Breast Density as a Predictor of Mammographic Detection: Comparison of Interval- and Screen-Detected Cancers

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Background: **Screening mammography is the best method to reduce mortality from breast cancer, yet some breast cancers cannot be detected by mammography. Cancers diagnosed after a negative mammogram are known as interval cancers. This study investigated whether mammographic breast density is related to the risk of interval cancer.** ***Methods:*** **Subjects were selected from women participating in mammographic screening from 1988 through 1993 in a large health maintenance organization based in Seattle, WA. Women were eligible for the study if they had been diagnosed with a first primary invasive breast cancer within 24 months of a screening mammogram and before a subsequent one. Interval cancer case subjects (n = 149) were women whose breast cancer occurred after a negative or benign mammographic assessment. Screen-detected control subjects (n = 388) were diagnosed after a positive screening mammogram. One radiologist, who was blinded to cancer status, assessed breast density by use of the American College of Radiology Breast Imaging Reporting and Data System.** ***Results:*** **Mammographic sensitivity (i.e., the ability of mammography to detect a cancer) was 80% among women with predominantly fatty breasts but just 30% in women with extremely dense breasts. The odds ratio (OR) for interval cancer among women with extremely dense breasts was 6.14 (95% confidence interval [CI] = 1.95–19.4), compared with women with extremely fatty breasts, after adjustment for age at index mammogram, menopausal status, use of hormone replacement therapy, and body mass index. When only those interval cancer cases confirmed by retrospective review of index mammograms were considered, the OR increased to 9.47 (95% CI = 2.78–32.3).** ***Conclusion:*** **Mammographic breast density appears to be a major risk factor for interval cancer. [J Natl Cancer Inst 2000;92:1081–7]**

Screening mammography is the best available method to reduce the incidence of late-stage breast cancer and mortality *(1)*, yet it is widely recognized that not all breast cancers can be detected by mammography. Interval cancers are those that are detected in the interval after a negative mammographic result. While some cases of interval cancer are inevitable, the success of mammography as a screening method relies heavily on keeping the rate of interval cancers low by maintaining a high sensitivity (i.e., high probability of screen detection among women with breast cancer). Factors that may lower the sensitivity of mammography include technical and interpretative errors *(2–6)*, rapid tumor-growth patterns *(6–11)*, and extensive mammographic breast density *(12–14)*.

The parenchymal pattern of the breast varies with the relative amounts of fat, which is radiolucent and appears dark on a mammogram, and connective and epithelial tissues, which are radiologically dense and appear light. Mammographic density changes over time, is higher among younger, premenopausal women *(15–17)*, and is increased by use of hormone replacement therapy (HRT) *(18)*. Several lines of evidence indicate that breast density increases the likelihood that cancer will be missed by mammographic screening. Radiologic studies *(12–14,19,20)* report high amounts of diffuse parenchymal density among women with interval cancers. In addition, screening sensitivity is lower among younger women *(21–23)* and among women who use HRT *(24)*.

In spite of these observations, the relationship between breast density and interval cancer risk is unclear. Only a handful of studies *(12–14,19,20,23)* have examined this association, and most were too small. (Identification of even 100 interval cancer patients requires a follow-up of 100 000–300 000 negative mammograms.) In addition, in several *(13,14,20)* of the previous studies, breast density was measured by more than one radiologist, which increased the variability of the measure. Furthermore, how screening sensitivity and interval cancer are defined varies widely. Factors that differ include the length of the follow-up interval, the definition of a negative mammogram, and whether the interval cancers were or were not detectable on review.

In this study, we investigated whether breast density increases interval cancer risk in a large sample of women with interval- and screen-detected cancers. Mammographic density was measured by one radiologist, and we used five definitions of interval cancer.

