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Original Article

Telomerase reverse transcriptase (TERT) rs2736100 polymorphism contributes to increased risk of glioma: evidence from a meta-analysis

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Abstract: The rs2736100 polymorphism in telomerase reverse transcriptase (TERT) gene has been implicated as a risk factor for glioma in previous epidemiological studies. However, the data from these studies were inconclusive for the precise association of TERT rs2736100 with glioma. Here we employed a meta-analysis aiming to evaluate such association. The PubMed, Embase, and Web of Science were systematically searched for eligible studies. The odds ratio (OR) and 95% confidence interval (95% CI) was estimated to assess the strength of this association in fixed or random effects models. A total of 5 studies in 16 articles including 7337 cases and 12062 controls were eventually collected. Our analyses showed that there was a significant association between TERT rs2736100 polymorphism and glioma in all five genetic models(homozygous model-GG vs. TT: OR=1.64, 95% CI=1.50~1.79, $P_{heterogeneity}$=0.253, I^2=17.5%; heterozygous model-GT vs. TT: OR=1.38, 95% CI=1.27~1.49, $P_{heterogeneity}$=0.235, I^2=19.1%; dominant model-GG+GT vs. TT: OR=1.46, 95% CI=1.36~1.57, $P_{heterogeneity}$=0.167, I^2=25.5%; recessive model-GG vs. GT+TT: OR=1.31, 95% CI=1.22~1.40, $P_{heterogeneity}$=0.796, I^2=0.0%; additive model-G allele vs. T allele: OR=1.27, 95% CI=1.21~1.32, $P_{heterogeneity}$=0.481, I^2=0.0%). Further subgroup analysis on control source and ethnicity, we found similar association in population-based, hospital-based and Caucasians groups. The result of heterogeneity test were in acceptable range (P<0.05 and I^2<50%). Egger's tests and Begg's funnel plot did not show any publication bias. Sensitivity analysis confirmed that our results were reliable. Taken together, our meta-analysis suggested that TERT rs2736100 polymorphism may greatly increase glioma risk.

Keywords: Glioma, telomerase reverse transcriptase, polymorphism, meta-analysis

Introductions

Glioma is the most common type of primary brain tumors in adults and is associated with high morbidity and mortality rates. Although clinical intervention, such as surgery, radiation and temozolomide (TMZ) chemotherapy, are effective, its prognosis still remains poor. Patients with glioblastoma multiforme (GBM), the most common histological subtype of high-grade gliomas (HGGs), only have median survival of 14 months from diagnosis [1]. Thus, diagnosis at the early stage becomes one of most important steps for treatment. Like many other types of cancers, the etiology of glioma remains largely unclear. In addition to high-doses of ionizing radiation exposure as an identified contributor [2-4], recent studies show that genetic susceptibility may play a significant role in the carcinogenesis of glioma. Telomerase reverse transcriptase (TERT), a telomerase catalytic subunit that maintains telomeres and cell immortalization, has been an important factor in glioma grade and prognosis [5, 6]. The TERT gene locates at chromosome 5p15.33. The rs2736100 polymorphism maps to intron 2 of the TERT gene. It was first published by Shete et al. [7] and indicated that TERT rs2736100 polymorphism may contribute to an increased risk of glioma simultaneously. After that, a number of studies have reported the role of this SNP and glioma risk [8-11], however, the results are inconclusive. In order to gain better evaluation of association between TERT rs2736100 polymorphism and risk of glioma, a meta-analysis including five genetic models on all eligible case-control studies was performed.

