lack of concordance across many of these studies reflects limitation in the studies, such as ethnic difference, phenotypic heterogeneity, small sample size, and study design. With the

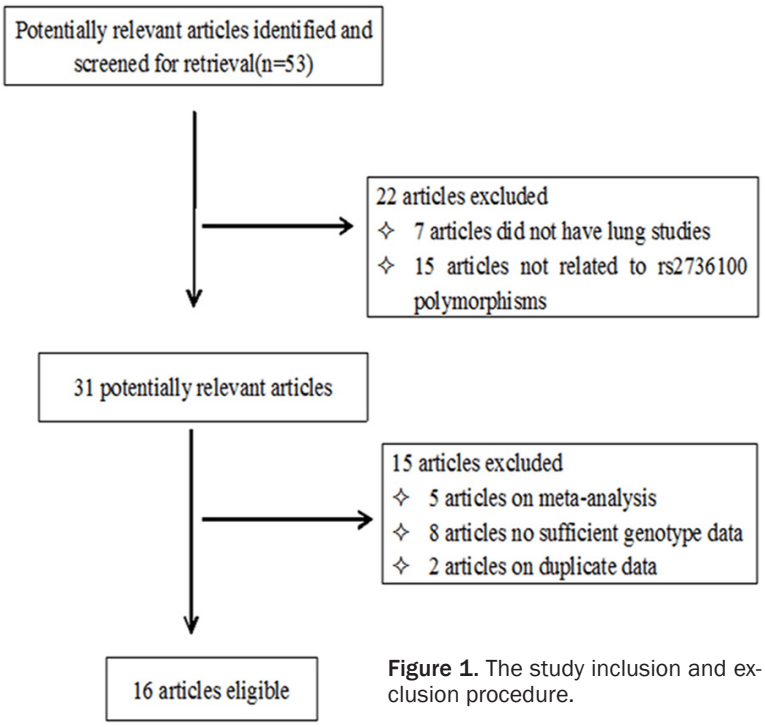

Figure 1. The study inclusion and exclusion procedure.

increased studies in recent years among Asians, and some other ethnic populations, there is a need to reconcile this inconsistency and to clarify the problems in previous studies. We therefore performed a meta-analysis of the published studies to clarify this inconsistency and to establish a comprehensive picture of the relationship between TERT rs2736100 polymorphism and lung cancer.

Materials and methods

Ethics statement

The use of human blood sample and the protocol in this study were strictly conformed to the tenets of the Declaration of Helsinki and were approved by the institutional ethical committees of the People's Hospital of Hainan Province and Northwest University. Written informed consent was obtained from each participant.

Study participants

We designed a case-control study of 554 individuals (male: 415, female: 138; Mean age: 54.87±9.47) with lung cancer (case group) and 693 healthy individuals (male: 392, female: 304; Mean age: 58.17±10.53), which were Han Chinese in Haikou City. The patients were examined and treated at the People's Hospital of Hainan Province. Control subjects were randomly selected from participants, without personal history of malignant disease. Then, a peripheral venous blood sample (5 ml) was obtained from each individual.

SNP genotyping

Genomic DNA was extracted from whole blood using the GoldMag® nanoparticle (GoldMag Co. Ltd., Xi'an City, China, based on the manufacturers' instructions. The quality and quantity of DNA were measured by using NanoDrop 2000. The Sequenom MassARRAY Assay Design 3.0 Software was used to design primers for PCR amplification [11]. Genotyping of SNPs was conducted using single-base primer extension chemistry matrix assisted laser desorption and ionization time of flight mass spectrometry detection by Sequenom MassARRAY RS1000 according to the manufacturer's protocol [12].

Statistical analysis

We used the SPSS 17.0 (SPSS, Chicago, IL) for statistical analysis. All *p*-values presented in this study were two-sided, and we used $P < 0.05$ as the cutoff for statistical significance. Hardy-Weinberg equilibrium (HWE) testing was carried out

for SNPs by the x^2 test in the control group. The allele frequencies within the case and control groups were assessed by the x^2 test [13]. Using unconditional logistic regression, we calculated ORs, and 95% CIs, adjusted for the case-control matching variables (age and gender), to estimate the relative risks of lung cancer associated with the SNP genotypes [14]. SNPstats, a web-based software tool (http://bioinfo.iconcologia.net/SNPstats_web), was used to test the associations between certain SNPs and the risk of lung cancer under five different genetic models [15].

