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# *CYP17* polymorphisms are associated with decreased risk of breast cancer in Chinese Han women: a case–control study

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Pengtao Yang,[1,*] Meng Wang,[1,*] Tian Tian,[1,*] Yanjing Feng,[2] Yi Zheng,[1] Tielin Yang,[3] Hongtao Li,[4] Shuai Lin,[1] Peng Xu,[1] Yujiao Deng,[1] Qian Hao,[1] Na Li,[1] Feng Guan,[5] Zhijun Dai[1]

[1]Department of Oncology, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, People's Republic of China; [2]Department of Cardiology, Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an 710004, People's Republic of China; [3]School of Life Science and Technology, Xi'an Jiaotong University, Xi'an 710049, People's Republic of China; [4]Department of Breast, Head and Neck Surgery, Affiliated Tumor Hospital of Xinjiang Medical University, Urumchi, 830000, People's Republic of China; [5]College of Life Science and Technology, Northwest University, Xi'an 710069, People's Republic of China

*These authors contributed equally to this work

**Introduction:** CYP17 is the second most important enzyme in estradiol synthesis. Epidemiological studies have shown the associations between *CYP17* polymorphisms and cancer risk. We conducted a case–control study to evaluate the relationship between *CYP17* polymorphisms (rs743572 and rs2486758) and breast cancer (BC) risk.

**Patients and methods:** This case–control study included 560 BC patients and 583 age-matched healthy controls from Northwest China. Two polymorphisms (rs743572 and rs2486758) of *CYP17* were genotyped by using Sequenom MassARRAY. ORs and 95% CIs were used to evaluate the relationship.

**Results:** Compared with the wild genotype of rs743572, we found a significantly reduced risk of BC associated with the variant genotypes (heterozygote model: OR=0.69, 95% CI=0.53–0.89; homozygote model: OR=0.68, 95% CI=0.49–0.95; dominant model: OR=0.69, 95% CI=0.54–0.87; overdominant model: OR=0.78, 95% CI=0.62–0.98; allele model: OR=0.79, 95% CI=0.66–0.93). For rs2486758 polymorphism, we did not find any difference in any of the genetic models. Further stratification analysis by clinical characteristics showed rs743572 was associated with estrogen receptor status (heterozygote model: OR=2.13, 95% CI=1.47–3.08; homozygote model: OR=3.29, 95% CI=1.94–5.58; dominant model: OR=2.39, 95% CI=1.69–3.37) and progesterone receptor status (homozygote model: OR=3.17, 95% CI=1.82–5.55), but there was no association between rs2486758 and clinical characteristics of BC. Haplotype analysis showed that $G_{rs743572}C_{rs2486758}$ haplotype was a protective factor of BC (OR=0.52, 95% CI=0.40–0.67). Survival analysis did not find that *CYP17* rs743572 polymorphism was associated with triple-negative BC, either in terms of overall survival or progression-free survival.

**Conclusion:** Our results suggest that *CYP17* polymorphisms may reduce the susceptibility to BC in Chinese women.

**Keywords:** *CYP17*, polymorphism, breast cancer, susceptibility

## Introduction

Breast cancer (BC) is the most common cancer in women worldwide and the second leading cause of cancer death in the United States.[1] In People's Republic of China, BC led to 70,700 deaths in 2015 and the estimated number of new cases is 272,400.[2] The development of BC is a complex interaction of genes, environment, and lifestyle.[3] Based on current research, it is certain that estrogen levels are associated with the occurrence and development of endometrial cancer and BC,[4] and estrogen metabolism-related genes which affect estrogen levels are considered to participate in the pathogenesis of BC. Among them, one of the most important gene is cytochrome P450, family 17 (*CYP17*).[5,6]

Correspondence: Zhijun Dai
Department of Oncology, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, People's Republic of China
Email dzj0911@xjtu.edu.cn

Feng Guan
College of Life Science and Technology, Northwest University, 229 North Taibai Avenue, Xi'an 710069, People's Republic of China
Email guanfeng@nwu.edu.cn

