Polymorphisms XRCC1-*R399Q* and XRCC3-*T241M* and the Risk of Breast Cancer at the Ontario Site of the Breast Cancer Family Registry

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Abstract

This study investigates the role of two nonsynonymous single nucleotide polymorphisms in DNA repair genes, X-ray repair cross-complementing group 1 (XRCC1)-*R399Q* and X-ray repair cross-complementing group 3 (XRCC3)-*T241M*, in breast cancer. Incident cases of invasive breast cancer in Caucasian women [*n* = 402, mean age = 45.7 (SD = 6.2) years] and female Caucasian controls [*n* = 402, mean age = 45.2 (6.5) years] frequency matched on 5-year age intervals were identified from the Ontario Familial Breast Cancer Registry. No evidence for a main effect of the XRCC1-*R399Q* genotype on breast cancer risk was observed. Estimates of risk for a family history (FH) of breast cancer compared with no FH differed by XRCC1-*R399Q* genotype (*P* value for interaction = 0.001). Homozygote XRCC1-399 *R*/*R* individuals and FH+ were at a 2.92-fold [95% confidence interval (95% CI) = 1.47–5.79] increased risk of disease compared with FH− individuals; the estimate of risk increased for *R*/*Q* heterozygotes with FH+ [odds ratio (OR) = 3.85, 95% CI = 1.94–7.65] but not for *Q*/*Q* homozygotes with FH+ (OR = 0.54, 95% CI = 0.20–1.47) compared with homozygous *R*/*R* and FH− individuals. A marginal positive association for XRCC3-241 *M*/*M* compared with *T*/*T* genotype was found (OR = 1.44, 95% CI = 0.94–2.19), but the heterozygous *T*/*M* was not associated with an increase in risk (OR = 0.96, 95% CI = 0.71–1.32). There was also some evidence for a combined effect of body mass index and XRCC3-*T241M* on estimates of risk. Our results suggest that these polymorphisms may influence breast cancer risk by modifying the effect of risk factors such as FH. There is a need for further study into the role of these polymorphisms as effect modifiers. (Cancer Epidemiol Biomarkers Prev 2004;13(4):583–591)

Introduction

Identifying genes associated with breast cancer continues to be a major goal of current research. Among unanswered questions are the number of genetic variants that may be involved in predisposition to the disease and their role in modifying the effect of environmental and life-style factors. Several studies have reported low penetrant variants, single nucleotide polymorphisms (SNPs), as potential cancer susceptibility factors including two variants involved in DNA repair: X-ray repair cross-complementing group 1 (XRCC1)-*R399Q* (arginine → glutamine, amino acid position 399; G → A, nucleotide position 28152) and X-ray repair cross-complementing group 3 (XRCC3)-*T241M* (threonine → methionine, amino acid position 241; C → T, nucleotide position18067; Refs. 1–31). These SNPs occur within functional domains of essential DNA repair proteins and result in nonsynonymous amino acid substitutions differing in volume, charge, and/or polarity at positions that are highly conserved within the Mammalia class.[2] How these SNPs relate to DNA damage phenotypes in human cells and tissues remains uncertain, but at least a few studies (12, 32, 33) have implied that the XRCC1-*Q399* and XRCC3-*T241* alleles have an important, potentially harmful phenotype.

The association between these polymorphic alleles and breast cancer has been reported in the peer-reviewed literature by a few case-control studies (6, 7, 21, 29, 34). Duell *et al.* (6) published the first results using a population-based case-control study design. This study did not show evidence of a main effect for the XRCC1-*R399Q* polymorphism among Caucasian women but did find a potential interaction between genotype and ionizing radiation (IR). The second study by Smith *et al.* (21) oversampled controls with a family history (FH) of breast cancer to investigate the combined effect

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of genotype (XRCC1-*R399Q* and XRCC3-*T241M*) and FH on risk estimates for the disease. Data stratified by FH were, however, limited in sample size and no significant association between breast cancer risk and genotype was observed. Kim *et al.* (7) reported results from a hospital-based case-control study of Korean women, which, unlike the other studies, found that homozygosity of the XRCC1-*Q399* allele placed women at a 2.4-fold risk [95% confidence interval (95% CI) = 1.20–4.72] for this disease and premenopausal women at a 3.8-fold risk (95% CI = 1.44–10.30). The authors of this study further report a synergistic interaction in breast cancer between XRCC1-*R399Q* polymorphism and alcohol consumption (data not shown). The Kuschel *et al.* (29) study was the only large population-based case-control study of the XRCC3-*T241M* polymorphism. The results showed that homozygous carriers of the XRCC3-*M241* allele were associated with an increased risk of 1.3-fold (95% CI = 1.1–1.6), but neither adjusted estimates nor gene exposure effects were reported. The most recent study to be published on the XRCC3-*T241M* polymorphism and the risk of breast cancer, by Jacobsen *et al.* (34), did not find evidence for an association. In summary, results are not consistent and studies vary significantly in methodology and analyses. As a result, what has been understood about the role of these alleles in the etiology of breast cancer is still unclear, and there is a need to resolve these inconsistencies.