Publication search

We conducted searches of PubMed, EMBASE, and the China National Knowledge Infrastructure (CNKI) using the following search terms:

Table 1. Association between rs2736100, a polymorphism in TERT, and Lung cancer risk under multiple models of inheritance

Model	Genotype	Group = control	Group = case	OR (95% CI)	*P*-value
Allele	T/G	693	554	1.19 (1.02-1.40)	0.029
Codominant	T/T	252 (36.4%)	159 (28.7%)	1	0.017
	G/T	317 (45.7%)	290 (52.4%)	1.47 (1.11-1.96)	
	G/G	124 (17.9%)	105 (18.9%)	1.50 (1.03-2.17)	
Dominant	T/T	252 (36.4%)	159 (28.7%)	1	0.004
	G/T-G/G	441 (63.6%)	395 (71.3%)	1.48 (1.13-1.94)	
Recessive	T/T-G/T	569 (82.1%)	449 (81%)	1	0.310
	G/G	124 (17.9%)	105 (18.9%)	1.19 (0.85-1.65)	
Overdominant	T/T-G/G	376 (54.3%)	264 (47.6%)	1	0.057
	G/T	317 (45.7%)	290 (52.4%)	1.28 (0.99-1.65)	
Log-additive	---	---	---	1.26 (1.05-1.51)	0.013

P < 0.05 indicates statistical significance.

"*TERT*", "telomerase reverse transcriptase", "rs2736100", "lung cancer", and "polymorphism". The search was completed in March of 2015. The articles selected for the subsequent meta-analysis were all published in English in the primary literature, focused on humans, and free of obvious overlap with the subjects of other studies. Two investigators independently selected articles containing information on the association between *TERT* and lung cancer morbidity and checked the corresponding reference lists. All studies providing estimates of odds ratios (ORs) and the corresponding 95% confidence intervals (CIs), or the information required to calculate them, were included in the meta-analysis. Multiple studies were published on the same population or subpopulation, only the most recent or informative study was included in the meta-analysis. A flowchart of the selection process for publications included in the meta-analysis is shown in **Figure 1**.

Inclusion and exclusion criteria

Articles were included in the meta-analysis if they: 1) examined the hypothesis that rs2736100 is associated with lung cancer risk, 2) followed a nested case-control, case-control, or cross-sectional study design, and 3) provided sufficient information on genotype/allele counts between cases and controls to estimate the ORs and corresponding 95% CIs. The exclusion criteria were: 1) non-case-control studies, 2) studies with a control population that included patients with a malignant tumor, and 3) duplicate studies.

Data extraction

Two investigators independently extracted the data from all of the publications that were eligible under the selection criteria. Any disagreement was resolved by discussion. We extracted the following information, when available, from each study: the first author's name, the year of publication, the country the study was performed in, the patients' ethnicities, and the numbers of cases and controls with the AA, AC, and CC rs2736100 genotypes.

Statistical analysis

All statistical analyses were performed using the STATA software (version 11.0; Stata Corporation, College Station, Texas). Two-sided *P* values less than 0.05 were considered statistically significant. For the case and control groups in each study, we calculated the allelic frequencies and assessed them for departure from Hardy-Weinberg equilibrium (HWE) using a Chi-square test [16]. The OR and 95% CI in each case-control study were employed to assess the strength of the associations between rs2736100 polymorphisms and lung cancer risk. The OR and 95% CI in each comparison were assessed in a codominant model, a dominant model, and a recessive model. Subgroup analyses were performed based on the source of the controls and the ethnicity of the study participants. The chi-square test-based Q-statistic was calculated to test for heterogeneity among the studies. If the studies were found to be heterogeneous ($P < 0.05$), then the pooled ORs were analyzed using a random-effects model [17]; otherwise, a fixed-effects model was used [16]. The I^2 statistic was then used to quantitatively estimate heterogeneity, with I^2 less than 25%, between 25% and 75%, and greater than 75% representing low, moderate, and high degrees of inconsistency, respectively [18, 19]. The significance of the combined OR was determined using a Z test ($P < 0.05$ was considered statistically sig-

