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# Polymorphisms of *ADPRT* Val762Ala and *XRCC1* Arg399Glu and risk of breast cancer in Chinese women: A case control analysis

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**Abstract.** Adenosine diphosphate ribosyl transferase (ADPRT) and X-ray repair cross-complementing 1 (XRCC1) are two major base excision repair (BER) proteins and act cooperatively in the BER processes. Polymorphisms of *ADPRT* Val762Ala and *XRCC1* Arg399Gln may alter their protein functions and BER activity, and were therefore hypothesized to be associated with breast cancer susceptibility. We examined the contributions of these two polymorphisms to breast cancer susceptibility in a case-control study of 302 breast cancer cases, 221 patients with benign breast disease (BBD) and 639 cancer-free controls in a Chinese population. We found that the variant genotypes of both *ADPRT* Val762Ala and *XRCC1* Arg399Gln were not significantly associated with the risk of breast cancer (adjusted OR 0.87, 95% CI 0.64 to 1.19 for *ADPRT* Val/Ala + Ala/Ala; adjusted OR 0.82, 95% CI 0.61 to1.11 for *XRCC1* Arg/Gln + Gln/Gln; and adjusted OR 0.70, 95% CI 0.45 to 1.10 for these two combined variant genotypes. Similarly, we did not find any significant associations of these two genotypes with BBD risk. These findings suggest that the *ADPRT* Val762Ala and *XRCC1* Arg399Gln polymorphisms may not play a role in the etiology of breast cancer.

## Introduction

Although the incidence rate of breast cancer in China is about one-third of that in the United States, it has been increasing significantly in the last two decades in both urban and rural areas (1,2). To date, the etiology of breast cancer is unclear, but it is well accepted that estrogen plays a central role in the development of breast cancer. One of the mechanisms involves estrogen metabolites that can induce oxidative DNA damage and single strand breaks (3,4). To safeguard the integrity of the genome by defending harmful consequences of DNA damage, humans have developed a set of complex DNA repair systems. Inherited differences in DNA repair capacity (DRC) were proposed to modify individual susceptibility to breast cancer (5,6).

Among DNA repair systems, the base excision repair (BER) pathway is responsible for repair of oxidative DNA damage and single strand breaks (7,8) and is most likely to be involved in estrogen-related breast cancer development. In this multi-step repair process, adenosine diphosphate ribosyl transferase (ADPRT) specifically binds to DNA strand breaks and recruits XRCC1-Lig3α complex, which is critical for stimulating and executing the BER process (9,10). Several genetic polymorphisms have been identified in the *ADPRT* coding region, with one being a T to C transition at codon 762 of *ADPRT* located in the COOH-terminal catalytic domain that causes a Val-to-Ala amino acid substitution (11,12). Although the functional relevance of this variant is still unknown, a study showed that this polymorphism was associated with altered ADPRT function, and the variant allele 762Ala contributed to prostate cancer susceptibility (13). There are a total of eight nonsynonymous SNPs in *XRCC1* (http://egp.gs.washington.edu). One of them leads to an amino acid substitution at codon 399 (exon 10, base G to A, amino acid Arg to Gln) located in the region of the BRCT-I interaction domain with poly(ADP-ribose) polymerase (14). This polymorphism has been extensively investigated both in its function and association with cancer risk, however, the results are conflicting and need to be further investigated in different populations (15).