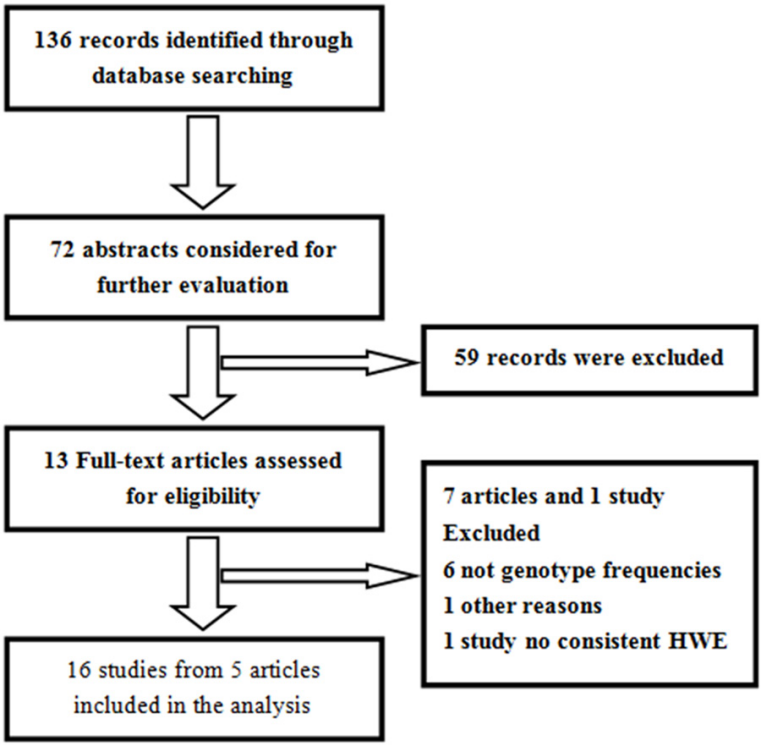

Figure 1. Flow diagram of the selection of studies and specific reasons for exclusion from this meta-analysis.

Methods

Publication search and inclusion criteria

We carried out a comprehensive literature search in electronic databases including PubMed, Embase, and Web of Science (the last search up to October 1, 2014). The search key words were limited as the following: "TERT OR rs2736100" AND "variant OR polymorphism OR mutation" AND "glioma". References of targeted publications on this topic were also reviewed. Literature selection had to meet the following criteria: (a) studies should concern the association of TERT rs2736100 polymorphism with glioma risk; (b) all of them must use case-control design (case-control or cohort); (c) sufficient data for estimating odds ratios (ORs) with 95% confidence interval (CI); (d) genotype distribution of control population must consistent with Hardy-Weinberg equilibrium (HWE). Articles that are not related to glioma research or lacking usable data of genotype frequencies were excluded.

Data extraction

Data were extracted by two authors independently. If encountered the contradictions, the agreement was reached by discussion; if agreement not reached, the third author was consulted to resolve the debate. The following data were collected from each study: the name of first author, publication year, ethnicity (Caucasian or Asian), source of controls (population or hospital-based controls), number of cases and controls with the TT, TG and GG genotypes, and the *P*-value of HWE.

Statistical analysis

The result of HWE test by chi-square test was applied to determine if observed distributions of genotypes in controls was significant when $P<0.05$. Studies that deviated from HWE were removed. The OR and 95% CI was used to measure the strength of the associations between the TERT rs2736100 polymorphisms and glioma risk in five genetic models including homozygous model (GG versus TT), heterozygous model (TG versus TT), dominant model (GG+TG versus TT), recessive model (GG versus TG+TT) and and additive model (G allele vs T allele). Subgroup analyses were performed based on the source of controls and ethnicity. Heterogeneity refers to the variation between different studies. It was checked by a Q-test. If the *P*-value of the Q-test was <0.05, the pooled ORs were analyzed using the random effects model (the DerSimonian and Laird method) [12]. Otherwise, if the Q-test revealed a *P*-value of more than 0.05, the fixed effects model was selected (the Mantel-Haenszel method) [13]. I^2 (I^2=100%×(Q-df)/Q) statistic was calculated to quantify the proportion of the total variation across studies due to heterogeneity. I^2 values of 25%, 50% and 75% were used as evidence of low, moderate, and high heterogeneity, respectively [14]. The statistical significance of the summary OR was determined by Z-test ($P<0.05$ was considered statistically significant). Sensitivity analyses were performed to assess the stability of the pooled results by omitting each individual study. The Begg's funnel plot and Egger's linear regression test were used to ana-

