The TERT rs2736100 Polymorphism and Cancer Risk: A Meta-analysis Based on 24 Case-Control Studies

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Running title: The TERT Polymorphism rs2736100 and Cancer Risk
Abstract

Background

The association between the TERT rs2736100 single nucleotide polymorphism (SNP) and cancer risk has been studied by many researchers, but the results remain inconclusive. In order to further explore this association, we performed a meta-analysis.

Results

A computerized search of PubMed and Embase database for publications on the TERT rs2736100 polymorphism and cancer risk was performed and the genotype data were analyzed in a meta-analysis. A significant association between the TERT rs2736100 polymorphism and cancer susceptibility was revealed by the results of the meta-analysis of the 24-case study (GG versus TT: OR = 1.74, 95% CI: 1.58, 1.92; P = 0.003; GT versus TT: OR = 1.38, 95% CI: 1.27, 1.49; P = 0.006; dominant model-TG+GG versus TT: OR = 1.47, 95% CI: 1.36, 1.59; P = 0.001; recessive model-GG versus TT+TG: OR = 1.39, 95% CI 1.30, 1.49; P = 0.032; additive model-2GG+TG versus 2TT+TG: OR = 1.31, 95% CI: 1.25, 1.37; P = 0.005). Moreover, increased cancer risk in all genetic models was found after stratification of the SNP data by cancer type, ethnicity and source of controls.

Conclusions

In all genetic models, the association between the TERT rs2736100 polymorphism and cancer risk was significant.

Background
Lung cancer is the leading cause of cancer death [1-3]. There are two main histologic subgroups of lung cancer: small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC); the latter includes the common types squamous cell carcinoma (SCC) and adenocarcinoma (ADC). Gliomas of astrocytic, oligodendroglial, and ependymal origin are derived from glial cells and account for ~80% of malignant primary brain tumors (PBT), which are the most common histologic type of brain tumors [4]. There is a dose-response relationship between ionizing radiation and the risk of an developing intracranial tumor [5], whereas familial aggregation of gliomas [6] is a result of a combination of low-risk variants.

Telomeres are special nucleoprotein structures located at the ends of eukaryotic chromosomes and are essential for protecting chromosomal termini against degradation, end to-end fusion and rearrangement [7]. Telomeres are made up of repetitive DNA (TTAGGG repeats) bound to abundant specialized proteins. The length of telomere repeats as well as the integrity of telomere-binding proteins are essential for telomere maintenance [8]. Telomerase recognizes the 3' hydroxyl (3’ OH) at the end of the G-strand overhang and adds telomeric repeat sequences onto chromosome ends. Telomerase expression can prohibit telomere erosion in most eukaryotic organisms. Functional telomerase is composed of the TERT (telomerase reverse transcriptase) protein and the telomerase RNA component (TERC) that acts as a template for DNA synthesis. In contrast to TERC, which is expressed rather ubiquitously, TERT expression is low in most normal human somatic tissues and is physiologically restricted to primary germ line cells and tissue stem cells and activated lymphocytes [9-14], leading researchers to consider TERT as the limiting factor for telomerase activity. The TERT
gene product contains three distinct structural domains: the RNA-binding domain (TRBD), the reverse transcriptase domain and the carboxy-terminal extension (CTE), which represents the putative thumb domain of TERT [15]. Tumor cells can prevent telomere loss through abnormal upregulation of telomerase [16], and telomerase has been found to be reactivated in majority of cancers, including those of the lung [7]. Activation of telomerase induced by the catalytic component TERT is a pivotal step during cellular immortalization and malignant transformation of human cells [17].

In the past decade, many investigators have explored factors contributing to inherited susceptibility to cancer [18]. The sequence variants in the TERT and CLPTM1L gene regions are associated with susceptibility to many types of cancer [19]. The rs2736100 polymorphism is localized to intron 2 of the TERT gene. McKay et al. [20] published the first study indicating that the TERT rs2736100 polymorphism may contribute to an increased risk of lung cancer. Since then, several research groups have reported associations between the SNP and cancer risk, but with inconclusive results [21-30]. Consequently, we performed a meta-analysis more precisely characterize this association.

