

RESEARCH ARTICLE

An Updated Meta-analysis on the Association of X-Ray Repair Cross Complementing Group 1 Codon 399 Polymorphism with Hepatocellular Carcinoma Risk

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Abstract

Background: A number of studies have reported the association of X-ray repair cross-complementing group 1 (XRCC1) Arg399Gln polymorphism with susceptibility to hepatocellular carcinoma (HCC). However, the results were inconsistent and inconclusive. The aim of this study was to comprehensively explore the association of XRCC1 Arg399Gln variant with HCC risk. **Materials and Methods:** Systematic searches of PubMed, Elsevier, Science Direct, CNKI and Chinese Biomedical Literature Database were performed. Pooled odds ratio (OR) with 95% confidence intervals (CI) was calculated to estimate the strength of association. **Results:** Overall, we observed an increased HCC risk among subjects carrying XRCC1 codon 399 Gln/Gln, Arg/Gln and Gln/Gln+Arg/Gln genotypes (OR=1.20, 95% CI: 1.05-1.38, OR=1.16, 95% CI: 1.05-1.28, and OR=1.14, 95% CI: 1.04-1.24, respectively) based on 20 studies including 3374 cases and 4633 controls. In subgroup analysis, we observed an increased risk of XRCC1 codon 399 Gln/Gln, Arg/Gln and Gln/Gln+Arg/Gln polymorphisms for HCC in hospital-based study (OR=1.25, 95% CI: 1.03-1.51, OR=1.21, 95% CI: 1.07-1.36 and OR=1.18, 95% CI: 1.06-1.31, respectively) and in Asian population (OR=1.19, 95% CI: 1.03-1.38, OR=1.17, 95% CI: 1.04-1.30 and OR=1.14, 95% CI: 1.04-1.25, respectively). Limiting the analysis to the studies with controls in agreement with Hardy-Weinberg equilibrium (HWE), we observed an increased HCC risk among Gln/Gln, Arg/Gln and Gln/Gln+Arg/Gln genotype carriers (OR=1.17, 95% CI: 1.05-1.29, OR=1.12, 95% CI: 1.00-1.25 and OR=1.11, 95% CI: 1.02-1.21, respectively). **Conclusions:** This updated meta-analysis results suggest that XRCC1 Arg399Gln variants may contribute to HCC risk. Well-designed studies with larger sample size were required to further verify our findings.

Keywords: Hepatocellular carcinoma - XRCC1 - genetic polymorphism - meta-analysis

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Introduction

Liver cancer in men is the fifth most frequently diagnosed cancer worldwide and the second most frequent cause of cancer death. It is the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death in women. An estimated 748,300 new liver cancer cases and 695,900 cancer deaths occurred worldwide in 2008. Half of these cases and deaths were estimated to occur in China. Among primary liver cancers, hepatocellular carcinoma (HCC) represents the major histological subtype, accounting for 70% to 85% of the total liver cancer burden worldwide (Jemal et al., 2011).

It has been known that chronic infection with hepatitis virus B (HBV) or hepatitis virus C (HCV) is the most common cause of HCC worldwide (Dominguez-Malagon et al., 2001). However, epidemiological data have exhibited that although a lot of people are exposed to these risk factors, only a minority of them develop HCC.

This indicates that an individual susceptibility might play a certain role in HCC carcinogenesis (Pang et al., 2008; Clifford et al., 2010). Recently, increasing evidence has been accumulated to support the hypothesis that common genetic polymorphisms in genes involved in DNA repair capacity may be of importance in determining individual susceptibility to develop HCC (Long et al., 2011; Huang et al., 2012; Wang et al., 2013).

