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Single-nucleotide polymorphisms in DNA repair genes and association with breast cancer risk in the web study

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Base excision repair (BER) and nucleotide excision repair (NER) pathways repair damaged DNA, and polymorphisms in these genes might affect breast cancer susceptibility. We evaluated associations between seven single-nucleotide polymorphisms in four DNA repair genes (*ERCC4* rs1799801, *XPC* rs2227998, rs2228001, rs2228000, *OGG1* rs1052133 and *XRCC1* rs25487 and rs25486) and breast cancer risk, examining modification by smoking and alcohol consumption, using data from the Western New York Exposures and Breast Cancer Study. Women aged 35–79 years with incident breast cancer ($n = 1170$) and age- and race-matched controls ($n = 2115$) were enrolled. Genotyping was performed using matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs). No significant associations were observed in premenopausal women. Among postmenopausal women, rs25487 and rs25486 (OR = 1.24; 95% CI 1.01–1.51 and OR = 1.23; 95% CI 1.01–1.49, respectively, for combined heterozygous and homozygous variant compared with reference) were associated with increased risk of breast cancer. Postmenopausal women carrying the variant allele of the synonymous *XPC* polymorphism (rs2227998) were also at borderline significantly increased risk (OR = 1.24; 95% CI 1.01–1.52, heterozygous variant compared with reference; OR = 1.22; 95% CI 1.01–1.48, for combined heterozygous and homozygous variant compared with reference). There was no evidence of genotype–smoking and genotype–alcohol consumption interactions for pre- and postmenopausal women. These results indicate that some of the variants in BER and NER genes may influence risk of postmenopausal breast cancer.

Introduction

Base excision repair (BER) and nucleotide excision repair (NER) are two mechanisms that repair single-stranded DNA by excising damaged sequences and using the complementary DNA strand as a template to fill the resulting gap. DNA damage can cause lesions that may or may not distort the double helix structure, and these are repaired by the BER and NER pathways, respectively. BER replaces short sequences of nucleotides, whereas NER replaces longer DNA sequences of 24–32 nucleotides (1,2). Multiple genes operate in DNA repair pathways, including excision repair cross-complementing rodent repair deficiency, complementation group 4 *(ERCC4)*, Xeroderma pigmentosum, complementation group C *(XPC)*, 8-oxoguanine DNA glycosylase *(OGG1)*, and X-ray repair complementing defective repair in Chinese hamster cells 1 *(XRCC1)*. These genes encode proteins with specialized functions for the repair of damaged DNA. During NER, *ERCC4* is part of a complex of proteins that creates the 5′ incision into the damaged DNA strand for subsequent excision and repair (3–6). *XPC* encodes a protein that is involved in early recognition of damage caused by bulky DNA adducts and triggers response by other proteins to repair the damage (5,6). *OGG1* is involved in the excision of 8-oxoguanine, a mutagenic byproduct of exposure to reactive oxygen that can form base-pairs with adenine, leading to G:C/T:A transversions. Decreased *OGG1* function could therefore lead to increased 8-oxoguanine lesions, which cause mutations that activate oncogenes or inactive tumor suppressor genes. *XRCC1* encodes a protein that acts as a scaffolding protein in base excision single-strand break repair pathways. These pathways function in the constitutive response to DNA damage caused by exogenous exposures as well as exposure to endogenous mutagens such as ionizing radiation and alkylating agents (7–9). Polymorphic variants exist for each of these genes, with some evidence of functional changes at the protein level. One single-nucleotide polymorphism (SNP) in the *XPC* gene (rs2228001) results in an amino acid change from lysine to glutamine. Individuals with the variant allele of this polymorphism have been found to have significantly increased DNA damage induced by exposure to benzo(a)pyrene diolepoxide and gamma-radiation in blood culture than individuals who were homozygous wild-type (10). The variant allele of another *XPC* SNP (rs2228000), causing an amino acid change from alanine to valine, has been associated with significantly decreased DNA damage induced by benzo(a)pyrene diolepoxide and gamma-radiation in blood culture (10). A serine to cysteine amino acid change in *OGG1* (rs1052133) may affect the ability of the *N*-glycosylase/DNA lyase enzyme to repair oxidative DNA damage, although evidence is conflicting (11–13). Polymorphisms in *XRCC1* have also been associated with reduced DNA repair capacity in some studies (13,14).

These two repair pathways address damage induced by oxidation and formation of DNA adducts. The presence of DNA adducts has been demonstrated in exfoliated breast ductal epithelial cells (15,16) and human breast tumor tissue (17). DNA adducts have also been associated with risk of breast cancer (18–20). Cigarettes contain known human carcinogens that have been shown to induce mammary tumors in rodents (21) and to lead to the formation of DNA adducts in human breast cells (22). Similarly, acetaldehyde, a metabolite of ethanol, has been shown to induce formation of DNA adducts (23). Ethanol exposure has also been associated with decreased DNA adduct repair capacity in human mammary epithelial cells (24), and an association between alcohol consumption and breast cancer risk has been demonstrated, with some consistency, in epidemiologic investigations (25–28). It is therefore possible that exposure to alcohol and carcinogens present in cigarettes increases the risk of breast cancer by affecting the formation of DNA adducts. Polymorphisms in DNA repair genes that result in suboptimal repair capacity or altered protein function might affect susceptibility to the damage induced by cigarette smoking and alcohol use, thereby influencing cancer risk.

