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Breast cancer risk polymorphisms and interaction with ionizing radiation among U.S. Radiologic Technologists

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Abstract

Genome-wide association studies are discovering relationships between single nucleotide polymorphisms (SNPs) and breast cancer, but the functions of these SNPs are unknown and environmental exposures are likely to be important. We assessed whether breast cancer risk SNPs interacted with ionizing radiation, a known breast carcinogen, among 859 cases and 1083 controls nested in the United States Radiologic Technologists cohort. Among eleven Breast Cancer Association Consortium risk SNPs, we found that the genotype-associated breast cancer risk varied significantly by radiation dose for rs2107425 in the *H19* gene ($p_{interaction}$=0.001). *H19* is a maternally expressed imprinted mRNA that is closely involved in regulating the *IGF2* gene and could exert its influence by this or by some other radiation-related pathway.

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Introduction

Genome-wide association studies (GWAS) are rapidly uncovering risk relationships between single nucleotide polymorphisms (SNPs) and several human diseases, including breast cancer (1). Some of the associations found were in genes or regions that were considered unlikely initial candidates, such as 8q24 (1,2), and more work is now being done to further replicate, elucidate function, or more precisely describe the risks (2). While the genetic contribution to complex diseases is gaining clarity, the contribution of environmental exposures on certain genetic backgrounds could also clarify situations where disease risk was increased. A statistical analysis strategy that combines known genetic risk variants and established environmental carcinogens for specific diseases may identify SNPs that are important when the environmental exposure is present. We evaluated gene-radiation interaction based on results from the Breast Cancer Association Consortium (BCAC)(1) among women exposed to ionizing radiation as radiologic technologists from a case-control study that is nested in the U.S. Radiologic Technologists (USRT) cohort. The breast cancer study was a component of BCAC and contributed data on the same breast cancer cases and controls as reported here. Ionizing radiation is an established breast cancer carcinogen (3,4) and occupational exposure to ionizing radiation been previously associated with breast cancer risk in the USRT cohort (5).

Materials and Methods

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 who were certified for at least two years between 1926 and 1982. The cohort members are predominantly white (95%) and their current mean age is 58 years. During 1984–1989 and during 1993–1998, postal surveys were conducted that included detailed questions related to work history as a radiologic technologist, family history of cancer, reproductive history, height, weight, other cancer risk factors and information regarding health outcomes. 69,524 of 98,233 (71%) and 69,998 of 94,508 (74%) known living female technologists responded to the first and second surveys, respectively (6). 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) that was confirmed based on pathology or medical records were eligible for inclusion. In December 1999, when biospecimen collection began, there were 1386 living (prevalent) breast cancer cases with diagnosis years ranging from 1955 to 1998. By the end of December 2003, 874 (63 %) breast cancer cases had provided informed consent, a blood sample, and completed a telephone interview collecting updated cancer risk factor and family cancer history information and selected work history data. Controls were technologists who had not reported a diagnosis of breast cancer prior to 1998 and were randomly selected and frequency matched to cases (ratio 1.5:1) by birth year in 5 year strata. There were 2268 living controls; 1094 (48 %) provided informed consent, a blood sample, and completed a telephone interview. We found few differences when we compared demographic and other characteristics among responders, nonresponders, and decedents, including race, education, marital status, age in 1999, cigarette smoking, alcohol consumption, age at menarche, age at first live birth, and number of live births. However, among cases and controls, the proportion of African-Americans was lower among responders than nonresponders, slightly more responders than nonresponders used oral contraceptives, and a higher percentage of technologists from the Midwest responded compared with those from the Northeast. Decedents who reported a breast

cancer but died before blood collection (N = 352) were significantly more likely to be older at breast cancer diagnosis, African-American, and smoked cigarettes longer than responders.

