

## RESEARCH ARTICLE

# The XRCC1 Arg399Gln Genetic Polymorphism Contributes to Hepatocellular Carcinoma Susceptibility: An Updated Meta-analysis

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### Abstract

The potential correlation of X-ray repair cross-complementing group 1 (XRCC1) Arg399Gln polymorphism with hepatocellular carcinoma (HCC) susceptibility is ambiguous. Taking account of inconsistent results of previous meta-analyses and new emerging literatures, we conducted a meta-analysis covering 15 case-control datasets to evaluate the relationship. Relevant studies from Medline, Embase and CNKI were retrieved. A fixed-effect model or a random-effect model, depending on between-study heterogeneity, were applied to estimate the association between XRCC1 polymorphism Arg399Gln and HCC risk with the results presented as odds ratios (ORs) and 95% confidence intervals (95% CIs). In accordance with Hardy-Weinberg equilibrium, 15 studies with data for 6,556 individuals were enrolled in this systematic review. For overall HCC, the XRCC1 polymorphism Arg399Gln was significantly associated with HCC susceptibility in a homozygote model as well as in a dominant model (G/G vs. A/A, OR=1.253,  $p=0.028$ ; G/G+A/G vs. A/A, OR= 1.281,  $p=0.047$ , respectively), but not in a heterozygote model (A/G vs. A/A, OR=1.271,  $p=0.066$ ) or a recessive model (G/G vs. A/G + A/A, OR= 1.049,  $p=0.542$ ). Similar results were also observed on stratification analysis by ethnicity (A/G vs. A/A, OR=1.357,  $p=0.025$ ; G/G vs. A/A, OR=1.310,  $p=0.011$ ; G/G+A/G vs. A/A, OR= 1.371,  $p=0.013$ ). However, no potential contribution of XRCC1 Arg399Gln polymorphism to HCC susceptibility in HBV/HCV subgroups was identified. No publication bias was found in this study. In conclusion, the XRCC1 Arg399Gln polymorphism contributes to HCC susceptibility. Due to the lack of studies in Western countries, further large-sample and rigorous studies are needed to validate the findings.

**Keywords:** Hepatocellular carcinoma - meta-analysis - SNPs - X-ray repair cross-complementing group 1

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### Introduction

Hepatocellular carcinoma (HCC) is a prevalent malignancy worldwide with a total of 28720 estimated new cases and ranks the fifth common cause resulting in male cancer death in USA (Siegel et al., 2012). Genome integrity and DNA damages have shed light on the mechanisms that concealed in HCC development (Price et al., 2013). Hepatitis B virus is the most common environmental cause of HCC susceptibility (>80%) which usually leads to DNA damages (McKillop et al., 2006). In addition, aflatoxin B1, alcohol consumption and cigarette smoking (Akinyinka et al., 2001; Lopez et al., 2004) also contribute pivotally to HCC occurrence due to unrepaired DNA damages (Stem et al., 2002; Lahtz et al., 2011). Different DNA damages could be revised by multiple regulatory pathways involved in the DNA repair system,

which is crucial for maintaining the integrity of genome and suppressing carcinogenesis (Smith et al., 2003). Base excision repair (BER) pathway is designated the most important safeguard against impairment resulted from ionizing radiation (IR), environmental toxins, or from other exogenous factors such as viruses (Seeberg et al., 1995). Mutations in BER component DNA repair genes are accompanied by amino acids substitution, which alter the functions of corresponding enzymes, and thereby damage the capability of the host to revise DNA damage and make it more susceptible to carcinogenesis (Miller et al., 2001).

