

DNA-Repair Genetic Polymorphisms and Breast Cancer Risk

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Abstract

Mammalian cells are constantly exposed to genotoxic agents from both endogenous and exogenous sources. Genetic variability in DNA repair contributes to deficient repair and breast cancer risk. Using samples collected in an ongoing, clinic-based, case-control study (253 cases and 268 controls), we tested whether breast cancer risk is associated with four amino acid substitution variants in three DNA repair genes, including *XRCC1 Arg194Trp* and *XRCC1 Arg399Gln* in base excision repair, *XRCC3 Thr241Met* in homologous recombination repair, and *ERCC4/XPF Arg415Gln* in nucleotide excision repair. Carriers of at least one variant allele of *XRCC1 Arg194Trp* [*Arg/Trp* and *Trp/Trp* versus *Arg/Arg*, odds ratio (OR) = 1.60, 95% confidence interval (CI) = 0.89–2.87] or two variant alleles of *XRCC3 241Met/Met* may have an increased risk of breast cancer (*Met/Met* versus *Thr/Thr* and *Thr/Met*, OR = 1.54, 95% CI = 0.94–2.52). No association between *XRCC1 Arg399Gln* genotype and breast cancer risk was observed. The genotype distribution of *ERCC4/XPF Arg415Gln* differed significantly between cases and controls ($P = 0.02$), and the *ERCC4/XPF 415Gln/Gln* genotype was found in only seven cases (3%) but not in controls. In addition, breast cancer risk was significantly associated with an increasing number of combined variant alleles of *XRCC1 Arg194Trp*, *XRCC3 Thr241Met*, and *ERCC4/XPF Arg415Gln* in a four-level model ($P_{\text{trend}} = 0.04$): OR = 1.0 for those without a variant allele (referent group); OR = 1.04 (95% CI = 0.67–1.61) for those with one variant allele; OR = 1.38 (95% CI = 0.83–2.29) for those with two

variant alleles; and age-adjusted OR = 2.60 (95% CI = 1.03–6.59) for those with three or more variant alleles after adjustment for age, family history, age at menarche, age at first live birth, and body mass index. We provide evidence that variants of *XRCC1*, *XRCC3*, and *ERCC4/XPF* genes, particularly in combination, contribute to breast cancer susceptibility.

Introduction

Breast cancer accounts for nearly one-third of all cancer cases diagnosed in American women (1). In 2003, approximately 211,300 women in the United States will be diagnosed with invasive breast cancer, and 39,800 will die of this malignancy (1). Although well-established risk factors, such as age at first child's birth, nulliparity, and FH⁷ may account for about 40% of United States breast cancer cases, the majority of cases are attributable to other risk factors (2). It is estimated that about 5% of breast cancer cases are related to rare but highly penetrant genes, such as *BRCA1* and *BRCA2* (3). However, low-penetrant cancer susceptibility genes may contribute to a large proportion of breast cancer cases because many of them are very common.

Eukaryotic cells are under constant mutagenic assault from endogenous and exogenous sources. IR, an established etiologic agent for breast cancer, and other suspected risk factors, such as chemical carcinogens, alcohol, estrogen, and diet, produce reactive oxygen species, oxidized bases, bulky DNA adducts, and DNA strand breaks (4). Mammalian cells have evolved distinct pathways to repair different types of DNA damage and maintain genomic integrity. Inherited reduction of DNA repair capacity may lead to deletions, amplifications, and/or mutations of critical genes that contribute to breast carcinogenesis (5, 6).

Previous studies have screened DNA repair genes for the presence of polymorphic alleles (7, 8). At least 125 amino acid substitution variants in 37 DNA repair genes have been identified in humans, including genes of NER, BER, and HRR for DSBs. We hypothesize that amino acid substitution variants of DNA repair genes could alter DNA repair capacity and/or fidelity, which may contribute to breast cancer susceptibility. Because different types of DNA damage produced by IR and other breast mutagens are repaired by multiple repair pathways, this study evaluated DNA repair genetic polymorphisms in three repair pathways: (a) X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*, exon 6, codon 194 *Arg/Trp* and exon 10, codon 399 *Arg/Gln*) for BER; (b) *XRCC3* (exon 7, codon 241 *Thr/Met*) for DSB/HRR; and (c) excision repair cross-complementing rodent repair deficiency,

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⁷ The abbreviations used are: IR, ionizing radiation; BER, base excision repair; CI, confidence interval; DSB, double-strand break; FH, family history; HWE, Hardy-Weinberg equilibrium; HRR, homologous recombination repair; NER, nucleotide excision repair; OR, odds ratio; SNP, single-nucleotide polymorphism; BMI, body mass index.

complementation group 4 (*ERCC4/XPF*; exon 8, codon 415 *Arg/Gln*) for NER.

