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META-ANALYSIS

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Telomere Reverse Transcriptase (TERT) rs2735940 Increases Cancer Risk

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1,2 Hui Yang
ABCDEF 1,2 Jing Li
BCDE 1,2 Ruihua Tang
BDE 1,2 Yaxiong Liu
BCD 1,2 Yan Shao
BC 1,2 Qingsheng Huang
D 1,2 Junling Shi

1 School of Life Sciences, Northwestern Polytechnical University, Xi'an, Shanxi, China
2 Key Laboratory for Space Bioscience and Biotechnology, Northwestern Polytechnical University, Xi'an, Shanxi, China

Corresponding Author: Hui Yang, e-mail: kittyyh@nwpu.edu.cn
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Background: Telomerase reverse transcriptase (TERT) rs2735940 polymorphism was found to be associated with increased cancer risk. However, recent studies reported controversial results. The aim of our study was to detect its relationship with cancer risk.

Material/Methods: EMBASE and PubMed databases were searched for all publications until October 2014. ORs and 95% CIs were applied to investigate the association in the random-effects model.

Results: Thirteen case-control studies with 19385 cases and 17558 controls were included in this study. We found a significant association between cancer risk and TERT rs2735940 polymorphism (OR=1.06, 95% CI 1.02–1.11, *P*=0.005). In the subgroup analysis by ethnicity, a marginal association was found in Caucasians (OR=1.05, 95% CI 1.00–1.10, *P*=0.05), but not in Asians (OR=1.01, 95% CI 0.82–1.24, *P*=0.93). In the subgroup analysis by cancer site, this polymorphism was significantly associated with lung cancer risk (OR=1.08, 95% CI 1.02–1.13, *P*=0.004).

Conclusions: TERT rs2735940 polymorphism was significantly associated with cancer risk, especially lung cancer.

MeSH Keywords: Breast Neoplasms • Lung Neoplasms • Polymorphism, Genetic • Telomerase

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Background

Cancer is a common disease, which results from interactions between genetic and environmental factors [1]. Telomerase is upregulated in the majority of cancers [2]. Human telomerase catalytic subunit, encoded by telomerase reverse transcriptase (TERT) gene, has been shown to be a rate-limiting determinant of telomerase activity and maintains genomic stability by adding the telomere repeat TTAGGG to telomere ends [3]. TERT was found to be over-expressed in non-small cell lung cancer [4, 5]. TERT was also an independent poor prognostic marker for disease-free survival [6]. TERT siRNA effectively suppressed the expression of TERT mRNA and TERT protein levels, reduced telomerase activity, and induced apoptosis of cancer cells [7,8]. Previous studies have shown that telomere length was associated with cancer risk [9]. Several TERT single-nucleotide polymorphisms had modest association with telomere length [10]. Therefore, TERT polymorphisms might influence the risk of cancers.

Recently, some meta-analyses have investigated the association between TERT polymorphisms and some cancers risks [11,12]. However, all of these meta-analyses focused on TERT rs2736098 and rs2736100. Many studies also assessed the relationship of TERT rs2735940 polymorphism and cancer risk and reported controversial results [10,13–24]. In addition, Zhang et al. indicated that TERT rs2735940 polymorphism was significantly associated with telomere length [20]. Thus, we did this meta-analysis to calculate the relationship between cancer risk and TERT rs2735940 polymorphism.

Material and Methods

Publication search

Two databases – PubMed and EMBASE – were searched to find relevant articles. The following keywords were used: ('telomerase reverse transcriptase'' or ''TERT'') and (''tumor'' or ''cancer'' or ''neoplasms'') and (''polymorphism'' or ''mutation''). The last search date was October 22, 2014. The language of the papers was not restricted. All references cited in these studies and previously published review articles were searched for additional eligible studies.

Study selection

Studies were included if they met the following criteria: (1) evaluation of the association of the TERT rs2735940 polymorphism and cancer risk; (2) a case-control study or a cohort study; (3) an available genotype or allele frequency. Studies were excluded if they were: (1) family or animal studies; (2) containing overlapping data; (3) reviews or abstracts.

Data extraction

Data would be extracted by 2 independent authors. The following data were extracted from each article: author, country, publication year, ethnicity, site of cancer, and numbers of the cases and controls.

