Polymorphisms in Apoptosis- and Proliferation-Related Genes, Ionizing Radiation Exposure, and Risk of Breast Cancer among U.S. Radiologic Technologists

Alice J. Sigurdson, Parveen Bhatti, Michele M. Doody, Michael Hauptmann, Laura Bowen, Steven L. Simon, Robert M. Weinstock, Martha S. Linet, Marvin Rosenstiel, Marilyn Stovall, Bruce H. Alexander, Dale L. Preston, Jeffrey P. Strewing, and Preetha Rajaraman

Introduction

In normal cells, growth and proliferation are controlled by a complex interplay of several pathways, including cell-cycle checkpoints, DNA damage sensing and repair, and apoptosis, inflammation, and proliferation. Using carefully reconstructed cumulative breast dose estimates from occupational and personal diagnostic ionizing radiation, we also investigated the joint effects of these polymorphisms on the risk of breast cancer.

Results: In multivariate analyses, we observed a significantly decreased risk of breast cancer associated with the homozygous minor allele of CASP8 D302H [rs1045485, odds ratio (OR), 0.3; 95% confidence interval (95% CI), 0.1-0.8]. We found a significantly increased breast cancer risk with increasing minor alleles for IL1A A114S (rs17561); heterozygote OR 1.2 (95% CI, 1.0-1.4) and homozygote OR 1.5 (95% CI, 1.1-2.0), P_{trend} = 0.008. Assuming a dominant genetic model, IL1A A114S significantly modified the dose-response relationship between cumulative personal diagnostic radiation and breast cancer risk, adjusted for occupational dose (P_{interaction} = 0.004).

Conclusion: The U.S. Radiologic Technologists breast cancer study provided a unique opportunity to examine the joint effects of common genetic variation and ionizing radiation exposure to the breast using detailed occupational and personal diagnostic dose data. We found evidence of effect modification of the radiation and breast cancer dose-response relationship that should be confirmed in studies with more cases and controls and quantified radiation breast doses in the low-to-moderate range.

(Cancer Epidemiol Biomarkers Prev 2007;16(10):2000–7)
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 2 years between 1926 and 1982. The cohort members are predominantly White (95%) and their current mean age is 56 years, owing to larger numbers who began working after 1970. During 1984 to 1989 and during 1993 to 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 (such as alcohol and tobacco use), and information regarding health outcomes, including breast cancer. The numbers of known living female technologists who responded to the first and second surveys are 69,524 of 98,233 (71%) and 69,998 of 94,508 (74%), respectively (see ref. 15 for other study participation details). This study has been approved annually by the human subject review boards of the National Cancer Institute and the University of Minnesota.

Cancer Confirmation and Recruitment for Nested Case-Control Study. All living female technologists reporting a primary breast cancer (ductal carcinoma in situ or invasive breast cancer) on one or more surveys that was confirmed based on pathology or medical records were eligible for inclusion. In December 1999, when biospecimen collection began, there were 1,386 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. Another 83 cases could not be located, had an unlisted telephone number, or did not respond to repeated correspondence inviting participation; 22 were too ill to participate, 358 refused, and 49 could not arrange a blood draw or the draw was unsuccessful.

Control Selection. As for cases, controls must have been alive and have completed one or more of the two survey questionnaires. Controls were selected randomly by birth year in 5-year strata corresponding to the case birth year distribution and frequency matched to cases (ratio 1.5:1). There were 2,268 living controls; 1,094 (48%) provided informed consent, a blood sample, and completed a telephone interview. There were 249 controls who could not be located or had an unlisted number and did not respond to repeated correspondence, 36 were too ill, 839 refused, and 50 could not arrange a blood draw or the draw was unsuccessful.

Sample Handling. 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). The samples were tracked by a unique ID code, and laboratory investigators were blinded to case-control status. Due to 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. The SNPs were selected for their common frequency in the population, results of previous epidemiologic studies, and for potential function based on amino acid substitution or location in promoter regions or splice sites. We chose 16 candidate variants in eight genes: AHR (rs2066853), CASP8 (rs13113, rs1045485), CDKN1A (rs1801279), DRA (rs4871857), IL1A (rs17561), TP53 (rs17882155, rs17883831), IGFBP3 (rs2854744, rs2132572, rs2471551, rs6413441), and TGFB1 (rs982073, rs1800471, rs1800472) involved in apoptosis or growth stimulation pathways, or both.

Samples were genotyped using standard TaqMan or MGB Eclipse assays. Genotyping methods for specific SNPs can be found online10 (16) and others were described previously (17). There were 115 quality control samples embedded randomly in the sample trays, composed of between 9 and 14 replicate samples from the same 10 individuals. All laboratory personnel were blinded to the location of the replicates. Of the replicated samples for the 16 assays, there were no discrepancies. For the various SNP assays, completion success ranged from a low of 86.9% for TGFB1 P25R and a high of 99.7% for IGFBP3 H158P. If the TGFB1 P25R assay is excluded, the average genotyping success was 98.4%.

