Risk of Subsequent Breast Cancer in Relation to Characteristics of Screening Mammograms from Women Less Than 50 Years of Age[1]

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Abstract

This investigation was conducted to assess the predictive value of calcifications and densities in mammograms from women <50 years of age for subsequent diagnosis of breast cancer. In a population-based study, prior screening mammograms taken before age 50 in 547 women with breast cancer and 472 controls were reviewed by a single radiologist. The relative risk (RR) of subsequent breast cancer increased with the percentage of the area of the mammogram that was mammographically dense [RR in succeeding quartiles of density = 1.0, 1.7 (1.1–2.6), 3.3 (2.2–5.0), and 4.0 (2.7–6.0)]; in relation to Wolfe parenchymal pattern class P2 [RR = 3.1 (2.2–4.3)] or DY [RR = 5.6 (3.2–10.0)]; and in relation to calcifications of class 1 (pleomorphic of any distribution) or class 2 (various morphological types that are regional, grouped, clustered, segmental, or linear in distribution) [RR = 3.0 (1.4–7.1), and 1.8 (1.2–2.6), respectively]. Women with radiographically dense mammograms and class 1 or 2 calcifications were at >10- and ~6-fold greater risk, respectively, than women with breasts of low density and no calcifications. Densities and parenchymal patterns were most strongly associated with

breast cancer being diagnosed in the next 3 years. Class 1 and 2 calcifications were most strongly predictive of an increased risk in 3–6 years. Class 1 calcifications were strongly predictive of the breast in which the subsequent cancer occurred. Women <50 years of age with class 1 or 2 calcifications or mammographically dense breasts, or both, should receive high priority for further evaluation and regular breast cancer screening.

Introduction

Although mammographic screening in women >50 years of age has been shown to reduce mortality from breast cancer by ~30% (1), it most probably is less efficacious in women <50 years of age (2). Furthermore, breast cancer occurs less frequently in younger than older women. Therefore, the number of screening mammograms required to save one life is considerably greater for women <50 (3–6). Despite the relative inefficiency of mammographic screening in women <50, screening women of ages 40–49 has been recommended by the American Cancer Society and the United States National Cancer Institute, and large numbers of young women have screening mammograms annually.

These recommendations are based solely on the value of mammograms to detect existing breast cancer at an early, potentially curable, stage. Mammograms are not generally used clinically to predict risk of subsequent breast cancer, although there is considerable evidence that certain mammographic features are associated with a subsequent increase in risk. If these features could be used to distinguish women <50 years of age who are at unusually high risk of breast cancer from women at lower risk, they could assist clinicians and radiologists in determining which women should receive intensive subsequent screening and which should not. This would enhance the value and efficiency of mammographic screening in young women.

Mammographic features that have been associated with increased risk of subsequent breast cancer include Wolfe classification of parenchymal pattern (7–12), the percentage of the area of the mammogram that is radiographically dense (9, 12–14), the amount of glandular tissue in the breast as judged from the appearance of mammographic densities (15), and the presence of certain types of calcifications (16). Although risk of breast cancer has been shown to increase with the percent density in mammograms taken in women <50 (12), the predictive value of calcifications and the joint influence of calcifications and densities on risk have not been evaluated in mammograms from women <50 years of age. In this report, we provide results from a population-based case-control study that was conducted to evaluate the predictive value for subsequent breast cancer of these features in mammograms from women screened for breast cancer before 50 years of age.

Materials and Methods

Cases and controls for this study were recruited from women who had participated in four previous population-based case-control studies of breast cancer in the Seattle area: BCYW[3] (17); WISH (18); HORMONE (19); and EMF (20). Cases from all four studies were identified through the Cancer Surveillance System, a population-based cancer registry sponsored by the Surveillance, Epidemiology, and End Results program of the National Cancer Institute that covers 13 counties of Western Washington State (21). Women with an initial diagnosis of either *in situ* or invasive disease were included in all four studies. Information on extent of disease was obtained from the registry records. Cases eligible for the BCYW study were female residents of King, Pierce, or Snohomish counties who were born after 1944 and who developed breast cancer from January 1983 through April 1990. Cases eligible for the WISH study were those from the same three counties <45 years of age who were diagnosed from May 1990 through December 1992. The HORMONE study included the cases 50–64 years of age residing in King County, diagnosed from January 1988 to June 1990. Cases eligible for the EMF study were female residents of King and Snohomish counties diagnosed from January 1993 to June 1995.

