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Nucleotide excision repair polymorphisms may modify ionizing radiation-related breast cancer risk in US radiologic technologists

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Abstract

Exposure to ionizing radiation has been consistently associated with increased risk of female breast cancer. Although the majority of DNA damage caused by ionizing radiation is corrected by the base-excision repair pathway, certain types of multiple-base damage can only be repaired through the nucleotide excision repair pathway. In a nested case–control study of breast cancer in US radiologic technologists exposed to low levels of ionizing radiation (858 cases, 1,083 controls), we examined whether risk of breast cancer conferred by radiation was modified by nucleotide excision gene polymorphisms *ERCC2 (XPD)* rs13181, *ERCC4 (XPF)* rs1800067 and rs1800124, *ERCC5 (XPG)* rs1047769 and rs17655; and *ERCC6* rs2228526. Of the 6 *ERCC* variants examined, only *ERCC5* rs17655 showed a borderline main effect association with breast cancer risk (OR_{GC} = 1.1, OR_{CC} = 1.3; *p*-trend = 0.08), with some indication that individuals carrying the C allele variant were more susceptible to the effects of occupational radiation (EOR/Gy_{GG} = 1.0, 95% CI = <0, 6.0; EOR/$Gy_{GC/CC}$ = 5.9, 95% CI = 0.9, 14.4; p_{het} = 0.10). *ERCC2* rs13181, although not associated with breast cancer risk overall, statistically significantly modified the effect of occupational radiation dose on risk of breast cancer (EOR/Gy_{AA} = 9.1, 95% CI = 2.1–21.3; EOR/$Gy_{AC/CC}$ = 0.6, 95% CI = <0, 4.6; p_{het} = 0.01). These results suggest that common variants in nucleotide excision repair genes may modify the association between occupational radiation exposure and breast cancer risk.

Exposure to ionizing radiation causes various types of damage to DNA,[1] and has been associated with increased risk of female breast cancer in several populations, including atomic bomb survivors, medically exposed populations and occupationally exposed cohorts.[2] The vast majority of DNA damage caused by ionizing radiation is corrected by the base-excision repair pathway. However, less common types of DNA damage from exposure to radiation, such as the formation of 5′,8-purine cyclodeoxynucleosides or malondialdehyde, can only be repaired through the nucleotide excision repair pathway.[1, 3]

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Additionally, recent evidence suggests that nucleotide excision repair may be involved in the repair of other types of oxidized DNA damage products, including O6-methylguanine, thymine glycol and the baseless sugar (AP site).[4–6]

We used data from a nationwide cohort of US radiologic technologists exposed to low levels of ionizing radiation from occupational sources, and personal medical diagnostic/therapeutic procedures to examine whether radiation-related risk of breast cancer was modified by single nucleotide polymorphisms in the nucleotide excision genes *ERCC2 (XPD*), *ERCC4 (XPF*), *ERCC5 (XPG*) and *ERCC6*. The detailed assessment of breast radiation dose in this study uniquely positioned us to be able to detect gene-radiation effects. This is the first study to our knowledge to evaluate the joint effects of polymorphisms in the nucleotide excision repair pathway and low-dose exposure to radiation.

METHODS

The study population, radiation dosimetry and blood specimen collection have been described in detail elsewhere.[7, 8] Study methods are briefly summarized below.

Study population

In 1982, the U.S. National Cancer Institute, in collaboration with the University of Minnesota and the American Registry of Radiologic Technologists, initiated a study of cancer incidence and mortality among 146,022 (106,953 female) U.S. radiologic technologists certified for at least 2 years between 1926 and 1982. During the years 1983–1989 and 1994–1998, surveys were mailed to all eligible cohort members to collect detailed information on work history as a radiologic technologist, family history of cancer, reproductive history, height, weight, other cancer risk factors (such as alcohol and tobacco use) and information regarding health outcomes, including breast cancer. 69,524 (71%) and 69,998 of 94,508 (74%) of female technologists known to be alive at the time of survey responded to the first and second surveys, respectively. This study has been approved annually by the human subjects review boards of the National Cancer Institute and the University of Minnesota.