Table 2. Characteristics of the studies on the association between *TERT* rs2736100 polymorphisms and cancer risk used in the meta-analysis

No	Study	Year	Population	Source of controls	Sample Size (case/control)	Control			Case			*P* value (HWE)
						AA	AC	CC	AA	AC	CC	
1	Wei R [25]	2014	American	HB	686/227	178	328	180	65	125	37	0.25
2	Yin Z [26]	2014	China	HB	524/524	186	255	83	139	273	112	0.78
3	Myneni AA [27]	2013	China	HB	352/447	157	212	78	122	141	89	0.66
4	Lan Q [28]	2013	China	HB	193/197	70	103	24	43	109	41	0.14
5	Ito H [29]	2012	Japanese	HB	716/716	279	329	108	248	340	128	0.50
6	Chen XF [5]	2012	China	PB	196/229	69	112	48	45	101	50	0.84
7	Bae EY [8]	2012	Korean	PB	1094/1100	422	522	156	402	501	191	0.79
8	Shiraishi K [24]	2012	Japan	PB	4648/12364	4,650	5,856	1,858	1,386	2,265	997	0.84
9	Kohno T [30]	2011	Japan	HB	370/320	116	165	39	142	175	53	0.09
10	Hu Z [31]	2011	China	PB	2323/3059	1,061	1,460	538	672	1,196	455	0.36
11	Hu Z [31]	2011	China	PB	2270/2234	751	1,126	357	665	1,121	484	0.06
12	Hu Z [31]	2011	China	PB	3966/4085	1,419	1,947	719	1,056	1,977	933	0.25
13	Truong T [32]	2010	Whites	PB	9126/11812	2,853	5,817	3,142	1,878	4,526	2,722	0.12
14	Truong T [32]	2010	Asian	PB	1686/2101	775	1,014	312	538	836	312	0.51
15	Yoon KA [33]	2010	Korean	PB	1425/3008	1,186	1,403	419	468	695	262	0.90
16	Wang Y [7]	2010	British	PB	239/553	136	259	158	42	115	82	0.15
17	Miki D [6]	2010	Asian	HB	1004/1900	696	890	314	291	498	215	0.30
18	Miki D [6]	2010	Asian	HB	525/7676	2,830	3,664	1,182	157	273	95	0.94
19	Miki D [6]	2010	Asian	HB	557/1458	567	692	199	174	277	106	0.60
20	Hsiung CA [34]	2010	Asian	PB	2308/2321	852	1,132	337	599	1,187	522	0.21
21	Jin G [35]	2009	Chinese	PB	1212/1339	450	658	231	353	627	232	0.72

P < 0.05 indicates statistical significance.

nificant). Additionally, sensitivity analyses were performed after the sequential removal of each study. Cumulative meta-analyses were performed through an assortment of all eligible cancer studies with case sample size. Finally, we produced a Begg's funnel plot and performed an Egger's test, to assess publication bias ($P < 0.05$ was considered to represent a significant publication bias) [17]. The Egger's test is based on the linear regression of the standard normal deviate against the precision of the standard normal deviate and can be used to test the symmetry of the Begg's funnel plot.

Results

Results of the case-control study

Using the x^2 test, we found rs2736100 was associated with increased the risk of lung: rs2736100 in *TERT* (OR = 1.19, 95% CI: 1.02-1.40, $P = 0.029$). Next, we assumed that the minor allele of rs2736100 was a risk factor and analyzed the association between the polymorphism and lung under multiple inheritance models. We found rs2736100 in *TERT* was associated with increased the risk of lung in a dominant model (OR = 1.48, 95% CI: 1.13-1.94, $P = 0.004$) (**Table 1**).

Study characteristics

We identified 16 articles, covering 21 case-control studies including 34961 cases and 58129 controls, which met the inclusion criteria. All of the studies in our meta-analysis focused solely on lung cancer. The characteristics of the studies are listed in **Table 2**. The alleles of interest were in HWE in all of the studies. The 21 studies included 3 studies of Caucasian populations, 18 studies of Asian populations. **Figure 1** shows the study selection procedure.

