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Mammographic Density and Risk of Second Breast Cancer After Ductal Carcinoma *in situ*

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Abstract

Background—We examined whether mammographic density predicts risk of second breast cancers among patients with DCIS.

Methods—The study included DCIS patients diagnosed during 1990–1997 and treated with breast-conserving surgery at Kaiser Permanente Northern California. Medical records were reviewed for clinical factors and subsequent breast cancers (DCIS and invasive). Ipsilateral mammograms from the index DCIS were assessed for density without knowledge of subsequent cancer status. Cox regression modeling was used to examine the association between mammographic density and risk of breast cancer events.

Results—Of the 935 eligible DCIS patients, 164 (18%) had a subsequent ipsilateral breast cancer, and 59 (6%) had a new primary cancer in the contralateral breast during follow-up (median 103 months). Those with the greatest total area of density (upper 20% of values) were at increased risk for invasive disease in either breast (hazard ratio (HR)=2.1, 95% CI 1.2–3.8) and for any cancer (DCIS or invasive) in the ipsilateral (HR=1.7, 95% CI 1.0–2.9) or contralateral (HR=3.0, 95% CI 1.3–6.9) breast compared to those with the smallest area of density (bottom 20%). HRs for these same endpoints comparing those in the highest vs. lowest BI-RADS category were 1.6 (95% CI 0.7–3.6), 1.3 (95% CI 0.7–2.6) and 5.0 (95% CI 1.4–17.9), respectively. There was a suggestion of increasing risk of contralateral, but not ipsilateral, cancer with increasing percent density.

Conclusions—Women with mammographically dense breasts may be at higher risk of subsequent breast cancer, especially in the contralateral breast.

Impact—Information about mammographic density may help with DCIS treatment decisions.

Keywords

Mammographic density; ductal carcinoma in situ; breast cancer; recurrence

Introduction

The diagnosis of ductal carcinoma in situ (DCIS) has increased over five-fold since the early 1980s, due mainly to the increase in mammographic screening (1). It is estimated that approximately 58,000 new cases of DCIS were diagnosed in the U.S. in 2008 (2).

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The use of breast-conserving surgery for DCIS also has increased dramatically over the last 25 years, and up to 70% of DCIS patients in the US are now treated with lumpectomy or wide excision (3;4). DCIS patients treated with breast-conserving surgery are at increased risk of invasive cancer in the involved, (i.e., ipsilateral) breast (5–7) and to a lesser extent in the uninvolved (i.e., contralateral) breast (8). Few strong predictors of these second cancers have been identified.

Mammographic density, or the proportion of the breast area in the mammogram that is occupied by radiologically dense breast tissue, is one of the strongest established risk factors for the development of a first primary invasive breast cancer (9), and probably for first primary DCIS, as well (10). The appearance of breast tissue on a mammogram is determined by the relative amounts of fat, collagen, and epithelial tissue (11;12). Collagen and epithelial tissue have high radiologic density, whereas fat appears translucent.

Mammographic density is influenced by genetic factors (11). It is inversely associated with age and body mass index (BMI) and is higher in nonparous than parous women (9;12). Density is reduced by tamoxifen (13) and by a gonadotropin-releasing hormone agonist (14) and is increased with estrogen plus progesterone, and to a lesser extent with estrogen alone, menopausal hormone therapy (15;16). Higher density appears to be associated with higher circulating levels of insulin-like growth factor (11;17) and prolactin (18). Given that it is influenced by some hormones and growth factors, it seems plausible that mammographic density might be related to risk of breast cancer progression, as well as risk of new primary disease.

In 2004, we reported that higher breast density was associated with increased risk of second breast cancers among a subset of DCIS patients participating in the National Surgical Breast and Bowel Project (NSABP) B-17 clinical trial (19). A more recent analysis of DCIS patients conducted among women in the Breast Cancer Surveillance Consortium also showed an increased risk of second breast cancers associated with higher density, but this increased risk was only observed for the contralateral breast (20).

The purpose of this study was to examine the association between mammographic density and risk of subsequent cancer in the ipsilateral and contralateral breast among a cohort of DCIS patients treated with breast-conserving surgery in the community setting.

