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.

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

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Xie T et al. XRCC1 polymorphisms and HCC

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide. It is accepted that the carcinogenesis of HCC is a multistep process, and multiple factors are involved in this complex process. 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. The progression of HCC might result from a complex interaction of both environmental (including HBV or HCV infection) and genetic factors. 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. 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. 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.

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. 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). 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). Numerous studies have focused on the association between these XRCC1 polymorphisms and development of cancer in humans. XRCC1 SNPs have been shown in the previous meta-analyses to be significantly associated with risk of gastric, breast, and lung 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 $\chi^2$ 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 ($P < 0.05$). For each polymorphism, the wild-type allele was set as A and the risk allele as B. The
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 $\chi^2$-based Q statistic was used to test for the between-study heterogeneity\textsuperscript{[20-30]}. When $P < 0.1$ or $I^2 > 50\%$, the heterogeneity was considered statistically significant\textsuperscript{[19]}\textsuperscript{[20-30]}. 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 included 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 $XRC\!C\!C\!1$ polymorphisms and HCC risk\textsuperscript{[20-30]}\textsuperscript{[26,31]}. 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 $XRC\!C\!C\!1$ gene: Arg194Trp, Arg280His, and Arg399Gln. The genotypes and allelic frequencies of these three $XRC\!C\!C\!1$ polymorphisms in the eligible studies are listed in Table 2. Three studies which respectively analyzed the Arg194Trp\textsuperscript{[22]}\textsuperscript{[30]}, the Arg280His\textsuperscript{[29]}\textsuperscript{[30]}, and the Arg399Gln polymorphisms\textsuperscript{[29]}\textsuperscript{[30]} significantly deviated from the HWE ($P < 0.05$).

### Arg194Trp

The Arg194Trp polymorphism is located on exon 6 of the $XRC\!C\!C\!1$ gene and has been investigated in association studies in patients with HCC. A positive association was initially noted by Kiran et al\textsuperscript{[22]} who reported an excess frequency of the Arg/Trp genotype in an Indian sample of HCC patients vs controls. Furthermore, Bo et al\textsuperscript{[24]} 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 $XRC\!C\!C\!1$ gene and HCC\textsuperscript{[29,30]}.

In this meta-analysis, four studies focused on the Arg194Trp polymorphism of $XRC\!C\!C\!1$ 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: 0.95–1.78).

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**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 $XRC\!C\!C\!1$ gene |
|---------------|---------------------|-------------------|----------------|-------------------|-----------------|-------------------------------------|
| Tang et al\textsuperscript{[24]} | China (Asian)       | PCR–RFLP          | 150/150        | Hospital          | Age matched, male and healthy | Arg194Trp, Arg280His, Arg399Gln |
| Bo et al\textsuperscript{[24]}   | China (Asian)       | PCR–RFLP          | 130/130        | Hospital          | Age matched and healthy | Arg194Trp |
| Zeng et al\textsuperscript{[29]} | China (Asian)       | TaqMan SNP        | 545/515        | Hospital          | Age, sex and residence matched and without cancer | Arg194Trp, Arg280His, Arg399Gln |
| Kiran et al\textsuperscript{[22]}| India (Asian)       | PCR–RFLP          | 63/155         | Hospital          | HBSAg (-), anti-HCV (-), and without renal or hepatic disease | Arg194Trp, Arg280His, Arg399Gln |
| Wu et al\textsuperscript{[22]}   | China (Asian)       | PCR–RFLP          | 100/60         | Hospital          | Age and sex matched, healthy and HBSAg (-) | Arg399Gln, Arg280His |
| Ren et al\textsuperscript{[29]}  | China (Asian)       | PCR–RFLP          | 50/92          | Hospital          | Healthy and HBSAg (-) | Arg399Gln |
| Borentain et al\textsuperscript{[26]} | France (Caucasian) | Sequencing       | 56/89          | Population        | Healthy and without chronic liver disease | Arg399Gln |
| Kirk et al\textsuperscript{[29]} | Gambia (African)    | PCR–RFLP          | 195/352        | Hospital          | Age and sex matched, normal $\alpha$-fetoprotein levels, and without clinical evidence of liver disease | Arg399Gln |
| Long et al\textsuperscript{[24]} | China (Asian)       | PCR–RFLP          | 140/536        | Hospital          | Age, sex and ethnicity matched and without cancer | Arg399Gln |
| Han et al\textsuperscript{[29]}  | China (Asian)       | PCR–RFLP          | 69/136         | Population        | Age, sex and residence matched | Arg399Gln |
| Yu et al\textsuperscript{[29]}   | China (Asian)       | PCR–RFLP          | 577/389        | Population        | Age and sex matched, HBSAg (+), and without HCC | Arg399Gln |