This study reports risk estimates for breast cancer using systematically collected data from the Ontario (Canada) site of the Breast Cancer Family Registry and population controls. Potential biologically plausible interactions between genotypes and exposures related to DNA repair capacity, including those examined previously by other studies, are evaluated. This study specifically looks at exposures during adolescence, a time where the breast tissue is more susceptible to DNA damage caused by exposure to tobacco carcinogens and low-dose IR. Furthermore, this study focuses on a younger population (under age 55) than the other studies, where the occurrence of breast cancer would more likely signify underlying genetic causes.

Methodology

Design/Population. Incident cases of breast cancer were identified from the Ontario Familial Breast Cancer Registry (OFBCR). The OFBCR is a population-based registry in Ontario, Canada that comprises one of six international sites of the NIH-funded Breast Cancer Family Registry. The OFBCR identified potential participants from the Ontario Cancer Registry (OCR), which registers virtually all cases of breast cancer in the province (97.5%; Ref. 35), and included all women aged 20–54 years, a 35% random sample of women aged 55–69 years, and all men diagnosed with invasive breast cancer aged 20–74 years. The majority of cases are reported to the OCR within 6 months of diagnosis. All cases were pathologically confirmed and diagnosed between 1996 and 1998. Pathology reports were reviewed to determine a physician involved in the care of each patient. Information about the OFBCR and a FH questionnaire were mailed to those patients once physician permission could be obtained. Questionnaires that were received were classified by whether they met criteria for ''genetic'' risk that had been established previously by the OFBCR (36, 37). Those individuals who qualified as ''genetic'' cases and a 25% random sample of ''nongenetic'' cases that were interested in further participating in the registry were telephoned to review their FHs. Epidemiological and diet questionnaires were mailed to these individuals. They were also asked for permission to contact relatives and about suitable arrangements for providing a blood sample.

In this study, we included only cases under age 55 at the time of diagnosis. Recruitment rates and other characteristics are described briefly in this report. There were 6219 individuals registered in the OCR that were diagnosed under age 55. Ninety-one percent of individuals (n = 5649) could be approached for possible participation in this study. FH questionnaires were completed and returned by 3609 (63.9%) individuals. All ''genetic'' cases (n = 1396) and a randomly selected sample of ''nongenetic'' cases (n = 529) were invited to complete an epidemiological questionnaire and provide a blood sample. Of the total cases, 1431 (74.3%) cases returned epidemiological questionnaires and 1212 (63.0%) provided a blood sample. About 2% of the population died at the various stages of recruitment. This study included all ''nongenetic'' (n = 315) and a 25% random sample of those who were ''genetic'' cases (n = 224) who had provided a blood sample to obtain a more representative sample of the breast cancer population under age 55. Out of a total of 539 individuals, cases of male breast cancers and those that did not identify themselves as Caucasians were excluded (n = 80; 14.8%). In addition, sufficient DNA could not be extracted from blood samples of 49 individuals (10.7%), and 8 individuals (1.7%) could not be genotyped.

Female population controls were recruited by calling randomly selected residential telephone numbers throughout the province of Ontario. Eligible controls were women with no history of breast cancer. They were frequency matched on 5-year age groups based on the age distribution of the entire OFBCR population. The total number of households contacted by telephone was 14,653. Sixteen percent (n = 2366) of households had an eligible participant willing to participate in the study. The majority (n = 7829; 53.4%) of households did not have an eligible participant. Among households not participating, 322 (2.2%) had an eligible participant. Eligibility could not be determined in the remaining 2194 (15.0%) households. Seventy-three percent (n = 1726) of individuals completed and returned questionnaires, and 52.4% (n = 1290) consented to providing a blood sample. Only a proportion, randomly selected from those under age 55 and agreeing to donate blood, were asked to do so (n = 676), and 62.3% (n = 421) in fact did. Ten (2.4%) samples were insufficient to extract DNA and 1 (0.2%) sample could not be genotyped.

