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Review Article

Association of TERT rs2736109 polymorphism with cancer risk: a meta-analysis

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Abstract: Several studies have demonstrated associations between the TERT rs2736109 polymorphism and susceptibility to cancer development. However, there are conflicting results. To derive a more precise estimation of the association, a meta-analysis was conducted. Eligible studies were identified by search of electronic databases. Overall and subgroup analyses were performed. Odds ratio (OR) and 95% confidence interval (CI) were applied to assess the associations between TERT rs2736109 polymorphism and cancer risk. This polymorphism was significantly associated with overall cancer risk (GG vs AA: OR = 1.49, 95% CI = 1.05-2.10; GA vs AA: OR = 1.12, 95% CI = 0.94-1.34; Dominant model: OR = 1.25, 95% CI = 0.98-1.58; Recessive model: OR = 1.33, 95% CI = 1.06-1.67). Moreover, in subgroup analyses by cancer types, the stronger significant association between the TERT rs2736109 polymorphism and gastric cancer risk was found. In the stratified analyses by race and quality scores, significant association was not found in Caucasians and high-quality studies. In summary, this meta-analysis suggests that TERT rs2736109 polymorphism may contribute to genetic susceptibility to cancer, especially to gastric cancer. Nevertheless, additional well-designed studies focusing on different ethnicity and cancer types are needed to provide a more exact and comprehensive conclusion.

Keywords: TERT, meta-analysis, cancer, polymorphism, susceptibility

Introduction

Cancer is a serious public health problem, with over 12 million new cases diagnosed worldwide each year [1]. Cancer is a multi-factorial disease, and the pathogenesis of these cancers is extremely complex. A variety of risk factors have been identified to contribute to cancer, including alcohol consumption, cigarette smoking, obesity, family history of cancer, and diet [2]. In recent years, researchers have focused on the molecular mechanism and new tumor biomarkers associated with tumor screening, diagnosis, prognosis, and evaluation of therapeutic effect [3, 4]. However, the exact mechanism of cancers is still unclear.

Telomeres are composed of short tandem repeats of the TTAGGG sequence. Telomeres present on the ends of chromosomes, which protect against coding sequence erosion and consequent DNA damage repair, leading to genome instability, chromosomal fusions, and rearrangements [5]. In most normal human somatic tissues, telomerase activity is undetectable, but it can be detected in almost all types of human cancers, suggesting the importance of telomerase in the tumorigenesis [6].

Recently, the relation of genetic polymorphisms to the risk of cancer has been widely studied. One of the genes critical for maintaining the telomerase function is the telomerase reverse transcriptase (TERT), which is located in chromosome 5p15.33 and encodes the catalytic subunit of telomerase. Overexpression of TERT and activation of telomerase was found in a variety of malignancies, which are related to the hallmarks of cancer including proliferation, anti-apoptosis, angiogenesis, and metastasis [7]. Previous meta-analysis suggested that TERT polymorphisms (rs401681 and rs2736098) are associated with cancer risk [8, 9].

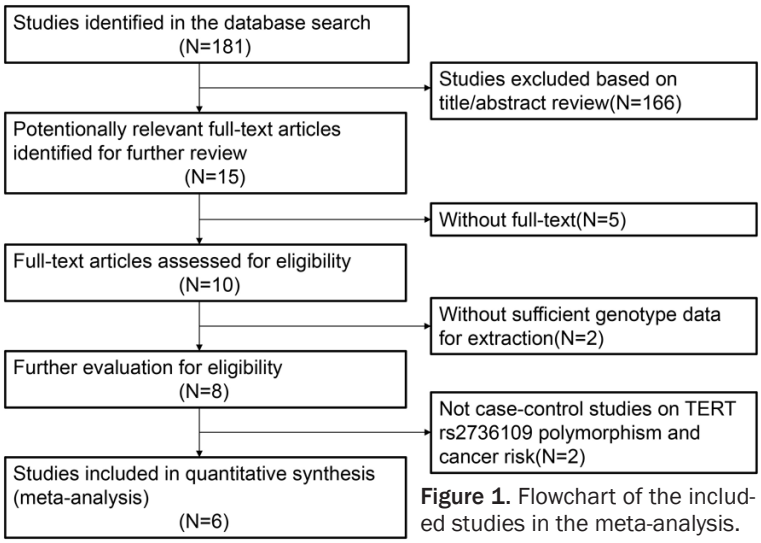

Figure 1. Flowchart of the included studies in the meta-analysis.