X-ray cross-complementing group 1 gene (XRCC1) is widely recognized as a critical constituent gene of BER (Vidal et al., 2001). It is located on chromosome 19q13.2 (Lamerdin et al., 1995) consisting of 17 exons and finally translates to a 70-kDa protein which contains 633

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amino acids (Lindahl et al., 1999). XRCC1 acts as a non-enzymatic, scaffold protein by recruiting and interacting with a variety of proteins important to the BER pathway, such as DNA glycosylase MPG, OGG1 (Whitehouse et al., 2001). Polymorphisms of XRCC1 were found to have reduced recruitment of XRCC1 interacting proteins, deteriorated overall efficiency of DNA damage restoration, and increased exposure to hepatocarcinogenesis (Chacko et al., 2005). Currently, it is reported that there are eight validated single nucleotide polymorphisms (SNPs) of XRCC1 gene. However, SNPs of XRCC1 in codon 194 (exon 6, C to T, Arg to Trp), codon 280 (exon 9, G to A, Arg to His) and codon 399 (exon 10, G to A, Arg to Gln) are the most common ones (Hu et al., 2005). Previous study has indicated that Arg399Gln in XRCC1 could impair the DNA repair capability and increase the susceptibility to cancer (Hu et al., 2005). Therefore, the polymorphism of XRCC1 Arg399Gln may have an impact on HCC susceptibility.

A considerable amount of epidemiological researches exploring the correlation between XRCC1 Arg399Gln polymorphism and HCC risk have been done worldwide, and the results are shown to be controversial or inconclusive. To investigate this relationship, five meta-analyses articles have been published in the last five years (Zhang et al., 2010; Liu et al., 2011; Xie et al., 2012; Li et al., 2013; Zeng et al., 2013). But the conclusions are paradoxical because of data duplicates, data missing, different original studies and different inclusion criteria. In order to address these issues, this updated meta-analysis including 15 eligible case-control studies was conducted to obtain robust evidence for such association.

## Materials and Methods

### Eligible Studies Selection

To include all eligible researches estimating the correlation of XRCC1 Arg399Gln to HCC, a comprehensive search was conducted in the Medline, Embase and CNKI databases (China National Knowledge Infrastructure) using the following key words: “X-ray repair cross-complementing group 1” or “XRCC1”, “liver cancer” or “hepatocellular carcinoma”, “polymorphism” or “variant”, “case-control” and “risk” (last search was updated on May 20, 2013). Relevant references in the retrieved reviews or articles were manually searched for supplementary data.

### Selection criteria

Studies in accordance with the following criteria were recruited in this meta-analysis: (a) written in English or Chinese; (b) case-control researches evaluating the correlation of XRCC1 Arg399Gln polymorphism to HCC susceptibility; (c) solid evidence for HCC diagnosis; (d) sufficient information for estimating odds ratio (OR) and 95% confidence interval (CI); and (e) genotypes distribution of control group was in agreement with Hardy-Weinberg equilibrium (HWE). Unpublished reports and abstracts were excluded. In addition, the latest study including the largest number of individuals was selected when studies had overlapping or same subjects.

### Data Extraction

The detailed information listed below was independently retrieved from each eligible study by two authors (Pan Y and Chen XM): year of publication, the first author, ethnicity, country/region, sample size, source of controls (HBV/HVC positive, negative or mixed), number of cases and controls, and HWE (Table 1). Discrepancy was addressed by discussion with another author (Zhao L).

### Statistical analysis

The correlation of XRCC1 Arg399Gln polymorphism to HCC susceptibility was evaluated by crude OR and 95% CI in a heterozygote model (A/G vs. A/A), a homozygote model (G/G vs. A/A), a dominant model (G/G + A/G vs. A/A) and a recessive model (G/G vs. A/G + A/A). In addition, stratification analyses were performed by ethnicity, country/region and source of controls subgroups. Chi square-based Q-test and I2 test was applied to estimate the heterogeneity among the included studies (Cochran et al., 1954; Higgins et al., 2003). If  $p < 0.05$ , the random effects model (DerSimonian et al., 1986) was applied. When  $p > 0.05$ , meta-analysis was performed using the fixed-effects model (Mantel et al., 1959). The consistence of the conclusions was tested by sensitivity analysis. The funnel plot, Begg's rank correlation method (Begg et al., 1994) as well as Egger's weighted regression method (Egger et al., 1997) were conducted to identify publication bias.