Main meta-analysis results

After pooling the 34961 cases and 58129 controls in the meta-analysis, we found a significant association between *TERT* rs2736100 polymorphisms and lung cancer risk in different genetic models (OR = 1.225, 95% CI: 1.170-1.283 for the allele model C vs. A; OR = 1.325,

Table 3. Stratified analyses of the association between *TERT* rs2736100 polymorphism and lung cancer risk

Population	Allele model (C VS. A)			Dominant model (AC+CC VS. AA)			Recessive model (CC VS. AA+AC)			Homozygote comparison (CC vs. AA)			Heterozygote comparison (AC vs. AA)		
	OR (95% CI)	*P*	I^2	OR (95% CI)	*P*	I^2	OR (95% CI)	*P*	I^2	OR (95% CI)	*P*	I^2	OR (95% CI)	*P*	I^2
Total	1.225 (1.170-1.283)	*P* < 0.05	75.90%	1.325 (1.285-1.365)	*P* < 0.05	63.30%	1.324 (1.225-1.431)	*P* < 0.05	73.10%	1.511 (1.376-1.659)	*P* < 0.05	75.30%	1.250 (1.210-1.290)	0.009	47.40%
Ethnicity															
Asian	1.251 (1.200-1.304)	*P* < 0.05	61.20%	1.365 (1.310-1.404)	0.001	58.80%	1.381 (1.296-1.471)	0.018	45.80%	1.577 (1.452-1.712)	0.001	58.80%	1.270 (1.224-1.317)	0.010	49.10%
Caucasus	1.056 (0.831-1.342)	0.001	85.60%	1.220 (1.146-1.302)	0.074	61.60%	0.973 (0.648-1.461)	0.001	86.50%	1.099 (0.662-1.823)	0.001	86.20%	1.183 (1.106-1.266)	0.506	0

P: test for heterogeneity; OR: odds ratio; CI: confidence interval.

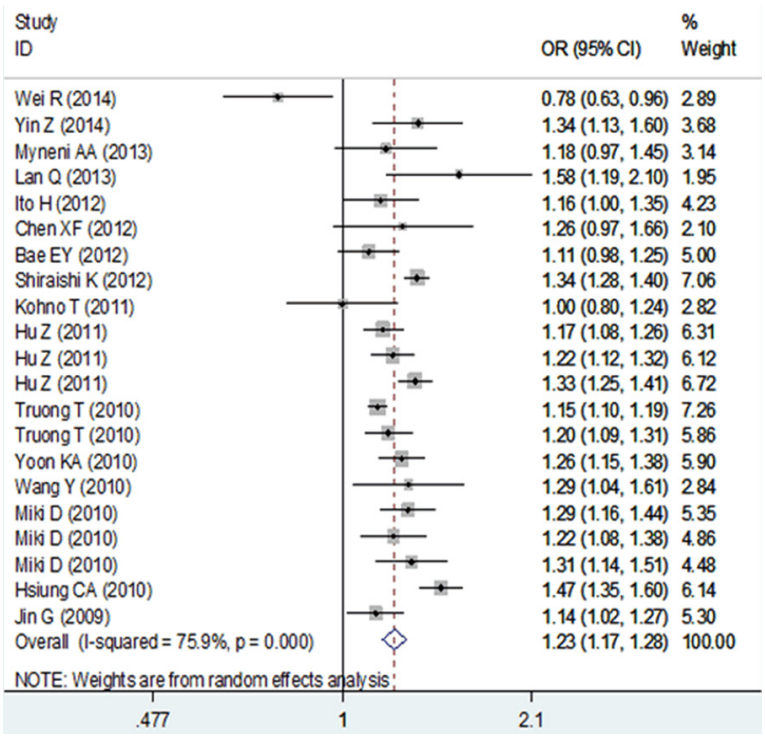

Figure 2. Forest plot of lung risk associated with the rs2736100 polymorphism (C vs. A).