Sample handling and SNP selection

After venipuncture, whole blood samples were shipped overnight with an ice pack to the processing laboratory in Frederick, MD. Blood components were separated and DNA was extracted using Qiagen Kits (Qiagen, Valencia, CA). The samples were tracked by a unique ID code, and laboratory investigators were blinded to case-control status. Due to biospecimen contamination, inadequate biospecimen quantity and incomplete survey data, the final sample size consisted of 859 cases and 1083 controls. Of the 30 variants that BCAC selected for stage 3 of their analysis, we chose 11 variants that showed evidence for association with breast cancer for our analysis (see Table 2 in Easton et al, 2007 (1); rs2981582, rs12443621, rs8051542, rs889312, rs3817198, rs2107425, rs13281615, rs981782, rs30099, rs4666451, and rs3803662). Genotyping methods have been previously described (1).

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 (7–9), but included some refinements for this work. Individuals without monitoring badge readings were assigned yearly doses using simulation techniques from probability distributions that described 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. Yearly breast doses were derived from the badge doses and were summed to derive a cumulative occupational breast dose for each person. Radiation exposure that occurred within 10 years of breast cancer diagnosis in the cases and an equivalent time period in controls was not included in the cumulative radiation dose. A 10 year lag for exposures was chosen because this is a generally accepted latency period for solid cancers (4,10,11).

We also derived a cumulative breast dose score as an estimate of organ dose from the numbers and calendar time periods of diagnostic x-ray procedures that study participants reported receiving on the cohort surveys. One unit of dose score approximates one Gy of ionizing radiation absorbed dose. Detailed methods used to derive the breast dose score have been previously published (12). For radionuclide and radiation therapy procedures we created “ever/never” variables because information on the number of procedures subjects underwent was not available. For all personal medical procedures, those procedures occurring 10 years prior to breast cancer diagnosis for cases and an equivalent time point for controls were excluded; a 10 year lag also minimizes potential bias from procedures performed because of pre-clinical disease symptoms (13).

Statistical Analysis

For each SNP, the rare allele among controls was considered the variant allele. The BCAC (1) study genotype main effects suggested co-dominant modes of inheritance; however, the odds ratios for the heterozygote and homozygote variant groups were quite similar, so to maximize the power to detect effect modification we assumed a dominant mode of inheritance in our analyses. We assessed Hardy-Weinberg equilibrium (HWE) among controls using chi-square tests.

Associations between SNPs and breast cancer were evaluated using unconditional logistic regression. To evaluate whether cumulative radiation breast organ dose in Gy (dose score) “high” vs. “low” modified the relation between genotype and breast cancer risk, we allowed the genotype-related odds ratio to vary by dose (dose score) level while adjusting for the

radiation effect. We stratified study subjects into "high" and "low" occupational dose and personal diagnostic dose score categories at the mean for each of these metrics among controls. Heterogeneity in genotype-breast cancer associations across dose and dose score categories was assessed using likelihood ratio tests (LRT).

All regression models were adjusted for year of birth. Models assessing effect modification of genotype associations with breast cancer by occupational radiation breast dose were adjusted for personal diagnostic radiation (in categories as seen in Table 1) and vice versa. Adjustment for radiation and radionuclide therapies, 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 did not substantially change genotype estimates, so these variables were not included in the final models. We used SAS 8.02 (SAS Institute, Cary, North Carolina) for all analyses.

Results

Distributions for covariates and radiation exposure variables are presented in Table 1, along with their corresponding ORs. Mean occupational breast doses and personal diagnostic dose scores in controls were 0.03 Gy (range 0 – 0.59 Gy) and 0.03 dose score units (range 0 –0.67), respectively.

The associations between the eleven SNPs and breast cancer in our study have been previously published as part of the BCAC GWAS analysis. Among U.S. radiologic technologists, breast cancer risk was significantly associated with four SNPs: rs2981582, rs889312, rs13281615, and rs3803662 (Table 2). We detected significant interaction by occupational radiation dose ($\leq$0.03 Gy versus >0.03Gy) with genotype for rs2107425 in the *H19* gene (p = 0.001, Table 3). We did not observe any significant modification of genotype effects by personal diagnostic radiation dose score (results not shown).