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Various enzymes mediate the conversion of cholesterol into estrogen and CYP17 is a key enzyme in estradiol synthesis.[7] It has two different catalytic reactions: the 17α-hydroxylase and 17,20-lyase reactions,[5] their ratio affects the final product of steroid hormone biosynthesis. A single-nucleotide polymorphism (SNP), *CYP17*-34T/C polymorphism (rs743572), is located in the 5'-untranslated promoter region, it creates a recognition site for the MspAI restriction enzyme resulting in two allelic variants: T (A1 allele) and C (A2 allele).[8] The A2 allele was considered to improve the transcription efficiency of the *CYP17* gene, thereby increasing the activity of related enzymes and the synthesis of estradiol,[9,10] therefore this SNP has received widespread attention. Another important SNP is rs2486758, which is mapped to the intergenic section near the 5' of the *CYP17* gene.[11] The previous study showed that the rs2486758 minor allele increased the expression of *CYP17* gene by affecting gene splicing and transcription factor binding or the sequence of noncoding RNA.[12]

Previous studies have confirmed the association between *CYP17* gene polymorphism and risk of various cancers.[8–10,13–17] Although there have been several studies about the relationship between *CYP17* gene polymorphism (rs743572) and BC susceptibility of Han Chinese,[18–24] the conclusions of these studies were not entirely consistent. Specifically, there were no studies regarding the association between rs2486758 and BC susceptibility of the Chinese. Therefore, we conducted this case–control study to investigate the relationship between the *CYP17* polymorphisms (rs2486758 and rs743572) and BC risk in a Northwest Chinese population.

# Patients and methods

## Ethics statement

The study was approved by the Institutional Review Board of the Xi'an Jiaotong University (Xi'an, People's Republic of China). During the time of recruitment, all participants signed a written informed consent form for the study.

## Study population

Our study consisted of 560 BC patients who were consecutively recruited between January 2013 and October 2014 at the Second Affiliated Hospital of Xi'an Jiaotong University, People's Republic of China. There was no age limit for recruiting patients. All patients were pathologically confirmed as having BC. Patients who received chemotherapy or radiotherapy before surgery or had other types of cancer were excluded. A total of 583 cancer-free healthy controls, who were receiving health care (without any underlying illnesses) from outpatient departments, were recruited. Controls were frequency aged-matched to the cases (±5 years). The methods were carried out in accordance with the approved guidelines.[34] After obtaining written informed consent, we obtained participants' relevant information through a self-administered questionnaire, including age, ethnicity, place of residence, education level, and other potential confounding factors of interest. Clinical characteristics were collected and regularly updated through follow-up, including menopausal status, tumor size, axillary lymph node metastasis, ER status, PR status, Her-2 status, and Ki67 status. In addition, 48 cases of TNBC were followed up every month by telephone up to October 31, 2017. OS was calculated from the date of pathological diagnosis to the date of death or the last follow-up. PFS was calculated from the date of pathologically confirmed diagnosis to the progression of the disease, death without progression, or last clinical follow-up. Survival distributions were estimated by using the Kaplan–Meier method and difference in the survival was tested using the log-rank test.

## Genotyping assay

The blood samples were collected from the peripheral vein and placed into EDTA-coated tubes. All samples were stored at −80°C, after centrifugation, whole blood cells were collected for further analysis.[35] Standard phenol–chloroform extraction method was used to extract genomic DNA from blood leukocytes. The DNA concentration was checked by spectrometry (DU530 UV/VIS spectrophotometer, Beckman Instruments, Fullerton, CA, USA), which we described in our previous studies.[25,36,37] Two tag-SNPs (rs2486758 and rs743572) were selected in our study based on minor allele frequency data from HapMap to achieve 80% power (http://www.hapmap.org).[38] Sequenom MassARRAY Assay Design 3.0 Software (Agena Bioscience, San Diego, CA, USA) was used to design multiplexed SNP MassEXTEND assay. *CYP17* genotyping was performed by using Sequenom MassARRAY RS1000 according to the manufacturer's standard recommended protocol. The corresponding primers for each SNP in this study were listed in Table 7. Sequenom Typer 3.0 Software (Sequenom Inc., San Diego, CA, USA) was used for data analysis.

