RESEARCH COMMUNICATION

Pro Variant of TP53 Arg72Pro Contributes to Gastric Cancer Risk in Asians: Evidence from a Meta-analysis

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Abstract

Background: Previous studies investigating the association between TP53 Arg72Pro polymorphism and gastric cancer (GC) risk in Asian population have reported controversial results. Thus, a meta-analysis was performed. Methods: A comprehensive literature search was conducted and 17 case-control studies were finally included, involving a total of 5,990 GC cases and 6,812 controls. Subgroup analyses were performed by the sample size. Results: Meta-analysis of all 17 studies showed variant genotypes of TP53 Arg72Pro to be associated with an elevated GC risk in three genetic comparison models ($OR_{Pro\ vs.\ Arg}$ =1.13, 95% CI 1.03-1.25, P_{OR}=0.01; $OR_{Homozygote\ comparison\ model}$ =1.33, 95% CI 1.07-1.64, P_{OR}=0.009; $OR_{Dominant\ genetic\ model}$ =1.13, 95% CI 1.05-1.22, P_{OR}=0.002). Besides, a more obvious association was observed after the heterogeneity was decreased (all P values less than 0.001). This association was further identified by both subgroup and sensitivity analyses. Conclusions: This meta-analysis suggests the Pro variant of TP53 Arg72Pro contributes to gastric cancer risk in Asians.

Keywords: Gastric cancer - TP53 Arg72Pro - polymorphism - meta-analysis - Asians

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Introduction

Gastric cancer (GC) was the sixth most common cancer worldwide (989,600 new cancer cases) and the second most frequent cause of cancer death worldwide (738,000 cancer deaths) in 2008 (Jemal et al., 2011). Over 70% of new cases and deaths occur in developing countries, and the highest incidence rate is in Eastern Asia (Jemal et al., 2011).

Despite of the emergence of new cytotoxic drugs and targeted biologic agents, GC remains one of the most clinically challenging cancers among all gastrointestinal malignancies and need multidisciplinary management (Hartgrink et al., 2009; Jiang and Ajani, 2010). Thus, GC still is a serious fatal disease worldwide and has caused serious damage to human health (Hartgrink et al., 2009). As a complex and multi-factorial process, the gastric carcinogenesis is still not fully understood. Epidemiological studies have revealed that Helicobacter pylori, smoking, diets and environmental risk factors play important roles in the development of GC (Fukase et al., 2008; Hartgrink et al., 2009; Wroblewski et al., 2010). However, only a small proportion of individuals exposed to the known risk factors develop GC, while many cases develop GC among individuals without those risk factors, which suggest genetic factors also play an important role in GC etiology (Resende et al., 2010).

The tumor suppressor p53 is a key player in stress responses and preserves genomic stability by responding to various insults including DNA damage, metabolic stress and oncogene activation (Vogelstein and Kinzler, 2004; Vousden and Lane, 2007). P53 can also interact with other cellular proteins, and these molecular interactions might contribute to the inhibitory role of p53 in carcinogenesis, while malfunction of the p53 pathway is an almost universal hallmark of human tumors (Chipuk et al., 2005; Riley et al., 2008). TP53 gene is a tumor suppressor gene encoding p53 and frequently mutates in various cancers, and those mutations can cause dramatic defects in p53 function and are often hallmarks of most human cancers (Chipuk et al., 2005; Riley et al., 2008). A polymorphism at codon 72 of the TP53 gene (Arg72Pro; rs1042522) has been most intensively investigated and reported to affect the functions of p53 network which is central to the development of cancer. TP53 Arg72Pro is a G-to-C polymorphism at the second position of codon 72 in exon 4 resulting in amino acid substitution from Arg to Pro. The current view is that the p53-Arg72 protein is more effective in inducing apoptosis and protecting cells from cancerization than the p53-Pro72 protein (Dumont et al., 2003; Whibley et al., 2009). A study published in 2004 showed that individuals with Pro/Pro genotype had a 2.98-fold higher risk of developing diffuse-type GC compared to individuals with Arg/Arg genotype (p=0.038) (Hiyama et al., 2002). Subsequently, nearly 20 studies have been published on this controversial issue, but it remains unclear whether there is an association between TP53 Arg72Pro polymorphism and GC risk (Hamajima et al., 2002; Hiyama et al., 2002; Gao et al., 2009). There were obvious inconclusive results among those studies,

