RESEARCH ARTICLE

Association between the TP53BP1 rs2602141 A/C Polymorphism and Cancer Risk: A Systematic Review and Meta-Analysis

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Abstract

Background: The p53-binding protein 1 (TP53BP1) gene may be involved in the development of cancer through disrupting DNA repair. However, investigation of associations between TP53BP1 rs2602141 A/C polymorphism and cancer have yielded contradictory and inconclusive outcomes. We therefore performed a meta-analysis to evaluate the association between the TP53BP1 rs2602141 A/C polymorphism and cancer susceptibility. Materials and Methods: Published literature from PubMed, Medline, the Cochrane Library, EMbase, Web of Science, Google (scholar), CBMDisc, Chongqing VIP database, and CNKI database were retrieved. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed or random-effects models. Publication bias was estimated using funnel plots, Begg's and Egger's test. Results: A total of seven studies (3,018 cases and 5,548 controls) were included in the meta-analysis. Our results showed that the genotype distribution of TP53BP1 rs2602141 A/C was not associated with cancer risk overall. However, on subgroup analysis, we found that TP53BP1 rs2602141 A/C was associated with cancer risk within an allele model (A *vs* C, OR=1.14, 95%CI: 1.01-1.29) and a codominant model (AA *vs* CC, OR=1.36, 95%CI: 1.06-1.74) in Asians rather than in Caucasians. Subgroup analysis by cancer type, genotype, and with or without adjustment for controls showed no significant association. Conclusions: The findings suggested an association between rs2602141 A/C polymorphism in TP53BP1 gene and increased risk of cancer in Asians.

Keywords: TP53-binding protein 1 - cancer - polymorphism - gene - meta-analysis

Asian Pac J Cancer Prev, **15 (6)**, 2917-2922

Introduction

It was reported that there was about 12.7 million new cancer cases and 7.6 million cancer deaths through out the world in 2008 (Ferlay et al., 2010). However, the etiology of cancer remains unknown and disease-modifying treatments are limited.

Previous researches suggested a more direct role of p53-binding protein 1 (TP53BP1) in the cellular response to DNA damage (Schultz et al., 2000; Rappold et al., 2001). In addition, studies suggested that TP53BP1 was a positive regulator of the BRCA1 promoter (Rauch et al., 2005) and a key transducer of the DNA damage checkpoint signal (Wang et al., 2002) and that it constitutively played an important role in the etiology of human cancers (DiTullio et al., 2002).

Since the involvement of cytokines in cancer was hypothesized, there were many candidate genes approach in designing a case-control association study of single nucleotide polymorphisms (SNPs) including TP53BP1. Previous researches have revealed that no association between the variant genotype of the TP53BP1 rs2602141 A/C SNPs and cancer risk (Frank et al., 2005; Ma et al., 2006; Chen et al., 2007; He et al., 2010), but Zhang et al. (2013) reported that the rs2602141 genotype increased lung cancer risk (Zhang et al., 2013). So published data were contradictory, and the association between TP53BP1 rs2602141 A/C polymorphism and cancer risk was still inconclusive. Therefore, we conducted a systematic review and meta-analysis to get a more precise estimate of the association between TP53BP1 rs2602141 A/C polymorphism and cancer susceptibility.

Materials and Methods

Selection of eligible studies

We searched Pubmed, Medline (US National Library of Medicine, Bethesda, MD), Embase, the Cochrane Library,

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Web of Science, Google (scholar), Chinese Biological Medicine, China National Knowledge Infrastructure, Wang Fang Data and Chongqing VIP database (Last search was updated on December 15, 2013) using the terms "p53-binding protein 1 or TP53BP1 or 53BP1", "Gln1136 Lys or rs2602141 or K1136Q", "cancer or tumor or carcinoma" and "polymorphism, variant, mutation or SNP". The search was done without restriction on language, but we only included published articles written in English or Chinese. We used the PubMed option "Related Articles" for each study to retrieve additional potentially relevant articles. Reference lists were checked and researchers contacted for additional literatures.

Selection criteria

Studies were selected if they met the following criteria: (1) association study with a case-control or cohort design; (2) the study investigated the association between rs2602141 polymorphisms of TP53BP1 and the risk of cancer; (3) in the case of multiple publications from the same study group, the most complete and recent results were used.

Exclusion criteria

The exclusion criteria were defined as: 1) abstracts, reviews and animal studies; 2) useless data reported, genotype number or frequency not included; 3) study without sufficient data for meta-analysis; and 4) genotype distribution in the control population not consistent with HWE. If more than one study was published by the same author using the same case series, only the most recent study or the study with the largest size of samples was included in our meta-analysis.