Methods

Study population and design

We conducted a cohort study within the membership of Kaiser Permanente of Northern California (KPNC). KPNC is a non-profit, integrated health services delivery organization that provides care for over 3 million members at 14 hospitals and 23 outpatient clinics. The KPNC membership is racially and ethnically diverse and is demographically similar to the general population of northern California, although it tends to under-represent the extremes of the socioeconomic spectrum (21–23). The study was approved by the Kaiser Permanente Institutional Review Board.

The KPNC tumor registry, a contributor to the Surveillance, Epidemiology, and End Results (SEER) program of cancer registries, was used to identify all female health plan members diagnosed with a first primary unilateral DCIS (International Classification of Diseases histology codes of 85002, 85012, 85032, 85042, 85072, and 85222) between January 1990 and December 1997. Patients were eligible if they were 20–84 years old at diagnosis, were treated with breast-conserving surgery, and had at least six months of membership in the health plan

after diagnosis. Women were excluded if they had bilateral breast cancer at diagnosis or had a prior cancer (breast or other site).

Information on the index DCIS, second cancers and other clinical factors

Information obtained from the KPNC tumor registry included diagnosis date, laterality, and treatment of the index DCIS. As with SEER registries, the KPNC tumor registry records information on new primary cancers only and cancer events considered to be recurrences are not captured. We therefore conducted a standardized review of patient medical records, including pathology reports, to confirm data from the registry and to identify all subsequent breast cancer events (DCIS or invasive disease), including those in the ipsilateral breast, regional or distant metastases and contralateral cancers. In addition, medical record information was obtained on several patient and clinical factors including reproductive history, family history of breast cancer, menopausal status, hormone use at diagnosis, height, weight, and history of benign breast disease. Data on surveillance mammography after DCIS were collected, and pathology reports of the index DCIS were reviewed by the study pathologist (author BP) to obtain information on status of surgical margins, histologic growth pattern, tumor size, nuclear grade, presence of microinvasion, microcalcifications, and necrosis. Breast cancer diagnosed within 6 months of the index DCIS was considered to be part of the initial disease episode. For example, if a woman had an invasive breast cancer in the first 6 months, she was excluded because she was considered to have invasive disease at diagnosis. If she had another DCIS within the first 6 months, this was considered to be part of the initial DCIS (i.e., re-excision of the initial lesion).

Density assessment

The diagnostic mammograms, including standard and magnification views, for the index DCIS were retrieved and reviewed by a Kaiser Permanente mammographer. Blinded to study outcomes, breast density was classified according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) system into four categories: almost entirely fat, scattered fibroglandular tissue, heterogeneously dense, extremely dense.

Films from the standard views of the involved breast were also sent to the mammographic density expert, Martine Salane. A manual compensating polar planimeter was used to measure the total breast area (in cm^2) and the total area of dense tissue (in cm^2) [as described in (24)]. Percent density was calculated as the area of dense tissue divided by the area of the breast. Note, the DCIS tumor was not excluded from the measurements of the approximately 28% of patients with a visible tumor mass. Parenchymal pattern assessment was based on criteria as defined by Wolfe et al (24). Briefly, the N1 pattern includes breasts composed primarily of fat; the P1 pattern includes breasts composed mainly of fat with prominent ducts occupying up to 25% of the breast; the P2 breast has prominent ducts occupying more than 25% of the breast; and, the DY breast is characterized by poorly defined sheet-like regions of densities admixed with areas of fat and without visible ducts. Unidentified for the readers, 10% of assessed films were sent for re-review by the mammographer and density expert, and 20% of films from the contralateral breast (in addition to those from the ipsilateral breast) were sent to the density expert for review. Of the 10% assessed films, the intraclass correlation coefficient of percent density=0.98; mean difference in percent density assessments =0.04%, 95% CI (0% to 1.08%). For parenchymal pattern assessments, kappa=0.7, 95% CI (0.6 to 0.9). The intraclass correlation coefficient of percent density between the ipsilateral and contralateral breasts is 0.96.