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which were probably due to limited sample sizes, ethnic difference or publication bias. Meta-analysis is a statistical procedure for combining results from published studies to acquire a precise estimation of the major effect (Stroup et al., 2000). Two meta-analyses were published to assess the association between TP53 Arg72Pro and GC risk, but there was obvious between-study heterogeneity (Zhou et al., 2007; Gao et al., 2009). Besides, several large scale case-control studies have been published to further assess the association between TP53 Arg72Pro and GC risk in Asian population, which is the highest incidence rate of GC, but the association above in Eastern Asia is still uncertain (Kim et al., 2010; Shirai et al., 2010; Song et al., 2011). Thus, to assess the evidence regarding the association TP53 Arg72Pro and GC risk and to investigate potential sources of heterogeneity, we conducted a comprehensive meta-analysis of epidemiological studies investigating this association.

Materials and Methods

Search strategy and selection criteria

We searched PubMed, Embase and CBM database using the following search strategy: ('gastric cancer' or 'stomach cancer' or 'gastric carcinoma' or 'stomach carcinoma') and ('p53' or 'TP53' or 'Arg72Pro' or 'codon 72') and ('polymorphism' or 'polymorphisms' or 'mutation') for papers published from January 1980 to July 2011. Additionally, we searched the internet for unpublished data. We also reviewed reference lists in those published articles. There was no language limitation. The inclusion criteria were: (1) case-control studies which evaluated the association between TP53 Arg72Pro polymorphism and GC risk; (2) used an unrelated case-control design; (3) had available genotype frequency for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) genotype distribution of the control population was in Hardy-Weinberg equilibrium (HWE). Overlapping study or studies comparing different laboratory methods were all excluded.

Data extraction and study design

The following information was extracted from included studies: first author, year of publication, number of cases and controls, characteristics of cases and controls, genotypes frequency and allele frequency of cases and controls. Difference was settled by reaching an agreement between all investigators. To test the population stratification in the controls, a chi-square test using a web-based program (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl) was applied to determine if TP53 Arg72Pro genotype distribution in the control population reported conformed to HWE ($P<0.05$ was considered significant). Subgroup analyses were mainly done by study size and published language. Study size was divided into those with at least 300 GC cases and those with fewer than 300 GC cases.

Statistical analysis

The strength of the association between TP53 Arg72Pro polymorphism and GC risk was measured by odds ratio (OR) corresponding to 95% confidence interval (CI). We assessed the association between Pro variant of Arg72Pro polymorphism and GC risk on allele genetic comparison model (Pro vs. Arg), the homozygote comparison model (Pro/Pro vs. Arg/Arg), the recessive genetic comparison model (Pro/Pro vs. Arg/Pro+Arg/Arg) and the dominant genetic comparison model (Pro/Pro + Arg/Pro vs. Arg/Arg).

