Distribution and susceptibility of ERCC1/XPF gene polymorphisms in Han and Uygur women with breast cancer in Xinjiang, China

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Abstract
This study aimed to explore the roles of ERCC1/XPF gene polymorphisms in the occurrence of breast cancer in the Uygur and Han ethnic groups in Xinjiang, China. Single nucleotide polymorphisms (SNPs) were detected by TaqMan real-time PCR. The rs11615 G>A and rs2276466 C>G variant frequencies were higher in Uygur patients with breast cancer than in Han patients, while the frequency of rs2298881 C>A was higher in Han patients. We found that rs2298881 C>A (CA vs. CC: OR = 0.35, 95% CI = 0.20-0.60; AA vs. CC: OR = 0.13, 95% CI = 0.04-0.34; CA + AA vs. CC: OR = 0.33, 95% CI = 0.18-0.51; AA vs. CA + CC: OR = 0.24, 95% CI = 0.08-0.62; CA vs. AA + CC: OR = 0.49, 95% CI = 0.29-0.82) was associated with a reduced breast cancer risk and rs3212986 C>A (AA vs. CC: OR = 4.80, 95% CI = 1.79-15.29; CA + AA vs. CC: OR = 1.71, 95% CI = 1.06-2.77; AA vs. CA + CC: OR = 4.12, 95% CI = 1.58-12.89) and rs11615 G>A (AA vs. GG: OR = 3.49, 95% CI = 1.54-8.55; GA + AA vs. GG: OR = 1.98, 95% CI = 1.21-3.27; AA vs. GA + GG: OR = 2.87, 95% CI = 1.30-6.85) were associated with an elevated breast cancer risk among Uygur individuals. In addition, Uygur patients with breast cancer with 2-3 combined risk genotypes of ERCC1 had a higher risk than patients with 0-1 risk genotypes (OR = 2.91; 95% CI = 1.54-5.71, p = 0.001). However, we failed to detect a statistically significant association between ERCC1/XPF polymorphisms and breast cancer risk in five genetic models among Han individuals. Our results showed that ERCC1/XPF gene polymorphisms predispose Uygur individuals to breast cancer; this finding should be verified by further large-scale analyses.

KEYWORDS
breast cancer, gene polymorphisms, Han, susceptibility, Uygur
Breast cancer is one of the most serious cancers threatening the health of women worldwide. According to the World Cancer Statistics, in 2018, approximately 2,100,000 women were diagnosed with breast cancer, accounting for 24.2% of all cancers, ranking first, and approximately 630,000 people died of breast cancer worldwide, accounting for 15% of the total cancer-related deaths, also ranking first. In 2015, there were about 268,600 new cases of breast cancer in women and 69,500 deaths in China. Compared with countries in Europe and the Americas, the incidence of breast cancer in China is relatively low. However, over the past 20 to 30 years, the incidence of breast cancer in China has increased at twice the average rate worldwide, and the mortality rate is also increasing. The detrimental effects of breast cancer on the health of women have become a serious public health issue in China. Although existing treatments have greatly improved prognosis, some patients with breast cancer still have poor outcomes.

Individual genetic factors may play an important role in breast cancer susceptibility, treatment responses, and prognosis. To date, genome-wide association studies (GWAS) and multiple large-scale repeated sequencing studies have identified more than 70 single nucleotide polymorphisms (SNPs) related to breast cancer, including the high-penetrace breast cancer-related genes BRCA1 (breast cancer associated gene 1) and BRCA2 (Breast cancer associated gene 2), moderate-penetrace genes CHEK2 (checkpoint kinase 2) and BRIP1 (BRCA1 interacting protein C-terminal helicase 1), and low-penetrace genes FGFR2 (fibroblast growth factor receptor 2), TNRC9 (also known as TOX3, TOX high mobility group box family member 3), MAP3K1 (mitogen-activated protein kinase kinase kinase 1), and LSP1 (lymphocyte specific protein 1). However, these susceptible genetic variants account for only a small proportion of variation in breast cancer risk; moreover, correction for multiple testing in GWAS can eliminate potential SNPs. Therefore, more gene polymorphisms associated with susceptibility to breast cancer need to be identified. The nucleotide excision repair pathway eliminates twisted helix DNA damage in a multi-step "shear and repair" reaction, and defects in the pathway may lead to cancer. Some previous studies indicate that SNPs in the nucleotide excision repair pathway are associated with susceptibility to certain cancers.