Occupational Ionizing Radiation Exposure. The occupational dosimetry system used to estimate absorbed dose to the breast has been described in detail elsewhere (18, 19), with some significant refinements (20) introduced for this work. The present dosimetry version incorporates new dose factors [i.e., Gray (Gy) to breast

10 http://www.snp500cancer.nci.nih.gov
per Sievert (Sv) of badge dose] that reflect temporal changes in X-ray machine tube potentials and filtration, more reliable estimates of photon transmission through protective aprons and shields, more precise estimates of individual-specific apron use during the years worked, and substantially greater number of occupational radiation monitoring badge readings from cohort members in the period before 1977.

In brief, the occupational dosimetry system derives probability density functions that represent the annual distribution of possible true breast doses for each study subject taking into account the individual’s monitoring badge readings (when available) and extensive data we collected by questionnaire on work history. Monte Carlo methods were used to simulate 100 dose realizations from each subject’s annual dose density function; the arithmetic mean of the 100 annual dose estimates was taken to be the annual mean breast dose for that individual. To derive a cumulative occupational breast dose for each person, we summed their derived arithmetic mean doses from each year they worked up to 10 years before breast cancer diagnosis for cases and an equivalent time point for controls.

### Personal Medical Radiation Exposure

From the two mailed surveys administered to the cohort, we used the self-reported numbers and calendar time periods of the diagnostic X-ray procedures to calculate a cumulative breast dose score as an approximation of organ dose. The cumulative score was calculated by multiplying the number of procedures by nominal estimates of breast doses from these procedures over time derived from earlier publications (refs. 23-25)\(^{11}\) and expert judgment by two medical radiation dosimetrists (M.S. and M.R.; Table 2). Although the breast dose score is an approximation of Gy, due to uncertainties in recall of various procedures and uncertainties with the nominal per procedure dose estimates, we prefer “cumulative breast dose score” rather than breast dose per se. Procedures occurring 10 years before breast cancer diagnosis for cases and an equivalent time point for controls were excluded from the cumulative score; a 10-year lag also minimizes potential bias from procedures done because of preclinical disease symptoms (26).

For radionuclide procedures, we created an “ever/never” variable because information on the number of procedure subjects underwent was not available. Calendar year was available, so if the reported year was during the 10 years before breast cancer diagnosis (or equivalent

### Table 1. Demographic and ionizing radiation exposure variable distributions among cases and controls, U.S. Radiologic Technologists study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (%; n = 859)</th>
<th>Controls (%; n = 1,083)</th>
<th>OR* (95% CI)</th>
<th>( P_{\text{trend}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>842 (98)</td>
<td>1,048 (97)</td>
<td>1.0 (Reference)</td>
<td>NA</td>
</tr>
<tr>
<td>African American</td>
<td>9 (1)</td>
<td>18 (2)</td>
<td>0.6 (0.3-1.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (1)</td>
<td>17 (2)</td>
<td>0.6 (0.3-1.4)</td>
<td></td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 1925 )</td>
<td>120 (14)</td>
<td>138 (13)</td>
<td>1.0 (Reference)</td>
<td>0.7</td>
</tr>
<tr>
<td>1926-1935</td>
<td>195 (23)</td>
<td>249 (23)</td>
<td>1.1 (0.9-1.5)</td>
<td></td>
</tr>
<tr>
<td>1936-1945</td>
<td>292 (34)</td>
<td>382 (35)</td>
<td>1.0 (0.8-1.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;1945</td>
<td>252 (29)</td>
<td>314 (29)</td>
<td>1.0 (0.8-1.3)</td>
<td></td>
</tr>
<tr>
<td>Occupational ionizing radiation breast dose (Gy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-0.05</td>
<td>665 (77)</td>
<td>859 (79)</td>
<td>1.0 (Reference)</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt;0.05-0.1</td>
<td>108 (13)</td>
<td>121 (11)</td>
<td>1.2 (0.8-1.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.1-0.2</td>
<td>65 (8)</td>
<td>83 (8)</td>
<td>1.0 (0.7-1.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.2</td>
<td>21 (2)</td>
<td>20 (2)</td>
<td>1.3 (0.7-2.5)</td>
<td></td>
</tr>
<tr>
<td>Personal diagnostic X-ray breast dose score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-0.05</td>
<td>686 (80)</td>
<td>908 (84)</td>
<td>1.0 (Reference)</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt;0.05-0.1</td>
<td>106 (12)</td>
<td>104 (10)</td>
<td>1.3 (1.0-1.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.1-0.2</td>
<td>46 (5)</td>
<td>51 (5)</td>
<td>1.2 (0.8-1.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.2</td>
<td>21 (2)</td>
<td>20 (2)</td>
<td>1.4 (0.8-2.6)</td>
<td></td>
</tr>
<tr>
<td>Radionuclide procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>721 (84)</td>
<td>937 (87)</td>
<td>1.0 (Reference)</td>
<td>NA</td>
</tr>
<tr>
<td>Ever</td>
<td>65 (8)</td>
<td>71 (7)</td>
<td>1.2 (0.8-1.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>73 (9)</td>
<td>75 (7)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>803 (93)</td>
<td>1,021 (94)</td>
<td>1.0 (Reference)</td>
<td>NA</td>
</tr>
<tr>
<td>Ever</td>
<td>24 (3)</td>
<td>14 (1)</td>
<td>2.1 (1.0-4.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>32 (4)</td>
<td>48 (4)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*All ORs are adjusted for year of birth categories; occupational dose and personal diagnostic dose score analyses are mutually adjusted (categorically); radionuclide procedure analysis is adjusted for occupational dose categories, personal diagnostic dose score categories, and radiation therapy categories; radiation therapy analysis is adjusted for occupational dose categories, personal diagnostic dose score categories, and radionuclide procedures categories.