Table 1. Main characteristics of all studies included in the meta-analysis

					case			control			
auther	year	source	ethnicity	reference	TT	TG	GG	TT	TG	GG	*P* (HWE)
Shete (French)	2009	PB	Caucasian	[7]	225	686	441	383	807	371	0.18
Shete (German)	2009	PB	Caucasian	[7]	91	240	160	133	269	163	0.28
Shete (Sweden)	2009	PB	Caucasian	[7]	120	326	177	212	367	185	0.29
Shete (USA)	2009	HB	Caucasian	[7]	230	645	372	546	1103	584	0.58
Schoemarker (Denmark)	2010	PB	Caucasian	[8]	22	58	39	31	74	41	0.82
Schoemarker (Finland)	2010	PB	Caucasian	[8]	8	56	33	23	53	19	0.25
Schoemarker (Sweden)	2010	PB	Caucasian	[8]	29	107	57	101	171	90	0.30
Schoemarker (UK-Nourth)	2010	PB	Caucasian	[8]	59	198	118	143	317	175	0.98
Schoemarker (UK-Sourth)	2010	PB	Caucasian	[8]	53	105	74	86	202	107	0.61
Chen	2011	HB	Asian	[9]	244	515	194	334	542	160	0.13
Safaeian (NCL)	2013	HB	Caucasian	[10]	70	152	100	96	181	107	0.27
Safaeian (NIOSH)	2013	PB	Caucasian	[10]	59	151	90	127	280	131	0.34
Safaeian (AHS)	2013	PB	Caucasian	[10]	2	13	3	9	20	6	0.37
Safaeian (ATBS)	2013	PB	Caucasian	[10]	11	18	8	339	626	304	0.65
Safaeian (PLCO)	2013	PB	Caucasian	[10]	22	68	43	218	404	232	0.12
Stefano	2013	HB	Caucasian	[11]	143	424	278	274	594	322	0.99

Note: PB population-based, HB hospital-based, HWE *P*-values for Hardy-Weinberg equilibrium for each study's control group.

lyze the publication bias statistically ($P<0.05$ was considered a significant publication bias) [15]. All statistical analyses were performed using the STATA software, version 12 (Stata Corporation, College Station, TX, USA), and all tests were two-sided.

Results

Literature search and study characteristics

A total of 16 eligible studies involving 7337glioma cases and 12062 controls were collected for meta-analysis. **Figure 1** shows the selection procedure. These 17 studies included 16 studies of Caucasians populations and 1 study of Asians population, 12 studies of population-based control and 4 studies of hospital-based control. The distributions of genotypes in the control groups were in accordance with HWE in all studies (all P>0.05). All characteristics of selected studies are summarized in **Table 1**.

Quantitative synthesis and subgroup analyses

All the main results of our meta-analysis for TERT rs2376100 polymorphism were listed in **Table 2**. A significantly increased glioma risk was revealed in five genetic models (homozygous model-GG vs. TT: OR=1.64, 95% CI= 1.50~1.79, $P_{heterogeneity}$=0.253, I^2=17.5%; heterozygous model-GT vs. TT: OR=1.38, 95% CI= 1.27~1.49, $P_{heterogeneity}$=0.235, I^2=19.1%; dominant model-GG+GT vs. TT: OR=1.46, 95% CI= 1.36~1.57, $P_{heterogeneity}$=0.167, I^2=25.5%; recessive model-GG vs. GT+TT: OR=1.31, 95% CI= 1.22~1.40, $P_{heterogeneity}$=0.796, I^2=0.0%; additive model-G allele vs. T allele: OR=1.27, 95% CI= 1.21~1.32, $P_{heterogeneity}$=0.481, I^2=0.0%).

When stratified by the source of controls, we found studies with population-based controls showed increased glioma risk in all genetic models (homozygous model-GG vs. TT: OR= 1.71, 95% CI=1.51~1.92, $P_{heterogeneity}$=0.150, I^2= 30.3%; heterozygous model-GT vs. TT: OR= 1.42, 95% CI=1.27~1.58, $P_{heterogeneity}$=0.102, I^2= 19.1%; dominant model-GG+GT vs. TT: OR= 1.51, 95% CI=1.37~1.67, $P_{heterogeneity}$=0.075, I^2=39.8%; recessive model-GG vs. GT+TT: OR= 1.34, 95% CI=1.22~1.47, $P_{heterogeneity}$=0.705, I^2= 0.0%; additive model-G allele vs. T allele: OR=1.29, 95% CI=1.22~1.37, $P_{heterogeneity}$=0.332, I^2=11.5%). Simultaneously, We could get the same conclusion in hospital-based subgroups (homozygous model-GG vs. TT: OR=1.56, 95% CI=1.37~1.77, $P_{heterogeneity}$=0.712, I^2=0.0%; heterozygous model-GT vs. TT: OR=1.33, 95% CI=1.19~1.49, $P_{heterogeneity}$=0.832, I^2=0.0%; dominant model-GG+GT vs. TT: OR=1.40, 95% CI=1.26~1.56, $P_{heterogeneity}$=0.804, I^2=0.0%; recessive model-GG vs. GT+TT: OR=1.27, 95% CI=1.14~1.40, $P_{heterogeneity}$=0.654, I^2=0.0%; additive model-G allele vs. T allele: OR=1.23, 95%

