Original Article

Impact of the *PARP1* rs1136410 and rs3219145 polymorphisms on susceptibility and clinicopathologic features of breast cancer in a Chinese population

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Background: Poly(ADP-ribose) polymerase-1 (*PARP1*) is the important one in the *PARP* family. *PARP1* participates in the development of tumors and its polymorphisms were reported to relate to various tumors risk. The case-control study aimed to examine whether the *PARP1* rs1136410 and rs3219145 polymorphisms had an association with breast cancer (BC) risk in a Chinese population.

Methods: We used the Sequenom MassARRAY to genotype the two polymorphisms in this study. We used SPSS 18.0 for statistical analyses and odds ratios (ORs) and 95% confidence intervals (CIs) for evaluating the strength of association between the two polymorphisms and the susceptibility to BC. The associations between the *PARP1* genotypes of the polymorphisms and patients' clinical characteristics were estimated by the χ^2-test and ORs and 95% CIs. The allele frequencies were assessed whether they deviated from the Hardy-Weinberg equilibrium (HWE) using the χ^2-test before analysis.

Results: There were significantly different between the genotype distributions of cases and controls for the *PARP1* rs1136410 polymorphism under the dominant (P=0.022, adjusted OR =0.73), recessive (P=0.028, adjusted OR =0.69) and allele models (P=0.005), the C/C genotype had a lower BC risk. Notably, this polymorphism exerted a more protective effect in the subgroup of older subjects (age ≥49 years) (P=0.003). The relationship of rs1136410 C/C genotype and less frequent lymph node involvement (OR =0.60, 95% CI: 0.37–0.99), less venous invasion (OR =0.55, 95% CI: 0.31–0.95), and lower Ki67 expression (OR =0.58, 95% CI: 0.35–0.96) was also observed. However, we did not observe any significant results with the *PARP1* rs3219145 polymorphism.

Conclusions: Our results suggest that the *PARP1* rs1136410 polymorphism may reduce the BC risk and delay BC progression rather than the rs3219145 polymorphism in the Chinese population.

Keywords: Poly(ADP-ribose) polymerase-1 (*PARP1*); polymorphism; susceptibility; breast cancer (BC)

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Introduction

Breast cancer (BC), with nearly 1.7 million incidence and 522,000 deaths (according to 2012 GLOBOCAN statistics), is the most frequently occurring cancer in women. Actually, the BC rates in Asia exceeded the historically high rates in the United States in recent generations (1,2). In China [2011], although BC was only the sixth leading cause of cancer death (mortality was 9.21/10^5) in females, it was the most common cancer among women overall (incidence was 37.86/10^5) (3). The etiology of BC, which is thought to be multifactorial, has not been completely elucidated. But it is widely known that genetic factors contribute to an increased or a decreased BC susceptibility, which means an important role of genetic variations to BC risk (4,5).

Poly(ADP-ribose) polymerase-1 (*PARP1*) is the main part of the *PARP* family. Activated by DNA breaks, it plays important roles in DNA repair and other cellular processes (6). *PARP1* can induce cell survival by repairing DNA, but it is degraded during apoptosis by caspases (7). Its overexpression contributes to the development of various tumors (8,9). In triple-negative BC and other human cancer types, the expression of *PARP1* was upregulated (10), and its nuclear expression was linked with chemotherapy response in invasive primary BCs (11). *PARP1/2* inhibitors (olaparib, for example) as therapeutic agents are currently used in clinical trials in breast and ovarian cancer (12,13). However, some studies revealed that *PARP1* participated in inhibiting malignancy in mice, and the reduction of *PARP1* activity in human peripheral blood lymphocytes is connected with various cancers (14,15). The explanation for these contrary findings remains undiscovered, but single nucleotide polymorphisms (SNPs) may play roles in the different functions of *PARP1*.