Previous epidemiological studies examining associations between heritable variation in DNA repair genes involved in the NER and BER pathways and the risk of breast cancer have been inconclusive. Some studies have demonstrated associations between variant alleles and increased or decreased susceptibility to breast cancer (29–33), whereas others have yielded null results (34–42). Similarly, results from studies investigating gene–environment interactions between

Abbreviations: BER, base excision repair; CI, confidence interval; NER, nucleotide excision repair; SNP, single-nucleotide polymorphism; OR, odds ratio; WEB, Western New York Exposures and Breast Cancer.

SNPs in NER and BER pathway genes, smoking and alcohol consumption on the risk of breast cancer have been inconsistent (5,30,40,43–45). In this large case–control study of breast cancer, we examined potential associations between genes in the NER and BER pathways and risk of breast cancer, as well as potential modification of risk by smoking and lifetime alcohol consumption. Variants in these genes may alter the function of the proteins encoded by *ERCC4*, *XPC*, *OGG1* and *XRCC1*, leading to the possibility that women with variant alleles may have diminished repair capacity and increased susceptibility to diseases such as cancer. Thus, we evaluated the associations between SNPs in four DNA repair genes in the NER and BER pathways [*ERCC4* (rs1799801); *XPC* (rs2227998, rs2228001, and rs2228000); *OGG1* (rs1052133); *XRCC1* (rs25487 and rs25486)] and risk of breast cancer in pre- and postmenopausal women using data from a case–control study of breast cancer, diet and environmental exposures [the Western New York Exposures and Breast Cancer (WEB) Study].

Materials and methods

The WEB Study was conducted between 1996 and 2001 and detailed descriptions of the study methods have been previously published (46–49). Eligible cases were ascertained from Erie and Niagara county hospitals in Western New York, and included women aged 35–79 years, diagnosed with incident, primary, histologically confirmed breast cancer, with no previous cancer diagnoses other than non-melanoma skin cancer, who were current residents of either Erie or Niagara counties. Nurse case finders identified cases through the pathology departments of participating hospitals. Upon identification, the patient's physician was contacted for verification of breast cancer diagnosis and permission to contact the woman, and all cases were interviewed within 1 year of diagnosis. Of 1627 eligible cases during the study period, 1170 participated (72%). Controls were also aged 35–79 years, residents of Erie and Niagara counties and frequency-matched to cases on age and race. They were randomly selected for recruitment from New York State drivers' license listings for participants under the age of 65 and from the Health Care Finance Administration Medicare rolls for participants age ≥65 years. Of 3331 eligible controls contacted, 2115 participated (63%). All participants provided informed consent, and the study protocol was approved by the Institutional Review Boards of the University at Buffalo and of all the participating hospitals.

During in-person interviews, trained interviewers collected data on demographics, breast cancer risk factors, anthropometric measures, alcohol consumption and smoking history. Body mass index was based upon height and weight measured at the time of interview and was calculated as weight (kg)/height (m^2). Women were considered to be postmenopausal if their menses had ceased permanently and naturally, or if they had undergone any of the following: a bilateral oophorectomy, a hysterectomy without removal of the ovaries if the woman was >50 years, or radiation or other medical treatment that resulted in the permanent cessation of menses if the woman was >55 years.

Data on alcohol consumption were collected using a detailed, computer-assisted interview assessing lifetime intake using the Cognitive Lifetime Drinking History, which has been described previously (49). Participants who had reported that they had not drunk at least 12 drinks in their lifetime were considered to be nondrinkers. The other participants reported their age when they first began drinking alcohol at least once a month for 6 months, and the ages at which their drinking patterns changed. Beginning from the time that they began drinking, participants provided information regarding the quantity and frequency of alcoholic beverage consumption for each interval. Beverage-specific drink size, proportion of drinks as beer, wine or liquor, and number of drinks consumed in a given 28 days period were used to create beverage-specific amounts of alcohol consumed. These estimates were summed to create a lifetime total for each participant up to 2 years before diagnosis for cases and date of interview for controls. In this analysis, participants were categorized into three categories based on the lifetime total amount of alcohol consumed: lifetime nondrinkers, 'lower' alcohol consumers (low alcohol) and 'higher' alcohol consumers (high alcohol). Cut-offs of 1001.6 and 1161.8 ounces, corresponding to lifetime intake of ∼4.0 and 3.0 drinks/month for pre- and postmenopausal women, respectively, were used to create these categories.

Smoking histories were ascertained by asking participants whether they had ever smoked at least 100 cigarettes, 20 cigars or 20 pipes in their lifetime; those who met these criteria were considered ever-smokers and those who smoked fewer were considered never-smokers. Ever-smokers were asked when they had begun smoking, and for each decade of life when they smoked, they reported the amount they smoked per day and any periods of time during that decade when they had stopped smoking. Ever-smokers were divided into current and former smokers. Current smokers were defined as those participants who reported smoking at the date of diagnosis for cases or the date of interview for controls, whereas former smokers had stopped smoking prior to those dates. Bias related to nonparticipation was assessed using a short telephone interview of both individuals participating and not participating at the time of contact. This interview ascertained current smoking habits and included several questions on alcohol consumption habits. Nonparticipating cases and controls had slightly fewer years of education (cases, 12.8 years for nonparticipants versus 13.6 for participants; controls, 12.6 years for nonparticipants versus 13.4 for participants), were more likely to be current smokers (cases, 16.4% nonparticipants versus 12.5% participants; controls, 20.3% nonparticipants versus 15.2% participants), and had lower monthly alcohol intake than participating cases and controls (cases, 2.9 drinks per month for nonparticipants versus 3.6 for participants; controls, 3.0 drinks per month for nonparticipants versus 3.9 for participants).

