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Association between the *WRAP53* gene rs2287499 C>G polymorphism and cancer risk: A meta-analysis

H.Y. Cao, S. Wang, Z.Y. Zhang and J.Y. Lou

Department of Gynecology and Obstetrics,
West China Second University Hospital, Sichuan University, Chengdu, China

Corresponding author: J.Y. Lou
E-mail: Loujiangyan1@aliyun.com

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ABSTRACT. The *TP53* 5'-untranslated region flanking the gene *WRAP53* (also known as *WDR79* and *TCAB1*) has been hypothesized to be associated with cancer risk due to its critical function in regulating p53 levels. In this review, we analyzed the association between the *WRAP53* gene rs2287499 C>G polymorphism and risk of cancer using five case-control studies, comprising seven datasets. All analyses were performed using RevMan software. In the overall analysis, no significant association between rs2287499 and risk of cancer was found. We then conducted subgroup tests, stratifying the data by cancer type, ethnicity, sample source, and quality score. Only the brain and breast cancer subgroups returned significant results, but with conflicting implications. Our concerns regarding this are discussed in detail. In conclusion, the rs2287499 polymorphism may be associated with risk of cancer. Further studies taking into consideration a broader range of cancer types and different ethnicities are warranted.

Key words: *WRAP53*; rs2287499; Gene polymorphism; Cancer

INTRODUCTION

An estimated 14.1 million new cases of cancer were diagnosed and 8.2 million cancer-related deaths occurred in 2012 (Ferlay et al., 2015). Over 20 million new cases are expected annually as early as 2025 (Bray et al., 2012). Cancer progression is a multi-step process, proceeding by multiple alterations, and characterized by many mutations in the form of substitutions, deletions, chromosomal translocations, and gene duplications. Tumor development is primarily caused by genetic and epigenetic modifications involving members of two broad gene categories: proto-oncogenes and tumor suppressor genes. The *TP53* gene is one of the most studied and commonly mutated tumor suppressor genes in human cancers (Olivier et al., 2009). Its 5'-untranslated region flanking gene, *WRAP53* (also known as *WDR79* and *TCAB1*), located on chromosome 17p13, performs an essential function in maintaining normal intracellular levels of p53 by targeting a specific region of p53 mRNA, thus protecting it from degradation (Mahmoudi et al., 2009). Single nucleotide polymorphisms (SNPs) have been confirmed to play important roles in the etiology of cancer and are therefore of great interest in this field. However, as opinions vary in regard to the significance of *WRAP53* SNPs, no unanimous conclusion can be drawn (Lan et al., 2009; Schildkraut et al., 2009; Rizzato et al., 2011; Mędrek et al., 2013; Saldaña-Meyer et al., 2014; Garvin et al., 2015). With this in mind, we performed the current meta-analysis to explore the relationship between the common non-synonymous C>G SNP in the first coding exon of *WRAP53* (Arg68Gly) and risk of cancer.

MATERIAL AND METHODS

Search strategy

To identify all articles having examined the association between the *WRAP53* polymorphism of interest and cancer risk, we conducted a literature search of PubMed, Google Scholar, and the Chinese Biomedicine Database. All relevant articles were retrieved using the following terms: ‘‘*WRAP53* or *TCAB1* or *WDR79*’’, “rs2287499 or R68G”, “cancer or tumor or carcinoma”, “polymorphism or variant or mutation”. References included in the retrieved publications were also screened to identify further relevant studies. In the case of multiple publications involving the same study population, only the largest-scale investigation was included. Selection of articles was carried out by two investigators independently, by assessing titles, abstracts, and full texts according to the inclusion and exclusion criteria below. Any dispute was resolved by discussion. Only research articles published in English or Chinese were included. Where a single article reported the results of several different studies, each study was treated as a separate dataset in our meta-analysis. And all included articles will be evaluated by a scoring system.

Inclusion criteria

The following inclusion criteria were applied when selecting studies for the current meta-analysis: publications had to 1) be a case-control study; 2) refer to the association between the rs2287499 polymorphism and cancer risk; 3) include details of case and control group sample sizes, along with allele/genotype distributions, and other information necessary to our analysis.