Excision repair cross-complementation group 1 (ERCC1) and XPF (also known as ERCC4, excision repair cross-complementation group 4) encode two proteins involved in the nucleotide excision repair pathway. Owing to the important role of the ERCC1/XPF complex in the DNA repair process, exploring the role of ERCC1/XPF gene polymorphisms in cancer risk has been a major focus of research.

In Xinjiang, China, the incidence of breast cancer is second only to cervical cancer. Han and Uygur are two major ethnic groups in Xinjiang, accounting for 90% of the total population. Although there is no definite epidemiological information about the incidence of breast cancer among Han and Uygur populations in Xinjiang, it is obviously lower in the Uygur population than in the Han population. According to the dynamic changes in the number of hospitalized individuals over the past 5 years, the number of patients with breast cancer of Uygur ethnicity has increased, with an average annual growth rate of 2.11%, while patients of Han ethnicity have fluctuated, with an average annual growth rate of -11.44%. Another study has shown that the incidence of breast cancer in Xinjiang Uygur women is low; however, the age of onset is relatively early (i.e., 36-50 years), most patients are stage II and III, and the prognosis is poor. Therefore, it is important to explore differences in risk factors for breast cancer between Xinjiang Uygur and Han populations. The purpose of our study was to explore the associations between ERCC1/XPF polymorphisms and breast cancer risk and to compare their distributions in Uygurs and Hans to improve our understanding of their roles in the pathogenesis of breast cancer in different races.
ki67) status, and P53 (also known as protein 53 or tumor protein 53) status. Information for individuals in the control group was obtained from the medical examination center system, including name, race, and age.

### 2.3 Genotyping assay

After the patients and healthy controls signed the informed consent form, we collected 5 ml of the subjects' peripheral blood into an EDTA-anticoagulation test tube. The dbSNP database (http://www.ncbi.nlm.nih.gov/) was used to select potential functional SNPs in ERCC1/XPF. A kit provided by Beijing Kangwei Century Biology Company (Beijing, China) was used to extract DNA from whole blood. SNP genotyping was performed by TaqMan real-time PCR. SNP primers were designed and synthesized by Applied Biosystems (Foster City). The probes for variant and wild-type allele were labeled with fluorescent dyes VIC and FAM, respectively. PCR reaction was performed with a 384-well plate (each well with a reaction volume of 5 μl). The PCR machine identified the genotypes based on the relative fluorescence intensity of VIC and FAM. Four negative controls and eight duplicate samples were set in each 384-well plate for quality control. Finally, four SNPs (rs2298881, rs3212986, and rs11615 in ERCC1 and rs2276466 in XPF) were successfully genotyped.

### 2.4 Statistical analysis

Hardy–Weinberg equilibrium (HWE) in the control population was evaluated. Six inheritance models were used to assess cancer susceptibility. The chi-squared test was used to assess differences in genotype and allele frequencies. Logistic regression, adjusting for age, was used to calculate the association between SNPs and breast cancer susceptibility. The GTEx (genotype-tissue expression, https://www.gtexportal.org/) portal was used to assess the biological effects of rs2298881 C>A and rs11615 G>A on ERCC1 gene expression. All statistical tests were two-sided, and statistical significance was evaluated at the 0.05 α-level. All results were calculated using R (version 3.5.1).