Molecular Analysis. DNA was extracted from peripheral blood lymphocytes. SNP genotyping was performed using matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectrometry (MS; Ref. 38). PCR primers [XRCC1: 5′-CCCAAGTACAGCCAGGTC-3′ (forward) and 5′-CCGCTCCTCTCAGTAGTC-3′

(reverse); XRCC3: 5′-GCTCGCCTGGTGGTCATC-3′ (forward) and 5′-GCTTCCGCATCCTGGCTAA-3′ (reverse)] were designed using the Oligo Primer Analysis Software (National Biosciences, Inc., Plymouth, MN). Multiplexed PCR reactions (10 μl) contained 10 ng genomic DNA, 1× reaction buffer, 0.20 unit Platinum Taq polymerase (Invitrogen Life Technologies, Burlington, Ontario, Canada), 0.40 μl deoxynucleotides (dNTPs), and 0.18 μM of each primer. Cycling conditions for PCR amplification consisted of 39 cycles (30 s at 94°C, 15 s at 58°C, and 10 s at 72°C). Products were purified using shrimp alkaline phosphatase (0.1 unit/μl; Amersham Biosciences, Bail d'Urfe, Quebec, Canada) and exonuclease I (0.5 unit/μl; Amersham Biosciences). Other primers (XRCC1: 5′-CGGCGGCTGCCCTCCC-3′ and XRCC3: 5′-ACTGCTCAGCTCACGAGC-3′) were designed to anneal to the targeted DNA immediately upstream of the SNP site to be extended by one or more nucleotides in the presence of dNTPs and dideoxynucleotides using the very short primer extension strategy (39). Multiplexed reactions (10 μl) contained 3.0 μl PCR products, 1× ThermoSequenase buffer, 1 unit ThermoSequenase (Amersham Biosciences), 8 μM dNTPs + dideoxynucleotides, and 0.12 μM of each primer. The extension products were purified using a cation exchange resin (DOWEX 50W8-200; Aldrich Chemical Co., Milwaukee, WI). About 1–2 μg of resin were added to each reaction tube and shaken for 10 s. A DNA MALDI-TOF MS matrix (3-hydoxypicolinic acid; Chemika, Seelze, Germany) was spotted (0.5 μl) on each of the 386-well plate (AnchorChip 400/384; Bruker Daltonics, Billerica, MA) for MS. The same amount of each sample was spotted on dried matrix. Samples were analyzed using the Reflex IV MALDI-TOF MS (Bruker Daltonics). The results were acquired by AutoXecute and analyzed by Genotools (Bruker Daltonics; Ref. 40). Inconclusive results were repeated by MS and/or using direct sequencing. Seventy-five percent of the population was also genotyped using the 5′ nuclease (Taqman) assay (ABI Prism 7700 system; PE Applied Biosystems, Foster City, CA) for the XRCC1-*R399Q* polymorphism. The two assays, MS and Taqman, yielded a 95% agreement; discordant results were genotyped using direct sequencing.

Exposure Information. Information about FH of cancer was obtained by self-report using a structured questionnaire. A separate questionnaire elicited information on age (cases, age at diagnosis less 1 year; controls, age at time the risk factor questionnaire was completed), ethnicity, height and weight, education, alcohol and tobacco use, medical and reproductive history, and radiation exposure. Participants were defined as adolescent smokers if they began smoking at least 1 cigarette/day for a 3-month period before age 20. Drinkers were defined as participants who consumed alcoholic beverages (beer, wine, or spirits) at least once a week for a 6-month period in their lifetime. Individuals who reported receiving X-rays to the breast/chest area under age 20 were classified as adolescents exposed to IR.

Statistical Analysis. χ^2 tests or Fisher's exact tests were used to examine the differences in the proportions of categorical variables between cases and controls. For continuous variables, Student's *t* test was performed. Tests for Hardy-Weinberg equilibrium among controls were conducted using observed genotype frequencies and a χ^2 test with 1 *df*. Both crude and adjusted odds ratios (ORs) and the 95% CI measuring the association between breast cancer and risk factors were estimated using unconditional logistic regression. $P < 0.05$ was used as the criterion of significance. Variables to be used in building multivariable models were selected *a priori*. The genotype of XRCC1-*R399Q* and XRCC3-*T241M* were variables of main interest; other risk factors for breast cancer related to DNA repair capacity [*i.e.*, age, body mass index (BMI), smoking status, alcohol status, IR exposure, and FH of breast cancer] were included in multivariable models. Entry of a confounding variable into the model was defined using Rothman and Greenland's (41) definition of confounding as a change of at least 10% in the β parameter estimates. Other potential risk factors evaluated but not included in the final models were menopausal status, parity, and age at first birth. Premenopausal women were defined as individuals not taking hormone replacement therapy whose last menses was within a year of the reference age. Postmenopausal women were individuals whose time since their last menses was more than 1 year from the reference age, and the reason for cessation was not because of a surgical procedure other than complete oophorectomy. None of these latter factors were identified as confounders in this study population. Only gene-environment interactions that were biologically reasonable were tested. Interaction effects were modeled by assuming a multiplicative effect on the logit scale and tests for interaction were performed using the likelihood ratio test. Individuals with missing data for non-genetic risk factors were excluded in multivariable analyses. All statistical analyses were performed using the Statistical Analysis System software (version 8; SAS Institute, Cary, NC).