Table 2. Stratified analyses of the rs2736100 polymorphism on glioma risk

Contrast models	Subgroup	Odds ratio		Heterogeneity		
		OR	[96% CI]	I^2	P_H	Model
GG vs. TT	overall	1.64	[1.50, 1.79]	17.5%	0.253	Fixed
(homozygous model)	PB	1.71	[1.51, 1.92]	30.3%	0.150	Fixed
	HB	1.56	[1.37, 1.77]	0.0%	0.712	Fixed
	Caucasian	1.63	[1.49, 1.79]	22.9%	0.199	Fixed
	Asian	1.66	[1.27, 2.17]	-	-	Fixed
GT vs. TT	overall	1.38	[1.27, 1.49]	19.1%	0.235	Fixed
(heterozygous model)	PB	1.42	[1.27, 1.58]	36.0%	0.102	Fixed
	HB	1.33	[1.19, 1.49]	0.0%	0.832	Fixed
	Caucasian	1.39	[1.28, 1.51]	23.2%	0.197	Fixed
	Asian	1.30	[1.06, 1.60]	-	-	Fixed
GG+GT vs. TT	overall	1.46	[1.36, 1.57]	25.5%	0.167	Fixed
(dominant model)	PB	1.51	[1.37, 1.67]	39.8%	0.075	Fixed
	HB	1.40	[1.26, 1.56]	0.0%	0.804	Fixed
	Caucasian	1.47	[1.36, 1.59]	29.4%	0.135	Fixed
	Asian	1.38	[1.14, 1.68]	-	-	Fixed
GG vs. GT+TT	overall	1.31	[1.22, 1.40]	0.0%	0.796	Fixed
(recessive model)	PB	1.34	[1.22, 1.47]	0.0%	0.705	Fixed
	HB	1.27	[1.14, 1.40]	0.0%	0.654	Fixed
	Caucasian	1.30	[1.21, 1.39]	0.0%	0.763	Fixed
	Asian	1.40	[1.11, 1.76]	-	-	Fixed
G allele vs. T allele	overall	1.27	[1.21, 1.32]	0.0%	0.481	Fixed
(Additive model)	PB	1.29	[1.22, 1.37]	11.5%	0.332	Fixed
	HB	1.23	[1.16, 1.31]	0.0%	0.791	Fixed
	Caucasian	1.27	[1.21, 1.32]	4.1%	0.407	Fixed
	Asian	1.26	[1.11, 1.43]	-	-	Fixed

CI=1.16~1.31, $P_{heterogeneity}$=0.791, I^2=0.0%). **Figure 2** shows the overall meta-analysis of TERT rs2736100 polymorphism and the risk of glioma stratified by source of controls in homozygous comparison model.

Additionally, in subgroup analysis by ethnicity, we suggested a positive correlation between the TERT rs2376100 polymorphism and glioma risk especially in Caucasians. The result of all genetic models support this view again (homozygous model-GG vs. TT: OR=1.63, 95% CI=1.49~1.79, $P_{heterogeneity}$=0.199, I^2=22.9%; heterozygous model-GT vs. TT: OR=1.39, 95% CI=1.28~1.51, $P_{heterogeneity}$=0.197, I^2=23.2%; dominant model-GG+GT vs. TT: OR=1.47, 95% CI=1.36~1.59, $P_{heterogeneity}$=0.135, I^2=29.4%; recessive model-GG vs. GT+TT: OR=1.30, 95% CI=1.21~1.39, $P_{heterogeneity}$=0.763, I^2=0.0%; additive model-G allele vs. T allele: OR=1.27, 95% CI=1.21~1.32, $P_{heterogeneity}$=0.407, I^2=4.1%). The Asian group only has one case-control study, so the pooled result did not provide any particular significance. **Figure 3** shows the association of TERT rs2736100 polymorphism and the glioma susceptibility stratified by sethnicity in homozygous comparison model.