Exclusion criteria

The following were excluded from our analysis: 1) articles involving duplication of previous publications; 2) comments, reviews, and editorials; 3) family-based studies of pedigrees; 4) investigations lacking detailed genotype data.

Data extraction

Three investigators (H.Y.C., S.W., and Z.Y.Z.) extracted all data independently, in compliance with the inclusion criteria listed above. Any discrepancy was resolved by discussion until an agreement was reached. The following information was collected from each publication: first author's name, publication year, location, ethnicity, cancer histology, study design, data adjustment, sample type, and genotype frequencies in case and control groups.

A quality assessment scale (Table 1) was employed based on previous research, to gauge the standard of eligible studies (Camargo et al., 2006; Gao et al., 2011; Guo et al., 2012; Shen et al., 2012).

Table 1. Criteria for quality assessment.

Parameter	Score
Source of cases	
Selected from population or cancer registry	2
Selected from oncology department or cancer institute	1
No description	0
Representativeness of controls	
Population-based	2
Population-hospital mixed	1.5
Hospital-based	1
No description	0
Diagnosis of cancer	
Histologically or pathologically confirmed	2
Patient medical record	1
No description	0
Specimens of cases for genotyping	
Peripheral blood or normal tissues	2
Tumor tissues or exfoliated cells	1
No description	0
Quality control of genotyping	
Different genotyping assays confirmed the result	2
Quality control by repeated assay	1
No description	0
Total sample size	
>1000	2
200-1000	1
<200	0

Statistical analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were pooled to evaluate the association between the rs2287499 polymorphism and risk of cancer. ORs were calculated for allele contrast (G *vs* C), homozygote (GG *vs* CC), dominant (GG+CG *vs* CC), and recessive (GG *vs* CC+CG) genetic models. Heterogeneity was assessed using the I^2 statistic, interpreted as the proportion of the total variation contributed by inter-study variation, and the Cochran chi-square *Q*-test, with a significance level of $P < 0.10$ and $I^2 > 50\%$. When significant

heterogeneity values were returned, the random-effect model was used to estimate pooled ORs (DerSimonian and Kacker, 2007). Otherwise, the fixed-effect model was employed. We conducted our meta-analysis according to the PRISMA (Moher D et al, 2009) checklist and followed the appropriate guidelines. Hardy-Weinberg equilibrium (HWE) was evaluated for each study by chi-square tests of control group data. $P < 0.05$ was considered to represent a significant departure from HWE. All statistical tests were performed with RevMan version 5.2 (The Cochrane Collaboration, 2012), and P values less than 0.05 were considered statistically significant.

RESULTS

Study inclusion and characteristics

As shown in Figure 1, five eligible articles concerning *WRAP53* rs2287499, including seven case-control datasets comprising 7107 cases and 10,737 controls were analyzed (Baynes et al., 2007; Garcia-Closas et al., 2007; Malmer et al., 2007; Rizzato et al., 2011; Sedaie Bonab et al., 2014). One of these articles, consisting of an investigation of different brain cancer types, was treated as three separate datasets in our analysis, all sharing the same group of controls. The main characteristics of the included studies are summarized in Table 2. Only one study was found to have a control group not conforming to HWE (Table 3).

