Mammographic Features and Breast Cancer Risk: Effects With Time, Age, and Menopause Status

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Background: **Mammographic images from women with a high proportion of epithelial and stromal breast tissues are described as showing high-density parenchymal patterns. Most past studies that noted an increase in breast cancer risk associated with mammographic parenchymal patterns showing high density either 1) lacked information on other breast cancer risk factors, 2) were too small, or 3) included insufficient follow-up time to adequately resolve persisting doubts whether mammographic features are "independent" measures of breast cancer risk and not a detection artifact.** ***Purpose:*** **The purpose of this study was twofold: 1) to evaluate the associations between mammographic features and other breast cancer risk factors and 2) to assess effects of mammographic features on breast cancer risk by time, age, and menopause status.** ***Methods:*** **To address these questions, we analyzed detailed information from a large, nested case–control study with 16 years of follow-up. This study used information from both screening and follow-up phases of the Breast Cancer Detection Demonstration Project, a nationwide program that offered annual breast cancer screening for more than 280 000 women from 1973 to 1980. Mammographic features were assessed from the base-line screening mammographic examination for 1880 incident case subjects and 2152 control subjects. Control subjects were randomly selected from women of the same age and race as each case subject. Control subjects attended the same screening center as the case subject and were free of breast cancer at the case subject's date of diagnosis. Odds ratios (ORs) with 95% confidence intervals (CIs) provided estimates of the relative risk of breast cancer.** ***Results:*** **Mammographic features were associated with known breast cancer risk factors. However, the high-density parenchymal pattern effects were independent of family history, age at first birth, alcohol consumption, and benign breast disease. The increased risk for women with Wolfe's two high-density parenchymal patterns, P2 (OR = 3.2; 95% CI = 2.5-4.0) and Dy (OR = 2.9; 95% CI = 2.2-3.9), was explained primarily by measured percent of the breast with dense mammographic appearance. Compared with women with no visible breast density, women who had a breast density of 75% or greater had an almost fivefold increased risk of breast cancer (95% CI = 3.6-7.1). These effects persisted for 10 or more years and were noted for both premenopausal and postmenopausal women of all ages.** ***Conclusions:*** **Of the breast cancer risk factors assessed in the participants, high-density mammographic parenchymal patterns, as measured by the proportion of breast area composed of epithelial and stromal tissue, had the greatest impact on breast cancer risk. Of the breast cancers in this study, 28% were attributable to having 50% or greater breast density. [J Natl Cancer Inst 1995;87:1622-9]**

The mammographic appearance of breast tissue depends on the relative degree of fat, connective, and epithelial tissues (*1*). Both the patterns of breast parenchymal tissue visible through mammographic examination as originally defined by Wolfe (*2*) and the proportion of the breast composed of dense tissue (percent breast density) have been associated with breast cancer incidence (*3-12*).

Despite a consistent twofold to sixfold increased risk of breast cancer associated with various categorizations of patterns of mammographic features (*4-6*), a persistent belief exists that recognized breast cancer risk factors, such as age at first birth and parity, might explain this increase (*13,14*). Another concern relates to possible "masking" of cancers by dense tissue. At an initial screen, prevalent cancers would be more readily detected in women with low-percent breast density. Therefore, the higher number of cases subsequently detected in follow-up screening among women with high-percent breast density may have included masked prevalent cases (*15*). Although these issues have been considered in some earlier studies or in theoretical explanations (*2,4-6,12,16*), most studies have not been large enough or included a long enough follow-up to resolve these concerns.

It is fairly well accepted that parenchymal patterns and percent density change with age and menopausal status (*17-20*). In particular, the high-risk Dy pattern often regresses to lower risk patterns (*19*). Whether the risk of breast cancer associated with high-density mammographic features differs by age and meno-

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See "Notes" section following "References."

pausal status, however, is not clear. Some studies (*9-11*) reported that the effects of mammographic features on breast cancer risk did not differ by age. In contrast, Brisson et al. (*8*), Boyd et al. (*7*), Horwitz et al. (*21*), and Brisson et al. (*22*) found that the risk associated with parenchymal patterns and percent density was restricted to effects in younger women (<50 years old), while Boyd et al. (*12*) reported higher risk estimates for older women. On this issue concerning differences in the effects of mammographic features on breast cancer by age and menopausal status, Sonnenschein and Toniolo (*23*) hypothesized that mammographic features determined before menopause would better predict postmenopausal breast cancer risk, and they indicated the need for a study with up to 10-15 years of follow-up.

To address these persistent questions, we examined the effects of both parenchymal patterns and percent breast density on breast cancer risk over the 16-year follow-up of participants in the Breast Cancer Detection Demonstration Project (BCDDP). The purpose of this study was twofold: 1) to evaluate the associations between mammographic features and other breast cancer risk factors and 2) to assess effects of mammographic features on breast cancer risk by time, age, and menopause status.

Subjects and Methods

This study was nested within both the screening and follow-up phases of the BCDDP, a nationwide breast cancer screening program cosponsored by the American Cancer Society and the U. S. National Cancer Institute (NCI). The parenchymal pattern and measured percent of the breast with mammographic density were assessed from the mammographic images obtained at entry into the screening program for 1880 women who subsequently developed breast cancer (incident case subjects) and 2152 matched control subjects.