Analysis

Entry into the cohort began 6 months after the index DCIS and ended at diagnosis of an invasive or in situ cancer (including lobular carcinoma in situ), end of membership in the health plan,

death, ipsilateral mastectomy for any reason, or date of last chart note (at time of review), whichever came first. Cox regression modeling was used to estimate hazard ratios, while controlling for confounding variables (25). Cumulative incidence curves were also generated (26;27). Time since diagnosis (in months) was used as the time axis in regression models and in the cumulative incidence curves. Endpoints of interest included the following: any second breast cancer (DCIS or invasive), any recurrence (ipsilateral or regional/distant disease), invasive breast cancer, ipsilateral breast cancer, and contralateral breast cancer. Mammographic density was examined when classified according to BI-RADS (almost entirely fat, scattered fibroglandular tissue, heterogeneously dense, extremely dense), parenchymal pattern (N1, P1, P2, DY), total area of density in quintiles, and percent density (0%, <25%, 25–49%, 50–74%, 75–88%). Although their addition to our models did not materially change the hazard ratio estimates, the following factors were included in all models because of their established strong association with density or recurrence: age (continuous), body mass index (BMI) (<20, 20–<25, 25–<30, 30–<35, 35+), diagnosis year (1990–91, 1992–93, 1994–95, 1996–97), radiotherapy (yes, no), tamoxifen therapy (yes, no). In addition, we examined the following as potential confounders: status of surgical margins (positive, negative), receipt of follow-up mammograms (yes, no in the 12 months prior to each failure time), race/ethnicity (white, black, Asian, other), menopausal status (premenopausal, postmenopausal), menopausal hormone use at diagnosis (none, former, current), history of first degree relative with breast cancer (yes, no), history of benign breast disease (yes, no), tumor size (<1 cm, 1–1.9 cm, 2+ cm), comedo necrosis (yes, no), nuclear grade (low, intermediate, high), and distribution of microcalcifications (none, cluster < 1 cm, > 1 cm, scattered). Missing values were included as a separate category. None of these potential confounders had any appreciable impact on hazard ratio estimates and were therefore not included in our final models.

The proportional hazards assumption was tested by fitting models containing cross-product terms between time (log) and the density measure. In general, there was no evidence of non-proportionality in any analysis with the exception of parenchymal pattern in relation to any 2nd breast cancer with a borderline Wald significance test for interaction (p=.07). These analyses should be interpreted as averaged over time, with the recognition that strength of associations varies somewhat over time.

We also conducted subanalyses to explore whether associations with density measures varied by adjuvant therapy, age, menopausal status, BMI, and time since DCIS diagnosis.

Results

A total of 1,221 potentially eligible DCIS patients were identified. Of these, 208 (18%) were ineligible for one or more of the following reasons: miscoding of DCIS in the tumor registry (n=27), prior breast cancer (n=88), bilateral breast cancer at diagnosis (n=6), treatment of index DCIS with mastectomy (n=34), age 85 years or older at diagnosis (n=14), and not followed within the health plan for at least 6 months (n=47). In addition, medical records were unavailable on 7 patients and mammograms could not be located or were not assessable for density on 71 patients. This left 935 patients in the final analytic cohort.

Approximately 60% of the study cohort was 55 years or older at diagnosis of DCIS, and 75% were non-Hispanic white (Table 1). The majority of DCIS was detected on a routine screening mammogram, and of those with tumor size available on the pathology report, 53% were less than 1 cm (not shown). Approximately half were treated with adjuvant radiotherapy, and 60% had two or more biopsies or surgeries (not shown). Final surgical margins were free of tumor in 91% of patients (not shown). Note, patients categorized as having free surgical margins included those with no evidence of disease on re-excision.

During a median follow-up of 103 months (range 6–189) after the index DCIS, there were 228 women who had a subsequent breast cancer as a first event. Median time to subsequent breast cancer was 43 months. Of these first events, 164 (72%) were in the ipsilateral breast, 5 (2%) were regional or distant metastases (without ipsilateral breast involvement), and 59 (26%) were in the contralateral breast. The cumulative incidence at 5 years was 0.13 for ipsilateral cancer, <0.01 for regional or distant disease, and 0.03 for contralateral cancer (not shown).