XRCC1 participates in BER as a scaffolding intermediate with DNA polymerase β , ADP-ribosyltransferase or poly-(ADP-ribose) polymerase, and DNA ligase III in the NH_2 -terminal, central, and COOH-terminal regions, respectively (9). Cells deficient in *XRCC1* display hypersensitivity to IR, UV, hydrogen peroxide, and mitomycin C (10). *XRCC3* is required for assembly of Rad51 complexes during DNA repair (11). Cells deficient in *XRCC3* are sensitive to IR (~2-fold) and extremely sensitive to cross-linking agents, such as nitrogen mustard and cisplatin (12, 13). *ERCC4/XPF* forms a tight complex with *ERCC1* to incise 5' to the damage site recognized and repaired by NER (7). The *ERCC4/XPF-ERCC1* complex is essential for interstrand cross-link repair mediated by recombination repair mechanisms. Chinese hamster cell lines defective in *ERCC1* or *ERCC4/XPF* are not only hypersensitive to UV but are also extremely sensitive to DNA interstrand cross-link (14).

To date, only five published studies have examined *XRCC1* and/or *XRCC3* variants and breast cancer risk (15–19). To the best of our knowledge, this study is the first examining the association between *ERCC4/XPF Arg415Gln* genotype and breast cancer risk. Importantly, we also explore the potential combined effect of these three DNA repair variants on breast cancer risk.

Materials and Methods

Study Population. Breast cancer cases and controls were recruited at North Carolina Baptist Hospital from November 1998 to April 2002. Controls were frequency-matched to cases by age (± 5 years) and race. The eligibility criteria included: (a) English-speaking and able to comprehend informed consent; (b) no personal history of any cancers, including skin cancer; and (c) at least 18 years of age. Study subjects received a detailed description of the study protocol and signed their informed consent as approved by the medical center's institutional review board. Newly diagnosed breast cancer cases were recruited at the Wake Forest University Breast Care Center. Cancer-free controls were recruited at the Outpatient Radiology-Breast Screening Center as they presented for routine screening mammography. Exclusion criteria for controls included any previous cancer history, chronic inflammatory diseases, and abnormal current mammogram results. Blood samples (20 ml) were collected from all study subjects. Each woman was asked to complete a self-administered questionnaire, containing demographic information, established breast cancer risk factors, medical history, and FH. A woman with at least one first-degree relative with breast cancer is classified as having a positive FH. Medical records and pathology reports were used to confirm case-control status. The laboratory personnel did not have knowledge of subjects' case-control status.

PCR-RFLP Genotyping Assays. Genomic DNA was isolated from 200 μl of whole blood, using the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA). The PCR-RFLP methods for *XRCC1* and *XRCC3* genotypes were described previously (15). The primer pairs used were: (a) *XRCC1 Arg194Trp*, F5'-GCCCGTCCCAGGTA-3' and R5'-AGCCCCAAGACCCTT-TCACT-3'; (b) *XRCC1 Arg399Gln*, F5'-TCTCCCTGGTC-TCCAACCT-3' and R5'-AGTAGTCTGCTGGCTCTGG-3'; (c) *XRCC3 Thr241Met*, F5'-GGTCGAGTGCAGTCCAAAC-3' and R5'-TGCAACGGCTGAGGGTCTT-3'; and (d) *ERCC4/XPF Arg415Gln*, F5'-GCACAGGGAAACTAGGA-GGA-3' and R5'-TCGACATCTCCTTCTCTTC-3'. PCR

products were digested with specific restriction enzymes that recognized and cut either the wild-type or variant sequence site. The restriction enzyme used for *ERCC4/XPF Arg415Gln* genotype was *XmnI*, and the restricted products of *Arg/Arg*, *Arg/Gln*, and *Gln/Gln* had band sizes of 96/284 bp, 96/284/380 bp, and 380 bp, respectively. Ten percent of random DNA samples were genotyped the second time, yielding complete agreement with the first set of genotype results.