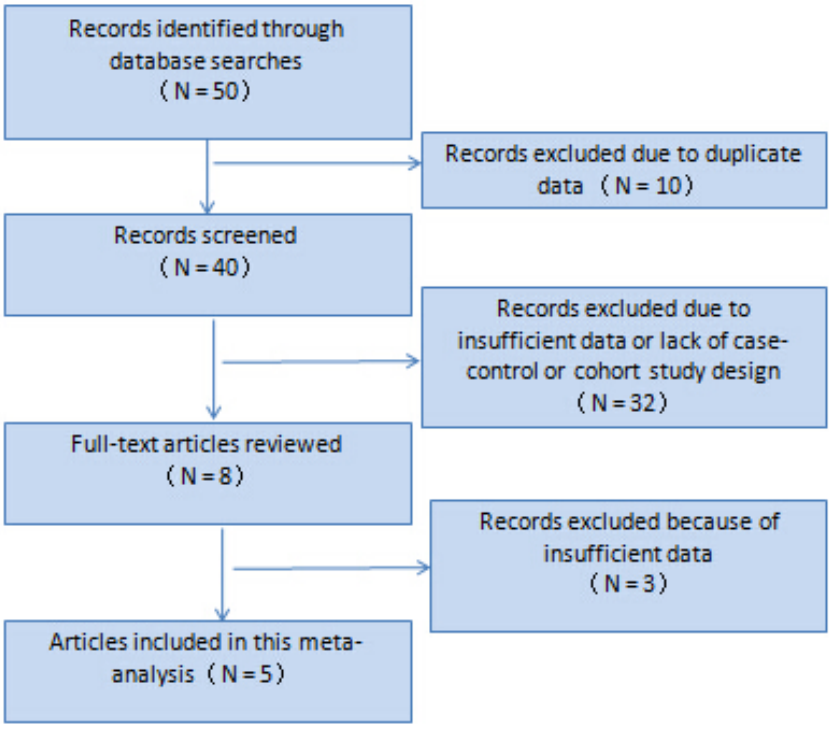

Figure 1. Flow chart demonstrating the process by which articles were selected for inclusion in the meta-analysis.

Table 2. Characteristics of the studies included in the meta-analysis.

First author	Year	Location	Ethnicity	Histology	Study design	Data adjustment	Sample type (cases)	Cases (N)	Controls (N)	Quality score
Baynes	2007	Mixed	Mixed	Breast cancer	Cancer registry	None	Blood	2274	2186	9
Garcia-Closas	2007	Mixed	Caucasian	Breast cancer	Hospital-based	Age, study population	Blood	2692	3367	10
Malmer glioblastoma)	2007	Mixed	Caucasian	Glioblastoma	Population-based	Age, sex, country	Blood	647	1483	10
Malmer (glioma)	2007	Mixed	Caucasian	Glioma	Population-based	Age, sex, country	Blood	275	1483	10
Malmer meningioma)	2007	Mixed	Caucasian	Meningioma	Population-based	Age, sex, country	Blood	484	1483	10
Rizzato	2011	Mixed	Caucasian	Basal cell carcinoma	Population-based	Age at diagnosis, gender, nationality, risk categories	Blood	529	532	8
Sedaie Bonab	2014	Iran	Caucasian	Breast cancer	Population-based	None	Mixed	206	203	9

Table 3. Distributions of *WRAP53* genotypes and alleles among cases and controls.

First author	CC (cases)	CG (cases)	GG (cases)	CC (controls)	CG (controls)	GG (controls)	P for HWE
Baynes	1699	453	34	1797	438	39	0.043
Garcia-Closas	2011	631	50	2595	732	40	0.146
Malmer (glioblastoma)	230	44	1	1154	306	23	0.6
Malmer (glioma)	530	111	6	1154	306	23	0.6
Malmer (meningioma)	380	98	6	1154	306	23	0.6
Rizzato	406	107	5	397	114	12	0.269
Sedaie Bonab	143	57	6	135	56	12	0.068

HWE = Hardy-Weinberg equilibrium.

Meta-analysis results

No significant association between any genotype of the rs2287499 polymorphism and cancer risk was found using the overall dataset (G *vs* C: OR = 0.94, 95%CI = 0.82-1.07, Figure 2A; CG *vs* CC: OR = 1.02, 95%CI = 0.94-1.10, Figure 2B; GG *vs* CC: OR = 0.76, 95%CI = 0.48-1.20, Figure 2C; GG+CG *vs* CC: OR = 0.94, 95%CI = 0.82-1.08, Figure 2D; GG *vs* GC+CC: OR = 0.77, 95%CI = 0.50-1.20, Figure 2E). The C allele was observed at a higher frequency than the G allele in both case and control groups, the former being the major allele and the latter the minor allele among the study population. Considering the possible impact of variation from factors such as cancer type, ethnicity, sample type, and quality score, we conducted four subgroup analyses (Table 4). Only the cancer type subgroup returned significant associations. The brain cancer dataset showed a modest risk reduction for individuals under allele contrast, codominant, and dominant models genotypes, while breast cancer data analyzed on its own revealed an increase in risk for allele contrast, codominant, and dominant models genotypes. Both of these results were obtained using a fixed-effect model.

