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BRIEF ARTICLE

X-ray repair cross-complementing group 1 polymorphisms and hepatocellular carcinoma: A meta-analysis

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Abstract

AIM: To perform a systematic meta-analysis to investigate the association between X-ray repair cross-complementing group 1 (*XRCC1*) polymorphisms and hepatocellular carcinoma (HCC) risk.

METHODS: Relevant studies extracted from PubMed, Embase, Wanfang, VIP and the Chinese National Knowledge Infrastructure databases up to March 2012 were included in the study. Stata software, version 11.0, was used for the statistical analysis. The odds ratios (ORs) and 95% confidence interval (CI) of the *XRCC1* polymorphisms in HCC patients were analyzed and compared with healthy controls. The meta-analysis was performed using fixed-effect or random-effect methods, depending on the absence or presence of significant heterogeneity.

RESULTS: Eleven studies with 2075 HCC cases and 2604 controls met our eligibility criteria (four studies, 888 cases and 938 controls for Arg194Trp, four studies, 858 cases and 880 controls for Arg280His, and nine studies, 1845 cases and 2401 controls for Arg399Gln). The meta-analysis revealed no associations between the Arg194Trp and Arg399Gln polymorphisms of the *XRCC1* gene and HCC risk under all contrast models (codominant, dominant and recessive models) in the overall analysis and sensitivity analysis (the studies with controls not in the Hardy-Weinberg equilibrium were excluded). For *XRCC1* Arg280His polymorphism, the overall analysis revealed the significant association between the His/His genotype and the increased risk of HCC (His/His *vs* Arg/Arg model, OR: 1.96, 95% CI: 1.03-3.75, $P = 0.04$). However, sensitivity analysis showed an altered pattern of result and non-significant association (OR: 2.06, 95% CI: 0.67-6.25, $P = 0.20$). The heterogeneity hypothesis test did not reveal any heterogeneity, and Begg's and Egger's tests did not find any obvious publication bias.

CONCLUSION: The *XRCC1* Arg194Trp and Arg399Gln polymorphisms are not associated with HCC risk. More rigorous association studies are needed to verify the involvement of *XRCC1* Arg280His polymorphism in HCC susceptibility.

Key words: X-ray repair cross-complementing group 1; Polymorphism; Hepatocellular carcinoma; Meta-analysis

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide[1]. It is accepted that the carcinogenesis of HCC is a multistep process, and multiple factors are involved in this complex process[2]. Epidemiological studies have indicated that chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV), heavy cigarette smoking, and alcohol abuse are associated with the risk of HCC[1]. The progression of HCC might result from a complex interaction of both environmental (including HBV or HCV infection) and genetic factors[2]. Loss of genomic stability and the gene alterations resulting from endogenous and/or exogenous damage appear to be crucial molecular and pathogenic steps that occur early in the carcinogenesis process of HCC[2]. Various enzymes and proteins involved in the DNA repair system play a pivotal role in maintaining the genome integrity in cells through the reversal of DNA damage[3]. The mutations and single-nucleotide polymorphisms (SNPs) in corresponding DNA repair genes may impair their repair or reversal capacity and increase the risk of cancer[4].

The X-ray repair cross-complementing group 1 (*XRCC1*) gene, located on chromosome 19 (19q13.2), encodes a crucial scaffold protein that is closely associated with the base excision repair (BER) pathway[5]. The XRCC1 protein is responsible for the repair of oxidative DNA damage and single-strand breaks through interacting with DNA ligase 3 and the complexes with DNA polymerase and poly (adenosine diphosphate-ribose) polymerase (PARP)[6,7]. Although more than 300 validated SNPs have been identified and described in the *XRCC1* gene, only three common SNPs have been extensively studied: Arg194Trp (rs1799782, C/T substitution at position 26304 on exon 6), Arg280His (rs25489, G/A substitution at position 27466 on exon 9), and Arg399Gln (rs25487, G/A substitution at position 28152 on exon 10)[8]. Numerous studies have focused on the association between these *XRCC1* polymorphisms and development of cancer in humans[9-16]. *XRCC1* SNPs have been shown in the previous meta-analyses to be significantly associated with risk of gastric[9], breast[12] and lung[16] cancer.

