Original Article
Lack of an association between XRCC2 R188H polymorphisms and breast cancer: an update meta-analysis involving 35,422 subjects

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Abstract: Purpose: Several studies have investigated the associations between XRCC2 R188H polymorphism and the susceptibility to breast cancer, but the results have been inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed. Methods: PubMed and China National Knowledge Infrastructure (CNKI) searches were carried out for relevant studies published before March 2015. Meta-analysis was performed with the Stata, version 11.0. Results: A total of 17 case-control studies, including 17,986 cases and 17,436 controls, were selected. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association in the homozygous model, dominant model, and recessive model. When all the studies were pooled into the meta-analysis, there was no evidence showing a significant association between XRCC2 R188H polymorphism and breast cancer risk (for homozygous model, OR=0.84, 95% CI=0.62-1.14; for dominant model: OR=0.76, 95% CI=0.53-1.09; and for recessive model: OR=1.04, 95% CI=0.98-1.10). In the subgroup analysis by ethnicity, no significant association was found between the polymorphism and breast cancer risk. Conclusions: In conclusion, this meta-analysis indicates that the XRCC2 R188H polymorphism is not a risk factor for developing breast cancer.

Keywords: XRCC2, polymorphism, breast cancer, susceptibility, meta-analysis

Introduction
Breast cancer is the most frequently diagnosed cancer among females [1]. The mechanism of breast carcinogenesis is still not fully understood. It is well established that breast cancer is induced by many endogenous and exogenous factors, such as the level of hormones and different genetic backgrounds [2]. Family studies found that the risk for those with first-degree relatives of affected individuals is more than two times higher than the risk of general population [3], confirming a strong genetic component underlying the etiology of breast cancer [4].

Evidence is converging supporting the central role of DNA damage in progression to breast cancer. It has been demonstrated that accumulation of unrepairped double-strand DNA breaks (DSB) can cause cell death and initiate malignancies [5]. Exposure to ionizing radiation, which can cause DSBs, increased the risk of developing breast cancer [6]. Homologous recombination (HR) and non-homologous end joining are two major mechanisms for the repair of DNA DSB, and genes involved in these repair pathways are predicted to have a genomic caretaker’s role [7]. X-ray repair cross-complementing (XRCC) group 2 is the member of the family of RAD51-related proteins that participate in HR [8]. Recently, several studies have focused on the influence of polymorphisms in the XRCC2 gene on genomic instability and tumorigenesis. There is a G to A transition located in exon 3 of the XRCC2 gene resulting in a substitution of histidine (His) by arginine (Arg), known as R188H (Arg188His, rs3218536), this polymorphism has been widely investigated to explore its potential impact on cancer susceptibility.

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XRCC2 polymorphism is not associated with breast cancer risk

A previous meta-analysis had reported the association between XRCC2 R188H polymorphism and breast cancer risk, whereas only twelve studies included in the analysis and some of these studies were departure from Hardy-Weinberg equilibrium, led to its limitation and the unexplained heterogeneity might reduce the validity of the conclusion [9]. Recently, there were some new literatures to evaluate the impact of the XRCC2 R188H polymorphism on the risks of breast cancer, so we conducted the update meta-analysis to draw a more concrete result.

Materials and methods

Studies identification

To identify all studies that examined the association of XRCC2 R188H polymorphisms with breast cancer, we conducted a literature search of the PubMed and China National Knowledge Infrastructure (CNKI) database, without a language limitation, covering all papers published up to March 2015, using the following keywords and subject terms: XRCC2, polymorphism, and breast cancer. We evaluated potentially relevant publications by checking their titles and abstracts, and then obtained the most relevant publications for a detailed examination. Furthermore, the reference lists of the selected papers were also screened for other potential articles that possibly have been missed in the initial search. Only published studies with full-text articles were included.

