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BRIEF REPORT

Mammographic breast density and breast cancer risk by menopausal status, postmenopausal hormone use and a family history of breast cancer

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Abstract
Purpose Few studies have investigated the association between breast density and breast cancer by a family history of breast cancer, menopausal status, and postmenopausal hormone use (PMH). We investigated if associations of breast density and breast cancer differ according to the status of these risk factors.
Methods This study included 1,481 incident breast cancer cases diagnosed within the Nurses' Health Study I and II cohorts and 2,779 matched controls. Breast density was measured from digitized film images with computerized techniques. Information on breast cancer risk factors was obtained prospectively from the biennial questionnaires before the date of the cancer diagnosis for cancer cases and their matched controls. The data were analyzed with logistic regression.
Results Breast cancer risk increased with increasing percent breast density in all strata (p for trend in all subsets <0.0001). The density-related risk of breast cancer was similar in women with and without a family history (OR = 4.00 [95 % CI 2.01–7.94] vs. 3.71 [95 % CI 2.79–4.94] for density ≥50 % vs. <10 %, p for interaction = 0.53). The magnitude of the association between density and breast cancer risk, however, appeared to be stronger in premenopausal women than in postmenopausal women without PMH history (OR = 5.49 [95 % CI 2.44–12.39] vs. 3.02 [95 % CI 1.62–5.63] for density ≥50 % vs. <10 %, p-heterogeneity = 0.17) and appeared to be stronger in postmenopausal women currently using hormones compared with postmenopausal women who never used PMH (OR = 4.50 [95 % CI 2.99–6.78] vs. 3.02, p-heterogeneity = 0.20) or with past hormone use (OR = 4.50 vs. 3.71 [95 % CI 1.90–7.23], p-heterogeneity = 0.23).
Conclusions Findings on associations by menopausal status/hormone use are suggestive and should be examined in additional larger studies.

Keywords Breast density · Breast cancer risk · Family history of breast cancer · Postmenopausal hormone use · Menopausal status

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Introduction

Mammographic breast density is a well-established and a strong predictor of breast cancer risk [1–4]. Appearance of the breast on the mammogram is a reflection of the amount of fat, connective, and epithelial tissue in the breast [3]. Light (non-radiolucent) areas on the mammogram represent the fibrous and glandular tissues ("mammographically dense"), whereas the dark (radiolucent) areas are primarily fat. Women with 75 % or greater percent density (proportion of the breast that appears dense on the mammogram out of the total breast area) are at 4–6 times greater risk of breast cancer compared with women with fatty breasts [3, 5, 6]. Whether breast density-related breast cancer risk differs by a family history of breast cancer and by menopausal status and a history of postmenopausal

hormone use is poorly understood [5–10]. A recent study by Kerlikowske et al. reported a stronger association of high breast density with breast cancer in premenopausal women and postmenopausal hormone users compared with postmenopausal women not on hormones [11]. In other studies, an increase in breast cancer risk in denser breasts was found both in women with and without a family history of breast cancer [12–15]. In a study by Martin et al., the association of density with the risk of breast cancer appeared four times stronger in women with a family history and denser breasts (≥50 %) as compared with women without a family history and low density (<10 %) [15]. We analyzed data from the Nurses' Health Study to determine if differences exist in the association between breast density and breast cancer risk by a family history of breast cancer, menopausal status and, among postmenopausal women, by a history of postmenopausal hormone (PMH) use.

Participants and methods

Participants for this nested case–control study were selected from the Nurses' Health Study I (NHS I) and the Nurses' Health Study II (NHS II) cohorts. These prospective cohorts followed registered nurses in the United States who were 30–55 years (NHS I) or 25–42 years old (NHS II) at enrollment. After administration of the initial questionnaire, the information on breast health risk factors and any diagnoses of cancer or other diseases was updated biennially [3, 16].

Breast cancer cases were confirmed through medical record review. We collected mammograms of breast cancer cases and controls from nested case–control studies in NHSI and NHSII. In both studies, breast cancer cases were matched to controls 1:1 or 1:2 on age at the time of blood collection, menopausal status and postmenopausal hormone use (current vs. not current) at blood draw, and day/time of blood draw. In total we obtained useable mammograms on 1,481 in situ or invasive breast cancer cases and 2,779 matched controls, which contributed to this analysis. This study excluded women with any prior cancer diagnosis (other than non-melanoma skin). This study was approved by the Committee on the Use of Human Subjects in Research at Brigham and Women's Hospital.