Over the past decade, a considerable number of epidemiological studies have focused on the association between *XRCC1* polymorphisms and HCC risk. However, the results remain either controversial or inconclusive. To address these issues, we carried out a systematic review and meta-analysis of all eligible case-control studies to estimate the risk of HCC associated with the *XRCC1* polymorphisms.

MATERIALS AND METHODS

Literature search

To identify the studies eligible for inclusion in the systematic review and meta-analysis, the following electronic databases were searched: PubMed, Embase, Wanfang (Chinese), VIP (Chinese) and the Chinese National Knowledge Infrastructure (CNKI) (up to Match 1, 2012). The following keywords were used: "X-ray repair cross-complementing group 1" or "XRCC1 and haplotype or polymorphism" and "liver cancer" or "hepatocellular carcinoma". The search was performed without restriction on language and all studies on human subjects were included. Additional studies were identified by a manual search of the references of the original studies. Of the studies with overlapping data published by the same investigators, only the most recent or complete study was included in this meta-analysis.

Inclusion/exclusion criteria

The included studies had to meet all the following criteria: (1) evaluated *XRCC1* polymorphisms and HCC risk; (2) case-control or cohort studies; and (3) contained sufficient published data for estimating an odds ratio (OR) with a 95% confidence interval (CI). The polymorphisms, for which eligible data were reported in at least three published studies, were included into the meta-analysis.

Data extraction

Information was carefully extracted independently by two investigators according to the inclusion criteria. The following data were collected: the first author's surname, year of publication, country of origin, ethnicity, mean age and type of cases and controls, and the number of cases and controls for each genotype of *XRCC1* polymorphisms. Ethnic origins were categorized as Caucasian, Asian, and African. If a study did not present the ethnic origin, or if it was not possible to separate the participants into a mono-ethnic group according to the phenotypes, the group reported was termed "mixed".

Statistical analysis

The Hardy-Weinberg equilibrium (HWE) in the control groups was calculated in our meta-analysis to determine selective bias in the control population. The χ^2 goodness-of-fit test was used to identify deviation from HWE ($P < 0.05$ was considered significant).

Associations between HCC risk and SNPs in Arg194Trp, Arg280His, and Arg399Gln were estimated by ORs and 95% CI. The statistical significance of the summary OR was determined with the *Z* test according to Thakkinstian's method[17] ($P < 0.05$). For each polymorphism, the wild-type allele was set as A and the risk allele as B. The

Table 1 Characteristics of eligible studies included in this study

Ref.	Country (ethnicity)	Genotyping method	Cases/controls	Source of controls	Type of controls	Polymorphisms of *XRCC1* gene
Tang *et al*[26]	China (Asian)	PCR-RFLP	150/150	Hospital	Age matched, male and healthy	Arg194Trp, Arg280His, Arg399Gln
Bo *et al*[30]	China (Asian)	PCR-RFLP	130/130	Hospital	Age matched and healthy	Arg194Trp
Zeng *et al*[29]	China (Asian)	TaqMan SNP Genotyping	545/515	Hospital	Age, sex and residence matched and without cancer	Arg194Trp, Arg280His, Arg399Gln
Kiran *et al*[22]	India (Asian)	PCR-RFLP	63/155	Hospital	HBsAg (-), anti-HCV (-), and without renal or hepatic disease	Arg194Trp, Arg280His, Arg399Gln
Wu *et al*[27]	China (Asian)	PCR-RFLP	100/60	Hospital	Age and sex matched, healthy and HBsAg (-)	Arg280His
Ren *et al*[25]	China (Asian)	PCR-RFLP	50/92	Hospital	Healthy and HBsAg (-)	Arg399Gln
Borentain *et al*[20]	France (Caucasian)	Sequencing	56/89	Population	Healthy and without chronic liver disease	Arg399Gln
Kirk *et al*[23]	Gambia (African)	PCR-RFLP	195/352	Hospital	Age and sex matched, normal α-fetoprotein levels, and without clinical evidence of liver disease	Arg399Gln
Long *et al*[24]	China (Asian)	PCR-RFLP	140/536	Hospital	Age, sex and ethnicity matched and without cancer	Arg399Gln
Han *et al*[21]	China (Asian)	PCR-RFLP	69/136	Population	Age, sex and residence matched	Arg399Gln
Yu *et al*[28]	China (Asian)	PCR-RFLP	577/389	Population	Age and sex matched, HBsAg (+), and without HCC	Arg399Gln

