Association Between TP53 Arg72Pro Polymorphism and Hepatocellular Carcinoma Risk: A Meta-analysis

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Abstract

Background: Previous studies on the association between the TP53 Arg72Pro polymorphism and hepatocellular carcinoma (HCC) risk obtained controversial findings. This study aimed to quantify the strength of the association by meta-analysis. Methods: We searched PubMed and Wangfang databases for published studies on the association between the TP53 Arg72Pro polymorphism and HCC risk, using the pooled odds ratio (OR) with its 95% confidence intervals (95% CI) for assessment. Results: 10 studies with a total of 2,026 cases and 2,733 controls were finally included into this meta-analysis. Overall, the TP53 Arg72Pro polymorphism was not associated with HCC risk (all P values greater than 0.10). However, there was no significant association between the TP53 Arg72Pro polymorphism and HCC risk in East Asians. No evidence of publication bias was observed. Conclusion: Meta-analyses of available data suggest an obvious association between the TP53 Arg72Pro and HCC risk in Caucasians. However, the TP53 Arg72Pro polymorphism may have a race-specific effect on HCC risk and further studies are needed to elucidate this possible effect.

Keywords: Hepatocellular carcinoma - TP53 Arg72Pro - polymorphism - meta-analysis - ethnicity
the following search strategy: ('liver tumor' or 'liver cancer' or 'hepatocellular carcinoma') and ('p53' or 'codon 72' or 'Arg72Pro' or 'rs1042522') and ('polymorphism' or 'polymorphisms' or 'mutation' or 'mutations' or 'SNP') for published studies. There was no language limitation. All references cited in the studies were also reviewed to identify additional published articles not indexed in the common database. The inclusion criteria were: (1) case-control studies which evaluated the association between TP53 Arg72Pro polymorphism and HCC risk; (2) used an unrelated case-control design; (3) had available genotype frequency for estimating an odds ratio (OR) with its 95% confidence interval (95%CI). Overlapping study or studies comparing different laboratory methods were all excluded. In studies with overlapping cases or controls, the most recent and/or the largest study with extractable data was included in the meta-analysis. In addition, family-based association studies were excluded because they use different study designs.

Data extraction
Two investigators independently extracted data, and disagreements were resolved through consensus. The following information was extracted from included studies: publishing year, ethnicity, inclusion criteria for HCC patients and controls, demographics, genotyping method, and the genotype distribution of TP53 Arg72Pro polymorphism. The frequencies of the alleles were extracted or calculated for cases and controls. Difference was settled by reaching an agreement between all investigators.

Statistical analysis
We performed a meta-analysis of the association between the TP53 Arg72Pro polymorphism and HCC risk under the allele contrast (Pro versus Arg), homozygote (ProPro versus ArgArg), heterozygote (ArgPro versus ArgArg), recessive (ProPro versus ArgPro/ArgArg), and dominant (ProPro/ArgPro versus ArgArg) models. We calculated the pooled OR with its corresponding 95%CI to assess this possible association. The significance of the pooled OR was determined by the Z test and a P value of less than 0.05 was considered significant. 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 (DerSimonian and Laird, 1986), while the fixed-effects model was conducted using the Mantel-Haenszel’s method (Mantel and Haenszel, 1959). To assess the between-study heterogeneity, the I² statistic were calculated, and I² values of 25%, 50%, and 75% were used as evidence of low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). The random-effects model was used to pool the data when obvious heterogeneity existed (I² value > 50%). Otherwise, the fixed-effects model was used to pool the data when low heterogeneity existed (I² value < 50%). For additional analyses, the cases and controls were subgrouped by ethnicity, and the ethnicity was categorized into Caucasians, East Asians, Africans and others. To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of individual studies or by omitting studies without high quality. Potential publication bias was assessed by visual inspection of the funnel plot, and an asymmetric plot suggested possible publication bias (Stuck et al., 1998). In addition, we also performed Egger linear regression test at the P < 0.10 level of significance to assess the publication bias (Egger et al., 1997). All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas). A P value < 0.05 was considered statistically significant, except where specified.

Results
Characteristics of included studies
With our search criterion, a total of 39 abstracts were identified from Pubmed and Wanfang databases. After discarding those overlapping records and those records which did not meet the criteria clearly, 14 publications were preliminarily identified for further detailed evaluation (Yu et al., 1999, Anzola et al., 2003, Leveri et al., 2004, Peng et al., 2004, Zhu et al., 2005, Zhu et al., 2005, Zhu et al., 2005, Zhu et al., 2005, Ezzikouri et al., 2007, Yoon et al., 2008, Di Vuolo et al., 2011, Ezzikouri et al., 2011, Xu et al., 2011, Sumbul et al., 2012). After extracting data and reviewing each original paper, 4 publications were further excluded for overlapping data (Zhu et al., 2005, Zhu et al., 2005, Ezzikouri et al., 2007). Finally, 10 studies with a total of 2,026 HCC cases and 2,733 controls were finally included into this meta-analysis (Yu et al., 1999, Anzola et al., 2003, Leveri et al., 2004, Peng et al., 2004, Zhu et al., 2005, Yoon et al., 2008, Di Vuolo et al., 2011, Ezzikouri et al., 2011, Xu et al., 2011, Sumbul et al., 2012). Ethnic groups among these studies were as following: 5 from Caucasians (Anzola et al., 2003, Leveri et al., 2004, Di Vuolo et al., 2011, Ezzikouri et al., 2011, Sumbul et al., 2012), and 5 from East Asians (Yu et al., 1999, Peng et al., 2004, Zhu et al., 2005, Yoon et al., 2008, Xu et al., 2011). The number of cases varied from 61 to 507 (mean, 203), and the number of controls varied from 111 to 548 (mean, 273).