Mammographic breast density assessment

To quantify mammographic density, the craniocaudal views of both breasts were digitized at 261 μm per pixel with a Lumisys 85 laser film scanner (bit depth of 12). The Cumulus software (University of Toronto, Toronto, ON, Canada) was used for computer-assisted determination of the percent mammographic density [3, 17]. During this assessment, the observer was blinded with respect to participant's case–control status. As reported previously, the measure of mammographic breast density was highly reproducible (within person intraclass correlation coefficient was 0.93) [3]. Since densities of the right and left breast are strongly correlated [17], the average percent density of both breasts was used in this analysis. The average time between the mammogram date and the date of breast cancer diagnosis was 4.8 years (interquartile range 2–7 years). The average time between mammogram and the reference date of controls was 3.9 years (interquartile range 1–7 years).

Covariate information

Information on breast health risk factors was obtained from the biennial questionnaires before the date of the breast cancer diagnosis (reference date) for cases and their matched controls. Women were considered postmenopausal if they reported (1) no menstrual periods within the 12 months prior to diagnosis date, if natural menopause, (2) having had bilateral oophorectomy, or hysterectomy with retention of at least one ovary, or (3) being 54 or 56 years or older if a smoker or nonsmoker, respectively. Family history of breast cancer was self-reported and referred to any 1st degree relative with breast cancer diagnosis.

Statistical analysis

The analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA). The difference in breast density distributions in cases and controls was tested with Wilcoxon-Mann–Whitney test. We used unconditional logistic regression to describe the association between breast density and breast cancer risk. The risk estimates were presented as odds ratios (ORs) and their corresponding 95 % Confidence Intervals (95 % CIs).

Variables that previously showed significant association with either breast cancer or breast density in previous studies, including those from NHS, were considered as potential confounders and included in adjusted logistic regression models. We included the following matching variables and potential confounders : age at diagnosis (continuous, years), body mass index (continuous, kg/m^2), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (i.e., age at the end of the first pregnancy lasting ≥6 months, modeled as nulliparous, 1–4 children with age at birth <25 years, 1–4 children with age at birth of 25–29 years, 1–4 children with age at birth of ≥30 years, ≥5 children with age at birth of <25 years, or ≥5 children with age at birth of ≥25 years), menopausal

status and PMH use (premenopausal, postmenopausal who never used hormones, postmenopausal who ever used hormones), age at menopause (<46, 46–<50, 50–<55, ≥55 years, unknown, including premenopausal women), a family history of breast cancer (yes or no), alcohol consumption (0, <5, 5–<15, or ≥15 g/day), and smoking status (ever vs. never).

The association of breast density with breast cancer risk was examined separately according to family history of breast cancer (any or none), menopausal status, and postmenopausal hormone use (premenopausal women, postmenopausal who never used hormones, postmenopausal with current hormone use, postmenopausal with past hormone use). The difference in the association of breast density with breast cancer risk by these risk factors was tested with two-way interactions and using Wald Chi-square test. Significance in all the analyses was assessed at 0.05 level.

Results

In this nested case–control study of 1,481 breast cancer cases and 2,779 matched controls, cases had a higher mean percent breast density (33.7 vs. 25.6 %, $p < 0.0001$) and higher proportion of women with density ≥25 % (χ^2 $p < 0.0001$). Among cases, there was a significantly larger proportion of postmenopausal women who had previously used hormones sometime before the reference date (date of diagnosis) (66.5 vs. 58.6 % in controls, $p < 0.0001$), women with a family history of breast cancer (17.4 vs. 12.7 %, $p < 0.0001$), and women with a prior benign breast disease (61.8 vs. 53.0 %, $p < 0.0001$). Cases and controls did not differ with respect to other covariates.

In the overall adjusted logistic regression analysis, the risk of breast cancer significantly increased with increasing percent breast density (≥50 % vs. <10 %: 3.74, 95 % CI 2.88–4.87, p for trend <0.0001). We next evaluated the association of breast density in women with and without a family history of breast cancer (Table 1). Breast cancer risk increased with increasing breast density regardless of family history (for density ≥50 vs. <10 %: OR = 4.00 [95 % CI 2.01–7.94] in women with a family history vs. 3.71 [95 % CI 2.79–4.94] in women without a family history). We observed no interaction of breast density with a family history of breast cancer (p for interaction 0.53). When the two risk factors were included in the analysis as a combined variable, the risk was 5.34 (95 % CI 3.46–8.25) times greater in women with a family history and dense breasts as compared with women with no family history and low density.

