A Population-Based Case-Control Study of the *Arg399Gln* Polymorphism in DNA Repair Gene *XRCC1* and Risk of Breast Cancer

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Abstract

XRCC1 (X-ray repair cross-complementing group 1) is a base excision repair protein that plays a central role in the repair of DNA base damage and strand breaks. A common polymorphism (Arg→Gln) at codon 399 of the *XRCC1* gene has been previously linked to functional changes of the gene product and risk of cancers. We evaluated the association between *XRCC1 Arg399Gln* polymorphism and breast cancer risk in the population-based Shanghai Breast Cancer Study involving 1088 cancer patients and 1182 community controls. Genomic DNA from peripheral blood was used in genotyping assays, and exposure information and anthropometrics were collected through in-person interview. Plasma estrogen and sex hormone-binding globulin (SHBG) levels were measured for 190 postmenopausal breast cancer patients who had donated a pretreatment blood sample and 407 postmenopausal controls. Conditional logistic regression model was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs) adjusting potential confounders. Approximately 27% of controls carried the variant allele (Gln), and cases and controls had a similar distribution for both allele type and genotype of this polymorphism. We found that 7.8% of cases and 6.3% of controls were homozygous for the variant allele, resulting in an OR of 1.20 (95% CI, 0.85–1.69). The OR was slightly higher among younger women [<45 years of age (OR, 1.39; 95% CI, 0.82–2.36)] than older women [≥45 years of age (OR, 1.07; 95% CI, 0.68–1.67)], but neither OR was statistically significant. No modifying effect of major breast cancer risk factors, including years of menstruation, body mass index, waist: hip ratio, and blood estrogen levels, was noted. Homozygosity for the variant Gln allele was associated with an elevated risk of postmenopausal breast cancer among subjects with a higher blood level of SHBG (OR, 3.27; 95% CI, 1.16–9.20) and a reduced risk among those with a lower level of SHBG (OR, 0.60; 95% CI, 0.18–1.97). The overall results of the study suggest that *Arg399Gln* polymorphism of the *XRCC1* gene alone may not play a substantial role in the risk of breast cancer among Chinese women.

Introduction

Breast cancer is the leading female cancer among women in many nations. Although it has been well accepted that estrogen plays a central role in the development of breast cancer, cumulative evidence suggests that genetic susceptibility may also play a major role. It has been recently recognized that the *BRCA1* and *BRCA2* genes, two well-known breast cancer susceptibility genes, play an important role in DNA repair (1). Defective DNA repair capacity has been found among both breast cancer patients and their first-degree relatives (2). DNA repair deficiency, therefore, may be involved in the development of breast cancer.

XRCC1 (X-ray cross-complementing group 1 protein) is involved in the repair of DNA base damage and single-strand DNA breaks by binding DNA ligase III at its carboxyl and DNA polymerase β and poly(ADP-ribose) polymerase at the site of damaged DNA (3). Deletion of the *XRCC1* gene in mice results in an embryonic lethal phenotype (4). Chinese hamster ovary cell lines with mutations in the *XRCC1* have shown a reduced ability to repair single-strand breaks in DNA and concomitant cellular hypersensitivity to ionizing radiation and alkylating agents (5). These suggest that *XRCC1* plays an essential role in the removal of endogenous and exogenous DNA damage. Three polymorphisms in coding regions of the *XRCC1* gene at codons 194 (*Arg* to *Trp*), 280 (*Arg* to *His*), and 399 (*Arg* to *Gln*) have been recently identified (6). These polymorphisms, involving an amino acid change at evolutionarily conserved regions, could alter the XRCC1 function. Codon 399 is located in the poly(ADP-ribose) polymerase-binding domain and within an identified *BRCA1* COOH terminus domain (6). Previous studies have reported that the *XRCC1 399 Gln* allele was significantly associated with a higher level of DNA adducts and glycophorin A mutations in erythrocytes (7, 8), increased sister chromatid exchange frequencies (9, 10), and higher sensitivity to ionizing radiation (11). However, a null association between *Arg399Gln* polymorphism and DNA adducts has been reported in other studies (8, 12). In this report, we describe the association of *Arg399Gln* polymorphism in the *XRCC1* gene with breast cancer risk using data from the Shanghai Breast Cancer Study.