**Methods**

**Study eligibility and identification**

Eligible studies were identified by searching PubMed, Embase, CNKI, and the Chinese Biomedicine Database (the last search update was performed on June 20, 2011), using the following search terms: (TERT OR "telomerase reverse transcriptase") AND polymorphism
using the limits, Humans, English, Cancer. The related reference articles were searched to identify other relevant publications. Unpublished data and further information were also obtained from the author. The case–control studies were selected if there was available data on the role of the TERT rs2736100 polymorphism in cancer risk.

In our meta-analysis, the following inclusion criteria were used for the selection of the studies: (1) articles about the TERT rs2736100 polymorphism and cancer risk, (2) case–control design, and (3) sufficient genotype data for estimating an odds ratio (OR) with a 95% confidence interval (CI). Articles that were not about cancer research, contained duplicated previous research, or did not include usable genotype data were excluded.

**Data extraction**

Two investigators independently extracted data from all eligible publications using the selection criteria listed above. Any disagreement was resolved by discussion. We extracted the following information from each study when available: the first author's name, year of publication, country, patient ethnicity (composed of either European or Asian), cancer type, source of control groups (population- or hospital-based controls or mixed (composed of both population- and hospital-based controls)), genotyping method and number of cases and controls with the TT, TG, and GG genotypes.

**Data synthesis**

All statistical analyses were performed using the STATA software (version 11; Stata Corporation, College Station, Texas). Two-sided $P$ values less than 0.05 were considered statistically significant. We first assessed Hardy–Weinberg equilibrium in the control groups
of each study. The OR and 95% CI in each case-control study were employed to assess the
strength of the associations between the TERT rs2736100 polymorphisms and cancer risk.
The OR and the 95% CI in each comparison were assessed in a codominant model (GG
versus TT; GT versus TT), a dominant model (GG + GT versus TT), a recessive model (GG
versus GT + TT) and an additive model (2GG+TG versus 2TT+TG). Subgroup analyses were
performed based on cancer type, the source of controls and ethnicity. The chi-square
test-based $Q$-statistic was calculated to test the heterogeneity between studies. If the result of
this heterogeneity test was $P < 0.05$, the pooled ORs were analyzed using the random effects
model (the DerSimonian and Laird method) [31]. Otherwise, if the result of this heterogeneity
test was $P > 0.05$, indicating that the between-study heterogeneity was not significant, then
the fixed-effects model was selected (the Mantel-Haenszel method) [32]. The $I^2 (I^2 = 100\% \times
(Q-df)/Q)$ statistic was then used to quantitatively estimate heterogeneity, with $I^2 < 25\%,$
25–75% and >75% to represent low, moderate and high degrees of inconsistency,
respectively [33, 34]. The significance of the combined OR was determined by Z test ($P <
0.05$ was considered statistically significant). Additionally, sensitivity analyses were
performed after sequential removal of each study. Cumulative meta-analyses were performed
through assortment of all eligible cancer studies with case sample size. Finally, The Begg’s
funnel plot and Egger’s test were performed to analyze the publication bias statistically
($P < 0.05$ was considered a significant publication bias) [35].

Results
Eligible studies

In total, 10 articles including 24 case-control studies in English with 14423 cases and 28896 controls met the inclusion criteria. Characteristics of the studies are listed in Table 1. Among the 24 studies, 13 focused only on lung cancer, 9 focused only on glioma and 2 focused on other cancers. The 24 studies collected in this meta-analysis included 14 studies of Asians and 10 studies of Europeans, 18 studies of population-based controls, 4 studies of hospital-based controls and 2 study of population-based and hospital-based controls. Figure 1 shows the study selection procedure.

Evidence synthesis

There was wide variation in the TERT rs2736100 polymorphism among the controls across different ethnicities. For European populations, the G allele frequency was 51.0% (95% CI = 49.6–52.4), which was significantly (P = 0.00) higher than that in Asian populations (39.5%, 95% CI = 38.2–40.8) (Figure 2).

