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Polymorphisms in oxidative stress and inflammation pathway genes, low-dose ionizing radiation, and the risk of breast cancer among US radiologic technologists

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Abstract

Objective—Ionizing radiation, an established breast cancer risk factor, has been shown to induce oxidative damage and chronic inflammation. Polymorphic variation in oxidative stress and inflammatory-mediated pathway genes may modify radiation-related breast cancer risk.

Methods—We estimated breast cancer risk for 28 common variants in 16 candidate genes involved in these pathways among 859 breast cancer cases and 1,083 controls nested within the US Radiologic Technologists cohort. We estimated associations between occupational and personal diagnostic radiation exposures with breast cancer by modeling the odds ratio (OR) as a linear function in logistic regression models and assessed heterogeneity of the dose–response across genotypes.

Results—There was suggestive evidence of an interaction between the rs5277 variant in *PTGS2* and radiation-related breast cancer risk. The excess OR (EOR)/Gy from occupational radiation exposure = 5.5 (95%CI 1.2–12.5) for the GG genotype versus EOR/Gy < 0 (95%CI < 0–3.8) and EOR/Gy < 0 (95%CI < 0–14.8) for the GC and CC genotypes, respectively, ($p_{\text{interaction}} = 0.04$). The association between radiation and breast cancer was not modified by other SNPs examined.

Conclusions—This study suggests that variation in *PTGS2* may modify the breast cancer risk from occupational radiation exposure, but replication in other populations is needed to confirm this result.

Keywords

PTGS2; COX-2; Inflammation; Breast cancer; Radiation

Introduction

Ionizing radiation causes DNA damage via the formation of reactive oxygen species [1]. Exposure to ionizing radiation has also been associated with long-term perturbations of the immune system, including persistently elevated levels of inflammatory markers [2–4]. Chronic inflammation is associated with an increased risk of cancer through hypothesized mechanisms including oxidative damage and aberrant cell cycle control [5,6]. We hypothesized that breast cancer risk associated with ionizing radiation exposure may be modified by polymorphic variation in genes involved in oxidative stress and inflammatory-mediated pathways but few studies have both the dosimetry and the genotype information necessary to examine this question. We evaluated this hypothesis in a nationwide cohort of US radiologic technologists (USRT) who have been exposed to protracted low-dose ionizing radiation from occupational sources and from personal medical radiologic procedures.

Materials and methods

The study population, radiation dose reconstruction, and blood specimen collection have been described in detail previously [7–11]. A brief summary of the study methods is provided below.

Study population

In the early 1980s, the National Cancer Institute, in collaboration with the University of Minnesota and the American Registry of Radiologic Technologists (ARRT), initiated the USRT study, which includes 146,022 (106,953 female) US radiologic technologists who were certified by the ARRT for at least 2 years between 1926 and 1982. Two postal surveys were mailed to all eligible participants during the years 1983–1989 and 1994–1998 to collect detailed information related to occupational history, family history of cancer, reproductive history, other cancer risk factors (e.g., alcohol and tobacco use), and information about breast cancer and other health outcomes [7]. Annual approval to contact cohort subjects was obtained from the human subjects review boards of the National Cancer Institute and the University of Minnesota.

Case and control recruitment

All living female technologists who reported a primary breast cancer on the first or second questionnaire that was confirmed as a ductal carcinoma in situ tumor or invasive breast cancer by pathology or medical records were eligible for inclusion in the case-control study. When biospecimen collection began in December 1999, there were 1,386 living (prevalent) breast cancer cases diagnosed between 1955 and 1998. By the end of December 2003, 874 (63%) of the women with breast cancer had provided informed consent, a blood sample, and had completed a telephone interview that updated information on cancer risk factors, family cancer history, and selected work history information.

Eligible controls included living female technologists who had completed at least one of the two questionnaires and reported no previous breast cancer diagnosis. Controls were randomly selected from among those who matched cases (ratio 1.5:1) according to birth year in 5-year strata. Of 2,268 living controls selected, 1,094 (48%) provided informed consent and a blood sample and completed a telephone interview.

Sample collection and handling

Following venipuncture, whole blood samples were shipped on ice overnight to the processing laboratory where blood components were separated and DNA was extracted using Qiagen Kits (Qiagen, Valencia, CA). A unique ID code was used to track samples and laboratory personnel were blinded to case-control status. The final analytic sample consisted of 859 cases and 1,083 controls after exclusion of samples with contamination ($n = 12$), inadequate quantity ($n = 12$), or incomplete survey data ($n = 2$).

