RESEARCH ARTICLE

The XRCC1 Arg280His Gene Polymorphism and Hepatocellular Carcinoma Risk: A Meta-analysis

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Abstract

  Many studies have suggested that the XRCC1 Arg280His gene polymorphism might be involved in the development of hepatocellular carcinoma (HCC). However, the results have been inconsistent. In this study, the authors performed a meta-analysis to assess the association between XRCC1 Arg280His and HCC susceptibility. Published literature from PubMed, EMBASE and CNKI Data was searched. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using fixed- or random- effects models when appropriate. Begg's test was used to measure publication bias. A total of 7 case-control studies covering 1,448 HCC cases and 1,544 controls were included. No significant variation in HCC risk was detected in any of the genetic models overall. In the stratified analysis, four studies with sample sizes over 300 produced similar results. The corresponding pooled ORs were not substantially altered after the exclusion of three studies deviating from Hardy-Weinberg equilibrium in the control group, which indicated reliability for our meta-analysis results.

Keywords: XRCC1 - Arg280His - polymorphism - HCC- meta-analysis

Introduction

  Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality in the world (Parkin et al., 2000). HCC is a significant health problem, the malignancy occurring more often among men than women, with the highest incidence rates reported in East Asia (Kiran et al., 2009).Both biological and biochemical evidence demonstrated that the major risk factors for HCC were alcoholism, hepatitis B and C, liver cirrhosis, hemochromatosis, aflatoxin and type 2 diabetics (Niwa et al., 2005). In addition, epidemiological studies provide strong evidence that genetic factors are important in the pathogenesis of HCC (Chen et al., 2012).

  The X-ray repair cross-complementing group 1 (XRCC1) protein plays a central role in DNA repair pathways.And XRCC1 gene is located on chromosome 19q13.2, spans a genetic distance of 32 kb, comprises of 17 exons, and encodes a 70-kDa protein consisting of 633 amino acids (Lindahl et al., 1999). Three common single nucleotide polymorphisms lead to amino acid substitutions in XRCC1 at codons 194 (exon 6, Arg-Trp), 280 (exon 9, Arg-His), and 399 (exon 10, Arg-Gln) .These variations could alter XRCC1 function, diminish repair kinetics, and result in altered efficiency of the protein, eventually induce the cancer development.

  Previous a systematic review suggested that XRCC1 Arg280His polymorphism may be biomarker of cancer susceptibility (Hu et al., 2005),the meta analysis according to cancer types suggested that XRCC1 Arg280His polymorphism was not significantly associated with risk of thyroid cancer, lung cancer, bladder cancer, gastric cancer, breast cancer, colorectal cancer, and cervical cancer (Zhang et al., 2012). However, to date, there is no meta analysis investigated the association between XRCC1 Arg280His polymorphism and HCC risk,the result has been inconsist.In this study,we performed a meta analysis to clarify the association.

Materials and Methods

Literature search

  We searched various databases including PubMed, EMBASE and CNKI Data to identify studies on XRCC1 Arg280His polymorphism and HCC published before 2013 without language restrictions, using the following key words: 'XRCC1' or 'Arg280His', 'hepatocellular carcinoma', 'HCC' or 'cancer' or 'tumor'. The reference lists of major textbooks, review articles, and included articles were identified through manual searches to find other potentially eligible studies.

Inclusion and Exclusion Criteria

  Titles and abstracts of all citations and retrieved studies were reviewed by two independent Researchers (Lu-Ping Li and Wei Wu). To be eligible for inclusion in

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Table 1. Characteristics of the Included Studies for Meta-analysis

Study included	Year	Area	Detection method	cases	controls	Genotypes for cases			Genotypes for controls			HWE test
						Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His	
Wu et al	2009	China	PCR-RFLP	100	60	77	22	1	47	13	0	0.35
Kiran et al	2009	India	PCR-RFLP	63	171	19	30	14	91	29	35	0.00
Zeng et al	2010	China	TaqMan	545	515	451	86	8	423	86	6	0.49
Tang et al	2011	China	PCR-RFLP	150	150	138	11	1	123	26	1	0.77
Bo et al	2012	China	PCR-RFLP	90	90	64	12	8	78	9	3	0.00
Yuan et al	2012	China	PCR-RFLP	350	400	272	73	5	329	64	7	0.07
Han et al	2012	China	PCR-CTPP	150	158	72	47	31	84	47	28	0.00
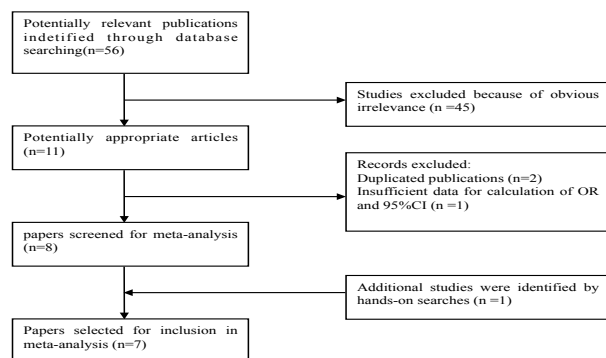
Figure 1. Flow Chart of Literature Search and Study Selection