To date, numerous studies have been performed to examine the relationship between the TERT rs2736109 polymorphism and risk of cancer. However, the available evidence reported to date is weak, due to sparse data or inconsistent research. In the present study, we investigated whether the TERT rs2736109 polymorphism is associated with cancer risk by performing this meta-analysis.

Materials and methods

Study identification and selection

Computer searches of PubMed and EMBASE were performed by two authors independently using the key words: "rs2736109", "cancer", "TERT", "single nucleotide polymorphism" and "genetic polymorphism". All eligible articles were retrieved and their references were retrieved simultaneously to find other related articles. Inclusion criteria were defined as follows: (1) case-control studies evaluating the association of TERT rs2736109 polymorphism with cancer risk; (2) research based on unrelated individuals; (3) sufficient published data to estimate an odds ratio (OR) with 95% confidence interval (CI). Reviews, reports, comments, and letters were excluded. For repeated studies, the study with the largest sample was included in this meta-analysis.

Data extraction

The following information from each study was extracted independently by two reviewers: first author, publication year, area, ethnicity, genotyping method, numbers of cases and controls, genotype frequency of cases and controls, HWE test and the type of cancer.

Quality evaluation

The authors used the methodological quality of each included article using the Newcastle-Ottawa quality assessment scale (NOS) [10]. An ultimate score of 6 stars or more was regarded as high-quality study.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was assessed via Fisher's exact test. The strength of the associations between this polymorphism and susceptibility to cancer was estimated by OR and 95% CI under a homozygote comparison (AA vs GG), a heterozygote comparison (AG vs GG), a dominant model (AA+AG vs GG) and a recessive mode (AA vs AG+GG) between groups. The Q-test was performed to evaluate heterogeneity. If heterogeneity was found among the studies (P>0.10), the pooled OR was estimated the pooled OR by the fixed-effects model. Otherwise, the random-effects model was used. Accuracy and stability of the analytic results were analyzed by sensitivity analysis. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset on the pooled ORs. Publication bias was examined by plotting Egger's funnel plot (P<0.05 was considered representative of statistically significant publication bias). All analyses were performed by STATA12.0 (STATA College Station, TX, USA).

Results

Study characteristics

Based on the search strategy, different databases were checked and a total of 181 articles were identified. Detailed search steps are described in **Figure 1**. In the next stage all of the abstracts were scanned, and 166 articles were excluded (based on review of abstracts, titles and keywords) and only 15 studies remained for further evaluation. In a further

Table 1. Characteristics of the included studies for meta-analysis

Author	Year	Area	Race	Cases/Controls	Genotyping method	Genotypes for cases			Genotypes for controls			HWE test	Cancer site
						AA	AG	GG	AA	AG	GG		
Savage	2007	Polish	Caucasian	1984/2277	Autopure LS DNA Purification System	664	963	357	702	1132	443	0.73	Breast cancer
Shen	2010	USA	Mixed	983/1054	TaqMan assays	125	450	408	194	550	310	0.07	Breast cancer
Beesley	2011	Australia	Caucasian	3950/6433	TaqMan assays	647	1895	450	1108	3156	2169	0.49	Breast cancer
Zheng	2012	USA	Mixed	1509/1383	Illumina GoldenGate Genotyping platform	20	310	1179	23	308	1052	0.93	Breast cancer
Bayram	2016	Turkey	Caucasian	104/209	PCR–RFLP	27	41	36	62	50	50	0.32	Gastric cancer
Zhang	2017	China	Asian	360/728	PCR–RFLP	180	136	44	473	219	50	0.11	Gastric cancer

HWE: Hardy-Weinberg equilibrium.

Table 2. Results of quality assessment by NOS for case-control

Study	Selection				Comparability	Exposure			Score
	Adequate definition of case	Representativeness of case	Selection of controls	Definition of controls	Control for important factors[a]	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Savage	-	☆	☆	☆	☆	-	☆	☆	6
Shen	-	☆	☆	☆	☆	-	☆	☆	6
Beesley	-	☆	-	-	-	-	☆	☆	3
Zheng	-	☆	-	☆	☆	-	☆	☆	5
Bayram	-	☆	-	☆	☆☆	-	☆	☆	6
Zhang	-	☆	☆	☆	☆☆	-	☆	☆	7

[a]A maximum of 2 stars can be allotted in this category, one for Age, the other for other controlled factors (gender, BMI, WHR and so on).

