Research Article

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# Family History, Mammographic Density, and Risk of Breast Cancer

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## Abstract

**Purpose:** Mammographic density is a strong and highly heritable risk factor for breast cancer. The purpose of this study was to examine the extent to which mammographic density explains the association of family history of breast cancer with risk of the disease.

**Subjects and Methods:** We carried out three nested case-control studies in screening programs that included in total 2,322 subjects (1,164 cases and 1,158 controls). We estimated the independent and combined associations of family history and percent mammographic density at baseline with subsequent breast cancer risk.

**Results:** After adjustment for age and other risk factors, compared with women with no affected first-degree relatives, percent mammographic density was 3.1% greater for women with one affected first-degree relative, and 7.0% greater for women with two or more affected relatives ($P$ = 0.001 for linear trend across family history categories). The odds ratios for breast cancer risk were 1.37 [95% confidence interval (95% CI), 1.10-1.72] for having one affected relative, and 2.45 (95% CI, 1.30-4.62) for having two or more affected relatives ($P$ for trend = 0.0002). Adjustment for percent mammographic density reduced these odds ratios by 16% and 14%, respectively. Percent mammographic density explained 14% (95% CI, 4-39%) of the association of family history (at least one affected first-degree relative) with breast cancer risk.

**Conclusions:** Percent mammographic density has features of an intermediate marker for breast cancer, and some of the genes that explain variation in percent mammographic density might be associated with familial risk of breast cancer. *Cancer Epidemiol Biomarkers Prev; 19(2); 456–63. ©2010 AACR.*

## Introduction

The tendency of breast cancer to cluster in families is widely recognized, and most of this familial aggregation is thought to reflect inherited susceptibility (1). However, it is estimated that only 20% to 25% of the excess risk of breast cancer in the first-degree relatives of women affected by the disease can be attributed to mutations in known genes, including the high-penetrance susceptibility genes *BRCA1* and *BRCA2*, as well as the moderate and low-penetrance genes identified to date (2-4). Much remains to be learned about why having a family history of the disease is a risk factor for breast cancer.

We consider here the association of family history of breast cancer with mammographic density, a strong risk factor for the disease that is highly heritable (5). Mammographic density refers to the extent of radiologically dense breast tissue, which varies greatly across women of the same age, reflecting differences in breast tissue composition (6). Stroma and epithelium attenuate X-rays more than fat and appear light in a mammogram, whereas fat appears dark (7). The extent of mammographic density is expressed as a percentage by determining the proportion of the total projected area in the breast that is occupied by dense tissue. Women with density in ≥75% of the breast have a risk of breast cancer four to six times that of women of the same age and body mass index with little or no density (8, 9).

Percent mammographic density (PMD) is associated with several factors that are also associated with risk of breast cancer. PMD is lower in women who are parous or postmenopausal (10, 11), is increased by the use of hormone therapy (12), and is reduced by the use of tamoxifen (13). Body weight and age, however, are inversely associated with PMD (14, 15). These factors account for only about 20% to 30% of the variance of PMD. Twin studies have shown that >60% of the residual variance after adjustment for age and other covariates can be explained by inherited factors (5). As PMD is a risk factor for breast cancer, and is highly heritable, it might account for some of the association of family history with risk of breast cancer. Some previous studies, using qualitative methods of classifying mammographic features, have shown that women with a family history of the disease

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have more extensive mammographic density than women with no family history (16-20), but other studies have failed to find this association (11, 21-25). PMD is associated with risk of breast cancer for women with a family history of the disease (24, 26, 27) and for women who carry deleterious mutations in *BRCA1* and *BRCA2* (28). However, the extent to which mammographic density might account for the association of family history with risk of breast cancer has not been previously examined. Consequently, the purpose of this study was to measure the association of family history of breast cancer with PMD, and to determine the extent to which the association of family history with breast cancer risk could be explained by PMD.

## Materials and Methods

### General Method

The methods have been described elsewhere (9) and are given only briefly here. We used data from three nested case-control studies carried out in screening populations to examine the association of family history and PMD at the time of entry to the screening program, and the independent and combined associations of these risk factors with the risk of breast cancer during subsequent follow-up. The populations included were the National Breast Screening Study (NBSS), a randomized trial of screening with mammography and physical examination (29, 30); the Screening Mammography Program of British Columbia (SMPBC); and the Ontario Breast Screening Program (OBSP). Ethical approval was obtained from the University of Toronto, University Health Network (Toronto), the OBSP, and the University of British Columbia.