## Statistical analyses

The differences in the distributions of demographic characteristics, selected variables, and frequencies of the two SNP genotypes between the cases and controls were compared using Student's *t*-test or $\chi^2$ test. In control subjects, any departure from HWE was tested by applying goodness of

fit $\chi^2$ test before analysis. The association between *CYP17* SNPs and BC risk were estimated by computing ORs and 95% CIs, using univariate and multivariate logistic regression analysis with adjustment for age and BMI Online SHEsis software (http://analysis.bio-x.cn/myAnalysis.php) was used to evaluate LD. Phase 2.1 (downloaded from http://stephenslab.uchicago.edu/phase/download.html) software was used for haplotype analysis and for each haplotype, an OR and 95% CI was estimated by using $\chi^2$ test. All the statistical analyses were performed using the software SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA), and a two-sided *P*-value <0.05 was considered statistically significant. GraphPad Prism 6 (https://secure.graphpad.com/) was used for survival analysis, the HR and 95% CI were calculated by univariate Cox proportional hazards model, multivariate Cox regression models were performed to compute HR and 95% CI, after adjusting for confounding factors.

# Results

## Characteristics of the patients and controls

The clinical and demographic characteristic of BC patients and controls were described in our previous studies.[25,26] The cases and controls were matched by age (Student's *t*-test, *P*=0.612). As shown in Table 1, there was no significant difference in the distribution of menopausal state between the two groups ($\chi^2$ test, *P*=0.716). However, the BMI was significantly different between BC patients and healthy controls (Student's *t*-test, *P*=0.038), which we considered may be related to the fact that most BC patients underwent modified radical mastectomy.

**Table 1** The characteristics of breast cancer cases and cancer-free controls

| Characteristics | Cases | Controls | *P*-value* |
|---|---|---|---|
| Number | 560 | 583 | |
| Age (mean ± SD) | 49.09±11.02 | 48.80±8.28 | 0.612 |
| Menopausal status | | | |
| Premenopausal | 264 | 281 | |
| Postmenopausal | 296 | 302 | 0.716 |
| Number of pregnancies | | | |
| <2 | 289 | 291 | 0.594 |
| ≥2 | 271 | 292 | |
| Body mass index (kg/m$^2$) | | | |
| (mean ± SD) | 22.52±2.84 | 22.95±3.21 | **0.038** |
| Tumor size | | | |
| <2 cm | 188 | | |
| ≥2 cm | 372 | | |
| LN metastasis | | | |
| Negative | 236 | | |
| Positive | 324 | | |
| ER | | | |
| Negative | 247 | | |
| Positive | 313 | | |
| PR | | | |
| Negative | 255 | | |
| Positive | 305 | | |
| Her-2 | | | |
| Negative | 389 | | |
| Positive | 171 | | |
| Ki67 | | | |
| <50% | 195 | | |
| ≥50% | 365 | | |

**Notes:** *t-test or two-sided $\chi^2$ test. The bold text indicates a statistically significant difference.
**Abbreviations:** LN, axillary lymph node; ER, estrogen receptor; PR, progesterone receptor.

## Association between *CYP17* polymorphisms and BC risk

The genotypes and allele frequencies of the *CYP17* rs2486758 and rs743572 polymorphisms are shown in Table 2. The genotype frequencies of both SNPs in controls were in accordance with Hardy–Weinberg Equilibrium (HWE) ($\chi^2$ test, for rs743572, *P*=0.49; for rs2486758, *P*=0.95 respectively). Compared with the wild genotype of rs743572, we found a significantly reduced risk of BC associated with the variant genotypes in all genetic models except recessive model ($\chi^2$ test, heterozygote model: OR=0.69, 95% CI=0.53–0.89; homozygote model: OR=0.68, 95% CI=0.49–0.95; dominant model: OR=0.69, 95% CI=0.54–0.87; overdominant model: OR=0.78, 95% CI=0.62–0.98; allele model: OR=0.79, 95% CI=0.66–0.93). These results suggested that the *CYP17* rs743572 polymorphism had a protective effect on BC risk. However, we did not observe a significant association between the *CYP17* rs2486758 polymorphism and BC risk in any genetic model.