Test of heterogeneity

There was no substantial heterogeneity among the association analysis between the TERT rs2736100 polymorphism and glioma risk in all genetic models and subgroups. **Table 2** described all results of heterogeneity.

Sensitivity analysis

Sensitivity analysis is a method used to evaluate the results of the stability. By omitting each individual study on the pooled OR, we could not examine any significant difference. This implies that our meta-analysis were sound and reliable (**Figure 4**).

Assessment of bias

Begg's funnel plots and Egger's linear regression test were used to assess the potential publication bias. For the homozygous model, the shape of the Begg's funnel plot seemed symmetrical (**Figure 5**) and T=-0.18, P=0.861, the 95% confidence interval (-1.50, 1.27) included zero, indicating no publication bias. Additionally, in other genetic models, the results still not show any evidence of publication bias.

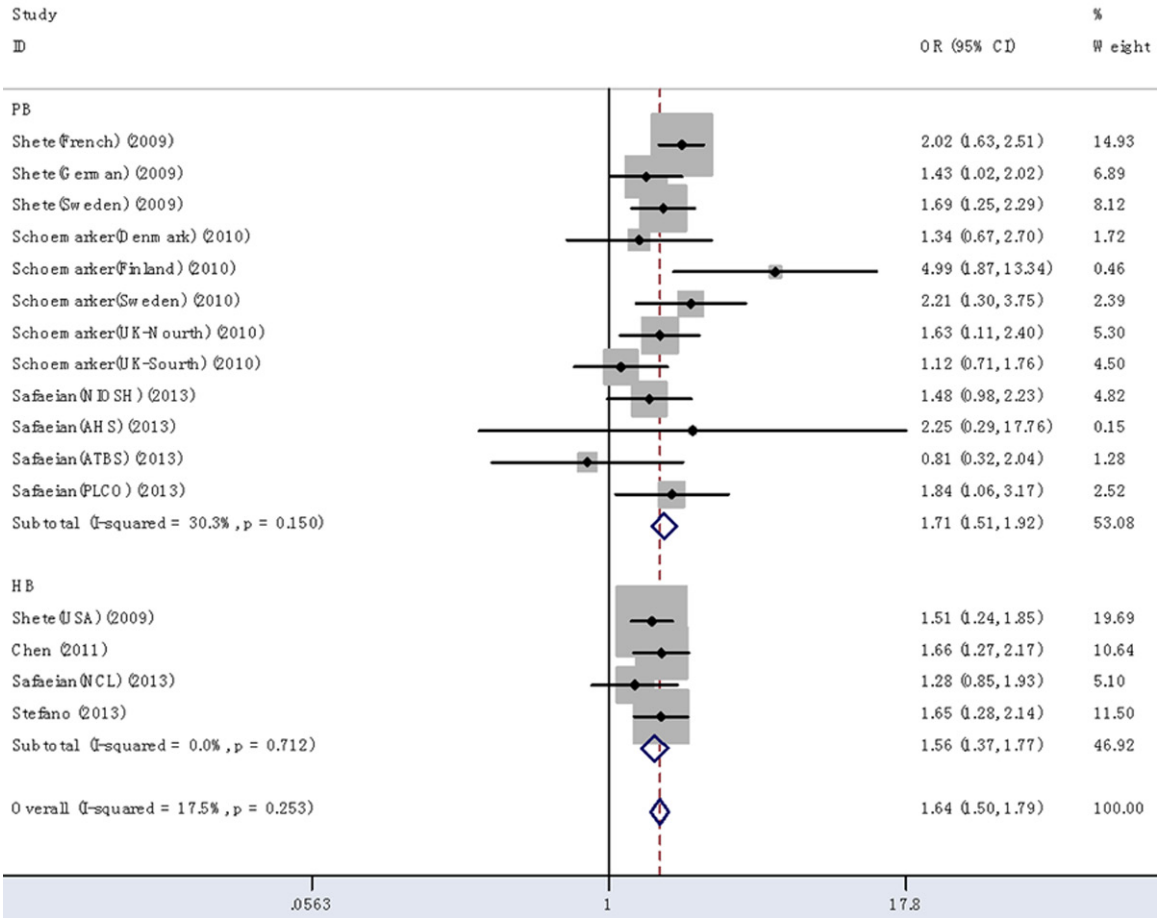

Figure 2. Forest plots for the association between TERT rs2736100 polymorphism and the risk of glioma stratified by source of controls using homozygous comparison model (GG vs. TT).

Discussion

Telomere is a DNA region with repetitive sequences at each end of eukaryotic chromosomes, which protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes [16]. Telomere shortening can lead to replicative senescence and blocks cell division. Moreover, shortened telomeres impair immune function that might also increase cancer susceptibility [17]. Telomerase is a ribonucleoprotein (RNP) which adding DNA sequence repeats "TTAGGG" repeats to the 3' end of DNA strands in the telomere regions [18, 19]. Telomerase activity is inhibited in normal human tissue, however, it becomes active in tumors. It suggests that telomerase may be involved in malignant transformation of tumor [19-21]. TERT is the catalytic component of telomerase and acts as the key determinant of telomerase activity [16]. It was recognized that overexpression of the TERT gene can possibly lead to unlimited cell division and carcinogenesis in many types of cancers. [22] Some scholars even found that TERT expression also correlates with glioma grade and prognosis [5, 23]. Single nucleotide polymorphisms (SNPs), the most common type of sequence variations in the human genome, caused human phenotypic differences [24], may contribute to an individual's cancer risk [25]. The TERT gene, located on chromosome 5p15.33, exhibits various genetic polymorphisms associated with cancers [26]. Among them, rs2376100 is one of the representatives. The research about the relationship between TERT rs2376100 polymorphism and glioma was a lot. By using a meta-analysis approach, we can get the most reliable conclusions.

The combined results based on 16 independent studies (from five articles) strongly sug-

