Association between *XRCC1* Arg280His polymorphism and risk of hepatocellular carcinoma: a systematic review and meta-analysis

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ABSTRACT. Hepatocellular carcinoma (HCC) is one of the most life-threatening malignancies worldwide. Defects in DNA repair genes may increase the risk of HCC. X-ray cross-complementing group 1 gene (*XRCC1*) is a major DNA repair gene involved in base excision repair. Recently, several studies have indicated that an association exists between *XRCC1* polymorphism and HCC, particularly the Arg280His polymorphism. However, the data is inconsistent and incomplete. In this study, we conducted a meta-analysis to investigate the association

between the *XRCC1* Arg280His polymorphism and HCC risk. A total of 10 case-control studies included 1848 HCC cases and 1969 controls were examined in this analysis. Our results suggest that variant genotypes of the *XRCC1* Arg280His gene are associated with a significantly increased risk of HCC in homozygote comparison (HisHis *vs* ArgArg, odds ratio, 1.55, 95% confidence interval, 1.10-2.18, P = 0.013); no heterogeneity was observed ($I^2 = 0\%$). Our analysis suggests that the *XRCC1* Arg280His polymorphism is associated with a higher risk of HCC.

Key words: Hepatocellular carcinoma; Meta-analysis; Single nucleotide polymorphism; *XRCC1*-Arg280His

INTRODUCTION

Hepatocellular carcinoma (HCC) is a major cancer worldwide because of its high-grade malignancy and lack of effectiveness of medical treatment. It is associated with poor prognosis, and its incidence is increasing in many countries (Siegel, et al., 2013). Hepatitis B virus infection is the predominant risk factor in Southeast Asia and China. However, hepatitis C virus infection has emerged as a more significant risk factor in Japan, North America, and Europe (Gomaa et al., 2008; Venook et al., 2010).

DNA is under constant threat from endogenous and exogenous DNA damaging agents. Mammalian cells have evolved highly conserved DNA repair systems to process DNA damage and maintain genomic integrity (Abbotts et al., 2014). These processes play a critical role in tumorigenesis and treatment resistance (Deans and West, 2011; Wilting and Dannenberg, 2012). Impaired DNA repair is a major factor in carcinogenesis and can promote aggressive cancer biology. The X-ray repair cross complementing group 1 (XRCC1), a key protein in the base excision repair system, serves as a scaffold protein for repairing base lesions induced by reactive oxygen species (David et al., 2007). More than 300 single-nucleotide polymorphisms have been identified in the *XRCC1* gene in the dbSNP database, but only 3 have been extensively studied, including Arg280His, Arg194Trp, and Arg399Gln (Li et al., 2012). These non-conservative amino acid changes may alter the function of the XRCC1 protein, diminish repair kinetics, and result in altered efficiency of the protein, eventually inducing cancer development.

In recent years, the association between the *XRCC1* Arg280His polymorphism and the risk of HCC has been investigated by several groups. However, because of limited sample sizes, varying geographic regions, and differences among research subjects, results regarding the association between the *XRCC1* Arg280His polymorphism and the risk of HCC have been inconsistent (Kiran et al., 2009; Yuan et al., 2012a,b; Li et al., 2012, 2013a). In this study, we performed a meta-analysis to clarify the association between the *XRCC1* Arg280His polymorphism and the risk of HCC. Our results suggest that the variant genotypes of the *XRCC1* Arg280His gene are associated with a significantly increased risk of HCC in the homozygote comparison model.