To eliminate women unlikely to have had access to mammographic screening before age 50 or to have had their mammograms in the too distant past for likely retrieval, cases diagnosed before 1985 in the BCYW study, those >54 years of age in the HORMONE study, and those >59 years of age in the EMF study were not considered eligible for this investigation.

Controls for all four studies were selected by random digit dialing, using a modification of the Waksberg (22) method. Controls were not matched to individual cases. They were selected from the counties from which the cases came, with stratification by age to yield a sample of women with an age distribution similar to that of the cases. For this investigation, the same criteria used to exclude cases unlikely to have retrievable mammograms were also used to exclude controls (except using a reference date comparable with the date of diagnosis in the cases instead of date of diagnosis).

Experienced interviewers had administered standardized questionnaires to all consenting study subjects after obtaining written informed consent. Although these questionnaires varied among the four prior studies, they were developed to ensure comparability on the standard risk factors for breast cancer. Information collected included marital, reproductive, menstrual and contraceptive history, use of exogenous hormones, lifestyle factors, prior breast biopsies (including, but not distinguishing, needle aspiration, biopsy of a lesion, and lumpectomy), socio-economic characteristics, and family history of breast cancer. Weight 1 year before interview and maximum height attained were also ascertained at interview, except in the WISH study, height was measured; and these data were used to calculate body mass index (weight in kilograms ÷ height in meters squared).

A history of prior mammographic screening had also been elicited from the women. Attempts were made to recruit into this investigation those who had given a history of a screening mammogram before 50 years of age and 1 year or more prior to the date of diagnosis (for the cases) or reference date (for the

controls). The women, or their next of kin if the woman was deceased, were sent a questionnaire to ascertain information on the time and place each screening mammogram was taken and a consent form giving their permission for us to contact the radiologists and request loan of the mammograms. Telephone calls were made to women who did not respond, and in some instances, the questionnaire was administered during the call.

Requests were sent to the mammographic facilities where each woman's earliest mammogram was taken and to facilities where subsequent screenings were performed if mammograms from the first facility were unavailable. The earliest available screening mammograms from each woman were used. Whether the mammograms were X-ray films or xeroradiographs was recorded.

Craniocaudal and mediolateral oblique or lateral views of each breast were reviewed by a single reference radiologist. All identifying information on the films was masked. The two views of the same breast were given the same code number and reviewed together, but the films from each breast were given different numbers and read independently. No special images were used.

The craniocaudal and mediolateral oblique or lateral views were both used to classify each breast according to the paren-chymal pattern classification of Wolfe (7, 23) as: N1 [mostly fat (radiolucent), few ducts]; P1 [ductal (linear) patterns occupying <25% of the breast area]; P2 [ductal (linear) patterns and nodular densities occupying >25% of the area]; and DY (dense sheets, no ductal pattern discernable). The reference radiologist received training from a colleague of Wolfe (Martine Salane) to enhance compatibility with prior investigations.

The two views were also used to record the morphological type and distribution of all calcifications. This information was subsequently used to classify all mammographic calcifications on a scale of 1–5 in descending order of suspicion for existing carcinoma. The system used combined entities in the Breast Imaging Reporting and Data System of the American College of Radiology (24). Class 5 calcifications are nonepithelial lesions (skin, vascular, or dystrophic) of any distribution. A variety of epithelial calcifications of low to intermediate suspicion of existing carcinoma were classified as class 4 if single, class 3 if diffuse or scattered, and class 2 if regional, grouped, clustered, segmental, or linear in distribution. These include calcifications that are punctate or round (probably representing fibrocystic disease, papillomatosis, or adenosis), lucent centered (most likely fat necrosis or calcified ductal debris), coarse/popcorn (usually involuting fibroadenoma), large rod-like (indicating duct ectasia and related changes), milk of calcium or polyhedral (usually cysts), and egg shell or rim (also cysts). Class 1 calcifications included those of any distribution that were pleomorphic. There were no linear branching, or casting type calcifications. The Breast Imaging Reporting and Data System designation of amorphous calcifications was not used.