Biospecimen collection and genotyping protocols have been described in detail elsewhere (50,51). As part of the WEB study, blood samples and mouthwash samples were collected at the time of the interview for DNA extraction. DNA was extracted from blood and mouthwash using the GenQuik DNA Extraction Kit (BioServe Biotechnologies Ltd, Beltsville, MD), and DNA was ultimately available for 1099 cases and 1945 controls. Genotyping for SNPs in NER pathway genes *ERCC4* and *XPC* [rs1799801 (NM_005236.2:c.2505T>C); rs2227998 (NM_004628.4:c.2061G>A); rs2228001 (NM_004628.4:c.2815C>A); *XPC* rs2228000 (NM_004628.4:c.1496C>T)] and BER pathway genes *OGG1* and *XRCC1* [rs1052133 (NM_002542.5:c.977C>G); rs25487 (NM_006297.2:c.1196A>G); rs25486 (NM_006297.2:c.1083-59G>A)] was performed on the 1099 cases and 1945 controls for whom DNA was available. Genotyping was performed using Homogenous MassExtend reactions to prepare real-time polymerase chain reaction products for matrix-assisted laser desorption ionization time-of-flight mass spectrometry on a MassARRAY iPLEX™ platform (Sequenom, San Diego, CA) according to the manufacturer's instructions. Primer sequences are provided in Table I. Controls were included on each plate for all genotypes, with four no-template controls per plate. Call rates ranged from 90.8 to 98.9%, and all SNPs were in Hardy–Weinberg equilibrium. Similar allele frequencies were observed when non-white participants were excluded. We also genotyped cases and controls for two SNPs in ERCC2 [NM_00400.3:c.1832-70C>T (rs1799787) and NM_00400.3:c.2251A>C (rs13181)]; these two SNPs were not in Hardy–Weinberg equilibrium and were subsequently omitted from further analyses.

Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). For comparison of descriptive variables between cases and controls, *t*-tests were used to test for differences in means of continuous variables and chi-squared tests were used for differences in categorical variables. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CIs), using homozygous common alleles as the reference category. We examined models of each genotype separately and also combined women with heterozygous and homozygous variant genotypes using a dominant model with homozygous common alleles as the referent. Potential covariates were identified based on previously published literature and included age at diagnosis for cases or age at interview for controls, years of education, race, body mass index, age at menarche, age at first birth, parity, history of benign breast disease, family history of breast cancer, cigarette smoking (never, former or current), lifetime alcohol consumption (lifetime nondrinker, low alcohol or high alcohol), and, for postmenopausal women, age at menopause and hormone therapy use. Analyses were stratified by menopausal status. In premenopausal women, final models were adjusted for age, race, years of education, age at first birth, family history of breast cancer, history of benign breast disease and smoking status, as these variables were associated with both genotype and case–control status or altered the OR estimate by at least 10% when added individually to the multivariate model. In postmenopausal women, final models were adjusted for this same list of covariates, as well as for age at menarche and hormone therapy use. Small numbers of non-white participants (6.4% of premenopausal and 9.3% of postmenopausal participants) precluded separate analyses of white and non-white participants. Sensitivity analyses excluding non-white participants were instead performed. We created joint classifications for genotype and smoking status (never, former and current) and for genotype and alcohol consumption (lifetime nondrinker, low alcohol group, high alcohol group) to examine effect modification of risk of breast cancer by smoking status and lifetime alcohol consumption, respectively. In these analyses, the homozygous common alleles/never-smoker category and homozygous common allele/lifetime nondrinker category were used as the referent. Interaction terms for genotype–smoking status and genotype–lifetime alcohol consumption interactions were included in logistic regression models and tested for

Table I. Primers used for polymerase chain reaction and homogenous MassExtend assays

Gene symbol	RefSNP number	PCR primers	MassExtend primers
ERCC4	rs1799801	5′-ACGTTGGATGTTATACTTCTCT-GACTCGGG-3′ 5′-ACGTTGGATGGAGCTGAAACAAAG-CAAGCC-3′	5′-CTGGCCATTACAGCAGATTC-3′
XPC	rs2227998	5′-ACGTTGGATGCACTCTTGCTTTCTT-CAGCC-3′ 5′-ACGTTG-GATGTTGTGTCCTGTGTTGGTTCC-3′	5′-CACACTCTGCATTCCAG-3′
XPC	rs2228001	5′-ACGTTGGATGAACTGGTGGGTGCCCCTC-TA-3′ 5′-ACGTTGGATGGGCCCAAGAAGAC-CAAAAGG-3′	5′-TTCCCACCTGTTCCCATTTGAG-3′
XPC	rs2228000	5′-ACGTTGGATGTACTGCTTGAAGAGCTT-GAG-3′ 5′-ACGTTGGATGAAAGGCTGGGTCCAA-GAGTG-3′	5′-GGACCCAAGCTTGCCAG-3′
OGG1	rs1052133	5′-ACGTTGGATGTCCTCCCCACACAGACTC-CA-3′ 5′-ACGTTG-GATGTTTCTGCGCTTTGCTGGTGG-3′	5′-GGCTCCTGAGCATGGCGG-3′
XRCC1	rs25487	5′-ACGTTGGATGATTGCCCAGCACAGGA-TAAG-3′ 5′-ACGTTGGATGTAAGGAGTGGGTGCTG-GACT-3′	5′-CGGCGGCTGCCCTCCC-3′
XRCC1	rs25486	5′-ACGTTGGATGAGTTAGGTGTGATCT-GAGGG-3′ 5′-ACGTTGGATGGTTTCTCCCACCT-CAATCTC-3′	5′-CTGTCTCCCCTGTCTC-3′