There were 257 patients (27%) who had 50% or more of the breast occupied by dense tissue and 21 patients (2%) whose breasts were classified as DY pattern; 125 patients (13%) had breast classified as extremely dense according to BI-RADS (Table 2). After adjusting for diagnosis year, age, body mass index at diagnosis of the index DCIS, and treatment (radiotherapy, hormonal) of the index lesion, those with the greatest area of density (upper 20% of values) were at approximately double the risk for a subsequent breast cancer or a subsequent invasive cancer, compared to those with the smallest area of density (bottom 20%). For any subsequent breast cancer, the strength of association was similar when comparing those in the highest to those in the lowest density category based on parenchymal pattern or when based on BI-RADS. In contrast, risk was not elevated in those with the highest vs. lowest category of percent density.

Associations between density and risk of second breast cancer appeared to differ by laterality of the cancer and were strongest for contralateral cancer (Table 3). Relative risks were not materially modified when we restricted the follow-up period to less than two years or to two or more years after the index DCIS. When analyses were restricted to patients without a visible tumor mass, associations were slightly weaker for parenchymal pattern, essentially the same for area of density, and slightly stronger for BI-RADS (not shown). Attempts to look at time intervals after diagnosis were limited by small numbers but did not reveal a clear pattern. Relative risks also did not vary appreciably across subgroups based on age, treatment, menopausal status, or BMI (not shown).

Discussion

Our results provide additional supporting evidence for an increase in risk of second breast cancers among DCIS patients with mammographically dense breasts. This association appears to be strongest and most consistent for risk of cancer in the contralateral breast. In addition, the association with risk of contralateral cancer is similar in strength to what has been previously reported for mammographic density and risk of primary breast cancer among women without a history of breast cancer.

Some limitations should be considered when interpreting our results. The study was conducted among patients treated in the community setting and follow-up was not standardized as is typical in clinical trials. However, we reviewed the medical records, including pathology and mammography reports, of all DCIS patients during their follow-up period and so should have complete ascertainment of subsequent breast cancer events. Our risk estimates were based on density assessments of diagnostic films of the involved or ipsilateral breast that did not exclude dense areas associated with a tumor mass. However, results were not materially changed when we restricted our analysis to patients without a visible mass. In addition, the concordance of density measurements was extremely high in the 20% random sample for which assessments were made in both the involved and uninvolved breast. Density assessments have been found to be quite variable in many studies that have not used radiologists or technicians trained in assessing density (28) and we therefore used an expert whose measurements are highly reproducible and have been strongly associated with risk in several breast cancer studies (24; 29–31). While the distribution of DCIS patients across density categories was very similar to what has been reported for healthy women of a similar age range (29), the number of patients

and breast cancer events in some of the density categories were quite small, resulting in risk estimates that were unstable.

Our results contrast somewhat with those from our previous study conducted among participants in the NSABP B-17 clinical trial (19). In that study, higher percent density, also measured centrally by the same density expert, was associated with a 3-fold increase in risk for both the ipsilateral and contralateral breasts, although the estimates for the contralateral breast were imprecise due to small numbers. In addition, the increased risk was only observed for women in the highest density category (≥ 75% dense tissue). It is not clear why the current study did not find an increased risk of either ipsilateral or contralateral cancer for those in the highest category of percent density, although small numbers of women in this category is a possible explanation. In the NSABP study, there was a more modest and non-statistically significant increase in risk of ipsilateral breast cancer among women with greater breast density based on parenchymal patterns and total area of breast density, although again numbers in some density categories were quite small. Density was not classified by BI-RADS in the NSABP B-17 study.

Our current BI-RADS findings of an increased risk only in the contralateral breast are largely in agreement with those found by Hwang et al (20). Whereas we did not collapse categories, BI-RADS categories in the Hwang et al study were collapsed into high (BI-RADS 3 and 4) and low density (BI-RADS 1 and 2). In that study, high versus low breast density was associated with a 3-fold increase in risk of contralateral invasive breast cancer among women treated with lumpectomy alone and among those treated with lumpectomy plus radiotherapy; density was not associated with risk of ipsilateral cancer. As in our study, they found that results did not change materially with time interval after initial DCIS.

Higher breast density also has recently been observed to be associated with increased risk of local but not distant recurrence among two relatively small studies of women with invasive breast cancer (32;33). Neither study reported on the association between density and risk of contralateral cancer.

