Association of XRCC1 Arg399Gln Polymorphism with Colorectal Cancer Risk: A HuGE Meta Analysis of 35 Studies

Mohammad Forat-Yazdi, Mohsen Gholi-Nataj*, Hossein Neamatzadeh, Parisa Nourbakhsh, Hossein Shaker-Ardakani

Abstract

Background: Non-synonymous polymorphisms in XRCC1 have been shown to reduce effectiveness of DNA repair and be associated with risk of certain cancers. In this study we aimed to clarify any association between XRCC1 Arg399Gln and colorectal cancer (CRC) risk by performing a meta-analysis of published case-control studies. Materials and Methods: PubMed and Google Scholar were searched to explore the association between XRCC1 and CRC. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association strength. Publication bias was assessed by Egger’s and Begg’s tests. Results: Up to January 2015, 35 case control studies involving 9,114 CRC cases and 13,948 controls were included in the present meta-analysis. The results showed that the Arg399Gln polymorphism only under an allele genetic model was associated with CRC risk (A vs. G: OR 0.128, 95% CI 0.119-0.138, p<0.001). Also, this meta-analysis suggested that the XRCC1 Arg399Gln polymorphism might associated with susceptibility to CRC in Asians (A vs G: OR 0.124, 95% CI 0.112-0.138, p<0.001) and Caucasian (A vs G: OR 0.132, 95% CI 0.119-0.146, p<0.001) only under an allele genetic model. Conclusions: This meta-analysis confirms the association between XRCC1 Arg399Gln polymorphism and CRC risk and suggests that the heterogeneity is not strongly modified by ethnicity and deviation from the Hardy-Weinberg equilibrium.

Keywords: Colorectal cancer - XRCC1 - Arg399Gln - polymorphism - meta-analysis.

RESEARCH ARTICLE

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Introduction

Colorectal cancer is the leading cause of cancer-related death worldwide. Overall, it ranks as the third most frequent cancer worldwide, and the third and second most frequent cancer in men and women respectively (Magaji et al., 2014). It remains an enormous financial burden on the health care system. Although many new and advanced techniques have been introduced for the management and surveillance of CRC, but local recurrence and distant metastasis are still considered major complications (Mehrabani et al., 2014; Omranipour et al., 2014).

Amongst the known genetic susceptibility to CRC, the x-ray cross-complementing group 1 and 3 (XRCC1 and XRCC3) have been studied most commonly (Gao et al., 2014). The X-ray repair cross-complementing group 1 (XRCC1) protein, which is encoded by the XRCC1 gene, is an important component of the base excision repair (BER) pathway. The XRCC1 gene is located on chromosome 19q13.2-13.3, spans a genetic distance of 33 kb, comprises of 17 exons and encodes a 70-kDa protein consisting of 633 amino acids. XRCC1 has been shown to have a large number of SNPs, and several have been extensively evaluated in cancer epidemiology association investigations because of their relative high frequency in the population (Ladiges et al., 2006). Although there are more than 300 validated polymorphisms in the XRCC1 gene only three of XRCC1 are most studied and lead to amino acid substitutions in XRCC1 at codon 194, codon 280 and codon 399, these non-conservative amino acid changes may alter XRCC1 protein function (li et al., 2014).

The XRCC1 Arg399Gln polymorphism has been the most studied of the XRCC1 variations and one of the most frequently studied SNPs among all DNA repair gene variations. XRCC1 Arg399Gln showed associations in different directions for different cancers (Ladiges et al., 2006). So, the XRCC1 Arg399Gln polymorphism is associated with an increased risk for CRC (Wang et al., 2010; Liu et al., 2013). Other studies found no relationship between this polymorphism and CRC risk. Limited and controversial results were obtained regarding the association between colorectal cancer risk and XRCC1 Arg399Gln polymorphism. To provide a comprehensive and objective assessment of the association between the XRCC1 gene Arg399Gln polymorphism and CRC risk, a meta-analysis of all eligible case-control studies was performed.
Materials and Methods

Study identification and selection

A comprehensive literature search was performed using PubMed and Google Scholar to identify studies that evaluated the association between XRCC1 Arg399Gln polymorphism and the risk of CRC up to February 1, 2015. The following key words were used: 'Colon cancer', 'X-ray repair cross-complementing group 1' or 'XRCC1', Arg399Gln and 'polymorphism' or 'variant'. The search was restricted to English and Chinese. The reference lists of reviews and retrieved articles were hand searched at the same time. Abstracts or unpublished reports were not considered. If more than one article was published by the same author using the same case series, we selected the study where the most individuals were investigated. The following criteria were used for the study selection: 1) only case-control studies; 2) studies should concern the association between XRCC1 Arg399Gln polymorphism and CRC risk; 3) papers should offer the sample sizes and the genetic distribution or the information that can help infer the results; 4) no overlapping data. If studies had the same or overlapping data, only the largest study should be included in the final analysis.