XRCC1 is a major DNA repair gene involved in base excision repair (Vidal et al., 2001). A common single nucleotide polymorphism leads to amino acid substitutions in XRCC1 gene at codon 399 (exon 10, G-A, and Arg-Gln) (Shen et al., 1998). This mutation could alter XRCC1 function, diminish repair kinetics and influence susceptibility to adverse health effect, such as cancer. To date, numerous studies have investigated the association between XRCC1 Arg399Gln polymorphism and HCC risk (Yu et al., 2003; Long et al., 2004; Yang et al., 2004; Kirk et al., 2005; Li, 2005; Long et al., 2006; Borentain et al.,

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2007; Ren et al., 2008; Kiran et al., 2009; Wu, 2009; Jia et al., 2010; Zeng et al., 2010; Pan et al., 2011; Tang et al., 2011; Bo et al., 2012; Guo et al., 2012; He et al., 2012; Bose et al., 2013; Gulnaz et al., 2013; Mohana Devi et al., 2013). However, the results from epidemiological studies have been inconsistent and controversial. Although, in recent year, several meta-analyses on XRCC1 Arg399Gln polymorphism related to HCC risk have been reported, conclusions drawn from them were not consistent. Four published meta-analyses failed to observe any positive association between XRCC1 Arg399Gln polymorphism and HCC risk (Zhang et al., 2010; Liu et al., 2011; Xie et al., 2012; Zeng et al., 2013). Two articles (Chen et al., 2011; Pan et al., 2013) reported that XRCC1 Arg399Gln polymorphism was associated with the susceptibility to HCC in total population, but several papers published before 2011 were not included in Chen et al's study; In Pan et al's paper, one overlapping paper was not excluded and Long et al's paper (Long et al., 2006) with controls being not in accordance with Hardy-Weinberg equilibrium (HWE) was mistakenly included in Pan et al's paper. Li et al found that XRCC1 Arg399Gln polymorphism was associated with HCC risk in East Asian population (Li et al., 2013), however, two overlapping studies were not excluded in that paper. Two meta-analyses found that XRCC1 Arg399Gln polymorphism was associated with HCC risk in Chinese population (Duan et al., 2012; Liu et al., 2012), but several published papers were missing and overlapping articles were not excluded in their study. Ever since, new studies have provided additional data on the association between XRCC1 Arg399Gln polymorphism and HCC risk. Therefore, it is required to clarify the association between XRCC1 Arg399Gln variations and HCC risk objectively and comprehensively. In this study, we used the most updated data to address this issue by performing meta-analysis.

Materials and Methods

Literature and methods

We carried out a systematic search in Pubmed/Medline, Elsevier, Science direct, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biomedical Literature Database, covering all papers published before December 1, 2013 with a combination of the following terms: "hepatocellular cancer" or "hepatocellular carcinoma" or "liver cancer" or "liver tumor", "polymorphism" and "XRCC1". Additional studies were identified by the references lists of the selected papers.

Data from studies were included in our meta-analysis only if the study met the following criteria: (1) The papers should include HCC risk and polymorphism of XRCC1 codon 399; (2) Only the case-control studies or cohort studies were considered; (3) The paper must offer the sample size, odds ratio (OR) with 95% confidence intervals (CI) or the information that can help infer the results; (4) When more than one article was identified for the same study population, we included the publication including more information.

Accordingly, articles that could not offer the numbers of case and control or other essential information were

excluded; reviews and overlapping literatures were excluded, too.

In total, 42 published studies were identified with the association between XRCC1 codon 399 polymorphisms and HCC risk. We reviewed all papers in accordance with the criteria defined above, and nine meta-analysis papers, two reviews and eleven overlapping studies were excluded. Therefore, 20 original articles were determined to enter our study.

Data extraction

Data were carefully extracted and tabulated by two investigators first, and then inputted into an electric database. The following information was subtracted from each study: authors, publishing year, country, ethnicity of subjects, source of controls, the extract data of total and exposure number in case and control groups, and OR with 95%CI. If the study provided stratum information, the data coming from similar stratum were added up to make a full use of the data. Characteristics of individual studies were presented in Table 1.