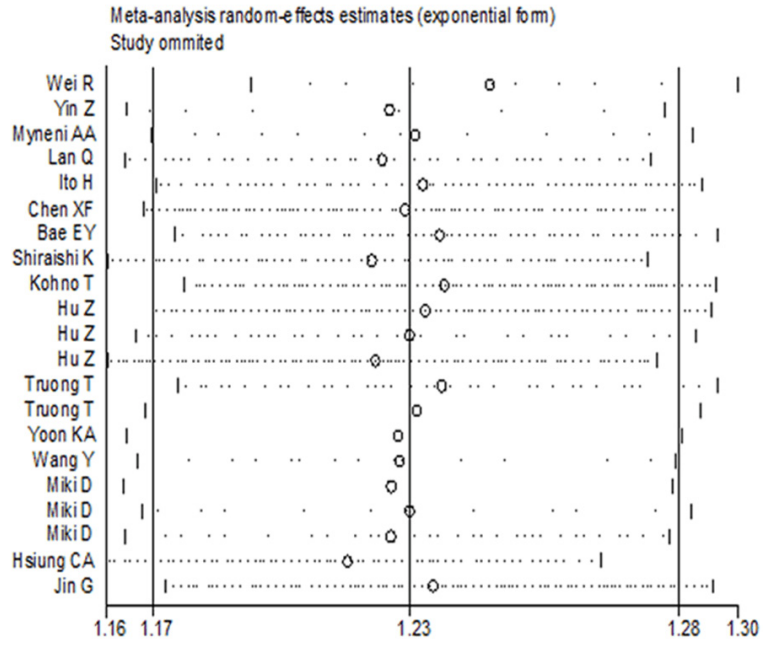

Figure 3. Sensitivity analysis of the summary OR on the association between the rs2736100 polymorphism and cancer risk under the allele model.

95% CI: 1.285-1.365 for the dominant model AC+CC vs. AA; OR = 1.324, 95% CI: 1.225-1.431 for the recessive model CC vs. AA+AC; OR = 1.511, 95% CI: 1.376-1.659 for Homozygote comparison CC vs. AA; and OR = 1.250, 95% CI: 1.210-1.290 for Heterozygote comparison AC vs. AA) (**Table 3**). The forest plots for rs2736100 in the allele model are shown in **Figure 2**.

When stratified by ethnicity, significantly increased risk was observed in the Asian population (OR = 1.251, 95% CI: 1.200-1.304 for C vs. A; OR = 1.356, 95% CI: 1.310-1.404 for AC+CC vs. AA; OR = 1.381, 95% CI: 1.296-1.471 for CC vs. AA+AC; OR = 1.577, 95% CI: 1.452-1.712 for CC vs. AA; and OR = 1.270, 95% CI: 1.224-1.317 for AC vs. AA). The association appeared to be less pronounced among Caucasians (OR = 1.05, 95% CI: 0.831-1.342 for C vs. A; OR = 0.973, 95% CI: 0.648-1.461 for CC vs. AA+AC; OR = 1.099, 95% CI: 0.662-1.823 for CC vs. AA) (**Table 3**).

Test for heterogeneity

Statistically significant heterogeneity was observed in trials using the following analyses with Q statistic tests (Allele model C vs. A: $P < 0.05$, $I^2 = 75.9\%$; dominant model AC+CC vs. AA: $P < 0.05$, $I^2 = 63.3\%$; recessive model CC vs. AA+AC: $P < 0.05$, $I^2 = 73.1\%$; homozygote comparison CC vs. AA: $P < 0.05$, $I^2 = 75.3\%$; heterozygote comparison AC vs. AA: $P = 0.009$, $I^2 = 47.4\%$) (**Table 3**).

Sensitivity analyses

The pooled OR values were not qualitatively changed by the elimination of any individual study, indicating that the final results of the meta-analysis were relatively stable and reliable (**Figure 3**).