A large number of studies have examined the association between mammographic density and risk of primary invasive breast cancer (34). To our knowledge, only one study has examined mammographic density (measured as percent density) and risk of new primary DCIS (10). In studies of invasive disease, associations generally have been stronger in those using quantitative measures of the percent of the breast occupied by dense tissue (29;35) than in those using parenchymal patterns. Associations have also been found to be substantially stronger in studies using percent density than in those using BI-RADS (34). Only a few studies have reported on the association between breast cancer risk and total area of density (29;36), and associations also have been weaker than what has generally been reported for percent density.

The biological mechanisms responsible for the relation between mammographic density and the risk of developing a new primary breast cancer have not been established, although several possible explanations have been proposed (11;29;37;38). Most established risk factors for breast cancer are hormone-related and others may act by modulating the activity of growth factors in breast tissue (37;39;40). It has been proposed that mammographic density principally reflects proliferation of breast stroma (37). The formation and maintenance of dense breast tissue may be the result of an interaction between breast stroma and epithelium via paracrine growth factors, and related to circulating levels of growth factors and hormones such as insulin-like growth factor and prolactin (11;37). Parenchymal patterns and percent mammographic density also may be related to breast cancer risk because they in part measure epithelial structures and the amount of epithelial tissue may be related to breast cancer risk (41).

Our finding of an increased risk of subsequent breast cancer among DCIS patients associated with highly dense breasts is consistent with several of the mechanisms noted above. However, these mechanisms do not provide a potential explanation for why the elevated risk of second cancer associated with high breast density appears to be greater for the contralateral than for the ipsilateral breast. It is possible that mammographic density is only related to new primary cancer and the more modest increase observed for the ipsilateral breast is due to an association with only those ipsilateral cancers that are new primaries (approximately 25%). It is also possible that BCS removes a materially important amount of dense tissue and therefore attenuates the associated risk in the ipsilateral breast. Further research will be needed to confirm our findings and to elucidate the biologic mechanisms.

Although breast cancer mortality rates are very low for women with a recent history of DCIS (42–44), those treated with breast-conserving surgery are at increased risk of subsequent invasive cancer in the ipsilateral and contralateral breast (8;45). To date, only a few modestly prognostic factors have been identified. Together with the findings from two other reports, our study results suggest that mammographic density assessment at diagnosis may aid in the prediction of risk for second cancers among women with DCIS. This information may be important to patients and doctors when making treatment decisions, especially given recent data suggesting increasing rates of contralateral prophylactic mastectomy in DCIS patients (46). However, precise and consistent estimates of risk for specific density categories will be needed before clinical utility can be established. Since higher mammographic density predicts lower sensitivity and specificity of screening mammography (47;48), high breast density may have clinical relevance regarding the accuracy of follow-up mammography for DCIS patients, as well.

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Table 1

Characteristics of DCIS cohort and crude rates of 2nd cancer in the ipsilateral and contralateral breasts

				2nd breast cancer			
	All DCIS Patients (n=935)			Ipsilateral* (n=164)		Contralateral (n=59)	
Characteristic (at index DCIS)	**N**	**Percent**	**Person-Years (py)**	**N**	**Rate per 1,000 py**	**N**	**Rate per 1,000 py**
Age at Diagnosis of							
<45	115	12.3%	905.5	28	30.9	5	5.5
45–54	258	27.6%	2,070.1	46	22.2	18	8.7
55+	562	60.1%	4,305.4	90	20.9	36	8.4
Diagnosis Year							
1990–91	149	15.9%	1,413.1	32	22.6	9	6.4
1992–93	207	22.1%	1,733.8	32	18.5	18	10.4
1994–95	274	29.3%	2,078.9	51	24.5	17	8.2
1996–97	305	32.6%	2,055.1	49	23.8	15	7.3
Race/Ethnicity							
Asian	104	11.1%	795.9	15	18.8	10	12.6
Black	68	7.3%	545.5	16	29.3	5	9.2
Hispanic	60	6.4%	499.3	9	18.0	3	6.0
White	700	74.9%	5,420.9	124	22.9	41	7.6
Unknown	3	0.3%	19.4	0	0.0	0	0.0
Mode of Detection							
Other	3	0.3%	33.6	1	29.7	0	0.0
Routine Mammogram	759	81.2%	5,998.6	126	21.0	48	8.0
Symptom/Exam	169	18.1%	1,209.2	37	30.6	11	9.1
Unknown	4	0.4%	39.6	0	0.0	0	0.0
Body Mass Index							
<25	390	41.7%	3,041.2	84	27.6	20	6.6
25–<30	292	31.2%	2,307.3	44	19.1	17	7.4
30+	195	20.9%	1,519.6	31	20.4	18	11.8
Unknown	58	6.2%	412.7	5	12.1	4	9.7
Radiotherapy							

