Introduction

Reactive oxygen species may be generated from estrogen metabolism through catechol estrogen redox cycling (1, 2). If not quenched, these reactive oxygen species may cause oxidative DNA damage and increase breast cancer risk. It has been suggested that 8-hydroxyguanine, a major product of oxidative DNA damage, plays an important role in carcinogenesis given its abundant and highly mutagenic properties (3). 8-Hydroxyguanine is subjected to base excision repair, especially via the 8-oxoguanine DNA glycosylase (hOGG1) catalyzing the release of 8-hydroxy-2’-deoxyguanosine and the cleavage of DNA at the AP site (3, 4). A common functional polymorphism (Ser326Cys) in exon 7 of the hOGG1 gene has been identified (5, 6). The Cys allele exhibits reduced DNA repair activity (5) and has been reported to be associated with the risk of cancers of the lung, prostate, esophagus, stomach, and orolarynx (6). Epidemiologic studies evaluating the hOGG1 polymorphism in relation to breast cancer risk are few and the sample sizes were small (7, 8). To evaluate the role of the Ser326Cys polymorphism and its joint effect with endogenous estrogen exposure and dietary antioxidant intake in relation to breast cancer risk, we analyzed data from the Shanghai Breast Cancer Study, a large population-based case-control study.

Materials and Methods

Cases and controls in this study were participants of the Shanghai Breast Cancer Study. Detailed study methods have been published elsewhere (9). Briefly, this study included 1,459 women between the ages of 25 and 64, who were diagnosed with breast cancer between August 1996 and March 1998, and 1,556 age frequency-matched controls. Cases were identified through a rapid case-ascertainment system supplemented by the population-based Shanghai Cancer Registry. Controls were selected using the Shanghai Resident Registry and were obtained from 1,193 (82%) cases and 1,310 (84%) controls who completed the in-person interviews. Usual dietary habits over the past 5 years were assessed using an in-person interview with a validated quantitative food frequency questionnaire (10).

The allelic discrimination of the hOGG1 gene Ser326Cys (rs1052133) polymorphism was assessed with the ABI PRISM 7900 Sequence Detection Systems (Applied Biosystems, Foster City, CA) using the fluorogenic 5’nuclease assay with primers and probes obtained from ABI (assay ID: C_3095552_1). The final volume for each reaction was 5 μL, consisting of 2.5 μL TaqMan Universal PCR Master Mix, 0.25 μL primers/TaqMan probes mix, and 2.5 ng genomic DNA. The PCR profile consisted of an initial denaturation step at 95°C for 10 minutes and 40 cycles of 92°C for 15 seconds and 60°C for 1 minute. The fluorescence level was measured with the ABI PRISM 7900HT sequence detector (Applied Biosystems). Allele frequencies were determined by ABI SDS software. Genotyping data were obtained from 1,102 cases and 1,167 controls. The concordance rate for the quality control samples was 96%.

Logistic regression models conditional on age were applied to estimate odds ratios and 95% confidence intervals. Analyses stratified by menopausal status were conducted to examine the homogeneity of the association. Additional analyses stratified by years of menstruation, body mass index, waist-to-hip ratio, and intake of fruits, vegetables, or antioxidant vitamins were conducted to evaluate the potential modifying effects. A composite dietary antioxidant index was derived to incorporate information of intake of four antioxidant nutrients (i.e., selenium and vitamins A, C, and E; refs. 11, 12). All statistical tests were two sided.

Table 1. Association of the hOGG1 polymorphism with breast cancer risk, the Shanghai Breast Cancer Study

<table>
<thead>
<tr>
<th></th>
<th>Case (n = 1,102)</th>
<th>Control (n = 1,167)</th>
<th>Odds ratio* (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser/Ser</td>
<td>186</td>
<td>214</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Ser/Cys</td>
<td>534</td>
<td>537</td>
<td>1.17 (0.93-1.47)</td>
</tr>
<tr>
<td>Cys/Cys</td>
<td>382</td>
<td>416</td>
<td>1.06 (0.83-1.35)</td>
</tr>
<tr>
<td>Premenopausal women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser/Ser</td>
<td>130</td>
<td>138</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Ser/Cys</td>
<td>347</td>
<td>344</td>
<td>1.08 (0.81-1.43)</td>
</tr>
<tr>
<td>Cys/Cys</td>
<td>255</td>
<td>268</td>
<td>0.99 (0.74-1.34)</td>
</tr>
<tr>
<td>Postmenopausal women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser/Ser</td>
<td>54</td>
<td>74</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Ser/Cys</td>
<td>186</td>
<td>191</td>
<td>1.37 (0.91-2.07)</td>
</tr>
<tr>
<td>Cys/Cys</td>
<td>126</td>
<td>148</td>
<td>1.18 (0.77-1.81)</td>
</tr>
</tbody>
</table>

*Adjusted for age, education level, menopausal status, and age at first live birth.
Table 2. Associations of breast cancer with the hOGG1 gene polymorphism, stratified by lifestyle factors, the Shanghai Breast Cancer Study

<table>
<thead>
<tr>
<th>hOGG1 polymorphism</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser/Ser</td>
<td>Ser/Cys</td>
</tr>
<tr>
<td>Years of menstruation*</td>
<td></td>
</tr>
<tr>
<td>Q1 (reference)</td>
<td>1.03 (0.62-1.70)</td>
</tr>
<tr>
<td>Q2 (0.58-1.98)</td>
<td>1.08 (1.00-2.00)</td>
</tr>
<tr>
<td>Q3 (0.81-2.57)</td>
<td>1.44 (0.99-2.12)</td>
</tr>
<tr>
<td>Q4 (0.91-2.08)</td>
<td>1.72 (1.26-2.37)</td>
</tr>
</tbody>
</table>