## Stratified analysis of *CYP17* polymorphisms and BC risk

Stratified analysis regarding the effect of rs743572 and rs2486758 polymorphisms on BC according to menopausal status are displayed in Table 3. The results indicated that rs743572 was associated with a decreased BC risk in both premenopausal and postmenopausal women ($\chi^2$ test, for premenopausal women, homozygote model: OR=0.40, 95% CI=0.23–0.71; dominant model: OR=0.69, 95% CI=0.48–0.96, and for postmenopausal women, heterozygote model: OR=0.62, 95% CI=0.43–0.89; dominant model: OR=0.70, 95% CI=0.50–0.97). However, there was no association between rs2486758 and BC risk in premenopausal patients or postmenopausal patients.

**Table 2** Genotype frequencies of *CYP17* polymorphisms in cases and controls

| Model | Genotype | Control (n, %) | Case (n, %) | OR (95% CI) | *P*-value* |
|---|---|---|---|---|---|
| **rs743572† HWE: *P*=0.49** | | | | | |
| **Co-dominant** | AA | 198 (34.0%) | 240 (42.9%) | 1.00 (reference) | |
| Heterozygote | GA | 276 (47.4%) | 231 (41.2%) | 0.69 (0.53–0.89) | **0.005** |
| Homozygote | GG | 108 (18.6%) | 89 (15.9%) | 0.68 (0.49–0.95) | **0.025** |
| **Dominant** | AA | 198 (34.0%) | 240 (42.9%) | 1.00 (reference) | |
| | GA +GG | 384 (66.0%) | 320 (57.1%) | 0.69 (0.54–0.87) | **0.002** |
| **Recessive** | AA + GA | 474 (81.4%) | 471 (84.1%) | 1.00 (reference) | |
| | GG | 108 (18.6%) | 89 (15.9%) | 0.83 (0.61–1.13) | 0.234 |
| **Overdominant** | AA+GG | 306 (52.6%) | 329 (58.8%) | 1.00 (reference) | |
| | GA | 276 (47.4%) | 231 (41.2%) | 0.78 (0.62–0.98) | **0.036** |
| **Allele** | A | 672 (57.7%) | 711 (63.5%) | 1.00 (reference) | |
| | G | 492 (42.3%) | 409 (36.5%) | 0.79 (0.66–0.93) | **0.005** |
| **rs2486758‡ HWE: *P*=0.95** | | | | | |
| **Co-dominant** | TT | 385 (66.2%) | 377 (67.4%) | 1.00 (reference) | |
| Heterozygote | TC | 177 (30.4%) | 162 (29.0%) | 0.94 (0.72–1.21) | 0.605 |
| Homozygote | CC | 20 (3.4%) | 20 (3.6%) | 1.02 (0.94–1.53) | 0.948 |
| **Dominant** | TT | 385 (66.2%) | 377 (67.4%) | 1.00 (reference) | |
| | TC +CC | 197 (33.8%) | 182 (32.6%) | 0.94 (0.74–1.21) | 0.644 |
| **Recessive** | TT+ TC | 562 (96.6%) | 539 (96.4%) | 1.00 (reference) | |
| | CC | 20 (3.4%) | 20 (3.6%) | 1.04 (0.55–1.96) | 0.897 |
| **Overdominant** | TT+CC | 405 (69.6%) | 397 (71.0%) | 1.00 (reference) | |
| | TC | 177 (30.4%) | 162 (29.0%) | 0.93 (0.72–1.20) | 0.597 |
| **Allele** | T | 947 (81.4%) | 916 (82.0%) | 1.00 (reference) | |
| | C | 217 (18.6%) | 202 (18.0%) | 0.96 (0.78–1.19) | 0.723 |

**Notes:** *Two-sided $\chi^2$ test for the distributions of genotype and allele frequencies. Adjusted for age and body mass index. †Genotype deletion: controls n=1. ‡Genotype deletion: controls n=1, cases n=1. The bold text indicates a statistically significant difference.
**Abbreviation:** HWE, Hardy–Weinberg Equilibrium.