$XRC\!C\!C\!1$: 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.
The Arg399Gln allele is located on the exon 10 of the XRC1 gene. Studies by Long et al. [28] and Tang et al. [29] reported significant associations among an Indian population and a significantly increased risk of HCC in the African population was reported by Kirk et al. [23]. The study by Borentain et al. [26] in a Caucasian population showed an increased frequency of the Arg/Arg genotype in HCC patients vs controls. Moreover, Kiran et al. [21] 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 XRC1 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 XRC1 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 bias.
| Arg194Trp | OR (95% CI) | Significance (Z test) | Heterogeneity (Q test) |
|----------|------------|----------------------|-----------------------|
| All      | 1.08 (0.73-1.60) | 0.39 0.69 | 13.64 78.0 0.00 |
|           | 1.03 (0.71-1.49) | 0.17 0.86 | 2.18 0.0 0.53 |
|           | 1.30 (0.68-2.48) | 0.79 0.42 | 17.86 83.2 0.00 |
|           | 0.88 (0.41-1.91) | 0.31 0.75 | 9.95 69.9 0.01 |
|           | 1.24 (0.70-2.02) | 0.76 0.44 | 15.45 80.6 0.00 |
|           | 0.93 (0.50-1.74) | 0.21 0.83 | 7.45 59.7 0.05 |
|           | 0.72 (0.36-1.43) | 0.92 0.36 | 23.78 87.4 0.00 |
| All HWE  | 0.89 (0.76-1.05) | 1.32 0.18 | 0.55 0.0 0.76 |
|           | 0.96 (0.66-1.43) | 0.18 0.85 | 0.39 0.0 0.82 |
|           | 0.94 (0.56-1.60) | 0.20 0.84 | 6.57 69.6 0.03 |
|           | 0.87 (0.36-2.13) | 0.29 0.77 | 9.95 79.9 0.00 |
|           | 0.88 (0.72-1.09) | 1.12 0.26 | 2.88 30.6 0.23 |
|           | 0.81 (0.43-1.59) | 0.56 0.57 | 5.86 65.9 0.05 |
|           | 0.92 (0.47-1.81) | 0.23 0.81 | 14.09 85.8 0.00 |
| Arg280His | 1.03 (0.62-1.70) | 0.11 0.90 | 12.73 76.4 0.00 |
|           | 1.96 (1.03-3.75) | 2.06 0.04 | 0.44 0.0 0.93 |
|           | 1.16 (0.47-2.86) | 0.33 0.74 | 26.36 88.6 0.00 |
|           | 1.13 (0.50-2.22) | 0.19 0.85 | 7.01 57.2 0.07 |
|           | 1.10 (0.52-2.33) | 0.25 0.80 | 20.36 85.1 0.00 |
|           | 1.23 (0.69-2.21) | 0.73 0.46 | 1.63 0.0 0.65 |
|           | 0.90 (0.38-2.11) | 0.23 0.81 | 24.71 87.9 0.00 |
| All HWE  | 0.83 (0.49-1.41) | 0.67 0.50 | 5.44 63.2 0.06 |
|           | 2.06 (0.67-6.25) | 1.28 0.20 | 0.43 0.0 0.80 |
|           | 0.74 (0.43-1.30) | 0.10 0.30 | 5.08 60.6 0.07 |
|           | 2.54 (0.80-8.04) | 1.59 0.11 | 0.07 0.0 0.96 |
|           | 0.78 (0.44-1.36) | 0.86 0.39 | 5.40 63.0 0.06 |
|           | 2.11 (0.69-6.43) | 1.32 0.18 | 0.36 0.0 0.83 |
|           | 1.34 (0.78-2.31) | 1.07 0.28 | 4.95 59.6 0.08 |