PCR, polymerase chain reaction.

statistical significance using Wald chi-square tests. All statistical tests were based on two-sided probability.

Results

Demographic characteristics for pre- and postmenopausal cases and controls are shown in Table II. Mean (SD) age in years at diagnosis or interview was 44.8 (4.6) and 44.1 (4.7) for premenopausal cases and controls and 63.1 (8.5) and 63.2 (8.9) for postmenopausal cases and controls. Cases did not differ from controls in terms of smoking status or alcohol consumption history for these broad categories of exposure. Postmenopausal cases had slightly more years of education, whereas premenopausal cases had slightly fewer years of education compared with controls, and both pre- and postmenopausal cases were more likely to have a personal history of benign breast disease and family history of breast cancer than controls.

Associations of genotype with breast cancer risk are shown in Table III. We did not observe any statistically significant associations among premenopausal women. Among postmenopausal women, polymorphisms in the *XRCC1* gene were associated with risk of breast cancer. A borderline significantly increased risk was observed for women who were either heterozygous or homozygous for the variant allele of *XRCC1* rs25487, compared with those homozygous for common alleles (OR = 1.24; 95% CI 1.01–1.51). Similarly, we observed increased risks of breast cancer among women with at least one copy of the variant allele of *XRCC1* rs25486 (OR = 1.23; 95% CI 1.01–1.49). Postmenopausal women carrying the variant allele of the synonymous polymorphism *XPC* rs2227998 were also at borderline significantly increased risk (OR = 1.24; 95% CI 1.01–1.52, heterozygous variant compared with reference; OR = 1.22; 95% CI 1.01–1.48, for combined heterozygous and homozygous variant compared with reference). We also tested for genotype–smoking status and genotype–lifetime alcohol consumption interactions; these data are presented in Tables IV and V, respectively. There was no evidence of an interaction of either smoking status or alcohol intake with the *XRCC1* SNPs (rs25487 and rs25486) or the *XPC* SNP rs2227998 among postmenopausal women nor did we detect statistically significant interactions for any of the other SNPs we investigated. Sensitivity analyses showed that the results were not appreciably different when the population was restricted to white participants.

Discussion

We found that there was a modest increase in risk of postmenopausal breast cancer associated with polymorphisms in two DNA repair genes, *XPC* (rs2227998) and *XRCC1* (rs25487 and rs25486); there were no associations with risk among premenopausal women. Consistent with our finding, in a recent meta-analysis of *XRCC1* polymorphisms and associations with breast cancer risk, the authors concluded that rs25487 was associated with increased risk of breast cancer, though in the Caucasian subgroup the effect was small and nonsignificant (OR = 1.08; 95% CI 0.95–1.22). Unlike our results, analysis by menopausal status did not alter this relationship (52). In two other meta-analyses, there was no association of *XRCC1* rs25487 with breast cancer risk in Caucasian populations, though a significantly increased risk was apparent among Asian populations (53,54). Similarly, increased risks associated with this polymorphism have been reported among Iranian (55) and Portuguese postmenopausal women (56). The *XRCC1* rs25487 polymorphism was not associated with risk in the Iowa Women's Health Study (40). In our study, we observed an ∼20% increase in risk of breast cancer for postmenopausal women with at least one of the variant alleles for rs25487 or rs25486; these polymorphisms in *XRCC1* are in high linkage disequilibrium. We did not observe any evidence of interaction between genotype and smoking status or genotype and lifetime alcohol consumption in either pre- or postmenopausal women. In one study, nonsmoking women heterozygous or homozygous for the *XRCC1* rs25487 variant allele were at significantly higher risk than women with common alleles; no interactions were observed for

Table II. Demographic characteristics of breast cancer cases and controls

Variable		Premenopausal		Postmenopausal	
		Cases ($N = 307$)	Controls ($N = 566$)	Cases ($N = 792$)	Controls ($N = 1379$)
Education, years (mean, SD)		13.9 (2.3)[a]	14.3 (2.2)	13.3 (2.7)[a]	13.0 (2.3)
Age at first birth, years (mean, SD)		20.5 (10.6)	21.7 (10.4)	19.6 (10.0)	21.1 (8.2)
Race, *n* (%)	White	282 (91.9)	535 (94.5)	731 (92.3)	1238 (89.8)
	Non-white	25 (8.1)	31 (5.5)	61 (7.7)	141 (10.2)
Smoking status, *n* (%)	Never	140 (45.6)	306 (54.1)	349 (44.1)	639 (46.3)
	Former	116 (37.8)	168 (29.7)	347 (43.8)	532 (38.6)
	Current	50 (16.3)	91 (16.1)	94 (11.9)	205 (14.9)
Lifetime alcohol consumption, *n* (%)[b]	Lifetime nondrinker	38 (12.5)	58 (10.4)	149 (19.1)	226 (17.1)
	Low	128 (42.2)	251 (44.9)	321 (41.2)	554 (41.8)
	High	137 (45.2)	250 (44.7)	309 (39.7)	544 (41.1)
History of benign breast disease, *n*(%)	Yes	110 (35.8)[c]	124 (21.9)	264 (33.3)[c]	311 (22.6)
	No	191 (62.2)	437 (77.2)	509 (64.3)	1064 (77.2)
Family history of breast cancer, *n*(%)	Yes	56 (18.2)[c]	56 (9.9)	149 (18.8)[c]	184 (13.3)
	No	221 (72.0)	489 (86.4)	593 (74.9)	1111 (80.6)