**Table 3** Stratification analysis by menopausal status and association between *CYP17* polymorphisms and breast cancer risk

| Menopausal status | Genotype distributions (case/control) | | | |
|---|---|---|---|---|
| | **AA** | **Aa** | **aa** | **Aa+aa** |
| **rs743572** | | | | |
| **Premenopausal** | 116/97 | 126/137 | 22/46 | 148/183 |
| OR (95% CI) | 1.00 (reference) | 0.77 (0.54–1.11) | **0.40 (0.23–0.71)** | **0.69 (0.48–0.96)** |
| *P*-value* | | 0.167 | **0.002** | **0.028** |
| **Postmenopausal** | 124/101 | 105/139 | 67/62 | 172/201 |
| OR (95% CI) | 1.00 (reference) | **0.62 (0.43–0.89)** | 0.88 (0.57–1.36) | **0.70 (0.50–0.97)** |
| *P*-value* | | **0.01** | 0.581 | **0.035** |
| **rs2486758** | | | | |
| Premenopausal | 167/175 | 85/94 | 12/11 | 97/105 |
| OR (95% CI) | 1.00 (reference) | 0.95 (0.66–1.36) | 1.14 (0.49–2.66) | 0.97 (0.68–1.37) |
| *P*-value* | | 0.783 | 0.831 | 0.86 |
| **Postmenopausal** | 210/210 | 77/83 | 8/9 | 85/92 |
| OR (95% CI) | 1.00 (reference) | 0.93 (0.64–1.34) | 0.89 (0.34–2.35) | 0.92 (0.65–1.31) |
| *P*-value* | | 0.711 | 1.0 | 0.720 |

**Notes:** *Two-sided $\chi^2$ test for the distributions of genotype frequencies. A: major allele; a: minor allele. The bold text indicates a statistically significant difference.

## Association between *CYP17* polymorphisms and clinical parameters of BC patients

In order to determine the effect of *CYP17* polymorphisms on the different clinical features of BC patients, we then analyzed the associations between the *CYP17* polymorphisms and a series of clinicopathological parameters, including tumor size, lymph node metastasis, estrogen receptor (ER) status, progesterone receptor (PR) status, and Her-2.

As shown in Table 4, we found that the mutational genotype frequency of rs743572 was significantly higher in patients with ER positive ($\chi^2$ test, heterozygote model:

OR=2.13, 95% CI=1.47–3.08; homozygote model: OR=3.29, 95% CI=1.94–5.58; dominant model: OR=2.39, 95% CI=1.69–3.37) and PR positive ($\chi^2$ test, homozygote model: OR=3.17, 95% CI=1.82–5.55). However, no significant relation was detected in other clinical parameters of BC patients. For rs2486758, we did not find any associated clinical parameters of BC patients (Table 5).

## Haplotype analysis of *CYP17* polymorphisms and BC risk

Linkage disequilibrium (LD) tests were conducted to evaluate LD, the results – D`=0.997, $r^2$=0.128 – showed that LD did not exist in the two SNPs. We further conducted haplotype analysis by using the Phase 2.1 software to explore whether the interaction of rs743572 and rs2486758 SNPs affected BC risk. Compared with the $A_{rs743572}T_{rs2486758}$ haplotype, $G_{rs743572}C_{rs2486758}$ haplotype showed a decreased risk of BC ($\chi^2$ test, OR=0.52, 95% CI=0.40–0.67, *P*<0.001, as shown in Table 6).

## Survival analysis of patients with *CYP17* rs743572 and triple-negative breast cancer (TNBC)

Compared to other molecular portraits of BC, TNBC patients have a poorer prognosis. Thus, we wanted to explore the relationship between SNPs and the prognosis of TNBC patients. A total of 48 TNBC patients were recruited, with mean age of 48.02. Patients underwent modified radical mastectomy or breast-conserving surgery, and received chemotherapy or radiotherapy after surgery. As shown in Figure 1, up to the follow-up time, there was no difference between the TNBC patients with *CYP17* rs743572 GA/GG (56.25%) and *CYP17* rs743572 AA (43.75%) in terms of the progression-free survival (PFS) (log-rank test, *P*=0.976; HR=0.98, 95% CI=0.33–2.92). Similar results were obtained in terms of overall survival (OS) (log-rank test, *P*=0.867; HR=1.08, 95% CI=0.45–2.57).