### Selection of Subjects

For the NBSS, informed consent was obtained at entry to the trial for research applications using the data collected, and all 354 women diagnosed with invasive breast cancer from 1984 to 1990, and their matched controls, were included (9). The criteria for selection of cases and controls for the NBSS were the same as those described below for the OBSP and SMPBC. For the OBSP and SMPBC, cases were women diagnosed with histologically verified invasive breast cancer diagnosed during the years 1992 to 1998 for the OBSP, and 1988 to 1999 for the SMPBC. Women diagnosed within 12 mo of their first screening examination were excluded.

Eligible cases and controls in the OBSP and SMPBC were contacted by mail and telephone, and asked for consent for the release of their mammogram and to complete a self-administered questionnaire (9). For each case, we selected up to 10 controls, individually matched according to year of entry to the screening program (within 1 y), screening center, age at entry to the program (within 1 y), and a duration of follow-up without breast cancer that was at least as long as the time the corresponding case subject had been in the program before cancer had been diagnosed. Controls for each case were contacted in random order until one control was recruited. Fifty percent of cases and 54% of controls selected from the OBSP and SMPBC agreed to take part.

### Data Collection

Information on breast cancer risk factors was obtained by self-administered questionnaire at the time of entry to the study for the NBSS, and at time of recruitment for the other two programs (with reference to the time of the first mammogram).

The cranio-caudal view of the unaffected breast for cases, and the corresponding breast for controls, taken at entry to the screening program (1 to 8 y prior to diagnosis of breast cancer) was used to measure PMD. Examination of the unaffected breast excludes the possibility of bias in the measurement of PMD where the presence of a cancer may add to the measurement of PMD in cases, and also unblinds the reader to the case-control status of the subject. The use of prediagnosis mammograms minimizes the effect of any molecular changes in the unaffected breast in breast cancer patients. Mammograms were digitized using a Lumisys 85 digitizer, and PMD was measured by one observer (NFB) using a previously described interactive thresholding technique (31). Reliability for measuring PMD, assessed by rereading a 10% random sample of images was 0.94 both within and between reads.

### Statistical Methods

Of the 2,418 subjects recruited, 96 with missing data for variables known to be strongly associated with PMD (body mass index, $n = 43$; parity, $n = 4$; menopausal status, $n = 28$; ever use of hormone therapy, $n = 31$) or for family history ($n = 2$) were excluded, leaving a total of 1,164 cases and 1,158 controls for analysis. For regression analyses, values were imputed for missing data for age at menarche ($n = 56$), age at first birth ($n = 10$), and age at menopause ($n = 184$) by using the mean value for each variable for subjects within the same screening population.

The characteristics of the case and control subjects were compared using two sample *t*-tests for symmetrically distributed continuous variables, Wilcoxon rank sum tests for continuous variables whose distributions were skewed, and $\chi^2$ test for categorical variables. The association of family history categories (0, 1, or $\geq 2$ affected first-degree relatives) with PMD was assessed using multiple linear regression. PMD was square root–transformed to improve normality and is shown after back-transformation in the tables. All *P* values were calculated from two-tailed tests of statistical significance.

The odds ratios (OR) for risk of breast cancer associated with family history and PMD, before and after adjustment for each other, were estimated using unconditional logistic regression. Although a matched study design was used, the results of unmatched analyses are presented as subjects were divided into categories of family history and PMD. Analysis of the matched data using conditional logistic regression showed similar results. In previous

work, percent mammographic density was divided into six categories (9), but due to small numbers of subjects in some categories of mammographic density and family history, we combined the lower two categories (0% and <10%) and the upper two categories (50-75% and >75%) for this paper. The association of family history with breast cancer risk was examined when number of affected first-degree relatives was considered as a binary variable (0 versus ≥1 affected first-degree relatives) and as a continuous variable (multiplicative model). The difference between the OR for family history and PMD before and after adjustment for each other was calculated as [(OR-1)-($OR_{adj}$-1)]/(OR-1). Attributable risk was calculated by the formula: attributable risk = (OR-1)$P_c$/OR; where OR denotes the odds ratio for the risk category compared with the baseline risk category (adjusted for breast cancer risk factors), and $P_c$ is the prevalence of the risk factor in case subjects (32). Attributable risk was calculated for at least one affected first-degree relative with breast cancer compared with no affected first-degree relatives and for percent mammographic density of >50% compared with <10%.