XRCC1: X-ray repair cross-complementing group 1; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; SNP: Single nucleotide polymorphism; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

A and B allele frequencies were first compared between the case and the control groups. Then, we evaluated the multiple comparisons including BB *vs* AA (codominant model), AB *vs* AA (codominant model), BB *vs* AB, (BB + AB) *vs* AA (dominant model), BB *vs* (AB + AA) (recessive model), and (BB + AA) *vs* AB (complete overdominant model).

The χ^2-based Q statistic was used to test for the between-study heterogeneity[18]. When $P < 0.1$ or $I^2 > 50\%$, the heterogeneity was considered statistically significant[19]. The data were analyzed using a random-effects model if heterogeneity existed. In the absence of heterogeneity, a fixed-effects model was used. Sensitivity analysis was performed to examine the effect of excluded specific studies, such as studies with controls that were not in HWE. The statistical significance of the summary OR was determined with the *Z* test ($P < 0.05$).

The publication bias was assessed qualitatively by the Begg's rank correlation method and the Egger's weighted regression method ($P < 0.05$). All statistical analyses were performed with Stata software (version 11.0; Stata Corporation, College Station, TX) using two-sided *P* values.

RESULTS

With the retrieval strategy, 60 potentially relevant papers were extracted (12 from PubMed, 15 from Embase, 16 from Wanfang, 3 from VIP and 14 from CNKI). Forty-seven studies were subjected to a full-text review and excluded according to the selection criteria stated above. Eleven studies were identified that examined the association between the *XRCC1* polymorphisms and HCC risk[20-30]. Table 1 summarizes the data from these studies, which included 2075 HCC patients and 2604 control subjects. The HCC was defined according to the clinical pathological examinations. Those with no clinical evidence of HCC served as controls.

These studies focused on three identified polymorphisms of the *XRCC1* gene: Arg194Trp, Arg280His, and Arg399Gln. The genotypes and allelic frequencies of these three *XRCC1* polymorphisms in the eligible studies are listed in Table 2. Three studies which respectively analyzed the Arg194Trp[30], the Arg280His[22], and the Arg399Gln polymorphisms[29] significantly deviated from the HWE ($P < 0.05$).

Arg194Trp

The Arg194Trp polymorphism is located on exon 6 of the *XRCC1* gene and has been investigated in association studies in patients with HCC. A positive association was initially noted by Kiran *et al*[22] who reported an excess frequency of the Arg/Trp genotype in an Indian sample of HCC patients *vs* controls. Furthermore, Bo *et al*[30] reported significant associations among a Chinese population between HCC and the Arg/Trp and Trp/Trp genotypes. However, another two studies of a Chinese population reported no association between the Arg194Trp polymorphism of the *XRCC1* gene and HCC[26,31].