| Arg399Gln | 1.07 (0.84-1.34) | 0.57 0.56 | 33.12 75.8 0.00 |
|           | 1.05 (0.71-1.56) | 0.29 0.77 | 14.84 46.1 0.06 |
|           | 1.13 (0.80-1.57) | 0.71 0.47 | 39.18 79.6 0.00 |
|           | 0.93 (0.71-1.21) | 0.52 0.60 | 6.32 0.0 0.61 |
|           | 1.11 (0.80-1.54) | 0.63 0.52 | 41.34 80.6 0.00 |
|           | 1.00 (0.78-1.28) | 0.03 0.97 | 7.87 0.0 0.44 |
|           | 0.85 (0.63-1.15) | 0.10 0.30 | 32.13 75.1 0.00 |
| All HWE  | 1.06 (0.79-1.41) | 0.40 0.69 | 32.61 78.5 0.00 |
|           | 1.06 (0.65-1.73) | 0.25 0.80 | 14.61 52.1 0.04 |
|           | 1.10 (0.73-1.68) | 0.49 0.62 | 38.85 82.0 0.00 |
|           | 0.96 (0.70-1.30) | 0.25 0.79 | 6.15 0.0 0.52 |
|           | 1.09 (0.72-1.64) | 0.43 0.66 | 40.82 82.9 0.00 |
|           | 1.02 (0.77-1.37) | 0.19 0.84 | 7.72 9.3 0.35 |
|           | 0.86 (0.60-1.24) | 0.77 0.44 | 31.84 78.0 0.00 |
| Asian    | 1.12 (0.87-1.44) | 0.89 0.37 | 25.85 76.8 0.00 |
|           | 1.13 (0.86-1.48) | 0.92 0.35 | 10.48 42.7 0.10 |
|           | 1.22 (0.83-1.78) | 1.04 0.29 | 33.10 81.9 0.00 |
|           | 0.92 (0.69-1.21) | 0.58 0.56 | 5.83 0.0 0.44 |
|           | 1.20 (0.83-1.73) | 0.98 0.32 | 33.84 82.3 0.00 |
|           | 1.02 (0.79-1.33) | 0.20 0.83 | 5.96 0.0 0.42 |
|           | 0.81 (0.57-1.13) | 1.21 0.22 | 28.55 79.0 0.00 |
| Asian HWE | 1.12 (0.81-1.54) | 0.69 0.49 | 24.80 79.8 0.00 |
|           | 1.16 (0.89-1.97) | 0.59 0.55 | 9.89 49.4 0.07 |
|           | 1.22 (0.74-2.00) | 0.78 0.43 | 22.23 84.5 0.00 |
|           | 0.95 (0.68-1.32) | 0.31 0.76 | 5.70 12.3 0.33 |
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\[9\]. 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\[9-30\].

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)\[12\]. 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, lung cancer and esophageal cancer, in the Chinese mainland population\[19\]. However, no associations were observed between the Arg194Trp polymorphism with skin\[19\], colorectal\[13\], and prostate cancer\[14\], 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\[13\]. 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\[9\] and nasopharyngeal carcinoma\[10\], but was not correlated with skin\[13\], gastric\[9\], and colorectal\[13\] cancer susceptibility for all genetic models. For prostate cancer, Wei et al.\[14\] 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\[19\] and indicated as a genetic determinant for developing breast cancer\[19\]. 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.

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