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X-ray repair cross-complementing group 1 (XRCC1) plays an important role in base excision and single-strand break repair, as a scaffold protein that brings together proteins of the DNA repair complex, and appears to be a candidate for cancer risk. However, studies on the association between polymorphisms in this protein and cancer have yielded conflicting results. We performed a meta-analysis to investigate the association between the breast cancer and the XRCC1 polymorphisms Arg194Trp (9411 cases and 9783 controls), Arg399Gln (22 481 cases and 23 905 controls) and Arg280His (6062 cases and 5864 controls) in different inheritance models. Our analysis suggested that Arg399Gln was associated with a trend of increased breast cancer risk when using both dominant [odds ratio (OR) = 1.06, 95% confidence interval (CI): 1.00–1.13] and recessive models (OR = 1.12, 95% CI: 1.02–1.23) to analyse the data. In ethnic subgroups and using recessive model analysis: Arg399Gln increased breast cancer risk in Asians (OR = 1.26, 95% CI: 0.96–1.64) and Africans (OR = 1.80, 95% CI: 0.97–3.32), and also while only slightly increasing the breast cancer risk in Caucasians (OR = 1.08, 95% CI: 0.95–1.22). However, Arg194Trp (recessive model, OR = 0.95, 95% CI: 0.75–1.20) and Arg280His (recessive model, OR = 1.28, 95% CI: 0.64–2.55) did not appear to be risk factors for breast cancer. Larger scale primary studies are required to further evaluate the interaction of XRCC1 polymorphisms and breast cancer risk in specific populations.

Introduction

Vineis et al. (1) conducted meta-analyses of 241 associations between variants in DNA repair genes and cancer and found sparse association signals with strong epidemiological credibility. X-ray repair cross-complementing group 1 gene (XRCC1) is one of these DNA repair genes. XRCC1 is involved in the repair of DNA base damage and single-strand DNA breaks by binding DNA ligase III at its carboxyl and by binding DNA polymeraseβ and poly [adenosine diphosphate (ADP)-ribose] polymerase at the site of damaged DNA (2). Deletion of the XRCC1 in mice results in an embryonic lethal phenotype (3). Chinese hamster ovary cell lines with mutations in the XRCC1 have shown a reduced ability to repair single-strand breaks in DNA and concomitant cellular hypersensitivity to ionizing radiation and alkylating agents (4). XRCC1 plays an essential role in removing endogenous and exogenous DNA damage. Three polymorphisms in XRCC1 gene at codons 194 (Arg to Trp), 280 (Arg to His) and 399 (Arg to Gln) have been identified (5). These polymorphisms, involving an amino acid change at evolutionarily conserved regions, could alter the XRCC1 function. Codon 399 is located in the poly (ADP-ribose) polymerase-binding domain and within an identified BRCA1 COOH terminus domain (5). Previous studies reported that the XRCC1 399Gln allele was significantly associated with a higher level of DNA adducts and glycoporphin. A mutations in erythrocytes (6,7) increased sister chromatid exchange frequencies (8) and higher sensitivity to ionizing radiation (9). However, no association between Arg399Gln polymorphism and DNA adducts has been reported in other studies (7).

Analysis of case–control studies is the most prevalent method of investigating the association between a disease and a specific gene. However, studies on XRCC1 polymorphisms in breast cancer so far have provided conflicting results. Saadat et al. (10) observed that 399Gln allele may act as a recessive allele and increase the breast cancer risk [Gln/Gln versus (Arg/Arg + Gln/Gln)], OR = 2.31, 95% confidence interval (CI): 1.21–4.35, \(P = 0.010\). But Costa et al. (11) observed that women carriers of XRCC1 399Gln genotypes have a protective effect concerning breast cancer (OR = 0.54, 95% CI: 0.35–0.84; \(P = 0.006\). Loizidou et al. (12) found that homozygous XRCC1 399Gln carriers had an increased risk of breast cancer (OR = 4.68, 95% CI: 1.01–21.7; \(P = 0.03\), but many studies [Thyagarajan et al. (13)] concluded that there was no significant association between the disease and these polymorphisms. However, some of these studies were based on small sample numbers of cases and controls, so a meta-analysis of all available studies will help to establish a more convincing result, and subgroup analysis based on ethnic and other factors may also yield more meaningful results.