Selection criteria

The following criteria were used to select literature for the background to further meta-analysis: (a) studies concerning the association between XRCC2 R188H and breast cancer; (b) case-control studies; (c) papers presenting the breast cancer diagnoses and the sources of cases and controls; (d) sufficient information to estimate odds ratios (ORs) and their 95% confidence intervals (CIs). Accordingly, the following exclusion criteria were also used: (a) the design and the definition of the experiments were obviously different from the others of the selected papers; (b) reviews and duplicated publications. After searching, we reviewed all papers in accordance with the criteria defined above for further analysis.

Data extraction

Data were carefully extracted from all eligible publications independently by two investigators according to the inclusion criteria mentioned above. For conflicting evaluations, an agreement was reached following discussion. The following data was collected from each study: first author’s name, year of publication, country of origin, ethnicity, control source (hospital-based or population-based) and numbers of cases and controls for each genotype. Studies containing two or more case-control groups were considered as two or more independent studies.

Statistical analysis

Firstly, the Hardy-Weinberg equilibrium (HWE) was assessed by Fisher’s exact test for each study in controls. Crude ORs with 95% CIs were used to assess the strength of association between the XRCC2 R188H polymorphism and breast cancer risk. A Chi-square-based Q statistic test was performed to assess heterogeneity. A P value greater than 0.05 for the Q-test indicates lack of heterogeneity among studies, so the pooled OR was calculated by the fixed-effects model (the Mantel-Haenszel method [10]). Otherwise, the random-effects model (the DerSimonian and Laird method [11]) was used. The pooled ORs were performed for homozygote comparisons (GG vs. AA), dominant model (GG+GA vs. AA) and recessive models (GG vs. GA+AA), respectively. Publication bias was assessed by visual inspection of funnel plots [12], in which the standard error of log(OR) of each study was plotted against its log(OR). An asymmetric plot indicates a possible publication bias. The symmetry of the funnel plot was further evaluated by Egger’s linear regression test (P<0.05 was considered representative of statistically significant publication bias) [13]. Statistical analysis was performed using the program STATA version 11.0 (Stata Corporation, College Station, TX). All statistical analyses were two sided and P<0.05 was considered significant.

Results

Study characteristics

Through literature search and selection based on the inclusion criteria, a total of 17 publica-
XRCC2 polymorphism is not associated with breast cancer risk