Data extraction

Necessary information was carefully extracted from all the eligible studies independently by 2 investigators according to the inclusion criteria. The following data were collected from each study: first author, publication year, country, racial descent (categorized as Asian, Caucasian, or mixed descent), numbers of cases and controls, genotype frequency of cases and controls, and the result of Hardy-Weinberg equilibrium test. If a consensus was not reached, another author was consulted to resolve the dispute; then, a final decision was made by the majority of the votes. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical methods

The strength of associations between XRCC1 Arg399Gln polymorphism and CRC risk were evaluated by crude ORs together with their corresponding 95% CIs. Also, the pooled ORs and 95% CIs for XRCC1 Arg399Gln polymorphism was calculated by homozygous model
(AA vs GG), heterozygous model (GA vs GG), dominant genetic model (AA vs GA+GG) and recessive model (GA+AA vs GG). HWE was evaluated for control subjects of each study, using the goodness-of-fit \( \chi^2 \) test, and \( P < 0.05 \) was considered representative of deviation from HWE. Heterogeneity was quantified with the \( I^2 \) statistic, a value that indicates what proportion of the total variation across studies is beyond chance. Specifically, 0 % indicates no observed heterogeneity, and larger values show increasing heterogeneity. When \( P \) value of the heterogeneity test was \( \geq 0.05 \), the fixed-effects model, based on the Mantel-Haenszel method was used, which assumes the same homogeneity of effect size across all studies. Otherwise, the random effects model, based on the DerSimonian and Laird method, was more appropriate, which tends to provide wider 95% CIs as the results of the constituent studies differ among themselves. Subgroup analyses were also performed by ethnicity. To assess the effects of individual studies on CRC risk, sensitivity analysis was performed by excluding each study at a time individually and recalculating the ORs and 95% CIs. Visual inspection of Begg’s funnel plots was performed for assessment of publication bias. An asymmetric plot suggested possible bias, in which case Egger’s test was used. All the analysis was performed using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey).

**Results**

Thirty five studies were included based on the search criteria for CRC susceptibility related to the XRCC1 Arg399Gln polymorphisms (Abdel-Rahman et al., 2000; Krupa et al., 2004; Hong et al., 2005; Skjelbred et al., 2006; Ren et al; Moreno et al., 2006; Jin et al., 2007; Stern et al., 2007; Yeh et al., 2007; Martinez-Balibrea et al., 2008; Pardini et al., 2008; Kasahara et al., 2008; Asaka et al., 2010; Stolzenberg-Solomon et al., 2010; Gutierrez et al., 2011; Kim et al., 2012; Morin et al., 2012; Yang et al., 2012; Suh et al., 2013; Sun et al., 2013; Yoon et al., 2013; Zhang et al., 2013; Wynn et al., 2014; Liao et al., 2014; Schanuel et al., 2014; Pang et al., 2014; Kim et al., 2015; Sato et al., 2015; Park et al., 2015; Gao et al., 2015; Guan et al., 2015; Wang et al., 2015; Zhao et al., 2015; Kim et al., 2016; Lee et al., 2016; Li et al., 2016; Kim et al., 2017; Zhang et al., 2017; Liu et al., 2017; Wang et al., 2017; An et al., 2018; Kim et al., 2018; Li et al., 2018; Kim et al., 2019; Zhang et al., 2019; Li et al., 2019; Kim et al., 2020; Zhang et al., 2020; Li et al., 2021; Kim et al., 2021; Zhang et al., 2021; Li et al., 2021; Kim et al., 2022; Zhang et al., 2022).