Here, we performed a meta-analysis including a subgroup analysis based on ethnicity and menopausal status and found that genotype Gln/Gln (Arg399Gln) might increase the risk of breast cancer regardless of ethnicity, and the homozygote genotype might specifically increase the risk of breast cancer in Asian women and African women. However, Arg194Trp and Arg280His polymorphisms might not be a risk factor for breast cancer.

Materials and methods

Selection of studies

All the case–control studies were identified by a computerized literature search of the PubMed, EBSCO and CGEMS database (prior to March 2009) using the following words and terms: ‘XRCC1’, ‘polymorphism’ and ‘breast cancer’. References of the retrieved publications were also screened. Only research articles were included and the language of publication was restricted to English. Studies had to be based on an unrelated case–control design, so pedigree data were excluded. The genotype distribution of the control population of the
studies had to be in Hardy–Weinberg equilibrium (HWE) \( (P > 0.05) \). Besides, we used the ‘Venice’ criteria (14) (Supplementary Table 1 is available at Mutagenesis Online) to evaluate the epidemiological significance of each study.

Data extraction

The following basic data were collected from the studies: first authors, journals, year of publications, ethnicities (categorized as Asians, Caucasians, Africans and not determined), amino types, ages and menopausal status.

Statistical analysis

For each study, the OR was first calculated to assess the association between the polymorphisms and the disease in Table I. In meta-analysis, we examined the association between allele Glu of Arg399Gln and the risk of breast cancer compared to that of allele Arg, as well as using additive (Gln/Gln versus Arg/Arg), recessive (Gln/Gln versus (Arg/Gln + Arg/Arg)) and dominant (Gln/Gln + Arg/Gln versus Arg/Arg) genetic models. The same method was applied to the other two polymorphisms. There are three widely used methods of meta-analysis for dichotomous outcomes: two fixed-effects methods (Mantel–Haenszel’s method and Petro’s method), which assume that studies are sampled from populations with the same effect size, making an adjustment to the study weights according to the in-study variance and one random-effects method (DerSimonian and Laird’s method), which assumes that studies are taken from populations with varying effect sizes, calculating the study weights both from the in-study and between-study variance, considering the extent of variation, or heterogeneity. In our study, both Mantel–Haenszel’s fixed-effects method and DerSimonian and Laird’s random-effects method were used in Stata 10.0 software. A chi-square-based Q-statistic test and an I\(^2\) test were both performed to evaluate the between-study heterogeneity of the studies. Venice criteria (14) for the I\(^2\) test included: \( I^2 < 25\% \) represents no heterogeneity, \( I^2 = 25–50\% \) represents moderate heterogeneity, \( I^2 = 50–75\% \) represents large heterogeneity and \( I^2 > 75\% \) represents extreme heterogeneity. So if \( P < 0.10 \) or \( P^2 > 25\% \), i.e. the between-study heterogeneity was considered to be significant, we choose the random-effects model to calculate the OR. Otherwise, when \( P > 0.10 \) and \( I^2 \leq 25\% \), i.e. the between-study heterogeneity was not significant, then the fixed-effects model was suitable. In the absence of between-study heterogeneity, the two methods yield similar results. In order to make a clear comparison, we present the OR of both the random-effects model and the fixed-effects model for every meta-analysis. A pooled OR obtained by meta-analysis was used to give a more reasonable evaluation of the association. A Z test was performed to determine the significance of the pooled OR \( (P \leq 0.05 \) suggests a significant OR). For each genetic comparison, subgroup analysis was performed according to racial descent and menopausal status. Funnel plots were used to access publication bias. Hardy–Weinberg equilibrium was tested by the chi-square test based on a programme (http://www.ihg.gsf.de/cgi-bin/hw/hwa1.pl). Analyses were performed by Stata 10.0 software.

Results

Eligible studies

Based on the search criteria, 37 studies were selected. Each subpopulation in these articles was treated as a separate study in our meta-analysis. Among all the eligible studies, 37 described the Arg399Gln polymorphism, 18 focused on Arg194Trp and 8 articles investigated on Arg280His. We extracted the eligible data, rejected datasets where HWE was very doubtful. All the studies were published from January 2000 to January 2009. Populations were divided into four ethnic categories: Caucasians, Asians, Africans and not determined (Table I).

Meta-analysis database

Table I shows the details of the cases and controls in the included studies, together with the ORs we calculated to make a primary evaluation. Supplementary Table 2 (available at Mutagenesis Online) is the summary of the meta-analysis of case–control studies examining the association between XRCC1 polymorphisms and breast cancer risk, with the comparison between different ethnicities, and between the combined studies and the studies excluding subjects not in HWE (Figure 1).