Genotyping

A total of 28 common variants were selected from 16 candidate genes. Common genetic variants were selected a priori based on a minor allele frequency of greater than 5% in the SNP500Cancer database (<http://snp500cancer.nci.nih.gov>), and previous associations with cancer outcomes, plausible relationship with breast cancer, or potential for modifying the relationship of ionizing radiation with breast cancer risk. Genotype analysis was performed using optimized TaqMan assays and analyzed on the ABI 7900HT platform (ABI, Foster City, CA). A description of genotyping methods is available on the SNP500Cancer website (<http://snp500cancer.nci.nih.gov>) [12]. A blinded duplicate analysis of 10% of study samples demonstrated greater than 99% concordance.

Occupational and personal diagnostic ionizing radiation exposure

A detailed description of the occupational dosimetry system used to estimate absorbed dose to the breast (in units of Gy) has been described previously [8,9]. Archival film badge measurements for monitoring of occupational exposures to ionizing radiation were obtained

for USRT study participants. Numerical simulation techniques using probability distributions to model dose-related parameters supplemented those data in order to derive estimates of yearly badge doses for individuals without badge readings. Annual breast doses were derived from badge doses using organ dose conversion coefficients that accounted for energy range and protection by lead aprons (where applicable) and were summed to derive a cumulative occupational breast dose for each person. We excluded doses within the 10 years prior to breast cancer diagnosis for cases and within an equivalent time period for controls. The 10-year lag for radiation exposure is an accepted latency period for solid cancers, including breast cancer [13–15].

Cumulative personal diagnostic medical radiation exposure was estimated using data obtained from the 1983–1989 and 1994–1998 mailed surveys. Self-reported numbers of diagnostic X-ray procedures and the calendar time periods when the examinations were received were used to calculate a cumulative breast dose score as an approximation of breast dose [10]. We excluded medical procedures involving radiation exposure within the 10 years prior to breast cancer diagnosis for cases and an equivalent time point for controls from the cumulative score as a lag period to minimize potential bias from diagnostic procedures performed because of pre-clinical disease symptoms [16]. The breast dose score is an approximation of Gy but due to greater uncertainties in recall of various procedures and uncertainties with the nominal per procedure dose estimates and variation in imaging mechanics over time and within individual hospitals and clinics, we were hesitant to imply any increased precision, and therefore it seemed preferable to call this “cumulative breast dose score,” maintaining a separation from the occupational dosimetry. Accuracy of self-report of personal diagnostic medical radiation exposures to the red bone marrow has been validated previously among US radiologic technologists in a separate effort [17]. Other personal medical radiation exposures including radionuclide procedures and radiation therapy were classified as “ever/never” variables. They were not included in the personal diagnostic X-ray breast score.

Statistical analysis

We examined departure from Hardy–Weinberg proportions among controls for each locus. To examine the association between a given SNP and breast cancer risk, we estimated the odds ratio (OR) and 95% confidence intervals (CI) using unconditional logistic regression. The rare allele among controls was considered the variant allele for each SNP. If the homozygous variant frequency of a given SNP among controls was <2%, the homozygous variant and heterozygous genotypes were combined for analysis. Tests for trend were conducted assuming a log-additive model for genotype.

The breast cancer risk associated with occupational breast dose and personal diagnostic radiation breast dose score was assessed by modeling the OR as a linear function of dose in logistic regression models:

$$OR = 1 + \beta \times D$$

where D is continuous radiation dose and β is the excess odds ratio (EOR) per unit dose (Gy, for occupational dose) or dose score (for personal diagnostic medical exposure).

To evaluate whether SNPs modified the association 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 and are denoted as

"<0". All regression models were adjusted for year of birth, and occupational radiation dose and personal diagnostic radiation dose score were adjusted for each other. Adjusting for exposure from radiation and radionuclide therapies had little effect on the estimated risks from occupational and personal diagnostic X-ray exposures. Additional potential confounders (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, height, alcohol consumption, and cigarette smoking) were examined but were not retained in the final model because they did not substantially alter the estimates. A two-tailed p -value ≤ 0.05 was considered statistically significant.

Confidence intervals for genotype risk estimates were Wald based, while confidence intervals for radiation risk estimates were derived from the profile likelihood method. Whereas the ORs are statistically significant when the confidence interval excludes 1.0, EOR estimates are statistically significant when the confidence interval excludes zero. We used EPICURE software (Hirosoft, Seattle, WA) for linear dose–response analyses and SAS software (SAS Institute, Cary, North Carolina, Release 8.02) for all other analyses.

Results

The distributions of selected demographic characteristics and radiation exposure are presented in Table 1. Cases were more likely than controls to have had a previous history of radiation therapy. Breast cancer risk increased significantly with increasing cumulative occupational radiation absorbed dose to the breast after adjustment for birth year and personal diagnostic radiation breast dose score (EOR/Gy = 3.0, 95%CI 0.04–7.8; $p = 0.046$). The association between personal diagnostic radiation breast dose score and breast cancer risk was not statistically significant (EOR/Gy = 1.3, 95%CI –0.4–4.0; $p = 0.3$). The two sources of radiation exposure were not significantly correlated ($r^2 = 0.02$).