Subjects and Methods

Selection of Study Subjects

Subjects were selected from women enrolled in the Group Health Cooperative of Puget Sound (GHC), a health maintenance organization with more than 400 000 members in western Washington state. Most mammographic screening at GHC is delivered through the Breast Cancer Screening Program (BCSP), which was established in 1985 *(25)*. The BCSP collects demographic data, health and screening histories, and risk-factor information through a self-administered survey mailed to women 40 years old or older and generates letters that invite women to begin breast cancer screening and remind them periodically. Eighty-five percent of eligible women completed the questionnaire and enrolled in

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the BCSP. Data on risk factors, screening examination results, and recommendations for additional evaluation are maintained in a central database. During the study period, women were sent reminders to come in for screening every 1–3 years on the basis of their breast cancer risk factors.

Screening consists of a two-view mammogram and clinical breast examination at dedicated centers within the GHC delivery system. GHC physicians may also order screening mammography in the course of usual care or to evaluate a symptomatic woman. These examinations occur within GHC radiology departments but outside the screening program.

Case subjects with interval cancer and control subjects with screen-detected cancer were drawn from women enrolled in the BCSP who underwent at least one screening mammographic examination between January 1, 1988, and December 31, 1993. Eligible study patients were those women diagnosed with a first primary invasive breast cancer within 24 months of a screening mammogram (the index mammogram) and before their subsequent one (either as part of the BCSP or through routine medical care). The study was restricted to women without a history of breast cancer who remained continuously enrolled at GHC for at least 24 months following their index mammogram or who had died from any cause during that 24-month period. Study patients were identified by linking the BCSP database with the Seattle–Puget Sound Surveillance, Epidemiology, and End Results (SEER)[1] cancer registry. Study procedures were approved by the GHC Institutional Review Board, in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

We classified women as interval- or screen-detected patients on the basis of the results of their index mammogram. Evaluations were made after assessment of additional views, if any. Information from the BCSP database and from patients' medical records was reviewed to reclassify the index mammograms of all patients previously diagnosed with interval cancer and all screen-detected breast cancer patients who were not diagnosed within 3 months of the index mammogram, according to the Breast Imaging Reporting and Data System (BI-RADS™) of the American College of Radiology *(26)*.

Women were classified as interval-detected patients if their cancers occurred after a negative (BI-RADS code 1) or benign (BI-RADS code 2) assessment of their index mammograms. Women whose normal follow-up intervals were 2 or 3 years but who were given 12-month follow-up recommendations after their index mammograms were considered to be negative because 12 months is a routine follow-up interval in many settings. We also counted as negative any interpretation where abnormalities noted by the radiologist were in the breast opposite the one in which cancer was eventually detected.

Women were classified as screen-detected patients if their breast cancers occurred after a positive screening mammogram (BI-RADS code 5: highly suggestive of malignancy) *(26)* or if they had a recommendation either for surgical evaluation (BI-RADS code 4: suspicious for malignancy) or for a 6-month follow-up examination (BI-RADS code 3: probably benign, short-interval follow-up suggested).

A total of 578 women with invasive breast cancer met the eligibility requirements. One woman was dropped from the study at her request; one woman was excluded because she was symptomatic at the time of the screening visit. Of the remaining 576 subjects, 414 were classified as screen-detected cancer case subjects, and 162 were classified as interval cancer control subjects. Women were further excluded from this study if breast implants were present at the time of diagnosis (three women with interval cancer and one woman with screen-detected disease), if index mammograms were unavailable for review (eight women with interval cancer and 18 women with screen-detected disease), or if they had bilateral breast cancer (two women with interval cancer and seven women with screen-detected disease). Thus, data from 149 women with interval cancer and from 388 women with screen-detected cancer were available for analysis.

Assessment of Breast Density

Index mammograms from study women were reviewed for breast density by one radiologist from the Division of Mammography Quality and Radiation Programs, U.S. Food and Drug Administration, Rockville, MD. This radiologist was blinded to screen-detected or interval cancer status and to the laterality of breast cancer. The density for each breast was classified into one of four groups as defined by the BI-RADS system: 1) almost entirely fat, 2) scattered fibroglandular tissue, 3) heterogeneously dense, or 4) extremely dense. The density in the cancer-free breast was used in all analyses.