ERCC4/XPF 415Gln/Gln Genotype Confirmation. To confirm the seven samples with the *ERCC4/XPF 415Gln/Gln* genotype, purified PCR products were sequenced using the ABI PRISM Big Dye Terminator Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) according to the manufacturer's instructions. Automated sequencing was done by cycle sequencing with Ampli-Taq, FS, whereby each dideoxynucleotide triphosphate contained a different fluorescent dye, and sequencing was performed in one tube. The reaction mixtures were denatured for 2 min at 96°C and then subjected to 25 cycles of denaturation at 96°C for 10 s, annealing at 50°C for 15 s, and extension at 60°C for 4 min. The reaction mixtures were then purified by gel filtration on a CentriSep column, and the filtrate was dried and resuspended in 85% formamide/4 mM EDTA pH (8.0)/8 mg/ml Blue Dextran. The samples were loaded onto a 5% Long Ranger sequencing gel containing urea and electrophoresed for 8 h at approximately 1700 V. The fluorescence data from each dideoxynucleotide triphosphate were read and collected in real time on an ABI PRISM 337 DNA sequencer (Applied Biosystems). The DNA synthesis core laboratory of the Comprehensive Cancer Center maintains the automated sequencer.

Statistical Analysis. Student's *t* tests, χ^2 tests, and Fisher's exact tests were used to compare demographic characteristics between cases and controls. χ^2 and Fisher's exact tests were used to test whether genotype data were consistent with HWE and compare the genotype distributions between cases and controls. Crude ORs and 95% CIs evaluating the association between genotype and cancer risk were calculated. Logistic regression was used to calculate ORs and 95% CIs after adjusting for subject characteristics. All two-way interactions between genotypes were considered. A backward-stepping algorithm was used to remove nonsignificant interactions from the model. All of the statistical analyses were carried out using the Statistical Analysis System (SAS Institute, Cary, NC) for personal computers.

Results

The general characteristics of cases and controls are summarized in Table 1. Age, FH, age at menarche, and parity did not significantly differ between cases and controls. However, age at first birth and BMI differed significantly between cases and controls ($P < 0.01$). Due to the small sample size of non-Caucasian study subjects (37 cases and 42 controls), we limited our analysis to Caucasian women. Surprisingly, we found 12 controls (35% with FH) who participated in mammographic screening ≤ 40 years of age. It is very likely that women who realize they are at increased risk for breast cancer may have regular mammographic screenings at a younger age.

Detailed genotype distributions are summarized in Table 2. Variant allele frequencies in cancer-free Caucasians were 5% for *XRCC1 194Trp*, 34% for *XRCC1 399Gln*, and 37% for *XRCC3 241Met*, consistent with previous studies (15–17). Genotype distributions of controls at each locus were consistent with the HWE. However, genotype distributions of *XRCC3 Thr241Met* ($P < 0.05$) and *ERCC4/XPF Arg415Gln* ($P < 0.01$)

Table 1 Demographic characteristics of study population

Characteristics	Categories	Cases (n = 253)	Controls (n = 268)	P ^a
Age (yrs)	Mean ± SD	59.12 ± 13.3	59.92 ± 12.3	0.47
	≤50	77 (30%)	75 (28%)	0.69
	51–60	54 (21%)	53 (20%)	
	61–70	67 (27%)	70 (26%)	
	≥71	55 (22%)	70 (26%)	
FH	None	192 (76%)	213 (79%)	0.77
	Mother or sister	52 (20%)	51 (19%)	
	Mother and sister	5 (2%)	4 (2%)	
	Missing	4 (2%)	0 (0%)	
Age at menarche (yrs)	≤12	113 (45%)	111 (41%)	0.13
	13–14	96 (38%)	125 (47%)	
	≥15	38 (15%)	30 (11%)	
	Missing	6 (2%)	2 (1%)	
	Parity	Nulliparous	37 (15%)	39 (15%)
≥1		212 (84%)	229 (85%)	
Missing		4 (1%)	0 (0%)	
Age at first live birth (yrs)	≤24	138 (55%)	111 (41%)	0.002
	25–29	50 (20%)	84 (31%)	
	≥30 or Nulliparous	59 (23%)	73 (27%)	
	Missing	6 (2%)	0 (0%)	
	BMI (kg/m ²)	Mean ± SD	27.41 ± 5.56	26.20 ± 5.25

^a P associated with either Student's *t*, χ^2 , or Fisher's exact test.