DISCUSSION

Antisense transcription, that is transcription from the strand opposite the sense strand, is an indispensable regulator of gene expression found in all kingdoms of life, and occurs in approximately 70% of all mammalian genes (Katayama et al., 2005). As a bidirectionally transcribed gene, *WRAP53* has been hypothesized to be associated with cancer risk due to the fact that it neighbors *TP53*. Much research has been conducted into this topic, yet no clear consensus has been reached. This was the issue that initially motivated this study.

Previous studies have provided evidence indicating that WRAP53 is a potential oncoprotein whose overexpression can induce cell transformation and promote cancer cell survival, and whose knockdown leads to massive cancer cell death (Mahmoudi et al., 2011). Mędrek et al. (2013) found *WRAP53* to be associated with ovarian cancer risk in a Polish population, although only in relation to its rs2287497 and rs2287498 polymorphisms. In

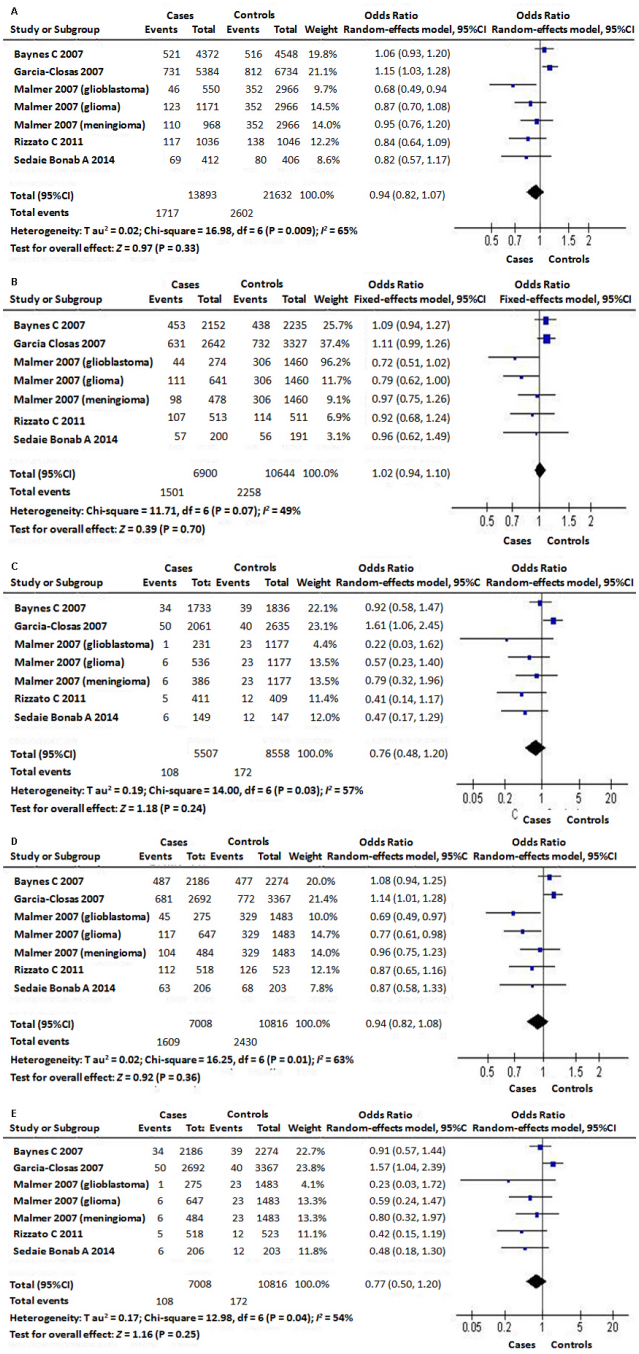

Figure 2. Forest plots of the association between cancer risk and the rs2287499 polymorphism in the overall study populationunder the following models: **A.** G *vs* C, **B.** CG *vs* CC, **C.** GG *vs* CC, **D.** GG+CG *vs* CC, and **E.** GG *vs* GC+CC. CI = confidence interval; d.f. = degrees of freedom.

