A Prospective Study of Breast Cancer Risk Using Routine Mammographic Breast Density Measurements

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Abstract

Mammographic breast density is a major risk factor for breast cancer but estimates of the relative risk associated with differing density patterns have varied widely. It is also unclear how menopausal status influences this association and to what extent the effects of density are due to its correlation with other risk factors. Most recent investigations of breast density have been case-control studies, which provide indirect estimates of relative risk. We have prospectively followed 61,844 women for an average of 3.1 years to directly estimate risk among women in the four mammographic breast density categories defined by the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS). The study was population-based and used density assessments routinely made by community radiologists. Cox regression was used to obtain age-adjusted relative risk estimates and to control for other risk factors. Risk increased with density and the risk associated with extremely dense breasts, relative to entirely fatty breasts, was 4.6 (95% confidence interval, 1.7–12.6) for premenopausal women and 3.9 (95% confidence interval, 2.6–5.8) for postmenopausal women. Estimates for pre- and postmenopausal women did not differ significantly. Although breast density was significantly related to body mass index, age at first childbirth, and postmenopausal hormone use ($P < 0.001$), adjustment for these variables only slightly altered the relative risk estimates. Our results correspond well to those from case-control studies using more quantitative measures of mammographic breast density and suggest that routine Breast Imaging Reporting and Data System density measurements may be useful in models for assessing breast cancer risk in individual women. (Cancer Epidemiol Biomarkers Prev 2004;13(5):715–22)

Introduction

Numerous studies have established that mammographic breast density is an important breast cancer risk factor. Women with radiologically dense breasts, indicative of large proportions of epithelial and connective tissue, are at substantially higher risk of developing breast cancer than women whose breasts are radiologically lucent with a large proportion of fatty tissue. However, estimates of the magnitude of the relative risk from different studies have varied widely, ranging from less than 2 to more than 12 (1, 2) and most studies have used mammograms taken during the 1970s and early 1980s. Subsequent improvements in imaging technology may have had an impact on breast density assessment, raising questions about the applicability of previous risk estimates to current density measurements. There are also questions about the influence of age and whether premenopausal or postmenopausal breast density is more predictive of risk. In addition, it is unclear to what extent the effects of breast density are due to its association with obesity, childbearing, use of hormone replacement therapy, and other established breast cancer risk factors.

Inconsistencies in relative risk estimates can arise due to differences in study design, breast density measurement, and statistical analysis. Most investigations of the risk associated with breast density have been case-control studies, some of which were nested within cohort studies. Only prospective studies that classify women according to breast density and follow them to document breast cancer incidence, can provide direct estimates of relative risk and are potentially the most accurate. Several breast density studies of this type have been conducted in the past (3–7) but some did not fully account for duration of follow-up and none have rigorously adjusted for age or changes in age during follow-up. This can influence results because age is strongly associated with both breast density and risk. In addition, although some of these prospective studies have examined the association between breast density and other risk factors, most did not adjust relative risk estimates for these potential confounders.

The most commonly used method for assessing breast density has been the classification scheme proposed by Wolfe which describes four parenchymal patterns: radiologically lucent (N1); ductal prominences involving less than a quarter of the breast (P1); ductal prominences

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involving more that a quarter of the breast (P2); and radiologically dense (DY) (8). Other studies have used more quantitative measures of breast density, including visual estimation of the proportion of the breast containing dense tissue and planimetry (9–12). The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) describes four categories similar to Wolfe's: (*a*) entirely fat; (*b*) scattered fibroglandular densities; (*c*) heterogeneously dense; and (*d*) extremely dense (13). The BI-RADS classification has the advantage of being routinely used by radiologists as part of their mammographic assessments, so is readily available for large numbers of women. We have previously used BI-RADS density measurements in a case-control study of breast cancer risk (14) but a more rigorous study was needed to determine the degree of risk associated with each density category.

In our current study, we have prospectively followed 61,844 women receiving mammograms in Vermont during 1996–2001 to directly ascertain breast cancer risk among women in different BI-RADS breast density categories, as assigned by community radiologists during routine practice. A person-years approach was used to rigorously account for both age and follow-up time. We investigated the influence of menopausal status on relative risk estimates and also examined the effect of breast density after adjustment for body mass index (BMI), nulliparity, age at first childbirth, family history of breast cancer in a first-degree relative, and use of hormone replacement therapy.