Body mass index

Q1 (reference) | 1.00 (0.74-1.37) | 1.00 (0.74-1.37) | 1.00 (0.74-1.37) |
Q2 (0.72-1.91) | 1.10 (0.85-1.42) | 1.08 (0.83-1.42) | 1.08 (0.83-1.42) |
Q3 (0.72-2.85) | 1.20 (0.94-1.55) | 1.18 (0.92-1.55) | 1.18 (0.92-1.55) |
Q4 (0.90-2.50) | 1.50 (1.14-2.00) | 1.48 (1.12-2.00) | 1.48 (1.12-2.00) |

Waist-to-hip ratio

Q1 (reference) | 1.00 (0.86-1.20) | 1.00 (0.86-1.20) | 1.00 (0.86-1.20) |
Q2 (0.66-1.20) | 1.06 (0.81-1.39) | 1.04 (0.80-1.39) | 1.04 (0.80-1.39) |
Q3 (0.83-1.60) | 1.12 (0.90-1.40) | 1.10 (0.88-1.40) | 1.10 (0.88-1.40) |
Q4 (0.90-2.00) | 1.20 (1.00-1.45) | 1.18 (0.98-1.45) | 1.18 (0.98-1.45) |

Carotenoids

Q1 (reference) | 1.00 (0.84-1.20) | 1.00 (0.84-1.20) | 1.00 (0.84-1.20) |
Q2 (0.66-1.50) | 1.06 (0.81-1.40) | 1.04 (0.80-1.40) | 1.04 (0.80-1.40) |
Q3 (0.90-1.60) | 1.12 (0.90-1.40) | 1.10 (0.88-1.40) | 1.10 (0.88-1.40) |
Q4 (0.90-2.00) | 1.18 (0.96-1.44) | 1.16 (0.94-1.44) | 1.16 (0.94-1.44) |

Antioxidant index1

Q1 (reference) | 1.00 (0.85-1.50) | 1.00 (0.85-1.50) | 1.00 (0.85-1.50) |
Q2 (0.66-1.30) | 0.95 (0.75-1.21) | 0.93 (0.73-1.21) | 0.93 (0.73-1.21) |
Q3 (0.90-1.60) | 0.98 (0.78-1.29) | 0.96 (0.76-1.29) | 0.96 (0.76-1.29) |
Q4 (0.90-2.00) | 1.03 (0.83-1.31) | 1.01 (0.81-1.31) | 1.01 (0.81-1.31) |

NOTE: The odds ratios (95% confidence intervals) and P values for interaction test were derived from logistic models, adjusting for age, education level, menopausal status, and age at first live birth. The cut points for categorical variables were based on quartile distributions among controls.

*Years of menstruation = menopausal age or age at interview for premenopausal women = menarche age.

1Dietary antioxidant index was derived using the method described in Material and Method section.

Results

Genotype distribution of the hOGG1 Ser326Cys polymorphism followed Hardy-Weinberg equilibrium for both cases and controls. No apparent difference in genotype frequencies between cases and controls was observed. Overall, the hOGG1 Ser326Cys polymorphism was not associated with breast cancer risk (Table 1).

As shown in Table 2, no significant interaction was found between the hOGG1 Ser326Cys polymorphism and endogenous estrogen exposure–related factors (P for interaction > 0.15). Similarly, no significant interaction was found between this polymorphism and the intakes of dietary antioxidant nutrients and dietary antioxidant index (P for interaction > 0.13).

Discussion

In this large-scale, population-based case-control study conducted among Chinese women, we did not find hOGG1 Ser326Cys polymorphism to be associated with breast cancer risk. Our result was supported by the reports from a case-control study conducted in Korean and Japanese populations (7) and a nested case-control study conducted in Denmark (8). The sample sizes of these two previous studies were small. We also did not find any significant interaction between this polymorphism and endogenous estrogen exposure–related factors or dietary antioxidant intake on breast cancer risk. The Ser326Cys polymorphism has been well documented to be related to major functional changes in the hOGG1 gene (5). The hOGG1 gene has been well characterized and no other major functional single-nucleotide polymorphisms have been found in the Chinese population (http://www.ncbi.nlm.nih.gov/SNP/). Therefore, it is unlikely that other polymorphisms in this gene would be related to a substantial risk of breast cancer.

The current study has many strengths: (a) the large sample size—our study has 80% statistical power to detect an odds ratio of 1.27 for any genotype of this polymorphism at a significance level of 0.05; (b) high participation rate and population-based study design, which reduce potential selection bias; (c) minimal confounding from ethnicity because >98% of women living in Shanghai are classified into a single ethnic group (Han Chinese); and (d) the extensive information on lifestyle factors which allowed a comprehensive evaluation of their interaction or confounding effects on the association of genetic polymorphisms and breast cancer risk. The risk estimates derived from age-adjusted and multivariable adjusted analyses were similar, indicating that the confounding effect is unlikely to be a concern in this study.

In summary, the functional Ser326Cys polymorphism in the hOGG1 gene may not play a substantial role in the risk of breast cancer among Chinese women.

Acknowledgments

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References

Functional Ser326Cys Polymorphism in the hOGG1 Gene Is Not Associated with Breast Cancer Risk

Qiuyin Cai, Xiao-Ou Shu, Wanqing Wen, et al.


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