Zhang *et al* reported that the *ADPRT* Val762Ala polymorphism was associated with altered lung cancer risk, and there is a super-multiplicative joint effect between the *ADPRT* Val762Ala and *XRCC1* Arg399Gln, indicating that

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Table I. Comparison of breast cancer patients, BBD cases and controls by selective characteristics.

| Variable | Controls n=639 | BBD n=221 | Breast cancer n=302 |
|---|---|---|---|
| Age, years | 47.14±12.76 | 44.03±11.58 | 52.34±11.04 |
| Age at menarche, years | 16.15±1.77 | 14.45±1.71 | 15.35±1.96 |
| Age at first live birth, years[a] | 24.31±2.43 | 26.08±2.80 | 25.38±3.63 |
| Age at menopausal, years[b] | 49.72±3.90 | 50.21±4.39 | 49.01±4.05 |
| Menopausal status | | | |
| Premenopausal | 369 | 177 | 153 |
| Postmenopausal | 270 | 44 | 149 |

All data shown as mean ± SD. [a]Age at first live birth information was available in 617 controls, 189 BBD patients and 290 breast cancer cases. [b]Age at menopausal information was available in 233 controls, 42 BBD patients and 143 breast cancer cases with postmenopausal status.

these two polymorphisms might jointly contribute to cancer susceptibility (16). In this case-control study of 302 breast cancer cases, 221 patients with benign breast diseases (BBD) and 639 cancer-free controls in a Chinese population, we simultaneously genotyped these two polymorphisms to test our hypothesis that these two polymorphisms independently or cooperatively play a role in the risk of breast cancer.

## Materials and methods

*Study population*. This hospital-based case-control study consisted of 302 patients with primary breast cancer, 221 patients with BBD and 639 cancer-free controls. All subjects were genetically-unrelated ethnic Han Chinese from Nanjing City and surrounding regions in southeast China. The breast cancer cases were consecutively recruited between January 2004 and December 2004 at the Cancer Hospital in the Jiangsu Province, the First Affiliated Hospital of Nanjing Medical University and the Nanjing Gulou Hospital, Nanjing City, China. BBD patients were those who underwent surgical treatment for a solitary mammary lump and were subsequently found to be non-malignant by pathological examination. All cases were incident breast cancer patients, histopathologically diagnosed and previously untreated by radiotherapy or chemotherapy with a response rate of 85.5% (523/612). Cancer-free controls were randomly selected from a pool of 10,500 individuals who participated in a community-based screening program for non-infectious diseases conducted in the Jiangsu Province during the same time period as the cases were recruited, with a response rate of 83.8%. These control subjects had no history of cancer and were frequency-matched to the cases on age (±5 years). Each subject was scheduled for an interview after informed consent was obtained, and a structured questionnaire was administered by interviewers to collect information on demographic data, menstrual and reproductive history and environmental exposure history. After the interview, an approximately 5-ml venous blood sample was collected from each subject. The study was approved by the Institutional Review Board of Nanjing Medical University.

*Genotype analyses*. Genomic DNA was extracted from the leukocyte pellet obtained from the buffy coat of each blood sample by centrifugation of 5-ml whole blood. The *ADPRT* Val762Ala was detected by using a primer-introduced restriction analysis (PIRA)-PCR assay (17). To induce a restricted endonuclease site, we changed the 3' end of the reverse primer from TCC to T*G*C, which created a *Hha*I cutting site. The primers used to detect this polymorphism were 5'-AGGTTTTCTCTGCCACCTGGGT-3' (forward) and 5'-CAGCAGGTTGTCAAGCATTT***G***C-3' (reverse). *XRCC1* Arg399Gln was detected using the PCR-restriction fragment length polymorphism (RFLP) assay with primers of 5'-CAC CTAACTGGCATCTTCACT-3' (forward) and 5'-ACAGGA TAAGGAGCAGGGTT-3' (reverse). The 108-bp (Val762Ala) and 190-bp (Arg399Gln) PCR products were then digested respectively by restriction enzymes of *Hha*I (for Val762Ala) and *Msp*I (for Arg399Gln) (New England BioLabs, Beverly, MA). The wild-type (762Val) allele produces a single 108-bp fragment, and the polymorphic (762Ala) allele produces two fragments of 87 and 21 bp. Similarly, the wild-type (399Arg) allele produces two fragments of 148 and 42 bp, while the variant (399Gln) allele produces a single 190-bp fragment. Genotyping was performed without knowledge of case/control status of the subjects. A 10% sample was randomly selected to perform duplicate assays, and the results were 100% concordant.