Discussion

Of the eleven SNPs that we analyzed, we observed a statistically significant interaction by occupational radiation dose with genotype for rs2107425 in the H19 gene. In the BCAC study (1), carrying one or two rs2107425 variant alleles was associated with a decreased risk of breast cancer, which we also observed in the low-dose group (OR=0.8, p = 0.05). In contrast, breast cancer risk in our study was increased in the high-dose group among carriers of the rs2107425 variant (OR= 1.6, p = 0.009). SNP rs2107425 of the *H19* gene was found to be only weakly statistically significant in stage 3 of the BCAC study after adjustment for rs3817198 in the *LSP1* gene (1). We did not observe significant interaction with rs3817198 or any of the other four SNPs found to be most significant in stage 3 of the BCAC study (1). We did not find any evidence of interaction between the *H19* SNP and personal diagnostic radiation breast dose score. This may be explained by the attenuated effect of personal diagnostic radiation breast dose score on breast cancer risk as compared to occupational radiation dose (see footnotes for Table 1).

The *H19* gene is located on 11p15, a region linked to Beckwith-Weidemann syndrome and is known to be associated with breast cancer and other cancer types by the so called "multiple tumor-associated chromosome region 1". *H19* is a maternally expressed imprinted non-coding mRNA whose specific function is unknown but is closely involved in regulating the insulin growth factor gene, *IGF2* (14). A polymorphism in *H19* that increases *IGF2* expression may promote carcinogenesis by allowing cells with radiation induced DNA damage to survive, proliferate, and maintain the malignant phenotype (15). This suggests that rs2107425 in *H19* may be important in a radiation-related pathway associated with breast cancer risk (15). Whole-

body radiation exposure in BALB/c mice was associated with an altered *H19* methylation pattern (16) and methylation status of *H19* in rats was related to hepatic neoplasms (17), suggesting that epigenetic phenomena might also play a role in radiation associated carcinogenesis as hypothesized by others (18). Further testing of the *H19* gene and the rs2107425 variant in biologically-based radiation assays may illuminate possible functional relevance for this gene.

Without replication of our finding and laboratory based studies of the 11p15 locus, there are few, if any clinical implications for our finding presently. Based on the apparent relationship with other genes and variants near the 11p15 locus, there could be complex polygenic factors underlying the interaction with occupational radiation exposure. As the number of convincing disease-SNP associations grow, further epidemiologic study of their potential interaction with other established risk factors and association with disease sub-types, ideally in prospective cohort settings where biases may be reduced, will be important to conduct. Such studies may give clues to the function of the variants/genes, potentially guiding laboratory analyses that can more definitively evaluate them and eventually lead to clinical applications.

Strengths of the present study are that the occupational breast doses are derived from a comprehensive dose reconstruction system and have been corroborated by biodosimetry in a separate effort (7). Limitations include the use of prevalent rather than incident breast cancer cases; however, the prevalence of genotype frequencies by survival time between breast cancer diagnosis and blood collection showed no significant differences (results not shown). A similar analysis considering occupational and personal diagnostic ionizing radiation exposures was not possible because increased survival time was associated with greater age, which is associated with greater cumulative exposure among our study subjects. However, an analysis considering all types of cancers among atomic bomb survivors demonstrated no association between survival time and radiation dose (19). Furthermore, this was an exploratory analysis with no prior hypothesis regarding radiation interaction with the 11 variants, so chance may explain our finding, which needs to be replicated in other groups.

This case-control study nested within the USRT cohort presented a unique opportunity to evaluate effect modification of SNPs conferring susceptibility to breast cancer by ionizing radiation, an established breast cancer carcinogen (3,4). We believe the *H19* gene may be a good candidate for functional studies because: the risk estimates for the *H19* SNP in the low dose group were consistent with the BCAC study, carefully reconstructed dose estimates were used, the *H19* SNP is unlikely to be a correlate of survival, and *H19* appears to be related to *IGF2* regulation and has some indirect relationships with ionizing radiation in animal models.