Data extraction

Two reviewers (Lei Liu and Dong Zhang) independently scrutinized studies on the associations between TP53BP1 rs2602141 A/C polymorphisms and cancer. When discrepancies were appeared, all investigators were recruited to assess the data. The following information was collected: First author, year of publication, location, ethnicity, characteristics, sample sizes of patients and controls, genotype numbers, *p* value for HWE.

The reviewers developed a quality assessment scale (Table 1), which was modified from previous studies (Camargo et al., 2006; Liu et al., 2011; Gao et al., 2011), to evaluate the quality of eligible studies.

The review and analysis were guided to conduct by the PRISMA statement for preferred reporting of systematic reviews and meta-analysis (Moher et al., 2009).

Statistical analysis

Odds ratio (ORs) with 95% confidence intervals (CIs) for genotypes and alleles were used to assess the strength of association between TP53BP1 rs2602141 A/C polymorphisms and risk of cancer. The ORs were performed for the allele contrasts, additive genetic model, as well as recessive genetic model and dominant genetic model, respectively. Heterogeneity was examined with I^2 statistic interpreted as the proportion of total variation contributed by between-study variation. We also measured the effect of heterogeneity using a quantitative measure, $I^2 = 100\% \times (Q\text{-}d\ f)/Q$. If there was a statistical difference in terms of heterogeneity ($p<0.10$, $I^2>50\%$), the random effects model would be used to estimate the pooled ORs (DerSimonian et al., 1986; 2007). Otherwise, the pooled ORs were estimated by the fixed effects model (Mantel et al., 1959). Sensitivity analysis was carried out by deleting one single study each time to examine the influence of individual data set on the pooled ORs. The possible publication bias was assessed with funnel plots and Egger's test. An asymmetric plot suggests a possible publication bias and the *p* value of Egger's test less than 0.05 was considered representative of statistically significant publication bias (Egger et al., 1997). All statistical tests were performed with RevMan version 5.0 (Review Manager, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2010) and Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood Cliffs, I.N.J., USA). All *p* values were two sided and a *p* value of smaller than 0.05 for any test was considered to be statistically significant.

Table 1. Scale for Quality Assessment

Paramete	Score
Source of cases:	
Selected from population o rcancer 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:	
Histological 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

Results

Study inclusion and characteristics

The study by He et al. (He et al., 2010) was divided into three studies according to cancer type. As showed in Figure 1, a total of seven studies were included in the meta-analysis including 3,018 cases and 5,548 controls (Frank et al., 2005; Ma et al., 2006; Chen et al., 2007; He et al., 2010; Zhang et al., 2013). The studies identified and their main characteristics were summarized in Table 2 and Table 3. Genotype distribution of any polymorphism did not differ from Hardy-Weinberg equilibrium with in both groups (all were greater than 0.05).

Quantitative data synthesis

As showed in Table 4, meta-analysis of the total

Table 2. Characteristics of the Included Studies for Meta-analysis

First author	Publication year	Location	Ethnicity	Histology	Study design	Study design	Adjusted	Genotyping method	TP53BP1 polymorphism	Cases(n)	Controls(n)	Quality score
Frank B	2005	Germany	Caucasian	breast cancer	HB	CC	No	Taqman	D353E (rs560191),G412S (rs689647), K1136Q (rs2602141)	353	960	10
Ma H	2006	China	asian	breast cancer	HB	CC	No	polymerase chain reaction	T-885G (rs1869258), Glu353 Asp (rs560191), rs2602141 A/C	404	472	9
Chen K	2007	USA	Caucasian	squamous cell carcinoma of the head and neck	HB	CC	age, sex, ethnicity	polymerase chain reaction	T-885G (rs1869258), Glu353 Asp (rs560191), rs2602141 A/C	818	821	10
Zhang H	2013	China	asian	lung cancer	HB	CC	gender, age, smoking status	Taqman	Glu353 Asp (rs560191), rs2602141 A/C, G412S (rs689647)	640	685	10
He C	2010	USA	Caucasian	melanoma	HB	CC	age	Taqman	rs3862138, rs17782975,G412S (rs689647), K1136Q (rs2602141), rs2242069,rs9999047	218	870	10
He C	2010	USA	Caucasian	squamous cell carcinoma	HB	CC	age	Taqman	rs3862138, rs17782975,G412S (rs689647), K1136Q (rs2602141), rs2242069, rs9999047	285	870	10
He C	2010	USA	Caucasian	basal cell carcinoma	HB	CC	age	Taqman	rs3862138, rs17782975,G412S (rs689647), K1136Q (rs2602141), rs2242069, rs9999047	300	870	10