Table 3. Summary ORs and 95% CI of the TERT rs2736109 polymorphism with cancer risk

Variables	N[a]	GG vs AA		GA vs AA		Dominant model		Recessive model	
		OR (95% CI)	Model	OR (95% CI)	Model	OR (95% CI)	Model	OR (95% CI)	Model
Total	6	1.49 (1.05-2.10)	R	1.12 (0.94-1.34)	R	1.25 (0.98-1.58)	R	1.33 (1.06-1.67)	R
Ethnicity									
Caucasian	3	1.05 (0.81-1.36)	R	0.97 (0.89-1.06)	F	0.99 (0.85-1.16)	R	1.07 (0.87-1.30)	R
Mixed	3	2.10 (1.37-3.20)	R	1.40 (1.17-1.68)	F	1.65 (1.39-1.95)	F	1.65 (1.09-2.48)	R
Cancer type									
Breast cancer	4	1.23 (0.88-1.74)	R	1.03 (0.89-1.18)	R	1.12 (0.90-1.40)	R	1.17 (0.94-1.45)	R
Gastric cancer	2	2.38 (1.24-4.55)	R	1.34 (0.82-2.20)	R	1.59 (1.06-2.39)	R	2.17 (1.54-3.05)	F
Scores									
High-quality	4	1.71 (0.90-3.27)	R	1.17 (0.85-1.60)	R	1.32 (0.87-2.00)	R	1.58 (0.98-2.53)	R
Low-quality	2	1.12 (1.00-1.25)	F	1.03 (0.92-1.15)	R	1.07 (0.96-1.19)	F	1.10 (1.02-1.18)	F

[a]Number of comparisons.

assessment, 5 articles were excluded because they had not full-text, 2 articles were excluded because they without sufficient genotype data for extraction, 2 articles were excluded because they were not case-control studies. Eventually, 6 non-duplicated studies met the predefined inclusion criteria including 20974 cases [11-16]. The main characteristics of the studies are presented in **Table 1**. The genotype distributions in the control population were consistent with HWE for TERT rs2736109 polymorphism.

Quality assessment

According to the NOS for case-control studies, the results of the quality assessment are shown in **Table 2**. The overall scores of the included studies ranged from three to seven stars. Of these studies, 4 were defined as high-quality.

Quantitative synthesis and analysis

As shown in **Table 3**, significant association was found between the TERT rs2736109 polymorphism and cancer risk in the overall population (**Figure 2**, GG vs AA: OR = 1.49, 95% CI = 1.05-2.10; GA vs AA: OR = 1.12, 95% CI = 0.94-1.34; the dominant model: OR = 1.25, 95% CI = 0.98-1.58; the recessive model: OR = 1.33, 95% CI = 1.06-1.67). In subgroup analysis by ethnicity, significant association was found between TERT rs2736109 polymorphism and cancer risk in mixed population (GG vs AA: OR = 2.10, 95% CI = 1.37-3.20; GA vs AA: OR = 1.40, 95% CI = 1.17-1.68; the dominant model: OR = 1.65, 95% CI = 1.39-1.95; the recessive model: OR = 1.65, 95% CI = 1.09-2.48), but not in Caucasian population. In the subgroup analysis stratified by NOS scores, significant association was found in low-quality studies (GG vs AA: OR = 1.12, 95% CI = 1.00-1.25; GA vs AA: OR = 1.03, 95% CI = 0.92-1.15; the dominant model: OR = 1.07, 95% CI = 0.96-1.19; the recessive model: OR = 1.10, 95% CI = 1.02-1.18), but not in high-quality studies. In the subgroup analysis stratified by cancer type, significant association was found in gastric cancer (**Figure 3**, GG vs AA: OR = 2.38, 95% CI = 1.24-4.55; GA vs AA: OR = 1.34, 95% CI = 0.82-2.20; the dominant model: OR = 1.59, 95% CI = 1.06-2.39; the recessive