	All DCIS Patients (n=935)			2nd breast cancer			
				Ipsilateral* (n=164)		Contralateral (n=59)	
Characteristic (at index DCIS)	**N**	**Percent**	**Person-Years (py)**	**N**	**Rate per 1,000 py**	**N**	**Rate per 1,000 py**
No	446	47.7%	3,251.0	109	33.5	22	6.8
Yes	485	51.9%	4,005.4	55	13.7	37	9.2
Unknown	4	0.4%	24.6	0	0.0	0	0.0
Hormonal Therapy							
No	891	95.3%	6,943.6	159	22.9	55	7.9
Yes	44	4.7%	337.4	5	14.8	4	11.9

*Excludes 2nd cancers (n=5) that were regional or distant metastases without ipsilateral breast involvement

Table 2

Hazard ratios of second breast cancers by four measures of mammographic density

	Full Cohort	Any 2nd Breast Cancer						2nd Breast Cancer - Invasive Only					
		Unadjusted			Adjusted*			Unadjusted			Adjusted*		
Density Measure	**N**	**N**	**HR**	**(95% CI)**	**HR***	**(95% CI)**	**P****	**N**	**HR**	**(95% CI)**	**HR***	**(95% CI)**	**P****
Parenchymal Pattern													
N1	97	15	1.0		1.0		0.06	10	1.0		1.0		0.44
P1	209	51	1.7	(0.9–3.0)	1.7	(0.9–3.0)		30	1.5	(0.7–3.0)	1.5	(0.7–3.1)	
P2	608	157	1.8	(1.1–3.1)	1.8	(1.0–3.2)		80	1.4	(0.7–2.7)	1.5	(0.8–3.1)	
DY	21	5	2.2	(0.8–6.1)	2.0	(0.7–5.8)		1	0.7	(0.1–5.3)	0.7	(0.1–5.5)	
Area of Density													
Quintile 1	185	34	1.0		1.0		0.02	20	1.0		1.0		0.02
Quintile 2	193	49	1.5	(1.0–2.3)	1.5	(1.0–2.4)		26	1.4	(0.8–2.4)	1.4	(0.8–2.6)	
Quintile 3	190	45	1.4	(0.9–2.2)	1.4	(0.9–2.2)		22	1.2	(0.6–2.2)	1.3	(0.7–2.5)	
Quintile 4	184	44	1.4	(0.9–2.2)	1.3	(0.8–2.1)		22	1.2	(0.6–2.2)	1.2	(0.6–2.3)	
Quintile 5	183	56	1.9	(1.3–3.0)	1.8	(1.2–2.9)		31	1.8	(1.0–3.2)	2.1	(1.2–3.8)	
Percent Density													
0	66	11	1.0		1.0		0.19	8	1.0		1.0		0.48
1–24	298	68	1.4	(0.8–2.7)	1.5	(0.8–2.8)		38	1.1	(0.5–2.4)	1.2	(0.5–2.5)	
25–49	314	78	1.6	(0.9–3.1)	1.7	(0.9–3.3)		41	1.2	(0.6–2.6)	1.4	(0.6–3.1)	
50–74	225	64	1.9	(1.0–3.6)	1.9	(0.9–3.7)		30	1.2	(0.6–2.7)	1.4	(0.6–3.3)	
75+	32	7	1.4	(0.5–3.5)	1.3	(0.5–3.6)		4	1.0	(0.3–3.5)	1.2	(0.3–4.4)	
BI-RADS Density													
Almost All Fat	165	28	1.0		1.0		0.03	16	1.0		1.0		0.16
Scattered fibroglandular	292	71	1.5	(1.0–2.4)	1.6	(1.0–2.5)		39	1.5	(0.8–2.6)	1.6	(0.9–3.0)	
Heterogeneously dense	328	91	1.7	(1.1–2.6)	1.8	(1.1–2.8)		50	1.6	(0.9–2.9)	1.9	(1.0–3.6)	
Extremely dense	125	36	1.8	(1.1–3.0)	1.9	(1.0–3.3)		15	1.3	(0.7–2.7)	1.6	(0.7–3.6)	

