RESEARCH ARTICLE

TERT rs2736098 Polymorphism and Cancer Risk: Results of a Meta-analysis

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Abstract

Objective: Several studies have demonstrated associations between the TERT rs2736098 single nucleotide polymorphisms (SNPs) and susceptibility to cancer development. However, there are conflicting results. A systematic meta-analysis was therefore performed to establish the cancer risk associated with the polymorphism. Methods: In this meta-analysis, a total of 6 case-control studies, including 5,567 cases and 6,191 controls, were included. Crude odds ratios with 95% confidence intervals were used to assess the strength of associations in several genetic models. Results: Our results showed no association reaching the level of statistical significance for overall risk. Interestingly, in the stratified analyses (subdivided by ethnicity), significantly increased risks were found in the Asian subgroup which indicates the TERT rs2736098 polymorphism may have controversial involvement in cancer susceptibility. Conclusions: Overall, this meta-analysis indicates that the TERT rs2736098 polymorphism may have little involvement in cancer susceptibility.

Keywords: Telomerase reverse transcriptase gene (TERT) - polymorphism - cancer - meta-analysis

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Introduction

Cancer is the end of a complex disease that results from intricate interactions, including multi-factorial, multi-genetic and multi-stage processes (Pharoah et al., 2004). Evidence suggests that genetic factors play a crucial role in cancer development. In recent years, several common low-penetrance genes, such as the telomerase reverse transcriptase gene (TERT), have been identified as potential cancer susceptibility genes. Many studies have determined that there is an association between the TERT polymorphism and cancer risk. Thus, a systematic statistical analysis is needed.

Telomeres are specialized structures at the end of eukaryotic chromosomes that protect chromosomes from degradation, end-to-end fusion and rearrangement (Lantuejoul et al., 2007). The TERT complex is a ribonucleoprotein polymerase that maintains telomere ends. It consists of a protein component with reverse transcriptase activity and an RNA component that serves as a template for the telomere repeat. The rs2736098 polymorphism is located on exon 2 of the TERT gene. It has been reported that the TERT rs2736098 (G>A) polymorphism is associated with susceptibility to multiple types of cancer (Rafnar et al., 2009). Variants in the TERT gene have been associated with basal cell carcinoma (Rafnar et al., 2009), lung cancer (McKay et al., 2008; Wang et al., 2008; Broderick et al., 2009; Jin et al., 2009; Landi et al., 2009; Rafnar et al., 2009), glioma (Shete et al., 2009; Chen et al., 2011), bladder cancer (Gago-Dominguez et al., 2011) and other tumors (Rafnar et al., 2009).

A study of individuals of Asian ancestry found that lung cancer, which is the leading cause of death in the world (Jemal et al., 2011) has a significant association with the TERT rs2736098 polymorphism (Jin et al.,2009). It has been reported that TERT rs2736098 may cause an increased risk of glioma in the Chinese population (Chen et al., 2011). Glioma, which develops from glial cells that surround and suppor neurons (Little et al., 1998), is the most common histological type of primary intracerebral neoplasm in China and the West, and accounts for nearly 80% of malignant primary brain tumors in humans (Xue et al., 1990). In a study of both Asian and European individuals, the TERT rs2736098 polymorphism was identified as a likely contributor to increased risk of developing bladder cancer in individuals of Asian ancestry (Gago-Dominguez et al., 2011). A study based on the European population found that TERT rs2736098 shows a borderline statistically significant association with reduced risk of breast cancer in analysis of all cases and controls; however, the association appeared to be stronger for individuals with a family history of breast cancer (Savage et al., 2007).

Although several studies in recent years have focused on the association between the TERT rs2736098

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polymorphism and cancer susceptibility, the results are inconclusive (Savage et al., 2007; Jin et al., 2009; Liu et al., 2010; Chen et al., 2011; Gago-Dominguez et al., 2011) . Therefore, this meta-analysis was performed to evaluate whether the TERT rs2736098 polymorphism is truly associated with cancer risk.