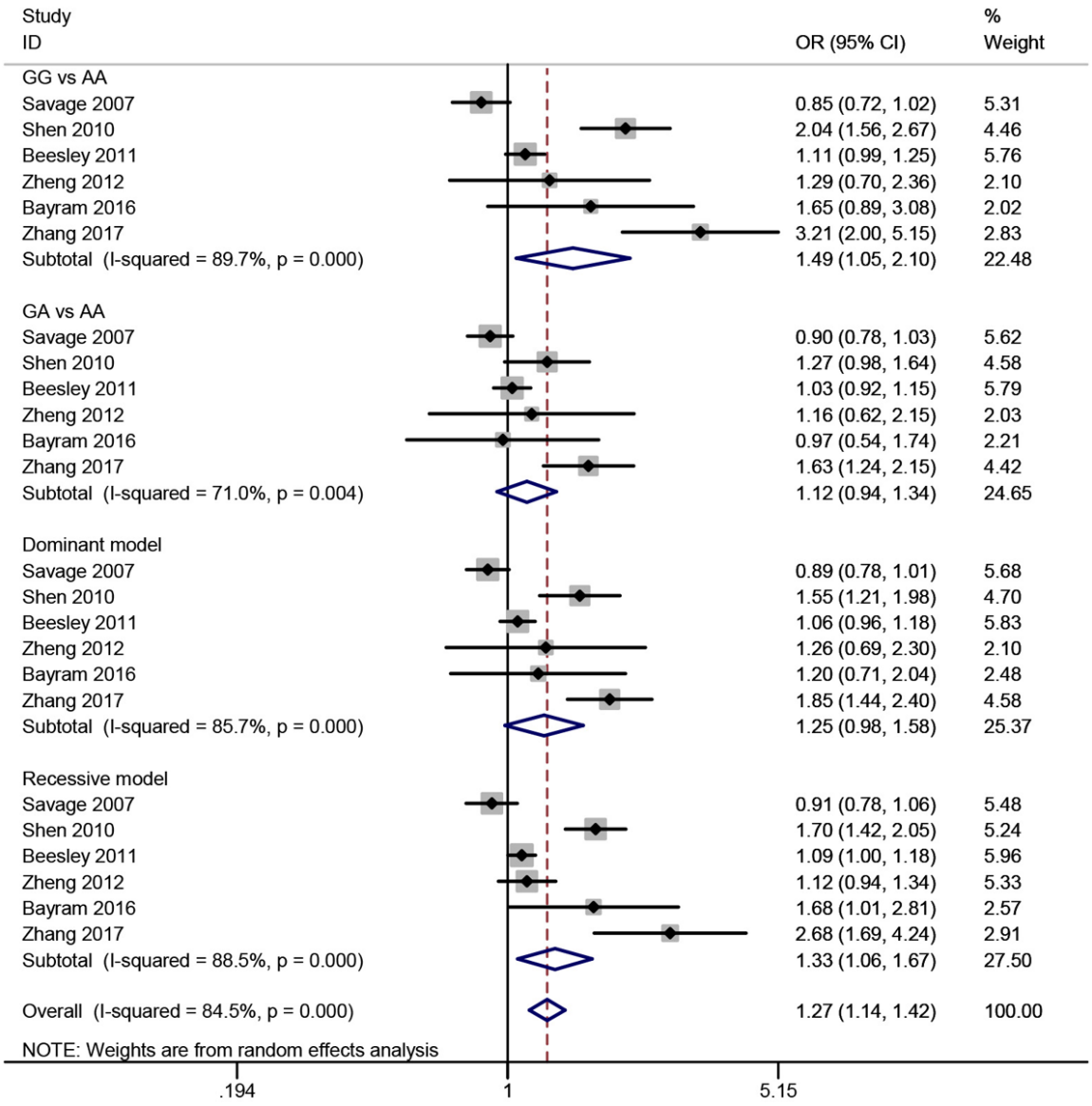

Figure 2. Forest plot for meta-analysis of the association between the TERT rs2736109 polymorphism and cancer risk.

model: OR = 2.17, 95% CI = 1.54-3.05), but not in breast cancer.

Sensitivity analysis

The statistical significance of the overall results did not change when any single study was omitted, indicating the result of our study was statistically significant (**Figure 4**).

Publication bias

Egger's funnel plot was performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (**Figure 5**).