Quantitative data synthesis

A meta-analysis of identified studies was conducted to estimate the strength of association between the polymorphisms of XRCC1 Arg399Gln and HCC risk. Data were combined using both a fixed-effects model and a random-effects model (DerSimonian et al., 1986). The Cochrane Q statistics test is used for the assessment of heterogeneity. The fixed-effects model is used when the effects are assumed to be homogenous, while the random-effects model is used when they are heterogeneous. The funnel plot was drawn to assess publication bias, Egger's test and Begg's test were used to test for the funnel plot symmetry (Begg et al., 1994; Egger et al., 1997). We tested whether genotype frequencies of controls were in agreement with HWE using the χ^2 test.

All of the statistical analyses were performed with STATA10.0 software package (Stata Corporation, College Station, Texas) and Review Manager (Version 5.0.24.0, the Cochrane Collaboration). All the tests were two-sided, a P value of less than 0.05 for any test was considered to be statistically significant.

Results

Meta-analysis databases

A database was established according to the extracted information from each article. Essential information was listed in Table 1, which showed first author, publishing year, source of control, country, ethnicity of subjects, the numbers of case and control. There were a total of 20 studies with 3374 cases and 4633 controls concerning the XRCC1 codon 399 polymorphisms related to HCC risk.

Test of heterogeneity

Table 2 showed the association of the XRCC1 codon 399 polymorphism with HCC susceptibility. The heterogeneity of XRCC1 codon 399 Gln/Gln versus Arg/Arg, Arg/Gln versus Arg/Arg, and Gln/Gln+Arg/Gln versus Arg/Arg was analyzed for 20 case-control studies.

Table 1. Studies on the Association Between Genetic Polymorphisms of XRCC1 Codon 399 and HCC Risk Included in Meta-analysis

First author	Year	Country	Ethnicity	Source of control	No. case	No. control	P value of HWE
(Yu et al., 2003)	2003	China	Asian	Population	577	389	0.497
(Long et al., 2004)	2004	China	Asian	Hospital	140	536	0.621
(Yang et al., 2004)	2004	China	Asian	Population	69	136	0.000
(Kirk et al., 2005)	2005	Gambia	African	Hospital	195	352	0.196
(Li, 2005)	2005	China	Asian	Population	98	200	0.848
(Long et al., 2006)	2006	China	Asian	Hospital	257	649	0.000
(Borentain et al., 2007)	2007	France	European	Population	56	89	0.807
(Ren et al., 2008)	2008	China	Asian	Population	50	92	0.281
(Kiran et al., 2009)	2009	India	Asian	Hospital	63	142	0.980
(Wu, 2009)	2009	China	Asian	Hospital	100	60	0.432
(Jia et al., 2010)	2010	China	Asian	Hospital	136	136	0.096
(Zeng et al., 2010)	2010	China	Asian	Hospital	500	507	0.053
(Bo et al., 2012)	2012	China	Asian	Hospital	60	60	0.000
(Pan et al., 2011)	2011	China	Asian	Hospital	202	236	0.457
(Tang et al., 2011)	2011	China	Asian	Hospital	150	150	0.429
(Guo et al., 2012)	2012	China	Asian	Hospital	410	410	0.000
(He et al., 2012)	2012	China	Asian	Population	113	113	0.000
(Bose et al., 2013)	2013	India	Asian	Hospital	55	209	0.040
(Gulnaz et al., 2013)	2013	Pakistan	Asian	Hospital	50	74	0.336
(Mohana Devi et al., 2013)	2013	India	Asian	Hospital	93	93	0.118

HWE, Hardy-Weinberg Equilibrium

Table 2. Summary Odds Ratios on the Relation of Polymorphisms of the XRCC1 Arg399Gln to Hepatocellular Carcinoma risk