We estimated the proportion of the association of family history with breast cancer that is explained by PMD by examining the effect of adjustment for PMD on the regression coefficient for family history as described by Freedman (33): proportion explained = ($\beta_{unadjusted}$ - $\beta_{adjusted}$)/$\beta_{unadjusted}$ × 100. The associated 95% confidence intervals (95% CI) were estimated using the Freedman (33, 34) and Bootstrap methods using 1,000 samples.

## Results

### Characteristics of Case and Control Subjects (Table 1)

Mean height, weight, and body mass index were similar in cases and controls. Compared with controls, cases

**Table 1.** Selected characteristics of cases and controls

| | Mean (SD) or % | | *P** |
|---|---|---|---|
| | Cases (*n* = 1,164)† | Controls (*n* = 1,158)† | |
| Age at mammogram (y) | 56.6 (9.1) | 56.8 (9.1) | 0.64 |
| Height (cm) | 162.3 (6.5) | 162.2 (6.7) | 0.77 |
| Weight (kg) | 65.8 (11.6) | 65.5 (11.3) | 0.81 |
| Body mass index (kg/m$^2$) | 25.0 (4.3) | 24.9 (4.3) | 0.95 |
| Age at menarche (y) | 12.9 (1.5) | 13.0 (1.5) | 0.03 |
| | *n* = 1,134 | *n* = 1,132 | |
| Parity (% parous) | 84.5 | 88.6 | 0.004 |
| Age at first birth‡ (y) | 24.8 (4.7) | 24.3 (4.4) | 0.04 |
| | *n* = 978 | *n* = 1,022 | |
| Number of live births‡ | 2.9 (1.5) | 3.1 (1.6) | 0.02 |
| | *n* = 983 | | |
| Menopausal status (% postmenopausal) | 74.3 | 75.9 | 0.37 |
| Age at menopause§ (y) | 46.4 (6.7) | 45.6 (6.9) | 0.02 |
| | *n* = 779 | *n* = 781 | |
| HRT use (% ever) | 35.7 | 32.4 | 0.09 |
| Duration of HRT use‖ (y) | 6.8 (7.6) | 7.1 (7.9) | 0.88 |
| | *n* = 389 | *n* = 344 | |
| Breast cancer in first-degree relatives (%) | | | 0.003 |
| 0 | 79.6 | 84.5 | |
| 1 | 17.8 | 14.2 | |
| ≥2 | 2.6 | 1.3 | |
| PMD (%) | 32.6 (19.7) | 26.8 (19.2) | <0.0001 |

Abbreviation: HRT, hormone replacement therapy; PMD, percent mammographic density.

*Two-sided two-sample *t*-test for age, height, age at menarche, and age at menopause. Two-sided Wilcoxon two-sample test for weight, body mass index, age at first birth, number of live births, duration of hormone replacement therapy use, and percent mammographic density; $\chi^2$ test for categorical variables.

†Total number of cases and controls. Data shown do include inputed values for missing data (see text). For variables with missing data, the number (*n*) of subjects with data is shown in the table.

‡Among parous women.

§Among postmenopausal women.

‖Among users of HRT.

**Table 2.** Percent mammographic density by number of first-degree relatives with breast cancer and case/control status

| | Number of affected first degree relatives | | | $P^{\dagger}$ |
|---|---|---|---|---|
| | 0 | 1 | ≥2 | |
| All | 27.78 (26.35-29.24) | 30.90 (28.65-33.23) | 34.73 (29.05-40.91) | 0.001 |
| | *n* = 1,904 | *n* = 372 | *n* = 46 | |
| Cases | 30.96 (29.26-32.70) | 31.97 (29.18-34.90) | 36.29 (29.43-43.87) | 0.09 |
| | *n* = 926 | *n* = 207 | *n* = 31 | |
| Controls | 24.57 (23.04-26.14) | 29.03 (26.09-32.12) | 30.56 (21.82-40.77) | 0.003 |
| | *n* = 978 | *n* = 165 | *n* = 15 | |
| *P** | <0.0001 | 0.12 | 0.32 | |

NOTE: The values are least squares mean (95% CI) for PMD; adjusted for age at mammogram, body mass index, age at menarche, parity (parous/nonparous), number of live births, age at first birth, menopausal status (pre-/post-menopausal), age at menopause, and HRT use (ever/never). The least squares means for cases and controls were estimated using data for all subjects and a regression model with an interaction between case/control status and family history category (0, 1 or ≥2). PMD was square root–transformed for analysis and the results are shown on back-transformed scale.

*Two-sided test of the difference between cases and controls within a column.