Discussion

The pathogenesis of the development and progression of cancer is not yet clear at present. Accumulated evidence suggests that it is a complex polygenic disorder for which genetic factors play an important role in etiology of the disease [17]. Telomeres are highly conserved functional structures that protect the ends of chromosomes, shorten with each cellular division, and signal cellular senescence [18]. A

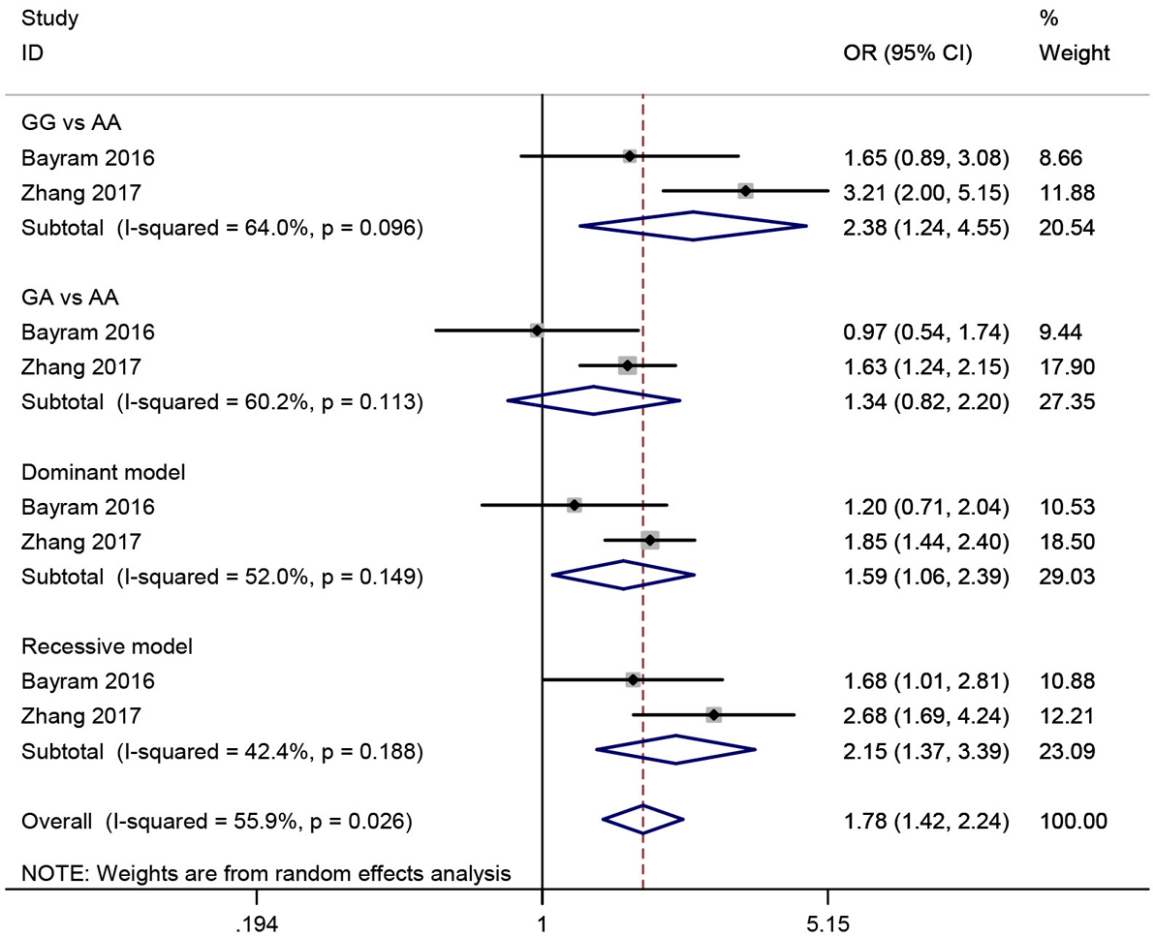

Figure 3. Forest plot for meta-analysis of the association between the TERT rs2736109 polymorphism and gastric cancer risk.