In our study, two models of meta-analysis for dichotomous outcomes were conducted: the random-effects model and the fixed-effects model. The random-effects model was conducted using the DerSimonian and Laird's method, which assumed that studies were taken from populations with varying effect sizes, calculating the study weights both from in-study and between-study variances, considering the extent of variation, or heterogeneity (DerSimonian and Laird, 1986). The fixed-effects model was conducted using the Mantel-Haenszel's method, which assumed that studies were sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance (Mantel and Haenszel, 1959). To assess the between-study heterogeneity more precisely, both the chi-square based Q statistic test (Cochran's Q statistic) to test for heterogeneity and the I2 statistic to quantify the proportion of the total variation due to heterogeneity were calculated (Cochran, 1954; Higgins and Thompson, 2002; Higgins et al., 2003). Heterogeneity was considered significant for $P_{\text{Cochran's Q statistic}} < 0.05$, and the random-effects model was used to pool the results; on the contrary, the fixed-effects model was used to pool the results when P value of Cochran's Q statistic was more than 0.05. The significance of the pooled OR was determined by the Z test and a p value of <0.05 was considered significant. Besides, Galbraith plot was also used to spot the outliers which were the sources of heterogeneity (Galbraith, 1988). To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of individual studies. Publication bias was investigated by funnel plot, and an asymmetric plot suggested possible publication bias in this meta-analysis. Publication bias was investigated by funnel plot, in which the standard error of logor of each study was plotted against its logor (Stuck et al., 1998). An asymmetric plot suggested possible publication bias. Furthermore, Funnel-plot asymmetry was assessed by the method of Egger's linear regression test (Egger et al., 1997).

Statistical analysis was performed with the software programs RevMan (version 5.1) and STATA (version 12). All the P values were two-sided.

Results

Characteristics of included studies

With our search strategy, 297 articles were found, but only 23 full-text articles were preliminarily identified for further detailed evaluation (Figure 1) (Hamajima et al., 2002; Hiyama et al., 2002; Li et al., 2004; Shen et al., 2004; Wu et al., 2004; Xi et al., 2004; Lai et al., 2005; Mu et al., 2005; Chung et al., 2006; Yi and Lee, 2006; Cao et al., 2007; Kim et al., 2007; Yang et al., 2007; Zhu et

Table 1. Characteristics of Studies Included in this Meta-analysis

Study	Country	Case group	Control group	Genotype method	P_{HWE}
Kexiang Z, 2011	China			PCR-TaqMan	0.31
140 patients (94 males, 46 females; median age, 58.6 years) with histologically confirmed gastric cancer from hospitals of Hexi area					
125 age- and gender-matched healthy controls (85 males, 40 females; median age, 59.1 years) confirmed by gastroscopy					
Song HR, 2011	Korea			PCR-TaqMan	0.48
2213 patients (1510 males, 703 females; median age, 60.2 years) with histologically confirmed gastric cancer					
1700 healthy controls (576 males, 118 females; median age, 52.2 years) recruited from the Thyroid Disease Prevalence Study of Korea					
Shirai O, 2010	Japan			PCR-CTPP	0.81
389 patients (285 males, 104 females; median age, 63.9 years) with histologically confirmed gastric cancer					
419 gender-matched healthy controls (315 males, 104 females; median age, 53.1 years) confirmed by gastroscopic biopsy					
Kim N, 2010	Korea			PCR-RFLP	0.07
535 patients (352 males, 183 females; median age, 59.5 years; 534 had DNA sample available) with histologically confirmed gastric cancer			535 age- and gender-matched healthy controls (352 males, 183 females; median age, 57.7 years; 531 had DNA sample available) recruited from volunteers undergoing gastroscopy	PCR-RFLP	0.81
Zhang WH, 2010	China				
385 patients (308 males, 77 female) with histologically confirmed gastric cancer					
412 age- and gender-matched healthy controls (332 males, 80 females)					
Kim JM, 2007	Korea			PCR-RFLP	0.78
120 patients (80 males, 40 female) with histologically confirmed gastric cancer					
145 age- and gender-matched healthy controls (99 males, 46 females)					
Cao YY, 2007	China			PCR-PIRA	0.86
275 patients (182 males, 93 females; median age, 60 years) with histologically confirmed gastric cardiac cancer					
635 age- and gender-matched healthy controls (409 males, 226 females; median age, 59 years) and confirmed by gastroscopy					
Yang M, 2007	China			PCR-RFLP	0.65
500 patients (430 males, 70 females) with histologically confirmed gastric cardiac cancer					
1000 age- and gender-matched cancer-free individuals (860 males, 140 females) selected from a cancer-screening program					
Chung WC, 2006	Korea			PCR-RFLP	0.68
84 patients (61 males, 23 females; median age, 61.1 years) with histologically confirmed gastric cardiac cancer					
43 H. pylori negative and healthy individuals (18 males, 25 females; median age, 54.9 years)					
Yi SY, 2006	Korea			PCR-RFLP	0.47
292 patients (171 males, 121 females; median age, 56 years) with histologically confirmed gastric cancer					
216 age- and gender-matched cancer-free individuals (128 males, 88 females; median age, 58 years) and confirmed by gastroscopic biopsy					
Mu LN, 2005	China			PCR-RFLP	0.1
206 patients (138 males, 68 females) with histologically confirmed gastric cancer					
417 age- and gender-matched healthy individuals (287 males, 128 females) recruited from the same areas					
Lai KC, 2005	China			PCR-RFLP	0.77
123 patients (81 males, 42 females) with histologically confirmed gastric cancer					
126 age-, and gender-matched healthy individuals					
Wu MT, 2004	China			PCR-RFLP	0.97
89 patients (51 males, 38 females) with histologically confirmed gastric cancer					
192 gender-matched cancer-free individuals (106 males, 86 females)					
Shen H, 2004	China			PCR-RFLP	0.73
324 patients with histologically confirmed gastric cancer					
317 cancer-free individuals					
Li XZ, 2004	China			PCR-RFLP	0.06
67 patients (56 males, 11 females; median age, 58.2 years) with histologically confirmed gastric cardiac cancer					
138 gender-matched healthy individuals (110 males, 28 females; median age, 59.0 years)					
Hiyama T, 2002	Japan			PCR-RFLP	0.93
117 gastric cancer patients (71 males, 46 females; median age, 61.2 years) with H. pylori and histologically confirmed gastric cancer					
116 age- and gender-matched cancer-free individuals(71 males, 45 females; median age, 58.4 years) with H. pylori					
Hamajima N, 2002	Japan			PCR-CTPP	0.91
144 patients (103 males, 41 females) with histologically confirmed gastric cancer					
241 non-cancer patients(118 males, 123 females) who underwent gastroscopy					