### 3 RESULTS

#### 3.1 Distribution of ERCC1/XPF polymorphisms in distinct ethnic groups

As determined by a chi-squared test, the distributions of ERCC1 rs2298881 C>A (p < 0.001), ERCC1 rs11615 G>A
(p < 0.001), and XPF rs2276466 C>G (p = 0.002) differed significantly between Uygur and Han patients with breast cancer. Similar results were found for the two alleles. The detailed results are shown in Table 1.

3.2 Associations between ERCC1/XPF polymorphisms and breast cancer susceptibility

We found significant associations between four SNPs and breast cancer susceptibility in the allelic genetic models among the Han and Uygur groups; the details are shown in Table 2. However, we failed to detect a statistically significant association between the four SNPs and breast cancer risk in the other five genetic models for the Han ethnicity (Table 3). As shown in Table 4, significant associations were observed between ERCC1 rs2298881 C>A (CA vs. CC: OR = 0.35, 95% CI = 0.20-0.60, p < 0.001; AA vs. CC: OR = 0.13, 95% CI = 0.04-0.34, p < 0.001; CA+AA vs. CC: OR = 0.33, 95% CI = 0.18-0.51, p < 0.001; AA vs. CA+CC: OR = 0.24, 95% CI = 0.08-0.62, p = 0.005; CA vs. AA+CC: OR = 0.49, 95% CI = 0.29-0.82, p = 0.007), rs3212986 (AA vs. CC: OR = 4.80, 95% CI = 1.79-15.29, p = 0.003; CA+AA vs. CC: OR = 1.71, 95% CI = 1.06-2.77, p = 0.028; AA vs. CA+CC: OR = 4.12, 95% CI = 1.58-12.89, p = 0.007), rs11615 (AA vs. GG: OR = 3.49, 95% CI = 1.54-8.55, p = 0.004; GA+AA vs. GG: OR = 1.98, 95% CI = 1.21-3.27, p = 0.007; AA vs. GA+GG: OR = 2.87, 95% CI = 1.30-6.85, p = 0.012) and breast cancer susceptibility in the Uygur population. In addition, we found that Uygur patients with breast cancer with 2-3 combined risk genotypes of ERCC1 had a higher risk than that of individuals with 0-1 risk genotypes (OR = 2.91; 95% CI = 1.54-5.71, p = 0.001).

3.3 Stratification Analysis

To further explore the association between ERCC1/XPF polymorphisms and breast cancer susceptibility, we performed a stratified analysis according to age, TNM stage, ER status, PR status, HER2 status, Ki67 status, and P53 status. As shown in Table 5, among the Han population, ERCC1 rs2298881 C>A was associated with a reduced risk of breast cancer in individuals ≥50 years old or with positive expression of P53. XPF rs2276466 C>G was also associated with a lower risk of breast cancer in patients aged <50 years, stage I+II, with positive expression of ER, positive expression of PR, or negative expression of Ki67. Similar associations for different P53 expression states were found. In the Uygur population, rs2298881 C>A was associated with a reduced risk of breast cancer with positive expression of HER2 or p53, irrespective of age, TNM stage, ER, PR, and P53 expression status. Rs312986 C>A was related to negative expression of PR, HER2, or Ki67. Rs11615 G>A was related to the risk of breast cancer in patients <50 years of age, with negative expression of ER, positive expression of PR, or positive expression of p53. A similar association was found for patients with breast cancer with different stages and Ki67 statuses; the details are shown in Table 6.

3.4 Expression quantitative trait loci

As shown in Figure 1, the GTEx portal was used to assess the effects of rs2298881 C>A and rs11615 G>A on ERCC1 gene expression. We found that both rs2298881 C>A and rs11615 G>A genotypes were significantly related to ERCC1 gene expression in breast-mammary and tissue- and cell-cultured fibroblasts.