HWE of genotypes distribution in control group from each individual research was evaluated using the Pearson's goodness-of-fit chi-square test. STATA software (version 12.0, Stata Corporation, USA) was used to perform the meta-analysis.  $P < 0.05$  was designated as significant difference.

## Results

### Characteristics of studies

After initial screening, 32 of 66 published articles regarding the correlation of XRCC1 polymorphism Arg399Gln and HCC susceptibility were identified, four of which were the postgraduate dissertations (Long et al., 2004; Wang et al., 2006; Su et al., 2008; Wu et al., 2009). Among these, five papers (Zhang et al., 2010; Liu et al., 2011; Xie et al., 2012; Li et al., 2013; Zeng et al., 2013) which were meta-analysis papers, four studies which were conducted (Yu et al., 2003; Han et al., 2004; Long

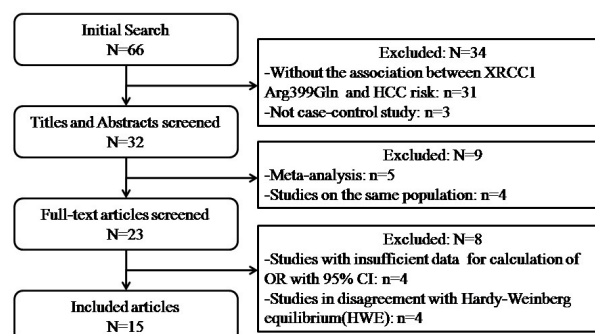


Figure 1. Flow Diagram of Study Selection

**Table 1. Distribution of XRCC1 Polymorphism Arg399Gln among HCC Cases and Controls Recruited in the Updated Meta-analysis**

| Author      | Year | Country/Region | Ethnicity | Sample size<br>(case/control*/control^) | Case |     |     | Control */Control^ |       |       | HWE   |
|-------------|------|----------------|-----------|---|------|-----|-----|--------------------|-------|-------|-------|
|             |      |                |           |   | A/A  | A/G | G/G | A/A                | A/G   | G/G   |       |
| Gulnaz      | 2013 | Pakistan       | Asian     | 50/74*/82^                              | 19   | 14  | 17  | 27/23              | 32/42 | 15/17 | 0.34  |
| Mohana Devi | 2013 | India          | Asian     | 93/93*                                  | 36   | 45  | 12  | 32                 | 51    | 10    | 0.12  |
| Li          | 2012 | Mainland China | Asian     | 150/158!                                | 32   | 78  | 40  | 46                 | 73    | 39    | 0.35  |
| Pan         | 2011 | Mainland China | Asian     | 202/236!                                | 45   | 105 | 52  | 68                 | 112   | 56    | 0.46  |
| Tang        | 2011 | Mainland China | Asian     | 150/150*                                | 41   | 94  | 15  | 84                 | 54    | 12    | 0.43  |
| Jia         | 2010 | Mainland China | Asian     | 136/136!                                | 53   | 66  | 17  | 78                 | 45    | 13    | 0.09  |
| Zeng        | 2010 | Mainland China | Asian     | 500/507 !/59^                           | 34   | 180 | 286 | 36                 | 167   | 304   | 0.053 |
| Kiran       | 2009 | India          | Asian     | 63/142 */174^                           | 25   | 33  | 5   | 45                 | 70    | 27    | 0.98  |
| Wu          | 2009 | Mainland China | Asian     | 100/60*                                 | 8    | 36  | 56  | 7                  | 23    | 30    | 0.43  |
| Ren         | 2008 | Mainland China | Asian     | 50/92*                                  | 32   | 14  | 4   | 46                 | 41    | 5     | 0.28  |
| Borentain   | 2007 | France         | Caucasian | 56/89*                                  | 27   | 21  | 8   | 27                 | 43    | 19    | 0.81  |
| Long        | 2006 | Mainland China | Asian     | 257/649*                                | 131  | 126 |     | 439                | 210   |       | >0.05 |
| Chen        | 2005 | Taiwan         | Asian     | 577/389^                                | 301  | 223 | 53  | 218                | 143   | 28    | 0.49  |
| Kirk        | 2005 | Gambia         | African   | 195/352!                                | 160  | 31  | 4   | 300                | 48    | 4     | 0.2   |
| Long        | 2005 | Mainland China | Asian     | 140/536*                                | 72   | 63  | 5   | 362                | 159   | 15    | 0.62  |