Case and control recruitment

All living female technologists reporting a primary breast cancer (ductal carcinoma *in situ* or invasive breast cancer) confirmed by pathology or medical records were eligible to be cases. 1,386 prevalent breast cancer cases (year of diagnosis 1955–1998) were known to be alive at the start of biospecimen collection in December 1996. By the end of December 2003, 874 (63%) breast cancer cases had provided informed consent and a blood sample, and had completed a telephone interview collecting updated information on cancer risk factors, family history of cancer and selected work history characteristics. Female controls identified from the URST cohort were frequency matched to cases (ratio 1.5:1) by birth year in 5 year strata. Of 2,268 living controls identified, 1,094 (48%) provided informed consent, a blood sample and completed a telephone interview. Participation details, nonresponder and responder characteristics, and comparisons with decedents have been published previously,[7, 8] and did not reveal any meaningful differences. For both cases and controls the proportion of African-Americans was lower among participants than nonparticipants, slightly more participants used birth control pills, and participants were more likely to be from the Midwest than the Northeast US. Nonparticipants and decedents did not differ from participants when comparing education, marital status, personal diagnostic ionizing radiation exposure, alcohol consumption, age at menarche, menopausal status, age at first live birth and number of live births.

Sample handling

Following venipuncture, whole blood samples were shipped on ice overnight to the processing laboratory in Frederick, MD. Blood components were separated and DNA was extracted using Qiagen Kits (Qiagen, Valencia, CA). Samples were tracked by a unique ID code, and laboratory investigators were blinded to case–control status. After exclusion of samples with biospecimen contamination ($n = 12$), inadequate biospecimen quantity ($n = 12$) and incomplete survey data ($n = 2$), the final sample size consisted of 859 cases and 1,083 controls.

Selection of candidate SNPs and sample genotyping

Candidate SNPs in the nucleotide excision pathway were selected based on a minor allele frequency >0.05, potential functional significance based on amino acid substitution or location in promoter regions or splice sites, and results of previous epidemiologic studies. Samples were genotyped using standard TaqMan or MGB Eclipse assays. Genotyping methods for specific SNPs can be found at http://www.snp500cancer.nci.nih.gov.[9] One hundred fifteen quality control samples composed of between 9 and 14 replicate samples from the same 10 individuals were embedded randomly in the sample trays. All laboratory personnel were blinded to the location of the replicates. Percent replication was 100% for each of the 6 SNP assays, and the sample completion rate ranged from 96.0% for ERCC6 (rs2228526) to 99.6% for ERCC5 (rs1047769). Hardy-Weinberg equilibrium (HWE) among controls was assessed using χ^2 or Fisher's exact test. Allele frequencies in controls did not deviate from expectation based on HWE except for *ERCC6* rs2228526 ($p = 0.01$).

Occupational and personal diagnostic ionizing radiation exposure

The occupational dosimetry system used to estimate absorbed dose to the breast (in units of Gray/Gy) has been described in detail elsewhere,[10, 11] but included some refinements for this work. As before, individuals without monitoring badge readings were assigned yearly doses using simulation techniques from probability distributions describing the plausible range of exposures. However, for the current study, the probability distributions that describe the variability in doses received in a given year were partitioned, where possible, into narrower distributions based on work history data, with the key determinants being calendar year of work, and use of protective shielding. Yearly breast doses were derived from real or simulated badge doses by applying dose conversion factors and were summed to estimate a cumulative occupational breast dose for each person. Doses up to 10 years prior to breast cancer diagnosis for cases and for an equivalent time point for controls were excluded. A 10-year lag for exposure was chosen because this is a generally accepted latency period for solid cancers following ionizing radiation exposure.[1, 12, 13] The occupational radiation doses are summarized in Table I.

Cumulative personal medical radiation exposure was estimated using data from the 2 surveys mailed to the cohort. Self-reported number and calendar time periods of diagnostic X-ray procedures were used to calculate a cumulative breast dose score as an approximation of organ dose. Although the breast dose score is an approximation of dose in Gy, the term "cumulative breast dose score" rather than "breast dose" is used to reflect uncertainties in recall of various procedures and uncertainties with the nominal per procedure dose estimates.[14] Procedures occurring less than or equal to 10 years prior to breast cancer diagnosis for cases and an equivalent time period for controls were excluded from the cumulative score in order to minimize potential bias from procedures performed because of preclinical disease symptoms.