In this meta-analysis, four studies focused on the Arg194Trp polymorphism of *XRCC1* gene in an Asian population, including 888 HCC cases and 938 controls. An evaluation of the association between the Arg194Trp polymorphism and HCC risk is presented in Table 3. No significant association was detected between HCC and the Arg/Trp or Trp/Trp genotype (the Arg/Trp *vs* the Arg/Arg model, fixed-effects OR: 1.30, 95% CI:

Table 2 Genotype distribution of X-ray repair cross-complementing group 1 polymorphisms used in this study

Polymorphism	Ref.	Ethnicity	Case			Control			HWE
Arg194Trp			Arg/Arg	Arg/Trp	Trp/Trp	Arg/Arg	Arg/Trp	Trp/Trp	
	Tang *et al*[26]	Asian	94	41	15	81	58	11	0.88
	Bo *et al*[30]	Asian	94	31	5	116	12	2	0.02
	Zeng *et al*[29]	Asian	305	200	40	275	202	38	0.91
	Kiran *et al*[22]	Asian	8	43	12	27	64	52	0.35
Arg280His			Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His	
	Tang *et al*[26]	Asian	138	11	1	123	26	1	0.76
	Zeng *et al*[29]	Asian	451	86	8	423	89	3	0.46
	Wu *et al*[27]	Asian	76	23	1	47	13	0	0.34
	Kiran *et al*[22]	Asian	19	30	14	91	29	35	0.00
Arg399Gln			Arg/Arg	Arg/Gln	Gln/Gln	Arg/Arg	Arg/Gln	Gln/Gln	
	Tang *et al*[26]	Asian	41	94	15	84	54	12	0.43
	Zeng *et al*[29]	Asian	312	196	37	309	169	37	0.04
	Kiran *et al*[22]	Asian	25	33	5	45	70	27	0.98
	Ren *et al*[25]	Asian	32	14	4	46	41	5	0.28
	Borentain *et al*[20]	Caucasian	27	21	8	27	43	19	0.80
	Kirk *et al*[23]	African	160	31	4	300	48	4	0.19
	Long *et al*[24]	Asian	72	63	5	362	159	15	0.62
	Han *et al*[21]	Asian	34	28	7	58	63	15	0.73
	Yu *et al*[28]	Asian	301	223	53	218	143	28	0.49

HWE: Hardy-Weinberg equilibrium.

0.68-2.48, $P = 0.42$; the Trp/Trp *vs* the Arg/Arg model, fixed-effects OR: 1.03, 95% CI: 0.71-1.49, $P = 0.86$). Furthermore, no significant results were observed in any other genetic models. Sensitivity analysis was performed after excluding the study conducted by Bo *et al*[30], because the controls were not in HWE.

Arg280His

The Arg280His allele is located on exon 9 of the *XRCC1* gene. A study by Kiran *et al*[22] in an Indian population showed that the Arg280His polymorphism of the *XRCC1* gene was positively associated with HCC. The Arg/His genotype was associated with a significantly increased risk of HCC. However, three studies in Chinese populations reported no association between the Arg280His polymorphism of the *XRCC1* gene and HCC[28,29,31].

In this study, the four studies on the Arg280His polymorphism of the *XRCC1* gene among Asian populations, included 858 HCC cases and 880 controls. Overall, significant association was found for the His/His *vs* Arg/Arg model (fixed-effects OR: 1.96, 95% CI: 1.03-3.75, $P = 0.04$) (Table 3). However, sensitivity analysis after exclusion of the study[22] with controls not in HWE did not suggest the association (the His/His *vs* Arg/Arg model, fixed-effects OR: 2.06, 95% CI: 0.67-6.25, $P = 0.20$). No significant results were observed in any other genetic models in the overall analysis and sensitivity analysis.

Arg399Gln

The Arg399Gln allele is located on the exon 10 of the *XRCC1* gene. Studies by Long *et al*[24] and Tang *et al*[26] reported an excess frequency of the Arg/Gln genotype of the *XRCC1* gene in HCC patients *vs* controls in Chinese populations. However, this observation was not replicated in four other studies[21,25,30,31] of the Chinese population. A positive association between the Arg/Gln genotype and a significantly increased risk of HCC in the African population was reported by Kirk *et al*[23]. The study by Borentain *et al*[20] in a Caucasian population showed an increased frequency of the Arg/Arg genotype in HCC patients *vs* controls. Moreover, Kiran *et al*[22] reported significant associations among an Indian population between HCC and the Gln/Gln genotype acting as a protective genotype for HCC.