*Statistical analysis*. Differences in demographic characteristics, selected variables and frequencies of the genotypes and alleles of *ADPRT* and *XRCC1* between the cases and controls were evaluated by using the $\chi^2$ test and/or Student's t-test. The associations between *ADPRT* and *XRCC1* variants and breast cancer risk were estimated by computing the ORs and their 95% CIs from both univariate and multivariate logistic regression analyses. Hardy-Weinberg equilibrium was tested by a goodness-of-fit Chi-square test to compare the observed genotype frequencies to the expected frequencies among control subjects. Stratification analysis was performed according to different groups of selected variants. All statistical analyses were performed with Statistical Analysis System software (v.8.0e; SAS Institute, Cary, NC).

*XRCC1* Arg399Gln and *ADPRT* Val762Ala genotype frequencies among controls, BBD cases and breast cancer

| Genotype | Controls (n=639) No. | % | BBD (n=221) No. | % | OR[a] (95%CI) | Breast cancer (n=302) No. | % | OR[b] (95%CI) |
|---|---|---|---|---|---|---|---|---|
| XRCC1 Arg399Gln | | | | | | | | |
| Arg/Arg | 347 | 54.3 | 118 | 53.4 | 1.00 | 173 | 57.3 | 1.00 |
| Arg/Gln | 240 | 37.6 | 84 | 38.0 | 1.08 (0.75-1.55 | 101 | 33.4 | 0.79 (0.57-1.08) |
| Gln/Gln | 52 | 8.1 | 19 | 8.6 | 1.38 (0.74-2.58) | 28 | 9.3 | 1.01 (0.60-1.70) |
| Arg/Gln + Gln/Gln | 292 | 45.7 | 103 | 46.6 | 1.13 (0.80-1.59) | 129 | 42.7 | 0.82 (0.61-1.11) |
| ADPRT Val762Ala | | | | | | | | |
| Val/Val | 197 | 30.8 | 65 | 29.4 | 1.00 | 100 | 33.1 | 1.00 |
| Val/Ala | 331 | 51.8 | 112 | 50.7 | 0.94 (0.63-1.39) | 153 | 50.7 | 0.88 (0.63-1.22) |
| Ala/Ala | 111 | 17.4 | 44 | 19.9 | 1.12 (0.68-1.84) | 49 | 16.2 | 0.85 (0.55-1.31) |
| Val/Ala + Ala/Ala | 442 | 69.2 | 156 | 70.6 | 0.98 (0.68-1.43) | 202 | 66.9 | 0.87 (0.64-1.19) |
| XRCC1 and ADPRT combinations | | | | | | | | |
| 399Arg/Arg and 762 Val/Val | 101 | 15.8 | 39 | 17.6 | 1.00 | 55 | 18.2 | 1.00 |
| Either variant genotype[c] | 342 | 53.5 | 105 | 47.5 | 0.78 (0.48-1.26) | 163 | 54.0 | 0.82 (0.55-1.23) |
| Both variant genotypes | 196 | 30.7 | 77 | 34.8 | 1.02 (0.61-1.69) | 84 | 27.8 | 0.70 (0.45-1.10) |

[a]Adjusted for age, age at menarche and menopausal status BBD patients vs controls. [b]Adjusted for age, age at menarche and menopausal status breast cancer patients vs controls. [c]Either variant genotype, an individual with any variant homozygote or heterozygote at one site and wild-type homozygote at the other site.