Genotype	Case/Control	Heterogeneity test		Summary OR(95% CI)	Hypothesis test			Egger's test		Begg's test	
		<i>Q</i>	<i>P</i>		<i>Z</i>	<i>P</i>	df	<i>t</i>	<i>P</i>	<i>Z</i>	<i>P</i>
Overall											
Gln/Gln: Arg/Arg	2111/3157	40.17	0.003	1.20(1.05-1.38)	2.66	0.008	19	0.11	0.911	0.42	0.673
Arg/Gln: Arg/Arg	2861/4027	58.54	0.000	1.16(1.05-1.28)	2.86	0.004	19	0.17	0.870	0.03	0.974
Gln/Gln+Arg/Gln: Arg/Arg	3374/4633	86.72	0.000	1.14(1.04-1.24)	2.94	0.003	19	0.06	0.954	0.16	0.871
Stratification by HWE											
Yes											
Gln/Gln: Arg/Arg	1451/1990	17.99	0.158	1.17(1.05-1.29)	2.88	0.004	13	0.52	0.613	0.33	0.743
Arg/Gln: Arg/Arg	2049/2669	40.42	0.000	1.12(1.00-1.25)	2.01	0.045	13	0.36	0.723	0.44	0.661
Gln/Gln+Arg/Gln: Arg/Arg	2410/3056	49.76	0.000	1.11(1.02-1.21)	2.37	0.018	13	0.05	0.963	0.00	1.000
Stratification by source of control											
Population-based control											
Gln/Gln: Arg/Arg	641/687	9.08	0.106	1.13(0.99-1.28)	1.82	0.069	5	1.15	0.315	0.38	0.707
Arg/Gln: Arg/Arg	781/783	8.21	0.145	1.05(0.94-1.18)	0.90	0.369	5	0.11	0.914	0.00	1.000
Gln/Gln+Arg/Gln: Arg/Arg	963/1019	12.27	0.031	1.04(0.93-1.17)	0.70	0.481	5	0.17	0.870	0.00	1.000
Hospital-based control											
Gln/Gln: Arg/Arg	1470/2470	25.39	0.020	1.25(1.03-1.51)	2.27	0.023	13	0.42	0.680	0.33	0.743
Arg/Gln: Arg/Arg	2080/3244	44.05	0.000	1.21(1.07-1.36)	2.96	0.003	13	0.02	0.983	0.22	0.827
Gln/Gln+Arg/Gln: Arg/Arg	2411/3614	57.78	0.000	1.18(1.06-1.31)	2.94	0.003	13	0.07	0.947	0.11	0.913
Stratification by ethnicity											
Asian											
Gln/Gln: Arg/Arg	1912/2807	38.23	0.002	1.19(1.03-1.38)	2.32	0.020	17	0.15	0.886	0.23	0.820
Arg/Gln: Arg/Arg	2641/3617	57.96	0.000	1.17(1.04-1.30)	2.73	0.006	17	0.09	0.931	0.23	0.820
Gln/Gln+Arg/Gln: Arg/Arg	3123/4192	86.36	0.000	1.14(1.04-1.25)	2.73	0.006	17	0.01	0.989	0.00	1.000

*HWE, Hardy-Weinberg Equilibrium

The results showed that XRCC1 codon 399 Gln/Gln versus Arg/Arg, Arg/Gln versus Arg/Arg and Gln/Gln+Arg/Gln versus Arg/Arg for total population, hospital-based study and Asian population, Gln/Gln+Arg/Gln versus Arg/Arg for population-based study, and Arg/Gln versus Arg/Arg and Gln/Gln+Arg/Gln versus Arg/Arg for control in agreement with HWE had heterogeneity with a P value less than 0.05, therefore, we analyzed the summary odds ratios for these with a random-effects model. Fixed-effects model was used to analyze the summary OR for the rest.