in cases were not consistent with the HWE; excess *ERCC4/XPF 415Gln/Gln* homozygotes were observed. Genotype distributions of *ERCC4/XPF 415Gln* ($P = 0.02$) differed significantly between cases and controls. The observation of deviation from HWE for *Thr241Met* and *Arg415Gln* in cases but not in controls indirectly suggests that variant alleles of these two SNPs may be associated with breast cancer risk. There was a weak association between *XRCC1 194Trp* allele and breast cancer risk (OR = 1.60 and 95% CI = 0.89–2.87 after adjustment for age, FH, age at menarche, age at first live birth, and BMI). No association between *XRCC1 Arg399Gln* genotype and breast cancer risk was observed. The *XRCC3 Met/Met* genotype showed a suggestive association with breast cancer risk (OR = 1.54 and 95% CI = 0.94–2.52 after adjustment for age, FH, age at menarche, age at first live birth, and BMI). The most interesting observation was that only seven breast cancer cases (3%), but not controls, carried the *ERCC4/XPF 415 Gln/Gln* genotype, which was confirmed by DNA sequencing.

Two-way interactions between three genotypes (*XRCC1 Arg194Trp*, *XRCC3 Thr241Met*, and *ERCC4/XPF Arg415Gln*) were then included in separate logistic models assessing cancer risk. The only significant two-way interaction was between

XRCC1 Arg194Trp and *ERCC4/XPF Arg415Gln* ($P < 0.05$). The data in Table 3 suggest a potential gene-gene interaction when we combined the variant alleles of *XRCC1*, *XRCC3*, and *ERCC4/XPF* in a four-level model ($P = 0.04$, test for linear trend): OR = 1.0 for those without any variant allele (referent group); OR = 1.04 (95% CI = 0.67–1.61) for those with one variant allele; OR = 1.38 (95% CI = 0.83–2.29) for those with two variant alleles; and OR = 2.60 (95% CI = 1.03–6.59) for those with three or more variant alleles after adjustment for age, FH, age at menarche, age at first live birth, and BMI. The odds of having cancer were not higher for subjects having one or two variant alleles than for subjects with no variant alleles; however, for subjects having three or more variant alleles, the odds of having cancer increased dramatically.

Discussion

Studies conducted over the past few years have identified variant alleles for a number of DNA repair genes, some of which may modify DNA repair capacity. Characterization of these genotypic variations in DNA repair functions and their association with cancer may help to elucidate cancer etiology

Table 2 DNA repair genotypes in breast cancer cases and controls

SNPs	Subjects	Genotype ^a			P ^b	WV vs. WW	VV vs. WW	WV/VV vs. WW	VV vs. WV/VV
		WW	WV	VV		OR (95% CI) ^c			
<i>XRCC1</i>	Controls	242	23	1		Referent	Referent	Referent	Referent
<i>Arg194Trp</i>	Cases	211	31	4	0.14	1.47 (0.80–2.70)	NA ^d	1.60 (0.89–2.87)	NA
<i>XRCC1</i>	Controls	115	123	29		Referent	Referent	Referent	Referent
<i>Arg399Gln</i>	Cases	99	122	30	0.69	1.02 (0.70–1.51)	1.07 (0.58–1.96)	1.03 (0.71–1.49)	1.05 (0.59–1.87)
<i>XRCC3</i>	Controls	104	129	35		Referent	Referent	Referent	Referent
<i>Thr241Met</i>	Cases	96	105	51	0.07	0.85 (0.57–1.27)	1.41 (0.83–2.42)	0.98 (0.67–1.41)	1.54 (0.94–2.52)
<i>ERCC4/XPF</i>	Controls	236	32	0		Referent	Referent	Referent	Referent
<i>Arg415Gln</i>	Cases	217	29	7	0.02	0.96 (0.54–1.69)	NA	1.23 (0.72–2.09)	NA

^a WW, wild-type/wild-type; WV, wild-type/variant; VV, variant/variant.

^b Fisher's exact test for genotype distributions.

^c OR adjusted for age, FH, age at menarche, age at first live birth, and BMI using logistic regression.

^d NA, not applicable.

Table 3 Number of DNA repair variant alleles and breast cancer risk

Total no. of variant alleles ^a	Controls (n = 266)	Cases (n = 246)	Adjusted OR (95% CI) ^b
0	87 (33%)	67 (27%)	Referent
1	114 (43%)	95 (39%)	1.04 (0.67–1.61)
2	57 (21%)	66 (27%)	1.38 (0.83–2.29)
3+	8 (3%)	18 (7%)	2.60 (1.03–6.59) ^c

^a *XRCC1 Arg194Trp*, *XRCC3 Thr241Met*, and *ERCC4/XPF Arg415Gln* genotypes were included in the model.