When stratified by menopausal status and PMH history (Table 2), breast cancer risk increased with increasing breast density in all categories, although the magnitude of the association was lowest among postmenopausal women who never used hormones. The risk of breast cancer associated with the highest breast density (≥50 %) in premenopausal women was 5.49 (95 % CI 2.44–12.39) relative to women with the lowest breast density. In contrast, the risk in postmenopausal women without a history of PMH use was 3.02 (95 % CI 1.62–5.63) (p-heterogeneity = 0.17). Associations in premenopausal women were similar to those in postmenopausal women with current hormone use (p-heterogeneity = 0.86) or past PMH use (p-heterogeneity = 0.36). Among postmenopausal women with either current or past PMH use, dense breasts (≥50 %), were associated with increased breast cancer risk relative to women with lowest density (current PMH: OR = 4.50, 95 % CI 2.99–6.78; past PMH: OR = 3.71, 95 % CI 1.90–7.23). The magnitude of the association appeared to be stronger in postmenopausal women with current hormone use compared with postmenopausal women with past PMH use or postmenopausal women with no PMH history, but these differences did not reach statistical significance (p-heterogeneity = 0.23 and p-heterogeneity = 0.20, respectively). We observed no overall interaction between breast density, menopausal status, and PMH history (p-heterogeneity = 0.51).

Discussion

In this nested case–control study with 1,481 breast cancer cases and 2,779 matched controls, we found no differences in the association of breast density with breast cancer risk by a family history of breast cancer. Although the differences in associations by menopausal status/PMH use did not reach statistical significance, the magnitude of the association between breast density and breast cancer risk appeared to be strongest in premenopausal women and postmenopausal women currently taking hormones.

Our results examining the association of breast density and breast cancer according to family history are similar to previous reports [12–15]. Previous studies with 1,047 [13] and 1,164 [15] cases suggested that the combined effect of breast density and a family history on the risk of breast cancer is greater than the risk associated with each of the individual risk factors [13, 15]. Although we observed no significant interaction between family history and breast density on breast cancer risk, consistent with a previous study [15], women with a family history and high breast density are at the highest risk of breast cancer. Proliferation of epithelium and stroma is regulated by both estrogens and growth factors [18–21]. Heritability of the mammographic breast density [22, 23] could in part result from genes regulating the breast tissue growth and differentiation. Along with other known genes associated with the family

Table 1 Association of categorical breast density with breast cancer, stratified by a family history of breast cancer (FamHx) [a]

Breast density categories (%)	Women without FamHx[b] 1,209 cases/2,408 controls		Women with FamHx 255 cases/353 controls	
	n cases/controls	Odds ratio (95 % confidence interval)	*n* cases/controls	Odds ratio (95 % confidence interval)
<10	133/465	Reference	30/64	Reference
10–24	286/710	1.49 (1.16–1.90)	68/108	1.64 (0.93–2.88)
25–49	491/814	2.61 (2.04–3.34)	96/125	2.52 (1.41–4.48)
≥50	299/419	3.71 (2.79–4.94)	61/56	4.00 (2.01–7.94)
		p for trend <0.0001[c]		*p* for trend <0.0001[c]

[a] Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (nulliparous, 1–4 children with age at first birth <25 years, 1–4 children with age at first birth of 25–29 years, 1–4 children with age at first birth of ≥30 years, ≥5 children with age at first birth of <25 years, or ≥5 children with age at first birth of ≥25 years), menopausal status and HRT use (premenopausal, postmenopausal who never used hormones, postmenopausal who ever used hormones), age at menopause (<46, 46–<50, 50–<55, ≥55, unknown, including premenopausal), alcohol consumption (0, <5, 5 to <15, or ≥15 g/day), and smoking status (ever vs. never)

[b] *p* for interaction between breast density and family history of breast cancer 0.53

[c] Two-sided test of linear trend with mammographic density as an ordinal variable, using median density level in each category

Table 2 Association of categorical breast density with breast cancer, stratified by menopausal status and postmenopausal hormone use (PMH)