The radiologist traced the outline of the dense areas on the craniocaudal view with a wax (China) marker. A single technician, who had also received training from Dr. Wolfe's associate, then measured the areas of the breast and of the dense area with a compensating polar planimeter (LASICO, Los Angeles, CA). A 10% sample of the mammograms was blindly read a second time by the reference radiologist. Within-observer variability in classifying mammograms was assessed using the Kappa statistic (25).

Data from the original interviews, the mammography evaluations, and (for cases) the cancer registry, were merged for analysis. Unconditional logistic regression (26) was used to

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[3] The abbreviations used are: BCYW, Breast Cancer in Young Women; WISH, Women's Interview Study of Health; HORMONE, Hormone Replacement Therapy and Breast Cancer in Middle Aged Women; EMF, Electric Power and Risk of Breast Cancer; CI, confidence interval; RR, relative risk.

Table 1 Distribution of cases and controls by age and prior study

	Cases		Controls	
	No.	%	No.	%
Age				
<40	101	18.5	73	15.5
40–44	254	46.4	222	47.0
45–49	78	14.3	72	15.3
50–54	89	16.3	90	19.1
55–59	25	4.6	15	3.2
Study				
EMF	231	42.2	213	45.1
HORMONE	37	6.8	31	6.6
BCYW	87	15.9	77	16.3
WISH	192	35.1	151	32.0
Total	547	100.0	472	100.0

Table 2 RRs of breast cancer in relation to percent density and Wolfe classification of prior mammograms

Feature of mammogram	No. of subjects		RR[a] (95% CI)	RR[b] (95% CI)
	Cases	Controls		
Percent density[c]				
≤26.7	53	118	1.0 (reference)	1.0 (reference)
26.8–50.1	92	118	1.8 (1.2–2.7)	1.7 (1.1–2.6)
50.2–70.2	176	118	3.5 (2.3–5.2)	3.3 (2.2–5.0)
≥70.3	226	118	4.4 (3.0–6.7)	4.0 (2.7–6.0)
Wolfe classification[d]				
N1 and P1	64	146	1.0 (reference)	1.0 (reference)
P2	420	302	3.2 (2.3–4.5)	3.1 (2.2–4.3)
DY	63	24	6.1 (3.5–10.8)	5.6 (3.2–10.0)

[a] Adjusted for age and study.
[b] Adjusted for age, study, and mammographic calcifications (see text).
[c] Mean of both breasts, classified into quartiles of controls.
[d] Highest of both breasts.

calculate odds ratios as estimates of RR in relation to various mammographic features and combinations of these features, controlling for age and study using the strata shown in Table 1 and for other mammographic features as appropriate. The potential confounding effects of other variables were assessed by including them as categorical variables, one at a time, in models containing age, study, and mammographic features. Confounding would have been considered present if inclusion of the additional variable had altered the RR estimate of interest by >5%, but no additional confounders were identified. For these analyses, the mean value of the percent density of both breasts was used, as was the most severe Wolfe class and calcification in the two breasts. In addition, to determine whether observed associations of risk with calcifications are breast specific, data on only the cases were used to compare the presence and types of calcifications in the breast ipsilateral and contralateral to the site of the subsequent neoplasm (no cases had bilateral carcinomas). Conditional logistic regression (26) was used to estimate the risk of breast cancer developing in the same side as the calcification, relative to the risk of it occurring on the opposite side (27). A similar analysis for Wolfe class and percent density could not be performed because values for these variables were highly correlated in the two breasts of each woman.

All study procedures were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Results

The percentages of eligible cases that were successfully interviewed for the BCYW, WISH, HORMONE, and EMF studies, and all studies combined, were 84, 87, 81, 78, and 82%, respectively. A history of having had a prior screening mammogram was given by 969 interviewed cases, 818 (84%) of whom agreed to have their mammograms reviewed. Screening mammograms of both breasts of satisfactory quality were obtained for 547 (67%) of the consenting cases, for an estimated overall response rate of 46% (0.82 × 0.84 × 0.67 × 100).