Additional Classification of Interval Cancers

For some analyses, we further classified interval cancer patients according to three factors: 1) index mammogram results (positive or negative), 2) duration of follow-up following a negative screening mammogram (12 or 24 months), and 3) whether or not the interval cancers were detected by a review by a second radiologist. When we reduced the follow-up period from 24 months to 12 months, 100 women who were diagnosed with breast cancer 13–24 months after their index mammograms were excluded from our study.

To classify interval cancers by whether or not they were detected by a second radiologist's review, an experienced study radiologist who was blinded to the cancer status of each mammography subject read a mixed group of mammograms: those of all interval cancer patients in the study plus 50 randomly selected screen-detected cancer patients and 50 randomly selected, age-stratified, cancer-free control subjects. Any additional views or ultrasound images obtained at the original assessment were available, but all marks on the films were removed. Films were interpreted by use of the five-category BI-RADS criteria. When a tumor was detected, its location was indicated on the study form. The index mammogram from one woman with interval cancer could not be obtained. Of the 148 cases of interval cancer included in this review, 100 (68%) were confirmed by assignment of BI-RADS code 1 (negative) or code 2 (benign) on both the initial assessment and the second review.

In a separate analysis, we combined patients with negative index mammograms with those initially interpreted as BI-RADS code 3 (probably benign, short-interval follow-up suggested) if there was no recommendation for further evaluation.

Risk Factors and Mammography Variables

Reproductive factors, oral contraceptive use, self-reported height and weight, and family history of breast cancer were ascertained from the BCSP Risk Factor Questionnaire. Body mass index (BMI) was calculated as (weight in kilograms)/(height in meters)^2. Race was obtained from the SEER cancer registry, which collects this information at medical record review. Mammography variables extracted from the BCSP database were age at index mammogram, year of index mammogram, and whether the mammogram was the woman's first or a subsequent screening mammogram.

Menopausal status at index mammogram was determined by a comparison of a woman's responses from two BCSP questionnaires, one prior to her index mammogram and the other following her diagnosis of breast cancer, supplemented by medical record abstraction when data were incomplete. Women with regular menstrual periods at the time of the index mammogram were considered to be premenopausal. Those with "less frequent" periods were considered to be perimenopausal. A woman was considered to be postmenopausal if she had had either natural cessation of menses, hysterectomy with bilateral oophorectomy, or hysterectomy without bilateral oophorectomy and was 50 years of age or older (the mean age at menopause in this population) at the time of her mammogram. Women with a hysterectomy without bilateral oophorectomy and under age 50 years were classified as "menopausal status unknown."

Use of HRT was determined from a computerized pharmacy database, operational at GHC since 1977, that records every prescription dispensed from the GHC pharmacy. HRT prescriptions at GHC are a 3-month supply of medications. The date of the index mammogram served as the reference date for ascertaining HRT use. Women were classified as current users if they filled at least two prescriptions for HRT in the 7 months prior to the mammogram index date. Former users comprised women with at least two prescriptions prior to the index mammogram but who were not current users. Never users were those who filled no more than one prescription prior to the index mammogram. Filling two prescriptions was the criterion for HRT use because a woman who filled only one prescription may have taken few or no pills before discontinuing use. Estrogen use was determined from the BCSP Risk Factor Questionnaire for women who had used HRT and stopped prior to 1977.

Statistical Analysis

Unconditional logistic regression analysis was used to analyze the association between breast density and the risk of interval- versus screen-detected cancers after adjustment for covariates. We present odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of interval cancer among women diagnosed with breast cancer. For ordered categorical-independent values, the statistical significance of the presence of a linear trend (P for trend) was tested by treating the factor as a single variable taking on

the values 1, 2, . . ., *n* equal to the category number; this is the logistic analog of the Mantel–Haenszel trend test. All *P* values are based on Z scores; $P<.05$ was considered to be statistically significant.