PCR-CTPP, PCR with confronting two-pair primers; PIRA-PCR, primer-introduced restriction analysis-polymerase chain; Restriction fragment length polymorphism

al., 2009; Kim et al., 2010; Mojtahedi et al., 2010 Shirai et al., 2010; Zhang et al., 2010; Zhou et al., 2010; Ihsan et al., 2011; Song et al., 2011; Ke-Xiang et al., 2012). According to the exclusion criteria, six articles were excluded including two studies containing overlapping data (Lai et al., 2005; Zhu et al., 2009), two studies from non-Asian population (Mojtahedi et al.; Ihsan et al., 2011), one without sufficient published genotype data (Xi et al., 2004) and one in which the genotype distribution of the control population was significantly deviated from HWE ($P < 0.0001$) (Zhou et al., 2010) (Figure 1). Finally, data were available from a total of 17 case-control studies including a total of 5,990 GC cases and 6,812 controls (Hamajima et al., 2002; Hiyama et al., 2002; Li et al., 2004; Shen et al., 2004; Wu et al., 2004; Lai et al., 2005; Mu et al., 2005; Chung et al., 2006; Yi and Lee, 2006; Cao et al., 2007; Kim et al., 2007; Yang et al., 2007; Kim et al., 2010; Shirai et al., 2010; Zhang et al., 2010; Song et al., 2011; Ke-Xiang et al., 2012). Table 1 summarized the main characteristics of those included studies. DNA

Table 2. Summary of Odds Ratios (OR) with Confidence Interval (CI) in the Meta-analysis