[a]$P < 0.05$, *t*-test for differences in means between cases and controls.
[b]Lifetime total alcohol consumption in ounces from birth to 2 years prior to diagnosis or interview for cases and controls, respectively. The cut-off for high/low alcohol consumption was 1001.6 and 1161.8 ounces, for pre- and postmenopausal women, respectively.
[c]$P < 0.05$, χ^2 for differences between cases and controls for categorical variables.

Table III. Association of DNA repair genotypes with breast cancer risk, stratified by menopausal status

Genotype	Premenopausal			Postmenopausal		
	Cases, *n* (%)	Controls, *n* (%)	OR[a] (95% CI)	Cases, *n* (%)	Controls, *n* (%)	OR[b] (95% CI)
ERCC4 Ser835Ser (rs1799801)						
TT	162 (54.6)	287 (51.7)	1.00	408 (53.3)	685 (50.4)	1.00
CT	113 (38.1)	210 (37.8)	0.95 (0.69–1.32)	301 (39.3)	557 (41.0)	0.94 (0.77–1.14)
CC	22 (7.4)	58 (10.5)	0.76 (0.43–1.33)	57 (7.4)	116 (8.5)	0.79 (0.55–1.14)
CT + CC	135 (45.5)	268 (48.3)	0.91 (0.67–1.24)	358 (46.7)	673 (49.5)	0.91 (0.75–1.10)
XPC Arg687Arg (rs2227998)						
GG	162 (56.3)	301 (55.4)	1.00	392 (52.4)	735 (55.9)	1.00
AG	114 (39.6)	210 (38.7)	1.01 (0.72–1.40)	302 (40.4)	487 (37.1)	1.24 (1.01–1.52)
AA	12 (4.2)	32 (5.9)	0.83 (0.39–1.77)	54 (7.2)	92 (7.0)	1.13 (0.77–1.66)
AG + AA	126 (43.8)	242 (44.6)	0.98 (0.72–1.35)	356 (47.6)	579 (44.1)	1.22 (1.01–1.48)
XPC Lys939Gln (rs2228001)						
AA	100 (34.5)	203 (37.3)	1.00	288 (38.2)	475 (35.6)	1.00
AC	136 (46.9)	263 (48.3)	1.10 (0.78–1.57)	361 (47.9)	650 (48.8)	0.92 (0.75–1.14)
CC	54 (18.6)	79 (14.5)	1.42 (0.89–2.25)	105 (13.9)	208 (15.6)	0.84 (0.62–1.12)
AC + CC	190 (65.5)	342 (62.8)	1.18 (0.85–1.64)	466 (61.8)	858 (64.4)	0.90 (0.74–1.10)
XPC Ala499Val (rs2228000)						
CC	167 (58.6)	317 (57.6)	1.00	437 (57.7)	793 (59.1)	1.00
CT	100 (35.1)	193 (35.1)	1.00 (0.71–1.39)	273 (36.0)	478 (35.6)	1.00 (0.81–1.22)
TT	18 (6.3)	40 (7.3)	0.90 (0.48–1.71)	48 (6.3)	72 (5.4)	1.16 (0.77–1.75)
CT + TT	118 (41.4)	233 (42.4)	0.98 (0.72–1.35)	321 (42.3)	550 (41.0)	1.02 (0.84–1.24)
OGG1 Ser326Cys (rs1052133)						
CC	184 (61.5)	325 (59.6)	1.00	450 (59.6)	800 (59.6)	1.00
CG	102 (34.1)	194 (35.6)	1.00 (0.72–1.38)	264 (35.0)	476 (35.5)	0.97 (0.79–1.19)
GG	13 (4.4)	26 (4.8)	1.17 (0.53–2.54)	41 (5.4)	66 (4.9)	1.19 (0.77–1.85)
CG + GG	115 (38.5)	220 (40.4)	1.01 (0.74–1.38)	305 (40.4)	542 (40.4)	0.99 (0.82–1.21)
XRCC1 Arg399Gln (rs25487)						
GG	126 (47.0)	227 (44.9)	1.00	291 (40.8)	587 (46.4)	1.00
AG	120 (44.8)	228 (45.1)	0.88 (0.62–1.24)	341 (47.8)	544 (43.0)	1.22 (0.99–1.51)
AA	22 (8.2)	51 (10.1)	0.79 (0.44–1.42)	82 (11.5)	133 (10.5)	1.31 (0.94–1.83)
AG + AA	142 (53.0)	279 (55.2)	0.86 (0.62–1.20)	423 (59.3)	677 (53.5)	1.24 (1.01–1.51)
XRCC1 A>G Intronic (rs25486)						
AA	131 (44.6)	241 (43.8)	1.00	301 (39.5)	594 (44.6)	1.00
AG	128 (43.5)	237 (43.1)	0.91 (0.65–1.27)	358 (47.0)	586 (44.0)	1.20 (0.97–1.47)
GG	35 (11.9)	72 (13.1)	0.91 (0.56–1.48)	103 (13.5)	152 (11.4)	1.36 (1.00–1.86)
AG + GG	163 (55.4)	309 (56.2)	0.91 (0.67–1.24)	461 (60.5)	738 (55.4)	1.23 (1.01–1.49)