## Results

Characteristics of the 302 breast cancer cases, 221 patients with BBD and 639 cancer-free controls included in the analysis are summarized in Table I. Because we frequency-matched the controls (on age) to all cases of breast disease (breast cancer + BBD cases), and the mean age of BBD patients (44.03±11.58 years) was significantly lower than that of breast cancer patients (52.34±11.04) (P<0.0001), the frequency matching on age between the breast cancer patients as well as BBD cases and controls was not adequate (P=0.0014 for BBD patients and P<0.0001 for breast cancer cases). Compared with the control subjects, both the patients with BBD and breast cancer had a lower age at menarche (P<0.0001 for both BBD and breast cancer patients) and a higher age at first live birth (P<0.0001 for both BBD and breast cancer patients). Within the 463 postmenopausal subjects, the menopausal age of breast cancer cases and BBD patients was not statistically different from that of controls (P=0.0921 for breast cancer cases and P=0.4630 for BBD patients, respectively).

The *XRCC1* Arg399Gln and *ADPRT* Val762Ala genotype distributions of cases and controls are shown in Table II. Allele frequencies of *XRCC1* 399Gln and *ADPRT* 762Ala were 0.269 and 0.433 in the controls, respectively, and the distribution of the genotypes was in agreement with the Hardy-Weinberg equilibrium (P=0.251 for *XRCC1* Arg399Gln and P=0.164 for *ADPRT* Val762Ala). For the *XRCC1* Arg399Gln polymorphism, the genotype frequencies were 54.3% (Arg/Arg), 37.6% (Arg/Gln) and 8.1% (Gln/Gln) among controls, which were not significantly different from those of BBD (53.4% Arg/Arg, 38.0% Arg/Gln and 8.6% Gln/Gln) (P=0.9627) and breast cancer patients (57.3% Arg/Arg, 33.4% Arg/Gln and 9.3% Gln/Gln) (P=0.4497). Logistic regression analyses revealed that compared with the 399Arg/Arg genotype, the adjusted ORs of breast cancer for subjects carrying Arg/Gln and Gln/Gln genotypes were 0.79 (95% CI 0.57 to 1.08) and 1.01 (95% CI 0.60 to 1.70), respectively. Similarly, no significant differences were observed for the genotype distribution of *ADPRT* Val762Ala between the cases and controls (P=0.6923 for BBD cases and P=0.7601 for breast cancer patients). There were also no significant associations between the variant genotypes of *ADPRT* and risk of developing breast cancer (adjusted OR 0.88, 95% CI 0.63 to 1.22 for 762Val/Ala and adjusted OR 0.85, 95% CI 0.55 to 1.31 for 762Ala/Ala).

We then examined the combined effects of *XRCC1* Arg399Gln and *ADPRT* Val762Ala genotypes on breast cancer risk. As shown in Table II, a joint effect was neither evident for patients with BBD nor breast cancer, with adjusted ORs associated with both variant genotypes of 1.02 (95% CI 0.61 to 1.69) for the BBD patients and 0.70 (95% CI 0.45 to 1.10) for breast cancer cases compared with those of both wild-type genotypes. In stratified analyses, no significant associations were observed between *XRCC1* or *ADPRT* genotypes and breast cancer risk for individuals categorized by age, menopausal status and age at menarche (Table III).

Table III. Stratified analysis on association between *XRCC1* Arg399Gln and *ADPRT* Val762Ala polymorphisms and risk of breast cancer.