Table 1. Main characteristics of all studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Controls</th>
<th>Case</th>
<th>Control</th>
<th>GG</th>
<th>GA</th>
<th>AA</th>
<th>GG</th>
<th>GA</th>
<th>AA</th>
<th>HWE (P)</th>
</tr>
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<td>Qureshi</td>
<td>2014</td>
<td>Pakistan</td>
<td>Asian</td>
<td>PB</td>
<td>156</td>
<td>150</td>
<td>131</td>
<td>20</td>
<td>5</td>
<td>137</td>
<td>12</td>
<td>1</td>
<td>0.217</td>
</tr>
<tr>
<td>Alexandra</td>
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<td>Russian</td>
<td>Caucasian</td>
<td>HB</td>
<td>659</td>
<td>656</td>
<td>594</td>
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<td>0</td>
<td>587</td>
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<td>Poland</td>
<td>Caucasian</td>
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<td>70</td>
<td>12</td>
<td>8</td>
<td>50</td>
<td>18</td>
<td>40</td>
<td>12</td>
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<tr>
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<td>HB</td>
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<td>166</td>
<td>280</td>
<td>160</td>
<td>184</td>
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<td>197</td>
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<td>207</td>
<td>13</td>
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<td>708</td>
<td>182</td>
<td>344</td>
<td>174</td>
<td>172</td>
<td>376</td>
<td>160</td>
<td>0.097</td>
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<td>314</td>
<td>290</td>
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<td>42</td>
<td>42</td>
<td>254</td>
<td>36</td>
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<td>4384</td>
<td>3590</td>
<td>610</td>
<td>32</td>
<td>3639</td>
<td>711</td>
<td>34</td>
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<td>Caucasian</td>
<td>PB</td>
<td>1108</td>
<td>1177</td>
<td>972</td>
<td>135</td>
<td>1</td>
<td>999</td>
<td>177</td>
<td>1</td>
<td>0.016</td>
</tr>
<tr>
<td>Brooks</td>
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<td>USA</td>
<td>Caucasian</td>
<td>NA</td>
<td>602</td>
<td>602</td>
<td>515</td>
<td>83</td>
<td>4</td>
<td>519</td>
<td>78</td>
<td>5</td>
<td>0.283</td>
</tr>
<tr>
<td>Montserrat</td>
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<td>USA</td>
<td>Caucasian</td>
<td>PB</td>
<td>1770</td>
<td>1402</td>
<td>1496</td>
<td>264</td>
<td>10</td>
<td>1177</td>
<td>214</td>
<td>11</td>
<td>0.711</td>
</tr>
<tr>
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<td>Poland</td>
<td>Caucasian</td>
<td>PB</td>
<td>1981</td>
<td>2280</td>
<td>1763</td>
<td>212</td>
<td>6</td>
<td>1983</td>
<td>281</td>
<td>16</td>
<td>0.085</td>
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<tr>
<td>Millikan</td>
<td>2005</td>
<td>USA</td>
<td>African</td>
<td>PB</td>
<td>765</td>
<td>678</td>
<td>744</td>
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<td>0</td>
<td>653</td>
<td>25</td>
<td>0</td>
<td>0.625</td>
</tr>
<tr>
<td>Millikan</td>
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<td>USA</td>
<td>Caucasian</td>
<td>PB</td>
<td>1268</td>
<td>1134</td>
<td>1084</td>
<td>176</td>
<td>8</td>
<td>982</td>
<td>145</td>
<td>7</td>
<td>0.516</td>
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<tr>
<td>Webb</td>
<td>2005</td>
<td>Australia</td>
<td>Caucasian</td>
<td>PB</td>
<td>1447</td>
<td>783</td>
<td>1251</td>
<td>187</td>
<td>9</td>
<td>675</td>
<td>101</td>
<td>7</td>
<td>0.145</td>
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<tr>
<td>Han</td>
<td>2004</td>
<td>USA</td>
<td>Caucasian</td>
<td>NA</td>
<td>952</td>
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<td>811</td>
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<td>7</td>
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<td>165</td>
<td>6</td>
<td>0.887</td>
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<tr>
<td>Rafii</td>
<td>2002</td>
<td>UK</td>
<td>Caucasian</td>
<td>PB</td>
<td>519</td>
<td>398</td>
<td>431</td>
<td>82</td>
<td>6</td>
<td>351</td>
<td>45</td>
<td>2</td>
<td>0.670</td>
</tr>
<tr>
<td>Kuschel</td>
<td>2002</td>
<td>UK</td>
<td>Caucasian</td>
<td>PB</td>
<td>1725</td>
<td>1811</td>
<td>1476</td>
<td>234</td>
<td>15</td>
<td>1538</td>
<td>267</td>
<td>6</td>
<td>0.117</td>
</tr>
<tr>
<td>Silva</td>
<td>2010</td>
<td>Portugal</td>
<td>Caucasian</td>
<td>HB</td>
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<td>548</td>
<td>243</td>
<td>46</td>
<td>0</td>
<td>445</td>
<td>103</td>
<td>0</td>
<td>0.015</td>
</tr>
</tbody>
</table>

PB: population based; HB: hospital based; NA: not available.

Meta-analysis results

To summarize the published data, we did a comprehensive meta-analysis. The overall data shown that the individuals who carried the GG genotype did not have a significantly increased breast cancer risk compared with those who carried the AA genotype for homozygous model, OR=0.84, 95% CI=0.62-1.14, (Figure 1); no significant association was found in the dominant model (OR=0.76, 95% CI=0.53-1.09) or the recessive model (OR=1.04, 95% CI=0.98-1.10). Then, the 17 studies were analyzed according to ethnicity. In the subgroup analysis based on ethnicity, no significant associations were detected too. The main results of the meta-analysis were listed in Table 2.

Sensitive analysis

Sensitivity analyses were conducted to determine whether modification of the inclusion criteria of the meta-analysis affected the final results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not materially altered (Figure 2), indicating that our results were statistically robust.

