Investigation on the role of XPG gene polymorphisms in breast cancer risk in a Chinese population

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ABSTRACT. We conducted a case-control study to investigate the role of XPG gene polymorphisms (rs2094258, rs751402, and rs17655) in the development of breast cancer. Patients with breast cancer (320) and control subjects (294) were consecutively selected from the Zhongshan Hospital between April 2013 and January 2015. The genotyping of XPG rs2094258, rs751402, and rs17655 was performed using polymerase chain reaction-restriction fragment length polymorphism. Using the chi-square test, we did not find any significant differences in the genotype distributions of XPG rs2094258 ($\chi^2 = 1.48$, $P = 0.48$), rs751402 ($\chi^2 = 0.65$, $P = 0.72$), and rs17655 ($\chi^2 = 0.01$, $P = 0.92$) genes between breast cancer patients and control subjects. The genotype distributions of XPG rs2094258, rs751402, and rs17655 did not deviate from the Hardy-Weinberg equilibrium in control subjects, and the P values were 0.58, 0.97, and 0.26, respectively. Using unconditional logistic regression...
analysis, we found that XPG rs2094258, rs751402 and rs17655 gene polymorphisms are not associated with the development of breast cancer after adjusting for potential confounding factors. In conclusion, we found that XPG rs2094258, rs751402, and rs17655 do not influence the development of breast cancer in a Chinese population.

Key words: XPG; Polymorphism; Breast cancer; Chinese population

INTRODUCTION

Breast cancer is the most common cancer and the third most common cause of cancer-related death for women in China (Siegel et al., 2014). Furthermore, the number of women in China suffering from breast cancer shows a tendency to increase, while the number of death tends to decrease (Matsen and Neumayer, 2013). The development of breast cancer is a complex process and depends on multiple factors, including age, family history of breast cancer, lack of physical activity, menstrual and reproductive history, and dense breast tissue (Abu Rabi et al., 2015; Zhang et al., 2015). However, not all individuals will develop breast cancer, even when exposed to the same risk factors for this type of cancer, which suggests that genetic factors are contributing to the development of breast cancer.

In humans, there are more than 130 genes involving in the DNA repair pathways. There are five common DNA repair pathways, including base excision repair, nucleotide excision repair (NER), mismatch repair, and double-strand break repair pathways. NER pathway plays an important role in removing DNA lesions caused by UV radiation or chemical agents (Friedberg et al., 2000). The XPG belongs to NER, and this gene has a function of extreme UV-sensitivity and a high genetic predisposition to sunlight-caused cancers (Cordonnier and Fuchs, 1999). Previous studies have shown that XPG gene polymorphisms are associated with development of several kinds of cancers, such as digestive system cancer, head and neck cancer, colorectal cancer, prostate cancer, laryngeal cancer, and bladder cancer (Du et al., 2014; Liu et al., 2014; Lu et al., 2014; Mirecka et al., 2014; Jiang et al., 2015; Yu et al., 2015). In particular, there are a few studies reporting on the association between XPG gene polymorphisms and the development of breast cancer, but the results are inconclusive (Kumar et al., 2003; Mechanic et al., 2006; Crew et al., 2007; Ding et al., 2011). In our study, we conducted a case-control study to investigate the role of XPG gene polymorphisms (rs2094258, rs751402, and rs17655) in the development of breast cancer.

MATERIAL AND METHODS

Subjects

This case-control study included 344 patients with breast cancer, and they were consecutively selected from the Zhongshan Hospital between April 2013 and January 2015. All the newly patients with breast cancer were independently confirmed by two pathologists through histopathological analysis. Patients who had secondary or recurrent tumors, a history of other malignant tumors, or serious infection diseases were excluded from this study. Finally, 320 patients with breast cancer were included in this study (participation rate was 90.02%). During the same period time, 294 females were consecutively randomly selected from
individuals who had a health check-up at our hospital. Controls who had a history of malignant
tumor, hyperplasia of mammary glands, and serious infection disease, kidney and liver diseases
were included into our study. Each patient and control subject signed a written informed consent
before participating in our study. The study protocol was approved by the Ethics Committee of
the Zhongshan Hospital and was according to the standards of the Declaration of Helsinki.

The demographic and clinical data of patients with breast cancer and control subjects
were collected from the medical records and from a structured questionnaire. The collected
information included age, menopause, age at menarche, age at first live birth, family history of
cancer, clinical stage, and tumor size.

