Polymorphisms in the ERCC1 and XPF Genes and Risk of Breast Cancer in a Chinese Population

Zecheng Yang,¹ Xuedong Fang,² Xinhong Pei,³ and Huixiang Li⁴

Inherited functional single-nucleotide polymorphisms (SNPs) in DNA repair genes may influence the capability of DNA repair and contribute to the risk of breast cancer. We therefore performed a case-control study to investigate the association of three in excision repair cross-complimentary group 1 (ERCC1) and three in xeroderma pigmentosum complementation group F (XPF) with the risk of breast cancer. Genotyping of ERCC1 (rs2298881, rs3212986, and rs11615) and XPF (rs2276465, rs6498486, and rs2276466) was performed in a 384-well plate format on the MassARRAY[®] platform. Odds ratios and their corresponding 95% confidence intervals were used to assess the effect of each SNP on breast cancer risk. The ERCC1 rs11615 variant A/A genotype was associated with increased breast cancer risk in codominant, dominant, and recessive models, and XPF rs6498486 variant C/C genotype carriers have a significantly increased breast cancer risk in codominant, dominant, and recessive models. Individuals with both the ERCC1 rs11615 A allele and XPF rs6498486 C allele had a heavy increased risk of breast cancer compared to double wild-type homozygotes. The present study shows that the ERCC1 rs11615 and XPF rs6498486 polymorphisms are associated with breast cancer risk in a Chinese population. Further large-scale studies are required to elucidate whether these ERCC1 and XPF SNPs interact with environmental factors in the development of breast cancer.

Introduction

BREAST CANCER IS one of the most common cancers among women worldwide and ranks second of all cancers (IARC, 2008). It is estimated that 1.38 million new breast cancer cases were diagnosed in 2008, and accounted for 25% of all cancers (IARC, 2008). In China, breast cancer is the second leading cause of cancer, and the incidence is as high as 21.6 per 10⁵ in 2008 (IARC, 2008). A complex interplay of genetics, environmental exposures, hormones, and behaviors may contribute to breast carcinogenesis during specific life phases (Benz, 2008).

Interindividual variations in DNA damage and repair genes, such as BRCA1, BRCA2, ATM, FANC, and CHEK2, are associated with susceptibility to breast cancer, and highlight the importance of DNA damage/repair in the development of the disease (Fortini *et al.*, 2003). Nucleotide excision repair (NER) is the most versatile DNA repair mechanism pathway responsible for removing a wide variety of DNA lesions, such as bulky adducts, crosslinks, oxidative DNA damage, alkylating damage, and thymidine dimers (De Silva *et al.*, 2000; Friedberg, 2001; Wood *et al.*, 2001). At least seven xeroderma pigmentosum (XP) complementation groups have been

identified during the NER mechanism (Cleaver, 2000). The excision repair cross-complimentary group 1 (ERCC1) gene encodes a subunit of the NER complex required for the incision step of NER, which forms a heterodimer with the xeroderma pigmentosum complementation group F (XPF) endonuclease to catalyze the 5' incision during the process of excising the DNA lesion (Wang *et al.*, 2011). It is reported that ERCC1 is a critical protein for NER, and polymorphisms in ERCC1 may influence the genomic stability, and thus enhance the susceptibility to cancer (Wood, 1997). Three common ERCC1 variants, rs11615, rs321986, and rs321961, have been investigated previously, which have function in the carcinogenesis of lung cancer, colorectal cancer, and head and neck cancers as well as gastric cancer (Zhang *et al.*, 2012). Four previous case-control studies indicated that the polymorphisms in ERCC1 are associated with breast cancer risk, including one study of 346 cases in a Korean population (Han *et al.*, 2012), one study of 1053 breast cancer cases in the United States (Crew *et al.*, 2007), one of 872 cases in Korea (Lee *et al.*, 2005a), and one of 426 cases in Iran (Mojgan *et al.*, 2012). However, no study explores the association between ERCC1 and breast cancer risk in the Chinese population. For the role of XPF polymorphisms on breast cancer risk, one previous

Departments of ¹Breast and ²General Surgery, the Second Hospital of Jilin University, Changchun, China.

Departments of ³Gastrointestinal Surgery and ⁴Pathology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China.

meta-analysis reported no association between XPF polymorphisms and breast cancer risk (Ding *et al.*, 2011).

Therefore, we performed a case-control study to investigate the association of ERCC1 and XPF polymorphisms with risk of breast cancer by genotyping six potential functional single-nucleotide polymorphisms (SNPs), three in ERCC1 and three in XPF in a Chinese population of 461 breast cancer cases and 504 cancer-free controls.