Table 4. Summary of odds ratios and 95% confidence intervals relating to the *WRAP53* gene rs2287499 polymorphism and cancer risk.

Study group	Allele contrast model				Codominant model								Dominant model				Recessive model			
	G/C				CG/CC				GG/CC				GG+CG/CC				GG/GC+CC			
	Fixed			Random	Fixed			Random	Fixed			Random	Fixed			Random	Fixed			Random
	OR (95%CI)	P_h	I^2	OR (95%CI)	OR (95%CI)	P_h	I^2	OR (95%CI)	OR (95%CI)	P_h	I^2	OR (95%CI)	OR (95%CI)	P_h	I^2	OR (95%CI)	OR (95%CI)	P_h	I^2	OR (95%CI)
Overall	1.01 (0.95-1.08)	0	65	0.94 (0.82-1.07)	1.02 (0.94-1.10)	0.1	49	0.97 (0.86-1.09)	0.93 (0.72-1.19)	0	57	0.76 (0.48-1.20)	1.01 (0.94-1.09)	0	63	0.94 (0.82-1.08)	0.92 (0.72-1.18)	0	54	0.77 (0.50-1.20)
Cancer type																				
Brain cancer	0.85 (0.74-0.98)	0.2	31	0.85 (0.72-1.01)	0.84 (0.72-0.98)	0.3	12	0.84 (0.71-0.99)	0.56 (0.31-1.03)	0.5	0	0.60 (0.33-1.11)	0.82 (0.70-0.95)	0	29	0.82 (0.68-0.98)	0.58 (0.32-1.07)	0.5	0	0.62 (0.34-1.14)
Basal cell carcinoma	0.84 (0.64-1.09)	NA	NA	0.84 (0.64-1.09)	0.92 (0.68-1.24)	NA	NA	0.92 (0.68-1.24)	0.41 (0.14-1.17)	NA	NA	0.41 (0.14-1.17)	0.87 (0.65-1.16)	NA	NA	0.87 (0.65-1.16)	0.42 (0.15-1.19)	NA	NA	0.42 (0.15-1.19)
Breast cancer	1.09 (1.01-1.18)	0.2	43	1.07 (0.95-1.21)	1.10 (1.00-1.20)	0.8	0	1.10 (1.00-1.20)	1.14 (0.85-1.54)	0	69	1.01 (0.56-1.82)	1.10 (1.01-1.20)	0	0	1.10 (1.01-1.20)	1.12 (0.84-1.51)	0.1	67	1.00 (0.56-1.77)
Ethnicity																				
Caucasian	1.00 (0.92-1.08)	0	70	0.90 (0.76-1.07)	0.99 (0.90-1.08)	0.1	52	0.93 (0.80-1.08)	0.93 (0.69-1.25)	0	64	0.67 (0.36-1.26)	0.98 (0.90-1.07)	0	67	0.90 (0.75-1.07)	0.93 (0.69-1.25)	0	61	0.69 (0.38-1.25)
Mixed	1.06 (0.93-1.20)	NA	NA	1.06 (0.93-1.20)	1.09 (0.94-1.27)	NA	NA	1.09 (0.94-1.27)	0.92 (0.58-1.47)	NA	NA	0.92 (0.58-1.47)	1.08 (0.94-1.25)	NA	NA	1.08 (0.94-1.25)	0.91 (0.57-1.44)	NA	NA	0.91 (0.57-1.44)
Sample source																				
Blood	1.02 (0.95-1.09)	0	68	0.95 (0.83-1.09)	1.02 (0.94-1.10)	0	57	0.96 (0.85-1.10)	0.97 (0.75-1.26)	0	58	0.81 (0.50-1.32)	1.01 (0.94-1.09)	0	68	0.94 (0.81-1.09)	0.97 (0.75-1.25)	0.1	55	0.83 (0.52-1.31)
Mixed	0.82 (0.57-1.17)	NA	NA	0.82 (0.57-1.17)	0.96 (0.62-1.49)	NA	NA	0.96 (0.62-1.49)	0.47 (0.17-1.29)	NA	NA	0.47 (0.17-1.29)	0.87 (0.58-1.33)	NA	NA	0.87 (0.58-1.33)	0.48 (0.18-1.30)	NA	NA	0.48 (0.18-1.30)
Quality score																				
≥10	1.03 (0.94-1.12)	0	77	0.92 (0.75-1.14)	1.00 (0.91-1.10)	0	70	0.91 (0.74-1.13)	1.10 (0.79-1.53)	0	64	0.83 (0.40-1.74)	1.00 (0.91-1.10)	0	78	0.90 (0.71-1.14)	1.10 (0.79-1.53)	0.1	59	0.86 (0.43-1.72)
<10	0.99 (0.89-1.11)	0.2	45	0.94 (0.79-1.13)	1.05 (0.92-1.19)	0.5	0	1.05 (0.92-1.19)	0.74 (0.50-1.08)	0.2	30	0.67 (0.39-1.15)	1.02 (0.90-1.15)	0	13	1.01 (0.87-1.16)	0.73 (0.50-1.07)	0.3	24	0.68 (0.41-1.13)

