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ORIGINAL ARTICLE

New evidence of TERT rs2736098 polymorphism and cancer risk: an updated meta-analysis

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Summary

Purpose: *Previous meta-analyses didn't suggest any significant association between TERT rs2736098 polymorphism and overall cancer risk, and the existing evidence lacks statistical power to draw a convincing conclusion.*

Methods: *Herein we performed an update meta-analysis to re-evaluate the association between rs2736098 polymorphism and the risk of overall cancer with all the case-control studies published before March 2015 according to PubMed and Embase databases.*

Results: *A total of 19 case-control studies were included in this analysis. We found that variant genotypes of rs2736098 (GA/AA) were significantly associated with an increased risk of overall cancer (GA/AA vs GG: OR=1.14; 95% CI=1.04-1.25). Additionally, the association was more significant in Asians (OR=1.20; 95% CI=1.07-1.34), while in subsequent analyses stratified by cancer type, the variant rs2736098 was definitely associated with increased lung cancer (OR=1.18; 95% CI=1.07-1.29) and hepatocellular carcinoma risk (OR=1.38; 95% CI=1.20-1.59).*

Conclusion: *These findings provided further evidence that TERT rs2736098 variant may modify the susceptibility to cancer.*

Key words: *cancer, meta-analysis, polymorphism, rs2736098, TERT*

Introduction

Genome-wide association studies (GWAS) have broadened our understanding of genetic variations that confer risk for different diseases [1]. During the past few years, the GWAS have identified numerous robust associations between specific chromosomal loci and different types of cancer [2]. Notably, pleiotropy has been observed for several loci, such as the region of 5p15.33 (*TERT-CLPTM1L*), 3q28 and 8q24. The telomerase reverse transcriptase (*TERT*) locus has initially been implicated in lung cancer risk [3,4]. In a subsequent meta-analysis on 19 studies including 49,869 cases and 73,464 controls, a significant association between *TERT* rs2736100 polymorphism and lung cancer risk was observed [5], while similar results were also observed for overall cancer risk [6]. In addition, the past several years have also witnessed an explosion of the associations between another variant rs2736098 at the *TERT* locus and cancer risk. However, the results of previous studies exploring this association were inconclusive. In a meta-analysis harboring 5 cancer types, the variant rs2736098 showed no association reaching statistical significance for overall cancer risk [7-9], probably due to the disparity in sample size in each of the published studies. Even so, an increasing number of replication studies have still paid special attention to the association between rs2736098 and cancer which consists of several common types, including lung cancer [10-

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15], breast cancer [16,17], hepatocellular carcinoma [18-20], bladder cancer [21,22], squamous cell carcinoma of the head and neck (SCCHN) [23,24], esophageal cancer [25], colorectal cancer [26] and glioma [27]. Therefore, we performed an update meta-analysis using all published data to date to more precisely characterize the association between rs2736098 and cancer risk.

Methods

Identification and eligibility of relevant studies

Relevant literature was collected by searching the PubMed and Embase databases (the last search update was March 30, 2015) using the keywords "*TERT*" or "telomerase reverse transcriptase" and "polymorphism" and "cancer" and selecting the following limits: Humans, English and Cancer. Furthermore, 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 study 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 main 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. Finally, data for meta-analysis were available from 19 studies, including 12,520 cancer cases and 14,968 controls.

Data extraction

Two investigators (T.L and Y.X) independently extracted data and reached consensus on all of the items. The following information was sought from each article: first author's name, year of publication, country of origin, ethnicity, cancer types, number of cases and controls, genotype frequency for cases and controls. Different ethnicity was categorized as Asians and Caucasians.

Statistics

The risk of cancer associated with rs2736098 polymorphism of *TERT* was estimated for each study by odds ratio (OR) together with its 95% confidence intervals (95% CI), respectively. A chi-square based Q statistic test was performed to assess the between-study heterogeneity, and it was considered significant for $p \leq 0.05$. We pooled the results using a fixed-effect model with the Mantel–Haenszel method or a random-effects model with the DerSimonian and Laird method. These two models provide similar results when heterogeneity between studies is absent; otherwise, the random-effects model is more appropriate. We firstly estimated