Genetic comparison models	Studies (No.)	Odds Ratio OR [95%CI]	P_{OR}	Heterogeneity I^2 (%)	P_H #	$P_{Egger's\ test}$
Total studies						
Pro vs. Arg	17(5990/6812)	1.13(1.03, 1.25)	0.01	65	0.0001	0.234
Pro vs. Arg (Adjustment for Heterogeneity*)	15(5648/6039)	1.11(1.05, 1.17)	<0.0001	20	0.23	0.768
Homozygote comparison mode	17(5990/6812)	1.33 (1.07, 1.64)	0.009	68	<0.0001	0.212
Homozygote comparison model (Adjustment for Heterogeneity*)	15(5648/6039)	1.32 (1.18, 1.47)	<0.0001	40	0.06	0.768
Recessive genetic comparison model	17(5990/6812)	1.21(0.99, 1.48)	0.06	73	<0.0001	0.427
Recessive genetic comparison mod el (Adjustment for Heterogeneity*)	14(5525/5913)	1.26(1.14, 1.39)	<0.0001	38	0.07	0.542
Dominant genetic comparison model	17(5990/6812)	1.13(1.05, 1.22)	0.002	31	0.11	0.35
Subgroup analyses by sample size Studies (case sample size≥300)						
Pro vs. Arg	6(4345/4379)	1.09(1.02, 1.16)	0.008	11	0.35	0.891
Homozygote comparison mode	6(4345/4379)	1.28(1.12, 1.45)	<0.0001	48	0.08	0.854
Recessive genetic comparison model	6(4345/4379)	1.22(1.01, 0.47)	0.03	56	0.04	0.891
Dominant genetic comparison model	6(4345/4379)	1.10(1.01, 1.20)	0.04	0	0.423	0.891

#P_H, the P value of heterogeneity test; *Adjustment for Heterogeneity was performed by excluding Cao YY's study and Li XZ's study as the outlier and the possible major source of heterogeneity

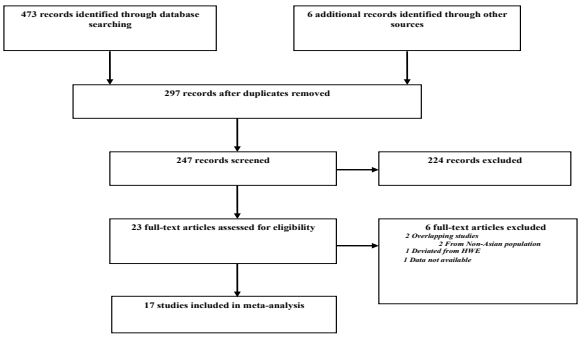

Figure 1. Flowchart of Selection of Studies for Inclusion in Meta-analysis

was all extracted from peripheral blood in those studies, and the main genotyping methods were PCR-RFLP (Table 1).

Meta-analysis results

Table 2 listed the main results of this meta-analysis.

When all 17 studies were pooled into meta-analysis, significant heterogeneity existed in three genetic comparison models, including Pro vs. Arg, the recessive genetic comparison model, and the homozygote comparison model; thus, the random-effects model was used to pool the results in these three comparison models except the dominant genetic comparison model (P_H=0.11>0.05, I^2=31%<50%). The combined results based on all studies showed the variant genotypes of TP53 Arg72Pro were associated with an elevated GC risk in three genetic comparison models ($OR_{Pro\ vs.\ Arg}$=1.13, 95%CI 1.03-1.25, P_{OR}=0.01; $OR_{Homozygote\ comparison\ model}$=1.33, 95%CI 1.07-1.64, P_{OR}=0.009) $OR_{Dominant\ genetic\ model}$=1.13, 95%CI 1.05-1.22, P_{OR}=0.002) (Figure 2). Subgroup analyses by sample also suggested the variant genotypes of TP53 Arg72Pro were associated with an elevated GC risk in all four genetic comparison models.