P_h = P value for test of heterogeneity, OR = odds ratio, CI = confidence interval, NA = not applicable.

addition, Garcia-Closas et al. (2007) established a significant association between rs2287499 and breast cancer. However, data generated by Jung et al. (2008) and Malmer et al. (2005) suggest no connection between this SNP and breast cancer risk.

With regard to our study, it may be inferred that cancer type constituted a source of heterogeneity, since the brain and breast cancer subgroups both returned modestly significant, contrasting results (Table 4). All things considered, we tend to accept the result obtained using the breast cancer dataset, since it is in accordance with our expectations. However, this should be interpreted with caution. Why the analyses of these two subgroups should lead to opposite conclusions remains a thought-provoking question (Ghert and Petrisor, 2012). First, although the three datasets in the brain cancer subgroup shared the same control group, thus leading to lower heterogeneity and more accurate conclusions, the small sample sizes involved may have resulted in a sampling effect and thereby, a conflicting outcome. Second, three types of brain cancer were included in this subgroup, which may have differed in clinical characteristics such as incidence, malignancy, diagnostic and prognostic parameters, and other factors such as age and gender of patient, besides intrinsic differences. Such disparity may cause clinical, statistical, and methodological biases, and might therefore represent one of the limitations of this meta-analysis. Interestingly, heterogeneity was significantly decreased in the low quality score subgroup. This odd finding may be due to methodological shortcomings, such as the unclear source and selection criteria of these cases, and deviation from HWE, which may be the result of non-random mating. In addition, of the few studies available concerning the association between rs2287499 and cancer risk, most have been conducted in Caucasian populations and involve a limited range of cancer types. All these factors may be responsible for the observed heterogeneity and only moderately significant results achieved in this meta-analysis (Higgins et al., 2002). With this in mind, many more studies are needed, particularly those involving a diverse range of other ethnicities and populations. Since allele frequencies vary between such groups, this data would certainly be helpful for future cancer prevention and treatment. Finally, we did not consider studies published in languages other than English and Chinese, which may have caused publication and language-related biases.

In conclusion, despite its limitations, the present meta-analysis suggests that the *WRAP53* rs2287499 polymorphism may be associated with cancer risk. Nevertheless, further larger-scale and well-designed studies should be carried out, which could help us better understand the association between this polymorphism and cancer risk.

Conflicts of interest

The authors declare no conflict of interest.

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