Quantitative data synthesis

Table 2 showed that the summary OR of XRCC1

codon 399 on the basis of 3374 cases and 4633 controls. We observed an increased HCC risk among subjects carrying XRCC1 399 Gln/Gln, Arg/Gln and Gln/Gln+Arg/Gln genotypes (OR=1.20, 95%CI: 1.05-1.38, OR=1.16, 95%CI: 1.05-1.28, and OR=1.14, 95%CI: 1.04-1.24, respectively) in total population (Figure 1a, 1b, 1c). In subgroup analysis, we observed an increased risk of XRCC1 399 Gln/Gln versus Arg/Arg, Arg/Gln versus Arg/Arg and Gln/Gln+Arg/Gln versus Arg/Arg polymorphisms for HCC in hospital-based study (OR=1.25, 95%CI: 1.03-1.51, OR=1.21, 95%CI: 1.07-1.36 and OR=1.18, 95%CI: 1.06-1.31, respectively) and in Asian population (OR=1.19, 95%CI: 1.03-1.38, OR=1.17, 95%CI: 1.04-

1.30 and OR=1.14, 95%CI: 1.04-1.25, respectively) (Table 2). Limiting the analysis to the studies with controls in agreement with HWE, we observed an increased HCC risk among Gln/Gln, Arg/Gln and Gln/Gln+Arg/Gln genotype carriers (OR=1.17, 95%CI: 1.05-1.29, OR=1.12, 95%CI: 1.00-1.25 and OR=1.11, 95%CI: 1.02-1.21, respectively), compared with Arg/Arg genotype carriers (Table 2).

Bias diagnosis

Publication bias was examined by using funnel plot. The shape of the funnel plot seemed to be approximately symmetrical (Figure 2a, 2b, 2c). The results from Egger's test and Begg's test indicated that publication biases may not have a significant influence on our current meta-analysis results (Table 2).

Sensitivity analyses

Sensitivity analyses were conducted to identify the effects of the individual dataset on the summary odds ratio by sequential omission of each study. The overall effects

were not modified when the studies were homogenous for Gln/Gln versus Arg/Arg, Arg/Gln versus Arg/Arg and Gln/Gln+Arg/Gln versus Arg/Arg polymorphisms among total population by removing some eligible studies (Figure S1, S2, S3).

Discussion

We performed a systematic literature review to evaluate the associations between sequence variants in XRCC1 codon 399 and the risk of HCC. We also evaluated possible effect modifications by controls in agreement with HWE, source of control and the ethnicity of subjects. In summary, we observed an increased risk of HCC among subjects carrying the XRCC1 codon 399 Gln allele, which is consistent with experiment evidence that this isoform exhibits decreased base excision repair activity (Lunn et al., 1999; Duell et al., 2000). However, Liu et al (Liu et al., 2011) did not find an association between XRCC1 Arg399Gln polymorphism and HCC risk based on 2208

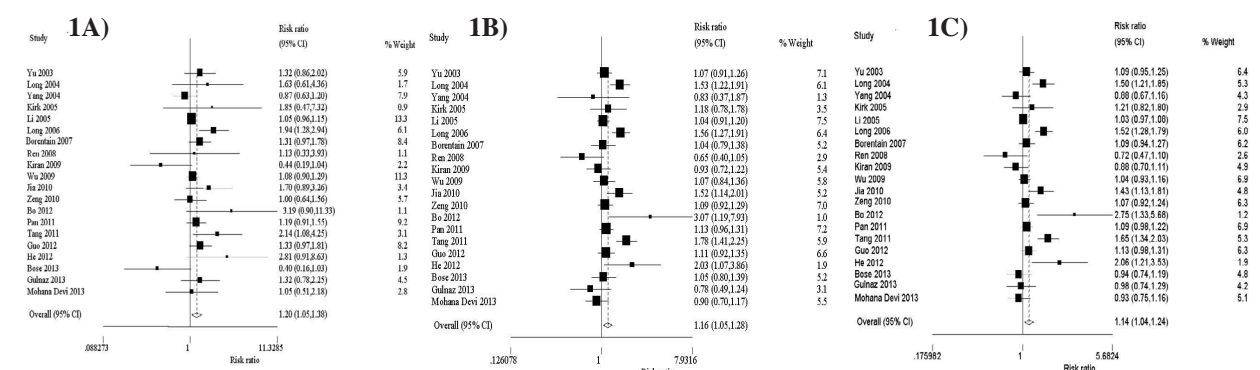


Figure 1. Forest Plots of Odds Ratios for Gln/Gln versus Arg/Arg (1A), Arg/Gln versus Arg/Arg (1B) and Gln/Gln+Arg/Gln versus Arg/Arg (1C) of XRCC1 Codon 399 Variant Associated with HCC Risk