\*controls: HBV/HCV negative (consisting of blood donors and healthy volunteers); ^controls: HBV/HCV positive (consisting of HBV/HCV carriers without HCC); !controls: HBV/HCV mixed (consisting of HBV/HCV-negative and HBV/HCV-positive)

**Table 2. Summary of the OR and P value for Various Influence of XRCC1 Polymorphism Arg399Gln on HCC Susceptibility**

| Variables          | No. | A/G vs. A/A         |       | G/G vs. A/A         |       | G/G+A/G vs. A/A     |       | G/G vs.A/G+ A/A     |       |
|--------------------|-----|---------------------|-------|---------------------|-------|---------------------|-------|---------------------|-------|
|                    |     | OR (95% CI)         | P     | OR (95% CI)         | P     | OR (95% CI)         | P     | OR (95% CI)         | P     |
| Total              | 15  | 1.271 (0.984-1.641) | 0.066 | 1.253 (1.025-1.531) | 0.028 | 1.281 (1.003-1.634) | 0.047 | 1.049 (0.900-1.222) | 0.542 |
| Ethnicity          |     |                     |       |                     |       |                     |       |                     |       |
| Asian              | 13  | 1.357 (1.039-1.772) | 0.025 | 1.310 (1.064-1.613) | 0.011 | 1.371 (1.067-1.760) | 0.013 | 1.059 (0.906-1.239) | 0.469 |
| non-Asian          | 2   | 0.805 (0.332-1.951) | 0.630 | 0.679 (0.310-1.491) | 0.335 | 0.795 (0.301-2.098) | 0.643 | 0.834 (0.395-1.758) | 0.632 |
| Country/region     |     |                     |       |                     |       |                     |       |                     |       |
| Mainland           | 9   | 1.649 (1.229-2.213) | 0.001 | 1.421 (1.101-1.835) | 0.007 | 1.632 (1.232-2.163) | 0.001 | 1.035 (0.867-1.234) | 0.705 |
| non-Mainland       | 6   | 0.921 (0.712-1.193) | 0.534 | 1.023 (0.739-1.415) | 0.891 | 0.926 (0.701-1.222) | 0.586 | 1.093 (0.803-1.486) | 0.572 |
| Source of controls |     |                     |       |                     |       |                     |       |                     |       |
| HBV/HCV positive   | 4   | 0.682 (0.366-1.270) | 0.227 | 1.037 (0.710-1.513) | 0.851 | 0.800 (0.483-1.324) | 0.385 | 1.210 (0.890-1.645) | 0.224 |
| HBV/HCV negative   | 10  | 1.143 (0.761-1.717) | 0.520 | 1.061 (0.798-1.409) | 0.684 | 1.159 (0.783-1.718) | 0.461 | 0.965 (0.796-1.170) | 0.718 |

et al., 2004; Han et al., 2012) on the same population, four (Long et al., 2008; Kiran et al., 2009; Ding et al., 2012; Jung et al., 2012) papers not providing adequate data for calculation of OR and 95% CI, and four (Yang et al., 2004; Su et al., 2008; Guo et al., 2012; Bose et al., 2013) studies not in accordance with HWE were excluded. A flow diagram summarizing the process of study selection was illustrated in Figure 1. As summarized in Table 1, the final data pooling consisted of 15 eligible publications (Long et al., 2005; Kirk et al., 2005; Chen et al., 2005; Long et al., 2006; Borentain et al., 2007; Ren et al., 2008; Wu et al., 2009; Kiran et al., 2009; Jia et al., 2010; Zeng et al., 2010; Pan et al., 2011; Tang et al., 2011; Li et al., 2012; Mohana Devi et al., 2013; Gulnaz et al., 2013) (eleven in English (Long et al., 2005; Kirk et al., 2005; Chen et al., 2005; Long et al., 2006; Borentain et al., 2007; Kiran et al., 2009; Jia et al., 2010; Pan et al., 2011; Li et al., 2012; Mohana Devi et al., 2013; Gulnaz et al., 2013) and four (Ren et al., 2008; Wu et al., 2009; Zeng et al., 2010; Tang et al., 2011) in Chinese) with a mount of 2719 HCC cases and 3837 controls.