As shown in Table 2, for the TERT rs2736100 polymorphism, all studies combined (14423 cases and 28896 controls) were pooled into the meta-analysis, and significantly increased cancer risk was found for all genetic models based on the studies (GG versus TT: OR = 1.74, 95% CI: 1.58, 1.92; P = 0.003; GT versus TT: OR = 1.38, 95% CI: 1.27, 1.49; P = 0.006; dominant model-TG+GG versus TT: OR = 1.47, 95% CI: 1.36, 1.59; P = 0.001; recessive model-GG versus TT+TG: OR = 1.39, 95% CI 1.30, 1.49; P = 0.032; additive model-2GG+TG versus 2TT+TG: OR = 1.31, 95% CI: 1.25, 1.37; P = 0.005). Figure 3 shows overall meta-analysis of the TERT rs2736100 polymorphism and cancer risk in the recessive
model.

**Subgroup analysis**

Specific data for the *TERT rs2736100* polymorphism were stratified by cancer type: the lung cancer subgroup, the glioma subgroup and the other cancer subgroup. The pooled odds ratios for the lung cancer, glioma, the other cancer were 1.47 (95% CI 1.35, 1.59; \( P = 0.062 \)), 1.34 (95% CI 1.24, 1.44; \( P = 0.174 \)) and 1.22 (95% CI 0.99, 1.51; \( P = 0.245 \)), respectively, when we assume a recessive genetic model. The meta-analysis results for other genetic models are listed in Table 2.

In the stratified analysis by source of controls, significantly increased risks were also found. The pooled odds ratios were 1.36 (95% CI 1.25, 1.48; \( P = 0.049 \)) in the population-based controls subgroup and 1.40 (95% CI 1.23, 1.60; \( P = 0.353 \)) in the hospital-based controls subgroups in a recessive genetic model. The Meta-analysis results for other genetic models are listed in Table 2.

We stratified the studies by the ethnicity of participants into two subgroups: Asian and European. The pooled odds ratios were 1.46 (95% CI 1.36, 1.58; \( P = 0.095 \)) and 1.31 (95% CI 1.22, 1.41; \( P = 0.160 \)) in a recessive genetic model, respectively. The meta-analysis results for other genetic models are listed in Table 2.

Lung cancer is classified into two main histologic groups: small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC), the latter of which includes squamous cell carcinoma (SCC) and adenocarcinoma (ADC), along with rarer subtypes. There is an association between familial risk and lung cancer histologic subgroups [36-39], but the
relationship between the inherited susceptibility factors and lung cancer histology is unknown. Adenocarcinoma is the most common histologic type of lung cancer and the relative proportion of ADC has steadily risen. Many investigators [21-25] have established an association between the \textit{TERT} rs2736100 polymorphism and risk of lung adenocarcinoma. Characteristics of these studies are listed in Table 3. As shown in Table 4, a significant association was observed between the \textit{TERT} rs2736100 polymorphism and adenocarcinoma susceptibility in all genetic models (GG versus TT: \textit{OR} = 1.91, 95\% CI: 1.73, 2.12; \textit{P} = 0.106; GT versus TT: \textit{OR} = 1.45, 95\% CI: 1.26, 1.66, \textit{P} = 0.007; dominant model-TG+GG versus TT: \textit{OR} = 1.57, 95\% CI 1.38, 1.78, \textit{P} = 0.008, recessive model-GG versus TT+TG: \textit{OR} = 1.54, 95\% CI: 1.41, 1.68, \textit{P} = 0.342; additive model-2GG+TG versus 2TT+TG: \textit{OR} = 1.38, 95\% CI: 1.31, 1.45; \textit{P} = 0.134).

\textbf{Sensitivity analysis}

Sensitivity analyses were performed after sequential removal of each eligible study. When we investigated the \textit{TERT} rs2736100 polymorphism and cancer susceptibility, the results suggested that the significance of pooled \textit{OR} was not influenced by any single study in a recessive genetic model. Sensitivity analyses indicated that the independent study contributing most to heterogeneity was conducted by Kohno et al. [23] (Figure 4). The heterogeneity was effectively decreased by exclusion of the study, \textit{OR}=1.39 (95\% CI: 1.30, 1.49; \textit{P} = 0.032; \textit{I}^2 = 38.0\%) and 1.36 (95\% CI: 1.29, 1.43; \textit{P} = 0.092; \textit{I}^2 = 29.4\%) before and after the removal of that study, respectively.