this meta-analysis, the following criteria were established: (1) case-control studies that addressed psoriasis cases and healthy controls; (2) studies on the association of XRCC1 Arg280His polymorphism and susceptibility to HCC; (3) and studies that included sufficient genotype data for extraction. The exclusion criteria were as follows: (1) not case-control studies that evaluated the association between XRCC1 Arg280His polymorphism and HCC risk; (2) case reports, letters, reviews, meta-analysis and editorial articles; (3) studies that were based on incomplete raw data and those with no usable data reported; (4) and animal studies were included in the studies.

Data Extraction

Two investigators extracted the data independently, and the result was reviewed by a third investigator. From each study, the following items were considered: first author's name, year of publication, area, study design, numbers of cases and controls, polymorphisms of gene and evidence of Hardy-Weinberg equilibrium (HWE) in controls.

Statistical Analysis

We assessed HWE in the controls for each study using x^2 test and a $P<0.05$ was considered as significant disequilibrium. The strength of the association between XRCC1 Arg280His polymorphism and HCC susceptibility was measured by ORs with 95%CIs under a homozygote comparison (His/His vs Arg/Arg), a heterozygote comparison (His/His vs Arg/His), a dominant model (Arg/Arg + Arg/His vs His/His) and a recessive mode (His/His + Arg/His vs Arg/Arg) between groups. Heterogeneity was quantified using I^2 test, $I^2<25\%$, no heterogeneity; $I^2=25\text{-}50\%$, moderate heterogeneity; $I^2=50\text{-}75\%$, large heterogeneity, $I^2>75\%$, extreme heterogeneity. When the effects were assumed to be homogeneous ($I^2>50\%$), the

fixed-effects model was used. Otherwise, the random-effects model was more appropriate. Subgroup analysis were performed according to the Sample size and HWE test. Begg's funnel plot was investigated to assess publication bias ($P<0.05$ was considered statistically significant). Sensitivity analysis was performed by removing the studies in the meta-analysis due to the genotype distribution in the control groups of the study deviating from HWE. All analyses were calculated using STATA Version 12.0 software (Stata Corp, College Station, TX).

Results

The characteristics of included studies

The search strategy retrieved 56 potentially relevant studies. According to the inclu¬sion criteria, 7 studies with full-text were included in this meta-analysis (Wu et al., 2009; Kiran et al., 2009; Zeng et al., 2010; Tang et al., 2011; Bo et al., 2012; Yuan et al., 2012; Han et al., 2012) and 45 studies were excluded. The flow chart for the study selection is summarized in Figure 1. These 7 case-control studies selected included a to¬tal of 1448 HCC cases and 1544 healthy controls. All studies were case-control studies, which evaluated the association between XRCC1 Arg280His Gene Polymorphism and HCC risk. The publishing year of the included studies ranged from 2009 to 2012. HWE test was conducted on genotype distribution of the controls in all included studies, all of studies performed HWE except three studies (Kiran et al., 2009; Bo et al., 2012; Han et al., 2012). The baseline characteristics of all studies included are summarized in Table 1.

Quantitative data synthesis

A summary of the meta-analysis findings of the association between XRCC1 Arg280His Gene Polymorphism and HCC risk is provided in Table 2. The heterogeneity is obvious under Recessive model ($I^2>50\%$), which might result from difference of country, source of controls, language and HWE test, so random effects model was used. The meta-analysis result showed that the XRCC1 Arg280His polymorphism was not related to HCC risk (His/His vs Arg/Arg: OR = 1.46, 95%CI: 0.99-2.13; His/His vs Arg/His: OR = 0.86, 95%CI: 0.58-1.28; Dominant model: OR = 0.83, 95%CI: 0.58-1.28; Recessive model: OR =1.23, 95%CI: 0.84-1.81). In the stratified analysis by limiting the analysis to the study sample size (> 300), we detected no significant association (His/His vs Arg/Arg: OR = 1.19, 95%CI: 0.74-1.90; His/

Table 2. Summary ORs and 95%CI of XRCC1 Arg280His polymorphism and hepatocellular carcinoma risk