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

Number	*First author*	*Year*	*Country*	*Ethnicity*	*Cancer type*	*Case/Control*	*Platform*
1	Hashemi	2014	Iran	Asian	Breast cancer	266/225	PCR-RFLP
2	Su	2014	China	Asian	HCC	201/210	TaqMan
3	Gao	2014	China	Asian	Lung cancer	309/310	Sequenom
4	Singh	2014	India	Asian	Bladder cancer	225/240	TaqMan
5	Yin	2014	China	Asian	Esophageal cancer	629/686	LDR
6	Zhang	2014	China	Asian	Lung cancer	366/366	Sequenom
7	Zhao	2014	China	Asian	Lung cancer	980/1000	TaqMan
8	Wu	2013	China	Asian	Lung cancer	539/627	TaqMan
9	Li	2013	China	Asian	Lung cancer	501/576	TaqMan
10	Zhang	2013	China	Asian	HCC	400/400	PCR-RFLP
11	Hofer	2012	Austria	Caucasian	Colorectal cancer	142/1793	TaqMan
12	Liu	2011	USA	Caucasian	SCCHN	888/885	TaqMan
13	Ding	2011	China	Asian	HCC	1300/1344	TaqMan
14	Chen	2010	China	Asian	Glioma	976/1057	Sequenom
15	Gago-Dominguez	2010	USA	Caucasian	Bladder	498/588	TaqMan
16	Gago-Dominguez	2010	China	Asian	Bladder	506/530	TaqMan
17	Liu	2010	America	Caucasian	SCCHN	1079/1115	TaqMan
18	Choi	2009	Korea	Asian	Lung cancer	720/720	PCR-RFLP
19	Savage	2007	Poland	Caucasian	Breast cancer	1995/2296	TaqMan

HCC: Hepatocellular carcinoma, SCCHN: Squamous cell carcinoma of the head and neck

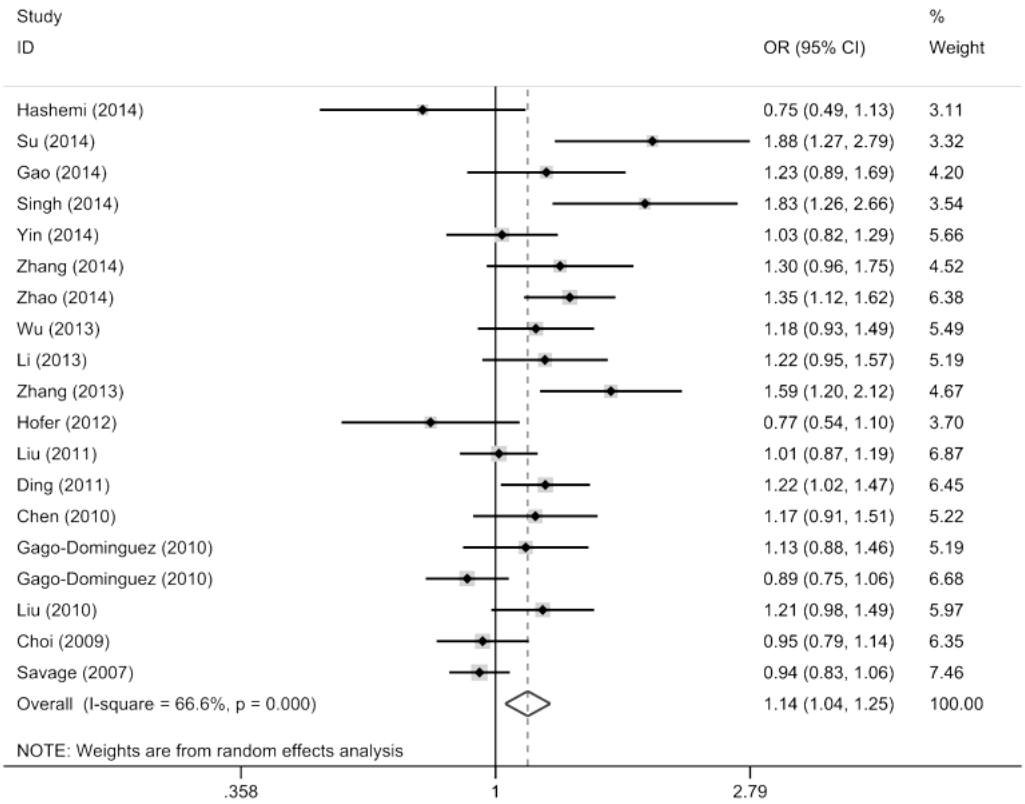

Figure 1. Forest plot of the *TERT* rs2736098 polymorphism and cancer risk

the risks of the GA and AA genotypes, compared with the GG genotype, respectively, and then evaluated the risks of combined GA and AA vs CG genotype, assuming dominant effects of the A allele. We also performed stratification analyses on ethnicity (divided into Asians and Caucasians) and cancer types. Egger's test and funnel plots were utilized to provide the evaluation of publication bias (Linear regression asymmetry test). All analyses were performed using the software Stata version 9.2 (Stata Corporation, College Station, TX, USA). All statistical evaluations were made assuming a two-sided test with the significance level of 0.05.