The associations between oxidative stress and inflammatory-mediated pathway SNPs and breast cancer risk, adjusted for birth year, are presented in Table 2. Few SNPs were associated with breast cancer risk. The TC (OR = 0.8, 95%CI 0.6–0.9) and CC (OR = 0.8, 95%CI 0.6–1.0) genotypes of rs5275 in *PTGS2* were associated with a reduced risk of breast cancer compared with the TT genotype ($p_{\text{trend}} = 0.01$). Haplotype analyses did not provide information beyond that obtained from single SNP analysis (not shown). Women with the TT genotype of rs1143634 in *IL1B* had an increased risk of breast cancer compared with the CC genotype (OR = 1.5, 95%CI 1.0–2.2; $p_{\text{trend}} = 0.05$). Compared with the CC genotype, the TT genotype of rs2070874 in *IL4* conferred a reduced risk of breast cancer (OR = 0.5, 95%CI 0.3–1.0; $p_{\text{trend}} = 0.03$). Other SNPs for which an association with breast cancer risk was suggested included rs2243250 in *IL4* and rs1800896 in *IL10*, but the p -values for the log-additive models were not statistically significant.

We evaluated whether any of the SNPs modified the association between occupational radiation dose or personal diagnostic breast score and breast cancer risk in models that adjusted for birth year, genotype main effect, and the other source of radiation (Table 3). With the exception of the rs5277 SNP in *PTGS2*, most SNPs showed little evidence of interaction. The EOR/Gy from occupational radiation exposure was 5.5 (95%CI 1.2–12.5) for the GG genotype compared with EOR/Gy < 0 (95%CI < 0–3.8) and EOR/Gy < 0 (95%CI < 0–14.8) for the GC and CC genotypes, respectively ($p_{\text{interaction}} = 0.04$). A similar pattern was observed for diagnostic radiation exposure, where the EOR/unit breast dose score for the GG genotype was 1.9 (95%CI < 0–5.7) compared with EOR/unit breast dose score = 0.4 (95%CI < 0–6.4) and EOR/unit breast dose score = 0.1 (95%CI < 0–18.8) for the GC and CC genotypes, respectively; however, the p -value for interaction was >0.5. Effect modification was also observed for rs1799983 ($p_{\text{interaction}} = 0.02$) and rs1549758 ($p_{\text{interaction}}$

= 0.04) in the *NOS3* gene, but the patterns were discordant between occupational and diagnostic radiation exposures.

Discussion

In this large case–control study nested within the USRT cohort, there was evidence of interaction between occupational radiation exposure and the rs5277 variant in *PTGS2*. The EOR/Gy was higher among women with the common GG genotype compared with the heterozygous GC or homozygous rare CC genotypes. A similar radiation breast cancer dose–response pattern was apparent for personal medical radiation exposure in that EOR/unit breast score was higher among women with the common GG genotype, but the relationship did not reach statistical significance. Except for the suggestive interaction with *PTGS2* (rs5277), we did not find that common variation in selected genes involved in inflammation and oxidative stress modified the radiation breast cancer risk relationship.

Consistent with previous studies [18–20], few of the SNPs examined were associated with breast cancer risk independent of radiation. Although the reduced risk of breast cancer among the TC and CC genotypes of the rs5275 variant in *PTGS2* compared with the TT genotype was reported in another case–control study [21], it was not confirmed by a meta-analysis of nine studies [20] or the Breast and Prostate Cancer Cohort Consortium [19]. Previous studies have not, however, evaluated these SNPs as potential effect modifiers of ionizing radiation. There is mounting concern over long-term health risks associated with increased exposures of the general population to medical sources of ionizing radiation [22,23]. Studies such as ours that evaluate genetic modification of radiation-related breast cancer risk can potentially contribute to the identification of susceptible sub-populations or additional genetic pathways of radiation action.

The *PTGS2* gene encodes the cyclooxygenase-2 (COX-2) enzyme which is elevated in a substantial proportion of invasive breast tumors, with some evidence of variation by hormone receptor status [24]. COX-2 converts arachidonic acid into prostaglandins; prostaglandin-driven production of inflammatory cytokines can lead to oxidative damage [6]. Prostaglandins have also been associated with increased aromatase expression in human and animal breast tissue studies [24]. Aromatization of androgens to estrogens constitutes the main source of endogenous estrogens in post-menopausal women. Animal studies also suggest that COX-2 promotes angiogenesis and inhibits apoptosis [24]. Ionizing radiation exposure has been shown to increase short-term COX-2 expression in vitro [25–27]. SNP variability in *PTGS2* may modify the radiation–COX-2 association.