To date, there are at least 400 SNPs, including 17 non-synonymous SNPs (nsSNPs) in the *PARP1*, but functional analyses have only been performed about the rs1136410 and rs3219145 polymorphisms (16). The impact of the *PARP1* polymorphisms is currently unclear. Some studies have demonstrated an association of that *PARP1* polymorphisms and an increased tumors risk including stomach (17), esophageal (18), cervical (19) and lung (20). In contrast, other studies have reported that *PARP1* polymorphisms are associated with reduced risk of malignancy including glioma and non-Hodgkin lymphoma (21,22). In some researches on BC, the *PAPR1* polymorphism (rs1136410) increased tumor risk among Saudi and Asian population, but decreased risk of cancer among Caucasians. Therefore, the *PAPR1* polymorphisms might play different roles in different ethnic populations and different cancer types (23,24). Because of these uncertain results, and the fact that only a few studies on BC involved Asian populations, we conducted this case-control study to determine the associations between the *PARP1* rs1136410 and rs3219145 polymorphisms and BC risk in a Chinese population.

Methods

Study participants

All 458 cases were consecutively recruited from August 2013 to September 2014 from the Second Affiliated Hospital of Xi'an Jiaotong University, while the 500 controls came from volunteers. These 958 participants signed informed consent documents during face-to-face interviews before recruitment and they understood the purpose of the research. All of the patients were sporadic BC by pathologically confirmation. Patients would be excluded if they ever had other types of cancer. For comparison, the control and case groups were frequency-matched based on age (48.96 *vs.* 47.90, P=0.061), as shown in *Table 1*. The basic information about the two groups is showed in *Table 1*. The Institutional Review Board of the Second Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) approved this research (No. 2015-010) (25-27).

SNP selection and genotyping

We selected two SNPs (rs1136410 and rs3219145) from the *PARP1* gene, which had previously been shown to be associated with various tumors (16-20,23). We used proteinase K digestion and phenol/chloroform extraction to isolate and purify genome DNA from peripheral blood leukocytes, as described previously (4,5), and measured the concentration using spectrophotometry (DU 530 UV/Vis spectrophotometer, Beckman instruments, Fullerton, CA, USA). The following corresponding primers were used for SNPs in this study: for rs1136410, forward primer: 5'-ACGTTGGATGCACCATGATACCTAAGTCGG-3' and, reverse primer: 5'-ACGTTGGATGATGTCCAGCAGGTTGTCAAG-3'; for rs321945, forward primer: 5'-ACGTTGGATGTGTTGCCATCTTAATCTCAG-3' and, reverse primer: 5'-ACGTTGGATGTTGAGTTTTGCCCCTCAGTC-3'. The two SNPs were genotyped by the Sequenom MassARRAY RS1000 (Sequenom, Inc., San Diego, CA, USA) following the manufacturer's instructions.

Table 1 Distributions of selected variables in BC cases and cancer-free controls

Variables	Cases (N=458) (%)	Control (N=500) (%)	P value*
Age (mean ± SD) (years)	48.96±8.85	47.90±8.57	0.061
<49	240 (52.4)	264 (53.0)	0.902
≥49	218 (47.6)	236 (47.0)	
Menopausal status			
Premenopausal	236 (51.5)	236 (47.2)	0.181
Postmenopausal	222 (48.5)	264 (52.8)	
Body mass index (mean ± SD) (kg/m^2)	23.05±2.89	22.33±2.48	0.315
Tumor size (cm)			
<2	152 (33.2)		
≥2	306 (66.8)		
Lymph node involvement			
Negative	184 (40.2)		
Positive	274 (59.8)		
Histological grade			
SBR 1–2	244 (53.3)		
SBR 3	214 (46.7)		
Venous invasion			
Negative	292 (63.8)		
Positive	166 (36.2)		
ER			
Negative	202 (44.1)		
Positive	256 (55.9)		
PR			
Negative	208 (45.4)		
Positive	250 (54.6)		
HER2			
Negative	330 (72.1)		
Positive	128 (27.9)		
Ki67			
<14%	164 (35.8)		
≥14%	294 (64.2)		

*, *t*-test or two-sided χ^2-test. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BC, breast cancer; SBR, Scarff-Bloom-Richardson.

The data was managed and analyzed by Sequenom Typer 4.0 software.

