RESEARCH ARTICLE

An Updated Meta-analysis Between the Association of XRCC1 Arg399Gln Polymorphism and Hepatocellular Carcinoma Risk

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Abstract

Background: Various studies have evaluated the relationship between X-ray repair cross-complementing group 1 (XRCC1) Arg399Gln polymorphism and hepatocellular carcinoma (HCC) risk, but the conclusions have been inconsistent and underpowered. The purpose of this updated meta-analysis was to examine whether XRCC1 Arg399Gln polymorphism confers susceptibility to HCC. Methods: Eligible studies extracted from PubMed, Embase, Cochrane Library, VIP (chinese) and CNKI (chinese) up to November 2013 were included in the study. Pooled odds ratio (OR) together with their 95% confidence interval (CI) were estimated to evaluate XRCC1 Arg399Gln polymorphism and HCC risk. Results: Finally, 21 studies with 4,170 cases and 5,030 controls were involved in our meta-analysis. The results demonstrated that there was significant association between Arg399Gln polymorphism and HCC risk under two contrast models in overall populations (AG *vs* GG: OR=1.265, 95%CI=1.036-1.545, *p*=0.021; AA+AG *vs* GG: OR=1.240, 95%CI=1.021-1.506, *p*=0.030). In subgroup analyses, significant association was found in Asians (A *vs* G: OR=1.175, 95%CI=1.013-1.362, *p*=0.033; AG *vs* GG: OR=1.317, 95%CI=1.070-1.622, *p*=0.009; AA+AG *vs* GG: OR=1.289, 95%CI=1.055-1.575, *p*=0.013) and Caucasians (A *vs* G: OR=0.591, 95%CI=0.361-0.966, *p*=0.036; AA+AG *vs* GG: OR=0.468, 95%CI=0.234-0.934, *p*=0.031). Conclusions: The results suggest that XRCC1 Arg399Gln polymorphism may increase HCC risk especially among Asians. However, XRCC1 Arg399Gln polymorphism might act as a protective role against HCC among Caucasians.

Keywords: XRCC1 - polymorphism - HCC - meta-analysis - risk

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most frequent diagnosed cancer in men and the seventh in women respectively, and the third most common cause of cancer-related death worldwide exceeded only by lung cancer and stomach cancer (Ferlay et al., 2010; Jemal et al., 2011). With a dramatic increase in incidence and mortality, HCC has become a global health challenge and has aroused growing public concern. It is accepted that HCC is a complex and multi-factorial disease, and its carcinogenesis still remains elusive (Sato et al., 2011; Forner et al., 2012). Risk factors enhance a person's chance of getting diseases. Some factors including chronic hepatitis B or C, obesity, diabetes, excessive alcohol consumption, pre-existing liver cirrhosis together with exposure to aflatoxin B1 are main known risk factors for HCC (Gomaa et al., 2008; Hagymasi et al., 2008; Caldwell et al., 2009; Forner et al., 2012). Besides, genetic factors have been reported to influence host's susceptibility and may play a vital role in the progression of HCC (Farazi et al., 2006; Sato et al., 2011; El-Serag 2011).

Recently, attention has focused on genetic variations in DNA repair pathways, as unrepaired DNA damage can lead to unregulated cell growth and even cancer (Hoeijmakers, 2001). The base excision repair (BER) pathway is one of the four major DNA repair pathways for the processing of small lesions caused by alkylation and oxidation damage (Almeida et al., 2007). The X-ray repair cross-complementing group 1 (XRCC1) is one of the key DNA repair proteins involved in BER and single-strand breaks (SSBs) repair through interacting with DNA ligaseIII and the complexes with DNA polymerase and poly (ADP-ribose) polymerase (PARP) (Masson et al., 1998; Vidal et al., 2001). Human XRCC1 gene spans 33 kb on chromosome 19q13.2-13.3 and composes of 17 exons (Mei et al., 2013; Li et al., 2013). The Arg399Gln polymorphism (rs25487) is G/A substitution at position 28152 on exon 10, which could alter XRCC1 function, diminish repair kinetics, and influence susceptibility to adverse health effect, such as cancer. To date, XRCC1 Arg399Gln polymorphism has been extensively explored the association with HCC risk (Long et al., 2004; Han et al., 2004; Chen et al., 2005; Kirk et al., 2005; Long

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et al., 2006; Borentain et al., 2007; Ren et al., 2008; Su 2008;Wu 2009; Kiran et al., 2009; Jia et al., 2010; Zeng et al., 2010; Pan et al., 2011; Tang et al., 2011; He et al., 2012; Han et al., 2012; Guo et al., 2012; Jung et al., 2012; Bose et al., 2013; Gulnaz et al., 2013; Mohana Devi et al., 2013). However, the sample sizes of these previous studies were limited and the molecular epidemiological studies into HCC risk are contradictory instead of conclusive. In addition, previous meta-analysis investigating this issue also generated conflicting results (Zhang et al., 2010; Li et al., 2013; Wu et al., 2013). In order to obtain a more accurate assessment of this relationship under different genetic models, an updated meta-analysis containing a total of 21 published studies was performed, which may provide more comprehensive evidence for the relationship of XRCC1 Arg399Gln variants with HCC risk.