Results

Characteristics of the published studies

The characteristics of the selected studies are listed in Table 1. The distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium for most of the studies except two studies by Zhang et al. [19] and Gago-Dominguez et al. [22]. These articles provided 19 case-control studies that included a total of 12,520 cancer cases and 14,968 controls harboring lung cancer, breast cancer, hepatocellular carcinoma, bladder cancer, SCCHN, esophageal cancer, colorectal cancer and glioma. There were 14 studies of Asians and 5 studies of Caucasians. Genotyping was performed using TaqMan for 12 studies, Sequenom and PCR-RFLP for each 3 studies and LDR for 1 study, respectively. The distribution of the genotypes and alleles of the *TERT* rs2736098 polymorphism for individual studies are listed in Table 2.

Quantitative synthesis

The evaluation of the associations between rs2736098 and cancer risk are presented in Table 3 and Figure 1. Overall, the A allele variant significantly increased the risk of cancer in all tested models (GA vs GG: OR=1.09; 95% CI=1.01-1.18; AA vs

GG: OR=1.30; 95% CI=1.10-1.54; GA/AA vs GG: OR=1.14; 95% CI=1.04-1.25). Because the variant genotypes (GA and AA) of rs2736098 consistently showed increased cancer risk, we used the dominant genetic model in further analyses.

We then evaluated the effect of the rs2736098 polymorphism on cancer risk among subgroups (Table 3). In stratified analyses with a dominant manner, a significantly increased cancer risk was observed in Asians (OR=1.20; 95% CI=1.07-1.34), however, for Caucasians, the rs2736098 variant showed no association reaching the level of statistical significance for cancer risk (OR=1.00; 95%

Table 2. Distribution of genotypes and alleles of TERT rs2736098 polymorphism

Number	*First author*	*Case/ Control*	*Case / Frequencies distribution of genotypes control*					
			GG	*AG*	*AA*	*GG*	*AG*	*AA*
			N(%)	*N(%)*	*N(%)*	*N(%)*	*N(%)*	*N(%)*
1	Hashemi	266/225	72(1.32)	140(2.64)	40(2.64)	51(0.73)	113(1.83)	58(4.03)
2	Su	201/210	75(1.37)	97(1.83)	29(1.92)	111(1.58)	76(1.23)	23(1.60)
3	Gao	309/310	122(2.24)	145(2.73)	42(2.77)	137(1.95)	143(2.32)	28(1.95)
4	Singh	225/240	77(1.41)	106(2.00)	42(2.77)	117(1.67)	95(1.54)	28(1.95)
5	Yin	629/686	245(4.49)	277(5.22)	78(5.15)	270(3.85)	306(4.96)	75(5.22)
6	Zhang	366/366	135(2.47)	173(3.26)	58(3.83)	157(2.24)	171(2.77)	36(2.50)
7	Zhao	980/1000	337(6.18)	438(8.25)	177(11.69)	406(5.79)	443(7.18)	106(7.37)
8	Wu	539/627	205(3.76)	232(4.37)	102(6.74)	263(3.75)	278(4.50)	86(5.98)
9	Li	501/576	173(3.17)	207(3.90)	88(5.81)	227(3.23)	250(4.05)	67(4.66)
10	Zhang	400/400	133(2.44)	206(3.88)	61(4.03)	177(2.52)	158(2.56)	65(4.52)
11	Hofer	142/1793	86(1.58)	45(0.85)	6(0.40)	963(13.72)	623(10.09)	119(8.28)
12	Liu	888/885	481(8.81)	351(6.62)	56(3.70)	468(6.67)	356(5.77)	61(4.24)
13	Ding	1300/1344	500(9.16)	563(10.61)	210(13.87)	526(7.50)	604(9.78)	198(13.77)
14	Chen	976/1057	351(6.43)	461(8.69)	141(9.31)	430(6.13)	486(7.87)	117(8.14)
15	Gago -Dominguez	498/588	217(3.98)	189(3.56)	43(2.84)	278(3.96)	210(3.40)	43(2.99)
16	Gago -Dominguez	506/530	178(3.26)	236(4.45)	85(5.61)	203(2.89)	270(4.37)	54(3.76)
17	Liu	1079/1115	588(10.78)	419(7.90)	72(4.76)	576(8.21)	461(7.47)	78(5.42)
18	Choi	720/720	311(5.70)	322(6.07)	87(5.75)	345(4.92)	320(5.18)	55(3.82)
19	Savage	1995/2296	1171(21.46)	699(13.17)	97(6.41)	1313(18.71)	811(13.14)	141(9.81)