A potential limitation of this study was the use of prevalent cases. Inclusion of prevalent cases could potentially distort the association estimated between the risk of breast cancer according to genotype and radiation exposure if any of these SNPs or radiation exposure were associated with breast cancer survival. It is reassuring, however, that analysis of allele frequencies over time showed no significant trends or differences (data not shown). This suggests that none of the genotypes were associated with breast cancer survival. With respect to radiation, analyses based on the atomic bomb survivors do not suggest that survival time varies by radiation exposure [28]. We also had limited power to detect interactions between rare variant alleles and radiation exposures as indicated by the wide confidence intervals for the estimated EORs/Gy stratified by genotype. Pooling data from this study together with other datasets that have both genotype and radiation data may offer an opportunity to evaluate gene by radiation interactions in a larger sample and thus obtain more precise estimates, thereby reducing the potential for missing interactions that might exist. While participation in the nested case–control study was 63% for cases and 48% for controls, it is reassuring that comparison of demographic characteristics between responders,

non-responders, and decedents did not reveal any meaningful differences [10,11]. Similarly, no evidence of an association between genotype and questionnaire response status has been previously demonstrated in this study population [29]. As this analysis was exploratory, results were not adjusted for multiple comparisons. Therefore, our findings of effect modification between the rs5277 SNP in *PTGS2* and radiation may be due to chance. Similarly, we cannot exclude the possibility that the main effects observed for rs5275 in *PTGS2*, rs2070874 in *IL4*, and rs1143634 in *IL1B* may have been chance findings, particularly as the literature does not provide strong evidence of associations for these SNPs with breast cancer [18–20].

A major strength of this study is the detailed characterization of occupational radiation dose to the breast [8]. The cumulative occupational breast dose and diagnostic radiation breast scores derived from questionnaire data [10] have been substantiated using biodosimetry assessing exposure to the red bone marrow [9,17]. The dosimetry, combined with the availability of genotype information, provides a unique opportunity to evaluate potential gene–radiation effects.

In summary, this study suggests that a variant in the *PTGS2* gene may modify the breast cancer risk from occupational radiation exposure. Given the potential role of chance, however, replication of this analysis in other study populations is needed to confirm this result.

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Table 1

Demographic and ionizing radiation exposure variable distributions among breast cancer cases and controls, US Radiologic Technologists study

Characteristic	Cases (%) (n = 859)	Controls (%) (n = 1,083)	p-value ^a	p-trend ^b
Ethnicity				
Caucasian	842 (98)	1,048 (97)	0.2	NA ^c
African American	9 (1)	18 (2)		
Other	8 (1)	17 (2)		
Year of birth				
≤1925	120 (14)	138 (13)	0.9	0.7
1926–1935	195 (23)	249 (23)		
1936–1945	292 (34)	382 (35)		
>1945	252 (29)	314 (29)		
Cumulative occupational ionizing radiation breast dose (Gy)				
0 to 0.05	687 (80)	894 (83)	0.2	0.1
>0.05 to 0.1	90 (10)	100 (9)		
>0.1 to 0.2	63 (7)	76 (7)		
>0.2	19 (2)	13 (1)		
Cumulative personal diagnostic radiation breast dose score				
0 to 0.05	686 (80)	908 (84)	0.1	0.05
>0.05 to 0.1	106 (12)	104 (10)		
>0.1 to 0.2	46 (5)	51 (5)		
>0.2	21 (2)	20 (2)		
Personal radionuclide procedures				
Never	721 (84)	937 (87)	0.3	NA
Ever	65 (8)	71 (7)		
Unknown	73 (9)	75 (7)		
Personal radiation therapy				
Never	803 (94)	1,021 (94)	0.01	NA
Ever	24 (3)	14 (1)		
Unknown	32 (4)	48 (4)		

^a Chi-square test

^b Mantel–Haenszel trend test

^c Not applicable

Table 2

Birth year-adjusted associations between oxidative stress and inflammatory-mediated pathway polymorphisms and breast cancer risk in the US Radiologic Technologists Study