Materials and Methods

Identification and eligibility of relevant studies

Relevant literature was collected by searching the PubMed and Embase databases (the last search update was July 10, 2011) using the keywords "TERT" or "telomerase reverse transcriptase" and "polymorphism" and selecting the following limits: Humans, English and Cancer. In addition, related unpublished data and further information were obtained. Finally, additional studies were selected by searching related reference articles for data involving the association between the TERT rs2736098 polymorphism with cancer risk in a case-control design. In this meta-analysis, the studies met the following standards: (1) involved the TERT rs2736098 polymorphism and cancer risk; (2) designed as a case-control study and (3) contained available genotype frequency. The chief reasons for exclusion of studies were: (1) not involving the TERT gene; (2) not involving rs2736098 polymorphism research; (3) not related to cancer research and (4) no relevant data reported.

Data Extraction

From the eligible literature, two authors independently selected data according to the inclusion criteria outlined above. Any disagreement was resolved by discussion between the two authors. If they could not reach a consensus, another author participated in the discussion and a final decision was made by the majority. The following data was collected: first author's name, year of publication, country in which study was conducted, ethnicity (Asian and European) of subjects, cancer type, source of control groups (population- or hospital-based), frequencies of genotypes in cases and controls, genotyping method, Hardy-Weinberg equilibrium (HWE) among controls and the numbers of cases and controls with the AA, AG, and GG genotypes. The work of Gago-Dominguez et al. (2011) included two separate case-control studies. All studies were considered separately for pooling analysis. Five cancer case-control publications provided six studies in the final meta-analysis. A summary of the individual studies is shown in Table 1. Two studies (Rafnar et al.,2009; Gudmundsson et al., 2010) were not included in our meta-analysis for reasons outlined in the Discussion section.

Statistical analysis

All statistical analyses in our study were two-sided, and P values less than 0.05 were considered statistically significant. For the control group of each study, the allelic frequency (A) was calculated and the observed genotype frequencies of the TERT rs2736098 polymorphism were assessed for Hardy–Weinberg equilibrium. We used crude odd ratios (ORs) with 95% confidence intervals (CIs) to assess the strength of association between the TERT rs2736098 polymorphism and cancer risk. The pooled OR and its 95% CI were performed for a heterozygote comparison (AG versus GG), a homozygote comparison (AA versus GG), an additive model (2*AA+AG versus 2*GG+AG), a dominant model (AA+AG versus GG) and a recessive model (AA versus AG+GG). Stratified analyses were performed according to ethnicity and source of controls. The chi-squared-based Q statistical test was performed to assess heterogeneity among studies (Lau et al., 1997). As a P value greater than 0.05 for the Q-test indicates a lack of heterogeneity among studies, the pooled OR estimate of each study was calculated using the fixed-effects model (the Mantel–Haenszel method (MANTEL et al.,1959)). Otherwise, the summary ORs estimate of each study was calculated by the random-effects model (the DerSimonian and Laird method), which is more appropriate when heterogeneity is present (DerSimonian et al., 1986). In the absence of heterogeneity, the two methods provide identical results. In addition, sensitivity analyses were performed to assess the stability of the results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the summary ORs. To test for publication bias, which indicates that non-significant or negative findings remain unpublished, both Begg's and Egger's tests are commonly used to assess whether smaller studies reported greater associations than larger studies (Egger et al., 1997). An estimate of potential publication bias was assessed by visual inspection of funnel plots (Munafo et al., 2004). An asymmetric plot suggests possible publication bias. Statistical analysis was performed using STATA version 11.