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Table 1

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

Characteristic	Cases (%) (n = 859)	Controls (%) (n = 1083)	Odds Ratio*	95% Confidence Interval		p-trend†
Ethnicity						
Caucasian	842 (98)	1048 (97)	1.0			N/A
African American	9 (1)	18 (2)	0.6	0.3	1.4	
Other	8 (1)	17 (2)	0.6	0.3	1.4	
Year of Birth						
≤ 1925	120 (14)	138 (13)	1.0			0.7
1926 – 1935	195 (23)	249 (23)	1.1	0.9	1.5	
1936 – 1945	292 (34)	382 (35)	1.0	0.8	1.3	
>1945	252 (29)	314 (29)	1.0	0.8	1.3	
Occupational Ionizing Radiation Breast Dose (Gy)§						
0 to 0.05	687 (80)	894 (83)	1.0			0.2
>0.05 to 0.1	90 (10)	100 (9)	1.2	0.9	1.7	
>0.1 to 0.2	63 (7)	76 (7)	1.1	0.7	1.6	
>0.2	19 (2)	13 (1)	1.9	0.9	4.0	
Personal Diagnostic x-ray Breast Dose Score§						
0 to 0.05	686 (80)	908 (84)	1.0			0.06
>0.05 to 0.1	106 (12)	104 (10)	1.3	1.0	1.8	
>0.1 to 0.2	46 (5)	51 (5)	1.2	0.8	1.8	
>0.2	21 (2)	20 (2)	1.4	0.7	2.6	
Radionuclide Procedures						
Never	721 (84)	937 (87)	1.0			NA
Ever	65 (8)	71 (7)	1.2	0.8	1.7	
Unknown	73 (9)	75 (7)	N/A			
Radiation Therapy						
Never	803 (93)	1021 (94)	1.0			NA
Ever	24 (3)	14 (1)	2.1	1.0	4.0	
Unknown	32 (4)	48 (4)	N/A			

*All Odds Ratios Adjusted for Year of Birth categories; Occupational Dose and Personal Diagnostic Dose Score analyses mutually adjusted (categorically); Radionuclide Procedure analysis adjusted for Occupational Dose categories, Personal Diagnostic Dose Score categories and Radiation Therapy categories; Radiation Therapy analysis adjusted for Occupational Dose categories, Personal Diagnostic Dose Score categories and Radionuclide Procedures categories

†Trend test with categories of interest modeled as continuous variables in logistic regression analyses; adjusted for applicable covariates as indicated above

§EOR/Gy (Excess Odds Ratio) for Occupational Dose is 3.0 (p = 0.05); EOR/dose score for personal diagnostic x-ray breast dose score is 1.3 (p = 0.2); OR = 1 + EOR*(dose)

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Table 2

Risk estimates for eleven SNPs showing an association with breast cancer in the Breast Cancer Association Consortium that were genotyped in the U.S. Radiologic Technologists study

Gene	Entrez SNP ID*	Genotype	Cases (%) (n=859)	Controls (%) (n=1083)	OR‡	95% CI		p- value
FGFR2	rs2981582	*CC*	267 (32)	407 (38)	1.0			
		TC/TT	555 (68)	670 (62)	1.3	1.0	1.5	0.02
TNRC91	rs12443621	*TT*	201 (24)	293 (27)	1.0			
		CT/CC	621 (76)	775 (73)	1.2	1.0	1.4	0.1
TNRC92	rs8051542	*GG*	235 (29)	339 (32)	1.0			
		AG/AA	586 (71)	735 (68)	1.1	0.9	1.4	0.2
MAP3K1	rs889312	*AA*	380 (46)	564 (52)	1.0			
		CA/CC	444 (54)	512 (48)	1.3	1.1	1.5	0.007
LSP1	rs3817198	*TT*	391 (47)	481 (45)	1.0			
		TC/CC	436 (53)	599 (55)	0.9	0.7	1.1	0.2
H19	rs2107425	*GG*	392 (48)	502 (47)	1.0			
		AG/AA	432 (52)	571 (53)	1.0	0.8	1.2	0.8
POU5F1P1	rs13281615	*AA*	269 (31)	398 (37)	1.0			
		GA/GG	576 (68)	683 (63)	1.2	1.0	1.5	0.02
HCN1	rs981782	*TT*	246 (30)	318 (30)	1.0			
		TG/GG	569 (70)	755 (70)	1.0	0.8	1.2	0.8
ITGA2	rs30099	*GG*	706 (85)	908 (84)	1.0			
		AG/AA	126 (15)	170 (16)	1.0	0.7	1.2	0.7
LOC388927	rs4666451	*CC*	339 (40)	419 (39)	1.0			
		CT/TT	502 (60)	659 (61)	0.9	0.8	1.1	0.5
TNRC93	rs3803662	*CC*	389 (47)	556 (52)	1.0			
		TC/TT	432 (53)	513 (48)	1.2	1.0	1.4	0.04

