Review Article
The association between TERT rs2853677 (A > G) and cancer risk: a meta-analysis

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Abstract: Polymorphisms in the telomerase reverse transcriptase (TERT) gene have been confirmed to be one of the key determinants of the occurrence of cancer. Among them, rs2853677 (A > G) is one of the most widely studied polymorphisms. Yet, the reports are controversial. Thus, we conducted a meta-analysis to assess the association of rs2853677 (A > G) with cancer susceptibility. Potential relevant case-control studies were retrieved from PubMed, Web of Science, the Cochrane Library, and the Chinese National Knowledge Infrastructure. We calculated odds ratios (ORs) with 95% confidence intervals (CIs) to verify the strength of the association in the dominant, recessive, homozygous, heterozygous, and allele models. A total of 11 articles met the eligibility criteria for inclusion in this meta-analysis, involving 7545 patients and 10129 controls. Overall, the results showed that rs2853677 (A > G) is not statistically associated with the risk of cancer under all genetic models but that it is associated with an increased susceptibility to lung cancer in the subgroup analyses. However, a decreased digestive system cancer risk was observed in the recessive model. Based on the analysis of the ethnicity, an increased cancer risk was found in Asians in five genetic models. However, the opposite result was observed in Caucasians. Taken together, our findings demonstrate that rs2853677 (A > G) might be a risk-conferring factor for the occurrence of lung cancer, and for cancer in Asians, but it might be a protective factor for digestive system cancer, and for cancer in Caucasians.

Keywords: Polymorphism, TERT, cancer, risk, meta-analysis

Introduction

In the 21st century, cancer is one of the most noteworthy public health issues worldwide, and there are an estimated 18.1 million new cancer patients and 9.6 million cancer-related deaths each year [1]. Cancer is projected to be the leading cause of death and the biggest obstacle to increasing life expectancy [1]. It is widely believed that cancer is a complicated multifactorial disease that is ascribed to the complicated interactive relation of genetic variants with environmental risk factors [2]. For the past few decades, numerous studies focusing on the full genome association (GWA) of cancer risk have been conducted, and among them, the telomerase reverse transcriptase (TERT) gene is one of the most important genes which had been extensively studied [3-6].

The TERT gene is located in an intronic region of chromosome 5p15.33, encoding the catalytic subunit of telomerase [7, 8]. The core components of ribonucleoprotein telomerase consist of a reverse transcriptase subunit and an individually encoded RNA template, which together with a series of related proteins leads to telomere lengthening and replenishment [9, 10]. Telomeres, located at the ends of eukaryotic chromosomes, are special chromatin structures which are composed of the TTAGGG repeat sequence [11]. They bind to a protein complex called shelterin, and they protect chromosome ends from DNA repair pathways and degradation to maintain chromosomal integrity [10, 11]. Telomerase is normally silenced in somatic cells and expressed in human embryonic stem cells, but it is detected in more than 85% of human cancers [10, 12]. This suggests that TERT transcription control is a key determinant of the occurrence of cancer [10].

Several single nucleotide polymorphisms (SNPs) in TERT have been shown to be related to cancer risk, such as rs2853669, rs2736098, rs2736100, and rs2735940 [13-16]. Mean-

while, another SNP, rs2853677 (A > G), and cancer risk have been widely studied, but the conclusions have been conflicting. Early in 2007, Savage et al. confirmed that this polymorphism was not related to the risk of breast cancer [17]. Also, Dong et al.'s research on hepatocellular carcinoma [18], Duan et al.'s research on gastric cancer [19], Wu et al.'s research on esophageal cancer [20], Martino et al.'s and Wu et al.'s research on renal cell carcinoma obtained similar results [21, 22]. However, several studies (Li et al.'s [23], Ye et al.'s [24], Li et al.'s [7], Li et al.'s [25]) observed that rs2853677 (A > G) is related to lung cancer susceptibility. And Campa et al. also obtained similar results for pancreatic cancer [26]. Thus, we carried out this meta-analysis to acquire a more precise evaluation of the relationship of rs2853677 (A > G) with cancer susceptibility by screening all of the relevant published data.

Methods

Search strategy

PubMed, Web of Science, the Cochrane Library, and the China National Knowledge Infrastructure were searched up through July 25, 2019. The following terms were used: ["polymorphisms" or "polymorphism" or "variants" or "SNP"], ["tumor" or "carcinoma" or "cancer"] and ["telomerase reverse transcriptase" or "TERT"]. Other potential studies were screened from reviews and references of related studies by hand-searching. No language restrictions were added during the process of search and retrieval.

Inclusion and exclusion criteria

In order to acquire eligible studies, the following inclusion criteria were used: (1) provides detailed genotype distributions; (2) the studies investigate the relation of rs2853677 with cancer risks; (3) in a case-control study design. The following exclusion criteria were used: (1) reviews, letters, or editorials; (2) incomplete genotype data; (3) duplicate publications.