CI=0.93-1.09). Notably, in subsequent analyses stratified by cancer type, the rs2736098 variant was significantly associated with increased lung cancer (OR=1.18; 95% CI=1.07-1.29) and hepatocellular carcinoma risk (OR=1.38; 95% CI=1.20-1.59), however, the rs2736098 variant showed no association reaching the level of statistical significance for other cancer types.

Publication bias

We used funnel plot and the Egger's test to address potential publication bias in the available literature. As shown in Figure 2, the shape of the funnel plot seemed symmetrical, suggesting absence of publication bias. The Egger's test also provided statistical evidence for funnel plot symmetry (p= 0.726).

Discussion

To date, most of the association studies that investigated the relationship between *TERT* polymorphisms and susceptibility to cancer have focused on the rs2736100 and rs2736098. However, in a previous meta-analysis that included 5 cancer types, the rs2736098 variant showed no association reaching statistical significance for overall cancer risk. Nevertheless, an increasing number of replication studies have still paid special attention to the association between rs2736098

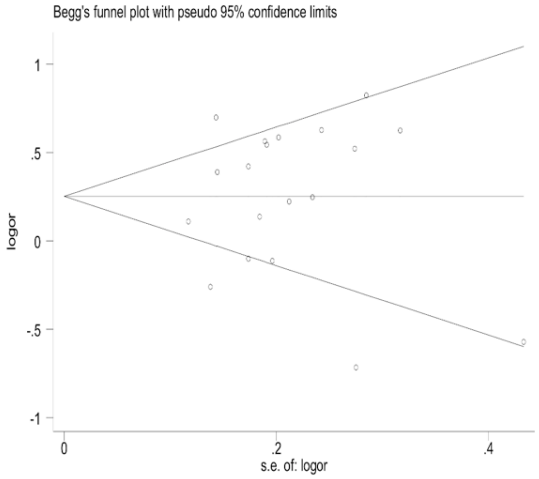

Figure 2. Funnel plot of the *TERT* rs2736098 polymorphism and cancer risk.

and cancer risk. In this study, we performed an update meta-analysis by pooling 19 studies with a total of 12,520 cancer cases and 14,968 controls, and demonstrated that the A allele of rs2736098 was associated with a significantly increased risk of cancer, mainly lung cancer and hepatocellular carcinoma.

The SNP rs2736098 at 5p15.33 is located at exon 2 of *TERT*. The 5p15.33 locus contains two known genes: the *TERT* gene and the *CLPTM1L* gene. *TERT* is the reverse transcriptase component of telomerase, making it essential for telomerase enzyme production and maintenance of telomeres [28]. The telomerase enzyme is responsible for telomere regeneration, and up to 90% of human tumor samples show telomerase activity, indicating that regeneration of telomeres is a vital step for most forms of carcinogenesis [29]. Notably, based on the Encyclopedia of DNA Elements (ENCODE) DNase I hypersensitive site (DHS) sequencing data set, we found that the SNP rs2736098 is within open chromatin regions associated with gene regulatory elements. It is plausible that variation in the SNP rs2736098 may result in aberrant activities of certain transcriptional factors. In turn, those factors may regulate the expression of the same target genes nearby or throughout the genome, hence activating crucial signaling pathways that drive carcinogenesis. However, these results are very preliminary and merit further investigations.

