



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 of 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 μ L 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 (χ^2) test. The genotype frequencies of XPG rs2094258, rs751402, and rs17655 confirmed with the Hardy-Weinberg equilibrium (HWE) were analyzed using the χ^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 ($\chi^2 = 3.36$, $P = 0.06$).

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

Characteristics	Patients (N = 320)	%	Controls (N = 294)	%	χ^2 test	P value
Age (years)						
<50	146	45.63	139	47.28		
\geq 50	174	54.38	155	52.72	0.17	0.68
Menopause						
No	241	75.31	184	62.59		
Yes	79	24.69	110	37.41	11.65	<0.001
Age at menarche						
<15	234	73.13	195	66.33		
\geq 15	86	26.88	99	33.67	3.36	0.06
Age at first live birth						
No children	40	12.50	9	3.06		
<30	98	30.63	119	40.48		
\geq 30	182	56.88	165	56.12	21.33	<0.001
Family history of cancer						
No	282	88.13	275	93.54		
Yes	38	11.88	19	6.46	5.33	0.02
Tumor size						
<2.0 cm	268	83.75				
\geq 2.0 cm	52	16.25				
Clinical stage						
I-II	227	70.94				
III-IV	93	29.06				

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 2. Genotype frequencies of XPG rs2094258, rs751402, and rs17655 gene polymorphisms between breast cancer patients and controls.

XPG	Patients (N = 320)	%	Controls (N = 294)	%	χ^2 test	P value	P for HWE
							In controls
rs2094258							
AA	157	49.06	127	56.16			
AG	136	42.19	96	38.51			
GG	27	8.44	15	5.33	1.48	0.48	0.58
rs751402							
CC	127	39.69	101	47.04			
CT	150	46.88	107	41.15			
TT	43	13.44	28	11.81	0.65	0.72	0.97
rs17655							
GG	116	36.25	84	43.6			
GC	145	45.31	107	40.75			
CC	59	18.44	46	15.65	0.01	0.92	0.26

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.

XPG	Patients (N = 320)	%	Controls (N = 294)	%	OR (95%CI) ¹	P value
rs2094258						
AA	157	49.06	127	56.16	1.0 (Ref.)	-
AG	136	42.19	96	38.51	1.15 (0.79-1.65)	0.45
GG	27	8.44	15	5.33	1.46 (0.71-3.08)	0.27
rs751402						
CC	127	39.69	101	47.04	1.0 (Ref.)	-
CT	150	46.88	107	41.15	1.11 (0.77-1.62)	0.55
TT	43	13.44	28	11.81	1.22 (0.69-2.19)	0.47
rs17655						
GG	116	36.25	84	43.6	1.0 (Ref.)	-
GC	145	45.31	107	40.75	0.98 (0.66-1.45)	0.92
CC	59	18.44	46	15.65	0.93 (0.56-1.54)	0.76

¹Adjusted 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 that XPG gene polymorphisms are associated with several kinds of cancers in different ethnicities, such as head and neck cancer, gastric cancer, bladder cancer, colon cancer, prostate cancer (Ma et al., 2012; He et al., 2012; Zhu et al., 2012; Liu et al., 2014; Steck et al., 2014; Zhang et al., 2014). Ma et al. (2012) conducted a case-control study of 1059 patients with head and neck cancer and 1066 control subjects, and they reported that XPG gene polymorphisms may not affect the risk of head and neck cancer in an American population. He et al. (2012) conducted a case-control study in a Chinese population, and they reported that rs2296147T>C and rs2094258C>T genetic variants may contribute to the risk of gastric cancer. Liu et al. (2014) conducted a meta-analysis with eight case-control studies and reported that the XPG rs17655 polymorphism was not associated with bladder cancer risk. Steck et al. (2014) did not find significant association between XPG gene polymorphisms and colon cancer risk. Zhang et al. (2014) reported that the XPG rs2296147 polymorphism was significantly correlated with prostate cancer susceptibility in a Chinese population. Zhu et al. (2012) suggested that XPG rs2296147 C variant genotypes were associated with a significantly lower ESCC risk in a Chinese population.

Several 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.

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