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Significant Association of *XPD* Asp312Asn Polymorphism with Breast Cancer in Taiwanese Patients

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Abstract

The DNA repair gene *XPD*, an important caretaker of the overall genome stability, is thought to play a major role in the development of human malignancy. Polymorphic variants of *XPD*, at Asp312Asn (rs1799793), Lys751Gln (rs13181), and promoter C-114G (rs3810366), were chosen to be studied of their association with breast cancer susceptibility in a central Taiwanese population. In this hospital-based case-control study, the associations of *XPD* Asp312Asn, Lys751Gln and promoter C-114G polymorphisms with breast cancer risk were investigated. In total, 1232 patients with breast cancer and 1433 healthy controls recruited from the China Medical Hospital in Central Taiwan were genotyped. We found a significant difference in the frequency of the *XPD* Asp312Asn genotype, but not the XPD Lys751Gln or promoter C-114G genotypes, between the breast cancer and control groups. Those who had G/A or A/A at *XPD* Asp312Asn showed a 1.78-fold (95% confidence interval = 1.53-2.08) increased risk of breast cancer compared to those with G/G. As for *XPD* Lys751Gln or promoter C-114G, there was no difference in distribution between the breast cancer and control groups. Our findings suggest that the heterozygous and homozygous A allele of the *XPD* Asp312Asn may be associated with the development of breast cancer and may be a useful marker for primary prevention and anticancer intervention.

Key Words: *XPD*, Asp312Asn, polymorphism, breast cancer Taiwanese

Introduction

Breast cancer is one of the most commonly diagnosed cancers all over the world (21). However, the etiology of breast cancer is still largely unknown. Breast cancer predisposition genes identified to date (*e.g.*, BRCA1 and BRCA2) are responsible for less than 5% of all breast cancer cases. Besides rare mutations, commonly occurring single nucleotide polymorphisms (SNPs) have also been shown to incrementally contribute to breast cancer risk (31, 40, 49). Polymorphisms exist in several genes involved in nucleotide excision repair (NER), the pathway mainly removes bulky DNA lesions typically generated from exposure to polycyclic aromatic hydrocarbons in tobacco smoke. Benzo[*a*]pyrene diolepoxide (BPDE) primarily reacts with guanine at the N^2 amino group to form bulky DNA adducts that distort the DNA double helix (32). Bulky BPDE-DNA adducts are repaired *via* either TCR or the global genome NER

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pathway depending on the location of the lesions (14, 32). Cigarette smoking contains may also induce a lot of oxidative damage causing DNA oxidative adducts together with single- and double-strand breaks (48, 51), which should be removed by base excision repair and double strand break repair systems, respectively (16, 18). Human DNA repair mechanisms protect the genome from DNA damage caused by endogenous and environmental agents. Mutations or defects in the DNA repairing system are essential for tumorigenesis. It is therefore logical to suspect that some genetic variants of DNA repair genes might contribute to breast cancer pathogenesis.

Sequence variants in DNA repair genes also are thought to modulate DNA repair capacity and consequently may be associated with altered cancer risk (20). *Xeroderma pigmentosum Group D* (*XPD*) gene, also known as excision repair cross-complementing rodent repair deficiency Group 2 (ERCC2), is important in environmentally induced cancer (17). The *XPD* gene product is a helicase that is a component of the TFIIH transcription factor complex. *XPD* plays a role in transcription and nucleotide excision repair (NER), which removes bulky adducts, such as those caused by environmental agents, UV-induced DNA damage, crosslinks and oxidative damage (35, 50). Mutations in the *XPD* gene can diminish the helicase activity, resulting in a defect in NER, in transcription and in an abnormal response to apoptosis (46). SNPs have been identified in several exons of the *XPD* gene, among which one in codon 312 of exon 10 and the other in codon 751 of exon 23 are commonly studied and result in amino acid changes (Asp312Asn and Lys751Gln, respectively) (37). These polymorphisms are associated with lower DNA repair capacity and a higher level of DNA adducts (28, 37). Some studies have reported significant associations between the Asp312Asn or Lys751Gln variants and predisposition to many types of cancer, including lung cancer (52), squamous cell carcinoma of the head and neck (43), melanoma (47) and bladder cancer (42). There are a few findings reporting the *XPD* polymorphisms in breast cancer in recent years. But an investigation of *XPD* genotypes in breast cancer Taiwanese is still lacking. The Asn/Asn genotype at *XPD* Asp312Asn is associated with a 2.06-fold breast cancer risk in a German population (23). Subjects with an Asp/Asn or Asn/Asn polymorphic genotype in *XPD* Asp312Asn had elevated levels of PAH-DNA adducts compared to subjects with the Asp/Asp genotype (45). The Lys/Lys and/or Lyn/Gln genotypes of *XPD* Lys751Gln is positively associated with breast cancer (33, 44), while other papers do not find any association (25, 29, 39). The association of the *XPD* Lys751Gln polymorphism with histological grade was also significant (15). In addition to to Asp312Asn and Lys751Gln, our group has previously investigated a novel SNP of *XPD*, promoter C-114G, which may have regulatory effects on the expression level of *XPD*. However, there is no association between *XPD* promoter C-114G and human myoma and prostate cancer (6, 19).