[a]ORs (premenopausal women) adjusted for age, education, race, smoking status, age at first birth, family history of breast cancer and history of benign breast disease.
[b]ORs (postmenopausal women) adjusted for age, education, race, smoking status, age at first birth, family history of breast cancer, history of benign breast disease, age at menarche and hormone therapy use.

Table IV. Genotype–smoking status interactions and breast cancer risk in pre- and postmenopausal women

Genotype	Premenopausal, OR (95% CI)[a]				Postmenopausal, OR (95% CI)[b]			
	Never-smoker	Former smoker	Current smoker	*P*-value[c]	Never-smoker	Former smoker	Current smoker	*P*-value[c]
ERCC4 Ser835Ser (rs1799801)								
TT	1.00	1.76 (1.09–2.85)	1.18 (0.64–2.12)	0.65	1.00	1.14 (0.86–1.52)	1.13 (0.76–1.69)	0.52
CT + CC	1.14 (0.73–1.77)	1.18 (0.73–1.91)	1.06 (0.54–2.08)		0.93 (0.70–1.23)	1.16 (0.86–1.55)	0.67 (0.42–1.07)	
XPC Arg687Arg (rs2227998)								
GG	1.00	1.40 (0.89–2.21)	1.41 (0.75–2.65)	0.26	1.00	1.38 (1.04–1.83)	0.98 (0.64–1.49)	0.47
AG + AA	1.09 (0.70–1.71)	1.57 (0.92–2.67)	0.76 (0.38–1.51)		1.42 (1.06–1.90)	1.36 (1.00–1.86)	1.38 (0.89–2.14)	
XPC Lys939Gln (rs2228001)								
AA	1.00	1.39 (0.76–2.56)	0.79 (0.37–1.68)	0.80	1.00	1.00 (0.71–1.40)	0.86 (0.53–1.40)	0.80
AC + CC	1.11 (0.70–1.75)	1.47 (0.91–2.36)	1.40 (0.75–2.59)		0.82 (0.61–1.11)	0.99 (0.73–1.35)	0.76 (0.50–1.15)	
XPC Ala499Val (rs2228000)								
CC	1.00	1.13 (0.71–1.77)	0.95 (0.52–1.74)	0.55	1.00	1.10 (0.84–1.44)	1.06 (0.72–1.56)	0.58
CT + TT	0.80 (0.51–1.26)	1.44 (0.86–2.34)	0.98 (0.49–1.97)		1.01 (0.75–1.35)	1.27 (0.95–1.69)	0.72 (0.44–1.17)	
OGG1 Ser326Cys (rs1052133)								
CC	1.00	1.47 (0.95–2.28)	1.23 (0.68–2.20)	0.94	1.00	1.15 (0.88–1.51)	1.06 (0.72–1.58)	0.80
CG + GG	1.09 (0.69–1.70)	1.47 (0.88–2.44)	1.03 (0.51–2.08)		1.04 (0.78–1.39)	1.20 (0.89–1.62)	0.79 (0.50–1.25)	
XRCC1 Arg399Gln (rs25487)								
GG	1.00	1.97 (1.17–3.29)	1.26 (0.62–2.56)	0.39	1.00	1.38 (0.99–1.91)	1.00 (0.63–1.59)	0.69
AG + AA	1.11 (0.69–1.78)	1.14 (0.67–1.96)	1.26 (0.65–2.46)		1.38 (1.02–1.87)	1.49 (1.09–2.03)	1.36 (0.87–2.14)	
XRCC1 A>G intronic (rs25486)								
AA	1.00	1.94 (1.17–3.22)	0.98 (0.49–1.97)	0.31	1.00	1.33 (0.97–1.84)	0.82 (0.51–1.31)	0.23
AG + GG	1.13 (0.72–1.78)	1.17 (0.71–1.93)	1.16 (0.61–2.18)		1.30 (0.97–1.74)	1.40 (1.04–1.90)	1.38 (0.91–2.10)	

[a]ORs (premenopausal women) adjusted for age, education, race, age at first birth, family history of breast cancer and history of benign breast disease.
[b]ORs (postmenopausal women) adjusted for age, education, race, age at first birth, family history of breast cancer, history of benign breast disease, age at menarche and hormone therapy use.
[c]*P*-value for genotype–smoking status interaction; Wald chi-square test.