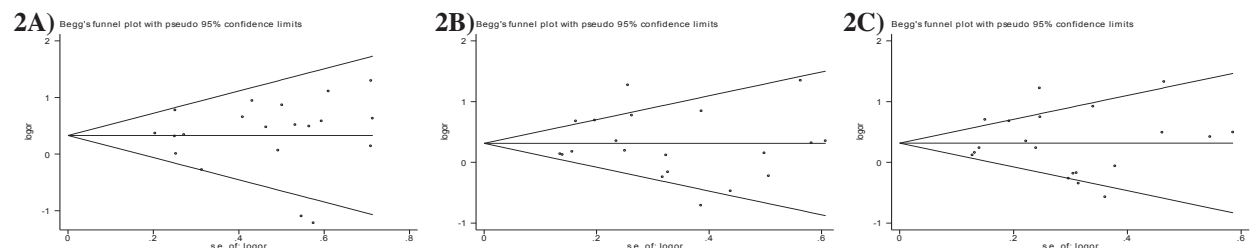


Figure 2. Funnel Plot Analysis to Detect Publication Bias for Gln/Gln versus Arg/Arg (2A), Arg/Gln versus Arg/Arg (2B) and Gln/Gln+Arg/Gln versus Arg/Arg (2C) of XRCC1 codon 399 Variant Associated with HCC Risk

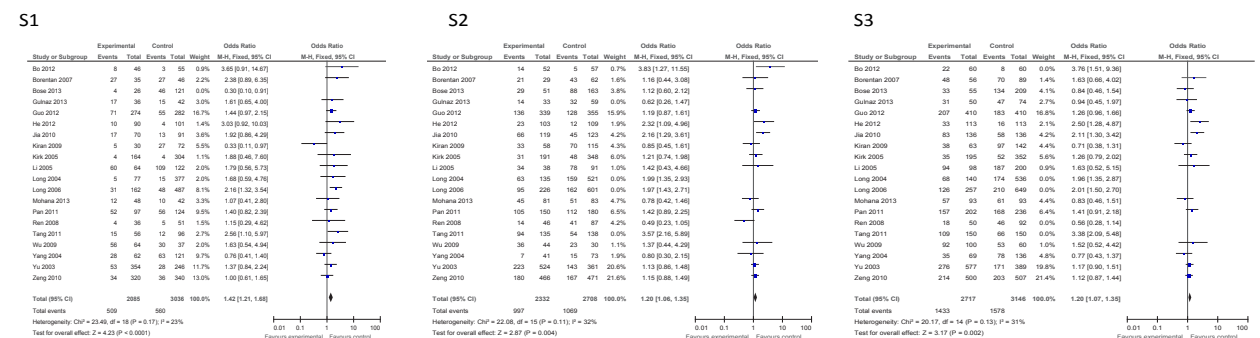


Figure S. Sensitivity Analyses were Performed. S1) The study was homogenous for Gln/Gln versus Arg/Arg, while excluding Bose (2013, 519: 231-237), the summary OR was 1.42 (95% CI: 1.21-1.68). **S2)** The study was homogenous for Arg/Gln versus Arg/Arg, while excluding Gulnaz (2013, 25: 166-179), Long (2004, 21: 313-315; 2006, 36: 48-55) and Tang (2011, 51: 19-20), the summary OR was 1.20 (95% CI: 1.06-1.35). **S3)** The study was homogenous for Arg/Gln+Gln/Gln versus Arg/Arg, while excluding Bo (2012, 22: 45-48), Long (2004, 21: 313-315; 2006, 36: 48-55), Ren (2008, 24: 361-364) and Tang (2011, 51: 19-20), the summary OR was 1.20 (95% CI: 1.07-1.35)