\(^{11}\) Trend test with categories of interest modeled as continuous variables in logistic regression analyses; adjusted for applicable covariates as indicated above.

year in controls) the subject was assigned to the “never” category.

We also created an ever/never variable for radiation therapy. Subjects were considered exposed if they received any cancer therapy or therapy for benign conditions in which breast tissue was likely to be located within the treatment field 10 years before breast cancer diagnosis (or equivalent year in controls). We assumed that radiation therapies for benign conditions in which breast tissue was not likely to be located within the treatment field would have been minor contributors to dose, and these procedures were not included. However, cancer therapy for sites more distant from breast tissue could result in significant scatter radiation to the breast because of higher treatment doses, so these procedures were included in the “ever” exposed category.

**Statistical Analysis.** For each SNP, the rare allele among controls was considered the variant allele. When <2% of the controls were homozygous variant, homozygous variant and heterozygous subjects were combined in one category. We assessed Hardy-Weinberg equilibrium among controls using \( \chi^2 \) or Fisher’s exact test.

Associations between SNPs and breast cancer were evaluated using unconditional univariate and multivariate logistic regression. Main effects of occupational breast dose and personal diagnostic radiation breast dose score were assessed by modeling the odds ratio (OR) as a linear function in logistic regression models:

\[
OR = 1 + \beta D
\]

where \( D \) is continuous radiation dose and \( \beta \) is the excess OR (EOR) per unit dose (Gy) or dose score. 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.

### Table 2. Nominal breast doses (Gy) applied to personal diagnostic radiographic procedures reported on questionnaires by radiologic technologists by calendar time period, U.S. Radiologic Technologists study

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures where most or all of breast tissue was within the beam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barium swallow</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Angiography (coronary)</td>
<td>NA</td>
<td>NA</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Routine chest X-ray</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
</tr>
<tr>
<td>Ribs X-ray</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>Thoracic spine X-ray</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>CT entire body</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
</tr>
<tr>
<td>CT chest (upper torso)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
</tr>
<tr>
<td>CT thoracic spine</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
</tr>
<tr>
<td>CT spine (if not otherwise stated)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
</tr>
<tr>
<td>Tomogram entire body</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>Tomogram chest (upper torso)</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>Tomogram thoracic spine</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>Tomogram spine (if not otherwise specified)</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>Mammogram</td>
<td>0.06</td>
<td>0.06</td>
<td>0.06 (1960-1969)</td>
<td>0.01 (1975-1980)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.03 (1970-1974)</td>
<td>0.005 (1981-1989)</td>
</tr>
<tr>
<td>Procedures where only part of breast tissue was within the beam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Cervical spine X-ray</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Abdomen X-ray</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Collar bone X-ray</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Shoulder X-ray</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Renal arteriogram</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Cholangiogram</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>I.v. retrograde pyelogram</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>KUB X-ray</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>CT abdomen</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>CT cervical spine, neck, clavicles</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>CT liver, spleen</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>CT kidney, renal</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>CT gall bladder, pancreas</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>CT unspecified site</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.002</td>
</tr>
<tr>
<td>Upper gastrointestinal series</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tomogram abdomen</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tomogram cervical spine, neck, clavicles</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tomogram liver, spleen</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tomogram gall bladder, pancreas</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tomogram kidney, renal</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
<tr>
<td>Tomogram, unspecified site</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Abbreviation: CT, computed tomography.

*Nominal per-procedure and time period-specific dose estimates from this table were multiplied by the number of self-reported procedures and summed to derive a cumulative personal diagnostic breast dose score.