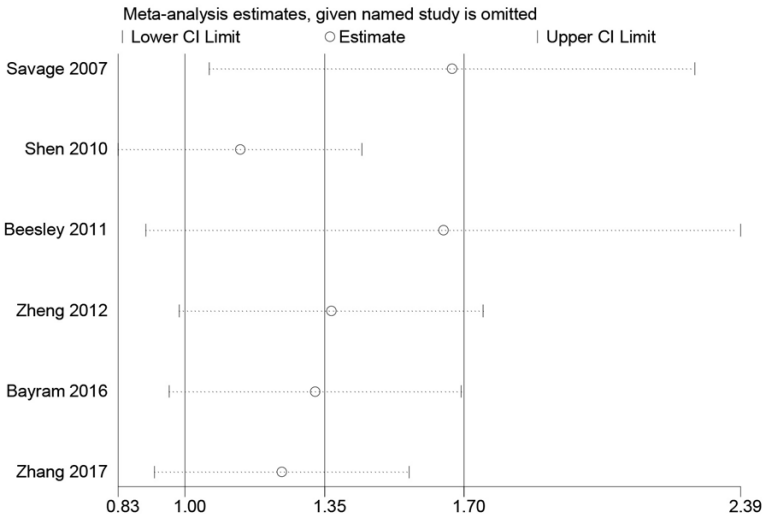

Figure 4. One-way sensitivity analysis of the pooled odds ratios and 95% confidence interval for TERT rs2736109 polymorphism, omitting each dataset in the meta-analysis.

recent study has revealed that telomerase regulation and telomere dysfunction, due to loss of telomeric sequence or telomere structure, have key roles in tissue regeneration during tumor initiation and progression [19]. Mounting evidence clearly shows that polymorphisms in the TERT gene are involved in the development of human cancer [20].

The relation of rs2736109 in the TERT gene to cancer risk has been investigated with either a relatively small or larger sample in different populations [21]. However, due to

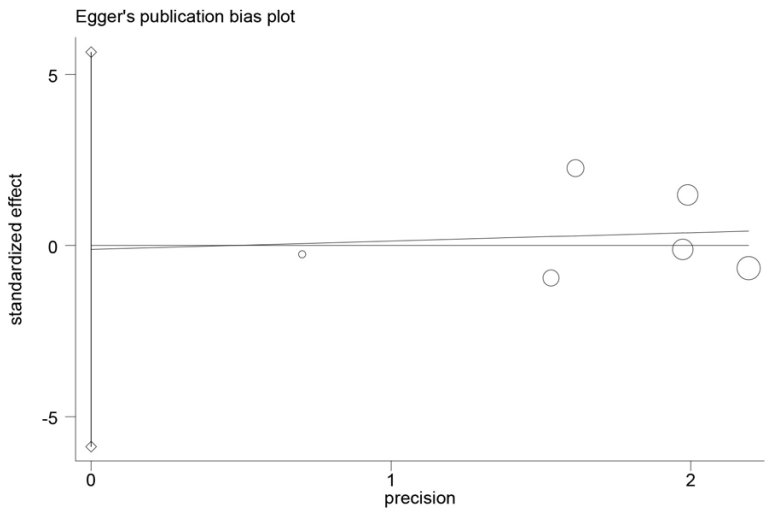

Figure 5. Egger's funnel plot analysis to detect potential publication bias.

There are several limitations in this meta-analysis. First, the number of studies and the number of samples contained in the meta-analysis were relatively small. Second, the meta-analysis was based on unadjusted estimates. A more precise analysis should be performed if more detailed individual data are available, which will allow for an adjusted estimate. Third, only published articles were included in our meta-analysis. Therefore, publication bias may have occurred, even though the use of a statistical test did not show it.

the difference in the number of participants and genetic background, the evidence provided by each study is insufficient to draw a convincing conclusion. Such an inconclusive connection led us to perform a comprehensive analysis consisting of published data to date, with an intention to clarify whether or not this cancer risk was related to rs2736109.

To date, only 6 studies have investigated the association between the TERT rs2736109 polymorphism and cancer susceptibility. Our findings suggest that this polymorphism is associated with increased cancer risk when all eligible studies were pooled into the meta-analysis. In stratified analyses by races, our findings indicated that TERT rs2736109 polymorphism had a significant association with cancer risk in the mixed population, but not in Caucasians. These differences may be induced by different genetic backgrounds and environmental factors. When stratifying by cancer type, this meta-analysis detect significant association between TERT rs2736109 polymorphism in the gastric cancer, but not in the breast cancer. Discrepancies between studies could possibly be due to a different role of this polymorphism in different cell types or tissues. When stratifying by NOS scores, the significant association between TERT rs2736109 polymorphism and cancer risk became null in the high-quality studies, suggests that the results should be interpreted with caution, further large and well-designed articles are needed to confirm these conclusions.

In conclusion, we found that the TERT rs2736109 polymorphism increase the risk of cancer, especially in the gastric cancer. Further studies are needed to verify these findings and explain the inconsistent results in different ethnicities and cancer types.

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