cases and 3265 controls. In addition, other three studies did not observe an effect modification with small sample sizes as well (Zhang et al., 2010; Xie et al., 2012; Zeng et al., 2013). Chen et al (Chen et al., 2011) found that XRCC1 Arg399Gln polymorphism was associated with the susceptibility to HCC on the base of 7 studies including 1342 cases and 2207 controls, but several papers published before 2011 (Wu, 2009; Jia et al., 2010; Zeng et al., 2010) were not included in their study. Pan et al also found a significant association between XRCC1 polymorphism and HCC risk containing 15 studies with 6556 individuals, but one overlapping paper was not excluded and one paper with controls being not in agreement with HWE was mistakenly included. Therefore, the conclusion drawn from Chen et al's paper and Pan et al's paper are not reliable. The present meta-analysis of 20 case-control studies including 3374 cases and 4633 controls might have sufficiently statistical power to detect the association of XRCC1 Arg399Gln polymorphism with HCC risk, owing to small random error in large sample sizes.

Similar to other systematic reviews and meta-analyses, there were some limitations in this present study. First, only published papers were included in this study. Therefore, publication bias is very likely to occur. To address this problem, Egger's test and Begg's test were conducted. Our results indicate that the likelihood of key publication bias might not be present in this meta-analysis. Secondly, each study had different eligibility criteria for subjects and different source of controls, which should be taken into account when explaining the combined estimates. When subgroup analysis was performed by source of control, we observed an association between XRCC1 codon 399 polymorphism and HCC risk in hospital-based study, but not in population-based study, maybe owing to too small sample size of population-based study (963 cases and 1019 controls in population-based study) to detect the modified effects. Thirdly, the summary ORs were based on individual unadjusted estimates, while a more precise analysis might be performed if detailed individual data were available, which could allow for an adjusted estimation by HBV status, age, smoking status, alcohol consumption and environment factors. Therefore, it is required for authors of all of the published papers to share their data.

Considering that the frequency of the XRCC1 399 Gln allele variant is significantly different among different ethnic population. Allele frequency patterns of XRCC1 Arg399Gln polymorphism vary greatly between major ethnic groups. The frequency of Gln allele was more than 0.3 in Caucasians (Zhang et al., 2006; Zienolddiny et al., 2006), but less than 0.2 in Asian population (Long et al., 2004; Yin et al., 2007). When stratified by ethnicity, we observed an association of XRCC1 polymorphism with HCC risk among Asian population. Results from previous meta-analysis based on 13 studies including 3011 case and 3619 controls showed that XRCC1 codon 399 polymorphism was associated with HCC risk in East Asian population (Li et al., 2013), however, two overlapping studies (Chen et al., 2005; Han et al., 2012) were not excluded in that paper, therefore, the results from that paper are not accurate. Only two published studies

included in this meta-analysis focused on the association of XRCC1 codon 399 polymorphism with HCC risk in Caucasian and African population, so, we did not perform meta-analysis in other ethnic population further.

It is widely acknowledged that, if the distribution frequency of genotypes in the control groups deviated from HWE, the results of genetic association studies might be spurious (Salanti et al., 2005). To address this problem, subgroup analysis was carried out in this study by HWE in controls. When the studies that were not in accordance with HWE were excluded from this present analysis, the results were persistent and robust, suggesting that this factor might not have significant effects on the overall estimates in the current meta-analysis.

In conclusion, this updated meta-analysis presented clear and comprehensive evidence that XRCC1 codon 399 variants were associated with the risk of HCC worldwide, especially in Asian population. Large scale studies with the pooling of individual study data should be taken into consideration in future association studies to confirm the results from this current meta-analysis.

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