Because of the small numbers in some subgroups, women whose breasts were categorized as "almost entirely fat" or with "scattered fibroglandular tissue" were combined to form the reference group, which we termed "predominantly fat." Potential confounding factors, such as age at index mammogram, BMI, and prior mammography experience, were entered individually as covariates in the model; those that changed the OR for interval cancer as a function of breast density by 10% or more were considered to be confounders and were included in the adjusted models. Two adjusted models that used data from the 149 women who were initially classified as interval-detected patients and the 388 initially classified as screen-detected patients are presented. The first model was adjusted for age at index mammogram (40–49, 50–59, 60–69, 70–79, or ⩾80 years), while the second model was adjusted for age at index mammogram (as above), BMI quartiles (<22.4, 22.4–24.8, 24.9–28.3, or ⩾28.4 kg/m^2), menopausal status (premenopausal or perimenopausal and postmenopausal), and use of HRT (never or former user and current user).

Subanalyses were also conducted to determine if observed associations between breast density and interval cancer risk varied with age, HRT use, or BMI. These analyses included tests for interaction to determine whether the measures of the association of breast density with interval cancer risk effect were uniform across variations in these factors.

RESULTS

Selected characteristics of the 149 women initially classified with interval breast cancer and the 388 women initially classified with screen-detected cancer are shown in Table 1. Women with interval breast cancer were younger, and 19% were premenopausal at the time of index examination compared with 5% of women with screen-detected cancer. Interval cancer case subjects were more likely to currently use HRT (39% versus 24% of screen-detected case subjects) and also more likely to report past use of oral contraceptives. Women with interval cancer were also less likely to be parous or to be overweight compared with screen-detected case subjects. The two groups were otherwise similar with respect to demographic and breast cancer risk factors.

Breast density was strongly associated with reduced mammographic sensitivity (i.e., probability of screen detection among women with breast cancer) and increased risk of interval cancer (Table 2). The overall mammographic sensitivity was 72%, but it declined sharply from 80% among women whose breasts were categorized as predominantly fat to 30% in women with extremely dense breasts.

Table 1. Comparison of women with interval cancer and with screen-detected cancer by demographic characteristics and factors related to breast cancer risk

	Interval cancer (n = 149)		Screen-detected cancer (n = 388)	
Characteristic	No.	%	No.	%
Age at index mammogram, y				
40–49	34	22.8	33	8.5
50–59	38	25.5	85	21.9
60–69	36	24.2	131	33.8
70–79	31	20.8	113	29.1
⩾80	10	6.7	26	6.7
Race*				
White	135	93.8	359	96.0
Black	5	3.5	7	1.9
Asian	4	2.8	8	2.1
Year of index mammogram				
1988 and 1989	27	18.1	84	21.6
1990 and 1991	49	32.9	128	33.0
1992 and 1993	73	49.0	176	45.4
Mammogram prior to index*				
Yes	94	63.1	209	54.4
No	55	36.9	175	45.6
Family history of breast cancer				
First degree	40	26.8	87	22.4
Second degree only	18	12.1	46	11.9
None	91	61.1	255	65.7
Parity				
Parous	117	78.5	338	87.1
Nulliparous or data missing	32	21.5	50	12.9
Oral contraceptive use, y				
None or <1	83	55.7	271	69.8
1–4	31	20.8	57	14.7
5–9	16	10.7	30	7.7
⩾10	19	12.8	30	7.7
Menopausal status				
Premenopausal	28	18.8	18	4.6
Perimenopausal or postmenopausal	121	81.2	370	95.4
Hormone replacement therapy use*,†				
Never or former user	74	61.2	282	76.2
Current user	47	38.8	88	23.8
Body mass index, kg/m^2*,‡				
<22.4	49	34.0	81	21.3
22.4–24.8	32	22.2	98	25.7
24.9–28.3	38	26.4	100	26.2
⩾28.4	25	17.4	102	26.8

*Women with missing information were excluded from column totals for calculation of percent.