MATERIAL AND METHODS

Data collection

For first-round exclusion, articles were searched in the NCBI Global Cross-data-

base, including PubMed, PMC, Gene, PubChem, etc. using "DNA polymorphism", "hepatocellular carcinoma", "HCC", and "XRCC1" as key words. All articles were published in English. We examined all articles whose primary topic was the association between DNA repair gene *XRCC1* polymorphism and HCC and identified a total of 162 articles. The following inclusion criteria were specified: case-control design with genotyping of HCC and studies that covered the *XRCC1* Arg280His polymorphism. We excluded studies that did not examine the association between hepatocellular carcinoma or did not include data for this specific DNA polymorphism. In cases of overlapping data, we retained that with the most extensive results. A total of 10 studies were included in our meta-analysis. The data collection flow chart is shown in Figure 1.
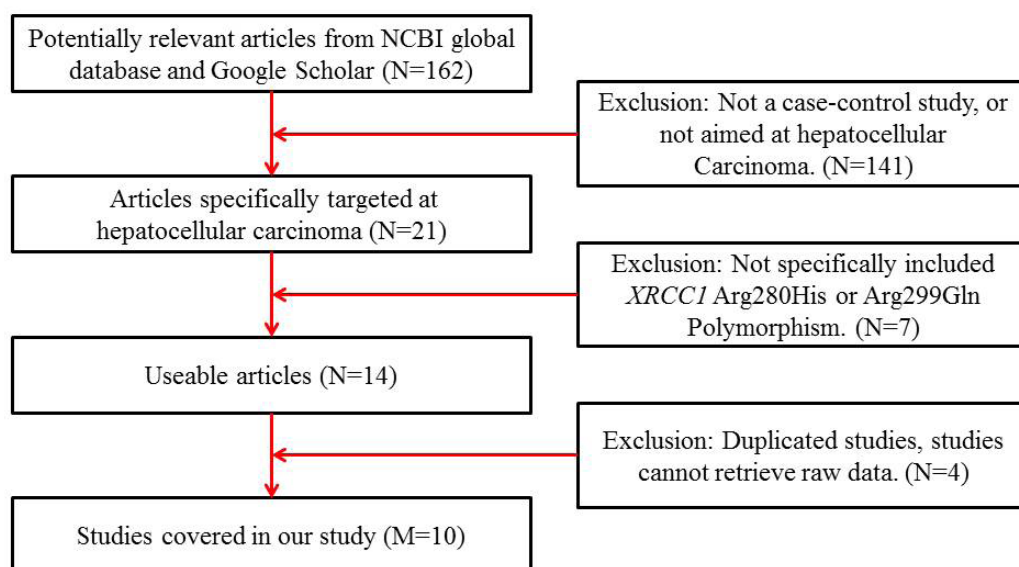
Figure 1. Flow chart of literature search and study selection. A total of 162 articles were searched for first-round exclusion. Ten studies were included in the final meta-analysis.

Study selection

Multiple electronic databases were searched for data collection. Ten case-control studies (1848 cases, 1969 controls) examining the Arg280His polymorphism were included in this meta-analysis. The association between the *XRCC1* Arg280His polymorphism and HCC was evaluated using the odds ratio (OR) derived from the recessive model (HisHis *vs* ArgArg+ArgHis), dominant model (HisHis+ArgHis *vs* ArgArg), and homozygote comparison (HisHis *vs* ArgArg). Statistical analysis was performed using STATA 12 version 12 (StataCorp, College Station, TX, USA). Heterogeneity was measured using the I^2 index. To account for significant heterogeneity, different analysis models were used: Mantel-Haenszel (M-H) fixed-effect model and DerSimonian and Laird (D-L) random-effect model were applied for the Arg280His dataset. A forest plot and Begg's funnel plot were generated to evaluate OR and publication bias. To better analyze publication bias, Egger's test was also completed for each dataset.