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2	P	OR	95% CI	z	P
Overall	His/His vs Arg/Arg	1448	1544	Fixed	0.0%	0.82	1.46	0.99-2.13	0.00	1.00
	His/His vs Arg/His			Fixed	14.7%	0.32	0.86	0.58-1.28	0.00	1.00
	Dominant model			Fixed	0.0%	0.85	0.83	0.58-1.28	0.00	1.00
	Recessive model			Random	74.0%	0.00	1.23	0.84-1.81	0.00	1.00
Sample size	His/His vs Arg/Arg	1195	1223	Fixed	0.0%	0.94	1.19	0.74-1.90	0.00	1.00
> 300	His/His vs Arg/His			Fixed	0.0%	0.75	1.06	0.65-1.75	0.00	1.00
	Dominant model			Fixed	0.0%	0.94	0.87	0.56-1.37	0.00	1.00
	Recessive model			Random	68.0%	0.03	0.97	0.66-1.42	0.00	1.00
Consistent with	His/His vs Arg/Arg	1145	1125	Fixed	0.0%	0.95	1.08	0.52-2.23	0.34	0.73
HWE	His/His vs Arg/His			Fixed	0.0%	0.73	1.04	0.49-2.19	0.34	0.73
	Dominant model			Fixed	0.0%	0.94	0.94	0.45-1.94	0.34	0.73
	Recessive model			Random	66.6%	0.03	0.92	0.61-1.40	0.34	0.73

His vs Arg/His:OR = 1.06, 95%CI: 0.65-1.75; Dominant model: OR = 0.87, 95%CI: 0.56-1.37; Recessive model: OR =0.97, 95%CI: 0.66-1.42). Sensitivity analysis was performed with controls in the HWE and the result was not altered, indicating the result of meta-analysis was statistically significant (Table 2).

Publication bias

The funnel plot and Begg's test was used to assess the publication bias of included studies. The shapes of the funnel plots in all genetic models did not reveal any evidence of obvious asymmetry (Table 2).The results implied that the publication bias was low in the present meta-analysis.

Discussion

The Arg280His Polymorphism could potentially alter the structure of XRCC1.To date, a number of case-control studies have investigated the association between Arg280His Polymorphism and HCC risk. However, the published results have been inconsistent. To assess the relationship between Arg280His Polymorphism and HCC, We conducted a comprehensive meta-analysis of 7 case-control studies with 1448 HCC cases and 1544 healthy controls. To our knowledge, this is the first meta-analysis considering XRCC1 Arg280His polymorphism and HCC risk. Finally, the results of our meta-analysis did not show any significant association between Arg280His Polymorphism and HCC risk. The results from our present meta-analysis did not support the significant association. This is most probably because our meta-analysis involved several small sample studies.There may be a high risk of selective bias for the relationship between Arg280His Polymorphism and HCC development, so this association should be reevaluated in studies with large sample sizes.And when stratifying by study sample size (≥300 subjects), this meta-analysis detects no significant association, suggesting there was not have small-study bias in our meta-analysis. Moreover, if the distribution of genotypes in the control groups were not in HWE, the results of genetic association studies might be spurious (Trikalinos et al., 2006), when limiting the analysis to the studies within HWE, no significant relationship was detected,suggesting that this factor probably had little effect in the present meta-analysis.

Potential function of XRCC1 Arg280His polymorphism might be affected via gene-gene and gene-environment interactions. A previous study demonstrated polymorphisms of both genes (hOGG1 ser326Cys and XRCC1 Arg 280His) increased HCC risk and found XRCC1 Arg 280His polymorphism alone didn't increase HCC risk (Srivastava et al., 2009). while XRCC1 280His polymorphism increases HCC risk in individuals with HBV infection and HCC family history (Yuan et al., 2012). However,one study could not included in our meta-analysis,further studies of gene-gene and gene-environment interactions should be taken into consideration for assessment of HCC risk.

There were still some limitations in our meta-analysis. First, although all cases and controls of each study were well defined with similar inclusion criteria, there may be potential factors that were not taken into account that may have influenced our results. Second, significance between-study heterogeneity was observed. Although we used the random-effect model to pool ORs, it may affect the precision of results. Finally, we did not estimate the influence of potential confounders because of data limitation.

In conclusion, our meta-analysis demonstrated that XRCC1 Arg280His polymorphism may not contribute to HCC susceptibility in the pooled population. Large-scale case-control and population-based association studies are warranted to validate the risk identified in the current meta-analysis and investigate the potential gene-gene and gene-environment interactions on HCC risk.

Acknowledgements

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