Materials and Methods

The subjects were recruited from an ongoing multicenter case-control study conducted in China. This study included 527 patients with newly diagnosed and histopathologically confirmed primary breast cancer recruited in the Second Hospital of Jilin University and the First Affiliate Hospital of Zhengzhou University of China between January 2008 and May 2012, and all patients were from North China and Central China. Finally, 461 breast cancer cases agreed to participate with a participation rate of 87.5%. A total of 552 cancer-free controls who sought for health examination in the Second Hospital of Jilin University and the First Affiliate Hospital of Zhengzhou University of China were selected during the same time period, and 504 patients agreed to participate (participation rate: 91.3%). Controls were matched with cases by age (± 5 years). All patients were asked to provide 5 mL of blood for genotyping, and they signed a written informed consent.

SNP selection and genotyping

The potentially functional SNPs of interest were recruited from NCBI dbSNP database and SNPinfo according to the following criteria: (1) the minor allele frequency (MAF) reported in HapMap was $\geq 10\%$ in the Chinese population; (2) affecting the microRNA binding sites activity; (3) not included in the published GWAS. For the ERCC1 and XPF genes, genomic DNA was extracted from the buffy coat fraction of the blood sample with a Qiagen Blood DNA Mini Kit (Qiagen, Inc., Valencia, CA) according to the manufacturer's instructions. DNA purity and concentration were conducted by spectrophotometric measurement of absorbance at 260 and 280 nm with a UV spectrophotometer (Nano Drop Technologies, Inc., Wilmington, DE). For the ERCC1 gene, we selected rs11615, rs3212986, and rs2298881. rs2298881 may be associated with the activity of TFBS, and rs11615 and rs3212986 may be related to transcript stability alterations and alternations of mRNA levels, respectively. For the XPF gene, rs2276465, rs6498486, and rs2276466 were selected, which may affect the activity of the miRNA binding site and TFBS. These six potential SNPs could capture other 40 nearby genes.

Five milliliter venous blood was drawn from each cases and controls. The blood was kept at -20°C , and EDTA with 1.5–2.2 mg/mL was used as anticoagulant. The DNA was extracted using a TIANamp blood DNA kit (Tiangen Biotech, Beijing, China). Genotyping of ERCC1 (rs11615, rs3212986, and rs2298881) and XPF (rs2276465, rs6498486, and rs2276466) were performed in a 384-well plate format on the MassARRAY[®] platform (Sequenom[®], San Diego, CA), which combined polymerase chain reaction (PCR) and matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry technologies (Fig. 1). PCR and single-base extension primers were designed using Sequenom Assay

Design 3.1 software (Sequenom) according to the manufacturer's instructions. The cycling program involved preliminary denaturation at 94°C for 2 min, followed by 35 cycles of denaturation at 94°C for 30 s, and annealing at 64°C for 30 s, with a final extension at 72°C for 10 min. PCR products were verified by 1.0% agarose gel electrophoresis, and the PCR products were visualized using ethidium bromide staining. For quality control, genotyping was repeated for a random sample of 5% of cases and controls, and the results were 100% concordant.

Statistical analysis

All statistical analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC). Continuous variables were presented as mean $\pm$ SD and analyzed using an independent sample *t*-test. Categorical variables were presented as *n* of subjects (%) and analyzed using the χ^2 -test. The Hardy-Weinberg equilibrium and between-group comparison of genotype distribution were analyzed using a goodness-of-fit χ^2 test. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were used to assess the effect of each SNP on breast cancer risk. Unconditional multivariate logistic regression models were performed to calculate the OR (95% CI) after adjusting for age, family history of breast cancer, history of breast disease, age at first full-term pregnancy, and number of full-term pregnancies. All comparisons were two sided, and $p < 0.05$ was regarded as statistically significant.

Results

The study included 461 patients with breast cancer (mean age 45.2 ± 8.2 years; age range 31–79 years) and 504 health control subjects (mean age 46.7 ± 8.5 years; age range 28–76 years). Baseline demographic characteristics of the study population are shown in Table 1. Elevated breast cancer risk was associated with those who had a family history of breast cancer (OR, 3.61; 95% CI, 1.64–8.78) compared with those without such a family history. Patients with breast cancer were significantly more likely to have a history of breast disease (OR, 1.48; 95% CI, 1.10–1.95), and age above 30 years at first full-term pregnancy (OR, 1.98; 95% CI, 1.42–2.76). However, those who had a history of full-term pregnancy were associated with reduced risk of breast cancer (OR, 0.42; 95% CI, 0.20–0.85 for one full-term pregnancy; OR, 0.38; 95% CI, 0.18–0.76).