Gene	Entrez SNP ID ^a	Genotype	Cases (%) (n = 859)	Controls (%) (n = 1,083)	OR ^b	95% CI	p-value	p-trend ^c
<i>IFNG</i>	rs1861494	AA	429 (51)	548 (51)	1.0			
		AG	342 (40)	429 (40)	1.0	0.8 1.2	0.8	
		GG	74 (9)	89 (8)	1.1	0.8 1.5	0.7	0.7
<i>IFNG</i>	rs2069705	TT	369 (45)	478 (45)	1.0			
		TC	352 (43)	468 (44)	1.0	0.8 1.2	0.8	
		CC	105 (13)	119 (11)	1.1	0.9 1.5	0.4	0.6
<i>IL1B</i>	rs16944	CC	370 (45)	456 (42)	1.0			
		TC	352 (43)	494 (46)	0.9	0.7 1.1	0.2	
		TT	98 (12)	127 (12)	1.0	0.7 1.3	0.7	0.4
<i>IL1B</i>	rs1143634	CC	463 (56)	636 (59)	1.0			
		TC	314 (38)	385 (36)	1.1	0.8 1.4	0.3	
		TT	57 (7)	53 (5)	1.5	1.0 2.2	0.05	0.05
<i>IL4</i>	rs2243250	CC	616 (74)	750 (70)	1.0			
		TC	206 (25)	289 (27)	0.9	0.7 1.1	0.2	
		TT	16 (2)	35 (3)	0.5	0.3 1.0	0.05	0.08
<i>IL4^d</i>	rs2243248	TT	721 (86)	928 (89)	1.0			
		GT/GG	115 (14)	120 (11)	1.2	0.9 1.6	0.1	0.2
		CC	600 (73)	763 (71)	1.0			
<i>IL4</i>	rs2070874	TC	206 (25)	288 (27)	0.9	0.7 1.1	0.4	
		TT	12 (1)	30 (3)	0.5	0.3 1.0	0.05	0.03
		GG	274 (33)	379 (35)	1.0			
<i>IL6^e</i>	rs1800795	CG	408 (49)	487 (45)	1.2	0.9 1.4	0.2	
		CC	156 (19)	211 (20)	1.0	0.8 1.3	0.9	0.6
		GG	272 (33)	393 (37)	1.0			
<i>IL6^f</i>	rs1800797	GA	395 (48)	478 (45)	1.2	1.0 1.5	0.09	
		AA	151 (18)	199 (19)	1.1	0.8 1.4	0.5	0.3
		CC	487 (59)	590 (56)	1.0			

Gene	Entrez SNP ID ^a	Genotype	Cases (%) (n = 859)	Controls (%) (n = 1,083)	OR ^b	95% CI	p-value	p-trend ^c
<i>IL10</i>	rs1800896	TC	288 (35)	394 (37)	0.9	0.7	1.1	0.2
		TT	54 (7)	75 (7)	0.9	0.6	1.3	0.5
		AA	219 (26)	322 (30)	1.0			
		GA	417 (50)	530 (50)	1.2	0.9	1.4	0.2
<i>IL12B</i>	rs3212227	GG	200 (24)	230 (21)	1.3	1.0	1.7	0.06
		AA	537 (64)	697 (64)	1.0			
		CA	263 (31)	335 (31)	1.0	0.8	1.2	0.9
		CC	36 (4)	50 (5)	0.9	0.6	1.5	0.8
<i>NFKB1</i>	rs230521	GG	321 (38)	401 (37)	1.0			
		CG	400 (47)	496 (46)	1.0	0.8	1.2	0.9
		CC	127 (15)	179 (17)	0.9	0.7	1.2	0.4
		TT	291 (34)	351 (33)	1.0			
<i>NFKBIE</i>	rs730775	CT	425 (50)	547 (51)	0.9	0.8	1.1	0.5
		CC	140 (16)	182 (17)	0.9	0.7	1.2	0.6
		AA	309 (37)	407 (38)	1.0			
		GA	400 (48)	490 (45)	1.1	0.9	1.3	0.5
<i>NOS2A</i>	rs944722	GG	123 (15)	182 (17)	0.9	0.7	1.2	0.3
		CC	526 (63)	675 (63)	1.0			
		TC	281 (34)	352 (34)	1.0	0.8	1.2	0.8
		TT	30 (4)	45 (4)	0.9	0.5	1.4	0.5
<i>NOS3</i>	rs1799983	GG	412 (50)	506 (47)	1.0			
		TG	329 (40)	449 (42)	0.9	0.7	1.1	0.3
		TT	77 (9)	122 (11)	0.8	0.6	1.1	0.1
		CC	418 (50)	516 (48)	1.0			
<i>NOS3</i>	rs1549758	TC	345 (41)	447 (42)	1.0	0.8	1.2	0.6
		TT	72 (9)	114 (11)	0.8	0.6	1.1	0.1
		CC	615 (76)	799 (74)	1.0			
		CA	181 (22)	260 (24)	0.9	0.7	1.1	0.3
<i>PTGS1</i>	rs5788	AA	17 (2)	20 (2)	1.1	0.6	2.1	0.8
		GG	610 (73)	794 (74)	1.0			
		GC	198 (24)	264 (24)	1.0	0.8	1.2	0.8