| | *XRCC1* Arg/Gln + Gln/Gln genotypes | | | | | *ADPRT* Val/Ala + Ala/Ala genotypes | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Breast cancer | | Controls | | | Breast cancer | | Controls | | |
| Variables | No. | % | No. | % | Adjusted OR (CI) | No. | % | No. | % | Adjusted OR (CI)[a] |
| Age | | | | | | | | | | |
| ≤48 | 48 | 45.28 | 160 | 45.07 | 0.92 (0.59-1.45) | 74 | 69.81 | 245 | 69.01 | 1.07 (0.66-1.74) |
| >48 | 81 | 41.33 | 132 | 46.48 | 0.84 (0.57-1.23) | 128 | 65.31 | 197 | 69.37 | 0.84 (0.56-1.26) |
| Menopausal status | | | | | | | | | | |
| Premenopausal | 63 | 41.18 | 165 | 44.72 | 0.83 (0.55-1.28) | 103 | 67.32 | 259 | 70.19 | 0.81 (0.52-1.28) |
| Postmenopausal | 66 | 44.30 | 127 | 47.04 | 0.82 (0.54-1.25) | 99 | 66.44 | 183 | 67.78 | 0.93 (0.60-1.44) |
| Age at menarche | | | | | | | | | | |
| <15 | 51 | 45.95 | 53 | 43.80 | 1.18 (0.67-2.07) | 70 | 63.06 | 83 | 68.60 | 0.65 (0.36-1.19) |
| ≥15 | 78 | 40.84 | 239 | 46.14 | 0.77 (0.55-1.10) | 132 | 69.11 | 359 | 69.31 | 0.98 (0.68-1.42) |

[a]Adjusted for the other covariates presented in this table in a logistic regression model for each stratum.

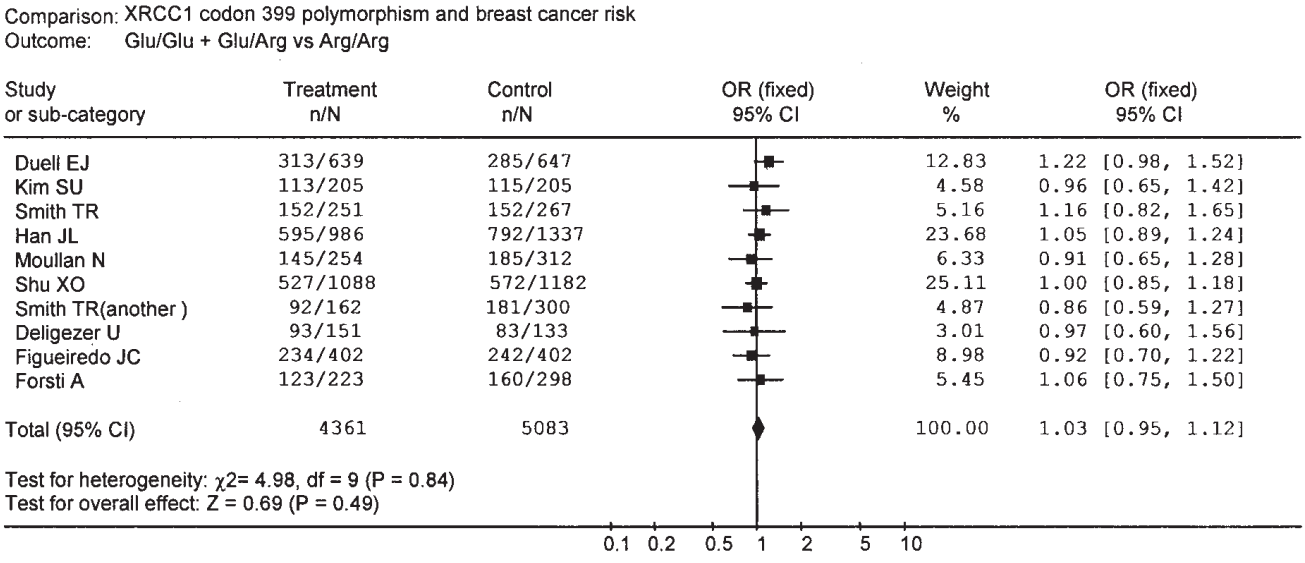


Figure 1. ORs on breast cancer cases associated with the *XRCC1* codon 399 variant for the combined Gln/Gln and Arg/Glu genotypes compared with the Arg/Arg genotype (a meta-analysis from 10 case-control studies)

## Discussion

In this case-control study of breast cancer, we investigated the associations between two nonsynonymous SNPs, *ADPRT* Val762Ala and *XRCC1* Arg399Gln, and the risk of breast cancer in a Chinese population. We found that neither of these two polymorphisms was independently or jointly associated with breast cancer risk, suggesting that these two variants may not play a major role in the etiology of breast cancer. To the best of our knowledge, this is the first molecular epidemiological study on *ADPRT* Val762Ala polymorphism and breast cancer risk.