# Discussion

CYP17 is a crucial estrogen-signaling regulatory enzyme, which mediates a variety of physiological and pathological processes. Several studies have demonstrated the association of *CYP17* rs743572 and rs2486758 polymorphisms with increased risk of various cancers,[12–16] and these two SNPs are the most common type of variation mutation. Related studies showed that rs743572 A>G SNP in *CYP17* may change the binding characteristics of the promoter region and then modify the gene's function.[27] This could lead to a change of estrogen levels and risk of BC. In addition, the rs2486758 minor allele has been reported to be associated with higher serum 17β-estradiol levels in premenopausal

**Table 4** The associations between the *CYP17* rs743572 polymorphism and clinical characteristics of breast cancer patients

| Characteristics | Genotype distributions | | | |
|---|---|---|---|---|
| | AA | GA | GG | GA+GG |
| **Tumor size (cm)** | | | | |
| <2/≥2 | 84/156 | 73/158 | 31/58 | 104/216 |
| OR (95% CI) | 1.00 (reference) | 1.17 (0.79–1.71) | 1.01 (0.61–1.68) | 1.12 (0.78–1.59) |
| *P*-value* | | 0.494 | 1.0 | 0.588 |
| **ER status** | | | | |
| Negative/positive | 135/105 | 87/144 | 25/64 | 112/208 |
| OR (95% CI) | 1.00 (reference) | **2.13 (1.47–3.08)** | **3.29 (1.94–5.58)** | **2.39 (1.69–3.37)** |
| *P*-value* | | **<0.0001** | **<0.0001** | **<0.0001** |
| **PR status** | | | | |
| Negative/positive | 115/125 | 120/111 | 20/69 | 140/180 |
| OR (95% CI) | 1.00 (reference) | 0.85 (0.59–1.22) | **3.17 (1.82–5.55)** | 1.18 (0.85–1.66) |
| *P*-value* | | 0.407 | **<0.0001** | 0.346 |
| **LN metastasis** | | | | |
| Negative/positive | 101/139 | 96/135 | 39/50 | 135/185 |
| OR (95% CI) | 1.00 (reference) | 1.02 (0.71–1.47) | 0.93 (0.57–1.52) | 1.0 (0.71–1.40) |
| *P*-value* | | 0.926 | 0.803 | 1.0 |
| **Her-2 status** | | | | |
| Negative/positive | 173/67 | 160/71 | 56/33 | 216/104 |
| OR (95% CI) | 1.00 (reference) | 1.15 (0.77–1.70) | 1.52 (0.91–2.55) | 1.24 (0.86–1.79) |
| *P*-value* | | 0.544 | 0.137 | 0.266 |

**Notes:** *Two-sided $\chi^2$ test for the distributions of genotype frequencies. The bold text indicates a statistically significant difference.
**Abbreviations:** LN, axillary lymph node; ER, estrogen receptor; PR, progesterone receptor; Her-2, human epidermal growth factor receptor 2.

**Table 5** The associations between the *CYP17* rs2486758 polymorphism and clinical characteristics of breast cancer patients