Data extraction

Two independent reviewers (Yi Xie and Ying Fu) extracted the data using standardized forms from the eligible studies, including: the author's surname, publication date, country, ethnicity, genotyping method, type of cancer, frequency

of rs2853677 (A > G) in cases and controls respectively, and Hardy-Weinberg equilibrium (HWE) for controls. When any discrepancies appeared, another reviewer (Jia Zhu) participated in the discussions, and we negotiated to resolve the disputes until a consensus was achieved.

Methodological quality assessment

Two reviewers (Yi Xie and Jia Zhu) performed the quality assessments of the eligible articles independently using the Newcastle-Ottawa Scale (NOS) [27, 28]. Three items were assessed in the scale: (1) the selection of subjects: 0-4 points, (2) subject comparability: 0-2 points, and (3) the clinical outcome: 0-3 points [27, 28]. The total possible score was 9 points, and scores of 5 points or more were regarded as good quality [28].
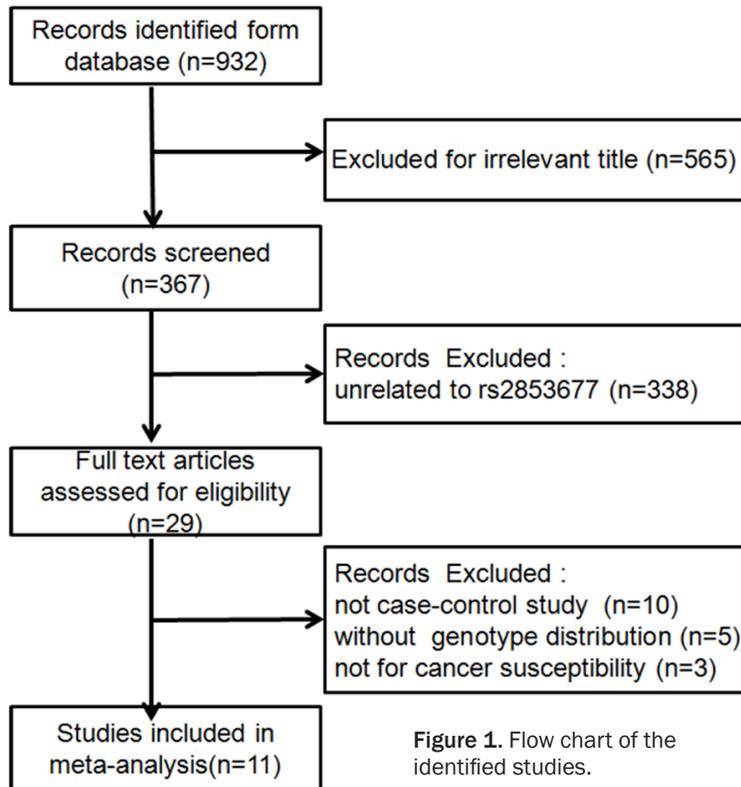
Statistical analysis

In this meta-analysis, all of the data were processed with Stata 11.0 (Stata Corporation, College Station, TX, USA). The relationships between rs2853677 (A > G) and cancer susceptibility were evaluated using pooled odds ratios (ORs) and their 95% confidence intervals (CIs) in five models containing dominant (GA+ GG vs. AA), recessive (GG vs. GA+AA), homozygous (GG vs. AA), heterozygous (GG vs. AA), and allele (G vs. A) models. And the pooled OR was assessed using Z-tests, and a P value <0.05 was recognized as having statistical significance [29]. I-squared (I^2) statistics and Q-tests were applied to analyze the heterogeneity. A random-effects model was performed to calculate the pooled OR, in cases where significant heterogeneity was detected ($I^2 > 50\%$). Otherwise, a fixed-effects model was appropriately performed [30]. Further, we used two methods, meta-regression and subgroup analyses, to analyze the sources of the heterogeneity. In addition, the reliability of the conclusions was evaluated using the sensitivity analysis method. Publication bias was assessed by means of Begger's funnel plots and Egger's linear regression test [31]. In the control groups, chi-square tests were applied to assess HWE when it was not reported [32].

Results

Characteristics of the eligible studies

The flow chart of the data collection is presented in **Figure 1**. Altogether 932 potentially rele-

Figure 1. Flow chart of the identified studies.

ods were categorized as MassARRAY, Taqman, and PCR.

Meta-analysis results

The results of the relationship of rs2853677 (A > G) with the risk of cancer are summarized in **Table 2**. We didn't detect any statistically significant association between rs2853677 (A > G) and overall cancer susceptibility under all the genetic models.