*XRCC1* encodes a scaffolding protein that plays a pivotal role in BER by bringing together *ADPRT*, DNA ligase 3, and DNA polymerase-ß at the site of DNA damage (9,18), suggesting that XRCC1 and ADPRT may play a joint role in the repair of oxidative damage and single strand breaks. Several molecular epidemiological studies have been conducted to evaluate the association between *XRCC1* Arg399Gln and breast cancer risk. We previously performed a meta-analysis on a total of 4,361 breast cancer cases and 5,083 control subjects from 10 published case-control studies (19-28) and showed that there was no significant effect for this polymorphism on breast cancer risk (Gln/Gln vs Arg/Arg, OR 1.10, 95% CI 0.96 to 1.26; Gln/Gln + Gln/Arg vs. Arg/Arg, OR 1.03, 95% CI 0.95 to 1.12) (Fig. 1; unpublished data), which is consistent with our current observation. ADPRT is a DNA-binding protein involved in the regulation of BER by detecting DNA strand breaks. The 762Val to Ala substitution located within the C-terminal catalytic domain was considered to be correlated with deficient enzyme functions (13). However, Cottet *et al* did not find a functional relevance for this polymorphism (12). A few studies have been conducted to evaluate the role of this polymorphism in

susceptibility, and the results were inconsistent -31). A study by Zhang *et al* reported that *ADPRT* Ala/Ala genotype was associated with a 1.68-fold (95% CI 1.27 to 2.23) increased risk with lung cancer compared with the Val/Val genotype, and a gene-gene interaction between *ADPRT* Val762Ala and *XRCC1* Arg399Gln was evident in a Chinese population (16). However, no significant associations with lung cancer were reported in a Korean or Japanese population (29,31). In the present study, we genotyped this *ADPRT* Val762Ala polymorphism in Chinese women and failed to find significant evidence of an association with breast cancer risk. The discrepancies between published studies might reflect differences in the disease mechanism and/or carcinogen exposure in different populations.

Genetic polymorphisms often vary between ethnic groups. In this study with 639 cancer-free controls, we reported that the allele frequency of *ADPRT* 762Ala was 0.43 among these southeast Chinese women, which is very close to that of Asian populations [0.39 among women in northern China, n=1000 (16); 0.44 in Korean women, n=352 (29); 0.40 in Japanese women, n=685 (31)], and significantly higher than that in U.S. Caucasians (0.15, n=427) and African-American women (0.05, n=100) (13). Likewise, the allele frequency of *XRCC1* 399Gln was also different among different ethnic populations. Here, we report the frequency of *XRCC1* 399Gln of 0.27 in Chinese women, which is similar to that of Asian populations [0.29 in Korean women, n=219 (20), and 0.28 in women of Shanghai China, n=1088 (23)], and significantly lower than that in Caucasians (0.35, n=386) (19).

Given the moderate sample size of our current study, we used an 80% power two-sided test ($\alpha$=0.05) to detect an OR of 1.61 for *ADPRT* Ala/Ala homozygotes, and OR of 1.87 for *XRCC1* 399Gln/Gln, and determine if the variant genotypes are risk genotypes. Because our study was a hospital-based case-control study and the cases were from hospitals and controls were from the surrounding community, the study subjects, particularly breast cancer cases, may not be representative of the target population. In addition, we cannot rule out the possibility that other unidentified alterations in genes involved in DNA repair pathways may influence the risk of developing breast cancer. Large population-based prospective studies are warranted to further elucidate the gene-gene interactions of *XRCC1* and *ADPRT* in breast cancer susceptibility.

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