In our meta-analysis, significant association existed among the overall analysis with *TERT* rs2736098 in all kinds of cancers, and the association was stronger in Asians, and no significant association was observed in Caucasians. In subsequent analyses stratified by cancer types, the rs2736098 was definitely associated with increased lung cancer and hepatocellular carcinoma risk in all genetic models, which was also associated with increased bladder cancer risk for the comparison of homozygous (AA vs GG), however, the association was not significant for other cancer types. There are several reasons for the inconsistent results. First, the difference may due to genetic heterogeneity between different ethnicities, as well as cancer types. Second, since only 2 studies, each of breast cancer and SCCHN, were included in our meta-analysis, which might not be large enough to make a convincing conclusion for stratified analysis. Nevertheless, further studies with large sample size are warranted to evaluate the relationship between rs2736098 and subgroup cancer risk, especially breast cancer, SCCHN, esophageal cancer, colorectal cancer and glioma.

When interpreting our results, several limitations need to be addressed. First, the lack of detailed information, such as age, gender, smoking habits, and alcohol consumption, in some studies

Table 3. Summary ORs of TERT rs2736098 polymorphism and cancer risk

Variables	*Studies*	*Sample size*	*GA vs GG*			*AA vs GG*			*Dominant model*		
			OR (95%CI)	*P**	I^2	*OR (95%CI)*	*P**	I^2	*OR (95%CI)*	*P**	I^2
Total	19	27,488	1.09(1.01,1.18)	0.005	0.512	1.30(1.10,1.54)	0.000	0.733	1.14(1.04,1.25)	0.000	0.666
Ethnicity											
Asians	14	16,209	1.16(1.05,1.27)	0.032	0.456	1.49(1.25,1.76)	0.001	0.634	1.20(1.07,1.34)	0.000	0.669
Caucasians	5	11,279	0.96(0.88,1.04)	0.501	0	0.87(0.74,1.03)	0.335	0.123	1.00(0.93,1.09)	0.123	0.448
Cancer type											
Lung cancer	6	7,014	1.13(1.02,1.25)	0.987	0	1.78(1.53,2.07)	0.893	0	1.18(1.07,1.29)	0.170	0.355
Breast cancer	2	4,782	0.96(0.85,1.09)	0.678	0	0.70(0.55,0.90)	0.138	0.546	0.92(0.82,1.04)	0.300	0.069
HCC	3	3,855	1.44(0.91,2.29)	0.000	0.872	1.20(0.99,1.45)	0.306	0.154	1.38(1.20,1.59)	0.079	0.606
Bladder cancer	3	2,587	1.17(0.98,1.38)	0.095	0.576	1.69(1.30,2.20)	0.273	0.229	1.19(0.82,1.71)	0.002	0.838
SCCHN	2	3,967	0.92(0.81,1.05)	0.577	0	0.90(0.70,1.16)	0.963	0	1.08(0.95,1.23)	0.184	0.434
Esophageal cancer	1	1,315	1.00(0.79,1.27)	--	--	1.15(0.80,1.65)	--	--	1.03(0.82,1.29)	--	--
Colorectal cancer	1	1,935	0.81(0.56,1.18)	--	--	0.57(0.24,1.32)	--	--	0.77(0.54,1.10)	--	--
Glioma	1	2,033	1.16(0.96,1.41)	--	--	1.48(1.11,1.96)	--	--	1.18(0.91,1.51)	--	--

HCC: hepatocellular carcinoma, SCCHN: squamous cell carcinoma of the head and neck, OR: odds ratio, CI: confidence interval, *Random-effects model was used when p value for heterogeneity test < 0.05; otherwise, fixed-effect model was used

limited further stratification analysis, and a more precise OR should be adjusted for those factors that may be associated with cancer risk. Second, different genotyping methods with differing accuracy were used in previous studies, which might lead to a bias to some extent. Despite these limitations, our study has several strengths. First, previous meta-analyses suggested that the *TERT* rs2736098 polymorphism is not associated with cancer risk, however, our update meta-analysis provided new evidence that the variant genotypes of *TERT* rs2736098 polymorphisms may significantly increase the risk of cancer, indicating the potential role of the *TERT* rs2736098 in carcinogenesis. Second, the well-designed search and selection method significantly increased the statistical power of this meta-analysis and the results did not show any evidence of publication bias, indicating that our results are reliable.

The overall results of this meta-analysis have shown that the *TERT* rs2736098 polymorphism is associated with cancer risk. Further studies are warranted to extend our findings and to evaluate the potential functional significance of the loci.

Acknowledgements

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