Gene	Entrez SNP ID ^a	Genotype	Cases (%) (n = 859)	Controls (%) (n = 1,083)	OR ^b	95% CI	p-value	p-trend ^c
<i>PTGS2</i>	rs5275	CC	23 (3)	20 (2)	1.5	0.8	2.7	0.2
		TT	387 (47)	437 (40)	1.0			0.6
		TC	348 (42)	501 (46)	0.8	0.6	0.9	0.01
<i>SOD1^d</i>	rs2070424	CC	96 (12)	144 (13)	0.8	0.6	1.0	0.06
		AA	712 (85)	931 (86)	1.0			0.01
		GA/GG	124 (15)	149 (14)	1.1	0.8	1.4	0.5
<i>SOD2</i>	rs4880	CC	206 (24)	285 (26)	1.0			0.4
		CT	422 (50)	539 (50)	1.1	0.9	1.3	0.5
		TT	217 (26)	256 (24)	1.2	0.9	1.5	0.2
<i>SOD2</i>	rs2758346	AA	210 (25)	289 (27)	1.0			
		GA	416 (50)	534 (49)	1.1	0.9	1.3	0.5
		GG	210 (25)	256 (24)	1.1	0.9	1.5	0.3
<i>SOD3</i>	rs2855262	CC	325 (40)	431 (40)	1.0			
		TC	398 (49)	516 (48)	1.0	0.8	1.2	0.8
		TT	81 (11)	128 (12)	0.9	0.7	1.3	0.7
<i>TNF</i>	rs1800629	GG	560 (69)	714 (67)	1.0			
		GA	229 (28)	313 (29)	0.9	0.8	1.1	0.5
		AA	28 (3)	36 (3)	1.0	0.6	1.6	0.9
<i>TNFD</i>	rs361525	GG	763 (91)	986 (91)	1.0			0.6
		GA/AA	79 (9)	96 (9)	1.1	0.8	1.5	0.7
		CC	682 (82)	898 (84)	1.0			
<i>TNFD</i>	rs1799724	TC/TT	148 (18)	174 (16)	1.1	0.9	1.4	0.4
								0.3

Bolded *p*-trend values indicate significance ≤ 0.05

^aEntrez SNP reference ID number (<http://www.ncbi.nlm.nih.gov/entry/query.fcgi?db=snp>)

^bAdjusted for year of birth

^c1 *df* test across genotypes

^dDominant model assumed due to prevalence of rare homozygotes <2%

^e*p*-value for Hardy–Weinberg equilibrium = 0.04

^f*p*-value for Hardy–Weinberg equilibrium = 0.03

Table 3

Analysis of interaction between oxidative stress and inflammatory-mediated pathway polymorphisms, breast radiation dose from occupation and dose score from personal diagnostic radiation, and breast cancer risk in US radiologic technologists

Gene	Entrez SNP ID ^a	Genotype	Cases (%)(n = 859)	Controls (%)(n = 1,083)	Occupational radiation effect modification			Diagnostic radiation effect modification		
					EOR/Gy ^b	95% Confidence interval	p-value ^c	EOR/unit breast dose score ^b	95% Confidence interval	p-value ^c
<i>IFNG</i>	rs1861494	AA	429 (51)	548 (51)	2.2	<0, 7.6	>0.5	2.2	<0, 7.1	>0.5
		AG	342 (40)	429 (40)	3.5	<0, 11.2		0.7	<0, 5.6	
		GG	74 (9)	89 (8)	1.1	<0, 18.1		0.8	<0, 9.7	
<i>IFNG</i>	rs2069705	TT	369 (45)	478 (45)	3.8	<0, 11.0	>0.5	3.4	<0, 9.6	0.4
		TC	352 (43)	468 (44)	2.3	<0, 8.7		<0	<0, 3.7	
		CC	105 (13)	119 (11)	<0	<0, 10.9		0.7	<0, 7.9	
<i>IL1B</i>	rs16944	CC	370 (45)	456 (42)	4.0	<0, 11.5	>0.5	0.4	<0, 4.4	>0.5
		TC	352 (43)	494 (46)	2.4	<0, 9.3		2.5	<0, 7.9	
		TT	98 (12)	127 (12)	1.5	<0, 13.9		0.8	<0, 11.2	
<i>IL1B</i>	rs1143634	CC	463 (56)	636 (59)	5.3	1.0, 12.8	0.2	<0	<0, 2.2	0.1
		TC	314 (38)	385 (36)	1.7	<0, 9.2		5.7	0.6, 14.5	
		TT	57 (7)	53 (5)	<0	<0, 8.0		1.8	<0, 24.9	
<i>IL4</i>	rs2243250	CC	616 (74)	750 (70)	2.4	<0, 7.4	>0.5	0.8	<0, 3.7	>0.5
		TC	206 (25)	289 (27)	0.8	<0, 8.5		3.6	<0, 13.4	
		TT	16 (2)	35 (3)	16.7	<0, >100		<0	<0, <0	
<i>IL4^d</i>	rs2243248	TT	721 (86)	928 (89)	3.4	0.1, 8.8	>0.5	1.3	<0, 4.5	>0.5
		GT/GG	115 (14)	120 (11)	1.8	<0, 13.2		1.1	<0, 9.8	
		CC	600 (73)	763 (71)	3.2	<0, 8.8	>0.5	1.0	<0, 4.1	>0.5
<i>IL4</i>	rs2070874	TC	206 (25)	288 (27)	1.3	<0, 9.6		3.7	<0, 13.6	
		TT	12 (1)	30 (3)	11.5	<0, >100		<0	<0, <0	
		GG	274 (33)	379 (35)	1.0	<0, 7.3	>0.5	1.6	<0, 7.7	0.4
<i>IL6^e</i>	rs1800795	CG	408 (49)	487 (45)	4.7	0.3, 12.5		<0	<0, 3.3	
		CC	156 (19)	211 (20)	2.0	<0, 10.8		3.3	<0, 12.1	
		GG	272 (33)	393 (37)	1.6	<0, 8.6	>0.5	2.4	<0, 9.3	>0.5
<i>IL6^f</i>	rs1800797	GA	395 (48)	478 (45)	4.4	0.1, 12.1		0.8	<0, 5.3	