Ethics. Approval for this study was obtained from the Research Ethics Board of Mount Sinai Hospital, Toronto, ON, Canada and the Advisory and Steering Committees of the NIH-funded Breast Cancer Family Registry.

Results

Selected characteristics of the case and control populations are listed in Table 1. A few individuals identified themselves as Caucasian as well as another ethnic group (Caucasian-Native: $n = 15$, Caucasian-Asian: $n = 3$, Caucasian-Black: $n = 2$). Cases and controls ranged in age from 25 to 54 years, with a third of the population past menopause. Fifteen (3.7%) cases had multiple diagnoses of breast cancer and 19 (4.7%) were known to be deceased to date. There were no significant differences between cases and controls in alcohol consumption or cigarette smoking and IR exposure before age 20 (data not shown); however, a significantly larger proportion of controls were overweight or obese (BMI > 25) compared with cases (40.6% *versus* 53.5%).

A χ^2 test of observed *versus* expected genotype frequencies for each polymorphism showed no deviations from Hardy-Weinberg equilibrium among controls. The allele frequency for the least common alleles, XRCC1-*Q399* and XRCC3-*M241*, was 0.37 and 0.39, respectively.

Table 1. Distribution of selected characteristics and risk factors in breast cancer cases and population controls

Category	Cases		Controls		P^a
	n	%	*n*	%	
Age (yr)					
≤40	81	20.2	89	22.1	0.77
41–45	87	21.6	92	22.9	
46–50	128	31.8	126	31.3	
>50	106	26.4	95	23.6	
Mean (SD)	45.7 (6.2)		45.2 (6.5)		0.2[b]
BMI (kg/m^2)					
<18.5	8	2.6	6	1.6	<0.01
18.5–25	178	56.9	174	45.0	
25–30	72	23.0	127	32.8	
>30	55	17.6	80	20.7	
Missing	89	–	15	–	
Mean (SD)	25.6 (5.4)		26.5 (5.6)		0.04[b]
Education					
Up to high school	122	35.7	109	27.1	0.07
Technical school	107	31.3	151	37.6	
Some college/university	25	7.3	35	8.7	
University degree	88	25.8	107	26.6	
Missing	60	–	0	–	
Menopausal status					
Premenopausal	224	66.5	256	67.4	0.80
Postmenopausal	113	33.5	124	32.6	
Uncertain	7	–	21	–	
Missing	58	–	1	–	
Parity (no. of live births)					
Nulliparous	70	20.4	70	17.4	0.50
1 child	55	16.0	61	15.2	
2 children	144	41.9	166	41.3	
≥3 children	75	21.8	105	26.1	
Missing	58	–	0	–	
FH of breast and/or ovarian cancer[c]					
No	313	77.9	357	88.8	<0.01
Yes	89	22.1	45	11.2	
FH of other cancers[c]					
No	202	50.2	247	61.4	<0.01
Yes	200	49.8	155	38.6	

[a] χ^2 test for homogeneity of proportions in contingency table.
[b] Student's *t* test (unequal variances).
[c] Only first-degree relatives.

Crude and adjusted ORs presented in Table 2 were borderline statistically significant for the XRCC3-*T241M* polymorphism but not significant for XRCC1-*R399Q*. Comparing the XRCC3 *T/M* genotype to *T/T*, the OR was 0.96 (95% CI = 0.71–1.32) and 1.44 (95% CI = 0.94–2.19) for the *M/M* genotype compared with *T/T*. Analyzed as a dichotomous variable by combining the XRCC3 *T/T* and *T/M* genotypes as the reference group, the *M/M* genotype represented a 1.47-fold increase in risk (95% CI = 1.00–2.15). Adjusted ORs and 95% CI for the heterozygous XRCC1 *R/Q* genotype and homozygous *Q/Q* compared with the wild-type homozygous *R/R* genotype were 0.91 (0.67–1.23) and 0.88 (0.57–1.37), respectively. Similarly, analyzed as a dichotomous variable (*Q/Q versus R/R + R/Q*), the risk estimate was close to unity (OR = 0.93, 95% CI = 0.62–1.40). Exclusion of mixed Caucasians showed similar results (data not shown).

The combined analysis of genotype and FH of breast cancer are presented in Table 3. Test of interaction showed a statistically significant interaction between FH of breast cancer and the genotype of XRCC1-*R399Q* (P = 0.01). No evidence of interaction between FH and XRCC3-*T241M* was found (P = 0.82). Due to a relatively small number of cases and controls with a positive FH (n = 120) compared with those with no history of the disease (n = 684), a common reference group was used in the analyses (FH− and wild-type genotype). Homozygote XRCC1-399 *R/R* individuals with a FH were at a 2.92-fold (95% CI = 1.47–5.79) increased risk compared with those with no FH. There was an increase in risk for *R/Q* heterozygotes with a positive FH (OR = 3.85, 95% CI = 1.94–7.65) but not for the *Q/Q* genotype with a positive FH (OR = 0.54, 95% CI = 0.20–1.47) compared with FH− XRCC1-399 *R/R* carriers.