| TABLE 2 | Allelic genetic models among the Han and Uygur nationalities |
|----------|-----------------|--------|--------|--------|--------|----------|--------|
| Gene     | SNP             | Allele | Case A | Case B | Control A | Control B | OR (95% CI) | p      |
|----------|-----------------|--------|--------|--------|-----------|-----------|-------------|--------|
| Han      | ERCC1           | rs2298881 | C    | A     | 336 | 309 | 448 | 280 | 1.47(1.19-1.82) | <0.001 |
|          | ERCC1           | rs3212986 | C    | A     | 350 | 353 | 496 | 224 | 2.23(1.80-2.77) | <0.001 |
|          | ERCC1           | rs11615 | G    | A     | 439 | 555 | 620 | 106 | 7.39(5.81-9.41) | <0.001 |
|          | XPF             | rs2276466 | C    | G     | 451 | 521 | 616 | 128 | 5.56(4.42-6.99) | <0.001 |
| Uygurs   | ERCC1           | rs2298881 | C    | A     | 191 | 86  | 147 | 105 | 0.63(0.44-0.90) | 0.011  |
|          | ERCC1           | rs3212986 | C    | A     | 182 | 178 | 215 | 65  | 3.24(2.29-4.57) | <0.001 |
|          | ERCC1           | rs11615  | G    | A     | 187 | 206 | 221 | 55  | 4.43(3.10-6.32) | <0.001 |
|          | XPF             | rs2276466 | C    | G     | 206 | 188 | 223 | 59  | 3.45(2.43-4.89) | <0.001 |

Bold font: p < 0.05.
4 | DISCUSSION

We performed the first case–control study of the role of ERCC1/XPF polymorphisms in Han and Uygur patients with breast cancer. In particular, we included 140 Uygur patients with breast cancer, 141 Uygur healthy controls, 265 Han patients with breast cancer, and 374 Han healthy controls. Our data showed that rs2298881 C>A was associated with a higher breast cancer risk, and rs3212986 C>A and rs11615 G>A were associated with a lower breast cancer risk in the Uygur population. In addition, the rs11615 and rs2276466 polymorphisms frequencies were higher in the Uygur group compared to Han patients.
TABLE 5  Stratification analysis for the association between *ERCC1/XPF* gene genotypes and Han breast cancer susceptibility.