We retrieved nine studies involving 1845 HCC cases and 2401 controls of different populations (one Caucasian, one African, and seven Asian) reporting detailed allele frequencies[20-26,28,29]. The overall meta-analysis did not suggest any association between the *XRCC1* Arg399Gln polymorphism and HCC susceptibility in all genetic models (Table 3). For example, the ORs of the HCC risks associated with the Arg399Gln polymorphism were 1.07 (random-effects, 95% CI: 0.84-1.34, $P = 0.56$) for the comparison of Arg allele *vs* Gln allele, 1.05 (random-effects, 95% CI: 0.71-1.56, $P = 0.77$) for the comparison of Gln/Gln *vs* Arg/Arg genotype, and 1.13 (random-effects, 95% CI: 0.80-1.57, $P = 0.71$) for the comparison of Arg/Gln *vs* Arg/Arg. The results were consistent after we excluded one study[29] with controls not in HWE.

By stratifying the meta-analysis by ethnicity, no significant association between *XRCC1* Arg399Gln polymorphism and HCC risk was observed in the Asian subgroup, which included 1594 HCC cases and 1960 controls. Sensitivity analysis was performed after one study was excluded[29]. This did not alter the pattern of the results.

Publication bias

The Begg's rank correlation method and Egger's weighted regression method were used to assess publication

Table 3 Associations between Arg194Trp, Arg280His and Arg399Gln polymorphisms of X-ray repair cross-complementing group 1 gene and hepatocellular carcinoma risk shown in the meta-analysis