Methods

This study used data from the Vermont Breast Cancer Surveillance System (VBCSS), which is part of the National Cancer Institute's Breast Cancer Surveillance Consortium (15). Since 1994, the VBCSS has collected information on all mammography and breast sonography performed in Vermont, and it began collecting BI-RADS breast density classification in 1996 (16). The VBCSS also collects breast pathology data from all pathology facilities in Vermont and cancer information from the Vermont Cancer Registry, as well as from the New Hampshire Cancer Registry because some women from eastern Vermont receive medical care in New Hampshire. In addition, risk factor information is obtained by asking the patient to complete a health history questionnaire at the time of her mammography. The Institutional Review Board at the University of Vermont approved the protocol for this project with an alteration of informed consent.

Women were eligible for the study if they had no prior history of breast cancer and had at least one mammogram with a breast density assessment in Vermont between April 1, 1996 and December 31, 2000. Of 94,253 women with the requisite mammogram, 3,749 indicated they did not wish their information to be used for research, 3,133 reported a prior history of breast cancer, and 110 who did not report a history of breast cancer had a previous malignant biopsy recorded in the VBCSS. For the remaining 87,261 women, date of entry into the study was defined as the date of their first mammogram with breast density information. Breast cancers diagnosed within a year of the entry date were considered prevalent cases, resulting in the exclusion of 792 women. For women who developed incident cancers, the date of diagnosis was defined by the date of the first malignant biopsy. Both invasive and *in situ* cancers were included, and most of the non-invasive cancers were ductal carcinoma *in situ* (DCIS). A woman who did not develop cancer remained under follow-up either until the date of her last mammogram before July 1, 2001 or the date of her last benign biopsy if it occurred after that mammogram. Although the VBCSS data used in the study were complete through June 30, 2002, an earlier cutoff date was used for the exit mammogram to be consistent with the study entry criteria, which required examination of a full year of subsequent biopsy data to ensure that the woman was cancer free at the time of the mammogram. There were 20,673 women who did not have an exit mammogram before July 1, 2001 or a biopsy before July 1, 2002. Without this verification that they still resided in Vermont, the absence of a malignant biopsy in the VBCSS could not be used to determine disease status. They were therefore considered lost to follow-up and excluded from the data analyses. An additional 3,952 were excluded because they had less than 1 year of follow-up, leaving a total of 61,844 women.

The women excluded from the study because of no or insufficient follow-up were younger than those in the study, with 58.3% under the age of 50 compared to 42.7% of the study subjects. However, there were only small differences in the breast density distributions of included and excluded women, and these were primarily attributable to menopausal status. Among excluded premenopausal women, 3.1% had entirely fatty breasts, 40.5% had scattered fibroglandular densities, 43.6% had heterogeneously dense breasts, and 12.8% had extremely dense breasts, similar to the density distribution for premenopausal women in the study (3.2%, 43.5%, 39.8%, and 13.4% in the four density categories, respectively). Among postmenopausal women, the corresponding percentages were 9.5%, 60.1%, 26.3%, and 4.1% for those excluded from the study, compared to 9.6%, 60.8%, 24.9%, and 4.7% for women in the study.

Statistical Analysis. Women were classified according to their BI-RADS density category at the time of entry into the study. Relationships of breast density with age and BMI were assessed by ANOVA, while relationships with categorical risk factors were assessed by χ^2 tests. Raw incidence rates were computed from the number of cancer cases and number of person-years of follow-up in each breast density category. Age-adjusted relative risk estimates were obtained by fitting a Cox regression model with age as the time variable and defining each risk set to include all women who were under observation at the specified age. A woman was therefore included in different risk sets according to her age at differing time points during follow-up. This analysis yields results equivalent to Poisson regression of person-year data with 1-year age strata. A Cox regression model including breast density and menopausal status at entry into the study, as well as their interaction, was fitted to compare the effects of breast density in women who were premenopausal and postmenopausal at the time of their density measurement. Other multivariate Cox regression models were used to estimate the relative risk associated

