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Short Communication

A genetic variant in the promoter of *APE1* gene (−656 T>G) is associated with breast cancer risk and progression in a Chinese population

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ABSTRACT

Background/aims: *APE1* is an important DNA repair protein in the base excision repair pathway. Genetic variations in *APE1* have been suggested to influence individuals' susceptibility to human malignancies. The present study was aimed to investigate the associations between two functional polymorphisms in *APE1* (−656 T>G and 1349 T>G) and breast cancer risk.

Methods: We genotyped the two polymorphisms in a case-control study of 500 breast cancer patients and 799 age-matched cancer-free controls using the TaqMan method. Unconditional logistic regression adjusted for potential confounding factors was used to assess the associations.

Results: We found that the variant genotypes of the −656 T>G were significantly associated with decreased breast cancer risk, compared with the wild genotype [TG/GG vs. TT: adjusted odds ratio (OR) = 0.71, 95% confidence interval (CI) = 0.56–0.91], and the protective effect of this polymorphism was more predominant among the subgroups of younger subjects (<52 years) (OR = 0.65, 95% CI = 0.46–0.92). Besides, we found that the variant genotypes were associated with less frequent lymph node metastasis ($P = 0.020$, OR = 0.64, 95% CI = 0.44–0.94). We did not observe any significant association between the 1349 T>G polymorphism and breast cancer risk.

Conclusion: Our results suggest that the *APE1* −656 T>G but not the 1349 T>G polymorphism may influence the susceptibility and progression of breast cancer in the Chinese population. Large population-based prospective studies are required to validate these findings.

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1. Introduction

Breast cancer is the most common malignancy affecting women worldwide and its incidence rate is increasing in both developed and developing countries in recent years (Jemal et al., 2011). The etiology of breast cancer has not been completely identified yet, but is thought to be multifactorial, with both environmental and genetic factors (Lichtenstein et al., 2000).

Human DNA repair systems play an important role in protecting the genome from DNA damage caused by endogenous and environmental agents (Wood et al., 2005). There are five major DNA repair pathways: direct repair, base excision repair (BER), nucleotide excision repair, mismatch repair, and double-strand break repair; among these repair systems, BER pathway is responsible for repairing small lesions such as oxidative damage, alkylation, or methylation (Hoeijmakers, 2001; Wilson and Bohr, 2007). AP endonuclease 1 (APE1), also known as APE, APEX, HAP1, or REF-1, is an important DNA repair protein in the BER pathway which acts as a 3′-phosphodiesterase to initiate repair of DNA single strand breaks producing either directly by reactive oxygen species or in directly through the enzymatic removal of damaged bases (Barzilay and Hickson, 1995). It also functions as a redox agent maintaining transcription factors involved in cancer promotion and progression in an active reduced state and is considered as a promising tool for anticancer therapy (Tell et al., 2010).

Genetic polymorphisms in DNA repair genes have been shown to influence the susceptibility to various carcinomas (Goode et al., 2002; Smith et al., 2003; Thompson et al., 2012). Up to data, a number of epidemiological studies have suggested that genetic polymorphisms in *APE1* were associated with the risk of cancer (Cao et al., 2011; Gu et al., 2009). The human *APE1* gene is located on chromosome 14q11.2–q12 and consists of five exons spanning 2.21 kb (Xi et al., 2004). A total of 18 single nucleotide polymorphisms (SNP) in *APE1* have been identified, but the most extensively studied polymorphisms are the 1349 T>G (rs1130409) in the fifth exon and the −656 T>G (rs1760944) in the promoter region. Gu et al. have conducted a meta-analysis on the association between the 1349 T>G polymorphism and cancer risk and suggested the

Abbreviations: SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; BER, base excision repair; APE1, AP endonuclease 1.

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polymorphism is a low-penetrance risk factor for cancer development (Gu et al., 2009). However, in a latter meta-analysis with a larger sample size performed by Zhou et al., they concluded that the *APE1* −656 T>G polymorphism has a possible protective effect on cancer risk whereas the 1349 T>G polymorphism did not contribute to the development of cancer (Zhou et al., 2011). There are also several studies that have investigated the association between the *APE1* 1349 T>G polymorphism and breast cancer risk; and the results from these are inconclusive. Recently, Wu et al. conducted a meta-analysis including 5 studies on this issue and suggested the *APE1* 1349 T>G polymorphism was not associated with breast cancer risk (Wu et al., 2012); however, only one of the studies was conducted in Asian population (Sangrajrang et al., 2008). As to the −656 T>G polymorphism, there is still a lack of study on its association with breast cancer risk. Herein, in the present study, we investigated the association of the two *APE1* SNPs (−656 T>G and 1349 T>G) with breast cancer risk in a case-control study in a Chinese population.

2. Materials and methods

2.1. Ethics statement

The study was approved by the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. At recruitment, written informed consent was obtained from all participants involved in this study.