†Two-sided test of linear trend across the rows, with three category family history as an ordinal variable.

had an earlier menarche, were more often nulliparous, and had a smaller number of live births, later menopause, and more frequent ever use of hormone therapy. The observed average age at menopause is lower than the median age expected for North American women (50 to 51 years; ref. 35). The average age at menopause in cross-sectional data is biased downward because not all women in the population have yet experienced menopause, and the women who have earlier menopause tend to be overrepresented compared with women who will experience later menopause. The number of first-degree relatives with breast cancer differed significantly between cases and controls. For cases, 207 subjects (17.8%) had one affected first-degree relative and 31 (2.6%) had two or more such relatives, whereas for controls 165 subjects (14.2%) had one affected first-degree relative and 15 (1.3%) had two or more. PMD was 5.8% greater in cases compared with controls.

### Family History and PMD

Table 2 shows the least squares means for PMD, adjusted for covariates described in the table legend, according to family history of breast cancer in all subjects and by case/control status. PMD was positively associated with the number of affected first-degree relatives in all subjects ($P = 0.001$), in cases ($P = 0.09$) and controls ($P = 0.003$), and was greater in cases compared with controls within each category of family history, although this difference was statistically significant only for the largest group of subjects with no first-degree relatives with breast cancer ($P < 0.0001$). There was no interaction between case-control status and number of affected first-degree relatives ($P = 0.20$).

### Risk of Breast Cancer According to Family History: Effect of Adjustment for PMD

Before adjustment for PMD (continuous variable), the ORs for risk of breast cancer were 1.37 (95% CI, 1.10-1.72) for those with one affected first-degree relative, and 2.45 (95% CI, 1.30-4.62) for those with two or more affected relatives (Table 3A). The attributable risk of breast cancer associated with having at least one affected first-degree relative was 6.4%. After adjustment for PMD, the OR for one affected first-degree relative became 1.31 (95% CI, 1.04-1.65), a reduction of 16%, and the OR for two or more affected first-degree relatives became 2.25 (95% CI, 1.19-4.27), a reduction of 14%. When we considered the number of first-degree relatives with breast cancer as a continuous variable (0, 1, ≥2 relatives), the OR for breast cancer risk was 1.44 (95% CI, 1.19-1.73; $P = 0.0002$) and was reduced to 1.37 (95% CI, 1.13-1.66; $P = 0.001$) after adjustment for PMD, a 16% difference.

The proportion of the association of family history (0 compared with ≥1 affected relatives) with breast cancer risk explained by PMD (as a continuous variable) was calculated using the Freedman method. This method estimated that 14% (95% CI, 4-39%) of the association of a first-degree family history on breast cancer risk was explained by PMD. When the number of first-degree relatives with breast cancer was considered as a continuous variable (0, 1, ≥2 relatives), the Freedman method estimated that 13% (95% CI, 3-35%) of the association of family history with breast cancer risk was explained by PMD. The upper and lower limits of the confidence intervals for these estimates were confirmed by Bootstrap using 1,000 samples (95% CI, 4-35% and 4-30%, respectively).

The association of having at least one affected first-degree relative versus none with breast cancer risk was not significantly different for women age ≤50 years compared with women age >50 years (OR, 1.70; 95% CI, 0.95-2.68, and OR, 1.33; 95% CI, 1.04-1.72, respectively; data not shown). The decrease in OR for having a first-degree relative with breast cancer after adjusting for PMD was similar in both age groups (14.3% and 15.2%, respectively). There were too few women age ≤50 with two or more affected first-degree relatives for a reliable OR to be calculated.

### Risk of Breast Cancer According to PMD: Effect of Adjustment for Family History

Adjustment for family history changed the OR for PMD (for ≥50% density compared with <10%) from 3.06 to 3.00, a 3% difference (Table 3B). The attributable risk of breast cancer associated with density in ≥50% of the mammogram versus <10% of the mammogram was 13.8%.

### Risk of Breast Cancer According to PMD and Family History

Table 4 shows the risk of breast cancer according to both PMD and a family history of breast cancer in first-degree relatives. Greater PMD was associated with increasing risk of breast cancer in women with ($P$ = 0.06) and without ($P$ <0.0001) a family history of the disease. Women with one or more affected first-degree relatives and PMD of ≥50% had a risk of breast cancer four times that of women with no affected relatives and PMD of <10%. There was no interaction between PMD and family history on risk of breast cancer ($P$ = 0.40).