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) of the controls was calculated by chi-square test. OR and 95% CI were applied to determine the strength of the association between the TERT rs2735940 polymorphism and cancer risk. The OR and respective 95% CI were calculated by comparing TT+CT *vs.* CC. We used Q statistic to assess the heterogeneity. A *P* value <0.1 was regarded as suggesting large heterogeneity. The random-effects model was adopted to assess the overall OR value. Subgroup analyses were performed by ethnicity and site of cancer. We carried out the cumulative meta-analysis. Sensitivity analysis was conducted. Funnel plot was used to assess evidence for potential publication bias. STATA 11.0 software was used to do all the statistical tests.

Results

Eligible studies

Thirteen studies with 19385 cases and 17558 controls were enrolled in our meta-analysis [10,13–24]. One study reported 5 independent case-control studies and 1 study reported 2 case-control studies; thus, a total of 18 case-control studies were included. Table 1 summarizes the characteristics of the included studies. Most of the studies were conducted in Caucasians, while 5 case-control studies conducted in Asians. There were 5 studies of lung cancer, 3 studies of breast cancer, 2 studies of prostate cancer, and 2 studies of bladder cancer. All studies were in HWE.

Meta-analysis

We found a significant association between cancer risk and TERT rs2735940 polymorphism (OR=1.06, 95% CI 1.02–1.11, *P*=0.005, Figure 1). In the subgroup analysis by ethnicity, a marginal association was found in Caucasians (OR=1.05, 95% CI 1.00–1.10, *P*=0.05), but not in Asians (OR=1.01, 95% CI 0.82–1.24, *P*=0.93). In the subgroup analysis by cancer site, this polymorphism was significantly associated with lung cancer risk (OR=1.08, 95% CI 1.02–1.13, *P*=0.004). No significant association was found in risk of breast cancer (OR=1.00, 95% CI 0.86–1.16, *P*=0.97), prostate cancer (OR=0.95, 95% CI 0.73–1.23, *P*=0.68), or bladder cancer (OR=0.99, 95% CI 0.84–1.16, *P*=0.87). Table 2 shows the main results of this study.

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Table 1. Characteristics of included studies.

Author	Year	Country	Ethnicity	Cases	Controls	Hardy-Weinberg equilibrium	Cancer site
Savage	2007	Poland	Caucasian	2202	2360	Yes	Breast
Hosgood	2008	China	Asian	121	110	Yes	Lung
Guey	2009	Spain	Caucasian	990	1033	Yes	Bladder
Rafnar	2009	Iceland	Caucasian	4912	1551	Yes	Basal cell carcinoma, bladder, cervix, lung, prostate
Choi	2009	Korea	Asian	720	720	Yes	Lung
Shen	2010	America	Mixed	978	1045	Yes	Breast
Pande	2011	America	Caucasian	1681	1235	Yes	Lung
Liu	2011	America	Caucasian	888	885	Yes	Head and neck
Hofer	2012	Austria	Caucasian	137	1705	Yes	Colorectal
Walsh	2012	America	African	1308	1241	Yes	Lung
Sheng	2012	China	Asian	569	669	Yes	Acute lymphoblastic leukemia
Iizuka	2013	Japan	Asian	1347	909	Yes	Mixed and prostate
Pellatt	2013	America	Mixed	3532	4095	Yes	Breast

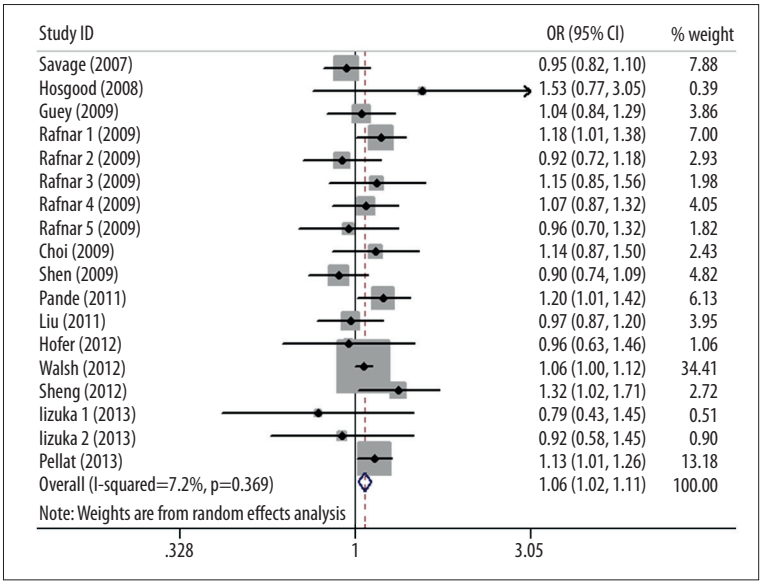

Figure 1. Meta-analysis of the association between TERT rs2735940 polymorphism and cancer risk.