Materials and Methods

Search of eligible studies

Eligible studies about XRCC1 Arg399Gln polymorphism and HCC risk were identified by systematic searches of PubMed, Embase, Cochrane Library, VIP (chinese) and CNKI (chinese) that contained all of the records published up to November 2013, using the following key words in both English and Chinese: XRCC1 or X-ray repair cross-complementing group 1, HCC or hepatocellular carcinoma and polymorphism. Although the search was initially performed without restrictions of language, the final analysis we only allowed the full-text articles published in English and Chinese. Additional eligible records were checked by a manual search of the references in the retrieved studies. Review articles were also inspected to find other relevant publications.

Selection criteria

The studies had to satisfy all the included criteria: (a) assessed the association between XRCC1 Arg399Gln polymorphism and HCC risk; (b) a case-control or cohort study; (c) studied on human beings; (d) provided sufficient data to calculate an odds ratio (OR) and a 95% confidence interval (CI); (e) published in English or Chinese language; (f) if more than one article reported on the same or overlapping data, only the study with the largest sample size was included. Family-based design study, meta-analysis, letters, case reports, reviews and editorials were excluded.

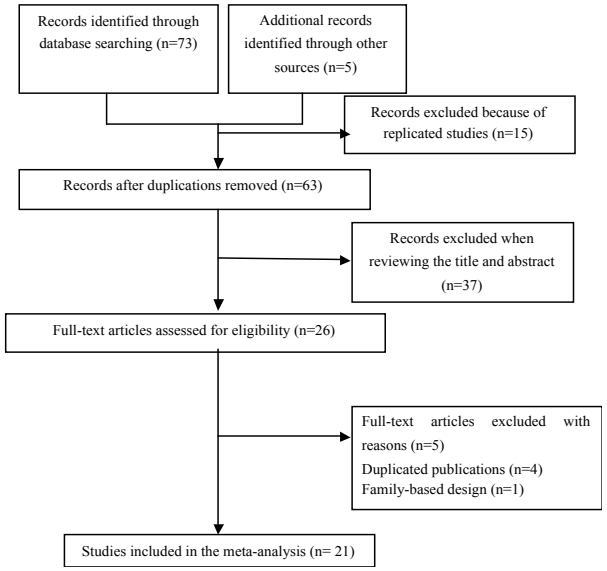

Figure 1. Flowchart of the Included Study

Data extraction

Based on the inclusion criteria, literature searches and identification of eligible articles were carried out by two independent reviewers (Xiaolian Zhang and Yu Lu). Then, two separate investigators extracted data from all eligible studies and the result was reviewed by a third reviewer (Xue Qin). The following data was extracted from each study: the first author's name, publication year, country, ethnicity, genotyping method, source of controls, number of cases and controls, genotypes frequency and Hardy-Weinberg equilibrium (HWE) of controls.

Statistical analysis

HWE was calculated for control groups of each study using the goodness-of-fit (χ^2 or Fisher's exact test), and $p<0.05$ was considered representative of deviation from HWE. The strength of association between the XRCC1 Arg399Gln polymorphism and HCC susceptibility was evaluated by odds ratio (OR) together with their 95 % confidence interval (CI) under the allele model (A *vs* G), the homozygous model (AA *vs* GG), the heterozygous model (AG *vs* GG), the dominant model (AA+AG *vs* GG) and the recessive model (AA *vs* GG+AG). The statistical significance of the pooled OR was determined by the Z test, and $p<0.05$ was considered statistically significant. A Q-test and the I^2 test were performed to assess statistical between-study heterogeneity assumption (Higgins et al., 2002; 2003). If the result of the Q-test was $p<0.10$ or I^2 >50%, indicating there was heterogeneity among studies, the pooled OR estimate of the each study was calculated by the a random-effects (the DerSimonian and Laird method) model (DerSimonian et al., 1986), otherwise fixed-effects model (the Mantel-Haenszel method) was applied (Mantel et al., 1959). Sensitivity analysis was performed to assess the stability of the results by sequential omission of individual studies. Potential publication bias was diagnosed by Egger's linear regression test ($p<0.05$ was considered representative of statistically significant publication bias) (Egger et al., 1997) and visual observation of Begger's funnel plot. All analyses were performed by STATA version 12.0 (Stata Corporation LP, College Station, Texas, USA). All the tests were two-sided, $p<0.05$ was considered statistically significant.