†Not applicable as these procedures were not done in certain calendar periods.
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. Because 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.” Based on genotype main effect associations from the present study or information from a large pooled study (11), we also analyzed selected SNPs assuming a dominant mode of inheritance; that is, the heterozygous and homozygous variant subjects were combined.

All regression models were adjusted for year of birth. Occupational radiation main effect estimates as well as occupational radiation effect estimates stratified by genotype were adjusted for personal diagnostic radiation dose score (categorically as seen in Table 1) and vice versa. Adjustment for 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 or radiation main effect estimates or radiation effect estimates stratified by genotype, so these variables were not included in the final models.

Confidence intervals (CI) for genotype risk estimates were Wald-based, whereas CIs for radiation risk estimates were derived from the profile likelihood method. We used EPICURE software (Hirosoft) for linear dose-response analyses and SAS software (SAS Institute, release 8.02) for all other analyses.

Results

Selected distributions of demographic and ionizing radiation exposure variables are shown in Table 1, along with their corresponding ORs. Compared with controls, cases were more likely to have a previous history of radiation therapy. Cumulative occupational breast organ dose and personal diagnostic radiation breast dose score were not statistically significantly associated with breast cancer risk in multivariate regression (EOR/Gy = 1.4; 95% CI, 0.4-4.0; \( P = 0.3 \); EOR/Gy = 1.3; 95% CI, 0.4-4.0; \( P = 0.3 \), respectively). The two sources of radiation exposure were not correlated with each other (\( r^2 = 0.02 \)).

Allele frequencies in controls did not deviate from expectation based on Hardy-Weinberg equilibrium. In multivariate analyses (Table 3), the minor allele of \( CASP8 \) D302H was associated with a significantly decreased risk of breast cancer (OR, 0.3; 95% CI, 0.1-0.8). The minor allele of \( CDKN1A \) S31R was present in seven controls and none of the cases; the upper bound of the 95% CI was 0.3. Risk of breast cancer was significantly associated with an increase in the number of the minor alleles for \( IL1A \) A114S (heterozygote OR, 1.2; 95% CI, 1.0-1.4 and homozygote OR, 1.5; 95% CI, 1.1-2.0; \( P_{\text{trend}} = 0.008 \)).

Interactions with ionizing radiation–associated breast cancer risk by genotype are shown in Table 4. Suggestive evidence of interaction with personal diagnostic X-ray radiation exposure score were observed for three genotypes based on likelihood ratio test \( P \) values: DR4 (rs4871857, \( P = 0.09 \)), \( IL1A \) (rs17561, \( P = 0.004 \)), and \( IGFBP3 \) IVS3-707→A (rs6413441, \( P = 0.03 \)) that all involved personal diagnostic X-ray exposure. No interaction was observed for occupational radiation exposure and genotype. When a dominant model was assumed for these SNPs, the likelihood ratio test \( P \) value for diagnostic radiation exposure was 0.03 for the DR4 genotype. The magnitude of the DR4 genotype–specific breast cancer risk estimates for occupational radiation dose and diagnostic radiation dose score for any minor allele (CG or CC) were similar, with an EOR/Gy of 2.2 (95% CI, <0–7.1) and an EOR/unit breast dose score of 2.7 (95% CI, 0.04-7.0), respectively. Assuming a dominant model for the \( IL1A \) genotype, the likelihood ratio test \( P \) value for diagnostic radiation exposure was 0.002. The \( IL1A \) genotype–specific breast cancer risk estimate for diagnostic radiation exposure score was strongest for the heterozygous group (EOR 7.8; 95% CI, 2.3-17). For \( IGFBP3 \), a dominant model was not used because only the homozygous variant subjects showed a significantly different EOR, suggesting a possible recessive effect. Subjects heterozygous for \( TGFB1 \) L10P had a significantly elevated EOR of 2.9 (95% CI, 0.4-9.6) for occupational radiation dose, but when analyzed in a dominant model the EOR did not differ from those homozygous for the major allele and was no longer statistically significant (EOR 1.6; 95% CI, <0–5.8).

Discussion

In our evaluation of common variants in apoptosis-related genes, we found a significantly decreased risk of breast cancer associated with the HH genotype of \( CASP8 \) D302H. The association with the minor allele of \( CASP8 \) D302H has been confirmed by a large breast cancer consortium in which the present study was included (11). As yet, the function of the \( CASP8 \) D302H variant is not known, but caspase-8 plays a central role in the extrinsic tumor necrosis factor family death receptor pathway leading to the activation of the effector caspases (27). We also found a significantly increasing risk associated with the minor alleles of \( IL1A \) A114S. Interleukin-1 possesses pleiotropic effects that are associated with infection, inflammation, and autoimmune processes. Interleukin-1α acts as an early-response proinflammatory cytokine, a transcription factor, and interleukin-1 plays a dominant role in mediating systemic inflammation (28). Several types of cancer have been associated with chronic inflammation (29). The \( IL1A \) A114S polymorphism is closely located to a protease cleavage site (30) and the A5 or S5 genotypes were associated with higher circulating levels of C-reactive protein than the AA genotype (31), suggesting a functional role for this variant. The rare allele of \( IL1A \) A114S was associated with a reduced risk of breast cancer in one previous study (32), an observation in the opposite direction of the present study. To our knowledge, no other studies have investigated the association of breast cancer and \( IL1A \) A114S.