In order to probe the origin of the heterogeneity, a stratified analysis were performed. As for the cancer types, increased lung cancer susceptibility was found under all five models: comparison (dominant model: OR = 1.323, 95% CI: 0.175-1.490, $P_{heterogeneity}$ = 0.915; recessive model: OR = 1.346, 95% CI: 1.147-1.581, $P_{heterogeneity}$ = 0.671; **Figure 2**; homozygous model: OR = 1.537, 95% CI: 1.289-1.832, $P_{heterogeneity}$ = 0.684; heterozygous model: OR = 1.264, 95% CI: 1.115-1.433, $P_{heterogeneity}$ = 0.932; additive model: OR = 1.240, 95% CI: 1.142-1.347, $P_{heterogeneity}$ = 0.826; **Table 2**). However, a decreased digestive system cancer risk was observed in the recessive model (OR = 0.875, 95% CI: 0.771-0.994, $P_{heterogeneity}$ = 0.393; **Table 2**; **Figure 2**). As for renal cell carcinoma and breast cancer, no statistical association was detected in the five genetic models (**Table 2**).

As for ethnicity, a significantly increased cancer risk was detected in the Asian population under the recessive model (OR = 1.213, 95% CI: 1.072-1.372, $P_{heterogeneity}$ = 0.420; **Table 2**; **Figure 3**), homozygous model (OR = 1.273, 95% CI: 1.031-1.572, $P_{heterogeneity}$ = 0.272; **Table 2**), and the additive model (OR = 1.126, 95% CI: 1.012-1.254, $P_{heterogeneity}$ = 0.014; **Table 2**). However, a contrast result was found in Caucasians under the recessive model (OR = 0.897, 95% CI: 0.817-0.985, $P_{heterogeneity}$ = 0.272; **Table 2**; **Figure 3**), and heterozygous model (OR = 0.882, 95% CI: 0.796-0.977, $P_{heterogeneity}$ = 0.272; **Table 2**).

vant articles were collected by searching four databases. After a preliminary screening, 565 studies were excluded for having irrelevant titles. We then read the abstracts in detail and excluded 338 additional studies for having no correlation with rs2853677 (A > G). The full texts of the remaining 29 articles were comprehensively reviewed. Of these, 10 were not case-control studies, 5 lacked any genotype distributions, and 3 did not report on cancer susceptibility. Finally, 7545 cancer patients and 10129 controls in a total of 11 articles were included in the present meta-analysis. The detailed characteristics and the allele and genotype distributions of all studies are shown in **Table 1**. Among these studies, there were 4 studies of lung cancer [7, 23-25], 4 studies of digestive system cancer (pancreatic cancer [26], hepatocellular carcinoma [18], gastric cancer [19], and esophageal cancer [20]), 2 studies of renal cell carcinoma [21, 22], and 1 study of breast cancer [17]. As for ethnicity, 8 studies were conducted on Asians and 3 studies on Caucasians. In addition, there were 5 hospital-based (HB) studies, 3 population-based (PB) studies, and 3 studies with other control sources (mixed and unknown). Furthermore, the genotyping meth-

Table 1. Characteristics of the eligible studies

Author	Year	Country	Ethnicity	Control	Genotyping method	Cancer type	Case				Control				HWE	Score*
							ALL	AA	GA	GG	ALL	AA	GA	GG		
Li Y [25]	2019	China	Asian	HB	TaqMan	Lung cancer	910	300	439	171	954	368	448	138	0.93	6
Li C [7]	2018	China	Asian	HB	TaqMan	Lung cancer	467	143	246	78	526	203	261	62	0.11	5
Wu Y [20]	2017	China	Asian	HB	MassARRAY	Esophageal cancer	381	140	179	62	495	202	222	71	0.44	5
Wu D [22]	2017	China	Asian	PB	MassARRAY	Renal Cell Carcinoma	292	112	132	48	495	202	222	71	0.44	7
Ye [24]	2017	China	Asian	PB	MassARRAY	Lung cancer	554	191	279	84	603	244	277	82	0.81	6
Duan [19]	2016	China	Asian	HB	MassARRAY	Gastric cancer	487	173	217	97	502	144	252	106	0.83	5
Li X [23]	2016	China	Asian	HB	PCR	Lung cancer	391	137	194	60	337	143	157	37	0.53	5
Martino [21]	2016	Austria	Caucasian	Others	PCR	Renal Cell Carcinoma	240	76	104	60	420	130	192	98	0.10	5
Campa [26]	2015	Mixed	Caucasian	Others	TaqMan	Pancreatic cancer	1658	581	804	273	3409	1021	1729	659	0.13	6
Dong [18]	2011	China	Asian	Others	PCR	Hepatocellular carcinoma	183	83	74	26	106	44	45	17	0.27	5
Savage [17]	2007	Poland	Caucasian	PB	TaqMan	Breast cancer	1982	294	950	738	2282	330	1062	890	0.65	6

*The score of the Newcastle-Ottawa Scale.