## Discussion

The established association between a history of breast cancer in first-degree relatives and increased risk of breast cancer is observed for women attending the three screening programs that were included in the present study. The magnitude of the increased risk was consistent with the risks estimated from the analysis of pooled data by the Collaborative Group on Hormone factors in Breast Cancer who found relative risks of 1.80, 2.93, and 3.90 for one, two, and three or more affected first-degree relatives, respectively (36). The extent of PMD, adjusted for the effects of other known influences, was also strongly associated with an increased risk of breast cancer. Women with mammographic density of >50% had a 3-fold higher risk of breast cancer then those with <10%. The magnitude of this association is similar to that observed by others who used quantitative methods to measure mammographic density (8).

We estimated the importance of family history and PMD as risk factors for breast cancer risk by calculating the proportion of breast cancer in the total population attributed to each risk factor (attributable risk). Six percent of breast cancers were associated with having at least one affected first-degree relative. For PMD, we arbitrarily selected PMD of >50% as the risk category and PMD of <10% as the baseline for comparison and calculated that 14% of breast cancers were attributable to

**Table 3.** Family history, percent mammographic density, and risk of breast cancer

| | Cases | Controls | OR* (95% CI) | $OR_{adj}$† (95% CI) | Difference‡ (%) |
|---|---|---|---|---|---|
| A. Number of affected first-degree relatives | | | | | |
| 0 | 926 | 978 | Ref | Ref | |
| 1 | 207 | 165 | 1.37 (1.10-1.72) | 1.31 (1.04-1.65) | 16.2 |
| ≥2 | 31 | 15 | 2.45 (1.30-4.62) | 2.25 (1.19-4.27) | 13.8 |
| $P$§ | | | 0.0002 | 0.002 | |
| B. Percent mammographic density (%) | | | | | |
| <10 | 154 | 266 | Ref | Ref | |
| 10-<25 | 310 | 348 | 1.63 (1.26-2.11) | 1.62 (1.25-2.09) | 1.6 |
| 25-<50 | 461 | 375 | 2.45 (1.89-3.18) | 2.40 (1.84-3.12) | 3.4 |
| ≥50 | 239 | 169 | 3.06 (2.21-4.23) | 3.00 (2.17-4.15) | 2.9 |
| $P$§ | | | <0.0001 | <0.0001 | |

*Odds ratios shown were adjusted for age at mammogram, body mass index, age at menarche, parity (parous/non-parous), number of live births, age at first birth, menopausal status (pre-/post-menopausal), age at menopause, and HRT use (ever/never).

† In addition to risk factors listed in footnote *, odds ratios were adjusted for continuous percent mammographic density in the analysis of family history and for family history in the analysis of percent mammographic density.

‡ Calculated as [(OR-1)-($OR_{adj}$-1)]/(OR-1).

§Two-sided test of linear trend within a column, with three category family history (A) or four-category percent mammographic density (B) as ordinal variables.

**Table 4.** Risk of breast cancer according to percent mammographic density and family history

| Number of affected first degree relatives | | Percent mammographic density (%) | | | | *P** |
|---|---|---|---|---|---|---|
| | | <10 | 10 to <25 | 25 to <50 | ≥50 | |
| 0 | Cases | 116 | 249 | 366 | 195 | |
| | Controls | 230 | 294 | 311 | 143 | |
| | OR† (95% CI) | Ref | 1.77 (1.33- 2.35) | 2.65 (1.98-3.53) | 3.30 (2.33-4.67) | <0.0001 |
| ≥1 | Cases | 38 | 61 | 95 | 44 | |
| | Controls | 36 | 54 | 64 | 26 | |
| | OR (95% CI) | 2.12 (1.27-3.56) | 2.37 (1.53-3.64) | 3.39 (2.27-5.06) | 4.08 (2.32-7.14) | 0.06 |

*Two-sided test of linear trend across the row, with four-category percent mammographic density as ordinal variable.
†Odds ratios shown were adjusted for age at mammogram, body mass index, age at menarche, parity (parous/non-parous), number of live births, age at first birth, menopausal status (pre-/post-menopausal), age at menopause, and HRT use (ever/never), and were estimated using all subjects.

PMD, a larger proportion than observed for family history of the disease.