| Variable | rs2298881* | rs3212986* | rs11615* | rs2276466* |
|----------|------------|------------|----------|------------|
|          | case/     | case/      | case/    | case/      |
|          | control   | control    | control  | control    |
|          | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Han      |            |            |          |            |
| Age      |            |            |          |            |
| <50      | 47/94      | 83/137     | 1.21(0.78-1.90) | 0.4     |
|          | 58/105     | 71/121     | 1.06(0.69-1.64) | 0.79    |
|          | 100/167    | 32/60      | 0.89(0.54-1.46) | 0.65    |
| ≥50      | 63/43      | 68/90      | 0.52(0.31-0.85) | 0.001   |
|          | 51/62      | 80/72      | 1.35(0.83-2.21) | 0.23    |
|          | 96/102     | 32/34      | 1.00(0.57-1.75) | 1       |
|          | 108/166    | 25/69      | 0.56(0.33-0.92) | 0.03    |
| Stage    |            |            |          |            |
| 0 + I+II | 77/137     | 107/227    | 0.81(0.56-1.18) | 0.27    |
|          | 80/167     | 104/193    | 1.16(0.80-1.67) | 0.43    |
|          | 137/269    | 47/94      | 1.04(0.68-1.57) | 0.87    |
|          | 143/256    | 44/116     | 0.62(0.41-0.94) | 0.03    |
| III+IV   | 33/137     | 42/227     | 0.72(0.43-1.21) | 0.21    |
|          | 29/167     | 45/193     | 1.42(0.85-2.40) | 0.19    |
|          | 57/269     | 17/94      | 0.91(0.49-1.63) | 0.76    |
|          | 50/256     | 26/116     | 1.09(0.63-1.83) | 0.76    |
| ER       |            |            |          |            |
| Negative | 29/137     | 48/227     | 0.89(0.53-1.52) | 0.68    |
|          | 33/167     | 42/193     | 1.14(0.68-1.92) | 0.62    |
|          | 59/269     | 18/94      | 0.96(0.52-1.72) | 0.9     |
| Positive | 81/137     | 101/227    | 0.74(0.51-1.07) | 0.11    |
|          | 76/167     | 107/193    | 1.27(0.88-1.83) | 0.21    |
|          | 135/269    | 46/94      | 1.02(0.67-1.54) | 0.92    |
|          | 147/256    | 38/116     | 0.54(0.35-0.82) | 0.005   |
| PR       |            |            |          |            |
| Negative | 47/137     | 70/227     | 0.82(0.53-1.29) | 0.39    |
|          | 53/167     | 63/193     | 1.08(0.70-1.67) | 0.73    |
|          | 89/269     | 30/94      | 1.04(0.63-1.68) | 0.89    |
| Positive | 63/137     | 79/227     | 0.74(0.50-1.10) | 0.14    |
|          | 56/167     | 86/193     | 1.37(0.92-2.05) | 0.13    |
|          | 105/269    | 34/94      | 0.98(0.61-1.53) | 0.92    |
|          | 117/256    | 26/116     | 0.47(0.28-0.75) | 0.002   |
| HER2     |            |            |          |            |
| Negative | 62/137     | 85/227     | 0.80(0.53-1.19) | 0.27    |
|          | 65/167     | 82/193     | 1.11(0.75-1.66) | 0.59    |
|          | 109/269    | 40/94      | 1.14(0.73-1.76) | 0.57    |
| Positive | 43/137     | 64/227     | 0.85(0.54-1.33) | 0.46    |
|          | 44/167     | 62/193     | 1.29(0.83-2.03) | 0.26    |
|          | 81/269     | 23/94      | 0.85(0.49-1.42) | 0.55    |
|          | 80/256     | 29/116     | 0.75(0.46-1.21) | 0.25    |
| Ki67     |            |            |          |            |
| Negative | 25/137     | 24/227     | 0.55(0.30-1.00) | 0.051   |
|          | 25/167     | 24/193     | 0.87(0.47-1.58) | 0.64    |
|          | 31/269     | 19/94      | 1.81(0.96-3.36) | 0.06    |
| Positive | 85/137     | 125/227    | 0.88(0.61-1.26) | 0.48    |
|          | 84/167     | 125/193    | 1.32(0.92-1.89) | 0.13    |
|          | 163/269    | 45/94      | 0.85(0.55-1.28) | 0.43    |
|          | 149/256    | 64/116     | 0.88(0.60-1.28) | 0.5     |
| P53      |            |            |          |            |
| Negative | 22/137     | 22/227     | 0.57(0.30-1.08) | 0.08    |
|          | 21/167     | 22/193     | 0.94(0.50-1.78) | 0.84    |
|          | 27/269     | 17/94      | 1.86(0.95-3.55) | 0.06    |
| Positive | 19/137     | 16/227     | 0.47(0.23-0.96) | 0.04    |
|          | 15/167     | 21/193     | 1.27(0.63-2.59) | 0.51    |

Bold font: *p* < 0.05. ER: estrogen receptor.
HER2, human epidermal growth factor receptor-2; PR, progesterone receptor.
than the Han group, while the opposite trend was observed for rs2298881.

ERCC1 is located on chromosome 19q13.32 and contains 10 exons. XPF maps to chromosome 16p13.12 and consists of 11 exons. The proteins ERCC1 and XPF act as structure-specific endonucleases in the form of heterodimers. The heterodimer catalyzes the formation of a 5’ incision in the process of nucleotide excision and repair. In the heterodimer, ERCC1 is a key DNA-binding subunit without endonuclease activity, while XPF has catalytic activity. Associations between genetic variation in ERCC1/XPF and several human genetic diseases have been shown in previous research.