Table 2. Results of the meta-analysis between rs2853677 and cancer risk

Study	N*	dominant model			recessive model			homozygous model			heterozygous model			additive model		
		OR (95% CI)	P_h #	I² (%)	OR (95% CI)	P_h	I² (%)	OR (95% CI)	P_h	I² (%)	OR (95% CI)	P_h	I² (%)	OR (95% CI)	P_h	I² (%)
Total	11	1.065 (0.917-1.237)	<0.001	76.7	1.084 (0.947-1.240)	0.007	58.5	1.126 (0.918-1.381)	<0.001	76.4	1.045 (0.915-1.194)	0.001	66.3	1.059 (0.954-1.176)	<0.001	79.4
Cancer type																
Lung cancer	4	1.323 (1.175-1.490)	0.915	0.0	1.346 (1.147-1.581)	0.671	0.0	1.537 (1.289-1.832)	0.684	0.0	1.264 (1.115-1.433)	0.932	0.0	1.240 (1.142-1.347)	0.826	0.0
Digestive system cancer	4	0.866 (0.703-1.067)	0.048	62.1	0.875 (0.771-0.994)	0.393	0.0	0.842 (0.654-1.084)	0.109	50.4	0.867 (0.714-1.052)	0.105	51.2	0.915 (0.796-1.051)	0.060	59.5
Renal cell carcinoma	2	1.045 (0.836-1.308)	0.556	0.0	1.131 (0.863-1.483)	0.800	0.0	1.129 (0.832-1.530)	0.624	0.0	1.008 (0.793-1.282)	0.556	0.0	1.062 (0.911-1.239)	0.622	0.0
Breast cancer	1	0.971 (0.819-1.151)	/	/	0.928 (0.820-1.050)	/	/	0.931 (0.774-1.120)	/	/	1.004 (0.839-1.202)	/	/	0.956 (0.876-1.043)	/	/
Ethnicity																
Asian	8	1.152 (0.985-1.347)	0.011	61.7	1.213 (1.072-1.372)	0.420	1.2	1.273 (1.031-1.572)	0.030	54.9	1.119 (0.967-1.296)	0.046	51.1	1.126 (1.012-1.254)	0.014	60.0
Caucasian	3	0.882 (0.755-1.030)	0.132	50.6	0.897 (0.817-0.985)	0.272	23.3	0.856 (0.695-1.054)	0.091	58.2	0.882 (0.796-0.977)	0.187	40.3	0.918 (0.830-1.015)	0.095	57.5
Control source																
HB	5	1.167 (0.930-1.465)	0.003	74.8	1.253 (1.084-1.449)	0.220	30.2	1.335 (0.982-1.814)	0.008	70.8	1.118 (0.905-1.381)	0.016	67.3	1.148 (0.984-1.338)	0.004	73.7
PB	3	1.076 (0.949-1.220)	0.158	45.8	0.967 (0.865-1.081)	0.323	11.5	1.025 (0.879-1.195)	0.178	42.0	1.088 (0.953-1.243)	0.290	19.2	1.054 (0.915-1.213)	0.073	61.8
Others	3	0.814 (0.726-0.912)	0.550	0.0	0.858 (0.746-0.987)	0.375	0.0	0.768 (0.657-0.899)	0.301	16.7	0.831 (0.737-0.938)	0.808	0.0	0.870 (0.805-0.939)	0.331	9.6
Genotyping method																
TaqMan	4	1.072 (0.824-1.395)	<0.001	88.6	1.076 (0.846-1.369)	<0.001	83.4	1.133 (0.780-1.646)	<0.001	90.1	1.052 (0.845-1.310)	0.001	81.5	1.057 (0.879-1.271)	<0.001	90.8
MassARRAY	4	1.057 (0.820-1.364)	0.013	72.2	1.078 (0.906-1.282)	0.725	0.0	1.091 (0.901-1.320)	0.127	47.5	1.039 (0.802-1.345)	0.020	69.5	1.055 (0.906-1.228)	0.047	62.3
PCR	3	1.111 (0.906-1.362)	0.166	44.3	1.175 (0.907-1.522)	0.378	0.0	1.206 (0.904-1.609)	0.166	44.3	1.074 (0.864-1.335)	0.283	20.9	1.104 (0.958-1.272)	0.136	49.8

*Number of studies included; #*p* value for heterogeneity.