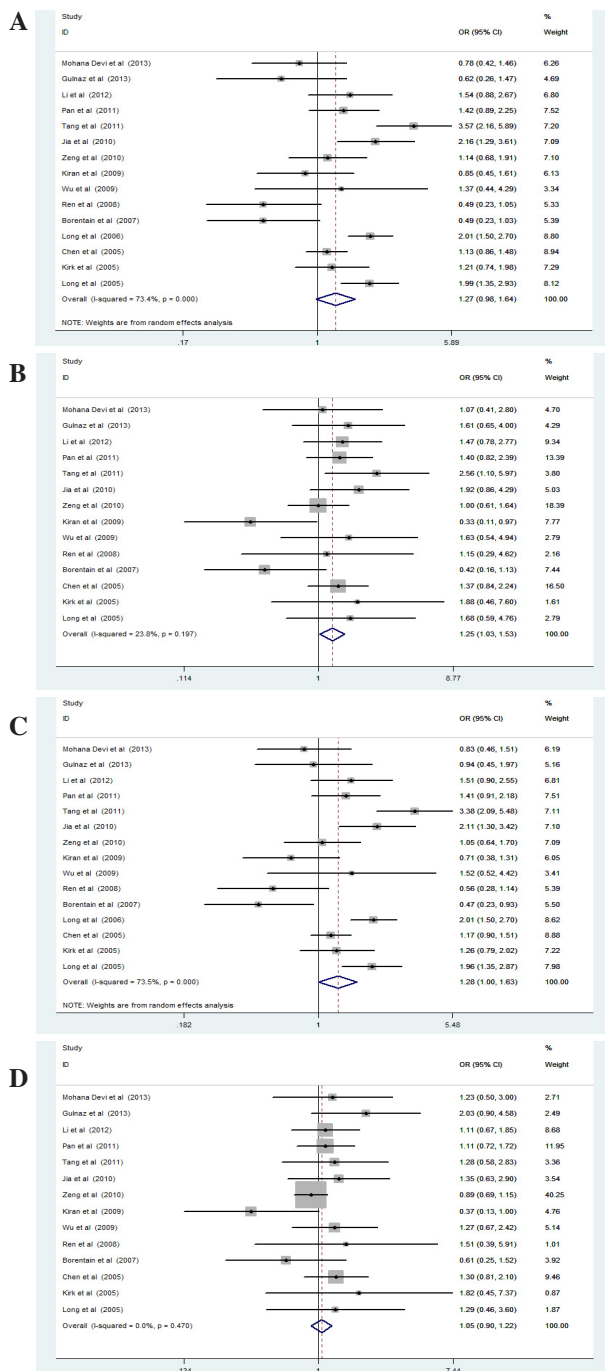
The case-control researches were performed in mainland China, India, France Taiwan, and Gambia. 13 studies from Asian population, one research of African population and one study consisted of Caucasian ethnicity.

The cases definition applied in each study were clinically or pathologically diagnosed with HCC. In respect of control's selection, ten studies recruited healthy volunteers or blood donors and four studies enrolled the HBV carriers. Among these 15 studies, controls in nine studies were selected from hospital-based people, while the rest were from population-based people. Among 11 studies, DNA in peripheral blood was extracted and tested the SNPs of XRCC1 using a classic polymerase chain reaction assay, namely restriction fragment length polymorphism assay (RFLP).