Previous studies have also reported a relationship between ERCC1/XPF gene polymorphisms and cancer risk. For example, individuals with rs11615 polymorphisms are predisposed to colorectal cancer. However, in another case–control study in the United States, no association was observed between ERCC1/XPF polymorphisms and endometrial cancer susceptibility. The inconsistencies among studies indicate that the same genetic polymorphism may have different effects on susceptibility depending on race or cancer type. Therefore, it is necessary to explore the contribution of ERCC1/XPF gene polymorphisms to breast cancer risk in specific populations, including the Xinjiang Uygur and Han groups.

This is the first study of the association between ERCC1/XPF polymorphisms and susceptibility to breast cancer in Uygur and Han populations in Xinjiang. We observed that rs2298881 C>A was related to a reduced breast cancer risk, and rs3212986 C>A and rs11615 G>A were related to an increased breast cancer risk among Uygur individuals. These results were consistent with those of previous studies. The opposite pattern observed for rs11615 G>A and rs2298881 C>A with respect to breast cancer susceptibility may be explained by eQTL results. The rs2298881 variant led to a decrease in ERCC1 expression, while the rs11615 variant led to an increase in ERCC1 expression. Among Han individuals, we failed to detect a statistically significant difference in five genetic models, contrary to the results of a previous study. This difference may be due to the different origins of the study population. Our Han group was from Xinjiang, whereas the previous
# Table 6
Stratification analysis for the association between ERCC1/XPF gene genotypes and Uygur breast cancer susceptibility

| Variable | rs2298881 case/ control | rs3212986 case/ control | rs11615 case/ control | rs2276466 case/ control |
|----------|--------------------------|--------------------------|-----------------------|-------------------------|
|          | CC | CA+AA | OR (95% CI)  | p  | CC | CA+AA | OR (95% CI)  | p  | CC | CA+AA | OR (95% CI)  | p  |
| Uygurs   |    |       |            |    |    |       |            |    |    |       |            |    |
| Age      |    |       |            |    |    |       |            |    |    |       |            |    |
| <50      | 42/27 | 29/62 | 0.30(0.15-0.57) | <0.001 | 37/58 | 46/42 | 1.72(0.96-3.10) | 0.07 | 36/66 | 47/32 | 2.69(1.48-4.98) | 0.001 |
| ≥50      | 33/16 | 18/24 | 0.30(0.12-0.71) | 0.007 | 24/22 | 32/18 | 1.63(0.72-3.72) | 0.24 | 35/26 | 20/14 | 1.06(0.45-2.51) | 0.89 |
| Stage    |    |       |            |    |    |       |            |    |    |       |            |    |
| 0 + I+II | 48/40 | 32/86 | 0.32(0.18-0.58) | <0.001 | 41/80 | 52/60 | 1.67(0.98-2.86) | 0.06 | 48/92 | 44/46 | 1.91(1.11-3.32) | 0.02 |
| III+IV   | 27/40 | 15/86 | 0.25(0.12-0.53) | 0.004 | 20/80 | 26/60 | 1.88(0.94-3.79) | 0.07 | 23/92 | 23/46 | 2.08(1.04-4.20) | 0.04 |
| ER       |    |       |            |    |    |       |            |    |    |       |            |    |
| Negative | 39/40 | 17/86 | 0.20(0.10-0.41) | <0.001 | 28/80 | 37/60 | 1.64(0.89-3.06) | 0.12 | 31/92 | 34/46 | 2.27(1.21-4.28) | 0.01 |
| Positive | 36/40 | 30/86 | 0.39(0.21-0.72) | 0.003 | 33/80 | 41/60 | 1.70(0.96-3.03) | 0.07 | 40/92 | 33/46 | 1.68(0.94-3.03) | 0.08 |
| PR       |    |       |            |    |    |       |            |    |    |       |            |    |
| Negative | 27/40 | 15/86 | 0.29(0.13-0.63) | 0.002 | 17/80 | 31/60 | 2.38(1.17-4.99) | 0.018 | 29/92 | 18/46 | 1.28(0.61-2.65) | 0.51 |
| Positive | 48/40 | 32/86 | 0.31(0.17-0.55) | <0.001 | 44/80 | 47/60 | 1.44(0.85-2.47) | 0.18 | 42/92 | 49/46 | 2.35(1.37-4.08) | 0.002 |
| HER2     |    |       |            |    |    |       |            |    |    |       |            |    |
| Negative | 16/40 | 15/86 | 0.46(0.21-1.04) | 0.06 | 12/80 | 23/60 | 2.44(1.13-5.51) | 0.025 | 25/92 | 11/46 | 0.89(0.38-1.95) | 0.77 |
| Positive | 27/40 | 19/86 | 0.40(0.18-0.84) | 0.02 | 21/80 | 30/60 | 2.01(1.00-1.14) | 0.05 | 30/92 | 20/46 | 1.60(0.76-3.34) | 0.21 |
| Ki67     |    |       |            |    |    |       |            |    |    |       |            |    |
| Negative | 13/40 | 14/86 | 0.50(0.21-1.17) | 0.11 | 16/80 | 13/60 | 1.08(0.48-2.42) | 0.85 | 12/92 | 17/46 | 2.84(1.26-6.60) | 0.013 |
| Positive | 62/40 | 33/86 | 0.25(0.14-0.45) | <0.001 | 45/80 | 65/60 | 1.98(1.19-3.34) | 0.01 | 59/92 | 50/46 | 1.84(1.09-3.15) | 0.02 |
| P53      |    |       |            |    |    |       |            |    |    |       |            |    |
| Negative | 28/40 | 22/86 | 0.37(0.19-0.73) | 0.004 | 26/80 | 30/60 | 1.62(0.86-3.06) | 0.14 | 35/92 | 22/46 | 1.28(0.37-2.43) | 0.45 |
| Positive | 41/40 | 20/86 | 0.23(0.12-0.44) | <0.001 | 31/80 | 41/60 | 1.73(0.97-3.11) | 0.07 | 30/92 | 40/46 | 2.95(1.62-5.49) | <0.001 |