Results

Characteristics of studies

Based on the search criteria, 78 records were identified during the initial search. When review the title and abstract, only 26 full-text studies were preliminarily identified for further detailed examination (Figure 1). Under the inclusion criteria, five of these articles were excluded: four were overlapped subjects (Yu et al., 2003;

Yang et al., 2004; Long et al., 2005; Li et al., 2012), one was family-based design study (Ding et al., 2012). At last, a total of 21 studies with 4,170 cases and 5,030 controls were included in the final meta-analysis. The eligible studies were published from 2004 to 2013. Of the 21 studies, there were 19 studies for Asians, one study for Africans and one study for Caucasians, respectively. 13 studies were English and eight were Chinese literatures. The distribution of genotypes for XRCC1 Arg399Gln polymorphism in the controls were in consistent with HWE except the six studies (Han et al., 2004; Long et al., 2006; Su 2008; He et al., 2012; Guo et al., 2012; Bose et al., 2013). The main characteristics of the 21 case-control studies were summarized in Table 1.

Meta-analysis results

The meta-analysis results and the test of heterogeneity were listed in Table 2. In the overall analysis, we found an increased risk of the XRCC1Arg399Gln polymorphism on the susceptibility to HCC under two contrast models (AG *vs* GG: OR=1.265, 95%CI=1.036-1.545, *p*=0.021; AA+AG *vs* GG: OR=1.240, 95%CI=1.021-1.506, *p*=0.030). In the subsequent stratified analysis by ethnicity, we also found that there was a significantly increased risk of HCC in Asian populationsv (A *vs* G: OR=1.175, 95%CI=1.013-1.362, *p*=0.033; AG *vs* GG: OR=1.317, 95%CI=1.070-1.622, *p*=0.009; AA+AG *vs* GG: OR=1.289, 95%CI=1.055-1.575, *p*=0.013). But in Caucasians, we observed a 0.591-fold decreased risk

Table 1. Basic Characteristics of the 21 Included Studies

First author	Year	Country	Ethnicity	Language	No. of cases/controls	Genotyping method	Source of controls	Cases			Controls			HWE
								GG	AG	AA	GG	AG	AA	
Long XD	2004	China	Asian	Chinese	140/536	PCR-RFLP	HB	72	63	5	362	159	15	0.62
Han YN	2004	China	Asian	Chinese	69/136	PCR-RFLP	PB	34	7	28	58	15	63	0
Chen CC	2005	China	Asian	English	577/389	PCR-RFLP	PB	301	223	53	218	143	28	0.5
Kirk GD	2005	Gambia	African	English	195/352	PCR–RFLP	HB	160	31	4	300	48	4	0.2
Long XD	2006	China	Asian	English	257/649	PCR–RFLP	HB	131	95	31	439	162	48	0
Borentain P	2007	France	Caucasian	English	56/89	Sequencing	PB	27	21	8	27	43	19	0.81
Ren Y	2008	China	Asian	Chinese	50/92	PCR–RFLP	HB	32	14	4	46	41	5	0.28
Su HY	2008	China	Asian	Chinese	100/111	PCR–RFLP	HB	40	53	7	69	31	11	0.01
Wu H	2009	China	Asian	Chinese	100/60	PCR–RFLP	HB	56	36	8	30	23	7	0.43
Kiran M	2009	India	Asian	English	63/142	PCR–RFLP	HB	25	33	5	45	70	27	0.98
Jia ZF	2010	China	Asian	English	136/136	PCR–RFLP	HB	53	66	17	78	45	13	0.1
Zeng XY	2010	China	Asian	Chinese	500/507	TaqMan	HB	286	180	34	304	167	36	0.05
Pan HZ	2011	China	Asian	English	202/236	PCR-CTPP	HB	45	105	52	68	112	56	0.46
Tang YT	2011	China	Asian	Chinese	150/150	PCR–RFLP	HB	41	94	15	84	54	12	0.43
He GZ	2012	China	Asian	Chinese	113/113	PCR–RFLP	PB	80	23	10	97	12	4	0
Han XC	2012	China	Asian	English	150/158	PCR-CTPP	HB	32	78	40	46	73	39	0.35
Guo LY	2012	China	Asian	English	410/410	PCR-CTPP	HB	203	136	71	227	128	55	0
Jung SW	2012	Korean	Asian	English	704/388	PCR	HB	417	248	39	212	147	29	0.62
Bose S	2013	India	Asian	English	55/209	PCR-RFLP	PB	22	29	4	75	88	46	0.04
Gulnaz A	2013	Pakistan	Asian	English	50/74	PCR-RFLP	HB	19	14	17	27	32	15	0.34
Mohaha Devi S	2013	India	Asian	English	93/93	PCR-RFLP	HB	36	45	12	32	51	10	0.12

