Genetic Polymorphisms in Base-Excision Repair Pathway Genes and Risk of Breast Cancer

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Abstract

Impaired base-excision repair (BER) function can give rise to the accumulation of DNA damage and initiation of cancer. We evaluated whether genetic variation in six BER pathway genes (XRCC1, ADPRT, APEX1, OGG1, LIG3, and MUTYH) is associated with breast cancer risk in two large population-based case-control studies in the United States (3,368 cases and 2,880 controls) and Poland (1,995 cases and 2,296 controls). A detailed evaluation was first done in a subset of 1,898 cases and 1,514 controls with mouthwash DNA samples in the U.S. study. Significant findings were followed up in the remainder of the U.S. study population that provided cytobrush DNA samples and in the Polish study. Using data from U.S. and Polish study participants with mouthwash DNA, we found no significant overall association between breast cancer risk and XRCC1 R280H and R194W, ADPRT V726W, APEX1 D148E, OGG1 S326C, LIG3 R780H, or MUTYH 5′ untranslated region. These data suggested a decreased risk for XRCC1 Q399R homozygous variants compared with homozygous wild-type in premenopausal women, but these findings were not confirmed when data from cytobrush DNA samples were added [combined odds ratio (OR), 0.8; 95% confidence interval (CI), 0.6-1.1] or in the Polish study (OR, 1.0; 95% CI, 0.7-1.5). Meta-analyses based on our data and published data from studies of two single nucleotide polymorphisms in XRCC1 showed no evidence of an overall association between breast cancer risk and homozygous variants versus wild-type for Q399R (OR, 1.1; 95% CI, 1.0-1.2) or R194W (OR, 1.0; 95% CI, 0.7-1.8), although there was a suggestion for an association in Asian populations for R194W (OR, 1.6; 95% CI, 1.1-2.4; P = 0.02). In conclusion, our results do not support that the polymorphisms evaluated in six BER pathway genes play a major role in breast carcinogenesis, particularly in Caucasian populations. (Cancer Epidemiol Biomarkers Prev 2006;15(2):353–8)

Introduction

Genetic variation in DNA repair genes could cause altered DNA repair function, resulting in accumulation of DNA damage, followed by programmed cell death (apoptosis) or unregulated cell growth and cancer. Base-excision repair (BER) is an important DNA repair pathway responsible for the repair of base damage resulting from x-rays, oxygen radicals, and alkylating agents (1-3). Two major processes are included in BER: releasing the damaged base by DNA glycosylases and poly(ADP-ribose) polymerase in BER (5-8). Two common genetic polymorphisms in XRCC1 (Q399R and R194W) have been evaluated in relation to breast cancer risk in several previous studies (9-20). The results, however, have been inconsistent. It has also been suggested that the relationship between XRCC1 Q399R and R194W and breast cancer risk might be modified by ethnicity or by family history (9-19). Polymorphisms of other genes in the BER pathway and breast cancer risk have been less explored. For this project, we analyzed eight SNPs in six BER genes (XRCC1, ADPRT, APEX1, OGG1, LIG3, and MUTYH) in one of the largest population-based case-control studies of breast cancer conducted to date, which includes 3,368 cases and 2,880 controls in the United States. We also evaluated polymorphisms in XRCC1 Q399R in a case-control study of 1,995 cases and 2,296 controls in Poland.

Materials and Methods

Study Population

The U.S. Breast Cancer Study. Eligible cases were English-speaking female residents of Wisconsin, western Massachusetts, or New Hampshire; of ages 20 to 74 years; and with a recent primary diagnosis of invasive or in situ breast cancer reported to the states’ mandatory cancer registries between...
1998 and 2001. Controls were randomly selected from population lists (licensed motor vehicle drivers for women of ages 20-64 years and Medicare beneficiaries for women of ages 65-74 years) in each state and frequency matched by 5 year categories to the age distribution of the cases. Women provided a telephone interview, covering known and suspected risk factors for breast cancer, and were invited to participate in a buccal cell collection at the end of the interview. Initially, buccal cells were collected using two buccal cytobrushes (June 1998-December 1999) with the collection method later changed to a mouthwash protocol to improve DNA quality (January 2000-March 2001). Samples were returned to a National Cancer Institute (NCI)-affiliated laboratory for processing. Collection, storage, and DNA isolation procedures have been previously described (21). The study was reviewed and approved by local institutional review boards (IRB) and the NCI IRB. All participants provided written informed consent.