Cumulative meta-analysis suggested that the results were stable (data not shown). Sensitivity analysis was also done; the results were not changed when each study was excluded, suggesting the robustness of the results (data not shown). The shape of the funnel plot did not show obvious asymmetry (Figure 2) and Begg's test also found no significant publication bias (P=0.75).

Discussion

In this meta-analysis with 19385 cases and 17558 controls, we investigated the association between cancer risk and TERT rs2735940 polymorphism. Results of this study indicate that individuals with the TERT rs2735940 polymorphism had an increased risk of cancer. In the subgroup analysis by ethnicity, a significant association was observed in Caucasians but not in Asians. However, only 5 studies on this polymorphism in

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Table 2. Summary of results from meta-analysis and subgroup analysis.

Comparison		No. of studies	No. of cases and controls	OR (95% CI)	P value	Pheterogeneity
TT+CT *vs.* CC	Overall	18	19385/17558	1.06 (1.02–1.11)	0.005	0.37
TT+CT *vs.* CC	Asian	5	2757/2408	1.01 (0.82–1.24)	0.93	0.03
TT+CT *vs.* CC	Caucasian	10	10810/8769	1.05 (1.00–1.10)	0.05	0.45
TT+CT *vs.* CC	Lung	5	4531/4857	1.08 (1.02–1.13)	0.004	0.55
TT+CT *vs.* CC	Breast	3	6712/7500	1.00 (0.86–1.16)	0.97	0.05
TT+CT *vs.* CC	Prostate	2	2235/1869	0.95 (0.73–1.23)	0.68	0.88
TT+CT *vs.* CC	Bladder	2	1453/2584	0.99 (0.84–1.16)	0.87	0.47

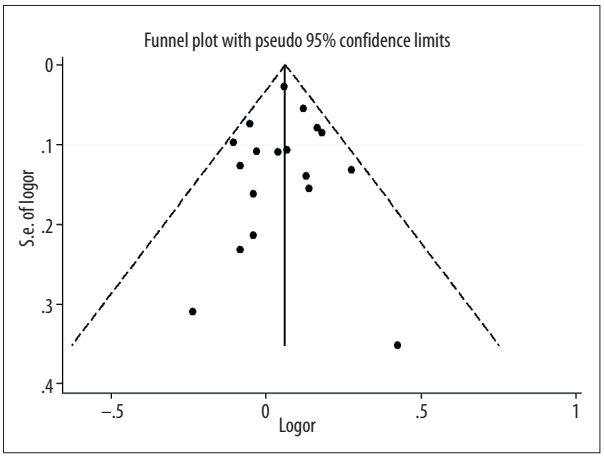

Figure 2. Funnel plot for the association between TERT rs2735940 polymorphism and cancer risk.

Asians were included. Thus, ethnic difference might be due to chance. In the subgroup analysis by site of cancer, we found TERT rs2735940 polymorphism exhibited increased lung cancer risk. This result indicates that TERT rs2735940 polymorphism may play the same role in the pathogenesis of lung cancer. Previous studies suggested that TERT rs2735940 polymorphism contributed to longer telomere length [25]. Longer telomere length was associated with the increased breast cancer risk and lung cancer risk [10,26]. Therefore, TERT rs2735940 polymorphism could increase the risks of lung cancer and breast cancer.

Sensitivity analysis and cumulative meta-analysis results revealed that our results were stable. Heterogeneity is an important issue in meta-analysis; however, no significant heterogeneity was detected in this meta-analysis. Funnel plots suggested that there was no significant publication bias. These results taken together show that the results of this meta-analysis are reliable.

There were also some limitations to this study. First, we only included published articles in this meta-analysis; thus, several unpublished studies might have been missed. Second, we did not assess the interactions of gene-gene and gene-environment due to lack of sufficient information. Finally, most of the included studies were carried out in Asians and Caucasians; therefore, further studies in different ethnic populations, especially Africans, are needed to confirm the results of this meta-analysis.

Conclusions

This study suggests that TERT rs2735940 polymorphism is associated with increased cancer risk. Future studies are warranted to validate this finding in different populations.

Conflict of interest

The authors declare that they have no conflicts of interest.

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