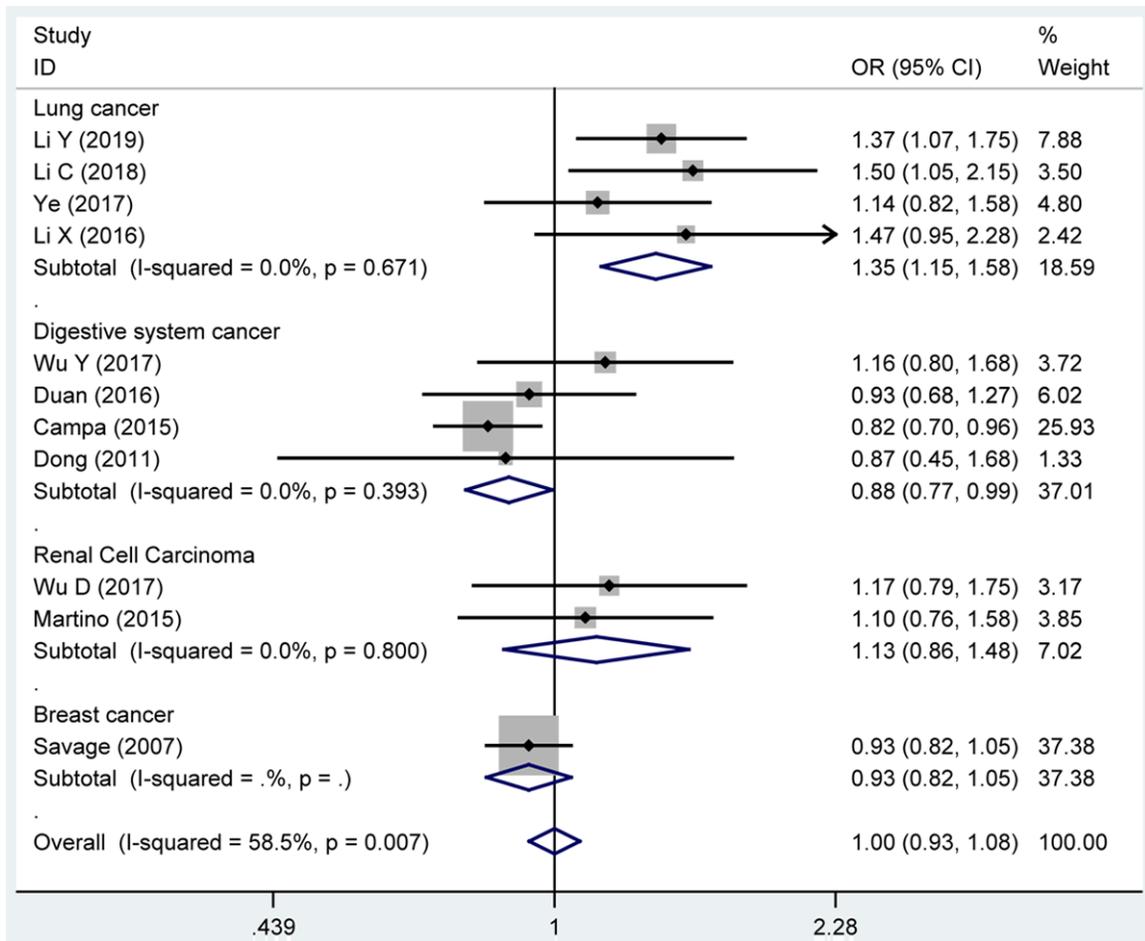## rs2853677 (A > G) and cancer risk

Figure 2. Forest plot of the cancer risk associated with rs2853677 (A > G) by cancer type for the recessive model, using a fixed-effects model.

As for the control source, a significant increase in cancer risk was found in HB under the recessive model (OR = 1.253, 95% CI: 1.084-1.449, $P_{heterogeneity}$ = 0.22; **Table 2**). And, as for the other control sources, a significant decrease in cancer risk was observed in each comparison (**Table 2**).

As for the genotyping method, no significant association was observed (**Table 2**).

Sensitivity analysis

A sensitivity analysis was performed by deleting any individual study in turn. And the estimated pooled OR were not substantially changed, suggesting the robust stability of the current results (**Table 3**).

Heterogeneity

As shown in **Table 2**, the substantial amount of heterogeneity was significant in the overall

comparisons under all five genetic models. After the subgroup analyses, the heterogeneity can be improved, but significant heterogeneity can still be detected. Due to this, a meta-regression analysis was carried out, and the results showed that heterogeneity was caused by the control source and the ethnicity, rather than by year, genotyping methods, or cancer type (**Table 4**).