Arg399Gln

There are 37 studies (22 481 cases and 23 905 controls) analysing the relation of XRCC1 Arg399Gln polymorphism and the risk of breast cancer. For each study, we investigated the association between Arg399Gln XRCC1 polymorphism and breast cancer risk, assuming different inheritance models of the 399Gln allele (Supplementary Table 2 is available at Mutagenesis Online). We did not use five studies that were not in HWE. In the dominant model of Gln Arg399Gln, there was between-study heterogeneity in the odds ratios (ORs) of individual studies \( (\chi^2 = 63.68, I^2 = 43.5\%, P = 0.002) \), so we analysed the data using the random-effect model and found that Gln Arg399Gln has a weak correlation with the risk of breast cancer \( (OR = 1.06, 95\% CI: 1.00–1.13) \). Meanwhile, when we analysed the data regarding the occurrence of XRCC1 Arg399Gln polymorphism and breast cancer using the recessive model and there was between-study heterogeneity in the ORs \( (\chi^2 = 61.30, I^2 = 41.3\%, P = 0.003) \), so we took the result from the analysis based on the random-effect model. The results of our meta-analysis showed that Gln Arg399Gln was slightly related with breast cancer \( (OR = 1.12, 95\% CI: 1.02–1.23) \) (Figure 1).

While we analysed the relationship of Arg399Gln polymorphisms and breast cancer in different ethnic subgroups, we excluded published studies that were not in HWE. Four articles dealing with Asians had no between-study heterogeneity \( (\chi^2 = 2.01, P = 0\%, P = 0.571) \), so we analysed the data using the fixed-effect model and found that Gln Arg399Gln [Gln/Gln versus (Arg/Gln + Arg/Arg)] increased the risk of breast cancer in Asians \( (OR = 1.26, 95\% CI: 0.96–1.64) \). Three articles dealing with Africans had no between-study heterogeneity \( (\chi^2 = 0.03, I^2 = 0\%, P = 0.896) \), and in the fixed-effect model meta-analysis, Gln Arg399Gln [Gln/Gln versus (Arg/Gln + Arg/Arg)] was also related with the occurrence of breast cancer \( (OR = 1.80, 95\% CI: 0.97–3.32) \). Fourteen articles dealing with Caucasians had between-study heterogeneity \( (\chi^2 = 20.61, I^2 = 36.9\%, P = 0.081) \), so we used the random-effect model. The results of meta-analysis showed that Gln Arg399Gln is weakly related with breast cancer \( [Gln/Gln versus (Arg/Gln + Arg/Arg), OR = 1.08, 95\% CI: 0.95–1.22] \).

We also analysed Arg399Gln polymorphism in pre-menopausal and post-menopausal subgroups (data not shown). Menopausal state did not influence the relation between the Arg399Gln polymorphism and the risk of breast cancer. However, few studies investigated the role of menopausal state and the number of studies may be too small to make a strong conclusion.

Arg194Trp

There are 18 studies (9411 cases and 9783 controls) analysing the relation between XRCC1 Arg194Trp polymorphism and the risk of breast cancer, but one study \( [\text{Zhang et al}. (32)] \) was not in HWE, so we excluded this study. In the recessive model of Trp Arg194Trp, there is no between-study heterogeneity between ORs of individual studies \( (\chi^2 = 11.52, I^2 = 0\%, P = 0.776) \), so we pooled the results using the fixed-effect model and found that Trp Arg194Trp was not related with breast cancer \( (OR = 0.95, 95\% CI: 0.75–1.20) \). Meanwhile, when we analysed the dominant of model of Arg194Trp, there was no between-study heterogeneity among ORs based on chi-square-based Q-statistic test \( (\chi^2 = 23.32, I^2 = 27.1\%, P = 0.105) \). But on \( I^2 \) test, there was moderate heterogeneity among ORs.
<table>
<thead>
<tr>
<th>Author et al.</th>
<th>Year</th>
<th>Population</th>
<th>Genotype distribution</th>
<th>OR (95% CI) Case</th>
<th>OR (95% CI) Control</th>
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<tr>
<td>Duell et al. (15)</td>
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<td>Smith et al. (20)</td>
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**ND**, not determined.

*The studies are not in HWE.
so we took the random-effect model and found that Trp Arg194Trp was not related with breast cancer (OR = 1.02, 95% CI: 0.93–1.16). This result was similar with the result of fixed-effect model (OR = 1.02, 95% CI: 0.93–1.11).