| Characteristics | Genotype distributions | | | |
|---|---|---|---|---|
| | TT | TC | CC | TC+CC |
| **Tumor size (cm)** | | | | |
| <2/≥2 | 123/254 | 61/101 | 4/16 | 65/117 |
| OR (95% CI) | 1.00 (reference) | 0.80 (0.55–1.78) | 1.94 (0.63–5.92) | 0.87 (0.60–1.26) |
| *P*-value* | | 0.276 | 0.327 | 0.504 |
| **ER status** | | | | |
| Negative/positive | 175/202 | 64/98 | 8/12 | 72/110 |
| OR (95% CI) | 1.00 (reference) | 1.33 (0.91–1.93) | 1.30 (0.52–3.25) | 1.32 (0.92–1.90) |
| *P*-value* | | 0.156 | 0.650 | 0.146 |
| **PR status** | | | | |
| Negative/positive | 172/205 | 75/87 | 8/12 | 83/99 |
| OR (95% CI) | 1.00 (reference) | 0.97 (0.67–1.42) | 1.26 (0.50–3.15) | 1.0 (0.70–1.43) |
| *P*-value* | | 0.925 | 0.653 | 1.0 |
| **LN metastasis** | | | | |
| Negative/positive | 165/212 | 64/98 | 7/13 | 71/111 |
| OR (95% CI) | 1.00 (reference) | 1.19 (0.82–1.73) | 1.45 (0.56–3.70) | 1.22 (0.85–1.75) |
| *P*-value* | | 0.393 | 0.495 | 0.315 |
| **Her-2 status** | | | | |
| Negative/positive | 263/114 | 111/51 | 15/5 | 126/56 |
| OR (95% CI) | 1.00 (reference) | 1.06 (0.71–1.58) | 0.77 (0.27–2.17) | 1.03 (0.70–1.51) |
| *P*-value* | | 0.839 | 0.803 | 0.922 |

**Note:** *Two-sided $\chi^2$ test for the distributions of genotype frequencies.
**Abbreviations:** LN, axillary lymph node; ER, estrogen receptor; PR, progesterone receptor; Her-2, human epidermal growth factor receptor 2.

**Table 6** The haplotype frequencies of *CYP17* polymorphisms and breast cancer risk

| Haplotypes | | Cases (N=1120) n, % | Controls (N=1164) n, % | OR (95% CI) | *P** |
|---|---|---|---|---|---|
| rs743572 | rs2486758 | | | | |
| A | T | 609 (54.4%) | 668 (57.4%) | 1.00 (reference) | |
| G | T | 309 (27.6%) | 279 (24.0%) | 1.22 (0.99–1.48) | 0.052 |
| G | C | 100 (8.9%) | 213 (18.3%) | **0.52 (0.40–0.67)** | **<0.001** |
| Others | | 102 (9.1%) | 4 (0.3%) | **27.97 (10.24–76.42)** | **<0.001** |

**Notes:** *Two-sided $\chi^2$ test for the distributions of haplotype frequencies. The bold text indicates a statistically significant difference.

**Table 7** Primers used in this study

| SNP_ID | 1st-PCRP | 2nd-PCRP | UEP_SEQ |
|---|---|---|---|
| **rs743572** | ACGTTGGATGTAGAGTTGCCACA GCTCTTC | ACGTTGGATGTAAGCAGCAAGAG AGCCACG | aAGGCAAGATAGACAGC |
| **rs2486758** | ACGTTGGATGCCTGAATCTGTCAT CTGTCC | ACGTTGGATGAGAGTGCGAATGG TATCTGG | tGCTTGGAACTTTCCATG |

**Abbreviation:** SNP, single-nucleotide polymorphism.

women.[11] In our study, we observed that variant genotypes of *CYP17* rs743572 were associated with decreased BC risk, but rs2486758 was not related to BC risk. In further stratification analysis by clinical characteristics, results showed that rs743572 was associated with ER and PR status, but there was no association between rs2486758 and any clinical characteristics of BC.

According to several published studies, rs743572 is the most commonly studied *CYP17* SNP. A significantly increased relationship was found with *CYP17* rs743572 and BC in Caucasian populations,[28] Feigelson et al also found an increased risk of advanced BC in women carrying an A2 allele in Caucasian populations.[10] However, Sangrajrang et al considered that there was no relationship between rs743572 and BC in Thai women.[17] In addition, in a study of a Chinese population, no evidence of relation was detected.[29] Tan et al, Hu et al, and Sakoda et al found a similar result.[20–22] In contrast, Zhang et al and Wang et al obtained the opposite result.[23,24] Our results