*PB, Population-based; HB, Hospital-based; HWE, Hardy-Weinberg equilibrium

Table 2. Meta-Analysis of the Association between XRCC1 Arg399Gln and HCC

Comparison	Population	N	Test of association			Model	Test of heterogeneity	
			OR	95 % CI	*p* value		*p* value	I^2
A ***vs*** G	Overall	21	1.148	0.994-1.326	0.06	R	0	74.9
	Asian	19	1.175	1.013-1.362	0.033	R	0	75
	African	1	1.286	0.837-1.974	0.251			
	Caucasian	1	0.591	0.361-0.966	0.036			
AA ***vs*** GG	Overall	21	1.167	0.926-1.471	0.190	R	0.005	49.9
	Asian	19	1.203	0.954-1.517	0.118	R	0.009	48.7
	African	1	1.875	0.463-7.597	0.379			
	Caucasian	1	0.421	0.158-1.126	0.085			
AG ***vs*** GG	Overall	21	1.265	1.036-1.545	0.021	R	0	73.3
	Asian	19	1.317	1.070-1.622	0.009	R	0	73.7
	African	1	1.211	0.741-1.978	0.445			
	Caucasian	1	0.488	0.232-1.030	0.06			
AA ***vs*** AG+GG	Overall	21	1.073	0.894-1.288	0.499	R	0.086	31.2
	Asian	19	1.084	0.898-1.309	0.400	R	0.08	33.3
	African	1	1.822	0.451-7.367	0.4			
	Caucasian	1	0.614	0.249-1.516	0.29			
AA+AG ***vs*** GG	Overall	21	1.24	1.021-1.506	0.03	R	0	75.9
	Asian	19	1.289	1.055-1.575	0.013	R	0	76.1
	African	1	1.262	0.789-2.018	0.331			
	Caucasian	1	0.468	0.234-0.934	0.031			

OR, odds ratio; CI, confidence interval; F, fixed effects model; R, random effects model

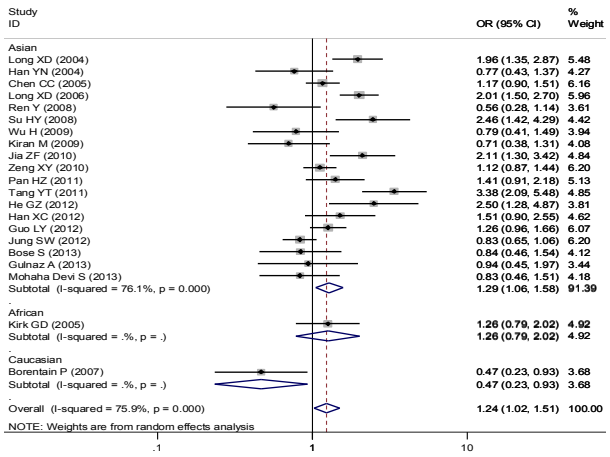

Figure 2. Forest Plot of XRCC1 Arg399Gln Polymorphism Associated with HCC Risk Under the Dominant Model (AA+AG vsGG)

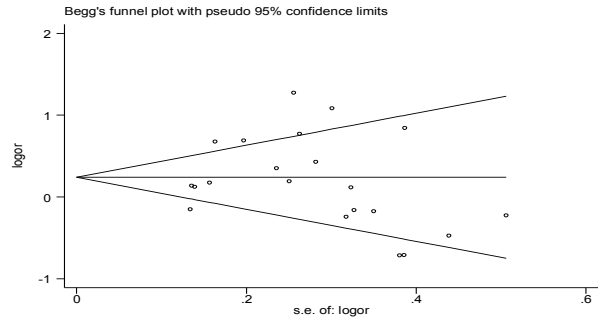

Figure 3. Begg's Funnel Plot of XRCC1 Arg399Gln Polymorphism and HCC Risk for Publication Bias in the Heterozygous Model (AG *vs* GG).

of HCC under the allele model (A *vs* G: OR=0.591, 95%CI=0.361-0.966, *p*=0.036) and 0.468-fold declined susceptibility under the dominant model (AA+AG *vs* GG: OR=0.468, 95%CI=0.234-0.934, *p*=0.031) (Figure 2).