The combined effects of genotypes and other covariates on estimates of risk are shown in Table 4. The XRCC1-*R399Q* genotype did not modify the effect of smoking or IR exposure during adolescence (under age 20), alcohol consumption, or BMI. There was also no evidence of an interaction between alcohol use and smoking or IR exposure before age 20 and the genotype of XRCC3-*T241M*. Individuals with BMI > 25 kg/m^2 were at approximately one-half the risk of individuals within normal BMI limits (18.5–25 kg/m^2) among individuals with either XRCC1-399 *R/R* and *R/Q* genotypes or XRCC3-241 *T/T* and *T/M* genotypes. Among normal weight individuals, the homozygous XRCC3-241 *M/M* genotype conferred an increased risk compared with the homozygous *T/T* genotype with an OR of 2.68

Table 2. Genotype frequencies and OR estimates for breast cancer risk

	Cases (n = 402) n (%)	Controls (n = 402) n (%)	P^a	OR	Multivariate adjusted OR[b]
XRCC3-*T241M*					
T/T	139 (34.6)	146 (36.3)	0.10	1.00	1.00
T/M	186 (46.3)	200 (49.8)		0.98 (0.72–1.33)	0.96 (0.71–1.32)
M/M	77 (19.2)	56 (13.9)		1.44 (0.95–2.19)	1.44 (0.94–2.19)
T/T + T/M	325 (80.9)	346 (86.1)	0.05	1.00	1.00
M/M	77 (19.2)	56 (13.9)		1.46 (1.02–2.13)	1.47 (1.00–2.15)
XRCC1-*R399Q*					
R/R	168 (41.8)	160 (39.8)	0.85	1.00	1.00
R/Q	179 (44.5)	185 (46.0)		0.92 (0.68–1.24)	0.91 (0.67–1.23)
Q/Q	55 (13.7)	57 (14.2)		0.92 (0.60–1.41)	0.88 (0.57–1.37)
R/R + R/Q	347 (86.3)	345 (85.8)	0.84	1.00	1.00
Q/Q	55 (13.7)	57 (14.2)		0.96 (0.64–1.43)	0.93 (0.62–1.40)

[a] χ^2 test for homogeneity of proportions in contingency table.
[b] Adjusted for ethnicity (Caucasian or Caucasian and other ethnic group), age (years), and FH of breast cancer (at least one first-degree relative).

Table 3. Effects of genotypes and FH on breast cancer risk

FH[a]	Genotype	Cases (n = 402) n (%)	Controls (n = 402) n (%)	OR	Multivariate adjusted OR[b]
XRCC3-*T241M*					
Negative	*T/T*	110 (27.4)	133 (33.1)	1.00	1.00
	T/M	148 (36.8)	180 (44.8)	0.99 (0.71–1.39)	0.97 (0.71–1.38)
	M/M	61 (15.2)	52 (12.9)	1.42 (0.91–2.22)	1.41 (0.90–2.20)
Positive	*T/T*	29 (7.2)	13 (3.2)	2.70 (1.34–5.44)	2.70 (1.34–5.46)
	T/M	38 (9.5)	20 (5.0)	2.30 (1.26–4.18)	2.26 (1.24–4.12)
	M/M	16 (4.0)	4 (1.0)	4.84 (1.57–14.89)	4.77 (1.55–14.70)
XRCC1-*R399Q*					
Negative	*R/R*	134 (33.3)	147 (36.6)	1.00	1.00
	R/Q	136 (33.8)	173 (43.0)	0.86 (0.62–1.19)	0.86 (0.62–1.19)
	Q/Q	49 (12.2)	45 (11.2)	1.20 (0.75–1.91)	1.17 (0.73–1.87)
Positive	*R/R*	34 (8.5)	13 (3.2)	2.87 (1.45–5.67)	2.92 (1.47–5.79)
	R/Q	43 (10.7)	12 (3.0)	3.93 (1.99–7.77)	3.85 (1.94–7.62)
	Q/Q	6 (1.5)	12 (3.0)	0.55 (0.20–1.50)	0.54 (0.20–1.47)

[a]At least one first-degree relative.
[b]Adjusted for ethnicity (Caucasian or Caucasian and other ethnic group) and age (years).

(95% CI = 1.45–4.94). Stratifying by BMI category (data not shown) showed that individuals with the XRCC3-241 *M/M* genotype were at an increase risk only if they were within normal BMI limits [adjusted OR comparing *M/M* to *T/T* + *T/M* for normal weight individuals: 3.55 (95% CI = 1.68–7.53) and overweight/obese individuals: 0.55 (95% CI = 0.16–1.91)]. The P value for interaction between BMI and XRCC3-*T241M* genotype was borderline statistically significant (P = 0.06). The combined analysis of XRCC1-*R399Q* and XRCC3-*T241M* genotypes presented in Table 5 showed no evidence of interaction.