Genotype distributions of six SNPs are shown in Table 2. In control subjects, the MAFs were consistent with published MAFs (available at www.ncbi.nlm.nih.gov/snp/), and in the Hardy-Weinberg equilibrium. The ERCC1 rs11615 and XPF rs6498486 genotype frequencies were significantly different between the breast cancer and control groups, with ERCC1 rs11615 A allele and XPF rs6498486 C allele frequencies significantly higher in the breast cancer group than controls (60.3% vs. 53.9% for rs11615 A allele; 37.3% vs. 30.7% for XPF rs6498486 C allele). There were no significant between-group differences in the frequencies of ERCC1 rs3212986, ERCC1 rs2298881, XPF rs2276465, or XPF rs2276466 (Table 2).

Table 3 shows the results of multivariate logistic regression analysis of the effects of the six SNPs on breast cancer risk, adjusted for age, family history of breast cancer, history of breast disease, age at first full-term pregnancy, and number of

Amplification **PCR Product** **SAP Treatment****iPLEX Reaction** **Sample conditioning, dispensing, and MALDI-TOF MS****Spectrum** **24-plex spectrum**

FIG. 1. Detection of single-nucleotide polymorphisms by matrix-assisted laser desorption/ionization time-of-flight-mass spectrometry (MALDI-TOF-MS).

full-term pregnancies. The ERCC1 rs11615 variant A/A genotype was associated with increased breast cancer risk in codominant, dominant, and recessive models (OR, 1.62; 95% CI, 1.14–2.31 for codominant model; OR, 1.31; 95% CI, 1.01–1.70 for dominant model; OR, 1.52; 95% CI, 1.09–2.10 for recessive model), and XPF rs6498486 variant C/C genotype carriers had a significantly increased risk of breast cancer in codominant, dominant, and recessive models (OR, 1.63; 95%

CI, 1.10–2.42 for codominant model; OR, 1.34; 95% CI, 1.02–1.77 for dominant model; OR, 1.57; 95% CI, 1.07–2.32 for recessive model). The results of multivariate logistic regression analysis of the combined effect of the combination effect of ERCC1 rs11615 and XPF rs6498486 on the breast cancer risk, adjusted for potential confounding factors are given in Table 4. Individuals with both ERCC1 rs11615 A allele and XPF rs6498486 C allele had a heavy increased risk of breast

TABLE 1. CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF INCLUDED SUBJECTS

Variables	Cases	%	Controls	%	OR (95% CI)	p-Value
Age, years (mean±SD)	45.2±8.2		46.7±8.5			
Family history of breast cancer						
No	432	93.7	495	98.3	1	
Yes	29	6.3	9	1.7	3.61 (1.64–8.78)	<0.001
History of breast disease						
No	301	65.3	370	73.5	1	
Yes	160	34.7	134	26.5	1.48 (1.10–1.95)	0.006
Age at menarche, years						
<12	232	50.3	241	47.8	1	
12~15	157	34.1	179	35.6	0.91 (0.68–1.22)	0.51
>15	72	15.6	84	16.6	0.89 (0.61–1.30)	0.53
Menopausal status						
Pre	139	30.1	140	27.7	1	
Post	322	69.9	364	72.3	0.89 (0.66–1.19)	0.42
Smoking history						
Never	381	82.7	438	86.9	1	
Ever	80	17.2	66	13.1	1.39 (0.96–2.02)	0.07
BMI (kg/m ²)						
<19	74	16.1	92	18.2	1	
19	241	52.3	270	53.6	1.10 (0.77–1.62)	0.56
≥24	146	31.6	142	28.2	1.28 (0.86–1.91)	0.21
Age at first full-term pregnancy						
<25	194	42.1	278	55.1	1	
25	133	28.8	129	25.6	1.48 (1.08–2.03)	0.012
≥30	134	29.1	97	19.3	1.98 (1.42–2.76)	<0.001
Number of full-term pregnancies						
0	31	7.8	14	2.8	1	
1	167	34.3	180	35.8	0.42 (0.20–0.85)	<0.001
≥2	262	57.9	309	61.4	0.38 (0.18–0.76)	<0.001

cancer than double wild-type homozygotes (OR, 2.29; 95% CI, 1.46–3.63).