	n[1]	Cases/controls	OR (95% CI)	Significance (Z test)[2]		Heterogeneity (Q test)		
				Z	P	Q	I^2 (%)	P
Arg194Trp								
All	4	888/938						
Trp *vs* Arg			1.08 (0.73-1.60)	0.39	0.69	13.64	78.0	0.00
Trp/Trp *vs* Arg/Arg			1.03 (0.71-1.49)	0.17	0.86	2.18	0.0	0.53
Arg/Trp *vs* Arg/Arg			1.30 (0.68-2.48)	0.79	0.42	17.86	83.2	0.00
Trp/Trp *vs* Arg/Trp			0.88 (0.41-1.89)	0.31	0.75	9.95	69.9	0.01
Arg/Trp + Trp/Trp *vs* Arg/Arg			1.24 (0.70-2.20)	0.76	0.44	15.45	80.6	0.00
Trp/Trp *vs* Arg/Trp + Arg/Arg			0.93 (0.50-1.74)	0.21	0.83	7.45	59.7	0.05
Trp/Trp + Arg/Arg *vs* Arg/Trp			0.72 (0.36-1.43)	0.92	0.36	23.78	87.4	0.00
All HWE	3	758/808						
Trp *vs* Arg			0.89 (0.76-1.05)	1.32	0.18	0.55	0.0	0.76
Trp/Trp *vs* Arg/Arg			0.96 (0.66-1.43)	0.18	0.85	0.39	0.0	0.82
Arg/Trp *vs* Arg/Arg			0.94 (0.56-1.60)	0.20	0.84	6.57	69.6	0.03
Trp/Trp *vs* Arg/Trp			0.87 (0.36-2.13)	0.29	0.77	9.95	79.9	0.00
Arg/Trp + Trp/Trp *vs* Arg/Arg			0.88 (0.72-1.09)	1.12	0.26	2.88	30.6	0.23
Trp/Trp *vs* Arg/Trp + Arg/Arg			0.83 (0.43-1.58)	0.56	0.57	5.86	65.9	0.05
Trp/Trp + Arg/Arg *vs* Arg/Trp			0.92 (0.47-1.81)	0.23	0.81	14.09	85.8	0.00
Arg280His								
All	4	858/880						
His *vs* Arg			1.03 (0.62-1.70)	0.11	0.90	12.73	76.4	0.00
His/His *vs* Arg/Arg			1.96 (1.03-3.75)	2.06	0.04	0.44	0.0	0.93
Arg/His *vs* Arg/Arg			1.16 (0.47-2.86)	0.33	0.74	26.36	88.6	0.00
His/His *vs* Arg/His			1.13 (0.30-4.22)	0.19	0.85	7.01	57.2	0.07
Arg/His + His/His *vs* Arg/Arg			1.10 (0.52-2.33)	0.25	0.80	20.16	85.1	0.00
His/His *vs* Arg/His + Arg/Arg			1.23 (0.69-2.21)	0.73	0.46	1.63	0.0	0.65
His/His + Arg/Arg *vs* Arg/His			0.90 (0.38-2.11)	0.23	0.81	24.71	87.9	0.00
All HWE	3	795/725						
His *vs* Arg			0.83 (0.49-1.41)	0.67	0.50	5.44	63.2	0.06
His/His *vs* Arg/Arg			2.06 (0.67-6.25)	1.28	0.20	0.43	0.0	0.80
Arg/His *vs* Arg/Arg			0.74 (0.43-1.30)	1.03	0.30	5.08	60.6	0.07
His/His *vs* Arg/His			2.54 (0.80-8.04)	1.59	0.11	0.07	0.0	0.96
Arg/His + His/His *vs* Arg/Arg			0.78 (0.44-1.36)	0.86	0.39	5.40	63.0	0.06
His/His *vs* Arg/His + Arg/Arg			2.11 (0.69-6.43)	1.32	0.18	0.36	0.0	0.83
His/His + Arg/Arg *vs* Arg/His			1.34 (0.78-2.31)	1.07	0.28	4.95	59.6	0.08
Arg399Gln								
All	9	1845/2401						
Gln *vs* Arg			1.07 (0.84-1.34)	0.57	0.56	33.12	75.8	0.00
Gln/Gln *vs* Arg/Arg			1.05 (0.71-1.56)	0.29	0.77	14.84	46.1	0.06
Arg/Gln *vs* Arg/Arg			1.13 (0.80-1.57)	0.71	0.47	39.18	79.6	0.00
Gln/Gln *vs* Arg/Gln			0.93 (0.71-1.21)	0.52	0.60	6.32	0.0	0.61
Arg/Gln + Gln/Gln *vs* Arg/Arg			1.11 (0.80-1.54)	0.63	0.52	41.34	80.6	0.00
Gln/Gln *vs* Arg/Gln + Arg/Arg			1.00 (0.78-1.28)	0.03	0.97	7.87	0.0	0.44
Gln/Gln + Arg/Arg *vs* Arg/Gln			0.85 (0.63-1.15)	1.02	0.30	32.13	75.1	0.00
All HWE	8	1300/1886						
Gln *vs* Arg			1.06 (0.79-1.41)	0.40	0.69	32.61	78.5	0.00
Gln/Gln *vs* Arg/Arg			1.06 (0.65-1.73)	0.25	0.80	14.61	52.1	0.04
Arg/Gln *vs* Arg/Arg			1.10 (0.73-1.68)	0.49	0.62	38.85	82.0	0.00
Gln/Gln *vs* Arg/Gln			0.96 (0.70-1.30)	0.25	0.79	6.15	0.0	0.52
Arg/Gln + Gln/Gln *vs* Arg/Arg			1.09 (0.72-1.64)	0.43	0.66	40.82	82.9	0.00
Gln/Gln *vs* Arg/Gln + Arg/Arg			1.02 (0.77-1.37)	0.19	0.84	7.72	9.3	0.35
Gln/Gln + Arg/Arg *vs* Arg/Gln			0.86 (0.60-1.24)	0.77	0.44	31.84	78.0	0.00
Asian	7	1594/1960						
Gln *vs* Arg			1.12 (0.87-1.44)	0.89	0.37	25.85	76.8	0.00
Gln/Gln *vs* Arg/Arg			1.13 (0.86-1.48)	0.92	0.35	10.48	42.7	0.10
Arg/Gln *vs* Arg/Arg			1.22 (0.83-1.78)	1.04	0.29	33.10	81.9	0.00
Gln/Gln *vs* Arg/Gln			0.92 (0.69-1.21)	0.58	0.56	5.83	0.0	0.44
Arg/Gln + Gln/Gln *vs* Arg/Arg			1.20 (0.83-1.73)	0.98	0.32	33.84	82.3	0.00
Gln/Gln *vs* Arg/Gln + Arg/Arg			1.02 (0.79-1.33)	0.20	0.83	5.96	0.0	0.42
Gln/Gln + Arg/Arg *vs* Arg/Gln			0.81 (0.57-1.13)	1.21	0.22	28.55	79.0	0.00
Asian HWE	6	1049/1445						
Gln *vs* Arg			1.12 (0.81-1.54)	0.69	0.49	24.80	79.8	0.00
Gln/Gln *vs* Arg/Arg			1.16 (0.69-1.97)	0.59	0.55	9.89	49.4	0.07
Arg/Gln *vs* Arg/Arg			1.22 (0.74-2.00)	0.78	0.43	32.23	84.5	0.00
Gln/Gln *vs* Arg/Gln			0.95 (0.68-1.32)	0.31	0.76	5.70	12.3	0.33