Statistical analysis

Associations between individual SNPs and breast cancer were evaluated using unconditional logistic regression, adjusted for year of birth. For each SNP, the rare allele among controls was considered the variant allele. When less than 2% of the controls were homozygous variant, heterozygous subjects and homozygous variants were combined into one category. Tests for trend were conducted assuming a log-additive model for genotype.

Main effects of occupational breast dose and personal diagnostic radiation breast dose score were assessed by modeling the odds ratio as a linear function in logistic regression models:

$$\mathrm{OR}=1+\beta \times D$$

where D is continuous radiation dose and β is the excess odds ratio (EOR) per unit dose (Gy) or dose score. Estimated doses of occupational radiation and personal diagnostic radiation were adjusted for each other.

To evaluate whether SNPs modified the relation between radiation and breast cancer risk, we allowed the radiation-related EOR to vary by genotype while adjusting for the genotype effect. EOR heterogeneity across genotype categories was assessed using likelihood ratio tests (LRT). Since some genotype categories contained small numbers of individuals, dose-response estimates were sometimes less than zero. In these instances the estimates were denoted as "< 0". To avoid unstable estimates caused by cells with few individuals, heterozygous and homozygous variant subjects were combined for the purposes of the interaction analyses. All regression models were adjusted for year of birth, and occupational radiation and personal diagnostic radiation dose score were adjusted for each other. Adjustment for cigarette smoking, alcohol consumption, age at menarche, number of live births, age at first birth, family history of breast cancer, history of benign breast disease, oral contraceptive use, hormonal replacement therapy, body mass index and height did not substantially change genotype or radiation main effect estimates or radiation effect estimates stratified by genotype, so these variables were not included in the final models. Confidence intervals for genotype risk were calculated based on the Wald test, and those for radiation risk were calculated using the LRT test. EPICURE software (Hirosoft, Seattle, WA) was used for linear dose-response analyses, and SAS software (SAS Institute, Cary, North Carolina, Release 8.02) was used for all other analyses.

RESULTS

Selected demographic and ionizing radiation exposure characteristics are summarized in Table I. Cases were more likely than controls to have a previous history of radiation therapy. In linear dose-response analyses, we found that breast cancer risk increased significantly with increasing cumulative occupational breast radiation dose (EOR/Gy = 3.0, 95% CI = 0.04–7.8, $p = 0.046$), but risk was not associated with personal diagnostic breast radiation dose score (EOR/Gy = 1.3, 95% CI = − 0.4 to 4.0, $p = 0.3$). The 2 sources of radiation exposure were uncorrelated ($r^2 = 0.02$).

Of the 6 *ERCC* variants examined, only *ERCC5* rs17655 showed a borderline main effect association with breast cancer risk ($OR_{GC} = 1.1$, $OR_{CC} = 1.3$; p-trend = 0.08) (Table II). There was some suggestion that individuals carrying the C allele variant of this SNP were more susceptible to the effects of occupational radiation, although the p-value for heterogeneity was not statistically significant ($EOR/Gy_{GG} = 1.0$, 95% CI = <0, 6.0; $EOR/Gy_{GC/CC} = 5.9$, 95% CI = 0.9, 14.4; $p_{het} = 0.10$, Table III). Although there was no main effect of *ERCC2* rs13181 on breast cancer risk, this SNP statistically significantly modified

the effect of occupational radiation dose on risk of breast cancer (EOR/Gy_{AA} = 9.1, 95% CI = 2.1– 21.3; $EOR/Gy_{AC/CC}$ = 0.6, 95% CI = <0, 4.6; p_{het} = 0.01). The pattern in risk was similar for personal diagnostic radiation, although the *p*-value for effect modification was not statistically significant.