The between-study heterogeneity was obvious in most comparisons before adjustment for heterogeneity. Galbraith plots spotted Cao YY's study and Li XZ's study as the outliers and the major source of the heterogeneity (Figure 3) (Li et al., 2004, Cao et al., 2007). Interestingly,

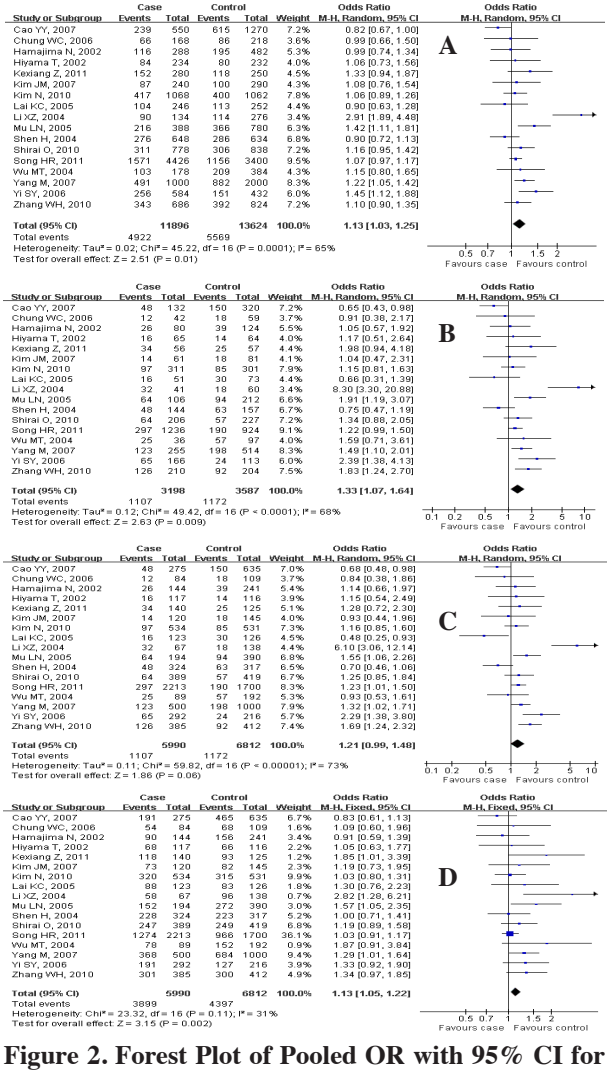

Figure 2. Forest Plot of Pooled OR with 95% CI for TP53 Arg72Pro Polymorphism with Gastric Cancer Risk (A, Pro vs. Arg, Random effects model; B, Homozygote comparison model, Random effects model; C, Recessive genetic comparison model, Random effects model; D, Dominant genetic model, Fixed effects model) (The squares and horizontal lines corresponded to the study-specific OR and 95% CI. The area of the squares reflected the study-specific weight (inverse of the variance). The diamond represented the pooled OR and 95% CI)

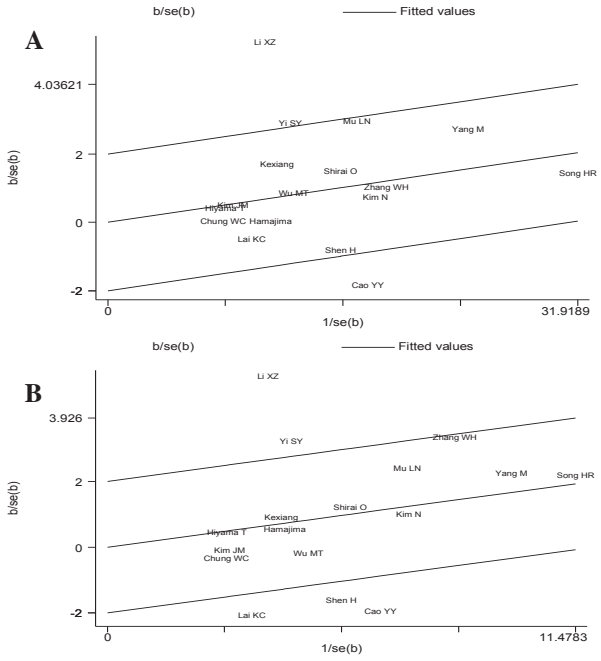

Figure 3. Galbraith Plot of TP53 Arg72Pro and Gastric Cancer Risk in Asians (A, Pro vs. Arg; B, Recessive genetic comparison model)