†Perimenopausal and postmenopausal women only.

‡Body mass index = (weight in kilograms)/(height in meters)^2.

Table 2. Odds ratio for risk of interval breast cancer associated with mammographic breast density among women diagnosed within 24 months of a screening mammogram

	Interval cancer (n = 149)		Screen-detected cancer (n = 388)		Odds ratio (95% confidence interval)	
	No.	%*	No.	%†	Age-adjusted	Adjusted for covariates‡
Predominantly fat§	72	19.7	294	80.3	1.00 (referent)	1.00 (referent)
Heterogeneously dense	61	41.2	87	58.8	2.57 (1.67–3.97)	3.02 (1.84–4.95)
Extremely dense	16	69.6	7	30.4	7.78 (2.98–20.3)	6.14 (1.95–19.4)
P for trend					<.001	<.001

*Row percent, constitutes proportion of women false negative at index screening mammogram.

†Row percent, constitutes sensitivity of index screening mammography.

‡Age at index mammogram, menopausal status, use of hormone replacement therapy, and body mass index quartile.

§Includes "almost entirely fat" and "scattered fibroglandular tissue."

Table 3. Odds ratios (ORs) for risk of interval breast cancer associated with mammographic breast density by subgroups based on age at index mammogram, use of hormone replacement therapy (HRT), and body mass index (BMI)

Breast density	Interval cancer No. (%)*	Screen-detected cancer, No. (%)†	Adjusted OR (95% confidence interval)	Interval cancer, No. (%)*	Screen-detected cancer, No. (%)†	Adjusted OR (95% confidence interval)
	Age 40–49 y‡			***Age 50 y and older§***		
Predominantly fat‖	13 (43.3)	17 (56.7)	1.00 (referent)	59 (17.6)	277 (82.4)	1.00 (referent)
Heterogeneously dense	13 (46.4)	15 (53.6)	1.05 (0.33–3.38)	48 (40.0)	72 (60.0)	3.01 (1.81–5.00)
Extremely dense	8 (88.9)	1 (11.1)	6.92 (0.68–70.7)	8 (57.1)	6 (42.9)	6.08 (1.93–19.2)
		P for trend = .17			*P* for trend <.001	
	Never or former user of HRT¶			***Current user of HRT¶***		
Predominantly fat‖	44 (16.1)	229 (83.9)	1.00 (referent)	18 (24.3)	56 (75.7)	1.00 (referent)
Heterogeneously dense	27 (35.5)	49 (64.5)	2.61 (1.42–4.80)	24 (44.4)	30 (55.6)	2.47 (1.00–6.10)
Extremely dense	3 (42.9)	4 (57.1)	4.31 (0.86–21.7)	5 (71.4)	2 (28.6)	8.55 (1.16–62.9)
		P for trend = .001			*P* for trend = .01	
	BMI <24.9 kg/m^2#			***BMI ≥24.9 kg/m^2#***		
Predominantly fat‖	34 (22.5)	117 (77.5)	1.00 (referent)	38 (17.7)	177 (82.3)	1.00 (referent)
Heterogeneously dense	39 (37.9)	64 (62.1)	2.17 (1.15–4.07)	22 (48.9)	23 (51.1)	4.94 (2.29–10.6)
Extremely dense	14 (70.0)	6 (30.0)	6.13 (1.72–21.8)	2 (66.7)	1 (33.3)	5.07 (0.28–92.1)
		P for trend = .001			*P* for trend <.001	

*Row percent, constitutes proportion of women false negative at index screening mammogram.

†Row percent, constitutes sensitivity of index screening mammography.

‡ORs adjusted for BMI quartile.