*Adjusted for age (continuous), BMI (<20, 20–<25, 25–<30, 30–<35, >=35), radiotherapy (yes, no), tamoxifen (yes, no), diagnosis year (90–91, 92–93, 94–95, 96–97)

**P-value for linear trend

Table 3

Hazard ratios of second breast cancers according to breast laterality by four measures of mammographic density

		Any Ipsilateral Breast Cancer						Any Contralateral Breast Cancer					
	Full Cohort	Unadjusted			Adjusted*			Unadjusted			Adjusted*		
Density Measure	**N**	**N**	**HR**	**(95% CI)**	**HR***	**(95% CI)**	**P****	**N**	**HR**	**(95% CI)**	**HR***	**(95% CI)**	**P****
Parenchymal Pattern													
N1	97	10	1.0		1.0		0.22	4	1.0		1.0		0.06
P1	209	38	1.8	(0.9–3.7)	1.8	(0.9–3.7)		12	1.5	(0.5–4.5)	1.7	(0.5–5.2)	
P2	608	111	2.0	(1.0–3.7)	1.7	(0.8–3.3)		43	1.9	(0.7–5.3)	2.8	(1.0–8.3)	
DY	21	5	3.3	(1.1–9.7)	2.7	(0.9–8.2)		0	0.0		0.0		
Area of Density													
Quintile 1	185	23	1.0		1.0		0.16	9	1.0		1.0		<0.01
Quintile 2	193	36	1.6	(1.0–2.8)	1.5	(0.9–2.6)		13	1.5	(0.6–3.5)	1.8	(0.8–4.4)	
Quintile 3	190	35	1.6	(1.0–2.8)	1.5	(0.8–2.6)		8	0.9	(0.4–2.4)	1.2	(0.5–3.2)	
Quintile 4	184	32	1.5	(0.9–2.6)	1.2	(0.7–2.2)		11	1.3	(0.5–3.1)	1.7	(0.7–4.3)	
Quintile 5	183	38	1.9	(1.2–3.2)	1.7	(1.0–2.9)		18	2.4	(1.1–5.3)	3.0	(1.3–6.9)	
Percent Density													
0	66	7	1.0		1.0		0.88	3	1.0		1.0		0.04
1–24	298	50	1.6	(0.8–3.6)	1.6	(0.7–3.6)		17	1.3	(0.4–4.5)	1.6	(0.4–5.4)	
25–49	314	57	1.9	(0.9–4.1)	1.7	(0.7–3.8)		20	1.6	(0.5–5.2)	2.3	(0.7–8.2)	
50–74	225	44	2.1	(0.9–4.6)	1.6	(0.7–3.8)		18	2.0	(0.6–6.8)	3.6	(1.0–13.1)	
75+	32	6	1.8	(0.6–5.5)	1.2	(0.4–4.1)		1	0.7	(0.1–6.6)	1.4	(0.1–14.6)	
BI-RADS Density													
Almost All Fat	165	22	1.0		1.0		0.32	5	1.0		1.0		0.02
Scattered fibroglandular	292	47	1.3	(0.8–2.1)	1.2	(0.7–2.1)		23	2.8	(1.0–7.2)	3.8	(1.4–10.2)	
Heterogeneously dense	328	66	1.6	(1.0–2.6)	1.4	(0.8–2.4)		23	2.4	(0.9–6.4)	3.9	(1.4–10.8)	
Extremely dense	125	27	1.8	(1.0–3.1)	1.3	(0.7–2.6)		8	2.3	(0.7–7.0)	5.0	(1.4–17.9)	

* Adjusted for age (continuous), BMI (<20, 20–<25, 25–<30, 30–<35, >=35), radiotherapy (yes, no), tamoxifen (yes, no), diagnosis year (90–91, 92–93, 94–95, 96–97)

** P-value for linear trend