A census was obtained from 96, 95, 96, 94, and 95% of the households selected by random digit dialing for each of the four studies, and for all studies combined, and interviews were obtained from 81, 89, 73, 75, and 80% of the controls selected from these households, respectively. A history of having had a prior screening mammogram was given by 823 interviewed controls that met the eligibility criteria for this investigation, and 672 (82%) of these controls agreed to have their mammograms reviewed. Screening mammograms of both breasts of satisfactory quality were obtained for 472 (70%) of the con-

senting controls for an estimated overall response of 44% (0.95 × 0.80 × 0.82 × 0.70 × 100). The main reason for not obtaining mammograms was that they had been discarded or could not be found. No facilities refused to make mammograms available.

As shown in Table 2, risk of breast cancer being diagnosed 1 or more years subsequent to a screening mammogram increased with the percentage of the area of the mammogram that was radiographically dense (percent density) and with the severity of the Wolfe classification. For the latter analysis, women with Wolfe classes N1 and P1 were combined because only 2 cases and 11 controls were classified as N1. The total area of the breast (as an indicator of total breast size) was associated with a slight decrease in risk of breast cancer. On the basis of the distribution of breast size in the controls, compared with women in the lowest quartile of breast size, RRs (and 95% CIs) of breast cancer in women in the second, third, and fourth quartiles were 1.1 (0.8–1.5), 0.7 (0.5–0.9), and 0.7 (0.5–1.0), respectively. RRs did increase with the absolute area of the mammographic density (presumably an indicator of the amount of glandular tissue in the breast). Compared with women in the lowest quartile of controls, RRs (and 95% CIs) were 1.8 (1.2–2.6), 3.4 (2.3–5.0), and 3.2 (2.2–4.8) in women in the second, third, and fourth quartiles. Because the risk of breast cancer was more strongly associated with percent density than absolute area of density, the former measurement was used in subsequent analyses presented.

As shown in Table 3, the risk in women with P1 Wolfe class did not vary by the extent of the breast density, but risk in women with a P2 class increased with the percentage of the mammogram that was dense. Also, among women with a similar percentage of the breast that was dense, risk was greater in those with a P2 than a P1 class and greater in those with a DY than a P2 class.

Risk of breast cancer was not associated with class 3, 4, or 5 calcifications but, as shown in Table 4, was significantly increased in women with class 1 and 2 calcifications. The RR estimates were not appreciably altered by controlling for Wolfe class or for percent density (not shown). Similarly, the strength of the associations of risk with percent density and Wolfe class were not greatly diminished by controlling for the presence of calcifications (Table 2). The RR estimates in Tables 2 and 4 were also not appreciably altered by controlling for number of live births, age at first live birth, current or past use of oral contraceptives or estrogens, duration of breast feeding, physical

Table 3   RRs of breast cancer in relation to combinations of Wolfe class and percent density on prior screening mammograms

Wolfe class and percent density	Cases	Controls	RR[a] (95% CI)
P1			
≤26.7%	47	102	1.0 (reference)
26.8–50.1%	15	33	0.9 (0.4–1.8)
P2			
26.8–50.1%	77	84	1.9 (1.2–3.1)
50.2–70.2%	171	115	3.1 (2.0–4.8)
>70.2%	168	98	3.4 (2.2–5.4)
DY			
>70.2%	58	20	5.8 (3.2–11)

[a] Adjusted for age, study, and mammographic calcifications.

Table 4   RRs of breast cancer in relation to presence of each specific type of calcification in either breast on prior mammogram

Calcification classification[a]	Number of subjects		RR[b] (95% CI)	RR[c] (95% CI)
	Cases (n = 547)	Controls (n = 472)		
No calcification	192	229	1.0 (reference)	1.0 (reference)
Nonepithelial, class 5	31	33	0.7 (0.4–1.2)	0.8 (0.5–1.4)
Epithelial, class 4	228	166	1.3 (1.0–1.7)	1.3 (1.0–1.7)
Epithelial, class 3	133	87	1.2 (0.9–1.7)	1.2 (0.8–1.6)
Epithelial, class 2	111	55	1.8 (1.3–2.6)	1.8 (1.2–2.6)
Epithelial, class 1	34	8	3.4 (1.6–8.0)	3.0 (1.4–7.1)

[a] Includes pleomorphic morphology of any distribution (class 1); other morphological epithelial calcification of regional, grouped, clustered, segmental, or linear distribution (class 2); of diffuse or scattered distribution (class 3); or as single entities (class 4); and any nonepithelial type (class 5).
[b] Adjusted for age, study, and other class of calcifications present.
[c] Adjusted for age, study, other type of calcification and Wolfe class (three categories: N1 + P1, P2, and DY).