**DNA extraction and genotyping**

A sample of peripheral blood (5 mL) was collected from each patient and control
subject, and the DNA was extracted from the collected blood samples using the TIANamp
Blood DNA Kit (Tiangen, Beijing, China) following the instructions. The genotyping of XPG
rs2094258, rs751402, and rs17655 was performed by polymerase chain reaction-restriction
fragment length polymorphism (PCR-RFLP). The primers of XPG rs2094258, rs751402, and
rs17655 were designed using the Primer premier v5.0 software (PREMIER Biosoft Ltd., Palo
Alto, CA, USA). The PCR for analysis was performed in a reaction of 25 µL solution of 10
pmol primers and 50 ng genomic DNA. The PCR condition was started at a denaturation
temperature of 94°C for 5 min, followed by 30 cycles of denaturation at 94°C for 30 s,
annealing at 60°C for 60 s, extension at 72°C for 60 s, and a final extension for 7 min at 72°C.
Digestion products were determined by electrophoresis using ethidium bromide staining, a 2%
agarose gel and observed by ultraviolet light.

**Statistical analysis**

The demographic and lifestyle information between breast cancer patients and
control subjects was compared using the chi-square ($\chi^2$) test. The genotype frequencies of
XPG rs2094258, rs751402, and rs17655 confirmed with the Hardy-Weinberg equilibrium
(HWE) were analyzed using the $\chi^2$ test with one degree of freedom. The association between
XPG rs2094258, rs751402, and rs17655 gene polymorphisms and the development of breast
cancer was analyzed using unconditional regression analysis, and the results were described
using odds ratios and 95% confidence intervals. The wide-type genotype of XPG rs2094258,
rs751402, and rs17655 was taken as the reference group. All the statistical analysis was
performing using the SPSS 16.0 statistical software (SPSS, Chicago, IL, USA), and a P value
<0.05 was considered as a significant difference.

**RESULTS**

The demographic and clinical characteristics of the breast cancer patients and control
subjects are presented in Table 1. Compared to the control subjects, breast cancer patients
were more likely to be in menopause ($\chi^2 = 11.65, P < 0.001$), have no children ($\chi^2 = 21.33, P <
0.001$), and have a family history of cancer ($\chi^2 = 5.33, P = 0.02$). No significant difference was
found between breast cancer patients and controls in terms of age ($\chi^2 = 0.17, P = 0.68$) and age
at menarche ($\chi^2 = 3.36, P = 0.06$).
Using the chi-square test, we did not find any significant difference in the genotype distributions of XPG rs2094258 ($\chi^2 = 1.48$, $P = 0.48$), rs751402 ($\chi^2 = 0.65$, $P = 0.72$), and rs17655 ($\chi^2 = 0.01$, $P = 0.92$) genes between breast cancer patients and control subjects (Table 2). The genotype distributions of XPG rs2094258, rs751402, and rs17655 did not deviate from the HWE in control subjects, and the $P$ values were 0.58, 0.97, and 0.26, respectively.

### Table 1. Demographic and clinical characteristics of breast cancer patients and controls in this study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (N = 320)</th>
<th>Controls (N = 294)</th>
<th>$\chi^2$ test</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>146</td>
<td>139</td>
<td>47.28</td>
<td></td>
</tr>
<tr>
<td>&gt;=50</td>
<td>174</td>
<td>155</td>
<td>52.72</td>
<td>0.17</td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>241</td>
<td>184</td>
<td>62.59</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79</td>
<td>110</td>
<td>37.41</td>
<td>0.17</td>
</tr>
<tr>
<td>Age at menarche</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>234</td>
<td>195</td>
<td>66.33</td>
<td></td>
</tr>
<tr>
<td>&gt;=15</td>
<td>86</td>
<td>99</td>
<td>33.67</td>
<td>3.36</td>
</tr>
<tr>
<td>Age at first live birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>98</td>
<td>119</td>
<td>40.48</td>
<td></td>
</tr>
<tr>
<td>&gt;=30</td>
<td>182</td>
<td>165</td>
<td>56.12</td>
<td>21.33</td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>59</td>
<td>52</td>
<td>47.06</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>212</td>
<td>175</td>
<td>52.94</td>
<td></td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>27</td>
<td>18</td>
<td>66.67</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>10</td>
<td>33.33</td>
<td></td>
</tr>
<tr>
<td>III-IV</td>
<td>93</td>
<td>74</td>
<td>22.22</td>
<td></td>
</tr>
</tbody>
</table>

Using unconditional logistic regression analysis, we found that XPG rs2094258, rs751402, and rs17655 gene polymorphisms could not influence the development of breast cancer, after adjusting for potential confounding factors (Table 3). Moreover, we performed
a gene-environmental interaction between XPG rs2094258, rs751402, and rs17655 gene polymorphisms and the demographic characteristics of breast cancer, but no significant interaction was found between them (P < 0.05).