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

†Amino acid sequence variation (regular font), nucleotide sequence variation (italics)

‡Adjusted for year of birth

§Genotype frequencies in controls did not comply with Hardy-Weinberg expectation, ($p < 0.001$)

Table 3

Effect modification of genotype and breast cancer risk relationships by occupational radiation dose to the breast of less and greater than 0.03 Gy for eleven SNPs from the Breast Cancer Association Consortium in the U.S. Radiologic Technologists study

Gene	Entrez SNP ID*	Genotype	Occupational Radiation Dose ≤0.03 Gy					Occupational Radiation Dose >0.03 Gy					effect modification p-value§
			Cases (n=601) †	Controls (n=783) †	OR‡	95% CI	p-value	Cases (n=258) †	Controls (n=300) †	OR‡	95% CI	p-value	
FGFR2	rs2981582	*CC*	189	283	1.0			101	156	1.0			0.3
		TC/TT	392	496	1.2	0.9, 1.5	0.2	140	140	1.5	1.1, 2.2	0.02	
TNRC9	rs12443621	*TT*	138	214	1.0			63	79	1.0			0.4
		CT/CC	445	557	1.2	1.0, 1.6	0.1	176	218	1.0	0.7, 1.5	0.9	
TNRC9	rs8051542	*GG*	169	241	1.0			66	98	1.0			0.4
		AG/AA	413	537	1.1	0.9, 1.4	0.5	173	198	1.3	0.9, 1.9	0.2	
MAP3K1	rs889312	*AA*	268	408	1.0			112	156	1.0			0.9
		CA/CC	314	371	1.3	1.0, 1.6	0.02	130	141	1.3	0.9, 1.8	0.1	
LSP1	rs3817198	*TT*	274	351	1.0			117	130	1.0			0.6
		TC/CC	310	429	0.9	0.7, 1.1	0.4	126	170	0.8	0.6, 1.1	0.2	
H19	rs2107425	*GG*	291	346	1.0			101	156	1.0			0.001
		AG/AA	292	431	0.8	0.7, 1.0	0.05	140	140	1.6	1.1, 2.2	0.009	
POU5F1B	rs13281615	*AA*	182	291	1.0			87	107	1.0			0.3
		GA/GG	413	490	1.3	1.1, 1.7	0.01	163	193	1.0	0.7, 1.5	0.8	
HCN1	rs981782	*TT*	177	236	1.0			69	82	1.0			0.8
		TG/GG	398	541	1.0	0.8, 1.2	0.8	171	214	0.9	0.6, 1.4	0.7	
ITGA2	rs30099	*GG*	494	647	1.0			212	261	1.0			0.7
		AG/AA	95	133	0.9	0.7, 1.2	0.6	31	37	1.0	0.6, 1.7	0.9	
LOC388927	rs4666451	*CC*	473	307	1.0			103	112	1.0			0.5
		CT/TT	355	236	1.0	0.8, 1.2	0.8	147	186	0.9	0.6, 1.2	0.4	
TNRC9	rs3803662	*CC*	265	395	1.0			124	161	1.0			0.6
		TC/TT	314	377	1.2	1.0, 1.5	0.05	118	136	1.1	0.8, 1.6	0.5	

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

†The numbers of cases and controls may not sum to total due to genotyping failures.

‡Odds Ratio (OR) adjusted for year of birth and medical diagnostic radiation exposure. A dominant genetic model was assumed for all analyses.

§Likelihood ratio test (LRT) comparing deviance of models with and without effect modification term

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