\textbf{Test of heterogeneity}
Significant heterogeneity existed in all five genetic models (GG versus TT, GT versus TT, TG+GG versus TT, GG versus TT+TG, 2GG+TG versus 2TT+TG) of the TERT rs2736100 polymorphism (Table 2). However, stratification based on the source of controls reduced the heterogeneity in the hospital-based controls subgroups (GG versus TT: $P$ heterogeneity = 0.803, $I^2 = 0.0\%$; GT versus TT: $P$ heterogeneity = 0.392, $I^2 = 0.0\%$; TG+GG versus TT: $P$ heterogeneity = 0.736, $I^2 = 0.0\%$; GG versus TT+TG: $P$ heterogeneity = 0.353, $I^2 = 8.1\%$; 2GG+TG versus 2TT+TG; $P$ heterogeneity = 0.951, $I^2 = 0.0\%$). When patients were stratified based on ethnicity, heterogeneity disappeared in the European (GT versus TT: $P$ heterogeneity = 0.266, $I^2 = 19.2\%$; TG+GG versus TT: $P$ heterogeneity = 0.077, $I^2 = 42.1\%$; GG versus TT+TG: $P$ heterogeneity = 0.160, $I^2 = 31.1\%$) and Asian subgroups (GG versus TT+TG: $P$ heterogeneity = 0.095, $I^2 = 35.0\%$). In the analysis of cancer type subgroups, heterogeneity disappeared in the glioma (GT versus TT: $P$ heterogeneity = 0.138, $I^2 = 35.0\%$; GG versus TT+TG: $P$ heterogeneity = 0.174, $I^2 = 30.6\%$) and lung cancer subgroups (GG versus TT+TG: $P$ heterogeneity = 0.062, $I^2 = 40.9\%$).

Neither cancer type, source of controls nor ethnicity could explain the significant between-study heterogeneity observed by meta-regression.

**Cumulative meta-analysis**

Cumulative meta-analyses were also conducted through the eligible studies sorted by case sample size (Figure 5). There is no obvious change in the 95% confidence intervals with increasing sample size.

**Assessment of bias**
The Begg’s funnel plot and Egger’s test were performed to assess the publication bias (Figure 6). The results did not show any evidence of publication bias ($t = 1.09$, $P = 0.289$ for GG versus GT+TT). The 95% confidence interval (95% CI: -0.68, 2.17) included zero, indicating no publication bias. In all genetic models, the results also did not show evidence of publication bias.

**Discussion**

Cancer is caused by a complicated interaction between genetic and environmental factors. There is individual variation in cancer susceptibility. Most genetic cancer risk results from the combination of many low-penetrance sequence variants [19]. It is well known that single nucleotide polymorphisms (SNPs) are the most common sources of human genetic variation, which may contribute to an individual’s susceptibility to cancer [40]. Thus genetic susceptibility to cancer has been extensively studied in the scientific community.

Telomerase is a ribonucleoprotein enzyme that synthesizes TTAGGG telomeric repeat sequences essential for genomic stability [41, 42]. Amplification of the $TERT$ gene, transcriptional activation and post-translational modifications contribute to the regulation of $TERT$ activity. Stringent transcriptional control via the $TERT$ promoter also modulates $TERT$ expression. Telomerase reexpression is a key factor in cancer cell biology, enabling malignant cells to proliferate indefinitely [7]. The commonly observed high expression of telomerase in lung cancer suggests that $TERT$ may have an important role in lung
Tumorigenesis [7, 43-45]. Telomerase activity is present in most glioma samples while absent in normal brain tissues [46]. TERT expression also correlates with glioma grade and prognosis [47, 48]. Moreover, the reduction of telomerase activity may inhibit glioma cell growth [49]. The biology of TERT makes it a compelling candidate gene for factors that influence cancer risk [50], and the association between TERT polymorphism and shorter telomere length has been recently reported [19]. A number of independent genome-wide association studies have implicated variants at the 5p15.33 locus (containing the TERT gene) in cancer risk at several different sites: lung cancer, basal cell carcinoma and pancreatic cancer show strong associations, while bladder, prostate and cervical cancer and glioma also show risk alleles in this region [51]. The association between the TERT rs2736100 single nucleotide polymorphism and cancer risk has been studied by many researchers, but the results remain unclear. In order to explore the association between the TERT rs2736100 polymorphism and cancer risk, we performed a meta-analysis. Ultimately 24 published studies encompassing 14423 cases and 28896 controls were used to examine the association. Table 2 shows the significantly increased cancer risk for all genetic model based on all studies. Moreover, increased cancer risk in all genetic models was found after stratification of the SNP genotype data by cancer type, ethnicity and source of controls.