#### Quantitative synthesis

In this meta-analysis, the variant G/G genotype of Arg399Gln was significantly correlated to HCC susceptibility comparing to the wild-type A/A (G/G vs. A/A, OR = 1.253, 95% CI = 1.025-1.531). Similarly, associations were observed in a dominant model (G/G + A/G vs. A/A, OR = 1.281, 95% CI = 1.003-1.634). However, no association was observed in a heterozygote model (A/G vs. A/A, OR = 1.271, 95% CI = 0.984-1.641) and a recessive model (G/G vs. A/G + A/A, OR = 1.049, 95% CI = 0.900-1.222) (Table 2, Figure 2).

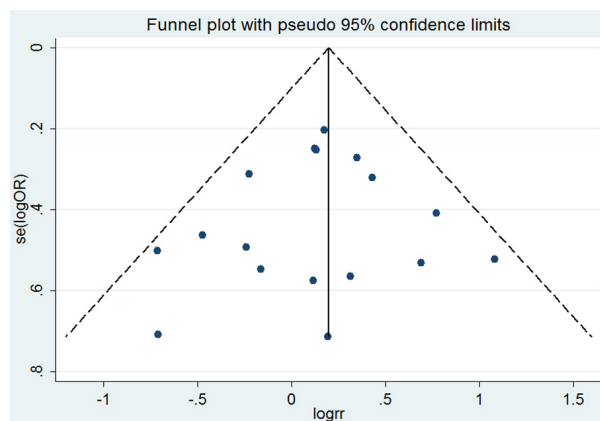
Challenged by the insidious exaggeration of the exact influence of XRCC1 Arg399Gln polymorphism on HCC



**Figure 2. Forest Plot of XRCC1 Arg399Gln Polymorphism Correlating to HCC Susceptibility in Different Genetic Models Analyses (A: A/G vs. A/A; B: G/G vs. A/A; C: A/G + G/G vs. A/A; D: G/G vs. A/G + A/A)**

susceptibility, subgroup analyses stratified by ethnicity, country/region, and source of controls were performed. Owing to the inadequate studies available for African and Caucasian populations, different ethnicities were divided into non-Asian and Asian subgroups. Similarly, different regions/countries were defined as non-Mainland and Mainland subgroups. Different sources of controls were classified as HBV/HCV negative and positive.

In stratification analyses, the variant genotypes (G/G and A/G) had similar significant correlation to HCC risk in ethnicity and country/region subgroups. Compared with the wild type, the heterozygote variant genotypes (A/G and G/G) in ethnicity subgroup (A/G vs. A/A, OR = 1.357,



**Figure 3. Funnel Plot for Publication Bias Test (G/G vs. A/A).** Each point represents an individual study involved in this updated meta-analysis

95% CI = 1.039-1.772; G/G vs. A/A, OR = 1.310, 95% CI = 1.064-1.613), and country/region subgroup (A/G vs. A/A, OR = 1.649, 95% CI = 1.229-2.213; G/G vs. A/A, OR = 1.421, 95% CI = 1.101-1.835) contribute significantly to HCC susceptibility. The correlation between XRCC1 polymorphism and HCC risk wasn't identified in HBV/HCV positive subgroup (Table 2, Figure 2).

*Heterogeneity analysis*

There was no heterogeneity among the included studies in overall comparison of the XRCC1 Arg399Gln polymorphism using a homozygote model or a recessive genetic model ( $\chi^2 = 23.8\%$ ,  $p = 0.197$  and  $\chi^2 = 0.0\%$ ,  $p = 0.470$  for heterogeneity test of G/G vs. A/A and G/G vs. A/G + A/A, respectively). Nevertheless, heterogeneity was existed in a heterozygote model or a dominant model ( $\chi^2 = 73.4\%$ ,  $p = 0.000$  and  $\chi^2 = 73.5\%$ ,  $p = 0.000$  for heterogeneity test of A/G vs. A/A and G/G + A/G vs. A/A respectively). To investigate the potential sources of heterogeneity among the studies, stratification comparisons by ethnicity, country/region, genotyping methods and source of controls were done in heterozygote model and dominant model. As a result, country/region (A/G vs. A/A:  $p = 0.001$ ; dominant model:  $p = 0.002$ ) rather than ethnicity, genotyping methods and source of controls was found contributing to substantial heterogeneity. In addition, results of meta-regression analyses indicated that stratified factor of country/ region could explain 48.81% (A/G vs. A/A) and 45.84% (dominant model) of the between-study heterogeneity.