Table 1. Characteristics of women at the time of entry into the study

	n	%
Age		
<40	3,764	6.1
40–44	11,689	18.9
45–49	10,976	17.7
50–54	9,642	15.6
55–59	6,846	11.1
60–64	5,568	9.0
65–69	5,075	8.2
70–74	4,161	6.7
≥75	4,134	6.7
Family history of breast cancer		
No	50,228	81.2
Yes	11,616	18.8
Age at first childbirth		
<21	15,295	24.8
21–30	31,396	51.0
>30	5,668	9.2
No children	9,219	15.0
Menopausal status		
Premenopausal	24,238	39.2
Postmenopausal	37,606	60.8
Postmenopausal hormone therapy		
Currently using	13,345	40.2
Formerly used	3,385	10.2
Never used	16,471	49.6
BMI (kg/m^2)		
<22.0	13,363	22.0
22.0–24.9	15,837	26.1
25.0–27.4	10,541	17.3
27.5–29.9	7,595	12.5
≥30	13,449	22.1
Breast density		
Entirely fat	4,409	7.1
Scattered	33,397	54.0
Heterogeneous	19,015	30.7
Extremely	5,023	8.1

with breast density after adjustment for other risk factors, including BMI (categorized as <22.0, 22.0–24.9, 25.0–27.4, 27.5–29.9, and ≥30 kg/m^2), family history of breast cancer, nulliparity, age at first childbirth (categorized as <21, 21–30, and >30), and postmenopausal use of hormone replacement therapy. Sample sizes for these analyses varied due to incomplete risk factor information for 5,267 (8.5%) of the subjects.

Results

The characteristics of women at the time of entry into the study are summarized in Table 1. Forty-three percent were under the age of 50 and 39.2% were premenopausal. Of the postmenopausal women, 40.2% said they were using hormone replacement therapy. A family history of breast cancer in a first-degree relative (mother, sister, or daughter) was reported by 18.8% of women. Fifteen percent of women were nulliparous and 9.2 had their first child after the age of 30. More than half (51.9%) of the women had BMI values over 25. BI-RADS breast density assessments for most women were either ''scattered fibroglandular densities'' (54.0%) or ''heterogeneously dense'' (30.7%). Only 7.1% had ''entirely fat'' breasts and 8.1% had ''extremely dense'' breasts.

Women in the four breast density categories differed significantly with respect to age and all of the other potential risk factors examined in the study except family history of breast cancer (Table 2). Most women with entirely fat breasts were postmenopausal (82.2% compared to 35.1% of women with extremely dense breasts) and if postmenopausal were less likely to be using hormone replacement therapy. Women with denser breasts were more likely to be nulliparous or to have begun childbearing after age 30. BMI was inversely

Table 2. Associations between breast density and other risk factors

	Breast density category								
	Entirely fat		Scattered		Heterogeneous		Extremely		
	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		*P* Value
Age	60.2 (11.6)		56.0 (12.0)		51.0 (11.0)		47.7 (9.6)		<0.001
BMI (kg/m^2)	31.2 (7.0)		27.4 (5.8)		25.0 (4.8)		22.8 (3.8)		<0.001
	n	%	*n*	%	*N*	%	*n*	%	*P* Value
Family history of breast cancer									
No	3,619	82.1	27,042	81.0	15,508	81.6	4,059	80.8	0.140
Yes	790	17.9	6,355	19.0	3,507	18.4	964	19.2	
Age at first childbirth									
<21	1,365	31.2	9,039	27.2	4,098	21.6	793	15.8	<0.001
21–30	2,233	51.1	17,468	52.5	9,428	49.8	2,267	45.3	
>30	259	5.9	2,618	7.9	2,101	11.1	690	13.8	
No children	514	11.8	4,129	12.4	3,320	17.5	1,256	25.1	
Menopausal status									
Premenopausal	784	17.8	10,544	31.6	9,651	50.8	3,259	64.9	<0.001
Postmenopausal	3,625	82.2	22,853	68.4	9,368	49.2	1,764	35.1	
Postmenopausal hormone use									
Currently using	1,307	36.1	10,470	45.8	4,973	53.1	1,000	56.7	<0.001
Formerly used	359	9.9	2,115	9.3	787	8.4	124	7.0	
Never used	1,959	54.0	10,268	44.9	3,604	38.5	640	36.3	

related to breast density with the average BMI decreasing from a mean of 31.2 in women with entirely fat breasts to 22.8 in women with extremely dense breasts.