While we analysed Arg194Trp polymorphism in stratified ethnic subgroups, there was still no evidence that Arg194Trp had risk relation with breast cancer. The OR values [TrpTrp versus (ArgTrp + ArgArg)] of Asians, Caucasians and Africans were 0.85 (95% CI: 0.64–1.12), 0.91 (95% CI: 0.57–1.44) and 0.59 (95% CI: 0.098–3.52), respectively (Supplementary Table 2 is available at Mutagenesis Online).

**Arg280His**

There are eight studies (6062 cases and 5864 controls) analysing the relation of XRCC1 Arg280His polymorphism and the risk of breast cancer. But one study [Loizidou et al. (12)] is not in HWE, so we excluded this study. In the dominant model analysis of His Arg280His, there was between-study heterogeneity among ORs of individual studies ($\chi^2 = 10.83$, $I^2 = 35.4\%$, $P = 0.094$), so we pooled the results using the random-effect model and found that His Arg280His was not a risk factor for breast cancer (OR = 1.10, 95% CI: 0.91–1.34). Meanwhile, when we analysed the

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**Fig. 1.** Meta-analyses for XRCC1 polymorphisms and breast cancer: each study is represented by a point estimate of the OR and the accompanying 95% CIs. (A) Comparison: Arg399Gln, GlnGln versus (ArgArg + ArgGln); outcome: combined population; random-effect model. (B) Comparison: Arg194Trp, TrpTrp versus (ArgArg + ArgTrp); outcome: combined population; fixed-effect model. (C) Comparison: Arg280His, HisHis versus (ArgArg + ArgHis); outcome: combined population; fixed-effect model. (D) Comparison: Arg399Gln, GlnGln versus (ArgArg + ArgGln); outcome: Asians; fixed-effect model. (E) Comparison: Arg399Gln, GlnGln versus (ArgArg + ArgGln); outcome: Africans; fixed-effect model. (F) Comparison: Arg399Gln, GlnGln versus (ArgArg + ArgGln); outcome: Caucasians; random-effect model. *The weight is displayed in a percentage form, not the real weight in the calculation of the pooled OR. The calculation of the weight for every study was different in the fixed-effects model and in the random-effects model. Weight_{MH} = \frac{W_i}{\sum_i W_i}$, Weight_{DL} = \frac{W_i}{\sum_i W_i + \sum_i \Delta_i^2}$, where MH, Mantel–Haenszel method, DL, DerSimonian and Laird method, $i$ was the number of the study, $a$ was the population of the case with intervention, $b$ was the population of the case without intervention, $c$ was the population of the control with intervention and $d$ was the population of the control without intervention. $N$ was the total number of cases and controls and $\Delta^2$ was the between-study variance of all the eligible studies. The pooled OR was influenced by the weights.
recessive model of XRCC1 Arg280His, there was no between-study heterogeneity among ORs ($\chi^2 = 4.89, I^2 = 0\%$, $P = 0.558$). And we found that His Arg280His was also not a risk factor for breast cancer (OR = 1.28, 95% CI: 0.64–2.55) Figure 2.

**Publication bias**

Funnel plots and Egger’s test were performed to assess publication bias (Figure 2, we discard the studies not in HWE). The data suggested that there might be publication bias for the comparison of 399Gln versus 399Arg ($t = 2.96, P = 0.006$). However, when we stratified 399Gln versus 399Arg according to different ethnic groups, there was no publication bias in each subgroup: Caucasians ($t = 0.88, P = 0.394$), Asians ($t = -0.54, P = 0.641$) and Africans ($t = -0.97, P = 0.511$). There was no publication bias for the comparison of 194Trp versus 194Arg ($t = 1.79, P = 0.093$) and 280His versus 280Arg ($t = 0.26, P = 0.802$) Figure 3.