*Sensitivity analysis*

To elucidate the differential influence of each individual studies on OR of HCC risk, sensitivity analysis was designed to examine such an effect through redoing the analysis and contrasting the corresponding results by omitting individual study, one at a time. The assessment confirmed that all results from this updated meta-analysis turned out to be stable. Furthermore, after inclusion of another 4 studies with unsatisfied HWE, no significant influence on between-study heterogeneity and the result of the meta-analysis was observed (G/G vs. A/A, OR = 1.182, 95% CI = 1.000-1.396; G/G + A/G vs. A/A, OR = 1.268, 95% CI = 1.032-1.559).



### Publication bias

The publication bias of all illegible articles was evaluated by funnel plot, Begg's test as well as Egger's tests. The symmetrical shape of the funnel plot (Figure3) indicated that no distinct publication bias was existed in this updated meta-analysis. In addition, the calculated results from Begg's test and Egger's test statistically validated the negative outcome (G/G vs. A/A:  $p = 0.702$ ,  $p = 0.832$ ; A/G vs. A/A:  $p = 0.547$ ,  $p = 0.466$ ; dominant model:  $p = 0.054$ ,  $p = 0.163$ ; recessive model:  $p = 0.622$ ,  $p = 0.285$ ).

## Discussion

Large amounts of studies were conducted to investigate whether the XRCC1 Arg399Gln polymorphism contributed to HCC susceptibility generated controversial or inconclusive results. Based on these studies, five meta-analyses were performed in last five years. However, the conclusions are unconvincing because of data duplications or data missing (Liu et al., 2011; Xie et al., 2012; Li et al., 2013), different original studies (Zhang et al., 2010; Liu et al., 2011; Xie et al., 2012; Li et al., 2013; Zeng et al., 2013) and different inclusion criteria (Xie et al., 2012; Li et al., 2013). Furthermore, new emerging articles on this association need to be included for reevaluation. In order to address these issues, current updated systematic review including eligible 15 studies including a amount of 2719 HCC cases and 3837 controls was conducted to explore the correlation between the XRCC1 Arg399Gln polymorphisms and HCC susceptibility. XRCC1 Arg399Gln polymorphism was significantly linked to HCC susceptibility in a homozygote model and a dominant model. Similarly, in stratification analyses of source of controls, ethnicity and country/region, consistent results were found. However, the potential correlation of XRCC1 Arg399Gln polymorphism to HCC susceptibility in HBV/HCV subgroup was not identified.

Dysfunction in DNA damage repair system is one critical element in the comprehensive process of carcinogenesis. XRCC1 is a crucial component of BER, which is the predominant DNA damage repair pathway for processing of small base lesions. XRCC1 polymorphisms contribute to carcinogenesis, such as lung cancer (Kiyohara et al., 2006), breast cancer (Saadat et al., 2009), and prostate cancer (Geng et al., 2009). Oppositely, it seems that XRCC1 polymorphisms didn't exert influence on the development of gastric cancer (Geng et al., 2008), bladder cancer (Wang et al., 2008), and colorectal cancer (Wang et al., 2010). Regarding to HCC, the correlations between XRCC1 polymorphisms and HCC susceptibility were also conflicting. Three previous meta-analyses found no association of XRCC1 Arg399Gln polymorphism with HCC susceptibility (Liu et al., 2011; Xie et al., 2012; Zeng et al., 2013) while other two studies got the inverse results that XRCC1 Arg399Gln polymorphism had significant contributions to HCC risk (Zhang et al., 2010; Li et al., 2013). However, there were some common problems in these previous meta-analyses such as data duplicates, data missing and inclusion of studies with unsatisfied HWE of the controls. Excluded the inappropriate studies and