*HB, hospital based; CC, case-control; PCR, polymerase chain reaction

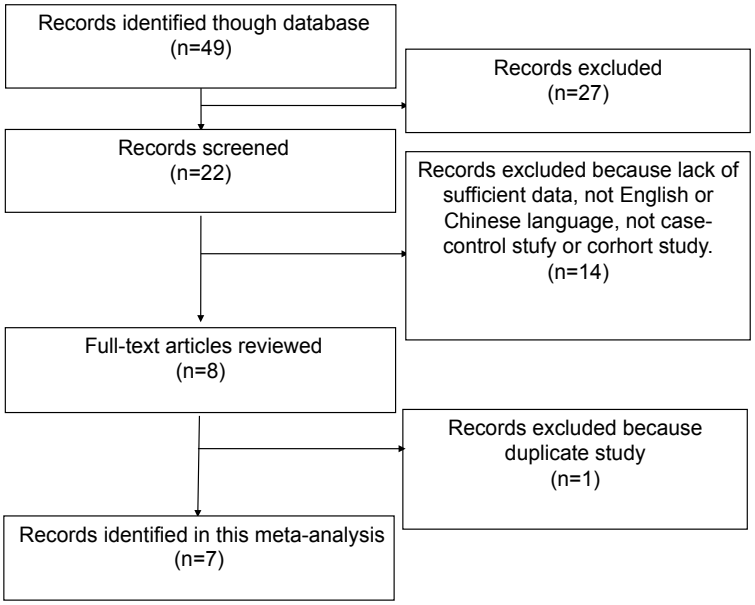

Figure 1. Flow Chart Demonstrating Those Studies That were Processed for Inclusion in the Meta-Analysis

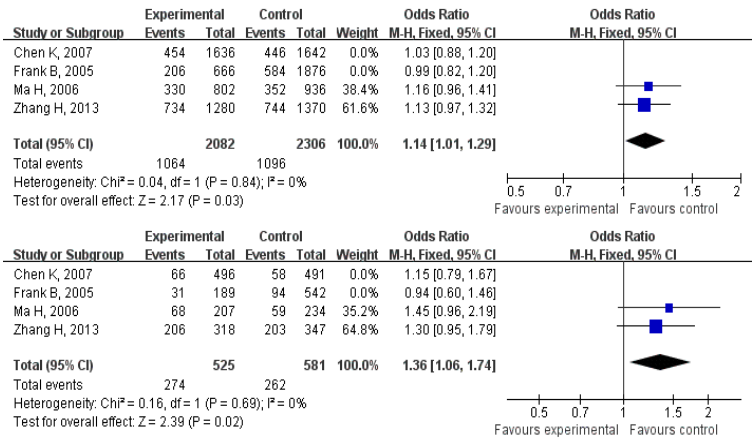

Figure 2. Forest Plot of the Association between Cancer and the rs2602141 A/C Mutation in Asian Population (A *vs* C); (AA *vs* CC)

studies showed that there was no association between rs2602141 A/C polymorphism and risk of cancer under all five genetic models in overall population (OR=1.08, 95%CI=0.99-1.17 for A *vs* C; OR=1.22, 95%CI=1.01-1.47 for AA *vs* CC; OR=1.11, 95%CI=0.94-1.32 for AA *vs* AC; OR=1.12, 95%CI=0.95-1.31 for recessive model; OR=1.03; 95%CI=0.91-1.17 for dominant model).

Subgroup analyses were performed of rs2602141 A/C polymorphism by ethnicity, showing that the rs2602141 A/C polymorphism was associated with elevated cancer risk in Asian (Figure 2) population (A *vs* C, OR =1.14, 95%CI =1.01-1.29; AA *vs* CC, OR =1.36, 95%CI =1.06-1.74) rather than in Caucasian.

In other subgroups analyses according to cancer type, adjusted with control or not, and genotyping methods, the results suggested that rs2602141 A/C polymorphisms were not associated with the risk of cancer (Table 4). The graphical funnel plots (Figure 3) and the results of Begg's and Egger's test (Begg, p=0.18; Egger, p=0.53) did not show any evidence of publication bias.