Publication bias

Symmetrical funnel plots were obtained for all of the models, which means that there was no significant publication bias. We then performed Egger's regression test and detected a positive result in the recessive model (P = 0.044; **Figure 4**). Further research showed that the study reported by Li [7] was the main reason for the publication bias. Excluding the study of Li, no evidence of publication bias was found (p = 0.080 for the recessive model, **Figure 5**), and
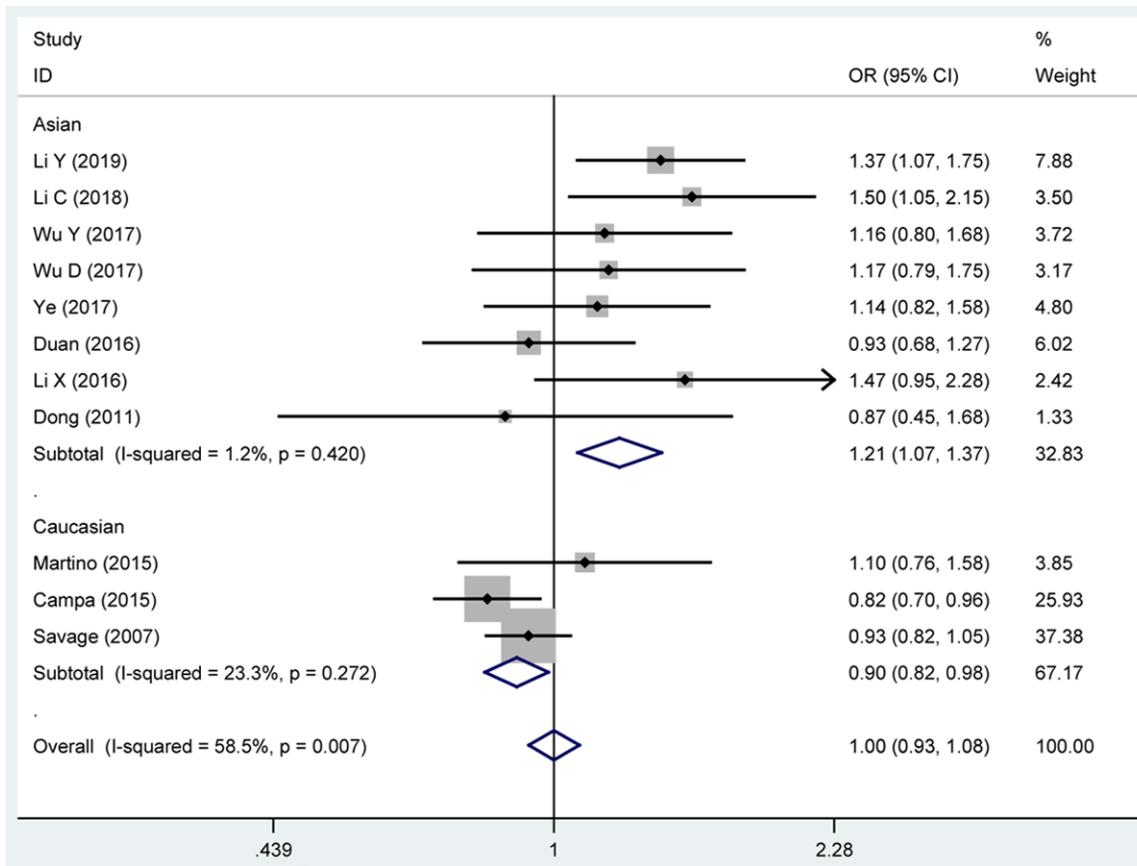
rs2853677 (A > G) and cancer risk

Study ID	OR (95% CI)	% Weight
Asian		
Li Y (2019)	1.37 (1.07, 1.75)	7.88
Li C (2018)	1.50 (1.05, 2.15)	3.50
Wu Y (2017)	1.16 (0.80, 1.68)	3.72
Wu D (2017)	1.17 (0.79, 1.75)	3.17
Ye (2017)	1.14 (0.82, 1.58)	4.80
Duan (2016)	0.93 (0.68, 1.27)	6.02
Li X (2016)	1.47 (0.95, 2.28)	2.42
Dong (2011)	0.87 (0.45, 1.68)	1.33
Subtotal (I-squared = 1.2%, p = 0.420)	1.21 (1.07, 1.37)	32.83
Caucasian		
Martino (2015)	1.10 (0.76, 1.58)	3.85
Campa (2015)	0.82 (0.70, 0.96)	25.93
Savage (2007)	0.93 (0.82, 1.05)	37.38
Subtotal (I-squared = 23.3%, p = 0.272)	0.90 (0.82, 0.98)	67.17
Overall (I-squared = 58.5%, p = 0.007)	1.00 (0.93, 1.08)	100.00

.439   1   2.28

Figure 3. Forest plot of the cancer risk associated with rs2853677 (A > G) by ethnicity for the recessive model, using a fixed-effects model.