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Materials and Methods

The Shanghai Breast Cancer Study is a population-based case-control study conducted among Chinese women in Shanghai. Details of study design have been described elsewhere (13). Briefly, through a rapid case ascertainment system, supplemented by the population-based Shanghai Tumor Registry, 1601 women who were newly diagnosed with breast cancer between the ages of 25 and 64 years during August of 1996 and March of 1998 were identified. In-person interviews were completed for 1459 of these women (91.1% response rate). One hundred and forty-two women were excluded from study because of refusal ($n = 109$; 6.8%), death before interview ($n = 17$; 1.1%), and inability to be located ($n = 17$; 1.1%). Cancer diagnosis was confirmed for all patients by two senior study pathologists through the review of tumor slides.

Age frequency-matched controls were randomly selected from the female general population according to the age distribution of the incident breast cancer cases reported to the Shanghai Tumor Registry between 1990 and 1993. The Shanghai Resident Registry, which keeps registry cards for all adult residents in urban Shanghai, was used to randomly select controls. Only women who lived at the listed address during the study period were eligible. In-person interviews were completed for 1556 of the 1724 eligible controls (90.2%). Among the 168 exclusions, there were 166 refusals (9.6%), 1 death, and 1 individual with a prior diagnosis of breast cancer (0.1%).

Exposure information and anthropometrics were taken during an in-person visit by trained interviewers. A structured questionnaire was used to elicit detailed information on demographic factors, menstrual and reproductive history, hormone use, dietary habits, prior disease history, physical activity, tobacco and alcohol use, weight, and family history of cancer. All interviews were tape-recorded for quality control (QC) purposes. Weight, circumferences of the waist and hip, and sitting and standing heights were measured twice for each study participant using a standard protocol. A third measurement was taken if the difference of the two measurements was greater than the tolerance limit (1 kg for weight and 1 cm for heights and circumferences). The averaged measurements were used in this analysis.

A fasting morning blood sample (10 ml from each woman) was collected using EDTA or heparin vacutainer tubes from 1193 (82%) cases and 1310 (84%) controls who completed the in-person interviews. These samples were processed on the same day, typically within 6 h after collection, at the Shanghai Cancer Institute; buffy coats (WBCs) and plasma for each participant were stored at −70°C.

Genomic DNA was extracted from buffy coat fractions using the Puregene DNA isolation Kit (Gentra Systems, Minneapolis, MN) following the manufacturer's protocol. DNA concentration was measured using PicoGreen dsDNA Quantitation Kit (Molecular Probes, Eugene, OR).

XRCC1 genotypes were examined using PCR-based RFLP assays. The primers were designed according to the human *XRCC1* gene sequence (GenBank accession number L34079). The sequences of primers were as follows: sense, 5′-GCATCGTGCGTAAGGAGTG-3′; and antisense, 5′-CCTTC-CCTCATCTGGAGTAC-3′. The PCR was performed in a Biometra TGradient Thermocycler. Each 25 μl of PCR mixture contained 10 ng of DNA, 1× PCR buffer [50 mM KCl and 10 mM Tris-HCl (pH 9.0)], 1.5 mM $MgCl_2$, 0.16 mM each deoxynucleotide triphosphate, 0.4 μM each primer, and 1 unit of Taq DNA polymerase. The reaction mixture was initially denatured at 94°C for 3 min, followed by 35 cycles of 94°C for 45 s, 60°C for 45 s, and 72°C for 45 s. The PCR was completed by a final extension cycle at 72°C for 7 min. Each PCR product (10 μl) was digested with 10 units of *Hpa*II restriction endonucleases (New England BioLabs, Beverly, MA) at 37°C for 3 h. The DNA fragments were then separated using 2% agarose gel containing ethidium bromide. The G→A substitution at nucleotide 28152 (GenBank accession number L34079) abolishes the *Hpa*II restriction site. The PCR product with 399Arg (*i.e.*, 28152 G) allele was digested to two fragments (177 and 59 bp), whereas the PCR product with 399Gln (*i.e.*, 28152 A) remained undigested (236 bp). Genotyping of *XRCC1* was completed for 1088 cases and 1182 controls.

The laboratory staff was blind to the identity of the subject. QC samples were included in genotyping assays. Each 96-well plate contains one water sample, two CEPH 1347-02 DNA, two blinded QC DNA, and two unblinded QC DNA samples. The blinded and unblinded QC samples were taken from the second tube of study samples included in the study. The *XRCC1* genotypes determined for the QC samples were in complete agreement with the genotypes determined for the study samples.