Table 5   RR[a] of breast cancer in relation to presence of class 1 and 2 calcifications, percent density, and Wolfe classification on prior screening mammograms

	No calcification	Class 2	Class 1
Percent density			
≤26.7	1.0 (reference)	2.3 (0.9–6.0)	∞ (0.16–∞)
	[19, 63]	[11, 11]	[1, 0]
26.8–50.1	1.7 (1.1–2.7)	3.0 (1.3–7.1)	2.4 (0.6–10.0)
	[34, 65]	[17, 12]	[7, 4]
50.2–70.2	3.2 (2.1–5.0)	6.1 (2.9–13.7)	14.1 (3.6–93.3)
	[65, 52]	[32, 12]	[13, 2]
≥70.3	4.3 (2.8–6.6)	5.6 (3.0–10.8)	10.9 (2.7–73.1)
	[74, 49]	[51, 20]	[13, 2]
Wolfe classification			
N1 and P1	1.0 (reference)	1.4 (0.6–3.3)	0.9 (0.04–10.5)
	[25, 73]	[11, 18]	[1, 2]
P2	2.8 (1.9–4.0)	5.4 (3.2–9.2)	7.3 (3.0–20.7)
	[143, 149]	[85, 32]	[28, 6]
DY	5.4 (2.9–10.3)	6.5 (2.3–21.1)	∞ (4.0–∞)
	[24, 7]	[15, 5]	[5, 0]

[a] Adjusted for age, study, and other types of calcifications. Numbers in parentheses, 95% CI; numbers in brackets, number of cases and controls.

activity, body mass index, number of alcoholic drinks/week, or years of schooling (not shown). The associations with class 1 or 2 calcifications did not vary significantly by the women's ages at screening mammogram, first live birth, or menopause; her menopausal status at reference date, body mass index, number of live births, or estimated months of ovulation; or whether she ever used oral contraceptives, received estrogen replacement therapy, exercised five or more times a week, or had a mother or sister with breast cancer (not shown).

As shown in Table 5, women with mammographically dense breasts and class 2 calcifications have an ~6-fold greater risk than women with radiolucent breasts and no calcification, and risk is elevated >10-fold in women with dense breasts and class 1 calcifications.

The two measures of mammographic density, Wolfe classification and percent density, were most strongly associated with risk of breast cancer in the first 3 years after the screening mammogram but were significantly associated with an increase in risk even 6 or more years after the screening mammogram (Table 6). Class 1 and 2 calcifications were most strongly associated with risk 3–6 years after being observed on a screening mammogram.

Sixty-two of the cases had *in situ* disease. When the analyses were confined to the 485 women with invasive disease, the results shown in Tables 2, 4, and 6 were virtually unchanged. There were too few women with *in situ* carcinomas to provide stable RR estimates for these lesions alone. Only 62 (11.3%) of the 547 cases and 43 (9.1%) of the 472 controls had xeroradiographic mammograms, and the results in Tables 2 and

4 were also not appreciably affected by controlling for type of mammogram.

Compared with women with no calcifications, risk was not significantly greater in women with any calcification in both breasts (RR, 2.0; 95% CI, 1.5–2.8) than in one breast (RR, 1.7; 95% CI, 1.2–2.2). Too few bilateral class 1 or class 2 calcifications occurred to provide stable estimates of RR in relation to the occurrence of these calcifications in both breasts, but the point estimates (and 95% CIs) of risks relative to women with no calcifications were actually slightly higher in women with unilateral than bilateral class 1 and 2 calcifications: 2.0 (1.4–3.0) and 1.0 (0.4–2.4) for unilateral and bilateral class 2 calcifications, respectively; and 3.8 (1.7–9.5) and 0.7(0.03–16.9) for unilateral and bilateral class 1 calcifications.