Statistical analysis

Three different models were examined, including the dominant model, recessive model, and homozygote comparison. In the dominant model, we used Arg/Arg as the reference genotype to investigate the distribution of the His/His+Arg/His genotype. In the recessive model, we chose Arg/Arg+Arg/His as the reference genotype and investigated the distribution of the His/His genotype. In the homozygote comparison, we used Arg/Arg as the reference genotype and investigated the distribution of the His/His genotype. For each study, the numbers of the 3 genotypes in the case and control groups were used as pooled data. For large samples, Peto's method may be misleading. In contrast, inverse variance method is only effective when examining continuous data. Another key factor in choosing analysis model is the heterogeneity involved in the studies. The M-H fixed-effect model can be applied to analyze datasets without significant heterogeneity, while the DerSimonian and Laird random-effects model should be applied for datasets showing obvious heterogeneity. In our analysis, the heterogeneity between studies was tested using the I^2 index; in the equation, Q is statistical data and df is degrees of freedom. A higher I^2 values indicates more significant heterogeneity. Values of $I^2 = 25$, 50, and 75% represent low, medium, and high heterogeneity, respectively. When $I^2 \leq 50\%$, there is no significant heterogeneity between pooled data. In this meta-analysis, 10 studies were included in the final analysis for codon Arg280. First, we used the M-H fixed-effect model to test heterogeneity, and then used a different model based on these results. ORs were calculated with each model within 95% confidence intervals. The available polymorphism data were analyzed using the STATA 12 software. Forest plots were generated using 3 statistical methods (dominant, recessive, and homozygote) to summarize the results. To evaluate publication bias, Begg's funnel plots were generated based on the analysis results and database size. Higher asymmetry in the funnel plot indicates more publication biases. Egger's test was also performed for further investigation.

RESULTS

Characteristics of studies included

The search strategy retrieved 162 potentially relevant studies. According to the inclusion criteria, 10 studies with full-text were included in this meta-analysis (Kiran et al., 2009; Li et al., 2012; Xie et al., 2012; Duan et al., 2012; Yuan et al., 2012a,b; Han et al., 2012; Gulnaz et al., 2012) and 152 studies were excluded. The flow chart for study selection is summarized in Figure 1. These 10 case-control studies selected included a total of 1848 HCC cases and 1969 healthy controls. All data in these studies were related to the association between the *XRCC1* Arg280His gene polymorphism and HCC risk. The characteristics of studies included are shown in Table 1.

Quantitative synthesis

First, the M-H fixed-effects model was applied to the dataset using 3 models to analyze heterogeneity. The results are shown in Table 2. Based on the results, we selected different methods (M-H fixed effect model, DerSimonian and Laird random-effects model) for analysis.
The analysis results using 3 different methods for the Arg280His polymorphism are

summarized in Table 3, including the results for the bias test. For the dominant model, the overall OR was 1.26 (95% confidence interval, 0.95-1.68, P = 0.115). Because of significant heterogeneity (I^2 = 65.7%), we used the random-effect model for analysis. For the recessive model, the overall OR was 1.30 (95% confidence interval, 0.94-1.80, P = 0.118), and no heterogeneity was observed (I^2 = 0%). For homozygote comparison, the overall OR was 1.55 (95% confidence interval, 1.10-2.18, P = 0.013), and no heterogeneity was observed (I^2 = 0%). The forest plots for all 3 models are shown in Figure 2. Based on homozygote comparison, the Arg280His showed an effect on HCC risk. These results showed that an association exists between the *XRCC1* Arg280His polymorphism and HCC according to the homozygote comparison model. Although patients with His showed a relatively higher risk of HCC compared to patients with Arg in both the dominant and recessive model, with ORs of 1.26 and 1.30, respectively, the results were not statistically significant, and further investigation is required.

Table 1. Pooled data for *XRCC1* Arg280His analysis.

Study/Year	Cases				Controls			
	Arg/Arg	Arg/His	His/His	Total	Arg/Arg	Arg/His	His/His	Total
Su 2008	79	20	1	100	87	21	3	111
Kiran 2009	17	30	14	50	91	29	35	155
Wu 2009	77	22	1	100	47	13	0	50
Zeng 2010	451	86	8	545	423	86	6	515
Tang 2011	138	11	1	150	123	26	1	150
Yuan 2012a	272	73	5	350	329	64	7	400
Bo 2012	64	12	8	84	78	9	3	90
Han 2012	72	47	31	150	84	47	28	159
Yuan 2012b	193	59	6	258	206	44	5	255
Gulnaz 2013	24	17	9	50	329	64	7	400