In an ancillary study of the Shanghai Breast Cancer Study, plasma levels of steroid hormones, sex hormone-binding globulin (SHBG), and other biomarkers were measured for 300 cases who had donated a pretreatment blood sample and for 300 controls matched to cases on age (years), date of blood collection (days), and menopausal status. Among them were 190 postmenopausal case-controls pairs. Plasma levels of estrogens and SHBG for all remaining postmenopausal Shanghai Breast Cancer Study controls ($n = 217$) were measured in another ancillary study. All assays for steroid hormones and SHBG were conducted at Diagnosed Laboratory Systems Inc. (TX), a reference lab certified by Clinical Laboratory Improvement Amendments and the International Standard ISO 9002. Each sample was tested in duplicate, and two internal QC samples were included in each run of the assay. Commercial radioimmunoassays from Diagnostic Systems Laboratories, Inc. were used for measuring steroid hormones, and an immunoradiometric assay from Diagnostic Systems Laboratories, Inc. was used for measuring SHBG. Plasma levels of estradiol, estrone, estrone sulfate, testosterone, and dehydroepiandrosterone sulfate were determined directly without any extraction procedures. The coefficients of variation for the intra- and interassay variations of these assays ranged from 1.1% to 11.5%, and the majority of coefficients of variation were <10%. Included in the present analyses are estrogen and SHBG data from the 190 postmenopausal breast cancer patients and 407 postmenopausal controls. Data from the premenopausal women were not included in the analysis because information on specific day of menstrual cycle when the blood was drawn was not available.

χ^2 statistics were applied to evaluate the difference in the distribution of *Arg399Gln* allele types and genotypes between cases and controls. Unconditional logistic regression was applied to derive odds ratios (ORs) and 95% confidence intervals (CIs) adjusting for age, the matching variable, and traditional breast cancer risk factors. The potential modifying effect of blood levels of estrogen and major breast cancer risk factors related to endogenous estrogen exposure on the gene-disease association was evaluated. All statistical tests were based on two-tailed probability.

Results

Presented in Table 1 are distributions of selected demographic characteristics and nongenetic breast cancer risk factors among

Table 1 Case-control comparison on demographics and selected risk factors for breast cancer

	Subjects with XRCC1 genotype information			Subjects with hormonal measurements		
	Cases (n = 1088)	Controls (n = 1182)	P	Cases (n = 190)	Controls (n = 407)	P
Age (mean ± SD)	47.7 ± 8.0	47.2 ± 8.7	0.15	56.8 ± 4.7	56.6 ± 5.3	0.61
Education						
<Elementary	134 (12.3)	171 (14.5)		55 (28.9)	139 (34.2)	
Middle & high	823 (75.6)	892 (75.5)		103 (54.2)	215 (52.8)	
>High	131 (12.0)	119 (10.1)	0.14	32 (16.8)	53 (13.0)	0.29
Family income (yuan)						
<10,000	122 (11.2)	119 (10.1)		25 (13.2)	50 (12.3)	
<10,001–19,990	433 (39.8)	484 (40.9)		61 (32.1)	169 (41.5)	
≥20,000	533 (50.0)	579 (49.0)	0.64	104 (54.7)	188 (46.2)	0.08
Family history of breast cancer among first-degree of relatives						
No	1051 (96.6)	1152 (97.5)		181 (95.3)	391 (96.1)	
Yes	37 (3.4)	30 (2.5)	0.23	9 (4.7)	16 (3.9)	0.65
BMI[a] (mean ± SD)	23.5 ± 3.4	23.2 ± 3.4	0.01	24.6 ± 3.7	24.1 ± 3.6	0.10
WHR (mean ± SD)	0.81 ± .006	0.80 ± 0.06	<0.01	0.82 ± 0.06	0.82 ± 0.06	0.24
Age at 1st live birth	26.8 ± 4.1	26.2 ± 3.8	<0.01	25.1 ± 4.9	24.2 ± 4.0	0.02
Age at menarche (mean ± SD)	14.5 ± 1.6	14.7 ± 1.7	<0.01	14.7 ± 1.8	15.1 ± 1.9	0.03
Age at menopausal age (mean ± SD)[b]	48.2 ± 4.6	47.6 ± 4.9	0.07	48.9 ± 4.4	47.6 ± 4.9	0.001
Physical activities						
No	875 (80.4)	877 (74.2)		129 (67.9)	236 (58.0)	
Yes	213 (19.6)	305 (25.8)	<0.01	61 (32.1)	171 (42.0)	0.02
Ever smoked						
No	1059 (97.3)	1152 (97.5)		179 (94.2)	392 (96.3)	
Yes	29 (2.7)	30 (2.5)	0.849	11 (5.8)	15 (3.7)	0.24
Ever drank						
No	1050 (96.5)	1136 (96.1)		183 (96.3)	386 (94.8)	
Yes	38 (3.5)	46 (3.9)	0.615	7 (3.7)	21 (5.2)	0.43