^b OR adjusted for age, FH, age at menarche, age at first live birth, and BMI using logistic regression.

^c $P = 0.04$, test for linear trend.

(20). With limited sample size, our current data suggest that amino acid substitution variants of DNA repair genes in three repair pathways, particularly in combination, may contribute to breast cancer susceptibility.

Our current data suggest that the *XRCC1 194Trp* allele may be associated with breast cancer risk, consistent with our previous findings with a different study population (15). However, the *XRCC1 Arg194Trp* was not associated with breast cancer risk in another study (16). The *Arg194Trp* resides in a hydrophobic region of the *XRCC1* protein, located between the DNA polymerase β and the ADP-ribosyltransferase-interacting domains (7). *XRCC1* coordinates the steps of BER through many protein-protein interactions. The functional significance of the *Arg194Trp* region is not clear, and more studies are needed to define its role in daily oxidative damage and DNA strand-break repair.

As a member of HRR, *XRCC3* is required for DSB repair and, thus, contributes to cellular genomic stability. Although the *XRCC3 Thr241Met* polymorphism does not reside in known *XRCC3* functional domains (7), our data support the previous results that indicated that homozygote individuals with the *Met/Met* genotype had an increased risk compared with carriers of the *Thr/Thr* genotype (17). We did not observe an age-dependent difference in the distribution of the *XRCC3 Thr241Met* genotype in cases aged less than 50 years compared with those aged 50 years and over ($P = 0.28$), as suggested previously (17). The data from a previous study demonstrated that cells expressing the *XRCC3 241Met* variant allele were active for DSB/HRR and were not more sensitive to the inter-strand cross-linking agent mitomycin C (21). However, their data showed a small but nonsignificant effect (13% decrease) of the *XRCC3 241Met* variant allele on homology-directed repair activity ($0.15 \pm 0.02\%$ for the wild-type allele versus $0.13 \pm 0.04\%$ for the variant allele) and mitomycin C hypersensitivity (survival fraction of 0.18 ± 0.005 for the wild-type allele versus 0.17 ± 0.001 for the variant allele, 6% difference; Ref. 21). Although these small differences may be within experimental error, their data suggest a potential functional role of the *XRCC3 Thr241Met* variant allele.

To the best of our knowledge, this study is the first to evaluate the *ERCC4/XPF Arg415Gln* polymorphism and breast cancer risk. The most intriguing observation is that only seven breast cancer cases (3%), but not controls, carry the *ERCC4/XPF 415 Gln/Gln* genotype. We have also pilot-tested this SNP in a prostate cancer case-control study (94 controls and 131 cases); no subjects with homozygous variants were identified in either group; the variant allele frequencies were 6.4% for controls and 8.0% for cases, respectively. It is not clear whether the *ERCC4/XPF 415 Gln/Gln* genotype may play a unique role in breast cancer. XPF patients show mild DNA repair deficiencies

and a later onset of skin cancer compared with patients from other XP complementation groups (22). Some XPF disease-related mutations are located near the *Arg415Gln* region within exon 8. Future studies are warranted to evaluate the functional significance of *ERCC4/XPF Arg415Gln* variant in DNA repair and breast cancer susceptibility.

Considering multiple pathways for repairing diverse DNA damages induced by endogenous and exogenous carcinogens, genetic variants in multiple repair pathways may have a joint or additive effect on breast cancer risk. Therefore, genotypes and phenotypes in different repair pathways must be evaluated simultaneously to fully assess cancer susceptibility. Although our results must be validated in larger population-based studies, our current data suggest a potential gene-gene interaction among variant alleles of *XRCC1*, *XRCC3*, and *ERCC4/XPF* in breast cancer risk. Because BER, HRR, and NER play critical roles in repairing various types of DNA damage, combined genetic variants of these three repair pathways may contribute to a greater risk of breast cancer.

The functional significance of DNA repair SNPs and human cancer risk is currently the subject of intense study, and many challenges must be overcome. In this study, we demonstrate that amino acid substitution variants of *XRCC1*, *XRCC3*, and *ERCC4/XPF* genes, particularly in combination, are associated with susceptibility to breast cancer. However, we should note that the sample size of our study has limited power for assessing gene-gene interactions. Therefore, our findings must be interpreted with caution, and larger studies are warranted to further test multiple DNA repair genetic variants in breast cancer susceptibility.

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BLOOD CANCER DISCOVERY

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