Arg/Gln + Gln/Gln *vs* Arg/Arg	1.20 (0.74-1.94)	0.75	0.45	32.66	84.7	0.00
Gln/Gln *vs* Arg/Gln + Arg/Arg	1.06 (0.78-1.46)	0.41	0.67	5.69	12.1	0.33
Gln/Gln + Arg/Arg *vs* Arg/Gln	0.80 (0.51-1.26)	0.93	0.35	27.84	82.0	0.00

[1]Number of studies; [2]Random-effects model was used when *P* value for heterogeneity test $P < 0.1$ or $I^2 > 50\%$; otherwise, fixed-effects model was used. HWE: Hardy-Weinberg equilibrium; OR: Odds ratio.

bias. There was no evidence of publication bias for these polymorphisms.

DISCUSSION

The XRCC1 protein is a key molecule of BER in the DNA repair process, which plays a key role in the integrity and stability of the genome and the pathogenesis and progression of human cancers[31]. Polymorphisms that can alter XRCC1 expression and function may contribute to the risk of cancers. Several studies have been conducted in recent years to evaluate the association between the *XRCC1* SNPs and HCC risk predisposition in different ethnic populations, but the results have been conflicting[20-30].

In the present study, we performed a systematic review and meta-analysis to examine the association between three *XRCC1* gene polymorphisms and HCC risk. These three polymorphisms of the *XRCC1* gene result in nonconservative amino-acid changes at evolutionary conserved regions: a C to T substitution in codon 194 of exon 6 (Arg to Trp), a G to A substitution in codon 280 of exon 9 (Arg to His), and a G to A substitution in codon 399 of exon 10 (Arg to Gln)[32]. Although the functional effects of these nonsynonymous polymorphisms in *XRCC1* are not well known, the nature of the amino acid substitutions may cause functional changes in the XRCC1 protein and impair DNA repair efficiency or accuracy, which could be implicated in the risk of cancer. However, previous meta-analysis showed inconsistent results in the association between the polymorphisms of the *XRCC1* gene and the risk of cancers.

These previous meta-analysis found that the carriers of homozygous Trp/Trp variant genotype of the Arg194Trp polymorphism had an increased risk of gastric cancer[9] and other cancers, especially lung cancer and esophageal cancer, in the Chinese mainland population[11]. However, no associations were observed between the Arg194Trp polymorphism with skin[15], colorectal[33], and prostate cancer[34], and nasopharyngeal carcinoma[10]. The Arg280His polymorphism was associated with an approximate 3.5-fold increase in skin cancer risk in homozygote codominant and recessive models[15]. However, the Arg280His polymorphism was not found to be a statistically significant risk factor for gastric cancer[9] and nasopharyngeal carcinoma[10]. The Gln/Gln genotype of the Arg399Gln polymorphism was associated with an increased risk of prostate cancer[34] and nasopharyngeal carcinoma[10], but was not correlated with skin[15], gastric[9], and colorectal[33] cancer susceptibility for all genetic models. For prostate cancer, Wei *et al*[34] concluded that the Gln allele of the Arg399Gln polymorphism might be a low-penetrant risk factor for prostate cancer only in Asian men, but was not related to overall prostate cancer risk.