Table V. Genotype–lifetime alcohol consumption interactions and breast cancer risk in pre- and postmenopausal women

Genotype	Premenopausal, OR (95% CI)[a]				Postmenopausal, OR (95% CI)[b]			
	Never drinker	Low alcohol	High alcohol[c]	*P*-value[d]	Never drinker	Low alcohol	High alcohol[c]	*P*-value[d]
ERCC4 Ser835Ser (rs1799801)								
TT	1.00	1.03 (0.48–2.19)	0.94 (0.44–2.02)	0.58	1.00	0.70 (0.48–1.01)	0.65 (0.44–0.95)	0.22
CT + CC	1.07 (0.43–2.68)	0.72 (0.35–1.56)	0.98 (0.45–2.12)		0.65 (0.40–1.03)	0.73 (0.50–1.06)	0.60 (0.41–0.87)	
XPC Arg687Arg (rs2227998)								
GG	1.00	0.94 (0.42–2.10)	0.98 (0.44–2.21)	0.93	1.00	0.90 (0.61–1.32)	0.82 (0.55–1.21)	0.47
AG + AA	1.13 (0.44–2.91)	0.77 (0.33–1.77)	0.98 (0.43–2.23)		1.28 (0.80–2.04)	1.14 (0.77–1.68)	0.89 (0.60–1.34)	
XPC Lys939Gln (rs2228001)								
AA	1.00	0.73 (0.33–1.63)	0.73 (0.32–1.65)	0.84	1.00	1.13 (0.70–1.81)	0.84 (0.52–1.36)	0.13
AC + CC	0.96 (0.38–2.42)	0.84 (0.39–1.79)	0.95 (0.44–2.04)		1.12 (0.69–1.84)	0.86 (0.55–1.36)	0.82 (0.52–1.30)	
XPC Ala499Val (rs2228000)								
CC	1.00	0.78 (0.40–1.52)	0.96 (0.49–1.86)	0.72	1.00	0.87 (0.61–1.24)	0.76 (0.53–1.09)	0.99
CT + TT	1.10 (0.40–3.03)	0.93 (0.48–1.83)	0.79 (0.39–1.59)		1.07 (0.66–1.74)	0.93 (0.64–1.35)	0.75 (0.51–1.10)	
OGG1 Ser326Cys (rs1052133)								
CC	1.00	0.66 (0.34–1.30)	0.78 (0.40–1.53)	0.71	1.00	0.79 (0.55–1.14)	0.61 (0.42–0.88)	0.18
CG + GG	0.71 (0.27–1.84)	0.82 (0.41–1.63)	0.80 (0.39–1.63)		0.69 (0.43–1.11)	0.74 (0.50–1.09)	0.76 (0.51–1.12)	
XRCC1 Arg399Gln (rs25487)								
GG	1.00	0.84 (0.36–1.96)	1.07 (0.46–2.51)	0.84	1.00	0.85 (0.55–1.33)	0.95 (0.61–1.48)	0.28
AG + AA	1.14 (0.43–3.04)	0.73 (0.31–1.69)	0.83 (0.36–1.93)		1.36 (0.84–2.21)	1.23 (0.80–1.88)	0.93 (0.60–1.44)	
XRCC1 A > G intronic (rs25486)								
AA	1.00	0.69 (0.31–1.50)	0.97 (0.44–2.14)	0.71	1.00	0.88 (0.56–1.36)	0.86 (0.55–1.34)	0.56
AG + GG	0.84 (0.33–2.12)	0.78 (0.36–1.70)	0.69 (0.32–1.50)		1.30 (0.81–2.10)	1.19 (0.78–1.81)	0.92 (0.60–1.41)	

[a]ORs (premenopausal women) adjusted for age, education, race, smoking status, age at first birth, family history of breast cancer and history of benign breast disease.
[b]ORs (postmenopausal women) adjusted for age, education, race, smoking status, age at first birth, family history of breast cancer, history of benign breast disease, age at menarche and hormone therapy use.
[c]Lifetime total alcohol consumption in ounces from birth to 2 years prior to diagnosis or interview for cases and controls, respectively. The cut-off for high/low alcohol consumption was 1001.6 and 1161.8 ounces, for pre- and postmenopausal women, respectively.
[d]*P*-value for genotype–lifetime alcohol consumption interaction; Wald chi-square test.

smoking women (40). However, a case–control study of patients in Finland found a significant increase in risk of breast cancer among ever-smoking women with the variant *XRCC1* rs25487 polymorphism compared with smoking women without that genotype (43). When we restricted our study population to former and current smokers, presence of the variant *XRCC1* rs25487 allele was nonsignificantly associated with decreased risk in premenopausal women and increased risk in postmenopausal women (data not shown). Modification of the

association of these variants with breast cancer risk by lifetime alcohol consumption has been less studied, although some studies have examined risk of breast cancer stratified by alcohol use. Alcohol consumption, defined as consuming at least one drink per week over a 6 months period (30) or as current weekly or daily consumption (43), has not been found to modify risk of breast cancer among women with the *XRCC1* rs25487 variant allele.

To our knowledge, *XPC* rs2227998 and *ERCC4* rs1799801 have not been studied previously in breast cancer. In our study, postmenopausal women with the variant allele of *XPC* rs2227998 were at increased risk of breast cancer, though these findings were only marginally significant. There was no evidence of an interaction with either smoking or alcohol consumption. In a recent study of bladder cancer, there was decreased risk of bladder cancer among individuals who were homozygous for the variant allele of *XPC* rs2227998 compared with those homozygous for common alleles (57). We did not observe any associations between *ERCC4* rs1799801 and breast cancer risk when we stratified by menopausal status. Only one other published report has examined the *ERCC4* Ser835Ser SNP in relation to breast cancer (58). In this Korean hospital-based case–control study, as in our study, *ERCC4* Ser835Ser was not associated with risk of breast cancer. Although not studied in breast cancer, alcohol intake has not been shown to modify associations between other *ERCC4* polymorphisms and laryngeal (59) and oral squamous cell carcinoma (60).