Results

Characteristics of studies

The search methods yielded 131 articles, and 5 articles were identified that met our inclusion criteria (Savage et al., 2007; Jin et al., 2009; Liu et al., 2010; Chen et al.,

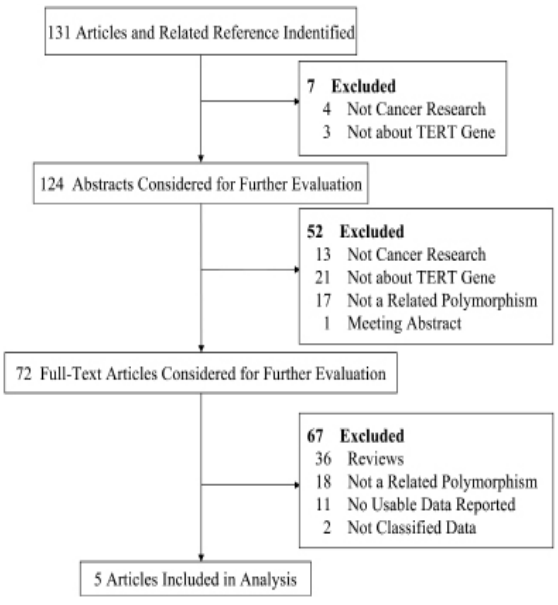

Figure 1. Study Inclusion and Exclusion Procedures

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

First author	Year	Country	Ethnicity	Cancer type	Source of controls	Matching criteria	Genotyping method	Cases	Controls	HWE
Chen, H	2011	China	Asian	Glioma	HB	Age, sex, and residential area	PCR	953	1033	0.25
Gago-Dominguez, M	2011	USA	European	Bladder cancer	PB	Age, gender and race/ethnicity	Taqman	449	531	0.71
				Bladder cancer		Age, gender and race/ethnicity				
Gago-Dominguez, M	2011	China	Asian		PB		Taqman	499	527	0.01
Liu, Z	2010	USA	European	SCCHN	PB	Matched by age and sex,	Taqman	1079	1115	0.27
Choi, J E	2009	Korea	Asian	Lung cancer	PB	Based on gender and age	PCR	720	720	0.1
Savage, S A	2007	Poland	European	Breast cancer	PB	City and 5-year age groups.	Taqman	1967	2265	0.29

PB, population based; HB, hospital based; SCCHN, Squamous cell cancer of the head and neck

Table 2. Stratified analyses of the TERT rs2736098 polymorphism on cancer risk

	AA versus GG		AG versus GG		dominant		recessive		additive	
	OR(95%CI)	P[a]	OR(95%CI)	P[a]	OR(95%CI)	P[a]	OR(95%CI)	P[a]	OR(95%CI)	P[a]
Total	1.25(0.93,1.69)[b]	0.000	1.02(0.94,1.10)	0.278	1.07(0.95,1.21)[b]	0.030	1.23(0.94,1.61)[b]	0.001	1.09(0.97,1.23)[b]	0.001
Source of controls										
Population based	1.21(0.84,1.74)[b]	0.000	0.99(0.91,1.08)	0.408	1.00(0.93,1.09)	0.074	1.20(0.86,1.69)[b]	0.001	1.07(0.93,1.22)[b]	0.002
Ethnicity										
Asian	1.63(1.34,1.98)	0.654	1.11(0.98,1.26)	0.654	1.20(1.06,1.35)	0.877	1.54(1.28,1.85)	0.420	1.21(1.11,1.32)	0.943
European	0.89(0.73,1.07)	0.173	0.97(0.88,1.06)	0.280	0.95(0.87,1.12)	0.191	0.90(0.75,1.08)	0.243	0.95(0.88,1.03)	0.142

[a]P value of Q-test for heterogeneity test; [b]Random-effects model was used when P value for heterogeneity test <0.05; otherwise, fix-effects model was used