**Table 2. Results of Meta-analysis for XRCC1 Arg399Gln Polymorphism and the Risk of Colorectal Cancer**

<table>
<thead>
<tr>
<th>Test of association</th>
<th>95% CI</th>
<th>Test of heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>A vs G</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.128</td>
<td>0.119</td>
</tr>
<tr>
<td>Asian</td>
<td>0.124</td>
<td>0.112</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.132</td>
<td>0.119</td>
</tr>
<tr>
<td>GA vs GG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.022</td>
<td>0.916</td>
</tr>
<tr>
<td>Asian</td>
<td>1.023</td>
<td>0.857</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.977</td>
<td>0.892</td>
</tr>
<tr>
<td>AA vs GG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.112</td>
<td>0.917</td>
</tr>
<tr>
<td>Asian</td>
<td>1.016</td>
<td>0.737</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.054</td>
<td>0.920</td>
</tr>
<tr>
<td>AA vs GA+GG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.100</td>
<td>0.929</td>
</tr>
<tr>
<td>Asian</td>
<td>1.067</td>
<td>0.922</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.031</td>
<td>0.901</td>
</tr>
<tr>
<td>GA+AA vs GG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1.041</td>
<td>0.942</td>
</tr>
<tr>
<td>Asian</td>
<td>1.046</td>
<td>0.891</td>
</tr>
<tr>
<td>Caucasian</td>
<td>0.984</td>
<td>0.903</td>
</tr>
</tbody>
</table>

**Figure 1. Forest Plots Showing the Association of the XRCC1 Arg399Gln Polymorphism with Risk of CRC**

(A: A vs G; B: GA vs GG; C: AA vs GG; D: AA vs GA+GG; E: GA+AA vs GG)
Meta-analysis results
Table 2 listed the main results of the meta-analysis for XRCC1 Arg399Gln polymorphism. The overall analysis investigating the allele model (OR=0.128 CI 90% 0.119-0.138 p=0.00) showed significant association between XRCC1 Arg399Gln polymorphism and increased CRC risk, although no evidence of associations was detected in the additive (OR=1.022 CI 90% 0.916-1.140 p=0.703), recessive (OR=1.112 CI 90% 0.917-1.347 p=0.281) and dominant (OR=1.100 CI 90% 0.929-1.303 p=0.268), and (OR=1.041 CI 90% 0.942-1.152 p=0.430) models. Next, stratified analyses by ethnicity were performed between XRCC1 Arg399Gln polymorphism and CRC risk. A significant association between XRCC1 Arg399Gln polymorphism and CRC susceptibility was found in Asian and Caucasian populations only in the allele model (Asians: OR=0.124 95% CI 0.112-0.138, p=0.00; Asian and Caucasian populations only in the allele model (A: A vs G and B: GA vs GG): p=0.379; GA vs GG: p=0.346; AA vs GG: p=0.324; AA vs GA+GG: p=0.329; GA+AA vs GG: p=0.283).

Discussion
XRCC1 plays an important role in the DNA damage repair pathway for the processing of small base lesions. The contradictory findings among case-control studies might be attributed to different sample size, source of controls, genotyping method and matching criteria of subjects, and so on. In addition, the potential gene-gene and gene-environment interactions may also play vital roles in the pathogenesis of CRC. Single study especially the one with relatively sample size may have not enough statistical power to identify a mild genetic association and introduce random errors. Inversely, meta-analysis by pooling all available data from eligible publications takes the advantage of achieving a more precise estimation for potential genetic associations. The advantages of this meta-analysis are that it is the most complete and the information from the eligible studies is utilized as much as possible through genetic model and stratified analysis. To help resolve the conflicting results this meta-analysis of published studies was conducted using a larger sample size. In this meta-analysis, it was focused on XRCC1 genetic polymorphism and provides the most comprehensive assessment of its association with CRC risk, by critically reviewing 35 studies on XRCC1 Arg399Gln polymorphism (a total of 9,114 cases and 13,948 controls).

Five meta-analyses previously have estimated the association between XRCC1 Arg399Gln polymorphism and CRC susceptibility (Liu et al., 2010; Wang et al., 2010; Wu et al., 2013; Zeng et al., 2013; Qin et al., 2015). However, the association remains not fully understood due to limited sample sizes and heterogeneity.
because of inconsistent results across independent studies. Compared with the previous meta-analyses, our meta-analysis involved a remarkably larger number of studies (35 studies) and provided a more comprehensive and reliable conclusion. We have found that the Arg399Gln polymorphism led to an increased risk in allele comparison (Table 2), which was in consistent with a previous meta-analysis among Chinese (Qin et al., 2015).