DISCUSSION

Although the vast majority of DNA damage caused by ionizing radiation is corrected by the base-excision repair pathway, nucleotide excision repair may be important for less common types of DNA damage, such as formation of 5′,8-purine cyclodeoxynucleosides, malondialdehyde and other types of oxidative DNA damage.[1, 3–6] This is the first study to our knowledge to evaluate the joint effects of polymorphisms in the nucleotide excision repair pathway and low-dose exposure to radiation. The detailed assessment of breast radiation dose in this nested-case control study of breast cancer uniquely positioned us to be able to detect gene-radiation effects. We found suggestive evidence that the C allele variant of *ERRC5 (XPG*) rs17655 was associated with increased risk of breast cancer overall, and may increase susceptibility to breast cancer in radiologic technologists exposed to low levels of ionizing radiation. While our borderline finding of increased risk with rs17655 is consistent with suggestive evidence of decreased DNA repair capacity in breast cancer cases with the C allele variant,[15] previous epidemiologic studies have been inconsistent; reporting significant evidence,[16] borderline evidence,[17] or no evidence[18, 19] of increased risk with the C variant. No previous studies have examined the interaction of the *ERRC5* rs17655 polymorphism with exposure to ionizing radiation.

Although suboptimal DNA repair has been reported for individuals with the C allele variant of *ERCC2 (XPD*) rs13181, and previous epidemiologic studies have observed a modest increase of borderline significance with the C allele,[17, 20, 21] we observed no main effect for the rs13181 polymorphism. However, we did find that *ERCC2 (XPD*) rs13181 modified the risk of breast cancer associated with occupational radiation, with the association between radiation and breast cancer risk being limited to individuals with the AA wild-type variant.

In this study of primarily female workers, we examined the interaction between low-dose radiation exposure and variants in the nucleotide excision repair pathway with regard to risk of breast cancer. Comparison of demographic characteristics did not reveal significant differences between participants and nonparticipants, and variants were not associated with participation in a questionnaire survey in this cohort.[22] Limitations of this study include the use of prevalent rather than incident breast cancer cases, and low power to detect effect modification for rare variants. Additionally, given that the majority of the cohort was exposed at low doses of ionizing radiation exposure, we could not assess effects at high doses of ionizing radiation. For these reasons, and because the role of nucleotide excision repair in correcting DNA damage induced by ionizing radiation is still not well understood, the associations observed here need to be confirmed in other studies with well-characterized exposure to radiation. Future studies should include additional genes in the nucleotide excision pathway, as well as more detailed coverage of SNPs in the genes studied here.

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TABLE I

DEMOGRAPHIC AND IONIZING RADIATION EXPOSURE VARIABLE DISTRIBUTIONS AMONG BREAST CANCER CASES AND CONTROLS. US RADIOLOGIC TECHNOLOGISTS STUDY, 1984–1998

Characteristic	Cases (%) (*n* = 859)	Controls (%) (*n* = 1083)	*p*-value[1]
Ethnicity			
Caucasian	842 (98)	1048 (97)	0.2
African American	9 (1)	18 (2)	
Other	8 (1)	17 (2)	
Year of birth			
≤ 1925	120 (14)	138 (13)	0.9
1926–1935	195 (23)	249 (23)	
1936–1945	292 (34)	382 (35)	
> 1945	252 (29)	314 (29)	
Occupational ionizing radiation breast dose (Gy)			
0 to 0.05	687 (80)	894 (83)	0.2
>0.05 to 0.1	90 (10)	100 (9)	
>0.1 to 0.2	63 (7)	76 (7)	
>0.2	19 (2)	13 (1)	
Personal diagnostic radialion breast dose score			
0 to 0.05	686 (80)	908 (84)	0.1
>0.05 to 0.1	106 (12)	104 (10)	
>0.1 to 0.2	46 (5)	51 (5)	
>0.2	21 (2)	20 (2)	
Radionuclide procedures			
Never	721 (84)	937 (87)	0.3
Ever	65 (8)	71 (7)	
Unknown	73 (9)	75 (7)	
Personal radiation therapy			
Never	803 (94)	1021 (94)	0.01
Ever	24 (3)	14 (1)	
Unknown	32 (4)	48 (4)	
Smoking			
Never	394 (46)	506 (47)	0.8
Former	172 (20)	204 (19)	
Current	263 (31)	343 (32)	
Unknown	30 (3)	30 (3)	

[1] x^2 test.