Gene	Entrez SNP ID ^a	Genotype	Cases (%) (n = 859)	Controls (%) (n = 1,083)	Occupational radiation effect modification			Diagnostic radiation effect modification		
					EOR/Gy ^b	95% Confidence interval	p-value ^c	EOR/unit breast dose score ^b	95% Confidence interval	p-value ^c
<i>IL10</i>	rs1800871	AA	151 (18)	199 (19)	1.3	<0, 9.1		2.0	<0, 9.6	
		CC	487 (59)	590 (56)	1.6	<0, 6.5	0.5	1.1	<0, 5.1	>0.5
		TC	288 (35)	394 (37)	4.5	<0, 13.9		1.2	<0, 6.5	
		TT	54 (7)	75 (7)	7.7	<0, 36.4		2.1	<0, 19.6	
<i>IL10</i>	rs1800896	AA	219 (26)	322 (30)	2.1	<0, 9.0	0.06	1.1	<0, 7.5	0.3
		GA	417 (50)	530 (50)	6.0	1.0, 14.4		3.1	<0, 8.9	
		GG	200 (24)	230 (21)	<0	<0, 3.4		<0	<0, 3.2	
		AA	537 (64)	697 (64)	3.9	0.3, 9.9	0.2	1.9	<0, 6.2	0.2
<i>IL12B</i>	rs3212227	CA	263 (31)	335 (31)	<0	<0, 5.3		<0	<0, 2.8	
		CC	36 (4)	50 (5)	7.0	<0, 45.7		7.1	<0, 44.5	
		GG	321 (38)	401 (37)	6.8	1.0, 17.0	0.2	2.7	<0, 9.0	>0.5
		CG	400 (47)	496 (46)	0.6	<0, 4.9		0.5	<0, 5.0	
<i>NFKB1</i>	rs230521	CC	127 (15)	179 (17)	3.6	<0, 17.0		0.4	<0, 6.6	
		TT	291 (34)	351 (33)	3.9	<0, 12.3	0.4	2.0	<0, 8.1	>0.5
		CT	425 (50)	547 (51)	1.7	<0, 6.9		0.9	<0, 4.7	
		CC	140 (16)	182 (17)	8.3	<0, 29.1		1.7	<0, 12.1	
<i>NOS2A</i>	rs944722	AA	309 (37)	407 (38)	5.0	<0, 14.6	0.3	2.2	<0, 7.4	>0.5
		GA	400 (48)	490 (45)	2.4	<0, 8.0		0.1	<0, 4.0	
		GG	123 (15)	182 (17)	-1.7	<0, 7.1		2.6	<0, 14.3	
		CC	526 (63)	675 (63)	1.4	<0, 6.6	0.4	0.3	<0, 3.3	0.5
<i>NOS2A</i>	rs2297518	TC	281 (34)	352 (34)	4.6	<0, 13.3		2.8	<0, 9.2	
		TT	30 (4)	45 (4)	7.5	<0, 43.4		6.6	<0, 54.2	
		GG	412 (50)	506 (47)	3.5	<0, 10.7	>0.5	2.1	<0, 7.3	0.02
		TG	329 (40)	449 (42)	3.1	<0, 10.2		<0	<0, 2.9	
<i>NOS3</i>	rs1799983	TT	77 (9)	122 (11)	0.3	<0, 12.1		19.7	3.7, 57.4	
		CC	418 (50)	516 (48)	3.9	<0, 11.3	>0.5	1.7	<0, 6.5	0.04
		TC	345 (41)	447 (42)	1.8	<0, 7.3		<0	<0, 2.8	
		TT	72 (9)	114 (11)	1.7	<0, 18.2		16.6	2.3, 50.4	
<i>PTGS1</i>	rs5788	CC	615 (76)	799 (74)	2.5	<0, 7.8	>0.5	1.4	<0, 4.9	>0.5