Discussion

In this study, we have found that polymorphisms in ERCC1 rs11615 and rs6498486 were associated with a pronounced increased risk of breast cancer. To our knowledge, this is the first study that ERCC1 rs11615 and XPF rs6498486 polymorphisms were found to be related with increased risk of breast cancer. It is reported that ERCC1 has a critical

function during the NER mechanism, these findings are biologically plausible. These findings suggest that variants of ERCC1 rs11615 and XPF rs6498486 may be useful genetic susceptibility markers for breast cancer, allowing for identification of high-risk individuals and the development of targeted therapies.

ERCC1 contains 10 exons and encodes a 297 acetaldehyde ammonia product, and has been mapped to chromosome 19q13.32, which is involved in correcting the excision repair deficiency of the NER pathway (van Duin *et al.*, 1986; Reed, 1998). While XPF is located on 16p13.12, contains 11 exons,

TABLE 2. GENOTYPE DISTRIBUTIONS OF SIX SNPs

Variants	Major/minor allele	MAF	Patients			Controls			p-Value	HWE (p-value) control
			A/A ^a	A/a ^b	a/a ^c	A/A	A/a	a/a		
ERCC1 rs11615	G/A	0.3617	183	166	112	232	184	88	0.02	0.22
ERCC1 rs3212986	C/A	0.2935	236	177	48	270	189	45	0.65	0.64
ERCC1 rs2298881	A/C	0.1928	300	105	56	338	112	54	0.69	0.7
XPF rs2276465	A/G	0.2647	296	101	64	339	98	67	0.57	0.09
XPF rs6498486	A/C	0.2637	289	95	77	349	98	57	0.03	0.13
XPF rs2276466	C/G	0.2248	294	103	64	326	108	70	0.91	0.27

^aWild genotype.

^bHeterozygous variant.

^cHomozygous variant.

ERCC1, excision repair cross-complementary group 1; XPF, xeroderma pigmentosum complementation group F; MAF, minor allele frequency; SNP, single-nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium.

TABLE 3. GENOTYPE FREQUENCIES AND OR (95% CI) FOR THE ASSOCIATION BETWEEN SIX SNPs AND BREAST CANCER RISK

Genes	Major/minor allele	Case	Control	OR (95% CI) ^a		
				Codominant	Dominant	Recessive
ERCC1 rs11615	G/G	183	232	—	—	—
	A/G	166	184	1.56 (0.86–1.55)	1.31 (1.01–1.70)	1.52 (1.09–2.10)
	A/A	112	88	1.62 (1.14–2.31)	—	—
ERCC1 rs3212986	C/C	236	270	—	—	—
	A/C	177	189	1.14 (0.70–1.84)	1.10 (0.85–1.43)	1.19 (0.76–1.86)
	A/A	48	45	1.22 (0.76–1.95)	—	—
ERCC1 rs2298881	A/A	300	338	—	—	—
	A/C	105	112	1.06 (0.77–1.45)	1.09 (0.83–1.44)	1.18 (0.77–1.79)
	C/C	56	54	1.19 (0.78–1.83)	—	—
XPF rs2276465	A/A	296	339	—	—	—
	A/G	101	98	1.18 (0.85–1.64)	1.15 (0.87–1.51)	1.05 (0.71–1.55)
	G/G	64	67	1.08 (0.73–1.60)	—	—
XPF rs6498486	A/A	289	349	—	—	—
	A/C	95	98	1.17 (0.84–1.64)	1.34 (1.02–1.77)	1.57 (1.07–2.32)
	C/C	77	57	1.63 (1.10–2.42)	—	—
XPF rs2276466	C/C	294	326	—	—	—
	C/G	103	108	1.07 (0.77–1.48)	1.05 (0.80–1.38)	1.0 (0.68–1.46)
	G/G	64	70	0.95 (0.60–1.50)	—	—

^aAdjusted for age, family history of breast cancer, history of breast disease, age at first full-term pregnancy, and number of full-term pregnancies.