There were a total of 192,343 person-years of follow-up for the 61,844 study subjects, with an average of 3.1 years. Breast cancer was diagnosed in 1,191 of the women and 891 (74.8%) of these were invasive cancers. As indicated by the age-adjusted relative risk estimates in Table 3, the risk of breast cancer increased steadily over the four BI-RADS breast density categories. Compared to women of the same age with entirely fat breasts, breast cancer was 2.19 times more likely in women with scattered densities [95% confidence interval (CI), 1.62–2.97], 2.97 times more likely in women with heterogeneously dense breasts (95% CI, 2.17–4.06), and 4.02 times more likely in women with extremely dense breasts (95% CI, 2.84–5.68). The age-adjusted relative risk estimates were somewhat higher for premenopausal women than postmenopausal women (*e.g.*, 3.70 *versus* 2.79 for the heterogeneously dense category and 4.61 *versus* 3.88 for the extremely dense category). However, there was no evidence of an interaction between the effects of density and menopausal status ($P = 0.74$), indicating that these differences were not statistically significant. After adjustment for BMI, the breast density relative risk estimates for postmenopausal women were somewhat increased, while for premenopausal women, the relative risk for the highest density category was reduced, resulting in smaller differences between the two groups (Table 4).

The effects of BMI on breast cancer risk in the premenopausal and postmenopausal women in our study differed markedly. Before adjustment for breast density, relative risk estimates for premenopausal women in the heavier BMI categories (>22.0) ranged from 0.64 to 0.68 and were statistically significant. After adjustment for breast density, only premenopausal women with BMI between 22.0 and 24.9 had a significantly lower risk than those with BMI under 22.0 (age-adjusted relative risk = 0.73). Similar relative risk estimates were obtained for higher BMI categories but they were not statistically significant (Table 4). In contrast, among postmenopausal women, relative risk estimates for the four higher BMI categories ranged from 1.07 to 1.19 before adjustment for breast density and were not statistically significant. After adjustment for the inverse relationship between BMI and breast density, breast cancer risk increased steadily with increasing BMI from 1.17 to 1.56, although the risks associated with BMI categories 22.0–24.9 and 25.0–27.4 were not significantly higher than for BMI <22.0. When postmenopausal women were grouped according to whether or not they were using hormone replacement therapy at the time of entry into the study, a significant relationship between BMI and breast cancer risk was observed only for those not using hormones, but breast density was significantly related to risk in both groups (Table 4). Women with missing information about hormone use were excluded from this analysis but were included in the analysis of all postmenopausal women.

Multivariate models including breast density, BMI, family history of breast cancer, nulliparity, age at first childbirth, and hormone replacement therapy indicated that all variables were significantly associated to breast cancer risk, independent of their relationships to the other risk factors (Table 5). Relative risk estimates for all variables except BMI were similar in premenopausal and postmenopausal women. The relative risk estimates for breast density, adjusted for all other risk factors, are very similar to the estimates in Table 3, which are only adjusted for age. The multivariate relative risk estimates for the other risk factors were also similar to those obtained from univariate analysis, indicating that after controlling for age, their associations with breast cancer risk are largely independent of breast density.

Discussion

This prospective study which rigorously controls for the effects of age provides the best estimates to date for the relative breast cancer risk associated with differing BI-RADS breast density categories. The lowest and highest BI-RADS categories represent very low and very high

Table 3. Raw incidence and relative risk of breast cancer by breast density category

Density	No. of women	No. of person-years	No. of cancer cases	Raw incidence per 100,000 person-years	Age-adjusted relative risk (95% CI)
All women					
Entirely fat	4,409	14,278	45	315	1.00
Scattered	33,397	105,222	635	603	2.19 (1.62–2.97)
Heterogeneous	19,015	56,953	486	678	2.97 (2.17–4.06)
Extremely	5,023	15,889	125	787	4.02 (2.84–5.68)
Premenopausal					
Entirely fat	784	2,502	4	160	1.00
Scattered	10,544	31,799	120	377	2.47 (0.92–6.69)
Heterogeneous	9,651	27,718	148	534	3.70 (1.37–9.98)
Extremely	3,259	10,120	65	642	4.61 (1.68–12.64)
Postmenopausal					
Entirely fat	3,625	11,776	41	348	1.00
Scattered	22,853	73,423	515	701	2.18 (1.58–2.99)
Heterogeneous	9,364	29,235	238	814	2.79 (2.00–3.88)
Extremely	1,764	5,769	60	1,040	3.88 (2.60–5.78)