As shown in Table 7, among women with breast cancer, the carcinoma was about three times more likely to occur in the same breast as a class 1 calcification than in the opposite breast, but breast cancer was not significantly more likely to occur in the ipsilateral than in the contralateral breast with a class 2 calcification. Class 1 calcifications were significantly predictive for >6 years of the breast in which a mammary carcinoma develops (Table 8).

Risk of subsequent breast cancer in women with a class 2 calcification was not appreciably different in women with and without a history of a breast biopsy. However, compared with women with no calcifications and no breast biopsy, the RR of breast cancer was 5.0 (95% CI, 1.9–17.4) in women with a class 1 calcification and no history of a benign breast biopsy but just 2.0 (95% CI, 0.6–7.6) in women with a class 1 calcification and a reported breast biopsy.

Discussion

Evidence is presented that mammograms from women <50 years of age can be used to identify individuals at unusually high risk for subsequent breast cancer. The P2 or DY Wolfe parenchymal patterns, the percent of the craniocaudal image that is radiographically dense, calcifications of any morphology that are confined to a localized area within the breast (class 2) and pleomorphic calcifications of any distribution (class 1) were independently associated with risk of subsequent breast cancer.

Table 6   RRs[a] of breast cancer in relation to percent density, Wolfe classification, and types of calcifications on screening mammograms by time since screening mammogram

| | Time since mammogram | | | | | | | | |
| | 1 to <3 years | | | 3 to <6 years | | | ≥6 years | | |
	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Percent density									
≤26.7	8	44	1.0 (reference)	27	49	1.0 (reference)	18	25	1.0 (reference)
26.8–50.1	31	52	3.2 (1.4–8.2)	43	46	1.7 (0.9–3.2)	18	20	1.4 (0.6–3.5)
50.2–70.2	61	49	6.8 (3.0–17)	69	36	3.9 (2.1–7.5)	46	33	2.3 (1.1–5.3)
≥70.3	72	35	12.6 (5.5–32)	89	50	3.4 (1.9–6.3)	65	33	2.9 (1.4–6.3)
Wolfe classification									
N1 and P1	10	58	1.0 (reference)	33	61	1.0 (reference)	21	27	1.0 (reference)
P2	149	116	7.9 (4.0–17)	169	110	3.1 (1.9–5.1)	102	76	1.9 (1.0–3.9)
DY	13	6	12.1 (3.9–43)	26	10	4.9 (2.2–12)	24	8	3.9 (1.4–11)
Calcification classification									
None	49	96	1.0 (reference)	80	84	1.0 (reference)	63	49	1.0 (reference)
Class 5	7	12	0.4 (0.1–1.2)	13	16	0.5 (0.2–1.2)	11	5	1.7 (0.6–5.7)
Class 4	85	55	2.2 (1.4–3.5)	90	62	1.3 (0.8–2.0)	53	49	0.7 (0.4–1.2)
Class 3	47	34	1.2 (0.7–2.1)	56	39	1.0 (0.6–1.7)	30	14	1.9 (0.9–4.0)
Class 2	39	23	1.8 (1.0–3.4)	45	18	2.2 (1.2–4.3)	27	14	1.5 (0.7–3.1)
Class 1	15	5	2.9 (1.0–9.5)	14	1	9.8 (1.9–179)	5	2	2.9 (0.6–22)

[a] Adjusted for age and study. RRs in relation to each class of calcification are also adjusted for other types of calcifications.

Table 7   Risk of breast cancer in ipsilateral breast, relative to risk in contralateral breast, in relation to type of mammographic calcification on screening mammogram[a]

Calcification classification	Ipsilateral breast	Contralateral breast	RR[b] (95% CI)
No calcification	291	293	1.0 (reference)
Nonepithelial, class 5	14	18	0.8 (0.4–1.7)
Epithelial, class 4	132	146	0.9 (0.7–1.2)
Epithelial, class 3	87	76	1.2 (0.8–1.7)
Epithelial, class 2	68	53	1.4 (0.9–2.1)
Epithelial, class 1	26	9	3.1 (1.5–7.4)

[a] Based on prior screening mammograms in 547 women with breast cancer.
[b] RR for each calcification class adjusted for other classes of calcifications in the same breast.