Gene	Entrez SNP ID ^a	Genotype	Cases (%) (n = 859)	Controls (%) (n = 1,083)	Occupational radiation effect modification			Diagnostic radiation effect modification		
					EOR/Gy ^b	95% Confidence interval	p-value ^c	EOR/unit breast dose ^b	95% Confidence interval	p-value ^c
PTGS2	rs5277	CA	181 (22)	260 (24)	3.3	<0, 12.6		1.5	<0, 8.4	
		AA	17 (2)	20 (2)	10.3	<0, >100		<0	<0, 24.3	
		GG	610 (73)	794 (74)	5.5	1.2, 12.5	0.04	1.9	<0, 5.7	>0.5
		GC	198 (24)	264 (24)	<0	<0, 3.8		0.4	<0, 6.4	
		CC	23 (3)	20 (2)	<0	<0, 14.8		0.1	<0, 18.8	
PTGS2	rs5275	TT	387 (47)	437 (40)	2.0	<0, 8.6	0.4	1.9	<0, 7.1	>0.5
		TC	348 (42)	501 (46)	2.9	<0, 9.1		0.5	<0, 4.5	
		CC	96 (12)	144 (13)	10.2	<0, 35.2		3.7	<0, 17.3	
		AA	712 (85)	931 (86)	1.8	<0, 6.4	0.3	1.50	<0, 4.6	>0.5
SOD1 ^d	rs2070424	GA/GG	124 (15)	149 (14)	6.5	<0, 22.7		0.5	<0, 11.0	
		CC	206 (24)	285 (26)	0.7	<0, 7.6	0.1	1.6	<0, 7.9	>0.5
		CT	422 (50)	539 (50)	6.0	1.3, 14.1		2.0	<0, 6.9	
		TT	217 (26)	256 (24)	<0	<0, 5.5		<0	<0, 4.3	
SOD2	rs2758346	AA	210 (25)	289 (27)	0.2	<0, 6.4	0.08	1.4	<0, 7.7	>0.5
		GA	416 (50)	534 (49)	6.1	1.3, 14.3		2.0	<0, 6.9	
		GG	210 (25)	256 (24)	<0	<0, 5.8		<0	<0, 4.8	
		CC	325 (40)	431 (40)	4.9	0.1, 13.8	>0.5	2.8	2.3, 4.9	0.1
SOD3	rs2855262	TC	398 (49)	516 (48)	2.0	<0, 7.3		1.0	0.6, 2.6	
		TT	81 (11)	128 (12)	3.5	<0, 33.0		<0	<0, not found	
		GG	560 (69)	714 (67)	2.4	<0, 7.5	>0.5	1.3	<0, 5.2	>0.5
		GA	229 (28)	313 (29)	3.1	<0, 11.7		1.4	<0, 7.3	
TNF	rs1800629	AA	28 (3)	36 (3)	8.5	<0, 75.3		<0	<0, 52.9	
		GG	763 (91)	986 (91)	3.3	0.08, 8.6	0.4	1.2	<0, 4.4	>0.5
		GA/AA	79 (9)	96 (9)	0.3	<0, 10.3		0.6	<0, 9.7	
		CC	682 (82)	898 (84)	2.7	<0, 8.2	>0.5	1.2	<0, 4.4	>0.5
TNFD	rs1799724	TC/TT	148 (18)	174 (16)	2.1	<0, 9.5		2.2	<0, 12.4	

Bolded p-values indicate significance ≤ 0.05

^aEntrez SNP reference ID number (<http://www.ncbi.nlm.nih.gov/entry/query.fcgi?db=snp>)

^b Adjusted for year of birth

^c χ^2 test across genotypes

^d Dominant model assumed due to prevalence of rare homozygotes <2%

^e p -value for Hardy–Weinberg equilibrium = 0.04

^f p -value for Hardy–Weinberg equilibrium = 0.03