Table 3. ORs (95% CI) of the sensitivity analyses

Excluding literature one by one	GA/GG vs. AA OR (95% CI)	GG vs. GA/AA OR (95% CI)	GG vs. AA OR (95% CI)	GA vs. AA OR (95% CI)	G vs. A OR (95% CI)
Total	1.065 (0.917-1.237)	1.084 (0.947-1.240)	1.126 (0.918-1.381)	1.045 (0.915-1.194)	1.059 (0.954-1.176)
Li Y [25]	1.042 (0.891-1.219)	1.040 (0.915-1.183)	1.083 (0.883-1.329)	1.027 (0.891-1.184)	1.040 (0.935-1.156)
Li C [7]	1.034 (0.890-1.202)	1.048 (0.920-1.193)	1.075 (0.880-1.313)	1.019 (0.891-1.166)	1.036 (0.934-1.150)
Wu Y [20]	1.054 (0.898-1.238)	1.080 (0.935-1.247)	1.115 (0.896-1.388)	1.035 (0.898-1.193)	1.052 (0.941-1.177)
Wu D [22]	1.061 (0.903-1.247)	1.079 (0.935-1.245)	1.119 (0.899-1.393)	1.043 (0.904-1.204)	1.056 (0.944-1.181)
Ye [24]	1.043 (0.892-1.221)	1.081 (0.935-1.251)	1.110 (0.891-1.381)	1.022 (0.891-1.172)	1.048 (0.938-1.171)
Duan [19]	1.105 (0.949-1.287)	1.105 (0.953-1.281)	1.173 (0.944-1.459)	1.083 (0.950-1.234)	1.083 (0.970-1.210)
Li X [23]	1.041 (0.892-1.215)	1.060 (0.926-1.213)	1.088 (0.884-1.338)	1.026 (0.894-1.178)	1.041 (0.935-1.158)
Martino [21]	1.074 (0.915-1.261)	1.086 (0.939-1.255)	1.135 (0.910-1.415)	1.055 (0.916-1.216)	1.063 (0.950-1.190)
Campa [26]	1.111 (0.973-1.268)	1.131 (0.990-1.291)	1.193 (0.990-1.437)	1.088 (0.965-1.226)	1.091 (0.990-1.202)
Dong [18]	1.079 (0.923-1.261)	1.094 (0.951-1.259)	1.147 (0.927-1.419)	1.055 (0.918-1.212)	1.070 (0.959-1.193)
Savage [17]	1.077 (0.907-1.279)	1.121 (0.955-1.317)	1.158 (0.908-1.476)	1.051 (0.902-1.226)	1.074 (0.948-1.216)

the pooled OR has no sense of statistics (OR = 1.048, 95% CI: 0.920-1.193).

Discussion

The TERT rs2853677 (A > G) polymorphism, located in the second intronic region of chromosome 5p15.33, is involved in encoding the protein subunit of telomerase, which is responsible for telomere synthesis to maintain telomere length [33, 34]. Telomerase is activated by altering the molecular of TERT promoter, induces the cancer cell escape from the normal senescence or apoptosis, and ultimately pro-

Table 4. Meta-regression analyses

Sub-groups	GA/GG vs. AA		GG vs. GA/AA		GG vs. AA		GA vs. AA		G vs. A	
	t value	p value	t value	p value	t value	p value	t value	p value	t value	p value
Year	1.41	0.193	1.82	0.103	1.68	0.127	1.08	0.309	1.74	0.115
Cancer type	-1.65	0.134	-1.75	0.115	-1.76	0.112	-1.43	0.188	-1.83	0.101
Ethnicity	-1.95	0.083	-3.41	0.008	-2.31	0.046	-1.79	0.106	-2.27	0.049
Control source	-1.94	0.084	-2.83	0.02	-2.35	0.043	-1.77	0.111	-2.23	0.053
Genotyping method	0.02	0.986	0.46	0.659	0.14	0.892	-0.02	0.985	0.15	0.885
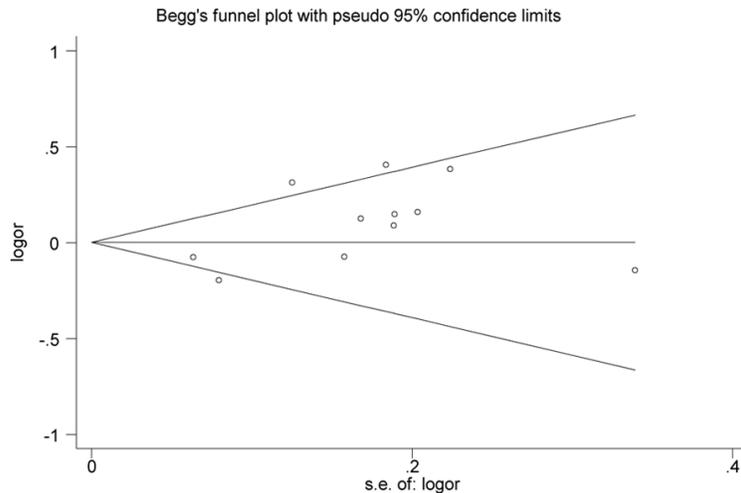
Figure 4. Begg's funnel plot for publication bias (recessive model). Funnel plot of all eligible studies, Egger's test P = 0.044.
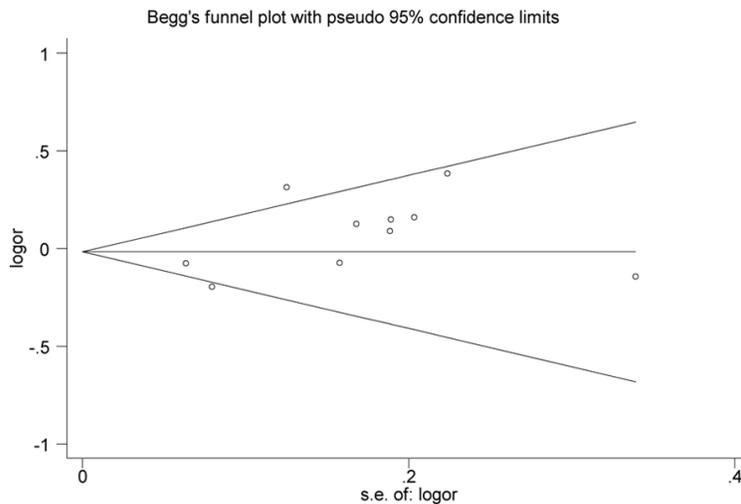
Figure 5. Begg's funnel plot for publication bias (recessive model). Funnel plot of 10 studies (Li C's study was excluded), Egger's test P = 0.080.