Table 4. Independent effects of breast density and BMI on breast cancer risk

	Age-adjusted multivariate relative risk (95% CI)			
	Premenopausal women (n = 24,006)	Postmenopausal women (all) (n = 36,867)	Postmenopausal women not using hormones (n = 19,437)	Postmenopausal women using hormones (n = 13,233)
BMI (kg/m^2)				
<22.0	1.00	1.00	1.00	1.00
22.0–24.9	0.71 (0.53–0.94)	1.17 (0.94–1.45)	1.06 (0.77–1.47)	1.25 (0.91–1.73)
25.0–27.4	0.77 (0.55–1.09)	1.25 (0.99–1.57)	1.33 (0.96–1.86)	1.04 (0.72–1.51)
27.5–29.9	0.79 (0.53–1.20)	1.43 (1.12–1.83)	1.43 (1.00–2.04)	1.35 (0.91–1.99)
≥30	0.85 (0.61–1.20)	1.54 (1.23–1.93)	1.67 (1.22–2.31)	1.30 (0.90–1.88)
Density				
Entirely fat	1.00	1.00	1.00	1.00
Scattered	2.49 (0.91–6.68)	2.26 (1.64–3.12)	2.06 (1.40–3.03)	2.35 (1.15–4.79)
Heterogeneous	3.64 (1.33–9.96)	3.08 (2.20–4.32)	2.41 (1.57–3.68)	3.80 (1.80–7.62)
Extremely	4.35 (1.55–12.20)	4.47 (2.96–6.74)	3.55 (1.99–6.36)	4.20 (1.90–9.30)

percentages of dense tissue and are thought to be similar to the N1 and DY parenchymal patterns described by Wolfe. The relative risk observed for the highest BI-RADS density category (extremely dense compared to entirely fat) therefore provides a good estimate for comparison with studies using these other methods for classifying breast density. In an extensive review, Boyd *et al.* (2) found that odds ratios from case-control studies ranged from 2.1 to 6.0 when women with a high percentage of density (defined as above 60%, 70%, or 75% in various studies) were compared to women with no or low percentage density. Our overall age-adjusted relative risk estimate of 4.0 for the extremely dense BI-RADS category falls in the middle of this range and was very similar to the odds ratios obtained from several studies using planimetry to quantify the percentage of dense tissue (9, 10, 12), as well as from a study by Boyd using a computer-assisted method to quantify percentage density (11). Case-control studies using Wolfe's classification and comparing the DY and N1 categories of density showed a wider range of odds ratios, from 1.9 to 12.2, which may be due to variations in the use of this classification (2). In a prospective study by Brisson *et al.* (6), Wolfe's DY and P2 categories were combined and compared to N1, yielding a relative risk of 2.7 after 2–3 years of follow-up. We obtained a slightly higher relative risk estimate (3.2) when we combined the two highest BI-RADS density categories. The general comparability of our estimates based on recent mammograms to those from earlier studies suggests that technical changes in mammography have not had a large impact on breast density assessment.

Studies examining the influence of age and/or menopausal status on the association between breast density and risk have shown inconsistent results. We found a somewhat stronger association in premenopausal women than in postmenopausal women, although the difference was not statistically significant. Very similar

Table 5. Multivariate relative risk estimates for all available risk factors

	Age-adjusted multivariate relative risk (95% CI)	
	Premenopausal women (n = 23,970)	Postmenopausal women (n = 32,607)
Family history of breast cancer		
No	1.00	1.00
Yes	1.65 (1.30–2.10)	1.40 (1.19–1.65)
Age at first childbirth		
<21	1.00	1.00
21–30	1.03 (0.75–1.42)	1.16 (0.97–1.39)
>30	1.76 (1.22–2.54)	1.52 (1.12–2.06)
No children	1.46 (1.02–2.09)	1.45 (1.14–1.85)
Postmenopausal hormone use		
Never or formerly used		1.00
Currently using		1.31 (1.13–1.53)
BMI (kg/m^2)		
<22.0	1.00	1.00
22.0–24.9	0.73 (0.55–0.97)	1.17 (0.93–1.47)
25.0–27.4	0.82 (0.58–1.16)	1.23 (0.96–1.57)
27.5–29.9	0.85 (0.56–1.29)	1.41 (1.08–1.84)
≥30	0.92 (0.65–1.30)	1.56 (1.23–1.98)
Breast density		
Entirely fat	1.00	1.00
Scattered	2.50 (0.92–6.82)	2.06 (1.47–2.89)
Heterogeneous	3.62 (1.32–9.92)	2.75 (1.93–3.92)
Extremely	4.21 (1.49–11.80)	3.48 (2.24–5.40)