§ORs adjusted for age at index mammogram, menopausal status, use of HRT, and BMI quartile.

‖Includes "almost entirely fat" and "scattered fibroglandular tissue."

¶ORs adjusted for age and BMI quartile.

#BMI = (mass in kilograms)/(height in meters)^2; ORs adjusted for age, menopausal status, and HRT use.

Density was strongly associated with the risk of interval cancer after adjustment for age (P<.001 for linear trend). Further adjustment for menopausal status, use of HRT, and BMI did not change the effect: Women with heterogeneously dense breasts had a threefold greater risk of interval cancer (OR = 3.02; 95% CI = 1.84–4.95), and women with extremely dense breasts had a sixfold greater risk (OR = 6.14; 95% CI = 1.95–19.4) (relative to women with predominantly fatty breasts, in both cases).

The association between breast density and interval cancer risk was similar in subgroups of women characterized by age (Table 3). For women 50 years old or older, extremely dense breasts were associated with ORs for interval cancer greater than 6 when compared with women with predominantly fatty breasts. This association was not statistically significant in women aged 40–49 years (OR = 6.92; 95% CI = 0.68–70.7). Older women with heterogeneously dense breasts had a greater risk of interval cancer than older women with predominantly fatty breasts, whereas younger women in these two categories were at similar risk.

Statistically significant trends between breast density and interval cancer risk were present among both current users of HRT, never or former users of HRT, women in the lower half of BMI values, and women in the upper half of BMI values. Tests for interaction between subgroups of women stratified by age, HRT use, and BMI value were not statistically significant.

To better characterize the association between mammographic density and interval cancer detection, alternative definitions of interval detection and screen detection were applied for the analyses that are presented in Table 4. Limiting analyses to interval cancer patients whose negative screening mammograms were confirmed by retrospective review strengthened the association of interval cancer risk with breast density (OR associated with extreme density = 9.47 [95% CI = 2.78–32.3]; P for trend <.001). A much smaller, and not statistically significant, association between interval cancer risk and breast density was observed for interval cancer patients for whom retrospective review revealed the apparently negative screening mammogram to be positive (P for trend = .06).

Shortening the screening interval from 24 to 12 months also strengthened the relationship between breast density and the risk of interval cancer (and increased the overall probability of screen detection among women with breast cancer to 85%). In contrast, when we combined patients whose index mammograms were negative with those initially interpreted as BI-RADS code 3 (probably benign, short-interval follow-up suggested) and for whom there was no recommendation for further evaluation, 43 women whose cancers were originally considered screen detected were reclassified as interval cancer patients, and the association between breast density and interval cancer detection was attenuated, although a statistically significant trend persisted.

Discussion

We found that mammographic density was a strong risk factor for breast cancer detected in the interval after a negative mammogram. Women with extremely dense breasts had a sixfold greater risk of interval cancer, independent of the effects of age, menopausal status, use of HRT, or BMI. The association of breast density with interval cancer risk was generally similar among subgroups of women known to have increased breast density (women under age 50 years, women currently using HRT, and lean women) and subgroups with lower density (older women, those not currently using HRT, and women with higher BMIs). Our finding that breast density increased the risk of interval cancer was consistent across

Table 4. Odds ratios (ORs) for risk of interval breast cancer associated with mammographic breast density by alternative definitions of interval cancer