Breast density categories (%)	Premenopausal[a] 239 cases/557 controls		Postmenopausal, no PMH history[b] 245 cases/584 controls		Postmenopausal, Current PMH users[b] 735 cases/1,120 controls		Postmenopausal, Past PMH users[b] 225 cases/481 controls	
	n cases/controls	Odds ratio (95 % confidence interval)	*n* cases/controls	Odds ratio (95 % confidence interval)	*n* cases/controls	Odds ratio (95 % confidence interval)	*n* cases/controls	Odds ratio (95 % confidence interval)
<10	12/58	Reference	59/164	Reference	52/189	Reference	39/114	Reference
10–24	15/78	1.15 (0.49–2.73)	75/218	1.11 (0.73–1.68)	186/346	2.00 (1.39–2.88)	72/170	1.46 (0.90–2.38)
25–49	97/211	3.83 (1.79–8.20)	84/158	2.00 (1.27–3.14)	327/418	3.15 (2.20–4.52)	74/14	1.99 (1.18–3.36)
≥50	115/210	5.49 (2.44–12.39)	34/48	3.02 (1.62–5.63)	170/167	4.50 (2.99–6.78)	40/49	3.71 (1.90–7.23)
		p for trend <0.0001[c]		*p* for trend <0.0001[c]		*p* for trend <0.0001[c]		*p* for trend <0.0001[c]

[a] Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (nulliparous, 1–4 children with age at first birth <25 years, 1–4 children with age at first birth of 25–29 years, 1–4 children with age at first birth of ≥30 years, ≥5 children with age at first birth of <25 years, or ≥5 children with age at first birth of ≥25 years), family history (yes or no), alcohol consumption (0, <5, 5 to <15, or ≥15 g/day), and smoking status (ever vs. never)

[b] Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, or >13 years), parity and age at first birth (nulliparous, 1–4 children with age at first birth <25 years, 1–4 children with age at first birth of 25–29 years, 1–4 children with age at first birth of ≥30 years, ≥5 children with age at first birth of <25 years, or ≥5 children with age at first birth of ≥25 years), age at menopause (<46, 46–<50, 50–<55, ≥55, unknown, including premenopausal), family history (yes or no), alcohol consumption (0, <5, 5 to <15, or ≥15 g/day), and smoking status (ever vs. never)

[c] Two-sided test of linear trend with mammographic density as an ordinal variable, using median density level in each category

Note: Overall interaction $p = 0.51$; *p*-values for two-way interaction between density and menopausal status/PMH use: premenopausal and postmenopausal with no PMH history $p = 0.17$; premenopausal and postmenopausal with current PMH use $p = 0.86$; premenopausal and postmenopausal with past PMH use $p = 0.36$; postmenopausal women with no PMH history and postmenopausal women with current PMH use $p = 0.20$; postmenopausal women with no PMH history and postmenopausal women with past PMH use $p = 0.68$; postmenopausal women with current PMH use and postmenopausal women with past PMH use $p = 0.23$

history of breast cancer, those additional genetic factors in women with denser breasts could result in an increased cancer risk in women with the family history of breast cancer as compared with women without the history.

Recent work by Kerlikowske et al. reported significant differences in the association between breast density and breast cancer risk according to menopausal status/hormone use among 14,090 cases and 573,279 controls [11]. Although our results are consistent with these findings and suggest stronger association among premenopausal women and postmenopausal women currently taking hormones, the differences in our study were not statistically significant. It is possible that we were underpowered. Studies of the effects of hormone therapy on breast density consistently show an increase in breast density among postmenopausal women on hormone therapy [24–27]. However, this hormone therapy-driven increase in breast density does not entirely explain the increase in breast cancer risk [28]. The additive effect of PMH and high breast density on breast cancer risk could result from stimulation of a larger number of epithelial and stromal cells in denser breasts by hormones [3, 29] and, thus, higher potential for mutation and, subsequently, a greater

breast cancer risk. This mechanism is consistent with results from our prior study which showed that women with high circulating hormone levels and high density were at the highest risk of breast cancer [3].

In conclusion, we investigated the association of breast density with breast cancer by a family history of breast cancer, menopausal status, and postmenopausal hormone therapy use. Our results show that the association of breast density with breast cancer risk is similar in women with and without a family history of breast cancer. Our findings, though not significant, suggest that breast density among premenopausal women and postmenopausal women currently using postmenopausal hormones may have a stronger association with breast cancer risk compared with postmenopausal women without history of hormone use.

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Conflict of interest The authors declare that they have no competing interests.

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