results were obtained when women under age 50 were compared to women aged 50 or older. This is contrary to the findings from two large, nested case-control studies that indicated a stronger association in older women (11, 12). It also differs from our prior results from a case-control study, which only showed an association between density and risk in postmenopausal women (14).

Adjustment for BMI had little influence on the relative risk associated with breast density, the largest effect being an increase from 3.9 to 4.5 for postmenopausal women with extremely dense breasts. The reverse effects of BMI on breast cancer risk in premenopausal and postmenopausal women observed in this study are consistent with other studies (17–20) and underscore the importance of considering menopausal status when using weight or BMI as a covariate in breast density studies. Several studies have reported the effects of weight or BMI on breast cancer risk after adjustment for breast density but only two previous studies, our case-control study (14) and a similar one by Brisson *et al.* (21), have compared the unadjusted and adjusted relative risk estimates. Both of these studies, as well as our current study, found that adjustment for breast density increased the positive association between obesity and breast cancer in postmenopausal women, indicating that obese women with dense breast are at particularly high risk. For premenopausal women, Brisson *et al.* obtained almost identical results as for postmenopausal women, which is contrary to the inverse relationship between body weight and premenopausal breast cancer risk seen in our current study. We found that the protective effect of a higher BMI in premenopausal women is reduced after adjustment for the effect of breast density, indicating that some of this benefit can be attributed to lower breast density among heavier women.

Further adjustments for family history of breast cancer, nulliparity, age at first childbirth, and postmenopausal use of hormone replacement therapy did not greatly affect the relative risk estimates for either breast density or BMI. The biggest change was in the relative risk among postmenopausal women with extremely dense breasts, which was 4.5 after adjustment for BMI and 3.5 after adjustment for the additional risk factors. The independent effects of family history of breast cancer, nulliparity, age at first childbirth, and use of hormone replacement therapy, as estimated from the multivariate models, were similar to those obtained from univariate models. This suggests that their age-adjusted effects on breast cancer risk are not primarily due to their joint associations with breast density, BMI, and each other, but interrelationships between risk factors are complex and further work is needed to understand their effects on risk. The magnitudes of the relative risks associated with family history of breast cancer, nulliparity, and age at first childbirth were consistent with estimates from other studies that adjusted for breast density (12, 22, 23), as well as from studies that did not include breast density (24, 25). Our estimate of the relative risk associated with postmenopausal hormone use (1.31) is nearly identical to the estimate of 1.26 from the Women's Health Initiative randomized trial (26).

We did not have information about age at menarche, which is inversely related to breast cancer risk. There is some evidence that later menarche is associated with denser breasts (27). If this is the case, adjustment for age at menarche might result in somewhat higher breast density relative risk estimates. Age at menopause is another risk factor that was unavailable for many of the women in our study. If later menopause is associated with denser breasts in postmenopausal women, adjustment for age at menopause might reduce the relative risk estimates for breast density. The VBCSS is currently collecting data on both these risk factors for use in future studies.

Some discrepancies across studies in relative risk estimates for breast density and other risk factors are expected due to differences in study population, study design, and the covariates used for adjustment. Nearly all studies have controlled for age, which is a major risk factor for breast cancer. However, because risk increases within fairly narrow age ranges, differing methods of adjustment for the effect of age may account for much of the variability in relative risk estimates, particularly those for breast density. By using Cox regression with age as the time variable, our current study strictly controls for age and takes into account aging during the follow-up period, so that all comparison are among women under observation at the same age. Our results therefore provide an accurate reflection of the relative risk associated with density, independent of the effect of age. Use of age rather than duration of follow-up as the time variable is appropriate in studies such as ours, in which entry dates are essentially arbitrary (28, 29) and it is not equivalent to alternative approaches that use age as a covariate or stratify by age. When we performed Cox regressions using duration of follow-up as the time variable and age as either a covariate or stratification variable, our breast density relative risk estimates were substantially lower for both premenopausal and postmenopausal women.