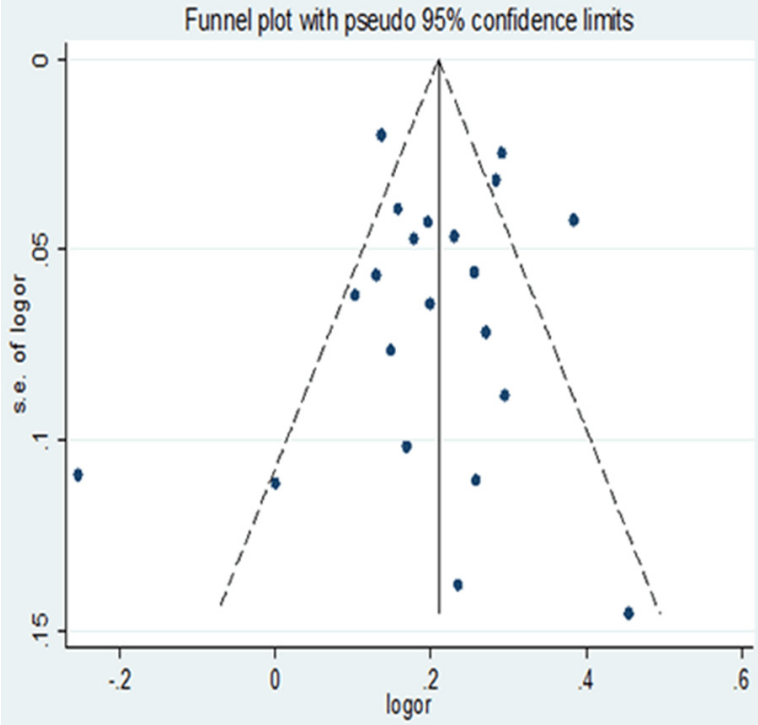

Figure 4. Funnel plot for publication bias (allele model).

Publication bias

The shape of the funnel plot was relatively symmetric and revealed no obvious publication bias (**Figure 4**). The Egger's test revealed no statistically significant asymmetry in the funnel plot for any of the genetic models (P = 0.747).

Discussion

It is well known that SNPs are the most common sources of human genetic variation, and that such variation can contribute to the susceptibility of individuals to cancer [20]. Hence, genetic susceptibility to cancer is studied extensively. Although rs2736100, located in intron 2 of *TERT*, is hypothesized by many researchers to be associated with the risk of lung cancer development, the results of tests of the hypothesis have been conflicting and heterogeneous. We analyzed pooled data from case-control studies to clarify the role of rs2736100 in determining lung cancer susceptibility. In our meta-analysis of 5454 cases and 14035 controls, we found that rs2736100 was significantly associated with an increased risk of developing lung cancer. Furthermore, we found that the increased risk was appeared using each of the genetic models in the subgroup analyses of ethnicity and control source.

TERT gene mapped to the 5p15.33 locus and consists of 16 exons and 15 introns spanning 35 kb of genomic DNA [21]. It encodes the catalytic subunit of telomerase, functions as telomere maintenance and may play a role in the determination of cancer risk. *TERT* gene has been recently identified to associate with multiple cancer types including glioma [22], urinary bladder [23], prostate [24], based on its critical role in the maintenance of telomere, chromosome stability, and ultimately preventing normal cell malignance.

In meta-analysis, heterogeneity evaluation was always conducted in statistical analysis. Thus, several subgroup meta-analyses were performed according to ethnicity and sample size. In the subgroup analysis, ethnicity was responsible for heterogeneity, and the ORs between different genetic models and sample size were consistent. When stratified by ethnicity, significantly increased risk was observed in the Asian population (OR = 1.251). The association appeared to be less pronounced among Caucasians (OR = 1.05), suggesting a similar role of the variant among different ethnicity with different genetic backgrounds.

In interpreting the results, some limitations of this meta-analysis should be addressed. First, as with any meta-analysis of published results, the quality of our meta-analysis depends on that of individual studies. Ideally, we would like to pool individual-level data. However, this is not possible for the present study. Second, our results were based on unadjusted estimates. A more precise analysis could be conducted if all individual raw data were available, which would allow for the adjustment by other covariants including age, drinking status, cigarette consumption, and other lifestyle factors. Third, only published studies were included in this meta-analysis. Therefore, publication bias may have

occurred, even though the use of a statistical test did not show it.

Despite these limitations, our result and the results of our meta-analysis show that the *TERT* rs2736100 polymorphism significantly associated with lung cancer risk. Further functional studies between this polymorphism and cancer risk are warranted.

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Disclosure of conflict of interest

None.

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