2.2. Study population

Our study consisted of 500 breast cancer patients which were consecutively recruited between Jan 2010 and September 2012 at the Second Affiliated Hospital, Medical School of Xi'an Jiaotong University. The Cases were recruited without the restriction of age. All of the patients were pathologically confirmed, sporadic breast cancer. Those patients that received chemotherapy or radiotherapy before surgery or had other type of cancer were excluded from the present study. For comparison, 799 cancer-free controls were recruited from subjects who were seeking health care in the outpatient departments at the hospital and were frequency-matched to the cases on age (±5 years). Before recruitment, a standard questionnaire was administered through face-to-face interviews by trained interviewers to obtain information on demographic data and related factors. The clinical information of the patients group and the demographic characteristics of both the cases and controls were present in Table 1.

2.3. Genotyping

Genomic DNA was isolated and purified from leucocytes of peripheral blood by proteinase K digestion and phenol/chloroform extraction. Genotyping of the two *APE1* polymorphisms was performed using the predesigned TaqMan probe assay (Applied Biosystems, Foster City, CA, USA). The sequences of primer and probe for the two SNPs are available on request. The reaction mixture of 10 μL contained 20 ng genomic DNA, 3.5 μL of 2×TaqMan Genotyping Master Mix, 0.25 μL of the primers and probes mix and 6.25 μL of double distilled water. The amplification was performed under the following conditions: 50 ºC for 2 min, 95 ºC for 10 min followed by 45 cycles of 95 ºC for 15 s, and 60 ºC for 1 min. Amplifications were performed in the 384-well ABI 7900HT Real Time PCR System (Applied Biosystems), following the manufacturer's instructions. After the completion of the amplification, the fluorescence intensity in each well of the plate was read and analyzed with SDS 2.4 automated software. Four blank controls were included in each plate to ensure accuracy of the genotyping. About 10% of the samples were randomly selected for repeated assays, and the results were in agreement with the results of the first assays.

2.4. Statistical analyses

SNP allele frequencies in the controls were tested against departure from the Hardy-Weinberg equilibrium (HWE) using a goodness-of-fit χ^2-test before analysis. Differences in the distributions of categorical variables such as smoking and drinking status and the frequencies of genotypes of the −656 T>G and 1349 T>G polymorphisms between the cases and controls were evaluated using the χ^2-test, and continuous variables such as age using the Student's *t*-test. The associations between the genotypes of the *APE1* −656 T>G and 1349 T>G polymorphisms and risk of breast cancer and patients' clinical characteristics were estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs) from unconditional logistic regression analysis with the adjustment for age and age at menarche. $P < 0.05$ was considered statistically significant, and all statistical tests were two sided. All of the statistical analyses were performed with the software SAS 9.1.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Association between APE1 polymorphisms and risk of breast cancer

Allele and genotype distributions of the *APE1* −656 T>G and 1349 T>G polymorphisms are presented in Table 2. The observed genotype frequencies of the two SNPs in the controls were in agreement with the HWE ($P = 0.294$ for the −656 T>G polymorphism and $P = 0.199$ for the 1349 T>G polymorphism). We found that the distributions of the *APE1* −656 T>G genotypes were significantly different between cases and controls ($P = 0.012$). Comparing with subjects with the −656 TT genotype, individuals with the variant GG genotype had a significant reduced breast cancer risk (adjusted OR = 0.63, 95% CI = 0.45–0.88). Furthermore, in a recessive model, the −656 TG/GG genotypes were also significantly associated with a decreased risk for breast cancer (OR = 0.71, 95% CI = 0.56–0.91). However, we did not observe significant associations between the 1349 T>G polymorphism and breast cancer risk in any comparison, as shown in Table 2.

Table 1
Distributions of select variables in breast cancer cases and cancer-free controls.

Variables	Case (*N* = 465), %		Control (*N* = 799), %		*P* [a]
Age at diagnosis or recruitment (year)					
Mean ± SD	52.0 ± 11.0		50.8 ± 13.2		0.110
<52	239	51.4	437	54.7	0.257
≥52	226	48.6	362	45.3	
Age at menarche (year)					
Mean ± SD	14.55 ± 1.84		14.89 ± 1.76		0.002
<14	136	29.3	183	22.9	0.012
≥14	329	70.7	616	77.1	
Tumor size					
Less than 2 cm	126	27.1			
2 to 5 cm	310	66.7			
More than 5 cm	29	6.2			
LN involvement					
Negative	251	54.0			
Positive	214	46.0			
ER					
Negative	162	34.8			
Positive	303	65.2			
PR					
Negative	209	44.9			
Positive	256	55.1			
HER-2					
Negative	309	66.4			
Positive	156	33.6			

[a] *T*-test or two-sided χ^2-test.

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