Statistical analysis

Statistical analyses were conducted with the Student's *t*-test for continuous variables and the χ^2-test for categorical variables by SPSS PASW Statistics v18.0 (SPSS Inc., Chicago, IL, USA). For controls, the allele frequencies were assessed whether they deviated from the Hardy-Weinberg equilibrium (HWE) using the χ^2-test before analysis. We performed unconditional logistic regression to evaluate the associations between the two *PARP1* polymorphisms and BC risk were evaluated by calculating odds ratios (ORs) and 95% confidence intervals (CIs), and P values were adjusted for age, menopausal status, and body mass index. The associations between the *PARP1* genotypes of the polymorphisms and patients' clinical characteristics were estimated by the χ^2-test and ORs and 95% CIs. Significance was taken when P<0.05, and all statistical tests were two-sided.

Results

Characteristics of the patients and controls

The basic characteristics of the two groups are showed in *Table 1*. There had no significant differences between the cases and controls for the age (P=0.061), the stratification of age (P=0.902) and the menopausal status (P=0.181). The percentages of patients with tumors <2 and ≥2 cm in size were 33.2% and 66.8%, respectively. About 47% of the patients had Scarff-Bloom-Richardson (SBR) 3 grade cancer. The percentages of patients with lymph node involvement and venous invasion were 59.8% and 36.2%, respectively. In addition, patients with estrogen receptor- (ER-), progesterone receptor- (PR-), human epidermal growth factor receptor 2- (HER2-) and Ki67-positive disease account for 55.9%, 54.6%, 27.9%, and 64.2% of the overall cases, respectively.

Association between the PARP1 polymorphism and the risk of BC

The genotype distributions and alleles of the *PARP1* rs1136410 and rs3219145 polymorphisms are presented in *Table 2*. The two SNPs' genotype distribution was in HWE in controls tested (the P values were 0.07 and 0.13 for the rs1136410 and rs3219145 polymorphisms, respectively). The frequencies of the *PARP1* rs1136410 genotypes were significantly different between the case and control groups (P=0.024). The same trend was also observed between cases and controls under the allele model (P=0.005). Subjects with the C/C genotype had a lower BC risk than those with T/T genotype (P=0.007, OR =0.61, 95% CI: 0.43–0.89) and TT/TC genotypes (P=0.028, OR =0.69, 95% CI: 0.50–0.96). However, we could not find any association between the *PARP1* rs3219145 polymorphism and BC risk in any comparison.

Stratified analysis of the PARP1 rs1136410 polymorphism and risk of BC

Stratified by age, we investigated the influence of the *PARP1* rs1136410 polymorphism on BC risk. As shown in *Table 3*, the protective effect of the *PARP1* rs1136410 C/C genotype was confirmed in older subjects (P=0.003, OR =0.47, 95% CI: 0.28–0.77) rather than younger subjects, which suggested that older individuals could benefit more from carrying the C/C genotype. The same analysis was also performed for the *PARP1* rs3219145 polymorphism, but got no significant observations (data not shown).

Association between the PARP1 rs1136410 polymorphism and clinical parameters of BC patients

On the basis of the clinicopathologic features of BC patients, we then analyzed the association between the *PARP1* polymorphisms and a series of clinicopathologic features including tumor size, lymph node involvement, histological grade, venous invasion, ER/PR, HER2, and Ki67. In patients with positive lymph node involvement, positive venous invasion and Ki67 index ≥14%, the frequencies of CC genotype were 13.5%, 11.4%, and 13.6% versus 86.5%, 88.6% and 86.4% in those with TT/TC genotypes, respectively. No other significant association between the *PARP1* polymorphisms and the clinical features was observed, as shown in *Table 4*.

Discussion

PARP1 is the main member of the *PARP* family and participates in DNA repair pathways. It can influence carcinogenesis and tumor biology by inducing cell survival or impacting apoptosis (10). Although the overexpression of *PARP1* was confirmed in numerous BC studies, some contrary results have also been reported (8-15). Therefore,

Table 2 Genotype and allele frequencies of the *PARP1* polymorphisms among the cases and controls and the associations with risk of BC