Breast density	Interval cancer No.	Interval cancer %*	Screen-detected cancer No.	Screen-detected cancer %†	Adjusted OR‡ (95% confidence interval)
Interval cancer detected ⩽24 mo after a negative screening mammogram (*confirmed* by retrospective review)					
Predominantly fat§	43	12.8	294	87.2	1.00 (referent)
Heterogeneously dense	43	33.1	87	66.9	3.69 (2.03–6.72)
Extremely dense	14	66.7	7	33.3	9.47 (2.78–32.3)
					P for trend <.001
Interval cancer detected ⩽24 mo after a negative screening mammogram (but *positive* on retrospective review)					
Predominantly fat§	28	8.7	294	91.3	1.00 (referent)
Heterogeneously dense	18	17.1	87	82.9	2.15 (1.01–4.57)
Extremely dense	2	22.2	7	77.8	2.00 (0.22–18.6)
					P for trend = .06
Interval cancer detected ⩽12 mo after a negative screening mammogram					
Predominantly fat§	29	9.4	280	90.6	1.00 (referent)
Heterogeneously dense	28	25.2	83	74.8	4.09 (2.06–8.14)
Extremely dense	10	58.8	7	41.2	8.37 (2.21–31.8)
					P for trend <.001
Interval cancer detected ⩽24 mo after a negative or "probably benign" screening mammogram‖					
Predominantly fat§	104	28.4	262	71.6	1.00 (referent)
Heterogeneously dense	72	48.6	76	51.4	2.34 (1.48–3.70)
Extremely dense	16	69.6	7	30.4	3.85 (1.25–11.9)
					P for trend <.001

*Row percent, constitutes proportion of women false negative at index screening mammogram.

†Row percent, constitutes sensitivity of index screening mammography.

‡Adjusted for age at index mammogram, use of hormone replacement therapy, menopausal status, and body mass index quartile.

§Includes "almost entirely fat" and "scattered fibroglandular tissue."

‖"Probably benign" finding corresponds to BI-RADS assessment code 3.

varied definitions of interval cancer and was highest when interval cancers identified upon review by the study radiologist were omitted. Our primary analyses were based on a 24-month screening interval, for which the overall sensitivity was 72%; however, this finding persisted in analyses with the more common 12-month follow-up interval, for which the overall sensitivity was 85%.

Several previous studies *(13,14,20,23, 27–29)* have examined mammographic density in relation to interval breast cancer; however, they differ with regard to how breast density was measured, how interval cancer was defined, consideration of potentially confounding factors, how the control population was chosen, and sample size. Ma et al. *(14)* compared 31 true interval cancer patients (i.e., those not identified on retrospective review) with a random sample of 84 patients with mammographically detected breast cancer. Breast density was coded by one radiologist into five categories. Women in the highest category (⩾75% breast density) had an increased risk of interval cancer when compared with women in the lowest category (⩽10% breast density; OR = 9.0 [95% CI = 1.8–44.3]) after adjustment for tumor characteristics. In a study of 77 patients originally considered interval-detected cancer patients whose cancers were identified by second radiologist and 121 randomly selected screen-detected cancer patients *(13)*, breast density was associated with an increased risk of missed cancer (crude OR = 4.4 for ⩾75% glandular tissue versus <25%; $P = .05$). Kerlikowske et al. *(23)* compared 20 interval cancer patients with 179 screen-detected cancer patients, with density determined by one radiologist by use of the 4-point BI-RADS system collapsed into two categories. Breast density was associated with interval cancer risk for women 50 years old or older (crude OR = 5.8 for the two upper versus the two lower categories of density; $P<.01$). Rosenberg et al. *(20)* studied 129 interval- and 464 screen-detected breast cancer patients who were participating in community screening. Since breast densities were ascertained at multiple radiology facilities with different coding schemes, a simple two-category system was used in the study. In a model controlling for age, ethnicity, and screening history, an interaction between the use of HRT and breast density was observed: Women in the upper level of density who were using HRT had an increased risk of interval cancer (OR = 3.0; 95% CI = 1.7–5.3) compared with women in the lower level of density who were not using HRT. Women with either HRT use or increased breast density alone were not at increased risk of interval cancer. Thus, despite the differences in design, each of these studies found a substantial association of breast density with interval cancer risk in some subgroups of women.