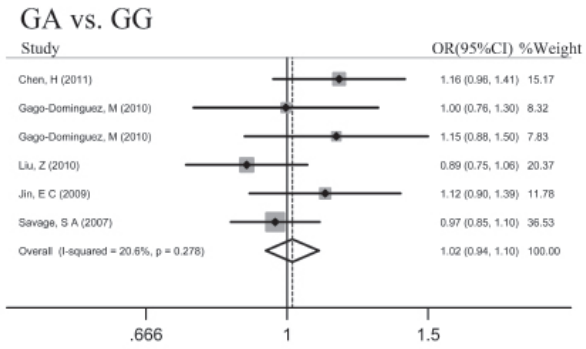

Figure 2. Overall Cancer Risk Associated with the TERT rs2736100 Polymorphism: GA vs. GG

2011; Gago-Dominguez et al., 2011), as shown in Table 2. These articles provided 6 case-control studies that included a total of 5667 cancer cases and 6191 controls. These 6 studies focused on bladder cancer, lung cancer, glioma, breast cancer, and squamous cell carcinoma of the head and neck (SCCHN) (2, 1, 1, 1, and 1 studies, respectively). These 6 studies include 3 studies each of Asian and European populations, 5 studies of population-based controls and 1 study of hospital-based controls. The study selection procedures are shown in Figure 1.

Quantitative synthesis

All 6 studies included in our meta-analysis were used to calculate individual risk estimates. The results are shown as forest plots in Figure 2. The overall results indicate that individuals who carry the AA genotype do not have a significantly increased cancer risk compared with those who carry the GG genotype (additive model, OR=1.09, 95% CI (0.97, 1.23)); no significant association was found in the dominant model (OR=1.07, 95% CI (0.95, 1.21)) or the recessive model (OR=1.23, 95% CI (0.94, 1.61)). In a stratified analysis by ethnicity, increased risks were observed for Asian populations (homozygote comparison: OR=1.63, 95% CI (1.34, 1.98); dominant model: OR=1.20, 95% CI (1.06, 1.35); recessive model: OR=1.54, 95% CI (1.28, 1.85); additive mode: OR=1.21, 95% CI (1.11, 1.32)). However, similar associations were not found among European populations. When stratified by controls, no significant association was found in any genetic model (Table 2).

Test for heterogeneity

There was significant heterogeneity for homozygote comparison (AA versus GG: Pheterogeneity< 0.001), dominant model comparison (AA+GA versus GG: Pheterogeneity=0.030), recessive model comparison (AA versus GA+GG: Pheterogeneity =0.001) and additive model comparison (2*AA+AG versus 2*GG+AG: Pheterogeneity=0.001). However, in heterozygote comparison analysis (AG versus GG: Pheterogeneity=0.278), the heterogeneity was not found. When we assessed the source of heterogeneity by ethnicity and source of controls, no significant heterogeneity was found except for the homozygote comparison (AA versus GG: Pheterogeneity< 0.001), recessive model comparison (AA versus GA+GG: Pheterogeneity =0.001) and additive model comparison (2*AA+AG versus 2*GG+AG: Pheterogeneity=0.002) of population-based controls.

Sensitivity analyses

Sensitivity analyses were performed to conclude whether modification of the inclusion criteria of the meta-analysis affected the final results. A single study involved in the meta-analysis was deleted each time the analysis was performed to reflect the influence of the individual data set on the pooled ORs. Most of the corresponding pooled ORs were not materially altered, indicating that our results were statistically robust. When we investigated the association between the TERT rs2736098 polymorphism and cancer susceptibility, we found that the importance of the pooled ORs was not influenced by any single study in a heterozygote genetic model. Sensitivity analyses indicated that the independent study that caused the majority of heterogeneity was conducted by Savage et