is linked to a longer relative telomere length in the population with cancer [33]. Also, many studies have revealed that telomere length is linked to various cancer risks, yet the results remain contradictory [36, 37]. Moreover, Li et al. reveled that the polymorphism increases lung cancer susceptibility by destroying snail1 binding and derepressing TERT expression [23]. Up until now, there has been no relevant meta-analysis of the relationship of rs2853677 (A > G) with cancer susceptibility.

Therefore, we conducted this meta-analysis which encompassed 11 studies with 7545 cases and 10129 controls [7, 17-26]. We demonstrated that there is no significant association of rs2853677 (A > G) with overall cancer susceptibility. Perhaps the explanation is that the occurrence of cancer is the result of the interaction of multiple genes, and the effect of a single gene is limited.

In the sub-groups of the cancer types, the rs2853677 (A > G) significantly increased lung cancer risk in the five genetic models. Our findings are consistent with the previous studies [7, 8, 23-25]. However, lung cancer was not further classified in this meta-analysis. Bhat et al. revealed that rs2853677 (A > G) is linked to a risk of non-small cell lung cancer, especially in the

motes the unlimited proliferation and immortality of cancer cells [8, 33, 35]. Wang et al. suggest that rs2853677 (A > G) with AA genotype

subtype of adenocarcinoma and squamous cell carcinoma, but not the undifferentiated carcinoma subtype [8]. And Li et al.'s also confirmed that it was linked to a risk of adenocarcinoma of the lungs [23]. One possible explanation of this result is that the risk allele G of rs2853677 (A > G), located in the snail1 binding site of the TERT enhancer, increases the susceptibility to adenocarcinoma by destroying the snail1 binding and derepressing the TERT expression [23]. Another potential reason is ethnicity. All four studies about lung cancer used Asian population cohorts, which had an increased risk of developing cancer. As for digestive system cancer, a significantly decreased risk with this polymorphism was observed in the recessive model. And no significant association was detected in renal cell carcinoma or breast cancer. The reason for this discrepancy is likely to be the TERT gene work on the different types of cancer through different mechanisms. And the small number of studies was not robust enough to show any statistical differences, which may be another reason.

In the sub-group of ethnicity, a higher cancer susceptibility was detected in the Asian population under all five genetic models. Nevertheless, a significantly decreased risk was found in the Caucasian population under the recessive and heterozygous models. There may be a lot of factors affecting the discrepancy in ethnicity such as genetic diversity, the different external environment, lifestyle, and different tumorigenesis mechanisms in different populations.

In this meta-analysis, there are still some limitations that should be mentioned. First, the results were derived from unadjusted estimates, without the raw data (e.g., age, sex, family history) and may cause a serious confounding bias. Second, there are publication bias and substantial heterogeneities in this meta-analysis. Third, although all available studies have been summarized, the quantity of studies was too small to yield reliable results, especially in the stratified analysis.

In conclusion, we demonstrate that the TERT rs2853677 (A > G) polymorphism may have no effect on overall cancer susceptibility. But it might be a risk-conferring factor for the development of lung cancer, and for cancer in Asians, and it might be a protective factor for digestive system cancer, and for cancer in Cau-

casians. Our findings revealed that rs2853677 (A > G) may contribute to the occurrence of cancer specific to ethnicity or cancer type. To confirm the association, it is necessary to carry out elaborate and large-scale studies involving the gene-gene gene-environment and gene-gene interaction.

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Disclosure of conflict of interest

None.

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