The two measures of mammographic densities were most strongly associated with breast cancer being diagnosed within the subsequent 3 years, and this is likely attributable to masking of pre-existing carcinomas (28). However, similar to others (12), we also observed an increase in risk after 6 years in relation to both P2 and DY parenchymal patterns and radiographic densities of any morphology occupying >50% of the breast area, suggesting that mammographic densities are also true predictors of subsequent breast cancer development. The most likely explanation for this is that proliferative epithelial changes and atypia occur more frequently in breasts with P2 and DY parenchymal patterns than in breasts with N1 and P1 patterns (8, 29), especially in younger women, and women with histologically diagnosed benign breast lesions with proliferative elements are at increased risk of subsequent breast cancer (30–33), particularly if there is evidence of atypia (32, 34, 35). Our observations that risk in women with P2 parenchymal patterns increased with the percentage of the breast that was radiographically dense, similar observations by others in women with P2 (12) and DY (9, 12) patterns, and an observation that risk increased with the amount of glandular tissue in the breast as judged by the appearance of mammographic densities (15) suggest that risk of breast cancer increases with the extent of the epithelial proliferative changes in the mammary tissue.

Although based on small numbers, both class 1 and class 2 calcifications were most strongly associated with breast cancer occurring 3–6 years later, suggesting that they did not represent existing invasive carcinomas that were missed at the time of the screening mammogram. Class 2 calcifications were not strongly predictive of the breast in which the subsequent cancer developed, suggesting that their presence is indicative of generalized ductal changes in both breasts. Some of these calcifications may represent sclerosing adenosis, which has been associated with calcifications and a somewhat increased risk of breast cancer (36). Most, however, likely represent ductal hyperplasia and atypia. Women with histological evidence of these lesions are at increased risk of cancer in either breast (35, 37), and these lesions are sometimes calcified (38). Furthermore, histological evidence of calcification in these lesions is associated with an additional increase in risk of breast cancer (31, 32, 34), which is consistent with the observation in this study that women with mammographically dense breasts (who are at increased risk of breast cancer) have an even higher risk if they also have class 2 calcifications. One previous study has also shown that mammographic calcifications likely representing fibrocystic disease with proliferative elements are associated with increased risk of breast cancer in either breast (16).

Class 1 calcifications (pleomorphic) were predictive of breast cancer developing in the same breast, even >6 years later, suggesting that these calcifications represent local lesions from which breast cancer develops. None of these lesions were accompanied by radiographically observed masses or calcifications that were of the linear branching or casting type, which are features more strongly indicative of existing carcinoma than only the presence of pleomorphic calcifications. Nonetheless, the natural history of these lesions observed in this study is similar to that of histologically diagnosed low-grade ductal carcinoma *in situ*; such lesions, if untreated, frequently are followed by the development of invasive carcinoma at the site of the biopsy (39), and the subsequent invasive carcinoma occurs primarily from 5 to 8 years later (40). It thus seems likely that pleomorphic calcifications represent an early stage in the devel-

Table 8   Risk[a] of breast cancer in ipsilateral breast, relative to risk in contralateral breast, in relation to presence of class 1 calcifications on screening mammograms by time since screening mammogram

| Calcification status | Time since mammogram | | | | | | | | |
| | 1 to <3 years | | | 3 to <6 years | | | ≥6 years | | |
	Ips[b]	Contra	RR (95% CI)	Ips	Contra	RR (95% CI)	Ips	Contra	RR (95% CI)
None	81	86	1.0 (reference)	120	125	1.0 (reference)	90	82	1.0 (reference)
Class 1	10	6	1.3 (0.4–4.4)	11	3	3.7 (1.1–17)	5	0	∞ (1.8–∞)

[a] RRs adjusted for all other classes of calcifications.
[b] Ips, ipsilateral; Contra, contralateral.

opment of ductal carcinoma *in situ* and warrant careful evaluation. The results of one previous study of mammographic calcifications (16) are consistent with these findings; clustered calcifications, considered most likely to represent ductal carcinoma *in situ* or precancerous ductal lesions, were associated with an increase in risk of subsequent mammary carcinoma in the same breast.