Present meta-analysis results were not consistent with a previous meta-analysis (81-86) on XRCC1 Arg399Gln polymorphism with CRC risk. Liu et al. (Liu et al., 2010) included 22 case-control studies with a total of 6,291 CRC cases and 10,289 controls concerning the XRCC1 Arg399Gln polymorphism. Their results suggested that XRCC1 Arg399Gln polymorphism was not associated with increased CRC risk and by ethnicity. In a meta-analysis, Qin et al retrieved 11 case-control studies with a total of 3194 CRC cases and 4472 controls in the Chinese Han population. They have not found a significant association between the XRCC1 Arg399Gln polymorphism and CRC risk in the population (Qin et al., 2015). Our results are inconsistent with the meta-analysis performed by Zeng et al., which 26 case-control studies with 6,979 cases and 11,470 controls were pooled in the meta-analysis. They have suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased risk of CRC in among high quality studies and in Asians, but not in Caucasians (Zeng et al. 2013). Lu et al, in a meta-analysis suggests that there is an obvious association between the XRCC1 Arg399Gln polymorphism and increased risk of CRC in East Asians (Lu et al., 2013). Wu et al, in an update meta-analysis suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased CRC (Wu et al., 2014).

Three polymorphisms in XRCC1 (Arg194Trp, Arg280His and Arg399Gln) have been frequently examined in the studies on cancer susceptibility. Liu et al. (Liu et al., 2013) included 22 case-control studies with a total of 6,291 CRC cases and 10,289 controls concerning the XRCC1 Arg399Gln polymorphism, 14 studies with a total of 4,814 CRC cases and 8,357 controls for Arg194Trp, seven studies with a total of 3,505 CRC cases and 4,636 controls for Arg280His. Their results suggested that these three SNPs evaluated are not associated with risk of CRC.

The statistically significant association between the XRCC1 Arg399Gln polymorphism and CRC risk was observed among studies with high quality and in all ethnicity. Sensitivity analyses by sequential omission of any individual studies not identified the significant association. Obviously, in all genetic models there were potential to moderate level heterogeneity. When we deleted 5 Asian studies which were not according to HWE any more, the heterogeneity of all genetic models was not decreased. Since the subjects came from different populations that perhaps have genetic heterogeneity, subgroup analyses were conducted on ethnicity. However, we found that ethnicity might not be the source of heterogeneity (Table 2). This further indicated that ethnicity and deviations from HWE might not be one source of heterogeneity. Other factors such as the sample sizes, diversity in study designs, inclusion criteria, and genotyping methods might be source of heterogeneity (Salanti et al., 2005).

Compared with two previous meta-analyses, our meta-analysis involved a remarkably larger number of studies and provided a more comprehensive and reliable conclusion. However, there are still some limitations in this meta-analysis. First, our meta-analysis included only studies with accessible full-text articles in English. Therefore, missing some otherwise eligible studies that were reported in other languages could lead to publication bias in the results. Second, lacking the original data for the included studies limited our further evaluation of potential interactions among gene-gene, gene-environment, or even different polymorphism loci of the same gene, which all may affect cancer risk. The joint effect between XRCC1 Arg399Gln and other repair genes genotypes on the risk of cancer was not addressed in the present study. However, the lack of individual data from the included studies limited the further evaluation of other potential interactions, as in other genes and environment factors. For instance, only two studies have reported the combined effect of XRCC1 Arg399Gln and other repair genes genotypes on the risk of cancer (Krupa et al., 2004; Kasahara et al., 2008; Wang et al., 2010). Third, due to the lack of detailed data in the primary articles, our results were based on single-factor estimates without adjustment for other risk factors such as age, gender, environmental factors and other variables, which might have caused serious confounding bias.

In summary, the meta-analysis suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased CRC, and the G allele probably acts as an important CRC risk factor.

References


polymorphism in intron 11 of the XPC gene plays a crucial role in the modulation of an individual’s susceptibility to sporadic colorectal cancer. *Mol Biol Rep*, 39, 527-534.