expanded the sample size, our study finally found that XRCC1 Arg399Gln polymorphism could be a HCC risk factor. Until now, the reasons for apparent difference in the influence of XRCC1 polymorphism on cancer risk are still unclear. It appears that following factors might contribute to the process of carcinogenesis. First of all, the influence of gene polymorphisms on the development of different kinds and stages of cancers are in variation. Secondly, the effect of the same gene polymorphism could be significantly different when studies were conducted under different ethnic compositions. Thirdly, methodological differences including the quality of original studies, inclusion criteria and small sample size might contribute to the discrepancy. Further rigorous studies are needed to resolve this inconsistency.

People of different ethnicities, different regions have various susceptibilities to carcinogenesis because of the differences of genetic backgrounds and the living environment (Hirschhorn et al., 2002). Therefore, stratification analyses by ethnicity or country/region were performed. The results, identical to the findings of Li et al (Li et al., 2013), showed that XRCC1 Arg399Gln polymorphism was significantly correlated to HCC susceptibility in Asian, especially in Mainland China. The null results in non-Asian ethnic subgroup may be explained for the limited available studies from Caucasian and African ethnics (Borentain et al., 2007; Kirk et al., 2005). More larger-sample and well-designed multicenter researches from non-Asian ethnics should be conducted to reevaluate the findings.

HBV or HCV chronic infection is the most overwhelming environmental factor for HCC susceptibility globally, especially in developing countries (McKillop et al., 2006). Theoretically, HBV/HVC carriers would be more susceptible to HCC. In this meta-analysis, a healthy population was mainly considered as the reference group (Long et al., 2005; Long et al., 2006; Borentain et al., 2007; Ren et al., 2008; Kiran et al., 2009; Wu et al., 2009; Zeng et al., 2010; Tang et al., 2011; Gulnaz et al., 2013; Mohana Devi et al., 2013), whereas in some others studies, chronic HBV/HCV carriers (Chen et al., 2005; Kiran et al., 2009; Zeng et al., 2010; Gulnaz et al., 2013) without HCC presented as the control group. To distinguish the possible influence from the confounding factor on HCC susceptibility, we conducted stratification analysis in different source of controls. The results revealed that XRCC1 Arg399Gln polymorphism was not associated with HCC susceptibility in controls who were chronic HBV/HCV carriers as well as healthy individuals.

It is widely believed that the conclusions from gene-cancer correlation studies could be unconvincing when the genotypes distribution in the control group was not in HWE (Salanti et al., 2005; Trikalions et al., 2006). The 15 studies involved in this meta-analysis were all in HWE. Here, we hope to increase the sample to reevaluate the findings by including other four studies that were not in HWE. However, the conclusion wasn't altered, suggesting that HWE probably had limited influence on the overall assessment in present meta-analysis.

No publication bias was identified in this systematic review. However, some limitations need to be mentioned.

On one hand, it is evitable to find that significant heterogeneity among the eligible studies was existed in a heterozygote model and a dominant model comparison. The source of heterogeneity was partially due to the different region distribution of the recruited population. On the other hand, the number of studies from Asian and non-Asian regions was not equilibrium and large enough for comprehensive analyses. Particularly, only two published studies focused on the Arg399Gln polymorphism and its relationship with HCC in Caucasian and African populations (Kirk et al., 2005; Borentain et al., 2007). Moreover, the current meta-analysis was carried out based on the unadjusted ORs, whereas a more rigorous analysis should be performed with available individual data. Finally, the influence of gene-gene and gene-environment interactions was not addressed in this meta-analysis because of the lack of sufficient studies.

In conclusion, this updated meta-analysis provided comprehensive and clear evidence that XRCC1 Arg399Gln polymorphism could be a genetic susceptibility for HCC worldwide, particularly in East Asian population. Further large-scale studies with the consideration of gene-gene and gene-environment interactions are necessary to validate the findings in the present meta-analysis.

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

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