**Table 3.** Association between XPG rs2094258, rs751402, and rs17655 gene polymorphisms and the development of breast cancer.

<table>
<thead>
<tr>
<th>XPG</th>
<th>Patients (N = 320)</th>
<th>%</th>
<th>Controls (N = 294)</th>
<th>%</th>
<th>OR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs2094258</td>
<td>AA</td>
<td>157</td>
<td>49.06</td>
<td>127</td>
<td>56.16</td>
<td>1.0 (Ref.)</td>
</tr>
<tr>
<td></td>
<td>AG</td>
<td>136</td>
<td>42.19</td>
<td>96</td>
<td>32.53</td>
<td>1.15 (0.79-1.65)</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>27</td>
<td>8.44</td>
<td>15</td>
<td>5.33</td>
<td>1.46 (0.71-3.08)</td>
</tr>
<tr>
<td>rs751402</td>
<td>CC</td>
<td>127</td>
<td>39.69</td>
<td>101</td>
<td>47.04</td>
<td>1.0 (Ref.)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>150</td>
<td>46.88</td>
<td>107</td>
<td>41.15</td>
<td>1.11 (0.77-1.62)</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>43</td>
<td>13.44</td>
<td>28</td>
<td>11.81</td>
<td>1.22 (0.69-2.19)</td>
</tr>
<tr>
<td>rs17655</td>
<td>GG</td>
<td>116</td>
<td>36.25</td>
<td>84</td>
<td>43.65</td>
<td>1.0 (Ref.)</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td>145</td>
<td>45.31</td>
<td>107</td>
<td>40.75</td>
<td>0.98 (0.66-1.45)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>59</td>
<td>18.44</td>
<td>46</td>
<td>15.65</td>
<td>0.93 (0.56-1.54)</td>
</tr>
</tbody>
</table>

1 Adjusted for age, menopause, age at first live birth, and family history of cancer.

**DISCUSSION**

Polymorphisms in the XPG gene can alter the expression of this protein and influence its function of correcting the excision repair deficiency, and thus cause a reduced DNA repair capacity and influence the cancer susceptibility (Mudgett and MacInnes, 1990; Takahashi et al., 1992). In the present study, we conducted a case-control study to investigate the association between three common SNPs (rs2094258, rs751402, and rs17655) in the XPG and the development of breast cancer in a Chinese population, and we found that the three SNPs do not contribute to the development of breast cancer.

Previous studies have reported the association between XPG gene polymorphisms and the development of breast cancer, but the results are inconclusive (Kumar et al., 2003; Mechanic et al., 2006; Crew et al., 2007; Ding et al., 2011; Xu et al., 2014). Kumar et al. (2003) conducted a case-control study with 220 breast cancer patients and 308 controls,
and reported that the XPG gene marginally significantly increased the development of breast cancer in a Swedish population. Mechanic et al. (2006) conducted a study in an African-American population, composed by 2311 cases and 2022 controls, and they did not observe a significant association between XPG gene polymorphisms and the development of breast cancer. Ding et al. (2011) suggested that the XPG rs17655 polymorphism is not associated with an increased breast cancer risk in a Chinese population. Xu et al. (2014) conducted a meta-analysis with 5235 breast cancer patients and 5685 control subjects, and they suggested that the XPG rs17655 polymorphism is not associated with breast cancer risk. In our study, no significant association was found between XPG rs2094258, rs751402, and rs17655 gene polymorphisms and breast cancer risk. The discrepancies of the above mentioned studies may be caused by different populations, selection of patients and controls, and sample sizes. Further studies are needed to confirm the findings of our study.

There are two limitations in our study. First, the selection bias could not be avoided, since the patients and controls were selected from one hospital. However, the genotype distributions of XPG rs2094258, rs751402, and rs17655 confirmed with the HWE in control subjects suggested that the study population could represent the general population. Second, the sample size is relatively small in our study, which may limit the statistical power to find differences between groups. The small sample size may explain no association between XPG rs2094258, rs751402, and rs17655 gene polymorphisms and risk of breast cancer in this study.

In conclusion, we found that XPG rs2094258, rs751402, and rs17655 do not influence the development of breast cancer in a Chinese population, and further studies with a large sample size and more ethnicities are needed to confirm our results.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank the staff in Zhongshan Hospital, and who help us to collect the blood samples from study subjects.

REFERENCES