Table 2. Heterogeneity test.

| Datasets	Heterogeneity (I^2)	P value	Suggested Model
Arg280His Dominant	65.7%	0.002	Random-effects model
Arg280His Recessive	0%	0.543	Fixed-effects model
Arg280His Homozygote	0%	0.517	Fixed-effects model

Publication bias

The funnel plot, Begg's test, and Egger's test were used to assess the publication bias of studies included. The funnel plot showed some scattering, which may indicate publication bias in this dataset because of the smaller sample size (Figure 3). Begg's and Egger's test results revealed no major publication bias in the present meta-analysis (Table 3).

Table 3. Analysis results for Arg280His polymorphism.

Method	Genotype	Reference	Overall OR	95%CI	P value	Begg's P value	Egger's P value
Dominant	His/His+Arg/His	Arg/Arg	1.26	0.95-1.68	0.115	0.721	0.683
Recessive	His/His	Arg/His+Arg/Arg	1.30	0.94-1.80	0.118	0.592	0.705
Homozygote	His/His	Arg/Arg	1.55	1.10-2.18	0.013	0.592	0.953
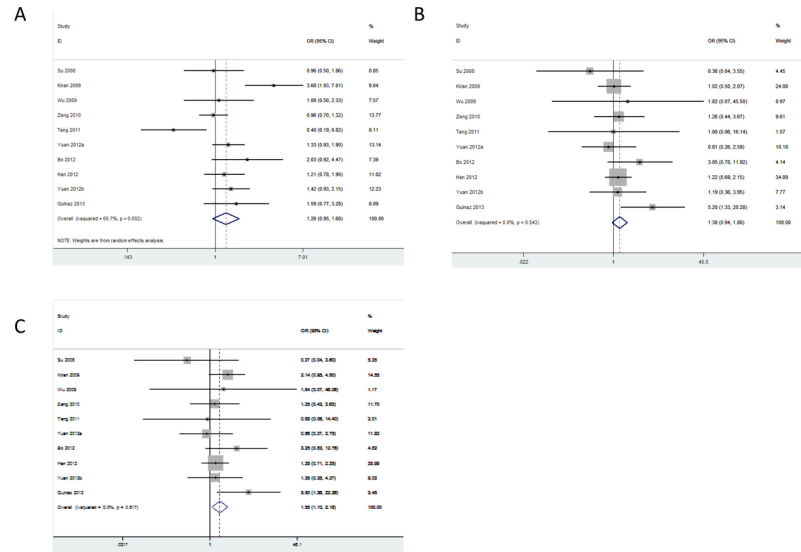
Figure 2. Forest plot of *XRCC1* Arg280His polymorphism and the risk of HCC in the (**A**) dominant genetic model (HisHis+ArgHis *vs* ArgArg), (**B**) recessive model (HisHis *vs* ArgArg+ArgHis), and (**C**) homozygote comparison (HisHis *vs* ArgArg). The center of each square represents the OR, the horizontal line indicates the 95%CI. OR, odds ratio; CI, confidence interval; weights are from random-effects analysis for the dominant model; weights are from the fixed-effects analysis for the recessive model and homozygote comparison.
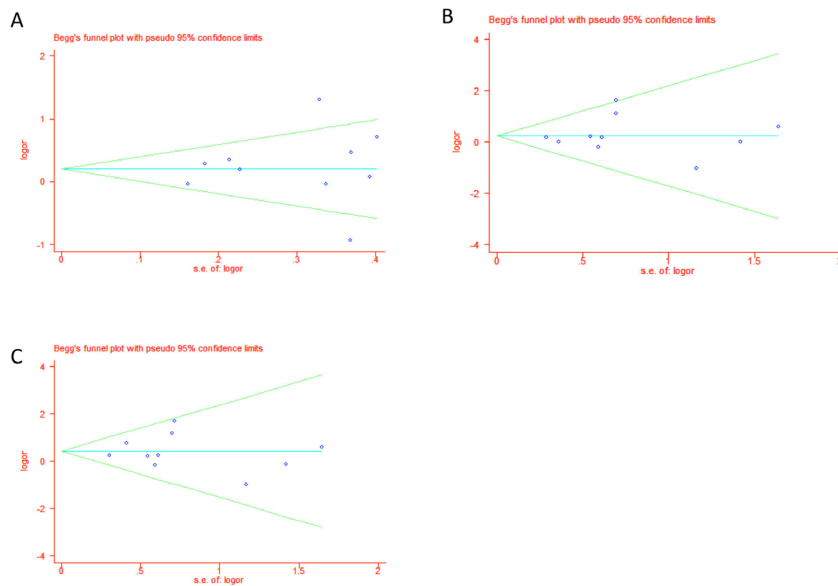
Figure 3. Funnel plot of *XRCC1* Arg280His polymorphism and HCC risk for dominant model (**A**), recessive model (**B**), and homozygote comparison (**C**). Each point represents a separate study for the indicated association. To determine publication bias in studies regarding the relationship between the *XRCC1* Arg280His polymorphism and HCC susceptibility, a funnel plot with pseudo-95% confidence limits was used.