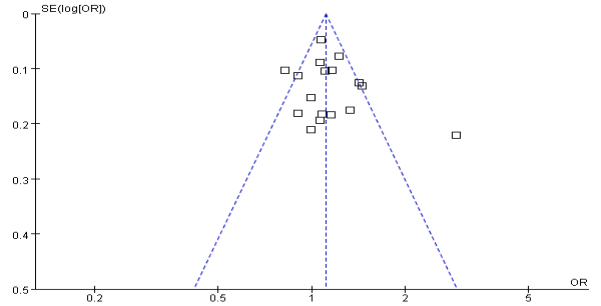

Figure 4. Funnel Plot for Publication Bias Test in the Meta-analysis Investigating the Association Between TP53 Arg72Pro and Gastric Cancer Risk (Pro vs. Arg, Each point represents a separate study for the indicated association)

the heterogeneity remarkably decreased in those three genetic comparison models after excluding Cao YY's study and Li XZ's study (Liet al., 2004, Cao et al., 2007), which further indicated that Cao YY's study and Li XZ's study were the major source of the heterogeneity (Table 2). Besides, a more obvious association was observed after the heterogeneity was decreased by excluding Cao YY's study and Li XZ's study in those three genetic comparison models above (Table 2).

Sensitivity analysis was performed by sequential omission of individual studies, and the significance of all pooled ORs was not influenced excessively by omitting any single study (data were not shown). Besides, sensitivity analysis was also performed by adding Zhou Y's study in which the genotype distribution of the control population was significantly deviated from HWE (Zhou et al., 2010), and the significance of all pooled ORs was also not influenced.

Publication bias

Funnel plot and Egger's test were performed to access the publication bias of this meta-analysis. The shape of the funnel plots for most genetic contrast models seemed symmetrical, and all the P values of Egger's tests were more than 0.05, providing statistical evidence of funnel plot symmetry. The results above suggested that publication bias was not evident in our meta-analyses. As shown in Figure 4, in the meta-analysis investigating the association between TP53 Arg72Pro and GC risk, the funnel plot's shape for the allele genetic comparison model (Pro vs. Arg) seemed symmetrical, suggesting no presence of publication bias; the P value of the Egger's test for the allele genetic comparison model was 0.236, providing statistical evidence for funnel plot's symmetry.

Discussion

The TP53 gene is one of the most widely investigated genes because of its role as a tumor suppressor gene, which plays a key role in the development and progression of cancers. TP53 gene is frequently mutated in various cancers, and it has been suggested that genetic polymorphisms in TP53 gene could affect the functions of p53 and TP53 gene variants have drawn increasing attention in the etiology of several cancers. Although there were many genetic association studies investigating the effect of TP53 genetic variants on GC cancer risk, the impact of TP53 Arg72Pro polymorphism on GC risk remained to be elucidated because the published data are controversial. Two meta-analyses were published to assess the association between TP53 Arg72Pro and GC risk, but there was obvious between-study heterogeneity. Besides, several large scale case-control studies have been published to further assess the association between TP53 Arg72Pro and GC risk in Asian population, which is the highest incidence rate of GC, but the association above in Eastern Asia is still uncertain (Zhou et al., 2007; Gao et al., 2009). Thus, to assess the evidence regarding the association TP53 Arg72Pro and GC risk and to investigate potential sources of heterogeneity, we conducted a comprehensive meta-analysis of epidemiological studies investigating this association. We performed a pooled analysis of all eligible studies. The present meta-analysis included 17 case-control studies including a total of 5,990 GC cases and 6,812 controls, providing the most comprehensive assessment of the association between TP53 Arg72Pro polymorphism and GC risk up to now. The outcomes of this meta-analysis indicate that variant genotypes of TP53 Arg72Pro were associated with an elevated GC risk in three genetic comparison models ($OR_{Pro\ vs.\ Arg}$ =1.13, 95%CI 1.03-1.25, P_{OR}=0.01; $OR_{Homozygote\ comparison\ model}$ =1.33, 95%CI 1.07-1.64, P_{OR}=0.009; $OR_{Dominant\ genetic\ model}$ =1.13, 95%CI 1.05-1.22, P_{OR}=0.002). Besides, a more obvious association was observed after the heterogeneity was decreased (All P values were less than 0.001). This association was further identified by both subgroup analyses and sensitivity analysis. Subgroup analyses were performed based on smoking status, study size, published language and study type, and the results of subgroup analyses further validated this statistically significant association (Table 2).