Sensitivity analysis

Sensitivity analysis was conducted to evaluate the influence of the individual studies on the pooled OR by sequential omission of each eligible study. The corresponding pooled OR were not changed when any single study was removed, indicating that the statistical results did not suggest significant effects, revealing the stability and credibility of the results.

Publication Bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of included studies in all comparison models. Begg's funnel plot is relatively straightforward to observe whether the publication bias is present, and Egger's test was used to provide statistical evidence of symmetries of the plots. The shape of the funnel plots showed no obvious asymmetry (Figure 3) and then result of Egger's test did not show statistical evidence for bias (AG *vs* GG: *p*=0.870).

Discussion

XRCC1 gene is a key DNA repair gene involved in BER, which play an important role in the stability and integrity of the genome and the pathogenesis and development of human cancers (Poehlmann et al., 2010). Three common single nucleotide polymorphisms (SNP) in the XRCC1 gene, including Arg399Gln (rs25487), Arg280His (rs25489) and Arg194Trp (rs1799782) are extensively studied in many studies and produced nonconservative changes (Shen et al., 1998). These mutations that can alter XRCC1 function may contribute to the risk of cancers.

Although chronic hepatitis B or C, obesity, diabetes, excessive alcohol consumption, pre-existing liver cirrhosis and exposure to aflatoxin B1 have been identified as significant risk factors, there is limited understanding on the molecular mechanisms HCC (Gomaa et al., 2008; Hagymasi et al., 2008; Caldwell et al., 2009; Forner et al., 2012). It is accepted that the carcinogenesis of HCC is a multistep process, and multiple factors including environmental and genetic factors are involved in this complex process (Sato et al., 2011). Many epidemiological studies investigating the association between XRCC1 Arg399Gln polymorphism and HCC risk have provided inconsistent results. Two previous meta-analysis (Zhang et al., 2010; Wu et al., 2013) both conducted with seven studies showed that the XRCC1 Arg399Gln polymorphism might not be risk factors for HCC. But another meta-analysis including 13 literatures (Li et al., 2013) obtained conflicting results. Previous meta-analysis did not contain all appropriate studies, and lack of stratified analysis by ethnicity, which may lead to a deviation to final result. Therefore, an updated meta-analysis including 21 studies with 4, 170 cases and 5, 030 controls was performed to comprehensively assess the relationship between XRCC1 Arg399Gln polymorphism and HCC risk. Subgroup analysis was categorized by ethnicity. Our meta-analysis statistical data showed that XRCC1 Arg399Gln genotypes were associated with an increased risk of HCC, especially among the Asians. However, a reduced risk was detected among the Caucasians and no association was found among the Africans. This indicated that different populations living in different environment and genetic backgrounds may influence the association between XRCC1 Arg399Gln polymorphism and HCC risk. However, the conclusion should be interpreted with caution, because the study which focused on Caucasians and Africans both had one included study with a small sample size. Our results of this meta-analysis also may cause by chance because studies with a small sample size may be underpowered or may have generated a fluctuated risk assessment, so that further studies need to be performed to improve the statistical power.

A comprehensive analysis was performed to show the association between XRCC1 Arg399Gln polymorphism and HCC risk, but some limitations remain. Firstly, only two published studies included in this meta-analysis focused on Caucasians and Africans. Secondly, the sources of heterogeneity that existed among the studies were not addressed. Thirdly, this meta-analysis was based on unadjusted data, whereas a more precise analysis stratified by gender, age, smoking status, and environmental factors could be conducted if individual data were available.

Finally, the controls were not uniformly defined. Most of the controls were chosen from healthy populations, but some were HBV or HCV positive, inpatient, and outpatient without HCC. Therefore, non-differential misclassification bias was possibly existed because these studies which including the controls may have different risks to develop HCC.

In conclusion, our meta-analysis of 21 case-control studies demonstrated that there was an increased risk between XRCC1 Arg399Gln polymorphism and HCC risk, especially in Asians, and a reduced risk in Caucasians. Due to limitations showed above in this analysis, it is necessary that well-designed and more-detailed studies with larger populations are needed to further evaluate the associations. Moreover, gene-gene and gene-environment interactions should be taken into consideration in future analysis.

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