DISCUSSION

In this meta-analysis, we reviewed published studies that examined the association between the *XRCC1* Arg280His polymorphism and susceptibility to HCC, which included a total of 1848 patients and 1969 controls in 10 studies. The overall data showed that the *XRCC1* Arg280His polymorphism was associated with an increased risk of HCC.

XRCC1 is an indispensable protein involved in the DNA repair process and plays an important role in base-excision repair (Parsons et al., 2010), homologous recombination (Fan et al., 2007), and genome stability as well as the pathogenesis and progression of human cancers (Figueiredo et al., 2004; Canalle et al., 2006). Polymorphisms that alter XRCC1 expression and function may contribute to cancer risk (Goode et al., 2002; Hu et al., 2005). The *XRCC1* Arg280His polymorphism is one of the most widely studied single-nucleotide polymorphisms and contributes to altered DNA repair capacity. Over the past 5 years, the *XRCC1* Arg280His polymorphism has been shown to be associated with the susceptibility to HCC. However, because of small sample sizes and difference in research subjects, previous studies provided limited information and showed controversial results. Therefore, a systematic meta-analysis of the available studies may provide more definitive answers.

Meta-analysis is a useful tool for investigating the association between genetic variants and cancer risk as it can combine the results of similar studies on the same topic in a quantitative manner (Kirkham et al., 2012). To date, a total of 3 published meta-analyses have been performed to investigate the association between the *XRCC1* Arg280His polymorphism and the risk of HCC (Li et al., 2012, 2013a,b). However, the results of these meta-analyses are either controversial or inconclusive. Li et al., 2012, 2013a,b) found no relationship between the *XRCC1* Arg280His polymorphism and the risk of HCC. In contrast, Xie et al. (2012) reported that the *XRCC1* Arg280 His polymorphism found a significant association between the His/His genotype and an increased risk of HCC (His/His *vs* Arg/Arg model, OR: 1.96, 95%CI: 1.03-3.75, P = 0.04). Thus, we collected a larger sample of studies for a meta-analysis to evaluate the association between the *XRCC1* Arg280His polymorphism and the risk of HCC. Our results indicated that the *XRCC1* Arg280His polymorphism is associated with an increased risk of HCC under the homozygote comparison model.

There were some limitations to our meta-analysis. First, selection bias may have played a role because all studies selected in this meta-analysis were published in English, and other studies that may have influenced the evaluation were excluded. Second, although all cases and controls in each study were well-defined with similar inclusion criteria, there may be factors that were not taken into account that could have influenced our results. Finally, the sample size of some subgroups in the stratified analyses was limited, which may have reduced the power of these analyses. Thus, further studies with large sample sizes and well-designed multicenter analyses are required to clarify the association between *XRCC1* genetic polymorphisms and the risk of HCC.

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