[a] BMI, body mass index; WHR, waist:hip ratio.
[b] Among postmenopausal women.

the 1088 cases and 1182 controls included in the current analysis. Cases and controls were well matched on age, with a respective mean age of 47.7 and 47.4 years, and had a similar distribution on education and family income. Cases (3.4%) were slightly but not significantly more likely to have a family history of breast cancer among first-degree relatives than controls (2.5%). Compared with controls, cases tended to have a higher body mass index and waist:hip ratios, younger age at menarche, older age at menopause, and older age at the first live birth and were less likely to engage in regular exercise during the past 10 years. The confounding effects of these variables and their interactive effect with *Arg399Gln* polymorphism on breast cancer risk were examined in subsequent analyses. Very few women (2.7% cases and 2.5% controls) ever smoked or drank (3.5% cases and 3.9% controls) regularly during their lifetime, and no confounding effect of smoking and drinking on the association under study was observed (data not shown). A similar pattern was found for the subgroup of postmenopausal women who had estrogen and SHBG measurements (Table 1).

Cases and controls had a similar allele distribution at *XRCC1* codon 399, and the distribution of the variant Gln allele was 28.1% and 27.3%, respectively, for cases and controls. The distribution of *Arg399Gln* genotype is consistent with Hardy-Weinberg equilibrium for both cases and controls. Approximately the same proportion of cases (7.8%) and controls (6.6%) had the *Gln/Gln* genotype, with an associated OR of 1.22 (95% CI, 0.87–1.71) in comparison with the *Arg/Arg* genotype. The association of *Gln/Gln* genotype with breast cancer did not vary with menopausal status. The OR associated with *Gln/Gln* genotype was slightly more elevated among women who were <45 years old (OR, 1.39; 95% CI, 0.83–2.34) than those who were ≥45 years old (OR, 1.11; 95% CI, 0.71–1.73); none of the associations reached statistical significance. Adjustment of all of the traditional breast risk factors did not alter the results (Table 2).

The association of *Arg399Gln* polymorphism with breast cancer risk was further evaluated on stratification by years of menstruation, waist:hip ratio, and body mass index, the major indicators of endogenous hormone exposure (Table 3). For postmenopausal women whose blood samples were measured for estrogens and SHBG, stratified analyses were performed using the median levels of these molecules to assess the genotype association. We did not find a noticeable and significant synergetic or agonistic effect between the *Gln/Gln* genotype and hormone-related indicators or hormonal measurements on breast cancer. The only exception was that the *XRCC1* genotype was related to a >3-fold increased breast cancer risk (OR, 3.27; 95% CI, 1.16–9.2) among postmenopausal women with a higher sex hormone-binding protein level but was related to a nonsignificantly reduced risk when SHBG level was low (OR, 0.60; 95% CI, 0.18–1.97; P for interaction = 0.06).

Discussion

DNA is continuously damaged by endogenous and exogenous mutagens and carcinogens. The damages are fixed by multiple DNA repair pathways including base excision repair, nucleotide excision repair, mismatch repair, and double-strand break repair (14). Cells with unrepaired DNA damage undergo either apoptosis or unregulated growth to malignancy. A defect or reduced efficiency in repairing DNA damage therefore plays a pivotal role in the development of cancer. Over the last decade, several common polymorphisms in several DNA repair genes have been discovered, and some of these polymorphisms have

Table 2 Association between XRCCI *Arg399Gln* polymorphism and breast cancer risk