Unique features of this study were its large size (859 cases and 1,083 controls), carefully reconstructed cumulative occupational radiation breast dose estimates (18, 19), cumulative questionnaire-based diagnostic radiation breast dose scores, and the availability of
detailed information about reproductive, demographic, and lifestyle factors derived from interviews of all subjects. Our risk estimates for both occupational and personal diagnostic radiation exposure were consistent with the entire cohort (data not shown) and from studies of radiation effects on breast cancer risk (ref. 33; reviewed in ref. 34). In addition, age at menarche, first degree relatives with breast cancer, number of live births, age at first live birth, history of benign breast disease, age at menopause, years of hormone replacement therapy, and body mass index were all associated with breast cancer risk in the direction and with the magnitude expected. We did not find an association with oral contraceptive use or alcohol consumption.

We found evidence of heterogeneity in the personal diagnostic radiation score dose-response relationship by two genotypes DR4 R209T and IL1A A114S, indicating possible effect modification. For the DR4 R209T polymorphism, the pattern and magnitude of the EOR/Gy were similar for both sources of radiation exposure in a dominant model, supporting the relationship between the genetic variant and radiation-associated breast cancer risk.

### Table 3. Age-adjusted associations between apoptosis-related SNPs and breast cancer risk in U.S. Radiologic Technologists

<table>
<thead>
<tr>
<th>Gene (alias)</th>
<th>Entrez SNP ID*</th>
<th>AA or nt variant ID</th>
<th>Genotype</th>
<th>Cases (n = 859)</th>
<th>Controls (n = 1,083)</th>
<th>Multivariateb, OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHR</td>
<td>rs2066853</td>
<td>R554K</td>
<td>GG</td>
<td>681 (82%)</td>
<td>870 (80%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GA</td>
<td>139 (17%)</td>
<td>199 (18%)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>13 (2%)</td>
<td>12 (1%)</td>
<td>1.5 (0.6-3.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>CASP8</td>
<td>rs13113</td>
<td>Ex14-271A&gt;T</td>
<td>TT</td>
<td>258 (32%)</td>
<td>329 (32%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AT</td>
<td>410 (50%)</td>
<td>520 (50%)</td>
<td>1.0 (0.8-1.3)</td>
<td>0.8</td>
</tr>
<tr>
<td>CASP8</td>
<td>rs1045485</td>
<td>D302H</td>
<td>GG</td>
<td>660 (77%)</td>
<td>802 (76%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GC</td>
<td>185 (22%)</td>
<td>232 (22%)</td>
<td>1.0 (0.8-1.2)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>7 (1%)</td>
<td>22 (2%)</td>
<td>0.3 (0.1-0.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>CDKN1A† (p21)</td>
<td>rs1801279</td>
<td>S31R</td>
<td>CA</td>
<td>110 (14%)</td>
<td>141 (13%)</td>
<td>0.9 (0.7-1.2)</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>0 (0%)</td>
<td>7 (1%)</td>
<td>(-0.3)</td>
<td></td>
</tr>
<tr>
<td>DR4 (TNFRSF10A; TRAIL-R1)</td>
<td>rs4871857</td>
<td>R209T</td>
<td>GG</td>
<td>244 (29%)</td>
<td>322 (30%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GC</td>
<td>411 (48%)</td>
<td>520 (48%)</td>
<td>1.1 (0.9-1.3)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CA</td>
<td>197 (23%)</td>
<td>236 (22%)</td>
<td>1.1 (0.8-1.4)</td>
<td>0.6</td>
</tr>
<tr>
<td>IL1A</td>
<td>rs17561</td>
<td>A114S</td>
<td>GG</td>
<td>392 (47%)</td>
<td>557 (52%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GC</td>
<td>343 (41%)</td>
<td>417 (39%)</td>
<td>1.2 (1.0-1.4)</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT</td>
<td>99 (12%)</td>
<td>100 (9%)</td>
<td>1.5 (1.1-2.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>TP53</td>
<td>rs17882155</td>
<td>P72R</td>
<td>AA</td>
<td>626 (75%)</td>
<td>805 (74%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG</td>
<td>185 (22%)</td>
<td>258 (24%)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>19 (2%)</td>
<td>22 (2%)</td>
<td>1.4 (0.9-2.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>CASP8</td>
<td>rs1045485</td>
<td>D302H</td>
<td>GG</td>
<td>660 (77%)</td>
<td>802 (76%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GC</td>
<td>185 (22%)</td>
<td>232 (22%)</td>
<td>1.0 (0.8-1.2)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>7 (1%)</td>
<td>22 (2%)</td>
<td>0.3 (0.1-0.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>TP53</td>
<td>rs17883831</td>
<td>IVS6+62A&gt;G</td>
<td>AA</td>
<td>626 (75%)</td>
<td>805 (74%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AG</td>
<td>185 (22%)</td>
<td>258 (24%)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>19 (2%)</td>
<td>22 (2%)</td>
<td>1.4 (0.9-2.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs2854744</td>
<td>−202A&gt;C</td>
<td>AA</td>
<td>207 (25%)</td>
<td>236 (22%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AC</td>
<td>408 (50%)</td>
<td>521 (48%)</td>
<td>0.9 (0.7-1.1)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>201 (25%)</td>
<td>238 (22%)</td>
<td>0.8 (0.6-1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs2132572</td>
<td>−670G&gt;A</td>
<td>GA</td>
<td>539 (64%)</td>
<td>664 (62%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AA</td>
<td>266 (31%)</td>
<td>353 (33%)</td>
<td>0.9 (0.8-1.1)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CC</td>
<td>72 (7%)</td>
<td>72 (7%)</td>
<td>0.9 (0.6-1.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs2471551</td>
<td>IVS2-17G&gt;C</td>
<td>CC</td>
<td>572 (67%)</td>
<td>705 (65%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GC</td>
<td>240 (29%)</td>
<td>333 (31%)</td>
<td>0.9 (0.8-1.1)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GG</td>
<td>25 (3%)</td>
<td>46 (4%)</td>
<td>0.7 (0.4-1.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs9282734</td>
<td>H158P</td>
<td>AA</td>
<td>817 (99%)</td>
<td>1,073 (99%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AC</td>
<td>7 (1%)</td>
<td>7 (1%)</td>
<td>1.3 (0.5-3.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs6413441</td>
<td>IVS4-707-&gt;A</td>
<td>CC</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AC</td>
<td>13 (2%)</td>
<td>12 (1%)</td>
<td>1.5 (0.6-3.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>TGFB1</td>
<td>rs982073</td>
<td>L10P</td>
<td>AA</td>
<td>122 (15%)</td>
<td>185 (17%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TC</td>
<td>291 (36%)</td>
<td>394 (37%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT</td>
<td>295 (38%)</td>
<td>506 (47%)</td>
<td>1.1 (0.9-1.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>TGFB1</td>
<td>rs1800471</td>
<td>P25R</td>
<td>GG</td>
<td>684 (85%)</td>
<td>730 (86%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GC</td>
<td>115 (14%)</td>
<td>113 (13%)</td>
<td>1.1 (0.8-1.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>TGFB1</td>
<td>rs1800472</td>
<td>T263I</td>
<td>CC</td>
<td>776 (99%)</td>
<td>996 (94%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CT</td>
<td>41 (5%)</td>
<td>59 (6%)</td>
<td>0.9 (0.6-1.4)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TT</td>
<td>0 (0%)</td>
<td>1 (-1%)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