In general, results from epidemiologic studies of heritable variation in DNA repair genes and risk of breast cancer have been inconsistent. Several of the SNPs analyzed in this study have been previously studied, including *XPC* rs2228001, *XPC* rs2228000, *OGG1* rs1052133 and *XRCC1* rs25487, but others, such as *ERCC4* rs1799801, *XPC* rs2227998 and *XRCC1* rs25486, are less well studied. We were unable to report findings for the ERCC2 rs13181 and rs1799787 polymorphisms, as these SNPs were not in Hardy–Weinberg equilibrium in our study and were therefore dropped from subsequent analyses. Our findings, particularly in premenopausal women, were largely null. It is possible that the significant associations we did detect are due to chance alone. It may also be that, for those polymorphisms in which null findings were observed, there is no true effect of those SNPs on breast cancer risk. Our findings may also be plausibly explained by reasoning that most of the SNPs chosen for this study did not have sufficient functional effect to alter the process of breast carcinogenesis. Our understanding of the functional effect of genetic variants is incomplete. Non-synonymous SNPs and those affecting regulatory regions are typically regarded as having functional effects (61), but SNPs located in introns or synonymous SNPs are not necessarily nonfunctional. Rather, they may exert effects by affecting the structure of messenger RNA or function and expression levels of proteins (62). A given genetic variant, however, is only one component of the spectrum of genetic and environmental causal factors that are required for disease development; individually, a single causal factor is often neither necessary nor sufficient (61,63,64), particularly for breast cancer. Environmental forces are more likely to strongly influence disease development rather than genetic variants, and as a consequence, the effect of any one variant is likely to be small and dependent on the surrounding environmental context (61,64). Inferring the role of a genetic variant in disease etiology is made more difficult by the lack of empirical data supporting an effect of the variant on protein function. If the actual functional effect of a variant on breast tumorigenesis is small, the variant's effect on the risk of developing breast cancer is also likely to be small and difficult to detect (61). If a variant lacks sufficient functional effect to impact the development of breast cancer, the effect on risk is likely to be null. An important goal for future research will be to evaluate the ways in which gene expression and protein function are affected by genetic variants. Confirming a functional role will provide additional support for inferring that a variant is causally related to disease (65).

Several of the SNPs we investigated are intronic or synonymous. We observed a significant association for one synonymous polymorphism, *XPC* rs2227998, in postmenopausal women, although there are no published studies evaluating the possible functional effects of this SNP. Using peripheral blood lymphocytes obtained from healthy men and women to assay DNA repair capacity for damage induced by irradiation and oxidation *in vitro*, the homozygous variant genotype of *XRCC1* rs25487 was shown to have significantly reduced rates of repair for irradiation-induced damage compared with common allele carriers (13). The *XRCC1* rs25487 homozygous variant genotype has also been shown to result in increased chromosomal abnormalities in peripheral blood lymphocytes assayed to determine cytogenetic damage induced by irradiation (14). This genetic variant was also associated with increased susceptibility to ionizing radiation, assayed by measuring prolonged cell cycle delay (66). These findings are consistent with the increased risk of breast cancer we observed for women with the variant allele of *XRCC1* rs25487 and *XRCC1* rs25486, which are in high linkage disequilibrium. DNA repair processes are fundamentally important for a cell to maintain genomic stability. Reduced repair capacity could lead to a predisposition to accumulate damage, mutations, and subsequently develop diseases such as cancer (67). Understanding the mechanisms by which somatic or inherited mutations and polymorphisms in DNA repair pathway genes influence carcinogenesis may lead to new chemopreventive targets or antitumor agents (67,68), making this a critical area of research.

The strengths of this study include the large sample size and population-based design. Limitations include the possibility of recall and selection biases, as well as misclassification in the self-reported exposure assessments and in assignment of genotype for the genes we studied. However, call rates for all of the genotypes we studied were $>$90%, and the concordance rate among blind duplicates ranged from 97.3 to 99.4%. We assessed selection bias due to nonparticipation by collecting general information in a short telephone interview from women who declined to participate. Nonparticipating cases and controls were more likely to be current smokers than those who participated, while participants tended to consume more drinks of alcohol per month than nonparticipants. There may have been recall bias in assessing lifetime alcohol consumption, although the same method of collecting this information was used for both cases and controls. Additionally, previous studies have documented minimal evidence for recall bias in the assessment of alcohol consumption for breast cancer case–control studies (69,70). Interviewers were also blinded to case and control status as well as to study hypotheses. It is unlikely that there were differences in recall related to genotype.

In conclusion, we found that polymorphisms in two DNA repair genes involved in the NER and BER processes, *XRCC1* and *XPC*, appear to influence risk of breast cancer in postmenopausal women. Our findings with respect to the *XPC* rs2227998 SNP suggest that synonymous polymorphisms may merit attention in future studies of breast cancer etiology. Because this SNP has not been well studied to date, future research is needed to confirm the associations we detected, as well as to elucidate the mechanisms by which these synonymous SNPs may act to affect the risk of breast cancer.

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