Meta-analysis results
Table 1 listed the main results of this meta-analysis. Overall, meta-analyses of total 10 studies showed the TP53 Arg72Pro polymorphism was not associated with HCC risk (For Pro versus Arg, OR = 1.07, 95%CI 0.92-1.23; For ProPro versus ArgArg, OR = 1.00, 95%CI 0.83-1.21; For ArgArg versus ProPro/ArgArg, OR = 0.99, 95%CI 0.87-1.13; For ProPro versus ProArg/ArgArg, OR = 1.04, 95%CI 0.72-1.18; For ProPro/ArgPro versus ArgArg, OR = 1.25, 95%CI 0.94-1.67) (Table 1).

Subgroup analysis by ethnicity showed that the TP53 Arg72Pro polymorphism was associated with HCC risk in Caucasians under three genetic models (For Pro versus Arg, OR = 1.20, 95%CI 1.03-1.41; For ProPro versus ArgArg, OR = 1.74, 95%CI 1.23-2.47; For ProPro versus ProArg/ArgArg, OR = 1.85, 95%CI 1.33-2.57) (Table 1, Figure 1). However, there was no significant association between the TP53 Arg72Pro polymorphism and HCC risk in East Asians (All P values were more than 0.10).
Publication bias

Funnel plot and Egger’s test were performed to assess 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. As was shown in Figure 2, in the meta-analysis investigating the association between the TP53 Arg72Pro polymorphism and HCC risk under the allele genetic comparison model (Pro vs. Arg), the funnel plot’s shape seemed symmetrical, suggesting no presence of publication bias, and the P value of the Egger’s test for the allele genetic comparison model was 0.944, providing statistical evidence for funnel plot’s symmetry (Figure 2). The results above suggested that publication bias was not evident in our meta-analyses.

Discussion

Although there were many genetic association studies investigating the effect of the TP53 Arg72Pro polymorphism on HCC cancer risk, the results from those studies were controversial (Yu et al., 1999, Anzola et al., 2003, Leveri et al., 2004, Peng et al., 2004, Yoon et al., 2008, Di Vuolo et al., 2011, Ezzikouri et al., 2011, Sumbul et al., 2012). Those conflicting results may partially due to the relatively small sample size of individual studies and sampling effects, because each of these studies typically involved a few cases and controls. 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). One meta-analysis was published to assess the association between the TP53 Arg72Pro polymorphism and HCC risk, but it only included 6 studies and failed to prove an obvious association between the TP53 Arg72Pro polymorphism and HCC risk in Caucasians and Asians (Chen et al., 2011). Besides, several large scale case-control studies have been published to further assess the association between the TP53 Arg72Pro and HCC risk since 2011 (Di Vuolo et al., 2011, Ezzikouri et al., 2011, Xu et al., 2011, Sumbul et al., 2012). Thus, to provide the evidence regarding the association the TP53 Arg72Pro and HCC risk, we conducted a comprehensive meta-analysis of...
epidemiological studies investigating this association.

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 (Whibley et al., 2009). It has been proven that TP53 genetic polymorphisms can affect the functions of p53 and TP53 gene variants have drawn increasing attention in the etiology of several cancers (Whibley et al., 2009). Somatic mutation of TP53 that results in the absence of its Arg counterpart (Dumont et al., 2003). Therefore, 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 (Dumont et al., 2003).

The present meta-analysis included ten case-control studies with a total of 2026 cases and 2733 controls, providing the most comprehensive assessment of the association between the TP53 Arg72Pro polymorphism and HCC risk up to now. Overall, meta-analyses of total 10 studies showed the TP53 Arg72Pro polymorphism was not associated with HCC risk (All P values were more than 0.10). Subgroup analyses by ethnicity showed that the TP53 Arg72Pro polymorphism was associated with HCC risk in Caucasians under three genetic models (For Pro versus Arg, OR = 1.20, 95CI 1.03-1.41; For ProPro versus ArgArg, OR = 1.74, 95CI 1.23-2.47; For ProPro versus ArgPro/ArgArg, OR = 1.85, 95CI 1.33-2.57). However, there was no significant association in East Asians (All P values were more than 0.10). Thus, meta-analyses of available data suggest an obvious association between the TP53 Arg72Pro and HCC risk in Caucasians, and the TP53 Arg72Pro polymorphism may have a race-specific effect on HCC risk and further studies are needed to elucidate this possible effect. Our analysis had several limitations that should be considered. Firstly, there were only five studies in Asians. More studies with large sample size and careful design are needed to further identify this association in Asians more comprehensively. Secondly, this meta-analysis was based on unadjusted estimates owing to the lack of adjusted estimates. However, a more precise analysis could be performed if adjusted estimates were available in all studies. Besides, serious variability in the study design and the selection of controls was revealed in this meta-analysis. The controls in some studies were selected from non-cancer patients, while the controls in other several studies were just selected from healthy individuals. Finally, misclassification bias was also possible in this meta-analysis, and most studies could not exclude latent cancer cases in the controls.

In conclusion, meta-analyses of available data suggest an obvious association between the TP53 Arg72Pro and HCC risk in Caucasians. TP53 Arg72Pro polymorphism may have a race-specific effect on HCC risk and further studies are needed to elucidate this possible effect.

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