	Cases (N = 1088)	Controls (N = 1182)	OR[a] (95% CI)	OR[b] (95% CI)
Allele frequency				
G(Arg)	1564 (71.9)	1718 (72.7)		
A(Glu)	612 (28.1)	646 (27.3)	P = 0.55	
Genotype				
Arg/Arg	561 (51.6)	610 (51.6)	1.00 (ref)[c]	1.00 (ref)
Arg/Glu	442 (40.6)	498 (42.1)	0.92 (0.77–1.09)	0.90 (0.76–1.08)
Glu/Glu	85 (7.8)	74 (6.3)	1.22 (0.87–1.71)	1.20 (0.85–1.69)
Premenopausal women				
Arg/Arg	373 (51.2)	368 (48.5)	1.00 (ref)	1.00 (ref)
Arg/Glu	295 (40.5)	340 (44.9)	0.79 (0.63–0.98)	0.79 (0.63–0.98)
Glu/Glu	61 (8.4)	50 (6.6)	1.20 (0.79–1.81)	1.19 (0.78–1.80)
Postmenopausal women				
Arg/Arg	188 (52.4)	242 (57.1)	1.00 (ref)	1.00 (ref)
Arg/Gln	147 (40.9)	158 (37.3)	1.21 (0.90–1.64)	1.19 (0.87–1.62)
Gln/Gln	24 (6.7)	24 (5.7)	1.19 (0.65–2.17)	1.13 (0.61–2.11)
Age < 45 yrs				
Arg/Arg	213 (48.9)	251 (51.2)	1.00 (ref)	1.00 (ref)
Arg/Gln	185 (42.4)	207 (42.2)	0.95 (0.72–1.26)	0.94 (0.70–1.24)
Gln/Gln	38 (8.7)	32 (6.5)	1.39 (0.83–2.34)	1.39 (0.82–2.36)
Age ≥ 45 yrs				
Arg/Arg	348 (53.4)	359 (51.9)	1.00 (ref)	1.00 (ref)
Arg/Gln	257 (39.4)	291 (42.1)	0.90 (0.72–1.13)	0.89 (0.71–1.12)
Gln/Gln	47 (7.2)	42 (6.1)	1.11 (0.71–1.73)	1.07 (0.68–1.67)

[a] OR, odds ratio; CI, confidence interval. Adjusted for age.
[b] Additional adjustment for education, family history of breast cancer, menopausal status, age at menarche, age at menopause, body mass index, waist:hip ratio, and physical activity.
[c] Ref, reference.

been suggested to affect DNA repair capacity and thus may determine an individual's susceptibility to carcinogens (2, 14).

The XRCC1 protein plays an important role in base-pair excision repair, fixing small DNA damage, such as oxidized or fragmented lesions or nonbulky adducts (14). Polymorphism in codon 399 of this gene has been studied in many epidemiological studies in relation to various cancers. The variant *Gln* allele has been linked to an increased risk of cancers of the lung

Table 3 Association between XRCC1 *Arg399Gln* polymorphism and breast cancer risk stratified by selected hormone-related factors and blood hormone levels[a]

	Arg/Arg		Arg/Gln		Gln/Gln	
	Case/control	OR	Case/control	OR (95% CI)	Case/control	OR (95% CI)
Years of menstruation						
<Median	217/296	1.00 (ref)[b]	190/238	1.02 (0.78–1.34)	44/39	1.57 (0.96–2.57)
≥Median	344/314	1.00 (ref)	252/260	0.87 (0.69–1.10)	41/35	1.06 (0.66–1.72)
Waist to hip ratio						
<0.84	403/479	1.00 (ref)	328/383	0.96 (0.78–1.18)	68/68	1.16 (0.80–1.68)
≥0.84	57/131	1.00 (ref)	113/114	0.87 (0.60–1.26)	17/6	2.48 (0.92–6.66)
Body mass index (weight/height^2)						
<25	387/451	1.00 (ref)	298/358	0.92 (0.74–1.13)	68/57	1.36 (0.93–2.01)
≥25	173/159	1.00 (ref)	143/139	0.88 (0.63–1.22)	17/17	0.92 (0.44–1.91)
Among postmenopausal women						
Body mass index (weight/height^2)						
<25	111/154	1.00 (ref)	74/97	1.06 (0.71–1.57)	17/16	1.50 (0.72–3.15)
≥25	77/88	1.00 (ref)	73/61	1.38 (0.85–2.22)	7/8	0.85 (0.28–2.58)
Estradiol[c]						
<Median	36/111	1.00 (ref)	42/79	1.56 (0.91–2.69)	4/12	0.88 (0.26–2.96)
≥Median	60/120	1.00 (ref)	37/74	0.98 (0.59–1.65)	9/11	1.68 (0.62–4.54)
Estrone[c]						
<Median	34/107	1.00 (ref)	31/73	1.38 (0.76–2.51)	6/9	1.85 (0.58–5.90)
≥Median	61/122	1.00 (ref)	48/79	1.13 (0.70–1.84)	7/14	1.10 (0.41–2.95)
Estrone sulfa[c]						
<Median	44/123	1.00 (ref)	27/72	1.03 (0.58–1.85)	4/8	1.45 (0.40–5.33)
≥Median	52/108	1.00 (ref)	51/81	1.31 (0.79–2.16)	9/15	1.42 (0.56–3.63)
SHBG[c]						
<Median	55/115	1.00 (ref)	48/69	1.50 (0.90–2.50)	4/14	0.60 (0.18–1.97)
≥Median	42/116	1.00 (ref)	32/84	1.12 (0.65–1.95)	9/9	3.27 (1.16–9.20)