It is difficult to interpret the reasons for these inconsonant results; nonetheless, several factors may influence the function of these polymorphisms of the *XRCC1* gene in various ways, including variation in the exposure of different populations to carcinogens and variation in different types of DNA damage associated with the initiation of different cancers. Further research is needed to clarify this inconsistency.

There has been no previous meta-analysis of the effect of the Arg194Trp and Arg280His polymorphisms of the *XRCC1* gene on the risk of HCC. Our data suggested that the Arg194Trp polymorphism might not be a risk factor for HCC. For the *XRCC1* Arg280His polymorphism, our meta-analysis on the available studies showed that the His/His genotype was significantly associated with increased HCC risk. However, the sensitivity analysis after exclusion of the study with controls not in HWE did not suggest this association. Our meta-analysis does not strongly support the association between the His/His genotype of the *XRCC1* Arg280His polymorphism and the increased risk in HCC. Although there is some evidence of association between the *XRCC1* Arg280His polymorphism and HCC, the above finding deserves further and more rigorous association studies. A previous meta-analysis study found that the Arg399Gln polymorphism had no association with HCC[13], which is similar to our current finding. Recently, another variant in the XRCC1 gene located in the 5'-untranslated region, -77 T to C, was identified[35] and indicated as a genetic determinant for developing breast cancer[14]. However, there is a lack of association study between the -77 T/C polymorphism of the *XRCC1* gene and HCC risk.

Similar to other systematic reviews and meta-analyses, there were some limitations in this study. Firstly, the sample sizes in the overall and subgroup analyses were small. Secondly, only two published studies included in this meta-analysis focused on the Arg399Gln polymorphism and its relationship with HCC in Caucasian and African populations. Thirdly, the sources of heterogeneity that existed among the studies for most polymorphisms were not addressed. Finally, this meta-analysis was based on unadjusted data, whereas a more precise analysis could be performed if individual data were available. Additional well-designed, more-detailed studies with larger populations and different ethnicities are needed to further evaluate the associations.

In conclusion, The XRCC1 Arg194Trp and Arg399Gln polymorphisms are not associated with HCC risk. More rigorous association studies are needed to clarify the involvement of XRCC1 Arg280His polymorphism in

HCC susceptibility. No publication biases regarding these three evaluated polymorphisms were found in this meta-analysis.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide. The X-ray repair cross-complementing group 1 (*XRCC1*) gene encodes a crucial scaffold protein that is responsible for the repair of oxidative DNA damage and single-strand breaks. Many studies have explored the association between the *XRCC1* polymorphisms and HCC risk, but the results remain either controversial or inconclusive. To address these issues, the authors carried out a systematic review and meta-analysis of all eligible case-control studies to estimate the association between the *XRCC1* polymorphisms and the risk of HCC.

Research frontiers

To date, a number of studies have assessed the association between the *XRCC1* polymorphisms and HCC risk among different populations; however, the results have been inconsistent and inconclusive.

Innovations and breakthroughs

This meta-analysis suggested that none of the Arg194Trp and Arg399Gln polymorphisms of *XRCC1* were significantly associated with a risk of HCC. More rigorous association studies are needed to verify the involvement of XRCC1 Arg280His polymorphism in HCC susceptibility.

Applications

This meta-analysis showed that the Arg399Gln and Arg194Trp polymorphisms of the *XRCC1* gene did not alter the susceptibility to HCC. The findings may provide valuable information about the etiology of HCC for both researchers and clinicians.

Peer review

This manuscript was a meta-analysis to analyze the association between X-ray repair cross-complementing group 1 polymorphisms and HCC. This is a scientifically interesting topic. Although the results show that this is a negative study, it is very important to systematically review these relevant reports.

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