Since DNA repair gene alterations have been shown to cause a reduction in DNA repair capacity, we hypothesized that DNA repair gene polymorphisms may be risk factors for breast cancer. To test this hypothesis, DNA samples from 1232 cases of breast cancer and 1433 age-matched healthy controls in a central Taiwan population were analyzed with a polymerase chain reaction-based restriction fragment length polymorphism method to determine the genotypic frequency of three polymorphisms of the *XPD* gene (Asp312Asn, Lys751Gln and promoter C-114G). To the best of our knowledge, this is the first study carried out to evaluate the *XPD* Asp312Asn, Lys751Gln and promoter C-114G polymorphisms at the same time and in a high prevalence Taiwanese population.

Materials and Methods

Study Population and Sample Collection

A total of 1232 patients diagnosed with breast cancer were recruited at the outpatient clinics of general surgery between 1998-2008 at the China Medical University Hospital, Taichung, Taiwan, Republic of China. The mean age of the breast cancer patients and the controls were 58.64 (SD = 9.61) and 55.31 (SD = 8.83) years, respectively. All patients voluntarily participated, completed a self-administered questionnaire and provided peripheral blood samples. At the same time, 1433 non-cancer healthy people as controls were selected by matching for age and gender after initial random sampling from the Health Examination Cohort of the hospital. Our study was approved by the Institutional Review Board of the China Medical University Hospital and written-informed consent was obtained from all participants.

Genotyping Assays

Genomic DNA was prepared from peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and Genotyping assays for the *XPD* polymorphisms (rs1799793, Asp312Asn; rs13181, Lys751Gln; rs3810366, 114 bp upstream of *XPD*) according to our previous paper (6). Briefly, the following primers were used for XPD Asp312Asn: 5'-TGGCCCCTGTCTGACTTGTCCC-3' and 5'-GACGGGGAGGCGGGAAAGGGACT-3'; for *XPD* Lys751Gln: 5'-ACTTCATAAGACCTTCTAGC-3'

Table 1. Allele frequencies for *XPD* Asp312Asn, 751 and promoter C-114G polymorphisms in the breast cancer and control groups

Allele	Cases (%) N = 2,464	Controls (%) N = 2,866	*P*-value[a]
XPD Asp312Asn			
Allele G (Asp)	1,636 (66.4)	2,165 (75.5)	< 0.0001
Allele A (Asn)	828 (33.6)	701 (24.5)	
XPD codon 751			
Allele A (Lys)	2,353 (95.5)	2,728 (95.2)	0.6384
Allele C (Gln)	111 (4.5)	138 (4.8)	
XPD promoter C-114G			
Allele C	1,345 (54.6)	1,581 (55.2)	0.6927
Allele G	1,119 (45.4)	1,285 (44.8)	

[a]*P*-value based on χ^2 test.

and 5'-GATTATACGGACATCTCCAA-3'; and for XPD promoter C-114G, 5'-ATGAATATTCAGCGA-GAGGC-3' and 5'-CTGGGTTCGATCAATACTCA-AT-3'. The following cycling conditions were performed: one cycle at 94°C for 5 min; 35 cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 30 sec; and a final extension at 72°C for 10 min. The PCR products were studied after digestion with Hpy99I, EarI, and Bme1580I, restriction enzymes for *XPD* Asp312Asn (cut from 250 bp A type into 188+62 bp G type), Lys751Gln (cut from 326 bp C type into 127+199 bp A type) and promoter C-114G (cut from 303 bp G type into 101+202 bp C type), respectively.

Statistical Analyses

To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *XPD* SNPs in the control subjects from those expected under the Hardy-Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's χ^2 test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *XPD* genotypes between cases and controls. Cancer risk associated with the genotypes was estimated as odds ratio (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. Data was recognized as significant when the statistical *P*-value was less than 0.05.

Results

The frequency of the alleles for the *XPD* Asp312Asn, Lys751Gln and promoter C-114G between breast cancer and control groups is shown in Table 1. The Asn allele at *XPD* Asp312Asn was significantly associated with breast cancer risk ($P = 2.32*10^{-13}$). In contrast, Lys or Gln at *XPD* Lys751Gln, or the C or G allele at *XPD* promoter C-114G, were not differently distributed in the breast cancer patient and control groups ($P > 0.05$).