One limitation to this study is the relatively short duration of follow-up (1–6 years with an average of 3.1 years). Short follow-up can lead to an overestimation of the risk associated with breast density if some cancers diagnosed during follow-up were present at the time of the entry mammogram but were masked by dense tissue. We sought to minimize this possibility by excluding cancers diagnosed within a year of the entry mammogram. A comparison of cancers occurring in the four breast density categories during follow-up revealed no significant differences in type of disease (invasive or *in situ*), size of invasive tumor, or time elapsed between entry into the study and cancer diagnosis. Thus, there was no indication that the cancers diagnosed in women with denser breasts were more likely to have been present at the time of entry into the study.

The short follow-up in this study precluded examination of how longer durations of follow-up might influence the association between breast density and risk. Mammographic breast density has been found to be stable over the short term (30) and Byrne *et al.* (12) have shown that density measurements can be predictive of risk for 10 years or longer. In contrast, Brisson *et al.* (6) found that for postmenopausal women, the association between density and risk decreased over 9 years of follow-up. The relative risk estimates we report may therefore remain applicable only for a few years following a density measurement. Subsequent density

measurement could periodically be used to re-evaluate a woman's risk of breast cancer, although the BI-RADS classification only distinguishes between substantially different breast densities and would not be useful for detecting small changes in risk. Other risk factors can also change over time and some women in our study almost certainly had changes in menopausal status or BMI during the follow-up period. Although it is unclear whether such changes have an immediate impact on risk, their occurrence could result in an underestimation of the effects of these risk factors.

Use of the VBCSS ensured good case ascertainment among women who remained in Vermont. To ensure that women not diagnosed with cancer were still resident in Vermont, we censored follow-up at the time of the last mammogram recorded in the registry before July 1, 2001. More than 23,000 potential subjects were excluded because they did not have another mammogram after their entry mammogram or had less than 1 year of follow-up. With these exclusion criteria, women who developed breast cancer were more likely to be in the study than those who did not. While this would be expected to inflate incidence rates, it would not affect relative risk estimates for breast density unless age-specific mammography rates differed among women in different breast density categories. The similarity in breast distributions between women excluded and included in the study indicates that this was not the case. To verify that the results were not biased by an association between breast density and exclusion from the study, we computed relative risk estimates without excluding women, using June 30, 2001 as the last date of follow-up for all women who did not develop cancer. The breast density relative risk estimates from this analysis differed from the reported results by 0.1 or less. In addition, the incidence rate for invasive cancer was similar to the 1997–2000 rate for SEER sites (standardized incidence ratio = 97.8), validating our basic study design and analytical approach (31).

The use of BI-RADS density categories, as assigned by community radiologists as part of routine practice, is both a strength and limitation of this study. BI-RADS density categories are semiquantitative and their interpretations are likely to vary among radiologists, particularly with regard to the types of parenchymal patterns included in the two intermediate categories: scattered fibroglandular and heterogeneously dense. The density assessments in this study are therefore more prone to misclassification error than those from studies using more quantitative methods and/or assessments from specially trained radiologists. Misclassification of breast density would attenuate the association between breast density and risk, so the actual relative risk may be higher than estimated in this study. However, the relative risk estimates increased consistently over the four BI-RADS categories and the estimate for the highest category corresponds well to studies using planimetry or computer-assisted methods to compare women with more than 75% density to women with zero density (11, 12). The BI-RADS density classification may therefore be as useful an indicator of risk as more quantitative measures, provided that radiologists accurately classify their patients. To help standardize classification, examples of mammograms corresponding to each density category were included in the 1998 edition of BI-RADS (13) and the most recent version includes additional descriptors, giving the corresponding percentage of glandular tissue for the four categories as <25%, 25–50%, 51–75%, and >75%, respectively (32).

Breast density is more strongly associated with breast cancer risk than most other risk factors. Relative risk estimates of similar or greater magnitude have been observed only for age, atypical hyperplasia, and germline mutations in BRCA genes (33). Our finding that the effect of breast density is largely independent of its relationship with other risk factors confirms the importance of breast density measurements for breast cancer risk assessment. Because BI-RADS breast density categories are routinely assigned when a women has a mammogram, the results of this study could aid the development of widely applicable models for assessing breast cancer risk in individual women.

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