Publication bias

Begg’s funnel plots and Egger’s tests were performed to assess publication bias. The shapes of the funnel plots revealed no obvious asymmetry (Figure 3). The Egger’s test was then used to statistically assess funnel plot symmetry. The results suggested no evidence of publication bias (P=0.575 for homozygous model). Results of recessive and additive model showed no significant publication bias either (data not shown).
XRCC2 polymorphism is not associated with breast cancer risk

Discussion

Previous study have reported conflicting results about the association between XRCC2 R188H polymorphism and the risk of breast cancer, which might have been influenced by the relatively small sample size and different genetic backgrounds in these studies. Meta-analysis is a powerful method for resolving inconsistent finding with a relatively large number of subjects. In this meta-analysis, we involved a total of 17,986 cases and 17,436 controls from 17

Figure 1. Forest plot of OR of breast cancer risk associated with XRCC2 R188H polymorphism for GG vs. AA. Horizontal lines represent 95% confidence intervals. Each square represents the OR point estimate and its size is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with confidence interval given by its width. The unbroken vertical line is at the null value (OR=1.0).

Table 2. Summary of ORs for XRCC2 R188H polymorphism and breast cancer risk

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Homozygous</th>
<th>Dominant</th>
<th>Recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>Ph</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>14</td>
<td>0.86 (0.60-1.25)</td>
<td>0.01</td>
<td>0.78 (0.49-1.25)</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>0.59 (0.18-1.91)</td>
<td>0.19</td>
<td>0.62 (0.21-1.85)</td>
</tr>
<tr>
<td>African</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>0.84 (0.62-1.14)</td>
<td>0.02</td>
<td>0.76 (0.53-1.09)</td>
</tr>
</tbody>
</table>

Ph: P value for the heterozygous analysis; NA: not available.
XRCC2 polymorphism is not associated with breast cancer risk

that the polymorphism was not significantly associated with breast cancer risk. And in the subgroup analysis by ethnicity, we did not find any association between the polymorphism and breast cancer risk.

XRCC2, located on 7q36.1, is an essential part of the homologous recombination repair (HRR) pathway and a functional candidate for involvement in tumor progression [8]. Common variants within XRCC2, particularly a coding SNP in exon 3 (R188H, rs3218536), have been identified as potential cancer susceptibility loci. Rafii et al. reported that the XRCC2 codon 188 His showed a slight decrease in repair of DNA damage induced by mitomycin C compared with the Arg allele [32]. This polymorphism had been shown to be associated with an increased risk of pharyngeal cancer [33], while it could reduce the risk of bladder cancer [34] and ovarian cancer [35]. So the polymorphism plays different role in different tumor.

There are some limitations to this meta-analysis. First, only published studies were included in the meta-analysis. It is possible that some related unpublished studies and investigated the associations between XRCC2 R188H polymorphism and breast cancer risk.

In the previous study by Yu et al [31], the publications inconsistent with HWE were also included in the meta-analysis which might result in potential bias. And in other analysis, He et al used some data without the original publication [9]. In this study, we excluded the publications which depart from HWE and the data without original publication, our results indicated...

Figure 2. Sensitivity analysis on the association between the XRCC2 R188H polymorphism and susceptibility of breast cancer (GG vs. AA). Horizontal line, the summary of the results as each study was deleted.

Figure 3. Begg’s funnel plot of XRCC2 R188H and breast cancer risk (GG vs. AA).
XRCC2 polymorphism is not associated with breast cancer risk

investigate the association of the polymorphism with breast cancer susceptibility. However, our meta-analysis also had some advantages. First, a substantial number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication bias was detected; indicating that the pooled result should be reliable.

Conclusions

In conclusion, this meta-analysis indicates that the XRCC2 R188H polymorphism is not a risk factor for the development of breast cancer. However, it is necessary to conduct large sample studies using standardized unbiased genotyping methods, homogeneous breast cancer patients and well-matched controls.

Acknowledgements

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Disclosure of conflict of interest

None.

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References