It is usually assumed that the association of a family history of breast cancer with risk of the disease primarily reflects the inheritance of genes that influence risk, but the role of nongenetic factors shared by relatives cannot be excluded. The apparently modest increased risk of breast cancer associated with a history of the disease in first-degree relatives can only occur if there are strong underlying genetic/familial risk factors for the disease (37), and the identification of these factors will be important for our understanding of the causes of breast cancer both in families, and in general. The high-penetrance susceptibility genes *BRCA1* and *BRCA2* are estimated to explain about 16% of familial breast cancer risk (2). The present data suggest that PMD explains about 14% (95% CI, 4-39%) of the association of family history with breast cancer risk, similar to these breast cancer genes.

PMD is a strong risk factor for breast cancer and is a highly heritable trait (5, 38) and therefore meets criteria for an intermediate phenotype for breast cancer (39). As the present data show, PMD is also associated with the number of first-degree relatives with breast cancer, and some proportion of the effect of family history on risk of breast cancer might be due to the inheritance of genes that influence mammographic density. This suggests that the genes that influence mammographic density might also influence risk of breast cancer. The number of genes that influence mammographic density might be smaller than the total number that influences the disease itself, and they might in consequence be easier to identify.

As reviewed in Martin and Boyd (40), mammographic density reflects the epithelial and stromal tissues in the breast, and genes that influence regulation of these tissues might be involved. Known influences of potential interest include blood and tissue levels of several known breast mitogens (41-43). Genes that regulate autocrine and paracrine growth factors in breast tissue, tissue modeling, the regulation of adipocyte formation and function, and the generation of mutagenic products of lipid peroxidation (44, 45) might also be appropriate candidates to examine. The search for genes associated with mammographic density is in its infancy, and few have been found to date (40). However, several large-scale genome-wide linkage and association studies are in progress and can be expected to report their findings within the next few years.

Although family history and PMD have some degree of overlap as risk factors for breast cancer risk, they also have strong independent effects. In agreement with earlier studies using qualitative measures of mammographic density (24, 27), PMD was associated with substantial differences in risk for those with or without a family history of breast cancer, and taken together these two risk factors were associated with larger gradients in risk than was either risk factor alone. It has also been reported that PMD is associated with breast cancer risk for women who carry deleterious mutations in *BRCA1* and *BRCA2* (28).

There are some potential limitations of this study related to the classification of family history and its limited range in the population. Overall, about 18% of subjects reported at least one first-degree relative with breast cancer, but the number of women with more than one first-degree relative with breast cancer was small (about 2% of subjects). Therefore, our analyses to assess the extent to which PMD explains the association of family history with breast cancer and the joint association of PMD and family history on breast cancer risk were limited to family history classified as at least one first-degree relative with breast cancer. To further elucidate the independent and combined associations of these factors with breast cancer risk, the association of mammographic density with breast cancer risk should be examined in studies with larger numbers of women with a strong family history and/or with *BRCA1* and *BRCA2* mutations.

The extent of family history may have been underestimated because breast cancer in second-degree relatives

was not considered. However, breast cancer in second-degree relatives is reported with less accuracy than that in first-degree relatives (46), and is associated with lower risk of breast cancer than that in first-degree relatives (47, 48). In one of the screening populations (NBSS) included in the present study, we have shown that compared with women with no family history, the relative risk of breast cancer for women with at least one affected first-degree was 1.44 (95% CI, 0.94-2.20) whereas for women with any first- or second-degree relative with breast cancer, the relative risk was only 1.14 (95% CI, 0.83-1.57; ref. 26).

Although PMD decreases with age, the risk of breast cancer associated with PMD is consistent across different ages (8). In contrast, the extent of family history of breast cancer tends to increase with age whereas the risk of breast cancer associated with family history is lower in women diagnosed at older ages (36). All the analyses were adjusted for age so that differences in these variables between subjects due to age are unlikely to have biased our results. However, the relationship of PMD and family history may be different in women diagnosed at younger ages where the association of family history with breast cancer risk is expected to be stronger than that observed in the present study where the average age at diagnosis was 57 years. We also did not consider the age at breast cancer diagnosis for relatives which can influence the breast cancer risk associated with family history (36). However, a recent population-based study suggested that the age of diagnosis of breast cancer in relatives does not substantially influence the risk of breast cancer associated with family history in women diagnosed over the age of 40 (48).

In two of the three populations examined in this study, information on family history of breast cancer was collected after diagnosis of breast cancer, and therefore recall bias could influence the estimate of risk associated with family history. A large pooled analysis of the association of family history with breast cancer showed that estimates of risk were similar in case-control and cohort studies, suggesting that recall bias does not have an important effect on the association of family history with breast cancer risk (36).