[a] Adjusted for age.
[b] Ref, reference; SHBG, sex hormone-binding globulin.
[c] Among 190 postmenopausal breast cancer patients who had donated a pretreatment blood sample and 407 postmenopausal controls.

(15–17), head, neck (18), and possibly the stomach (19). On the other hand, this allele was reported to be associated with a reduced risk of bladder cancer (20), esophageal cancer (21), and nonmelanoma skin cancer (22). Null association was also reported for lung cancer (23–26). Studies have shown that cigarette smoking may modify the association between *Arg399Gln* polymorphism and lung cancer risk (17, 26). Several estrogen metabolites, such as catechol estrogens, are known to generate reactive oxygen radicals that can cause DNA damage (27, 28). To date, only three studies have evaluated the association between *XRCC1* polymorphism and breast cancer risk (29–31). The *Gln* allele was found to be associated with an increased risk of breast cancer among African-American women (29), but not white women (29, 31). Unexpectedly, Duell *et al.* (29) found that the association of smoking and radiation and breast cancer was stronger among African-American women with the *Arg/Arg* genotype than among those with other genotypes. In a hospital-based case-control study conducted among Korean women (205 cases and 205 controls), the *Gln* allele was associated with a 3.8-fold increased risk of breast cancer among premenopausal women, and a possible interaction between *Gln* allele and alcohol drinking was suggested (30). In our population-based case-control study of 1088 cases and 1182 controls, we did not find a significant association between *Arg399Gln* polymorphism and breast cancer risk among both pre- and postmenopausal women, with the exception of a 3.27-fold elevation of risk for postmenopausal women who had a higher level of SHBG. We also did not find any potential modifying effect of blood estrogen levels or surrogate measurement of endogenous estrogen exposure on the association between *Arg399Gln* and breast cancer risk. We do not have a ready explanation for the observed modifying effect of blood SHBG on the gene-cancer association, and additional studies are needed. It is worth noting that the frequency of the *Gln/Gln* genotype among our controls (6.6%) is remarkably similar to that observed among controls of the Korean study (6.8%). The different findings of our study and the Korean study, therefore, are attributed to differences in case groups. Differences in study design (hospital-based *versus* population-based), participation rate, and eligibility criteria may contribute to the inconsistent results.

At least two more polymorphisms in coding regions of the *XRCC* [*i.e.*, at codons 194 (*Arg* to *Trp*) and 280 (*Arg* to *His*)] have been reported (6, 14), and the *Arg194Trp* polymorphisms have been linked to a reduced risk of cancers of the lung and stomach (14). The *Arg194Trp* polymorphism was found to be associated (although in a statistically insignificant fashion) with breast cancer in opposite directions in two United States studies (29, 31) and was unrelated to breast cancer among Korean women (29). A potential interaction between the XRCC1 194Trp allele and XRCC3 241Met allele was suggested (31). The inability to take into consideration the effect of these multiple polymorphisms and other DNA repair genes may be a limitation of the study. However, our study has many strengths (14). The population-based study design and high study participation rate minimized the selection biases. The large sample size and extensive exposure data also allowed a comprehensive evaluation of the effect of polymorphism on breast cancer along with surrogate and direct measurements of estrogen. The homogenous ethnic background (98% of study participants belonged to Han) also prevented confounding from ethnicity.

In conclusion, we did not find an apparent association between *XRCC1 Arg399 Gln* polymorphism and breast cancer risk among women in Shanghai. No clear interaction between this polymorphism and estrogen measurements on breast cancer was observed. Our study suggests that this polymorphism alone may not play a significant role in the risk of breast cancer among Chinese women. Additional studies are needed to evaluate the potential interaction of this polymorphism with other genetic factors in relation to the risk of breast cancer.

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