Approximately 80% of eligible breast cancer cases and 75% of eligible controls completed the interview. Respective participation rates for buccal cell collection in cases and controls who completed the interview were 73% and 64% for cytobrush samples and 71% and 61% for mouthwash samples. Because of insufficient DNA quantity or quality, 596 of 2,097 cases and 588 of 1,993 controls with a cytobrush sample and 22 of 1,986 cases and 14 of 1,573 controls with a mouthwash sample were excluded from genotype analyses. To limit heterogeneity, analyses were further restricted to Caucasian women, mostly of central European ancestry, resulting in a total of 1,470 cases (1,311 invasive and 159 in situ) and 1,366 controls with cytobrush DNA and 1,898 cases (1,061 invasive and 237 in situ) and 1,514 controls with mouthwash DNA samples included in the analyses.

The Polish Breast Cancer Study. Eligible cases were women 20 to 74 years of age, residents of Warsaw and Lodz in Poland, and newly diagnosed with either histologically or cytologically confirmed in situ or invasive breast cancer between January 2000 and January 2003. Cases were recruited through a rapid identification system organized at participating hospitals. The Cancer Registry in Warsaw was used to identify the eligible cases missed by the rapid case identification system in each hospital. The Polish Electronic System, a database with demographic information from all residents of Poland, was used to randomly select controls stratified by city and age in 5 year categories on a quarterly basis from January 2000 to September 2003. Women provided a personal interview on known and suspected risk factors. Venous blood samples were collected by a trained nurse and DNA was isolated from buffy coat or whole blood samples. The study protocol was reviewed and approved by local and NCI IRBs. All participants provided written informed consent. Of the 3,037 eligible cases and 3,639 controls, 2,386 (79%) cases and 2,502 (69%) controls who completed the interview were 73% and 64% for cytobrush samples and 71% and 61% for mouthwash samples. Because of insufficient DNA quantity or quality, 596 of 2,097 cases and 588 of 1,993 controls with a cytobrush sample and 22 of 1,986 cases and 14 of 1,573 controls with a mouthwash sample were excluded from genotype analyses. To limit heterogeneity, analyses were further restricted to Caucasian women, mostly of central European ancestry, resulting in a total of 1,470 cases (1,311 invasive and 159 in situ) and 1,366 controls with cytobrush DNA and 1,898 cases (1,061 invasive and 237 in situ) and 1,514 controls with mouthwash DNA samples included in the analyses.

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Results

As shown in Table 1, analysis of data from mouthwash DNA samples in the U.S. study participants (1,470 cases and 1,366 controls) showed no significant association between XRCC1 Q399R and R194W. Peer-reviewed studies published in June 2005 in English on the relationship between XRCC1 and breast cancer risk were located using PubMed. Crude ORs and 95% CIs were calculated for all studies using published frequencies for cases and controls by the genotype of interest. Analyses were conducted overall and separately in Caucasian and Asian women. A random-effect model (24) in STATA (Version 8.2, Special Edition) was employed to estimate summary ORs and 95% CIs by weighing each study result by a factor of within- and between-study variance. Homogeneity of study results in different groups was assessed by the Q test and publication bias by Begg’s test (25) and Egger’s test (26).

Meta-analyses. Meta-analyses were done to summarize our findings along with those of published studies of the association between breast cancer risk and two polymorphisms in XRCC1 (Q399R and R194W). Peer-reviewed studies published in June 2005 in English on the relationship between XRCC1 and breast cancer risk were located using PubMed. Crude ORs and 95% CIs were calculated for all studies using published frequencies for cases and controls by the genotype of interest. Analyses were conducted overall and separately in Caucasian and Asian women. A random-effect model (24) in STATA (Version 8.2, Special Edition) was employed to estimate summary ORs and 95% CIs by weighing each study result by a factor of within- and between-study variance. Homogeneity of study results in different groups was assessed by the Q test and publication bias by Begg’s test (25) and Egger’s test (26).