Many of the existing models for predicting risk of female breast cancer include having a family history of the disease (49-51). The addition of mammographic density to some models, including the Gail model, has to date shown only slight improvements in prediction (52-55), although the predictive value of density alone has been found to be similar to that of the other variables in the Gail model combined (52). Limitations of these studies include missing data (53, 54), the use of qualitative methods of classifying density (55), and the short-term nature of the predictions made (54). Further, all studies are constrained by the limitations of the current methods of measuring mammographic density. Although these methods have reliably shown mammographic density to predict breast cancer risk, they are subjective, and measure only the projected area of the breast rather than volume. Improvements in imaging and measurement might result in stronger estimates of risk associated with mammographic density, might show that mammographic density explains a larger proportion of the association of family history with breast cancer risk, and will increase the power of studies examining the associations of genetics and other factors with mammographic density.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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## References

1. Pharoah PD, Antoniou AC, Bobrow M, Zimmern RL, Easton DF, Ponder BA. Polygenic susceptibility of breast cancer and implications for prevention. Nat Genet 2002;31:33–6.
2. Stratton MR, Rahman N. The emerging landscape of breast cancer susceptibility. Nat Genet 2008;40:17–22.
3. Ahmed S, Thomas G, Ghoussaini M, et al. Newy discovered breast cancer susceptibility loci on 3p24 and 17q23.2. Nat Genet 2009;41:585–90.
4. Thomas G, Jacobs KB, Kraft P, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 2009;41:579–84.
5. Boyd NF, Dite GS, Stone J, et al. Heritability of mammographic density, a risk factor for breast cancer. N Engl J Med 2002;347:886–94.
6. Li T, Sun L, Miller N, et al. The association of measured breast tissue characteristics with mammographic density and other risk factors for breast cancer. Cancer Epidemiol Biomarkers Prev 2005;14:343–9.
7. Johns PC, Yaffe MJ. X-ray characterisation of normal and neoplastic breast tissues. Phys Med Biol 1987;32:675–95.
8. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:1159–69.
9. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med 2007;356:227–36.
10. El-Bastawissi AY, White E, Mandelson MT, Taplin SH. Reproductive and hormonal factors associated with mammographic breast density by age (United States). Cancer Causes Control 2000;11:955–63.
11. Brisson J, Sadowski NL, Twaddle JA, Morrison AS, Cole P, Merletti F. The relation of mammographic features of the breast to breast cancer risk factors. Am J Epidemiol 1982;115:438–43.
12. Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 2003;95:30–7.