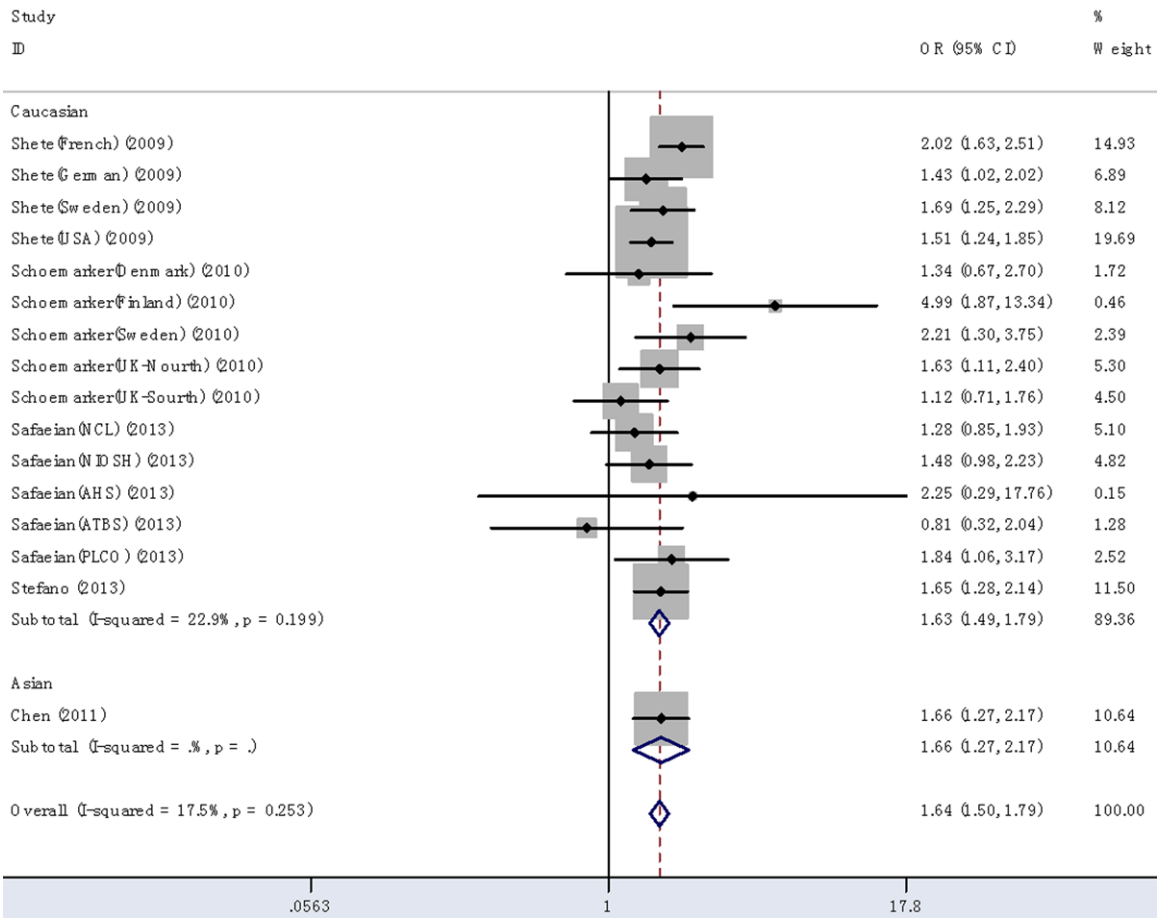

Figure 3. Forest plot for the association between TERT rs2736100 polymorphism and the risk of glioma stratified by ethnicity using homozygous comparison model (GG vs. TT).

gested that the rs2736100 polymorphism was associated with glioma risk in all genetic models. Subgroup analyses based on source of controls and ethnicity were applied to find potential sources of between-study heterogeneity. As for ethnicity, rs2736100 polymorphism was associated with increased risk of glioma among Caucasians in all genetic models. For Asian population, this meta-analysis only included one eligible study, so the conclusion for Asian population was insufficient. Thus, more studies in Asian-population are needed. In the stratified analysis by source of controls, significantly increased risk was observed for hospital-based and population-based subgroups in all genetic models. When analyzed the result of population-based subgroups, we found that low heterogeneity ($25\%<I^2<50\%$) were exist in homozygous model ($I^2=30.3\%$), heterozygous model ($I^2=36.0\%$) and dominant model ($I^2=39.8\%$). However, these low heterogeneity could not affect the reliability of pooled result.