†Amino acid sequence variation (regular font), nucleotide sequence variation (italics).
‡Adjusted for year of birth.
¶Upper 95% OR bound (Epicure) for homozygote variants = 0.3.
#ORtrend: 1.2 (95% CI, 1.0-1.4; P = 0.008).
{Rare homozygous variant carriers combined with heterozygotes.

Cancer Epidemiology, Biomarkers & Prevention 2005;16(10). October 2007

Downloaded from cebp.aacrjournals.org on June 20, 2017. © 2007 American Association for Cancer Research.
risk. However, the main effect for DR4 R209T in this and a previous study (35) was not significant, with the genotype-specific radiation-breast cancer risk relationship decreased for one group and increased in the others (Table 4), suggesting possible statistical variability.

The IL1A A114S polymorphism, despite an overall association with breast cancer risk, showed a dissimilar pattern between the EOR/Gy by genotype for personal diagnostic radiation dose score compared with occupational radiation dose. It is possible that the low protracted exposures that characterize chronic occupational exposure may not activate DNA repair, inflammatory or apoptotic mechanisms (36), whereas somewhat higher and typically acute doses associated with many personal diagnostic or therapeutic radiological procedures (e.g., gastrointestinal series, mammograms, fluoroscopically guided procedures) may be sufficient to induce cellular or tissue reactions.