Results

As shown in Table 1, analysis of data from mouthwash DNA samples in the U.S. study participants (1,470 cases and 1,366 controls) showed no significant association between XRCC1 R280H, ADPRT V762A, APEX1 D148E, OGG1 S326C, LIG3 R780H, and MUTYH 5’ UTR and breast cancer risk overall or by menopausal status. However, in premenopausal women, those who carried the homozygous A genotype of XRCC1 Q399R had a significantly reduced risk of breast cancer compared with women who carried the homozygous G genotype (OR, 0.6; 95% CI, 0.4-0.9). The interaction between menopausal status and XRCC1 Q399R was not statistically significant (P_interaction = 0.20). Further assessment of this finding, using the cytobrush DNA available from the U.S. study (1,470 cases and 1,366 controls), showed no significant reduction in risk overall or for either premenopausal or postmenopausal women. We also found little evidence of an association when the mouthwash and cytobrush data were combined. Further evaluation of the
Table 1. Associations between genetic polymorphisms in BER pathway and risk of breast cancer among Caucasians in the U.S. breast cancer study

<table>
<thead>
<tr>
<th>SNP (dbSNP ID)</th>
<th>Genotype</th>
<th>Overall Cases/Controls</th>
<th>OR* (95% CI)</th>
<th>Premenopausal Cases/Controls</th>
<th>OR* (95% CI)</th>
<th>Postmenopausal Cases/Controls</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XRCC1 (Q399R)¹</td>
<td>GG</td>
<td>659/505</td>
<td>1.0</td>
<td>252/159</td>
<td>1.0</td>
<td>366/307</td>
<td>1.0</td>
</tr>
<tr>
<td>(rs25487)</td>
<td>AG</td>
<td>769/590</td>
<td>1.0 (0.9-1.2)</td>
<td>310/234</td>
<td>0.8 (0.7-1.1)</td>
<td>408/322</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>P_HWE = 0.36</td>
<td>AA</td>
<td>207/192</td>
<td>0.9 (0.7-1.1)</td>
<td>72/75</td>
<td>0.6 (0.4-0.9)</td>
<td>122/97</td>
<td>1.1 (0.8-1.5)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRCC1 (Q399R)²</td>
<td>GG</td>
<td>555/549</td>
<td>1.0</td>
<td>223/177</td>
<td>1.0</td>
<td>289/344</td>
<td>1.0</td>
</tr>
<tr>
<td>(rs25487)</td>
<td>AG</td>
<td>664/583</td>
<td>1.2 (1.0-1.4)</td>
<td>254/184</td>
<td>1.1 (0.9-1.5)</td>
<td>352/358</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>P_HWE = 0.50</td>
<td>AA</td>
<td>185/168</td>
<td>1.1 (0.9-1.4)</td>
<td>77/51</td>
<td>1.2 (0.8-1.9)</td>
<td>97/109</td>
<td>1.0 (0.8-1.4)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XRCC1 (Q399R)³</td>
<td>GG</td>
<td>1,214/1,054</td>
<td>1.0</td>
<td>475/336</td>
<td>1.0</td>
<td>655/651</td>
<td>1.0</td>
</tr>
<tr>
<td>(rs25487)</td>
<td>AG</td>
<td>1,433/1,173</td>
<td>1.1 (0.9-1.2)</td>
<td>564/418</td>
<td>1.0 (0.8-1.2)</td>
<td>760/680</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>P_HWE = 0.25</td>
<td>AA</td>
<td>392/360</td>
<td>0.9 (0.8-1.1)</td>
<td>149/126</td>
<td>0.8 (0.6-1.1)</td>
<td>219/206</td>
<td>1.1 (0.8-1.3)</td>
</tr>
<tr>
<td>P_trend</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE: P_HWE, P value for departures of Hardy-Weinberg equilibrium among control populations.
*Adjusted for age and study site.
+ Including subjects in mouthwash study.
† Including subjects in cytobrush study.
§Including subjects in both mouthwash and cytobrush studies.

association using the data from Poland also showed no significant association overall or by menopausal status (Table 2).

In postmenopausal women, those who carried the heterozygous or homozygous T genotype of XRCC1 R194W, compared with those who carried the homozygous C genotype, had a nonsignificantly reduced risk of breast cancer [OR, 0.8 (95% CI, 0.6-1.0) and OR, 0.5 (95% CI, 0.2-1.4), respectively; Table 1] although the test of linear trend was significant ($P_trend = 0.03$).