The origins of heterogeneity may consist of many factors, besides differences in the observational methods, alternatively, it could be attributed to genetic backgrounds, living environment and patients' characteristics and so on [27]. In the course of this meta-analysis, a article of Wang et al. [28] get relevant research for association between TERT rs2736100 polymorphism and reproductive factors in famale glioma patients. After adding supplement data of this article, we found moderate heterogeneity in homozygous models and dominant models. We conscientiously analyzed the causes of heterogeneity on the research of Wang et al., put forward the following several possible factors: (a) Unlike other studies, the research object of the Wang et al. only in White females. The interaction of race and gender genotype may be the first main reason for this difference. (b) Wang's research data compose by two case-control studies from National Cancer Institute

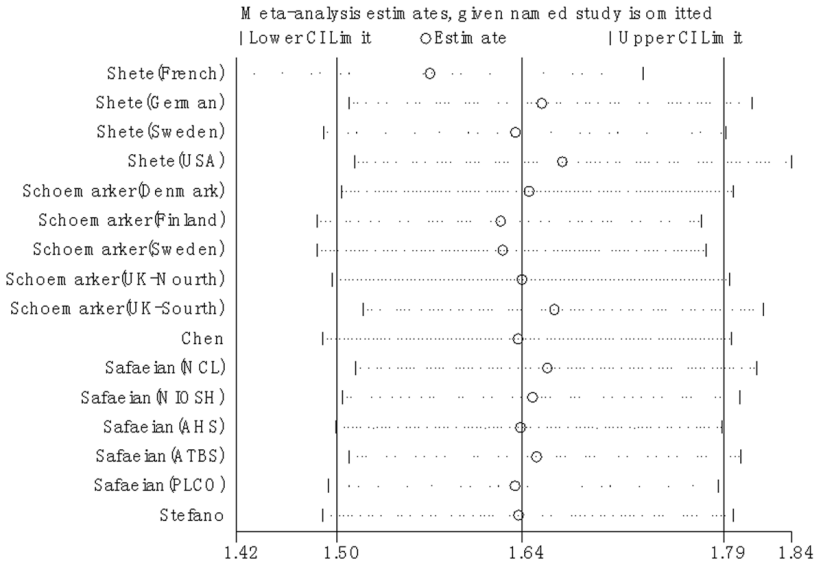

Figure 4. Sensitivity analysis of the summary OR coefficients on the association between TERT rs2736100 polymorphism and glioma risk.