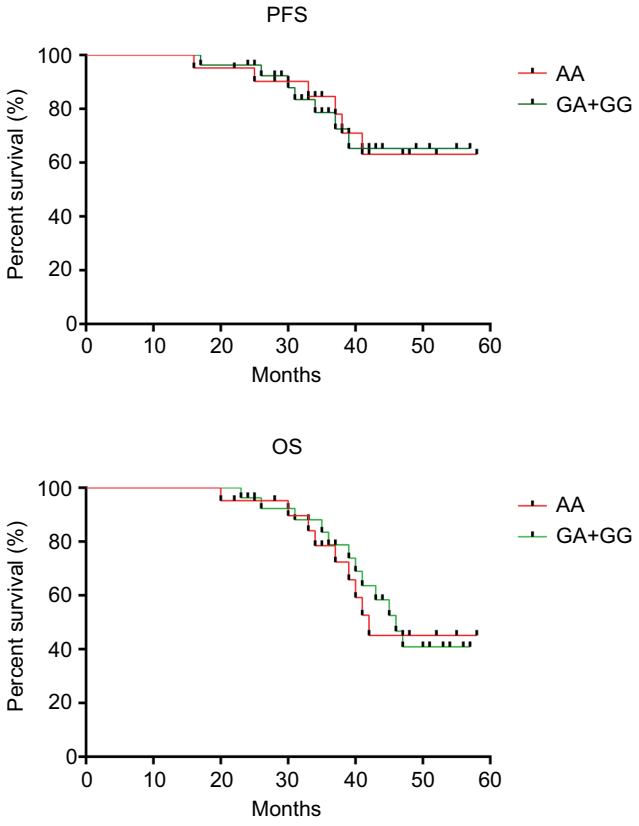


**Figure 1** Kaplan–Meier analysis of overall survival (OS) and progression-free survival (PFS) are shown for *CYP17* rs743572.
**Notes:** n=48, for PFS: *P*=0.976; HR=0.98, 95% CI=0.33–2.92; for OS *P*=0.867; HR=1.08, 95% CI=0.45–2.57.

have demonstrated the negative association between *CYP17* rs743572 SNP and BC risk in a Northwest Chinese population. The differences may be attributed to the geographical and lifestyle differences in different regions of the People's Republic of China, which may have led to differences in the frequencies of genetic variations. It was also indicated that *CYP17* rs743572 was a key site in the process of estrogen biosynthesis and metabolism, and thus may affect the development of various malignant tumors, which may offer evidence for clinical treatment and prognosis evaluation.

rs2486758 is another frequently studied *CYP17* SNP, which is localized in the intergenic section near the 5′ of *CYP17*. rs2486758 minor allele affects the *CYP17* gene's splicing and transcription, leading to an increase in the expression of *CYP17*.[12] Iversen et al found that *CYP17* rs2486758 minor allele was related to higher 17β-estradiol levels, modification of the minor allele of *CYP17* rs2486758 may have significant implications for the prevention of BC in women.[11] Another cohort study did not support any evidence about the association between *CYP17* rs2486758 and BC.[30] As shown in our study, there was also no association between rs2486758 and any clinical characteristics of BC, which is consistent with the previously mentioned study. Mechanistically, the risk of prostate cancer is based on the location of rs2486758 in the promoter region of *CYP17*A1,[31] while there was no other study to prove the relation between *CYP17* rs2486758 and BC, we considered *CYP17* rs2486758 was not affect the transcription of genes.

TNBC is a unique subtype of BC with poor survival, which is not affected by hormone metabolism.[32,33] As *CYP17* is a key enzyme in estradiol synthesis,[5] and the occurrence and development of TNBC does not depend on estrogen levels, we hypothesized that *CYP17* polymorphisms and TNBC survival are not directly related, which was confirmed by our results.

Our study had some limitations. First, it had a single-center design that only recruited Northwest Han Chinese women, which may preclude application of our conclusion in other ethnic populations. Second, survival analysis study was conducted only on patients with TNBC, thus, the effect of *CYP17* rs743572 and rs2486758 on the prognosis of other molecular portraits of BC patients needs further study. Third, our sample size was relatively small, which may have limited the power to detect associations. Thus, we need to conduct a large, well-designed study to verify the associations between *CYP17* polymorphisms and BC risk.

In summary, our case–control study indicates that the *CYP17* rs743572 polymorphism may reduce BC susceptibility in Chinese Han women. Further functional studies and large, well-designed studies are still required to further elucidate the impact of *CYP17* polymorphisms on BC.

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## Disclosure

The authors report no conflicts of interest in this work.

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