PARP1 polymorphism	Cases (N=458) (%)	Control (N=500) (%)	P value*	OR (95% CI)†
rs1136410				
Codominant				
T/T	182 (39.7)	163 (32.6)	–	1.00 (reference)
T/C	201 (43.9)	227 (45.4)	0.109	0.79 (0.60–1.05)
C/C	75 (16.4)	110 (22.0)	0.007	0.61 (0.43–0.89)
Dominant				
T/T	182 (39.7)	163 (16.3)	–	1.00 (reference)
C/C-T/C	276 (60.3)	337 (33.7)	0.022	0.73 (0.56–0.96)
Recessive				
T/T-T/C	383 (83.6)	390 (78.2)	–	1.00 (reference)
C/C	75 (16.4)	110 (21.8)	0.028	0.69 (0.50–0.96)
Allele				
T	565 (61.7)	553 (55.3)	–	1.00 (reference)
C	351 (38.3)	447 (44.7)	0.005	0.77 (0.64–0.92)
rs3219145				
Codominant				
G/G	297 (64.8)	327 (65.4)	–	1.00 (reference)
A/G	143 (31.2)	148 (29.6)	0.663	1.06 (0.81–1.41)
A/A	18 (4.0)	25 (5.0)	0.466	0.79 (0.42–1.48)
Dominant				
G/G	297 (96.1)	327 (95.0)	–	1.00 (reference)
A/A-A/G	161 (3.9)	173 (5.0)	0.858	1.03 (0.79–1.34)
Recessive				
G/G-A/G	440 (96.1)	475 (95.0)	–	1.00 (reference)
A/A	18 (3.9)	25 (5.0)	0.424	0.78 (0.42–1.44)
Allele				
G	737 (80.5)	802 (80.2)	0.887	1.00 (reference)
A	179 (19.5)	198 (19.8)	–	0.98 (0.79–1.23)

*, two-sided χ^2-test for the distributions of genotype and allele frequencies; †, adjusted for age, menopausal status and body mass index. PARP1, poly(ADP-ribose) polymerase-1; BC, breast cancer; OR, odds ratio; CI, confidence interval.

the role of *PARP1* remains uncertain, and the same is true for *PARP1* polymorphisms. There were significantly different of the *PARP1* rs1136410 genotypes between the case and control groups. Compared to individuals with the C/C and CC/TC genotypes, those with the C/C genotype had a more decreased BC risk. However, we could not find any relationships between the *PARP1* rs3219145 polymorphism and BC susceptibility in any comparison. Interesting, our results were in contrast to those of Alanazi (24), who found in a Saudi population that the *PARP1* rs1136410 increased

Table 3 Stratification analyses on age between the *PARP1* rs1136410 polymorphism and risk of BC

PARP1 rs1136410	Cases (N=458) (%)	Control (N=500) (%)	P value*	OR (95% CI)†
Age <49	240 (52.4)	264 (52.8)		
T/T-T/C	192 (80.0)	209 (79.2)	0.817	1.00 (reference)
C/C	48 (20.0)	55 (20.8)	–	0.95 (0.62–1.47)
Age ≥49	218 (47.6)	236 (47.2)		
T/T-T/C	191 (87.6)	181 (76.7)	0.003	1.00 (reference)
C/C	27 (12.4)	55 (23.3)	–	0.47 (0.28–0.77)

*, two-sided χ^2-test for the distributions of genotype and allele frequencies; †, adjusted for age, menopausal status and body mass index. PARP1, poly(ADP-ribose) polymerase-1; BC, breast cancer; OR, odds ratio; CI, confidence interval.

the risk of BC. Recently, a meta-analysis found evidence that the association of the *PARP1* polymorphism with risk of cancer was contrary in different populations (23). Our results provide the first evidence that the *PARP1* rs1136410 polymorphism was associated with a decreased risk of BC in a Chinese population. V762A (rs1136410) based on T to C transition at codon 762 in exon 17 in *PARP1*, this transition resulted in the substitution of alanine for valine in the catalytic domain of *PARP1* protein and was associated with an altered activity of *PARP1*. This might be the molecular mechanism of the protective role of *PARP1* rs1136410 in BC, but further experiments are needed to verify.