Discussion

Our findings suggest that the XRCC3-*T241M* polymorphism may be a risk factor for breast cancer. Some but not all previous studies have also found evidence to suggest that this polymorphism is a cancer risk factor including cancer of the breast (29), bladder (12, 30), squamous cell carcinoma of the head and neck (31), and melanoma (20). Our study is in agreement with Kuschel *et al.* (29), which found a statistically significant increased risk for breast cancer associated with the XRCC3-241 *M* allele [OR for *T/M versus T/T* = 1.16

Table 4. Effects of genotypes and environmental exposures on breast cancer risk

Exposure[a]	XRCC1-*R399Q*				XRCC3-*T241M*			
	Genotype	Cases n (%)	Controls n (%)	Multivariate adjusted OR[b]	Genotype	Cases n (%)	Controls n (%)	Multivariate adjusted OR[b]
Adolescent smoking								
No	*R/R + R/Q*	163 (48.1)	180 (44.9)	1.00	*T/T + T/M*	155 (45.7)	184 (45.9)	1.00
	Q/Q	25 (7.4)	29 (7.2)	0.89 (0.50–1.60)	*M/M*	33 (9.7)	25 (6.2)	1.50 (0.85–2.65)
Yes	*R/R + R/Q*	132 (38.9)	165 (41.2)	0.88 (0.64–1.21)	*T/T + T/M*	119 (35.1)	161 (40.2)	0.87 (0.63–1.20)
	Q/Q	19 (5.6)	27 (6.7)	0.76 (0.41–1.44)	*M/M*	32 (9.4)	31 (7.7)	1.24 (0.72–2.13)
Alcohol consumption								
No	*R/R + R/Q*	137 (40.1)	178 (44.3)	1.00	*T/T + T/M*	125 (35.6)	168 (41.8)	1.00
	Q/Q	19 (5.6)	24 (6.0)	1.04 (0.54–1.99)	*M/M*	31 (9.1)	34 (8.5)	1.21 (0.70–2.09)
Yes	*R/R + R/Q*	160 (46.8)	167 (41.5)	1.24 (0.90–1.70)	*T/T + T/M*	151 (44.2)	178 (44.3)	1.12 (0.81–1.54)
	Q/Q	26 (7.6)	33 (8.2)	0.93 (0.53–1.66)	*M/M*	35 (10.2)	22 (5.5)	2.09 (1.16–3.78)
BMI								
Normal	*R/R + R/Q*	152 (60.8)	151 (50.2)	1.00	*T/T + T/M*	138 (55.2)	156 (51.8)	1.00
	Q/Q	26 (10.4)	23 (7.6)	1.03 (0.56–1.93)	*M/M*	40 (16.0)	18 (6.0)	2.68 (1.45–4.94)
Overweight/ obese	*R/R + R/Q*	65 (26.0)	110 (26.0)	0.54 (0.36–0.79)	*T/T + T/M*	61 (24.4)	113 (37.5)	0.59 (0.39–0.87)
	Q/Q	7 (2.8)	17 (5.7)	0.40 (0.16–1.01)	*M/M*	11 (4.4)	14 (4.7)	0.75 (0.32–1.77)
Adolescent IR exposure								
No	*R/R + R/Q*	181 (70.7)	232 (68.8)	1.00	*T/T + T/M*	164 (64.1)	242 (71.8)	1.00
	Q/Q	22 (8.6)	44 (13.1)	0.63 (0.36–1.10)	*M/M*	39 (15.2)	34 (10.1)	1.67 (1.00–2.78)
Yes	*R/R + R/Q*	41 (16.0)	55 (16.3)	0.97 (0.61–1.53)	*T/T + T/M*	40 (15.6)	51 (15.1)	1.16 (0.73–1.85)
	Q/Q	12 (4.7)	6 (1.8)	2.56 (0.93–7.03)	*M/M*	13 (5.1)	10 (3.0)	2.02 (0.86–4.76)

[a]Definition of variables: smoking (at least 1 cigarette/day for a 3-month period) under age 20; alcohol consumption (at least 1 beer/glass of wine/liquor once a week for at least a 6-month period); BMI (normal: 18.5–25 kg/m^2, overweight/obese: >25 kg/m^2); FH of breast cancer (at least one first-degree relative with breast cancer); and IR exposure (X-rays to the breast area) under age 20.
[b]Adjusted for ethnicity (Caucasian or Caucasian and other ethnic group), age (years), and FH of breast cancer (at least one first-degree relative).