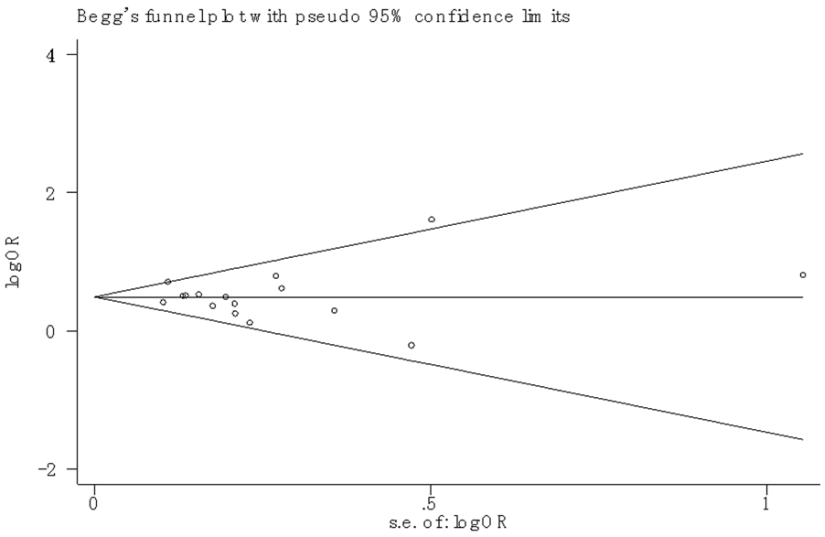

Figure 5. Begg's funnel plots to determine publication bias in homozygous comparison model (GG vs. TT).

(NCL; 1994-1998) and National Institute for Occupational Safety and Health (NIOSH; 1995-1997), as well as 2 cohort studies from Agricultural Health Study (AHS; 1993-1997) and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO; 1993-2001). By failing to provide appropriate data for each study, we can only be analyzed as a whole. The effect of different observational methods may be the second reason for heterogeneity. (c) Wang's research data mixed by population and hospital based controls. Thus, special mixed sources of controls may be the third factor for heterogeneity. By discussions with other authors of our meta-analysis, finally, we decided to exclude this article. Through this case, proving once again that the generation of heterogeneity is multifactorial. Simultaneously, these warned us that more detailed stratification research should be attention in the future.

The strength of our meta-analysis are summarized as follows. Above all, by means of well-designed search and selection method, we could sought to find publications as precision as possible. Subsequently, Egger's tests and Begg's funnel plot did not show any publication bias. At last, sensitive analysis did not change the results. Thus, we concluded that the results of our meta analysis were sound and reliable. Nevertheless, some potential limitations of our meta-analysis are still inevitable. First, glioma is known as a multifactor disease, more accurate OR should be corrected for age, sex, allergy, autoimmune, viral infection [29], gene-gene and gene-environment interactions that may affect cancer risk. Second, the number of researched studies was insufficient especially for analyses of ethnicity subtype. Owing to only one study for Asian population, the result of Asian subgroup was not convincing enough. Third, due to limited conditions, we just collected the studies which were indexed by the selected databases. However, some relevant published studies or unpublished studies

which may have biased our results were missed.

In conclusion, our meta-analysis suggested that TERT rs2736100 polymorphism may greatly enhance glioma susceptibility. Moreover, more studies should be explore the effects of rs2736100 polymorphisms in Asian population in the future.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

TERT, Telomerase reverse transcriptase; OR, Odds ratio; CI, Confidence interval; HWE, Hardy-Weinberg equilibrium; PB, Population-based; HB, Hospital-based.

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