Further analyses in the U.S. breast cancer study stratified by family history of breast cancer in first-degree relatives did not modify the associations between SNPs in XRCC1, ADPRT, APEX1, OGG1, LIG3, and MUTYH genes and breast cancer risk (data not shown). Findings were also similar for in situ and invasive breast cancer (data not shown). Pairwise $D' \times$ values, estimated using HaploView (27), indicated that the three XRCC1 SNPs are in strong linkage disequilibrium in the U.S. breast cancer study ($D' > 0.96$) although the correlation between SNPs was low ($r^2 < 0.05$).

Meta-analyses. Results from meta-analyses of two polymorphisms (Q399R and R194W) in the XRCC1 gene are presented in Table 3. The meta-analyses summarize the data presented here from the U.S. and Polish studies, data from 12 studies (9-20) that investigated the relationship between Q399R and breast cancer risk and 9 studies (9-12, 14, 17-20) that investigated the relationship with XRCC1 R194W. Summary estimates showed no significant associations between these two SNPs and breast cancer risk in all women (total of 10,934 cases and 11,543 controls for Q399R and total of 5,752 cases and 6,050 controls for R194W) or in separate analyses of Caucasian women (total of 7,824 cases and 8,226 controls for Q399R and total of 3,822 cases and 4,015 controls for R194W). However, in Asian women (total of 1,567 cases and 1,643 controls), we noted a significant 60% increased risk for women who carried homozygous G genotype of XRCC1 R194W.

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Using data from two large population-based case-control studies of Caucasian women in the United States and Poland,
Table 2. Association between XRCC1 Q399R genotype and breast cancer risk in the Polish breast cancer study

<table>
<thead>
<tr>
<th>SNP (dbSNP ID)</th>
<th>Genotype</th>
<th>Overall</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases/Controls</td>
<td>OR* (95% CI)</td>
<td>Cases/Controls</td>
</tr>
<tr>
<td>XRCC1 (Q399R)</td>
<td>GG</td>
<td>772/947</td>
<td>1.0</td>
<td>191/273</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>933/1,030</td>
<td>1.1 (1.0-1.3)</td>
<td>236/289</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>280/313</td>
<td>1.1 (0.9-1.4)</td>
<td>63/90</td>
</tr>
</tbody>
</table>

P_HWE = 0.15

*p trend = 0.13

NOTE: P_HWE, P value for departures of Hardy-Weinberg equilibrium among control populations.

*Adjusted for age and study site.