As shown in Table 4, the strongest risk association was observed between the TERT rs2736100 polymorphism and adenocarcinoma in all genetic models. TERT gene amplification occurred in 57% of NSCLC, but was more common among ADC (75%). TERT gene amplification is responsible for TERT mRNA overexpression in a majority of ADC,
while epigenetic factors at the transcriptional or post-transcriptional levels significantly affect
*TERT* expression in NSCLC cells [52]. The re-expression of *TERT* may indicate progression
from bronchiolo-alveolar carcinoma to adenocarcinoma [7, 53].

In our meta-analysis, the origins of heterogeneity may include many factors, such as the
differences in control characteristics and diverse genotyping methods. We attempted to
explain the heterogeneity using meta-regression; however, neither cancer type, source of
controls nor ethnicity could explain significant between-study heterogeneity. In addition, the
small sample size (<100 cases and controls) studies appear to overestimate the true
association because of deficiencies in statistical power.

There are some limitations of this meta-analysis that should be discussed. First,
misclassifications of the histologic type of the cancers reported may influence the results.
Second, the lack of detailed information, such as age and sex of the patients, in some studies
limited further stratification, and a more accurate OR would be corrected for age, sex and
other factors that are associated with cancer risk. Third, different genotyping methods could
lead to heterogeneity. Based on the limitations of the present study listed above, detailed
studies are warranted to confirm our findings. Nevertheless, our meta-analysis has some
advantages. First, the well-designed search and selection method significantly increased the
statistical power of this meta-analysis. Second, the distribution of genotypes in the controls
was consistent with Hardy-Weinberg equilibrium in all studies. Third, the results did not
show any evidence of publication bias. In conclusion, the overall results of this meta-analysis
have shown that the TERT rs2736100 polymorphism is associated with cancer risk.
COMPETING INTERESTS

The authors declare that there are no competing interests

Authors' contributions

Peng Zou participated in collection of data and manuscript preparation.

Guixiang Ji and Lin Zhao performed the statistical analysis.

Peng Zhao and Aihua Gu participated in study design and critically revised the manuscript.

Peng Zhao and Ailin Lu participated in study design and manuscript preparation

All authors read and approved the final manuscript.

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References


Figure legends

**Figure 1.** The study inclusion and exclusion procedures.

**Figure 2.** Frequencies of the variant alleles among controls stratified by ethnicity.

**Figure 3.** Overall meta-analysis of the TERT rs2736100 polymorphism and cancer risk in the recessive model.

**Figure 4.** Influence analysis for GG versus GT/TT 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 the 95% CI. Open circles indicate the pooled OR when the study indicated on the left is omitted from the meta-analysis. The lines indicate the 95% CI values when the study indicated is omitted from the meta-analysis.

**Figure 5.** Results of the cumulative meta-analysis of associations between the TERT rs2736100 polymorphism and cancer risk in the recessive model. The studies were sorted based on case sample size (small to large).

**Figure 6.** Funnel plot of the TERT rs2736100 polymorphism and cancer risk data for publication bias.
152 Articles and Related Reference Identified

20 Excluded
11 Not Cancer Research
9 Not about TERT Gene

132 Abstracts Considered for Further Evaluation

64 Excluded
10 Not Cancer Research
24 Not about TERT Gene
30 Not a Related Polymorphism

68 Full-Text Articles Considered for Further Evaluation

58 Excluded
20 Reviews
1 Previous Publication
22 Not a Related Polymorphism
13 No Usable Data Reported
1 Not in Agreement with HWE
1 Meta-Analysis

10 Articles Included in Analysis
### Recessive model: GG vs. GT+TT

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<th>Study</th>
<th>OR(95% CI)</th>
<th>%Weight</th>
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<td>1.14 (0.93, 1.39)</td>
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**NOTE:** Weights are from random effects analysis.
Begg's funnel plot with pseudo 95% confidence limits.

Figure 6
Additional files provided with this submission:

Additional file 1: table.doc, 148K
http://www.biomedcentral.com/imedia/172484862592751/supp1.doc