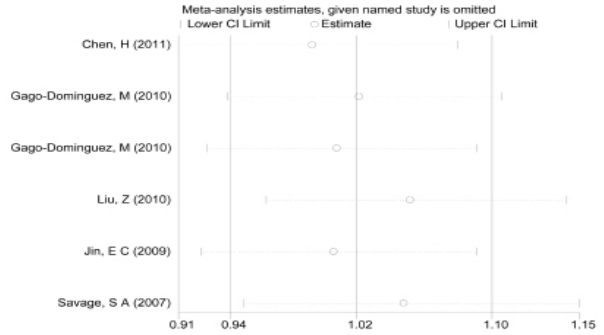

Figure 3. Influence Analysis for GA vs. GG in the Overall Meta-analysis. This figure shows the influence of individual studies on the summary OR. The middle vertical axis indicates the overall OR and the two vertical axes indicate its 95% CI. Open circles indicate the pooled OR when the left study is omitted in this meta-analysis. The two ends of the dotted lines represent the 95% CI

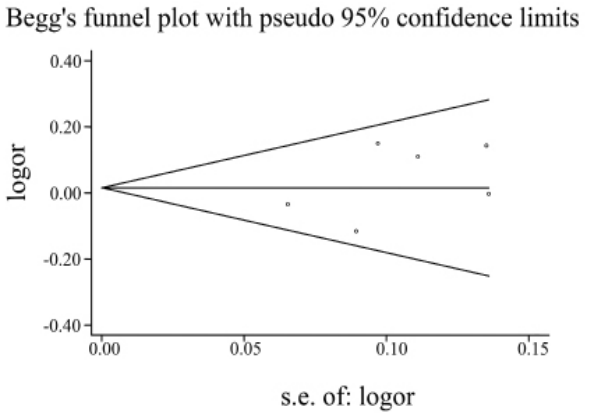

Figure 4. Funnel Plot of the TERT rs2736098 Polymorphism and Cancer Risk for Publication Bias

al. (2007) (Figure 3). The heterogeneity was effectively decreased by exclusion of the study. The following values were obtained before and after the removal of that study: OR 0.83 (95% CI: (0.65, 1.07)) and 0.76 (95% CI: (0.62, 0.92)), respectively.

Publication bias

Begger's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shapes of the funnel plots revealed no obvious asymmetry (Figure 4), suggesting that there was no obvious publication bias (t=1.21, P=0.294, 95% CI (-2.65, 6.72) for AG versus GG).

Discussion

Genetic factors may be the most important cause of cancer; however, in many cases, the roles of these factors are unclear. There are multiple lines of evidence suggesting that single nucleotide polymorphisms are the most common sources of human genetic variation that may increase the risk of cancer (Wu et al., 2009). In an attempt to clarify the exact mechanism by which genetic variation influences an individual's susceptibility to cancer, many extensive studies have been performed worldwide.

Telomere protection requires a minimal length of TTAGGG repeats to allow the binding of shelterin, which prevents the activation of the DNA damage response (DDR) at chromosome ends. When the integrity of the DDR is compromised, the resulting dysfunctional telomeres can lead to cancer. Research over the past two decades has revealed that telomerase regulation and telomere dysfunction, due to loss of telomeric sequence or telomere structure, have important roles in tissue regeneration during tumor initiation and progression (Martinez et al., 2011).

In a study of the association between the TERT rs2736098 polymorphism and cancer susceptibility (Rafnar et al., 2009), the authors selected two other SNPs (rs2736100 and rs4975616) to tag rs2736098 for an indirect test of its association with basal cell carcinoma (BCC), giving a P value of 3.9×10^{-8}. Such methods have been used in other cases involving five cancer types. In these subjects, rs2736098 [A] was associated with shorter telomeres with nominal significance (P= 0.027) (Rafnar et al., 2009), which resulted in cancer and dysfunction of telomeres in some conditions.