TABLE II

AGE-ADJUSTED ASSOCIATIONS BETWEEN NUCLEOTIDE EXCISION REPAIR POLYMORPHISMS AND BREAST CANCER RISK IN US RADIOLOGIC TECHNOLOGISTS, 1984–1998

Gene	Entrez SNP ID[1]	AA variant	Genotype	Cases (*n* = 858)	Controls (*n* = 1083)	Multivariate[2]			
						OR	95% CI		*p*-trend
ERCC2	rs13181	K751Q	AA	342 (41%)	428 (40%)				0.7
			AC	377 (45%)	494 (46%)	1.0	0.8	1.2	
			CC	120 (14%)	158 (15%)	1.0	0.7	1.3	
ERCC4	rs1800067	R415Q	GG	714 (85%)	922 (86%)				0.6
			GA/AA	124 (15%)	147 (14%)	1.1	0.8	1.4	
ERCC4	rs1800124	E875G	AA	792 (96%)	1044 (97%)				0.9
			AG	29 (4%)	27 (3%)	1.0	0.6	1.7	
ERCC5	rs1047769	M254V	AA	792 (93%)	1011 (93%)				0.6
			AG/GG	60 (7%)	71 (7%)	1.1	0.8	1.5	
ERCC5	rs17655	D1104H	GG	482 (59%)	674 (62%)				0.08
			GC	288 (35%)	352 (33%)	1.1	0.9	1.4	
			CC	49 (6%)	53 (5%)	1.3	0.9	2.0	
ERCC6	rs2228526[3]	M1097V	AA	510 (65%)	704 (66%)				0.6
			AG	241 (31%)	312 (29%)	1.1	0.9	1.3	
			GG	39 (5%)	54 (5%)	1.0	0.7	1.5	

[1] Entrez SNP reference ID number (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp).

[2] Adjusted for year of birth.

[3] HWE *p*-value in controls = 0.01.

TABLE III

ANALYSIS OF INTERACTION BETWEEN NUCLEOTIDE EXCISION REPAIR SNPS, OCCUPATIONAL BREAST RADIATION DOSE AND PERSONAL DIAGNOSTIC X-RAYS DOSE-SCORE, AND BREAST CANCER RISK IN US RADIOLOGIC TECHNOLOGISTS

Gene	Entrez SNP ID[1]	AA or nt variant ID[2]	Genotype	Occupational radiation effect modification			Diagnostic radiation effect modification		
				EOR/Gy[3]	95% CI	*p*-value[4]	EOR/unit breast dose score[3]	95% CI	*p*-value[4]
ERCC2	rs13181	K751Q	AA	9.1	2.1, 21.3	0.01	1.9	<0, 7.6	>0.5
			AC/CC	0.6	<0, 4.6		0.7	<0, 4.2	
ERCC4	rs1800067	R415Q	GG	4.5	0.8, 10.4	0.07	1.8	<0, 5.2	0.4
			GA/AA	<0	<0, 4.8		<0	<0, 5.9	
ERCC4	rs1800124	E875G	AA	2.8	<0, 7.7	>0.5	1.3	<0, 4.3	0.3
			AG	4.9	<0, 69.2		<0	<0, 11.7	
ERCC5	rs1047769	M254V	AA	3.6	0.3, 9.1	0.2	1.7	<0, 4.9	0.08
			AG/GG	<0	<0, 7.5		<0	<0, 2.3	
ERCC5	rs17655	D1104H	GG	1.0	<0, 6.0	0.1	0.9	<0, 4.7	>0.5
			GC/CC	5.9	0.9, 14.4		1.8	<0, 6.8	
ERCC6	rs2228526	M1097V	AA	4.7	0.6, 11.7	0.2	2.1	<0, 6.3	0.2
			AG/GG	1.1	<0, 7.3		<0	<0, 3.6	

[1] Entrez SNP reference ID number (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=snp).

[2] Amino acid sequence variation (regular font), nucleotide sequence variation (italics).

[3] Excess Odds Ratio (OR = 1 + EOR), adjusted for year of birth and occupational or personal diagnostic radiation dose.

[4] Likelihood ratio test comparing the genotype specific EOR. Because of the small numbers of individuals in some genotype categories, dose-response relationships were sometimes estimated as being below zero.