Sensitivity analysis

In order to examining the influence of the individual data set to the pooled ORs, we deleted every single study each time in this meta-analysis. According to sensitivity analysis, we found that there was no

Table 3. Distributions of TP53BP1 Genotype and Allele Among Cases and Controls

First author	Study groups	Distribution of TP53BP1 genotypes (n)				Frequency of TP53BP1 alleles (n)		HWE
		AA	AC	CC	AC+CC	A	C	
Chen K	Case	430	322	66	388	1182	454	0.6
	Control	433	330	58	388	1196	446	0.65
Frank B	Case	158	144	31	175	460	206	0.82
	Control	448	396	94	490	1292	584	0.64
Ma H	Case	139	194	68	262	472	330	0.98
	Control	175	234	59	293	584	352	0.15
Zhang H	Case	112	322	206	528	546	734	0.47
	Control	144	338	203	541	626	744	0.88
He C	Case	86	NA	NA	124	NA	NA	NA
melanoma	Control	389	NA	NA	449	NA	NA	NA
			NA	NA		NA	NA	NA
He C	Case	143	NA	NA	130	NA	NA	NA
SCC	Control	389	NA	NA	449	NA	NA	NA
			NA	NA		NA	NA	NA
He C	Case	154	NA	NA	142	NA	NA	NA
BCC	Control	389	NA	NA	449	NA	NA	NA

NA: not applicable; HWE: Hardy-Weinberg equilibrium; SCC: squamous cell carcinoma; BCC: basal cell carcinoma

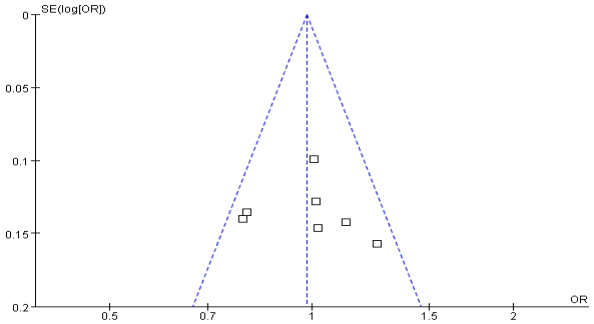

Figure 3. A Funnel Plot of Studies Conducted on the Association between rs2602141 A/C Mutation and Cancer Risk

substantial modification of estimates after exclusion of individual studies, indicating that the results were stable (data not shown).

Discussion

TP53BP1 gene has played an important role in both DNA repair and cell cycle control and also mediates the DNA damage checkpoint through cooperation with damage sensors and signal transducers (Miwa et al., 2013). The TP53BP1 contains two BRCA1 C-terminal (BRCT) domains, which is essential for tumor suppressor functions (Williams et al., 2001). The SNPs for TP53BP1 gene may play an important role in the etiology of cancer because of a direct role of TP53BP1 in the cellular response to DNA damage.

To the best of our knowledge, some researches that aim at the role of rs2602141 A/C polymorphism in cancer risk have been performed, but the results are controversial. This is the first meta-analysis to evaluate on the association between the rs2602141 A/C polymorphisms and cancer risk.

Although we have not found a significant association between TP53BP1 rs2602141 A/C polymorphism and cancer risk in overall population, we performed subgroups analyses based on different ethnicity, adjusted with control or not, genotyping methods and cancer type factors. Interestingly, the results showed us that rs2602141 A/C polymorphisms were associated with the risk of cancer in Asian population rather than that in Caucasian, suggesting that this polymorphism might be biologically functional in ethnicity. The genotype distributions of rs2602141 A/C in different ethnicity might account for this.

Table 4. Summary ORs and 95%CI of the rs2602141 Polymorphism in the TB53BP1 Gene and Cancer Risk