Some limitations of our study were that cases must have survived from the time of breast cancer diagnosis to blood collection, which averaged 21.5 years. However, analysis of allele frequencies over time showed no significant trends or differences (data not shown), suggesting none of the genotypes were correlates of survival. 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

### Table 4. Analysis of interaction between apoptosis-related SNPs, breast radiation dose from occupation and dose score from personal diagnostic X-rays, and breast cancer risk in U.S. Radiologic Technologists

<table>
<thead>
<tr>
<th>Gene</th>
<th>Entrez SNP ID*</th>
<th>AA or nt variant ID †</th>
<th>Genotype</th>
<th>Occupational radiation interaction</th>
<th>Diagnostic radiation interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>EOR/Gy ‡ (95% CI)</td>
<td>Px</td>
</tr>
<tr>
<td>AHR</td>
<td>rs2066853</td>
<td>R554K</td>
<td>GG</td>
<td>1.8 (&lt;0-6.3)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>GA/AA</td>
<td></td>
<td></td>
<td>0.3 (&lt;0-6.3)</td>
<td>&lt;0</td>
</tr>
<tr>
<td>CASP8</td>
<td>rs13113</td>
<td>Ex14-271A&gt;T</td>
<td>TT</td>
<td>&lt;0 (&lt;0-4.3)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>AT</td>
<td></td>
<td>3.0 (&lt;0-9.3)</td>
<td>0.4</td>
<td>0.5 (&lt;0-3.9)</td>
</tr>
<tr>
<td>CASP8</td>
<td>rs1045485</td>
<td>D302H</td>
<td>GG</td>
<td>1.3 (&lt;0-5.4)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>GC/CC</td>
<td></td>
<td>1.7 (&lt;0-9.0)</td>
<td>&gt;0.5</td>
<td>0.5 (&lt;0-3.9)</td>
</tr>
<tr>
<td>CDKN1A</td>
<td>rs1801279</td>
<td>S31R</td>
<td>CC</td>
<td>0.9 (&lt;0-4.6)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>CA/AA</td>
<td></td>
<td>3.3 (&lt;0-17.6)</td>
<td>&gt;0.5</td>
<td>0.3 (&lt;0-13.4)</td>
</tr>
<tr>
<td>DR4</td>
<td>rs4871857</td>
<td>R209T</td>
<td>GG</td>
<td>0.04 (&lt;0-4.5)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>GA/AA</td>
<td></td>
<td>2.2 (&lt;0-7.8)</td>
<td>&gt;0.5</td>
<td>2.7 (&lt;0-8.0)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td></td>
<td>2.3 (&lt;0-12.1)</td>
<td>&gt;0.5</td>
<td>2.7 (&lt;0-11.6)</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td></td>
<td>1.1 (&lt;0-5.5)</td>
<td>&gt;0.5</td>
<td>&lt;0 (&lt;0-1.0)</td>
</tr>
<tr>
<td></td>
<td>TG</td>
<td></td>
<td>0.6 (&lt;0-6.1)</td>
<td>&gt;0.5</td>
<td>7.8 (2.3-16.8)</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td></td>
<td>0.0 (&lt;0-7.7)</td>
<td>&gt;0.5</td>
<td>1.7 (1.4-14.4)</td>
</tr>
<tr>
<td>TP53</td>
<td>rs17882155</td>
<td>P72R</td>
<td>GG</td>
<td>2.5 (&lt;0-8.0)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td></td>
<td>0.4 (&lt;0-5.0)</td>
<td>&gt;0.5</td>
<td>2.8 (&lt;0-9.4)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td></td>
<td>0.7 (&lt;0-16.4)</td>
<td>&gt;0.5</td>
<td>&lt;0 (&lt;0-9.2)</td>
</tr>
<tr>
<td>TP53</td>
<td>rs17883831</td>
<td>IVS6-62A&gt;G</td>
<td>AA</td>
<td>1.9 (&lt;0-6.4)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>AG/GG</td>
<td></td>
<td>0.0 (&lt;0-5.5)</td>
<td>&gt;0.5</td>
<td>0.08 (&lt;0-4.4)</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs2854744</td>
<td>−202A&gt;C</td>
<td>AA</td>
<td>2.7 (&lt;0-11.8)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td></td>
<td>1.3 (&lt;0-6.2)</td>
<td>&gt;0.5</td>
<td>1.8 (&lt;0-6.6)</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td></td>
<td>0.4 (&lt;0-6.8)</td>
<td>&gt;0.5</td>
<td>0.2 (&lt;0-5.5)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td></td>
<td>1.2 (&lt;0-5.6)</td>
<td>&gt;0.5</td>
<td>2.9 (&lt;0-7.5)</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td></td>
<td>1.0 (&lt;0-6.7)</td>
<td>&gt;0.5</td>
<td>0.8 (&lt;0-5.8)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td></td>
<td>5.2 (&lt;36.7)</td>
<td>&gt;0.5</td>
<td>&lt;0 (&lt;0-2.5)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td></td>
<td>1.3 (&lt;0-5.5)</td>
<td>&gt;0.5</td>
<td>1.2 (&lt;0-4.7)</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td></td>
<td>1.9 (&lt;0-9.5)</td>
<td>&gt;0.5</td>
<td>1.7 (&lt;0-8.0)</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td></td>
<td>&lt;0 (&lt;15.5)</td>
<td>&gt;0.5</td>
<td>&lt;0 (&lt;0-19.7)</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs9282734</td>
<td>H138P</td>
<td>AA</td>
<td>1.0 (&lt;0-4.7)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td></td>
<td>14.6 (&lt;443)</td>
<td>&gt;0.5</td>
<td>0.2 (&lt;0-150)</td>
</tr>
<tr>
<td>IGFBP3</td>
<td>rs6413441</td>
<td>IVS3-707-&gt;A</td>
<td>-/-</td>
<td>0.4 (&lt;0-5.6)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>-/-A</td>
<td></td>
<td>0.4 (&lt;0-8.0)</td>
<td>&gt;0.5</td>
<td>2.7 (&lt;0-7.7)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td></td>
<td>0.6 (&lt;0-9.1)</td>
<td>&gt;0.5</td>
<td>&lt;0 (&lt;0-9.2)</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td></td>
<td>1.3 (&lt;0-6.2)</td>
<td>&gt;0.5</td>
<td>1.1 (&lt;0-5.6)</td>
</tr>
<tr>
<td></td>
<td>GC</td>
<td></td>
<td>2.9 (0.4-9.6)</td>
<td>&gt;0.5</td>
<td>2.4 (&lt;0-7.8)</td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td></td>
<td>&lt;0 (&lt;0-3.3)</td>
<td>&gt;0.5</td>
<td>&lt;0 (&lt;0-7.3)</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>rs982073</td>
<td>L10P</td>
<td>GG</td>
<td>1.2 (&lt;0-5.4)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td></td>
<td>1.0 (&lt;0-10.6)</td>
<td>&gt;0.5</td>
<td>&lt;0 (&lt;0-19.7)</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>rs1800471</td>
<td>P25R</td>
<td>GG</td>
<td>1.5 (&lt;0-5.3)</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>rs1800472</td>
<td>T263I</td>
<td>CC</td>
<td>0.3 (&lt;0-23.7)</td>
<td>&gt;0.5</td>
</tr>
</tbody>
</table>