PARP1 expression has been correlated with clinicopathologic characteristics, outcome, and some DNA repair proteins' expression. In particular, *PARP1* expression was positively related to younger premenopausal patients, and those with larger size tumors and higher tumor grade (28), whether *PARP1* rs1136410 would have similar associations with clinicopathologic features of BC. In the current study, we found that the frequency of the C/C genotype was significantly lower in patients with lymph node involvement, venous invasion, and Ki67 positivity, suggesting that the variant genotype of this polymorphism may play a protective role during the BC progression. We found no other associations between the *PARP1* polymorphisms and the clinical features of BC. Lymph node involvement, venous invasion, and Ki67 are poor prognostic factors. Our results indicated the higher expression of Ki67 and the more lymph node involvement with the lower expression of C/C type, this result was agree with the absence of C/C protective role. However, the molecular mechanism remains to be studied. Fortunately, the variant genotype (C/C) had a protective impact in this population. Although *PARP1* inhibitors as therapeutic agents are being used in clinical trials, especially for patients with triple-negative BC, in we did not find any association between *PARP1* rs1136410 and ER/PR/HER2. In patients with BRCA1- or BRCA2-mutated HER2-negative advanced BC, the *PARP1* inhibitor (olaparib) combined with carboplatin in a randomized phase II trial acquired positive results (29), but in other research patients without BRCA1- or BRCA2-mutation the *PARP1* inhibitors were also effective (30). Whether this phenomenon was related to the *PARP1* polymorphisms remained unknown, so future studies with a more specific focus on these topics will be useful.

In the subgroup analysis, we also found that the older individuals (age ≥49 years) could benefit more from carrying the CC genotype. As it is known that more DNA lesions occur as individuals' age, our results suggest that the CC genotype might play a protective role during this process, and the risk of BC development in younger individuals is influenced by other factors.

Our study does have a particular limitation that should be considered. Since our study was a case-control design, there may exist some bias, for example selection bias, which may result from selected participants with a particular genotype. However, the genotype distributions of *PARP1* polymorphisms in our control group all in HWE, suggesting that the selection bias would not be a major concern.

Conclusions

In conclusion, our results suggest that the *PARP1* rs1136410 reduce the BC risk and delay BC progression rather than the rs3219145 polymorphism in the Chinese population. Although we demonstrated a statistically significant

Table 4 Associations between the *PARP1* rs1136410 polymorphism and clinical characteristics of BC patients

Clinicopathologic features	PARP1 rs1136410 polymorphism (%)		P value*	OR (95% CI)†
	TT/TC	C/C		
Tumor size (cm)			0.861	
<2	125 (82.2)	27 (17.8)		1.00 (reference)
≥2	258 (84.3)	48 (15.7)		0.51 (0.51–1.46)
Lymph node involvement			0.043	
Negative	146 (79.3)	38 (20.7)		1.00 (reference)
Positive	237 (86.5)	37 (13.5)		0.60 (0.37–0.99)
Histological grade			0.202	
SBR 1–2	199 (81.6)	45 (18.4)		1.00 (reference)
SBR 3	184 (86.0)	30 (14.0)		0.72 (0.44–1.19)
Venous invasion			0.032	
Negative	236 (80.8)	56 (19.2)		1.00 (reference)
Positive	147 (88.6)	19 (11.4)		0.55 (0.31–0.95)
ER			0.132	
Negative	163 (80.7)	39 (19.3)		1.00 (reference)
Positive	220 (85.9)	36 (14.1)		0.69 (0.42–1.12)
PR			0.078	
Negative	167 (80.3)	41 (19.7)		1.00 (reference)
Positive	216 (86.4)	34 (13.6)		0.64 (0.39–1.01)
HER2			0.581	
Negative	274 (83.0)	56 (17.0)		1.00 (reference)
Positive	109 (85.2)	19 (14.8)		0.85 (0.48–1.50)
Ki67			0.032	
<14%	129 (78.7)	35 (21.3)		1.00 (reference)
≥14%	254 (86.4)	40 (13.6)		0.58 (0.35–0.96)

*, two-sided χ^2-test for the distributions of genotype and allele frequencies; †, adjusted for tumor size, lymph node, histological grade, venous invasion, ER/PR, HER2 and Ki67. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; *PARP1*, poly(ADP-ribose) polymerase-1; BC, breast cancer; OR, odds ratio; CI, confidence interval; SBR, Scarff-Bloom-Richardson.

association in our study, it needs to be confirmed by other larger scale studies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.09.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board of the Second Affiliated Hospital of Xi'an Jiaotong University (Xi'an, China) approved this research (No. 2015-010) and written informed consent was obtained from all patients.

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