Table 5. Analysis of joint effects for XRCC1-*R399Q* and XRCC3-*T241M* genotypes on breast cancer risk

Genotype		Cases (n = 402) n (%)	Controls (n = 402) n (%)	P[a]	OR (95% CI)	Multivariate adjusted OR (95% CI)[b]
XRCC1-*R399Q*	XRCC3-*T241M*					
R/R + R/Q	*T/T + T/M*	282 (70.2)	303 (75.4)	0.12	1.00	1.00
R/R + R/Q	*M/M*	65 (16.2)	42 (10.5)		1.66 (1.09–2.53)	1.66 (1.08–2.54)
Q/Q	*T/T + T/M*	43 (10.7)	43 (10.7)		1.07 (0.68–1.69)	1.03 (0.65–1.64)
Q/Q	*M/M*	12 (3.0)	14 (3.5)		0.92 (0.42–2.03)	0.92 (0.42–2.05)

[a] χ^2 test for homogeneity of proportions in contingency table.
[b] Adjusted for ethnicity (Caucasian or Caucasian and other ethnic group), age (years), and FH of breast cancer (at least one first-degree relative).

(95% CI = 1.00–1.36) and OR for *M/M versus T/T* = 1.28 (95% CI = 1.02–1.60)]; null results were found by Smith *et al.* (21) and Jacobsen *et al.* (34). No association was also reported for studies of lung cancer (2, 26, 27) and melanoma (28). The discordant results between cancer studies reflect differences in methodologies, and our incomplete understanding of the biological function of these alleles makes it difficult to further interpret potentially meaningful differences that may be tissue specific.

Studies investigating cancer risk by XRCC1-*R399Q* genotype have not consistently shown evidence of an association. Among Caucasians, there is some evidence that this SNP may decrease risk for nonmelanoma skin cancer (19) and therapy-related acute myeloblastic leukemia (23) and increase risk for melanoma skin cancer (20). Inconsistent results have been found for lung cancer (2, 4, 8, 25, 26) and cancers of the head and neck (13, 14), and there appears to be no effect for bladder cancer (11, 12), prostate cancer (22), or breast cancer (6, 7, 21). The latter study by Duell *et al.* (6) concluded that the relationship between XRCC1-*R399Q* genotype and breast cancer risk might be complicated by other factors. The authors of this study suggest that potential XRCC1 codon 399-dependent risk effects should account for biologically plausible interactions with other genetic and environmental factors because the mechanism by which this SNP functions is unknown at this time and unlikely to be independent of such factors. However, evaluation of the significance of gene-gene and gene-environment interactions in our study as in preceding studies needs to be interpreted with caution but is an important starting point meant to encourage the design of other studies with a larger sample size for relevant subgroups.

Our findings suggest that the effect of the XRCC1-*R399Q* polymorphism on breast cancer risk differs by FH of the disease. The possibility of an interaction between XRCC1-*R399Q* and FH was also explored by Smith *et al.* (21). This study specifically targeted controls with a positive FH and their analyses showed that controls with a FH had a very similar genotype distribution as cases, further supporting the hypothesis that these SNPs may contribute to FH-related susceptibility to breast cancer. A possible interpretation for the presence of such an association in the subgroup with FH may be that FH, particularly first-degree, broadly represents shared genes and environmental factors, and the presence of a single polymorphism, with likely weak effects on the individual's phenotype, may not be measurable except in the context of these supporting factors. Among individuals without a familial predisposition, the effect may be hidden by sum effects of other unidentified genetic and environmental factors.

There were several reasons to investigate other potential gene-environment interactions. Cigarette smoking, alcohol consumption, and IR exposure are associated with the production of free radical intermediates, including hydroxyethyl free radicals and reactive oxygen species that induce base damage and single- and double-strand breaks (42–46), which are corrected in part by the involvement of XRCC1 and XRCC3. Several reports suggest that free radicals and oxidative stress play an important role in the pathogenesis of breast cancer (47). Furthermore, alcohol consumption and IR exposure are known risk factors for the disease and there is some evidence that adolescent smoking could increase risk (48–50). Although this study was unable to show evidence for these gene-environment interactions, other studies agree that these are important hypotheses to examine (51–53) and should be a subject of further research.

This study also investigated a potential interaction between genotypes and BMI. A recently published study showed improved DNA repair capacity in marginally undernourished individuals (low BMI), which the authors suggest may improve longevity by postponing the age-dependent damage to DNA (54). Therefore, we reasoned that there might be a difference when comparing normal weight and overweight individuals by DNA repair genotypes. Our hypothesis was that if either SNP is functional and contributes to a deficient DNA repair phenotype then among individuals with less efficient repair DNA damage (*i.e.*, overweight individuals), the effect of a single SNP may be stronger than among normal weight individuals. Our results provide preliminary evidence for a potential interaction between XRCC3-*T241M* polymorphism and BMI. However, contrary to expectation, normal weight individuals were at an increased risk if they were XRCC3-241 *M/M* carriers compared with XRCC3-241 *T/T* or *T/M* carriers (OR = 2.68, 95% CI = 1.45–4.94), but among overweight or obese individuals, the risk of the disease did not appear to depend on the genotype of this polymorphism.