OR, odds ratio; 95% CI, 95% confidence intervals.

and encodes a 916 acetaldehyde ammonia product. It is well known that ERCC1 encodes a subunit for the NER complex that is required for the incision step of the NER pathway (Constantinou *et al.*, 1999; Kamangar *et al.*, 2009). A heterodimer of ERCC1 and XPF catalyzes the 5' incision during the process of excising DNA lesions in recombinational DNA repair and repairing interstrand crosslinks (O'Donovan *et al.*, 1994; Friedberg, 2003; Isla *et al.*, 2004). Therefore, it is possible that variants of ERCC1 and XPF can reduce the activity of DNA damage repair and genomic NER, and contribute to the development of carcinogenesis (Friedberg, 2003). Our study has reported that carrying both the ERCC1 rs11615 A allele and the XPF rs6498486 C allele had a 2.3-fold risk of breast cancer when compared with double wild-type homozygotes, which proved the combination effect of variants of ERCC1 and XPF on breast cancer risk.

Previous studies have indicated that ERCC1 rs11615 variant was found to be associated with the risk of various can-

cers, such as lung cancer, gastric cancer, and prostate cancer (Zhou *et al.*, 2005; Woelfelschneider *et al.*, 2008; He *et al.*, 2012; Yin *et al.*, 2012). Previous studies have reported that the association between variants of ERCC1 and breast cancer risk and the results are inconsistent (Lee *et al.*, 2005a; Crew *et al.*, 2007; Han *et al.*, 2012; Mojgan *et al.*, 2012). Lee *et al.*, (2005a) reported that the ERCC1 8092 A/A genotypes and ERCC1 354 T allele were associated with increased risk of breast cancer. One study conducted in the United States with 1053 breast cancer cases and 1102 population-based controls reported that ERCC1 rs3212986 C/A was associated with an increased risk of breast cancer (Crew *et al.*, 2007). Another study conducted in Iran with 300 breast cancer patients indicated that ERCC1 rs3212981 A/A genotype was associated with a heavy enhanced risk of breast cancer (Mojgan *et al.*, 2012). Our study found that ERCC1 rs11615 A/A was associated with a 1.62-fold risk of breast cancer in a codominant model, indicating that the ERCC1 rs11615 has a role in the development of breast cancer.

XPF, also known as ERCC4, is involved in the NER pathway and is linked to susceptibility to XP and a rare recessive syndrome that includes photosensitivity and malignant tumor development (Zhu *et al.*, 2003). It is reported that XPF is critical for recombination repair, mismatch repair, and possibly immunoglobulin class switching due to the function of identifying damage sites (Kornguth *et al.*, 2005). Previous studies have reported the association between polymorphisms in XPF and breast cancer risk (Smith *et al.*, 2003; Lee *et al.*, 2005b; Mechanic *et al.*, 2006; Jorgensen *et al.*, 2007; Romanowicz-Makowska *et al.*, 2007). However, the results of these studies are inconsistent. Smith *et al.* (2003), Jorgensen *et al.* (2007), and Romanowicz-Makowska *et al.* (2007) did not find the association between XPF polymorphisms and breast cancer risk, while Lee *et al.* (2005b) and Mechanic *et al.* (2006) reported a significant

TABLE 4. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF THE COMBINED EFFECT OF ERCC1 rs11615 AND XPF rs6498486 POLYMORPHISMS ON BREAST CANCER RISK

SNP		Cases, n	Controls, n	OR (95% CI) ^a
ERCC1 rs11615	XPF rs6498486			
GG	AA	102	127	—
GG	C allele	80	105	0.95 (0.63–1.43)
A allele	AA	187	222	1.05 (0.75–1.47)
A allele	C allele	92	50	2.29 (1.46–3.62)

^aAdjusted for age, family history of breast cancer, history of breast disease, age at first full-term pregnancy, and number of full-term pregnancies.

association between variants of XPF and breast cancer risk. However, we found that polymorphisms in XPF rs6498486 were associated with cancer risk in our study. The inconsistency of these studies may be explained by differences in the population background, the source of control subjects, and the sample size. Further studies are required to confirm the present findings.

The current study has several limitations. First, the study was conducted in two hospitals in China, and this cohort may not be representative of China as a whole. Second, breast cancer is a disease induced by multiple genes and environmental factors, and other genetic and environmental factors may be considered in a further study.

In conclusion, the present study shows that the ERCC1 rs11615 and XPF rs6498486 polymorphisms are associated with breast cancer risk in a Chinese population. Carrying both ERCC1 rs11615 A allele and XPF rs6498486 C allele had a heavy increased risk of breast cancer more than double that for wild-type homozygotes. Further large-scale studies are required to elucidate whether these ERCC1 and XPF SNPs interact with environmental factors in the development of breast cancer.

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Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:

Xuedong Fang, PhD

General Surgery Department

The Second Hospital of Jilin University

No. 18 Ziqiang Street

Changchun 130041

China

E-mail: xhpei99@163.com