Table 3. Meta-analysis of the effects of XRCC1 Q399R and R194W on breast cancer risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG vs GG</td>
<td>cAA vs GG</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>XRCC1 Q399R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chacko 2005</td>
<td>India</td>
<td>Asian</td>
<td>123</td>
<td>123</td>
<td>2.0 (1.2-3.5)</td>
<td>0.01</td>
<td>2.7 (1.1-6.4)</td>
<td>0.03</td>
<td>18</td>
</tr>
<tr>
<td>Deligezer 2004</td>
<td>Turkish</td>
<td>Asian</td>
<td>151</td>
<td>133</td>
<td>0.9 (0.5-1.5)</td>
<td>0.65</td>
<td>1.3 (0.6-2.6)</td>
<td>0.52</td>
<td>17</td>
</tr>
<tr>
<td>Smith 2003</td>
<td>United States</td>
<td>Caucasian</td>
<td>162</td>
<td>302</td>
<td>0.8 (0.5-1.2)</td>
<td>0.33</td>
<td>1.1 (0.6-2.1)</td>
<td>0.78</td>
<td>12</td>
</tr>
<tr>
<td>Kim 2002</td>
<td>Korea</td>
<td>Asian</td>
<td>205</td>
<td>205</td>
<td>0.8 (0.5-1.2)</td>
<td>0.20</td>
<td>2.4 (1.2-4.7)</td>
<td>0.01</td>
<td>10</td>
</tr>
<tr>
<td>Forsi 2004</td>
<td>Finland</td>
<td>All</td>
<td>223</td>
<td>298</td>
<td>1.1 (0.8-1.6)</td>
<td>0.60</td>
<td>0.9 (0.5-1.7)</td>
<td>0.71</td>
<td>20</td>
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<tr>
<td>Smith 2003</td>
<td>United States</td>
<td>Caucasian</td>
<td>253</td>
<td>268</td>
<td>1.2 (0.8-1.7)</td>
<td>0.45</td>
<td>1.2 (0.7-2.1)</td>
<td>0.53</td>
<td>11</td>
</tr>
<tr>
<td>Duell 2001</td>
<td>United States</td>
<td>Black</td>
<td>253</td>
<td>266</td>
<td>1.5 (1.1-2.3)</td>
<td>0.03</td>
<td>2.1 (0.6-7.3)</td>
<td>0.24</td>
<td>9</td>
</tr>
<tr>
<td>Moullan 2003</td>
<td>France</td>
<td>Caucasian</td>
<td>254</td>
<td>312</td>
<td>0.9 (0.6-1.3)</td>
<td>0.57</td>
<td>1.0 (0.6-1.6)</td>
<td>0.87</td>
<td>13</td>
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<tr>
<td>Duell 2001</td>
<td>United States</td>
<td>Caucasian</td>
<td>386</td>
<td>381</td>
<td>1.1 (0.8-1.5)</td>
<td>0.46</td>
<td>0.9 (0.5-1.3)</td>
<td>0.44</td>
<td>9</td>
</tr>
<tr>
<td>Figueiredo 2004</td>
<td>Canada</td>
<td>Caucasian</td>
<td>402</td>
<td>402</td>
<td>0.9 (0.7-1.2)</td>
<td>0.39</td>
<td>0.9 (0.6-1.4)</td>
<td>0.7</td>
<td>16</td>
</tr>
<tr>
<td>Han 2003</td>
<td>United States</td>
<td>Caucasian</td>
<td>1,004</td>
<td>1,385</td>
<td>1.0 (0.9-1.2)</td>
<td>0.66</td>
<td>1.1 (0.8-1.4)</td>
<td>0.61</td>
<td>14</td>
</tr>
<tr>
<td>Shen 2005</td>
<td>United States</td>
<td>All</td>
<td>1,067</td>
<td>1,110</td>
<td>1.1 (0.9-1.3)</td>
<td>0.38</td>
<td>1.0 (0.7-1.3)</td>
<td>0.79</td>
<td>19</td>
</tr>
<tr>
<td>Shu 2003</td>
<td>China</td>
<td>Asian</td>
<td>1,088</td>
<td>1,182</td>
<td>1.0 (0.8-1.1)</td>
<td>0.69</td>
<td>1.2 (0.9-1.7)</td>
<td>0.19</td>
<td>15</td>
</tr>
<tr>
<td>This study</td>
<td>Poland</td>
<td>Caucasian</td>
<td>1,995</td>
<td>2,296</td>
<td>1.1 (1.0-1.3)</td>
<td>0.11</td>
<td>1.1 (0.9-1.3)</td>
<td>0.33</td>
<td>16</td>
</tr>
<tr>
<td>This study</td>
<td>United States</td>
<td>Caucasian</td>
<td>3,568</td>
<td>2,880</td>
<td>1.1 (0.9-1.2)</td>
<td>0.31</td>
<td>0.9 (0.8-1.1)</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis

All studies (N = 14) 10,934 11,543 1.1 (1.0-1.1) 0.13 1.1 (1.0-1.2) 0.24
Studies of Caucasian populations (N = 8) 7,824 8,226 1.1 (1.0-1.1) 0.13 1.0 (0.9-1.1) 0.81
Studies of Asian populations (N = 4) 1,567 1,643 1.0 (0.8-1.4) 0.85 1.6 (1.1-2.3) 0.02

XRCC1 R194W

CT/TT vs CC*

Chacko 2005 India Asian 123 123 2.0 (1.1-3.5) 0.02 18
Deligezer 2004 Turkish Asian 151 133 0.5 (0.2-1.2) 0.11 17
Duell 2001 United States Black 161 166 0.7 (0.4-1.2) 0.23 9
Smith 2003 United States Caucasian 162 302 1.1 (0.6-2.0) 0.69 12
Duell 2001 United States Caucasian 205 205 1.1 (0.7-1.6) 0.69 10
Forst 2004 Finland All 223 298 1.3 (0.6-2.6) 0.52 20
Duell 2001 United States Caucasian 251 234 0.7 (0.3-1.4) 0.32 9
Smith 2003 United States Caucasian 253 268 1.7 (1.0-2.9) 0.07 11
Moullan 2003 France Caucasian 254 312 1.0 (0.6-1.7) 0.91 13
Han 2003 United States Caucasian 1,004 1,385 0.8 (0.6-1.0) 0.1 14
Shen 2005 United States All 1,067 1,110 0.9 (0.7-1.2) 0.61 19
This study United States Caucasian 1,898 1,514 0.9 (0.7-1.1) 0.46 19