Study groups	Variables		Allele Model A *vs* C			Codominant model AA *vs* CC (fixed model)				Recessive model AA *vs* AC			Dominant model AA *vs* AC+CC			Variables CC+AC *vs* AA			Dominant model* CC+AC *vs* AA			
			OR(95%CI)	Ph	I2%	Model	OR(95%CI)	Ph	I2%	Model	OR(95%CI)	Ph	I2%	Model	OR(95%CI)	Ph	I2%	Model	OR(95%CI)	Ph	I2%	Model
Overall		4	1.08(0.99-1.17)	0.57	0	F	1.22(1.01-1.47)	0.51	0	F	1.11(0.94-1.32)	0.54	0	F	1.12(0.95-1.31)	0.48	0	F	1.03(0.91-1.17)	0.93	0	F	7	0.98(0.89-1.08)	0.22	28	F
Ethnicity																											
	Caucasian	2	1.01(0.90-1.14)	0.76	0	F	1.05(0.79-1.40)	0.49	0	F	1.05(0.78-1.40)	0.4	0	F	1.05(0.80-1.38)	0.43	0	F	1.01(0.87-1.18)	0.97	0	F	5	0.96(0.86-1.07)	0.13	44	F
	Asian	2	1.14(1.01-1.29)	0.84	0	F	1.36(1.06-1.74)	0.69	0	F	1.51(0.93-1.41)	0.26	20	F	1.15(0.94-1.41)	0.21	37	F	1.07(0.88-1.31)	0.63	0	F	2	1.07(0.88-1.31)	0.63	0	F
Cancer type																											
	Breast cancer	2	1.07(0.94-1.23)	0.26	23	F	1.18(0.88-1.59)	0.16	50	R	1.15(0.86-1.54)	0.16	49	F	1.16(0.76-1.76)	0.14	54	R	1.06(0.88-1.28)	0.58	0	F	2	1.06(0.88-1.28)	0.58	0	F
	Others	2	1.08(0.97-1.20)	0.4	0	F	1.24(0.97-1.57)	0.6	0	F	1.09(0.89-1.35)	0.7	0	F	1.09(0.89-1.33)	0.71	0	F	1.01(0.86-1.19)	0.94	0	F	5	0.95(0.85-1.07)	0.13	43	F
Study with matching																											
	Yes	2	1.08(0.97-1.20)	0.4	0	F	1.24(0.97-1.57)	0.6	0	F	1.09(0.89-1.35)	0.7	0	F	1.09(0.89-1.33)	0.71	0	F	1.01(0.86-1.19)	0.94	0	F	5	0.95(0.85-1.07)	0.13	43	F
	No	2	1.07(0.94-1.23)	0.26	23	F	1.18(0.88-1.59)	0.16	50	R	1.15(0.86-1.54)	0.16	49	F	1.16(0.76-1.76)	0.14	54	R	1.06(0.88-1.28)	0.58	0	F	2	1.06(0.88-1.28)	0.58	0	F
Genotyping																											
	PCR	2	1.08(0.96-1.22)	0.34	0	F	1.28(0.97-1.68)	0.41	0	F	1.27(0.96-1.67)	0.53	0	F	1.27(0.98-1.66)	0.45	0	F	1.4(0.89-1.22)	0.52	0	F	2	1.04(0.89-1.22)	0.52	0	F
	Taqman	2	1.07(0.95-1.21)	0.29	11	F	1.17(0.90-1.51)	0.23	31	F	1.03(0.83-1.27)	0.54	0	F	1.03(0.84-1.26)	0.56	0	F	1.02(0.84-1.23)	0.97	0	F	5	0.95(0.84-1.07)	0.14	43	F

*The study bt He et al. was included; Ph: p value for test of heterogeneity; PCR: polymerase chain reaction; OR: odds ratio; CI: confidence interval; F: fixed-effects model; R: radom-effects model

When stratified by adjusted with control or not, genotyping methods and cancer type factors, the results showed no significant association between rs2602141 A/C polymorphism and cancer risk in all comparison models tested. That may be because only one study (Zhang et al., 2013) reported that the rs2602141 A/C polymorphism was associated with a risk of cancer. Therefore, further studies are needed to confirm our results.

Some studies indicate that TP53BP1 variants may have protective effects on squamous cell carcinoma of the head and neck (SCCHN) risk but such effects were confined to TP53 variant allele/haplotype carriers(Chen et al., 2007; Zhang et al., 2013). As the reason for few studies were performed and there were many meta-analysis related on TP53 gene polymorphism and cancer risk (Weng et al., 2012; Zhao et al., 2013), we could not use meta-analysis to analyze the relationship between TP53BP1 rs2602141 A/C polymorphism combined with TP53 gene polymorphism and cancer. In addition, Rudd et al. (Rudd et al., 2006) and Truong et al. (Truong et al., 2010) found that rs2602141 polymorphism was associated with lung cancer risk. However, because lack of sufficient data from these two studies, we could not include these studies in this meta-analysis. That may be another reason for the conclusion in this meta-analysis.

There are several limitations in this meta-analysis that should be considered. First, cancer is a multi-factorial disease from complex interactions between environmental exposure and genetic factors. In this meta-analysis, we had insufficient data to perform an evaluation of such interactions for the independent role of TP53BP1 rs2602141 A/C polymorphisms in cancer development. Second, the number of current studies is relative small. Thus, more studies are needed to further identify this association more comprehensively. Third, we did not consider studies published in languages other than English/Chinese or data presented in abstracted form; thus, publication and potential language biases may occur.

In conclusion, the findings suggested an association between rs2602141 A/C polymorphism in TP53BP1 gene and increased risk to cancer in Asian population. To verify these results, large scale case-control studies with detailed individual information are needed.

Acknowledgements

Thanks to Xiaomei Wu, Ph.D, Professor of the Department of Clinical Epidemiology and Evidence Medicine in the First Affiliated Hospital of China Medical University. Thanks to the editors and anonymous reviewers.

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