† Amino acid sequence variation (regular font), nucleotide sequence variation (italics).
‡ Excess OR adjusted for year of birth and occupational or personal diagnostic radiation dose; significance of EOR/Gy is denoted when the 95% CI (profile likelihood bounds) exclude the null value of zero.
¶ Likelihood ratio test comparing the genotype-specific EORs.
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. Although it is impossible to know with certainty that genotypes did not vary differentially among the decedents, a recent analysis did not show significant differences in SNP genotype frequencies with respect to levels of response in control groups from three different study groups, including the present one (37). It is possible that the associations we observed between personal diagnostic radiation dose score and breast cancer risk were confounded by other breast cancer risk factors that are associated with increased screening for breast cancer, such as family history of breast cancer and history of benign breast disease. Inclusion of these variables, however, did not appreciably alter the regression point estimates.

Our study of the joint effects of genotypic variants and quantitative estimates of breast occupational radiation dose and personal diagnostic radiation dose scores to the breast in the U.S. Radiologic Technologists cohort is among the first to assess potential gene and low-dose radiation interaction. We identified two polymorphisms, DR4 R209T and IL1A A114S, that may modify the radiation-associated breast cancer risk. These findings need to be replicated in studies with substantially larger numbers of women with information on personal diagnostic procedures or occupational radiation doses to the breast in the low- to moderate-dose range.

Acknowledgments

We thank the radiologic technologists who participated in the U.S. Radiologic Technologists Study; Jerry Reid of the American Registry of Radiologic Technologists for continued support of this study; Diane Kampa and Allison Iwan of the University of Minnesota for data collection and study coordination; and Chris McClure of Research Triangle International, Inc., for tracing and data management.

References

Polymorphisms in Apoptosis- and Proliferation-Related Genes, Ionizing Radiation Exposure, and Risk of Breast Cancer among U.S. Radiologic Technologists

Alice J. Sigurdson, Parveen Bhatti, Michele M. Doody, et al.


**Updated version**
Access the most recent version of this article at: [http://cebp.aacrjournals.org/content/16/10/2000](http://cebp.aacrjournals.org/content/16/10/2000)

**Cited articles**
This article cites 32 articles, 9 of which you can access for free at: [http://cebp.aacrjournals.org/content/16/10/2000.full.html#ref-list-1](http://cebp.aacrjournals.org/content/16/10/2000.full.html#ref-list-1)

**Citing articles**
This article has been cited by 8 HighWire-hosted articles. Access the articles at: [http://cebp.aacrjournals.org/content/16/10/2000.full.html#related-urls](http://cebp.aacrjournals.org/content/16/10/2000.full.html#related-urls)

**E-mail alerts**
Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.