13. Cuzick J, Warwick J, Pinney E, Warren RML, Duffy SW. Tamoxifen and breast density in women at increased risk of breast cancer. J Natl Cancer Inst 2004;96:621–8.
14. Brisson J, Morrison AS, Kopans DB. Height and weight, mammographic features of breast tissue, and breast cancer risk. Am J Epidemiol 1984;119:371–81.
15. Boyd NF, Lockwood GA, Byng JW, Yaffe MJ, Tritchler DL. The relationship of anthropometric measures to radiological features of the breast in premenopausal women. Br J Cancer 1998;78:1233–8.
16. Gravelle IH, Bulstrode JC, Bulbrook RD. The relation between radiological patterns of the breast and body weight and height. Br J Radiol 1982;55:23–5.
17. Carlile T, Kopecky KJ, Thompson DJ, et al. Breast cancer prediction and the Wolfe classification of mammograms. JAMA 1985;254: 1050–3.
18. Hainline S, Myers L, McLelland R, Newell J, Grufferman S, Shingleton W. Mammographic patterns and risk of breast cancer. Am J Roentgenol 1978;130:1157–8.
19. Ziv E, Shepherd J, Smith-Bindman R, Kerlikowske K. Mammographic breast density and family history of breast cancer. J Natl Cancer Inst 2005;95:556–8.
20. Crest AB, Aiello EJ, Anderson ML, Buist DS. Varying levels of family history of breast cancer in relation to mammographic breast density (United States). Cancer Causes Control 2006;17:843–50.
21. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. Am J Roentgenol 1987;148:1087–92.
22. de Waard F, Rombach JJ, Collette HJA, Slotboom B. Breast cancer risk associated with reproductive factors and breast parenchymal patterns. J Natl Cancer Inst 1984;72:1277–82.
23. Ernster VL, Sacks ST, Peterson CA, Schweitzer RJ. Mammographic parenchymal patterns and risk factors for breast cancer. Radiology 1980;134:617–20.
24. Brisson J. Family history of breast cancer, mammographic features of breast tissue, and breast cancer risk. Epidemiol 1991;2:440–4.
25. Breuer B, Miller DG, Salane M, Wolfe JN. Mammographic parenchymal patterns and family history of breast cancer. Cancer 1992;69:602.
26. Boyd NF, Lockwood GA, Martin LJ, et al. Mammographic densities and risk of breast cancer among subjects with a family history of this disease. J Natl Cancer Inst 1999;91:1404–8.
27. Saftlas AF, Hoover RN, Brinton LA, et al. Mammographic densities and risk of breast cancer. Cancer 1991;67:2833–8.
28. Mitchell G, Antoniou AC, Warren R, et al. Mammographic density and breast cancer risk in BRCA1 and BRCA2 mutation carriers. Cancer Res 2006;66:1866–72.
29. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. CMAJ 1992;147:1459–76.
30. Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. CMAJ 1992;147:1477–594.
31. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. The quantitative analysis of mammographic densities. Phys Med Biol 1994;39: 1629–38.
32. Rothman KJ, Greenland S. Modern epidemiology. Lippincott-Raven Publishers; 1998.
33. Freedman LS, Graubard BI, Schatzkin A. Statistical validation of intermediate endpoints for chronic diseases. Stat Med 1992;11:167–78.
34. Buyse M, Molenberghs G. Criteria for the validation of surrogate endpoints in randomized experiments. Biometrics 1998;54:1014–29.
35. Richardson SJ. The biological basis of the menopause. Bailliere Clin Endocrinol Metabol 1993;7:1–16.
36. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. Lancet 2001;358: 1389–99.
37. Hopper JL, Carlin JB. Familial aggregation of a disease consequent upon correlation between relatives in a risk factor measured on a continuous scale. Am J Epidemiol 1992;136:1138–47.
38. Kataoka M, Antoniou A, Warren R, et al. Genetic models for the familial aggregation of mammographic breast density. Cancer Epidemiol Biomarkers Prev 2009;18:1277–84.
39. Boyd NF, Rommens JM, Vogt K, et al. Mammographic breast density as an intermediate phenotype for breast cancer. Lancet Oncol 2005; 6:798–808.
40. Martin LJ, Boyd N. Potential mechanisms of breast cancer risk associated with mammographic density: hypotheses based on epidemiological evidence. Breast Cancer Res 2008;10:1–14.
41. Byrne C, Colditz GA, Willett WC, Speizer FE, Pollak M, Hankinson SE. Plasma insulin-like growth factor (IGF) I, IGF-binding protein 3, and mammographic density. Cancer Res 2000;60:3744–8.
42. Boyd NF, Stone J, Martin LJ, et al. The association of breast mitogens with mammographic densities. Br J Cancer 2002;87:876–82.
43. Diorio C, Pollak M, Byrne C, et al. Insulin-like growth factor-I, IGF-binding protein-3, and mammographic breast density. Cancer Epidemiol Biomarkers Prev 2005;14:1065–73.
44. Boyd NF, McGuire V. Evidence of lipid peroxidation in premenopausal women with mammographic dysplasia. Cancer Lett 1990;50:31–7.
45. Boyd NF, Connelly P, Byng J, et al. Plasma lipids, lipoproteins, and mammographic densities. Cancer Epidemiol Biomarkers Prev 1995; 4:727–33.
46. Murff HJ, Spigel DR, Syngal S. Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. JAMA 2004;292:1480–9.
47. Pharoah PDD, Day N, Duffy S, Easton D, Ponder BAJ. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer 1997;71:800–9.
48. Welsh ML, Buist DSM, Aiello Bowles EJ, Anderson ML, Elmore JG, Li CI. Population-based estimates of the relation between breast cancer risk, tumor subtype, and family history. Breast Cancer Res Treat 2009;114:549–58.
49. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81:1879–86.
50. Claus EB, Risch N, Thompson D. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am J Hum Genet 1991;48: 232–42.
51. Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer: updates and extensions. Br J Cancer 2008;98:1457–66.
52. Tice JA, Cummings SR, Ziv E, Kerlikowske K. Mammographic breast density and the Gail model for breast cancer risk prediction in a screening population. Breast Cancer Res Treat 2005;94:115–22.
53. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. J Natl Cancer Inst 2006;98:1215–26.
54. Barlow WE, White E, Ballard-Barbash R, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. J Natl Cancer Inst 2006;98:1204–14.
55. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical risk factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. Ann Intern Med 2008;148:337–47.