Bold font: $p < 0.05$. ER: estrogen receptor. HER2, human epidermal growth factor receptor-2; PR, progesterone receptor.
study included individuals from Henan Province. This suggests that genetic polymorphisms within the same ethnic group in different regions have different effects on cancer susceptibility. Extensive evidence suggests that a single SNP may not have sufficient capacity to explain the overall cancer risk, and a combination of multiple SNPs may be a more useful predictor.\textsuperscript{29} Therefore, we further analyzed the combined effect of risk genotypes for \textit{ERCC1}. We found that Uyghur patients with breast cancer with 2-3 combined risk genotypes of \textit{ERCC1} had a higher risk. Similar conclusions have been reported for other cancers.\textsuperscript{30,31}

However, our study had some limitations. First, as a single-center study, selection bias is inevitable. Second, the size of the Uyghur group was relatively small compared to that of the Han group. Thus, our conclusions, especially those for the Uyghur population, need to be verified using a larger sample size. Third, the number of SNPs analyzed in this study was limited, and it is necessary to evaluate links between additional SNPs and breast cancer susceptibility. Finally, our conclusions should be interpreted with caution because the population was from Xinjiang and generalizability to other populations has not been established.

5 | CONCLUSIONS

In summary, our study showed that \textit{ERCC1/XPF} gene polymorphisms in the Uyghur group predispose individuals to breast cancer. This finding should be verified in a larger sample, and further studies are needed to determine the mechanism by which \textit{ERCC1/XPF} influence breast cancer susceptibility as well as the causes of differences among races. Finally, our research deepens our understanding of the role of genetic variation in different races in cancer and may contribute to future research focused on cancer occurrence and prevention.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

H.-T. L. and L.-H. Z. performed experiments, analyzed data and wrote the paper; performed some experiments and analyzed data; B.-L. M. and Z.-J. D. initiated the study, designed experiments. J. M., Y.-Y. Z., J.-J. F., N. L., Y. Z., T. S., and Z. Z. read and approved the final manuscript.

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