Only three studies *(20,23,27)* examined the relationship between breast density and interval cancer risk in younger women. Kerlikowske et al. *(23)* reported that breast density did not influence the sensitivity of mammography among women under age 50 years. At least two factors may have affected this finding. First, only nine cancer patients missed by mammography in screened women under 50 years of age were available for analysis, so that the statistical power to detect an association in younger women was weak. Second, grouping women with extremely dense breast tissue with women with heterogeneously dense breast tissue may have diminished the magnitude of risk of interval cancer associated with breast density. However, both the Swedish Two-County Trial *(27)* and Rosenberg et al. *(20)* reported lower sensitivity of

mammography in women 40–49 years old with increased breast density. In our study, the ORs for interval cancer associated with extremely dense breasts were similar for women under age 50 years and those older (Table 3). However, women under age 50 years with heterogeneously dense breasts were not at increased risk, and no density-related trend for interval cancer risk was apparent for this age group, although few women were in the highest density category. Thus, it is not clear whether breast density plays as great a role in interval cancer risk in younger women as it does in older women.

Rosenberg et al. *(20)* observed an interaction between HRT use and breast density in their study. Our study partially supports their findings, since the combination of current HRT use and increased breast density appears to lead to substantially elevated risk of interval cancer (Table 3); however, we also found evidence of increased risk and a statistically significant trend among never/former users.

Cancer is generally detected in the interval after a negative mammogram because readers miss subtle or minimal signs on the screening mammogram *(5,6,10),* because tumors that are present are masked by characteristics of the breast or the tumor *(5,10,28),* or because rapid tumor growth leads to cancers that truly do arise in the interval after screening *(6,10,11).* Certainly, one way by which mammographic density increases the risk of interval cancer is by obscuring the tumor. Partial masking would also contribute to readers' missing the signs of malignancy. Past studies *(5,10,13,14,29–31)* as well as our study have found that 25%–50% of interval cancers could be seen on the screening mammogram in retrospect. In our study, a strong association between breast density and interval cancer (OR associated with extreme density = 9.47 [95% CI = 2.78–32.3]; P for trend <.001) was observed when we omitted interval cancers that were identified only retrospectively (i.e., cancer patients negative at index mammogram but positive on retrospective review). In contrast, when we limited our analysis to cancer patients identified only in retrospect (i.e., negative at index mammogram but positive at retrospective review), no statistically significant association with breast density was observed. These results suggest that breast density obscures the tumor, even when the mammogram is read by a second, experienced radiologist, although it may also play a role in reader error.

It is biologically plausible that breast density is associated with rapidly growing tumors that truly arise in the interval after screening. Density is a measure of stromal and epithelial breast tissues, and the histologic feature most responsible for density is stromal fibrosis *(32,33).* One possible mechanism that could link an increase in breast stroma to tumor aggressiveness is through the actions of growth factors produced in stroma *(33).* Past studies *(7,8,10)* and a separate analysis of the current study *(34)* show that tumors that are detected in the interval after a negative screening result have higher proliferation than screen-detected tumors. Further study of tumor cell proliferation in mammographically lucent and dense tissue is needed to better understand how these factors play a role in interval cancer risk.

Our study has at least two limitations. Despite its being, to our knowledge, among the largest studies of interval cancer conducted to date, some subanalyses were based on small samples and, consequently, had wide CIs around estimates of effect. In addition, we used the standard BI-RADS assessment of breast density by one study radiologist, but there is evidence that methods that quantify breast density may result in higher reproducibility and greater precision *(35,36),* although a recent review of studies that used variable definitions of breast density *(37)* showed consistency across study results.

Our findings, combined with results of previous studies, suggest that breast density is one of the strongest, if not the strongest, predictor of the failure of mammographic screening to detect cancer. There is evidence that short-term cessation of HRT *(38)* or timing of the mammogram based on a woman's menstrual cycle *(39)* may reduce breast density, and current studies are testing whether these approaches improve the accuracy of mammography. Future developments in breast imaging to improve screening of dense breasts may also contribute to a reduction in the frequency of interval cancers.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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