Class 1 calcifications were more strongly predictive of subsequent breast cancer in women without than with a history of a prior benign breast biopsy. One possible explanation for this is that histologically benign tissue that was destined to undergo malignant change was removed by the biopsy. Alternatively, the class 1 calcifications in women included in this study with a prior benign breast biopsy were more likely to have been innocuous than other class 1 calcifications because women with a biopsied class 1 calcification with a histological diagnosis of a malignancy would have, by design, not been included in the study (because women with a previous breast cancer were not eligible). Either interpretation further supports the contention that pleomorphic calcifications warrant careful evaluation.

It is unlikely that the low overall response rates influenced our results. The response rates in each of the four original studies were high, and cases and controls that were included in this study did not differ appreciably from the cases and controls in those studies that were not included with respect to any of the variables available from the original in-person interviews (not presented). These include: ages at menarche, first live birth, and menopause; parity; duration of lactation and total months of ovulation; use of oral contraceptives and estrogen replacement therapy; body mass index and physical activity; use of alcohol; level of education; or family history of breast cancer.

Confounding by other risk factors for breast cancer is also an unlikely explanation for our results. Information was collected on nearly all generally accepted and suspected risk factors for breast cancer, and adjustment for none of them appreciably affected the RR estimates. For confounding by an unidentified variable to explain our findings, it would have to be unrelated to the potential confounders that were considered and be more strongly associated with breast cancer than the mammographic features under study.

The mammographic assessments by the reference radiologist for this study were highly reproducible, and the within-observer variability was no greater than that reported by others (41). On the basis of blind second readings of 256 mammograms, the weighted kappa coefficients for Wolfe classification (four categories), percent density (four categories), and most severe class of calcification present were 0.76, 0.78, and 0.77, respectively. The level of agreement between first and second readings was not appreciably different in mammograms from cases and controls. The weighted kappa coefficient for the

calcification classifications was somewhat larger in mammograms with a N1 or P1 classification (0.81) than in those with a P2 or DY classification (0.75), suggesting that more calcifications may have been misclassified in women with radiodense than radiolucent mammograms. This would have had the effect of underestimating the RR of breast cancer in relation to class 1 and 2 calcifications in women with mammographically dense breasts.

Pleomorphic calcifications (class 1) on screening mammograms, even in the absence of discernable masses, should be carefully evaluated. In addition, women <50 years of age with either class 1 or class 2 calcifications or mammographically dense breasts, or both, should receive high priority for regular screening. This would actually be somewhat more efficient than selecting women with a mother or sister with breast cancer for screening. For example, in this study, women in the upper two quartiles of percent density on their mammograms, who also had a class 1 or 2 calcification, constituted 7.4% of the controls and 18.3% of the cases. By comparison, 12.7% of the controls had a sister or mother with breast cancer, as did 21.7% of the cases. This implies that one would have to screen 44% more women with a family history than with these high-risk mammographic features to detect the same number of breast cancers. This estimate, of course, assumes equal efficacy of screening in the groups being compared. Whether screening women with high-risk mammographic features should be by standard mammography or by other means depends on the efficacy of such screening in young women with dense breasts, and this requires further evaluation.

Several models have been developed to estimate a woman's risk of breast cancer (42, 43). They did not originally include mammographic variables. Methods to include mammographic densities into the Gail model have been described, and such densities were shown to be independent risk factors when added to that model (44). These models could also probably be improved by the addition of factors for mammographic calcifications.

The predictive value of specific types of mammographic calcifications for risk of subsequent breast cancer has now been observed in two independent studies and a third showed risk to be increased in relation to any type of calcification (12). Further research thus seems warranted. Relationships between class 1 and 2 calcifications and other risk factors for breast cancer should be investigated further. The specific components of class 2 calcifications most strongly predictive of subsequent breast cancer should be identified, and the classification system might then be modified to make it a more sensitive and specific predictor of subsequent cancer, easier to use, and more reproducible. Efforts should also be made to identify the underlying morphological and molecular changes associated with those calcifications that are predictive of subsequent mammary carcinoma.

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Risk of Subsequent Breast Cancer in Relation to Characteristics of Screening Mammograms from Women Less Than 50 Years of Age

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