**Discussion**

XRCC1 is very important for efficient base excision and single-strand break repair. The interactions of XRCC1 and its substrate result in assembly of the repair complex at the site of damage and regulate the activity of several repair enzymes, particularly poly (ADP-ribose) polymerase 1 (PARP1), ligase III and polynucleotide kinase 3'-phosphatase (2). Cells of rodents lacking XRCC1 are very sensitive to genotoxins and show increased genetic instability (2,42). A recent report provides data showing that the E2F1 transcription factor regulates XRCC1 and promotes DNA repair (43). A XRCC1 deletion mutation in null homozygous mice is embryonic lethal (3). XRCC1 has two BRCA1 carboxyl-terminal (BRCT) domains (BRCT1 and BRCT2), located centrally and at the C-terminal end, respectively (Figure 3). BRCT2 is responsible for binding and stabilizing DNA ligase III and is required for single-strand breaks and gaps repair (SSBR), specifically
during the G0/G1 phases of the cell cycle (44). The centre of BRCT1 domain binds to and down-regulates the single-strand breaks and gaps recognition protein PARP1 and is required for efficient SSBR during both G1 and S/G2 phases of the cell cycle. The polymorphism Arg399Gln is located close to BRCT1’s C-terminal boundary. The mutation in this domain will change XRCC1’s structure and maybe disrupt the combination of BRCT1 and PARP1. Arg194Trp and Arg280His are located in a domain that separates but connects the XRCC1 NH2 terminal and BRCT. These mutations will also change XRCC1’s structure but maybe not influence the function of XRCC1.
In the synopsis of Vineis et al. (1), there are >10,000 subjects in the study dealing with association of XRCC1 codons 194 and 399 and breast cancer and 1000–10,000 subjects dealing with the association of XRCC1 codon 280 and breast cancer. Vineis et al. (1) proposed that cancers at several sites may be associated with variants in the same genes, in particular ERCC2, XRCC1, XRCC3 and TP53, though some of these associations had weak credibility. Investigators from the Breast Cancer Association Consortium (41) reported that there was no evidence of an association of breast cancer with the XRCC1 Arg399Gln polymorphism. However, they based their conclusion on a small number of samples (9451 controls and 9510 cases). In a large meta-analysis (20,837 patients and 22,879 controls), Saadat et al. (45) concluded that the XRCC1 codon 399 polymorphism was associated with breast cancer risk in studies from Asian countries (recessive model, OR = 1.49, 95% CI: 1.22–1.81) but not in studies from Western countries (recessive model, OR = 0.99, 95% CI: 0.91–1.08). From our meta-analysis, Arg399Gln in the combined population was associated with a trend of increased breast cancer risk, regardless of ethnic subgroups division. Based on our results, individuals who have the Gln allele were
more likely to have breast cancer (dominant model: OR = 1.06, 95% CI: 1.00–1.13; recessive model: OR = 1.12, 95% CI: 1.02–1.23). Furthermore, in the recessive model analysis of stratified subgroups, Arg399Gln had a higher risk correlation with breast cancer in the Asians (OR = 1.26, 95% CI: 0.96–1.64) and Africans (OR = 1.80, 95% CI: 0.97–3.32) than in Caucasians (OR = 1.08, 95% CI: 0.95–1.22). Previously, it was reported that XRCC1 Arg399Gln was associated with lung cancer among Asians, but not among individuals from Western countries (46). In our study, genotypes and allele frequencies of cases and controls of Arg399Gln allele Gln had a higher presentation in Caucasians (36%) than in Asians and Africans (28 and 17%, respectively). There is an obvious publication bias between the total Arg399Gln codon 399 studies, but when we stratified the studies into different ethnic subgroups, the publication bias disappeared (Figure 2). Moreover, though there was moderate heterogeneity between the combined studies of XRCC1 Codon399, when we analysed the Arg399Gln polymorphism in different ethnic subgroups, the between-study heterogeneity decreased markedly. These results suggest that the publication bias and heterogeneity may be partly due to the variable effects of stratified ethnic subgroups, and some genetic polymorphisms may be associated with risk of some diseases in a specific ethnic subgroup.

In conclusion, the research of the relationship of XRCC1 polymorphisms and breast cancer is very popular but conflicting (47,48) at present. Our meta-analysis suggested that both under recessive and dominant models, the Arg399Gln polymorphism associates with an increased risk of breast cancer. The menopausal status did not affect the association of the Arg399Gln polymorphism with breast cancer. Arg194Tnp and Arg280His had no obvious association with breast cancer. According to the Venice criteria (14), our meta-analysis dealing with the association of the three polymorphisms and breast cancer belongs to the category of large-scale evidence and is highly stringent to the requirements of replication and protection from bias. However, the studies included in the subgroups analysis are limited and the results are sensitive to study selection. More comparative studies are needed to evaluate interactions of XRCC1 polymorphisms and breast cancer risk in specific populations.

**Supplementary data**

Supplementary Tables 1 and 2 are available at Mutagenesis Online.

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