Meta-analysis

All studies (N = 11) 5,752 6,050 1.0 (0.8-1.2) 0.87
Studies of Caucasian populations (N = 6) 3,822 4,015 0.9 (0.8-1.1) 0.54
Studies of Asian populations (N = 3) 479 461 0.9 (0.6-1.4) 0.7 16

*CT and TT genotypes were combined because some studies did not show data for the two genotypes separately.
ethnic groups (Caucasian, 36%; Asian, 30%; African, 14%; P = 0.0006), which was very similar with the number from a recently published meta-analysis of XRCCL polymorphisms and cancer risk (28). Summary estimates for XRCCL Q399R homozygous variants versus wild-type and overall cancer risk presented in that meta-analysis (28) are consistent with an increased risk in Asian (OR, 1.16; 95% CI, 0.98-1.38) or African (OR, 1.43; 95% CI, 0.68-2.99) populations, but not in European populations (OR, 0.96; 95% CI, 0.37-1.19). However, it is unclear that the observed differences by race have a biological basis and genetic effects for complex diseases tend to be consistent across human populations (29). Therefore, further evidence is needed to make a conclusion about potential differences in risk by race.

Studies of XRCCL R194W and breast cancer risk have been inconsistent, with some suggesting an increased risk (11, 18), a reduced risk (9, 14, 17), or no association (10, 13, 19). We found no association in the U.S. women, and summary estimates from our meta-analysis provided no evidence of an association either among all populations [OR, 1.0 (95% CI, 0.8-1.2)], based on 5,752 cases and 6,050 controls] or Caucasians [OR, 0.9 (95% CI, 0.8-1.1), based on 3,822 cases and 4,015 controls] this result was also supported by a previous meta-analysis (28).

Very few studies have investigated associations between other genetic variants in BER pathway and breast cancer risk. One study in Asians (125 cases and 123 controls) found no association between XRCCL R280H and breast cancer risk (18). One study among Caucasians (254 cases and 312 controls) reported an 80% increased risk associated with the XRCCL R280H homozygous or heterozygous A genotype (13). However, this increased risk was not confirmed in the present study of U.S. women. We also found no association between OGG1 S326C and breast cancer risk, consistent with a previous study of 434 cases and 434 controls (22).

A strength of our investigation is the availability of two large population-based studies in Caucasian populations with good participation rates. The mouthwash component of the U.S. study that was used to screen for potentially interesting findings had sufficient power to detect small to moderate associations between the genetic polymorphisms evaluated and risk of breast cancer. Additional samples from women with cytobrush DNA in the U.S. study allowed a substantial increase in sample size to assess potential associations, and the Polish study served as an independent replication study. The analytic strategy also minimized the probability of reporting false-positive findings. Finally, compared with a recently published meta-analysis (28), our meta-analyses had substantially larger number of breast cancer cases (2,382 in Hu et al’s study versus 10,934 in ours for Q399R and 2,476 versus 5,752 for R194W) and controls (2,780 versus 11,543 for Q399R and 2,122 versus 6,050 for R194W). The meta-analyses for associations evaluated in previous studies permitted a more definite conclusion about these associations. Although this is a large study, the power to detect associations with rare SNPs (i.e., XRCCL R280H, XRCCL R194W, LIG3 R780H, and MUTYH 5’ UTR) was limited, resulting in relatively wide confidence intervals. We used an approach that preferentially selected coding SNPs in candidate genes and did not perform a dense survey of SNPs intended to characterize haplotype diversity. Therefore, it is possible that common genetic variation in the BER genes not captured by our approach could be related to breast cancer risk. Other alternative approaches, such as selecting haplotype tagging SNPs, should be considered.

In summary, we provide evidence against a substantial association between XRCCL Q399R and R194W and breast cancer risk, with the possible exception of an association for Q399R in Asian populations. The U.S. breast cancer study also showed no evidence for an association with SNPs evaluated in other BER genes and the results were not changed after stratified by menopausal status and family history.

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Genetic Polymorphisms in Base-Excision Repair Pathway Genes and Risk of Breast Cancer

Yawei Zhang, Polly A. Newcomb, Kathleen M. Egan, et al.


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