In recent years, the association between TERT and cancer susceptibility has been reported in many studies, and TERT has been identified as a potential cancer susceptibility gene. Over-expression of the TERT gene and telomerase activity has been recognized in many types of cancers, and can possibly lead to unlimited cell division and carcinogenesis (Liu et al., 2010). In addition, telomerase may play a role in tumor progression and metastasis by activation of the glycolytic pathway and in suppression of tumor cell differentiation (Nosrati et al., 2004; Bagheri et al., 2006; Liu et al., 2010). The role of TERT rs2736098 expression has been well documented in the tumorigenesis of various cancers (Savage et al., 2007; Jin et al., 2009; Rafnar et al., 2009; Liu et al., 2010; Chen et al., 2011; Gago-Dominguez et al., 2011), but the influence of the TERT rs2736098 polymorphism in the development of cancer has been evaluated by only a few meta-analysis studies..

To date, only 6 studies included in 5 articles have investigated the association between the TERT rs2736098 polymorphism and cancer susceptibility. A hospital-based case-control study of 953 cases and 1033 controls showed an increased risk of glioma in the Chinese population (Chen et al., 2011). In a population-based study of bladder cancer among both Asian and European individuals (499 cases and 527 controls, 449 cases and 531 controls, respectively), the TERT rs2736098 polymorphism seems to contribute to increased susceptibility to bladder cancer in individuals of Asian but not European ancestry (Gago-Dominguez et al., 2011). In addition, a study of SCCHN with 1079 cases and 1115 controls showed only a borderline-significant association between TERT A variant genotypes and SCCHN risk. Little is known about the effect of the TERT A allele on the expression of telomerase activity (Liu et al., 2010). Moreover, a population-based study of 720 lung cancer patients and 720 cancer-free controls indicated that the TERT rs2736098 polymorphism is significantly associated with an increased risk of lung cancer in Asian individuals (Jin et al., 2009). A study with a sample including 1967 cases and 2265 controls showed a borderline-significant association with the risk of breast

cancer in individuals of European ancestry; in stratified analysis, the association between the TERT rs2736098 A allele and a reduced risk of breast cancer was found among individuals with a family history of breast cancer (Savage et al., 2007). Furthermore, two articles lacking usable data were not used in our meta-analysis. One article studying 5009 cases and 41334 controls showed that the TERT rs2736098 polymorphism is associated with prostate cancer (Gudmundsson et al., 2010), The other article studied 11290 cancer patients and 31162 controls and showed that TERT rs2736098 A variant genotypes are associated with significant increases in risk for basal cell carcinoma, lung cancer, bladder cancer and prostate cancer but not of cervical cancer in the European population.

Our results suggest that the TERT rs2736098 polymorphism is not associated with cancer risk. However, in the subgroup analysis by ethnicity, statistically significant increased risks were found in all genetic models except for the heterozygote comparison (AG versus GG) in Asians but not in Europeans. The complicated nature of cancer allows the same polymorphism to play different roles in cancer susceptibility among different ethnic populations.

The limitations of our meta-analysis should be considered. First, only published studies were included in our meta-analysis. It is likely that relevant unpublished studies that might meet our inclusion criteria were overlooked. As a result, some publication bias may have been present even though our analysis showed no publication bias and an exhaustive literature search was done. Second, lack of a large enough sample size may contribute to an uncertain conclusion. As only 5 articles containing 6 studies were included in our meta-analysis, the size of the sample we studied may be too small. Third, the data we selected from the studies did not provide detailed information, such as age and sex of different genotypes, which may limit further estimates. Despite these limitations, our meta-analysis has several strengths. First, a substantial number of cases and controls were pooled from different studies that were carefully selected based on the inclusion criteria, and our data analysis methods significantly increased the statistical power of the analysis. Second, the tests did not show any evidence of publication bias, indicating that our results are reliable.

In conclusion, our meta-analysis suggests that the TERT rs2736098 polymorphism is not associated with cancer risk. Asian individuals seem to have an increased susceptibility to cancer. However, additional studies comparing larger samples of cancer patients that are standardized, unbiased and homogenous with well-matched controls are necessary to validate our findings.

Acknowledgements

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