Our last objective was to investigate a possible joint effect of the SNPs on breast cancer risk considering that base excision repair and double-strand break repair are thought to be involved in coordinated activities. A potential partnership has been supported by evidence showing that base excision repair activity in human and

murine cell extracts closely parallels their levels of endogenous *p53* (55). Evidence for an interaction has also been found in studies of *Schizosaccharomyces pombe* (56). Furthermore, these particular genes, XRCC1 and XRCC3, are both associated with RAD51 (57–59), which is itself associated with the high penetrant breast cancer susceptibility genes, BRCA1 and BRCA2; therefore, there is reason to speculate possible additive effects of these SNPs on disease risk estimates. Indeed, at least one study of breast cancer risk has shown a statistically significant interaction between XRCC1 polymorphism: -*R194W* and XRCC3-*T241M* (21).

The functional differences between alleles has not be entirely understood; consequently, although variants leading to diminished XRCC1 or XRCC3 function may be predicted to confer an increased risk of cancer due to accumulated levels of DNA damage, it is also plausible that these cells may be more likely to undergo apoptosis rendering them potentially protective alleles. Considering that many genes are involved in repair of DNA damage, there is also the possibility that these polymorphisms might be in linkage disequilibrium with other causative factors. Evidence for linkage disequilibrium has been suggested by Duell *et al.* (6). This study found a positive association for XRCC1-399 *Q/Q* and breast cancer only among African American women, pointing to unmeasured genetic and environmental factors as potentially responsible for the observed effect. Another possibility is that the risk associated with specific genotypes analyzed in this study may have been obscured by other factors that could not be accounted for in this study such as those influencing the expression and function of the corresponding DNA repair enzymes. However, for these two SNPs, XRCC1-*R399Q* and XRCC3-*T241M*, there is reason to believe that they may be at least partially related to overall DNA repair functioning as measured by various *in vitro* and *in vivo* assays (32, 33, 51, 52, 60, 61). Other studies have not agreed (62–66), and further studies on the potential functional role of these SNPs in tissue-specific cells are required.

The main concern about our results is the representativeness of the cases and controls. The representativeness of the OFBCR as a population-based registry has been evaluated in two studies (37, 67). The former study by Knight *et al.* (37) examined characteristics such as age, sex, ethnicity, and FH of breast or ovarian cancer in association with response at different stages of the recruitment process for cases diagnosed in 1996. Results showed that women whose ethnicity was not white and men were less likely to participate compared with white women. Furthermore, the response rate at the FH questionnaire stage was lower than expected, but there was no evidence of systematic differences in response according to age and sex. The second study by Mancuso *et al.* (67) investigated potential biases of FH and ethnicity at this stage (*i.e.*, FH questionnaire) among individuals diagnosed in 2001. Similarly, their results showed that those who do not respond to the OFBCR mailed FH questionnaire do not have substantially different genetic or FH profiles than those who do respond but are more likely to be white. Therefore, there is no evidence to suggest that cases are nonrepresentative of Caucasians in spite of losses at each stage of the OFBCR. Furthermore, results from the crude analysis of nongenetic variables were in agreement with the published literature, and genotypes are in Hardy-Weinberg equilibrium and similar to other studies in Caucasians. Another concern may be loses due to death, but survivorship for breast cancer is relatively high and the OFBCR has estimated that only ~2% of potential cases were lost during various recruitment stages. It should also be noted that nongenetic exposures might be misclassified because of recall bias. Reporting factors, such as adolescent smoking and X-ray exposure, alcohol use, and BMI because there is public knowledge of their role in healthy life-style and disease risk, may be influenced by disease status. However, studies that have investigated differential recall between cases and controls have found minimal bias (68).

This study represents an addition to previous published work on XRCC1-*R399Q* and XRCC3-*T241M* and breast cancer. Our findings support the hypothesis that XRCC3-*T241M* may be related to breast cancer susceptibility and suggest that the effect of the XRCC1-*R399Q* polymorphism differs by FH of the disease. In comparison with the other two population-based case-control studies of breast cancer by Duell *et al.* (6) and Kuschel *et al.* (29), our results are in complete agreement. This study provides further support for the role of SNPs in modifying the effects of other factors such as FH and possibly BMI. We suggest that improving our measurements of relevant exposures to account for interactions so that future studies can better assess gene-exposure effects may be an important goal.

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Polymorphisms XRCC1-*R399Q* and XRCC3-*T241M* and the Risk of Breast Cancer at the Ontario Site of the Breast Cancer Family Registry

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