The frequency of the genotype of *XPD* Asp312Asn, Lys751Gln and promoter C-114G polymorphisms in the breast cancer and control groups is shown in Table 2. Using 312G as the reference group, there was an obvious association between the homozygotes and heterozygotes of 312A of *XPD* and breast cancer risk. A combination of the homozygotes and heterozygotes of A (with A) showed that the A allele at *XPD* Asp312Asn conferred a 1.78-fold risk factor for breast cancer (Table 2). Neither hetero- nor homozygotes of 751G of *XPD* seemed to be risky genotypes for breast cancer, as was also the case in promoter C-114G (Table 2).

Discussion

The *XPD* Asp312Asn Asn/Asn genotype is associated with prostate (34) and breast cancer risk (23). In this study, the genotype distribution of the A allele at *XPD* Asp312Asn (33.6%) was significantly higher in the breast cancer group than in the control group (24.5%) (Table 1). It was also found that participants homozygous Asn at *XPD* Asp312Asn had 1.69-fold higher risk of breast cancer (Table 2). As for the Asp/Asn heterozygotes, the risk was almost the same level, a 1.83-fold increased risk. After combining the heterozygous and homozygous participants in both case and control groups, there was still an obvious increased risk of 1.78 fold (Table 2). The data from such a large population suggested that Asn at *XPD* Asp312Asn was a marker for breast cancer. As long as 312Asn was detected, no matter whether is hetero- or homozygotes, the carriers were more susceptible to breast cancer.

In regard of *XPD* Asp312Asn polymorphism in breast cancer, our findings are consistent with the previous reports investigating populations in China (53) and American (12, 38). On the contrary, a group in German which also reported that *XPD* Asp312Asn polymorphism was associated with breast cancer found that Asp/Asp was the risky genotype (23). There were also some null studies in Caucasian (41), France (7), Poland (13), Korean (24, 27), UK (26), American (22, 28, 30, 36, 45), African-American (30, 41) populations. Very possibly, the population we investigated is more close to that in China, which is of much similar genetic origin and distributions of genotypic frequency, leading to the similar susceptibility to breast cancer. Apart from the potential involvement of genetic factors (*e.g.*, differences in

Table 2. Association of *XPD* Asp312Asn, codon 751, promoter C-114G polymorphisms and breast cancer risk

Genotype	Cases (%)	Controls (%)	Odds Ratio (95% CI)[a]	Adjusted Odds Ratio (95% CI)[b]
XPD Asp312Asn				
G/G	624 (50.6)	925 (64.5)	1.00 (ref)	1.00 (ref)
G/A	388 (31.5)	315 (22.0)	1.83 (1.53-2.19)[c]	1.88 (1.49-2.26)[c]
A/A	220 (17.9)	193 (13.5)	1.69 (1.36-2.10)[c]	1.73 (1.28-2.34)[c]
with A	608 (49.4)	508 (35.5)	1.77 (1.52-2.07)[c]	1.93 (1.43-2.88)[c]
XPD codon 751				
A/A	1136 (92.2)	1316 (91.8)	1.00 (ref)	1.00 (ref)
A/C	81 (6.6)	96 (6.7)	0.98 (0.72-1.33)	1.01 (0.76-1.28)
C/C	15 (1.2)	21 (1.5)	0.83 (0.43-1.61)	0.78 (0.52-1.44)
With C	96 (7.8)	117 (8.2)	0.95 (0.72-1.26)	0.98 (0.76-1.21)
XPD promoter C-114G				
C/C	347 (28.2)	417 (29.1)	1.00 (ref)	1.00 (ref)
C/G	651 (52.8)	747 (52.1)	1.05 (0.88-1.25)	1.12 (0.83-1.22)
G/G	234 (19.0)	269 (18.8)	1.05 (0.83-1.31)	1.03 (0.87-1.35)
With G	885 (71.8)	1,016 (70.9)	1.05 (0.88-1.24)	1.08 (0.89-1.26)

[a]CI, confidence interval; [b]Adjusted for age; [c]$P < 0.05$.

allelic frequencies, or with extension of linkage disequilibrium in different populations, or both), different kinds of exposures to environmental carcinogens could also differ among the populations, leading to inconsistent results concerning the role of *XPD* polymorphisms in breast cancer.

These results has added evidence showing that genetic variants involved in DNA repair pathways may also be involved in cancer etiology (1-6, 8-11). We have reported that non-homologous end-joining DNA repair capacities of each person may associated with their susceptibility to breast cancer (2). Therefore, it is interesting for our team to provide evidence about the NER repair capacities of each person in the future to preclude chance findings, particularly those among subgroups, and clarify the detail mechanisms involved.

In conclusion, this is a large population study which focuses on the SNPs of *XPD* and breast cancer in Taiwan, and the presence of the A allele of Asp312Asn was associated with a higher risk of breast cancer. The A allele of Asp312Asn may be a useful marker in breast oncology for anticancer application, and early cancer detection.

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