Heterogeneity is a potential problem when interpreting the results of all meta-analyses, and finding of the source

of heterogeneity is one of the most important goals of meta-analysis (Ioannidis et al., 2007). The present meta-analysis showed that significant heterogeneity existed in most analyses before we excluded Cao YY's study and Li XZ's study (Li et al., 2004, Cao et al., 2007), and Galbraith plot also spotted Cao YY's study and Li XZ's study (Li et al., 2004, Cao et al., 2007)as the outliers and further identified it as the major source of the heterogeneity (Figure 4). Therefore, Cao YY's study and Li XZ's study (Li et al., 2004, Cao et al., 2007) were the major source of the heterogeneity in this meta-analysis and might have some differences from other studies in the selection of controls, prevalence of lifestyle factors, or other aspects. Besides, heterogeneity between studies in the pooled analysis of total studies was removed after we excluded Cao YY's study and Li XZ's study (Table 2).

Somatic mutation of TP53 that results in the absence or dysfunction of p53 is one of the most common mechanisms by which the p53 pathway is damaged during carcinogenesis. The two alleles of TP53 Arg72Pro differ not only biologically but also functionally in their ability to bind components of the transcriptional machinery, to activate transcription, to induce apoptosis and to repress the transformation of primary cells. The Arg allele induces apoptosis more effectively than the Pro variant, suggesting that the TP53 Pro variant might be a weaker tumor suppressor than its Arg counterpart. Thus, there is obvious biological evidence for the different effects on cancer development between the two different variants and the TP53 Pro variant might be a weaker tumor suppressor compared with Arg allele. In 2008, Ioannidis JP et al suggested an interim guideline to develop guidance criteria for assessing cumulative epidemiologic evidence in genetic associations, such as the amount of biological evidence, epidemiological credibility and clinical public-health impact (Ioannidis et al., 2008). As is argued above, there is obvious biological evidence that the TP53 Pro variant might be a weaker tumor suppressor compared with Arg allele. In addition, our pooled analysis adds strong epidemiological evidence for the association between TP53 Arg72Pro polymorphism and GC risk in Asians. Finally, there are studies suggesting p53 codon 72 Pro/Pro is associated with poor relapse-free survival and overall survival, and there is also convincing evidence of clinical relevance between TP53 Arg72Pro polymorphism and GC (Huang et al., 2009; Kim et al., 2009). Thus, biological evidence, epidemiological evidence, and clinical evidence all confirm the association between Arg72Pro polymorphism and GC risk.

However, some possible limitations in our meta-analysis should be acknowledged. Firstly, the eligibility criteria for inclusion of controls were different from each other. The controls in some studies were selected from non-cancer patients who underwent gastroscopy, while the controls in other several studies were just selected from asymptomatic individuals (Table 1). Additionally, misclassification bias was possible. For example, most studies could not exclude latent cancer cases in the controls (Table 1). Finally, gene-gene and gene-environmental interactions were not fully addressed in this meta-analysis for the lack of sufficient data. As we know, aside from genetic factor, smoking is a major risk factor for GC; however we didn't perform subgroup analyses in smokers or nonsmokers owing to the limited reported information on such associations in the included studies.

Despite of those limitations, this meta-analysis suggests the Pro variant of TP53 Arg72Pro contributes to gastric cancer risk in Asian population.

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The author(s) declare that they have no competing interests.

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