Brief Background of the BCDDP

From 1973 to 1975, more than 280 000 women volunteered to have annual breast cancer screening for 5 years, consisting of both physical and mammographic examinations that were conducted at one of 29 U.S. centers. Among screening phase participants, the NCI conducted a case–control study that included in-home interviews to assess risk factor information (*24,25*). In 1980, at the end of screening, the 59 907 women selected for long-term follow-up included three groups: 1) women who had a benign breast biopsy specimen during the BCDDP screening (n = 25 114), 2) women who had a recommendation for surgical consultation but for whom a breast biopsy was not performed (n = 9628), and 3) women who had no breast surgery and did not receive a recommendation for surgical consultation (n = 25 165). In the first phase of follow-up conducted from 1980 to 1986, 96% of the eligible women provided information concerning any surgical procedures on the breast and changes in breast cancer risk factors through annual telephone interviews. Between 1987 and 1989, 85% of the women who had at least one telephone interview completed a mailed questionnaire that assessed breast cancer outcomes and changes in breast cancer risk factors since the last interview. Extensive tracing efforts included a National Death Index search of all nonrespondents. In addition, pathology reports were sought for all breast procedures.

Study Description

Of the 29 original screening centers, 22 sent mammographic images to the central BCDDP resource facility. For this study, eligible women included all women who attended one of these 22 participating centers, had no breast cancer diagnosis before or during the 1st year of screening, and completed either the screening phase case–control interview or the base-line follow-up interview. Owing to the high concordance (97.2%) between self-reporting of breast cancer and pathologic confirmation, the 5% of self-reported breast cancers with no available pathology were included. From screening, there were 1280 case subjects individually matched with a control subject on study center, race, age (year of birth), date of entry, and number of screening visits. For each of the 1281 eligible case subjects diagnosed during the BCDDP follow-up, a control subject was randomly selected from women who were disease free at the time of the case subject's diagnosis and who were from the same center and follow-up group and of the same race and age (year of birth) as the case subject (*26*). No eligible control subjects existed for three follow-up case subjects. Thus, when we combined screening and follow-up, 2561 case subjects and 2558 control subjects were eligible for this nested case–control study of mammographic features. The initial screening mammographic examination was available for 1880 (73%) eligible case subjects and 2152 (84%) eligible control subjects. The presence of mammographic calcifications was noted on the original BCDDP mammographic evaluation form completed at each screening center.

Because of the number of mammographic images that needed to be reviewed for this study, only one side of the breast could be reviewed for each woman. The decision on whether to use the contralateral or ipsilateral side was based on the weighing of two potential sources of bias. In choosing to evaluate the contralateral side, it is necessary to consider an unknown degree of misclassification. Others have noted the mammographic appearance of a woman's two breasts to be associated; however, the mammographic features of each breast are not necessarily identical (*4*). To the degree that the features of each breast differ, using the contralateral side of the breast would add an unknown element of misclassification to the exposures of interest in this study. In contrast, choosing to use the ipsilateral side, as this study did, made it necessary to consider the possibility of a reviewer bias. While all case subjects were diagnosed at least 1 year after the mammographic examination used in this study, it is possible that the reviewers may have seen indications of the cancer in a small percentage of the case subjects and thus may have been biased in their assessment. This bias would be most likely to occur in cases diagnosed close in time to the screening examination. Therefore, analyses stratified by time would indicate the magnitude of the effect of this potential reviewer bias.

Parenchymal pattern and measured percentage of the breast area with dense mammographic appearance were assessed from the initial screening mammographic examination, taken at BCDDP entry. Without knowledge of the subsequent status of case or control subjects, one of three trained reviewers evaluated the cranio-caudal and medio-lateral mammographic images from the side where breast cancer subsequently developed in the case subjects and the ipsilateral side for their matched control subjects. The mammographic appearance was classified as either N1, P1, P2, or Dy, according to Wolfe's (*2*) definition of parenchymal patterns, which is independent of other radiologic indicators such as calcifications. Wolfe (*2*) described the N1 breast as being composed predominantly of fat with little, if any, dense areas, the P1 breast as mainly being composed of fatty tissue with dense areas of ductal prominence making up less than 25% of the total breast, the P2 breast as consisting of dense areas of ductal prominence encompassing 25% or more of the total breast area, and the Dy breast as having 25% or more of the breast area containing homogeneous sheetlike areas of density with no signs of ductal prominence. Each reviewer recorded the mammographic method, quality of the image, and the parenchymal pattern and outlined the dense area of the breast on the cranio-caudal mammogram. A random sample of 100 mammographic examinations was used to train and evaluate staff in the use of the computerized planimeter (LASICO 1280-12; Los Angeles, CA) to measure the total breast area and the marked area on each mammogram. Staff were considered trained when their intrameasurer agreement was more than 95% and their intermeasurer agreement was more than 90%.

To verify the ability to determine the mammographic features used in this study, we evaluated the mammographic images from a 10% random sample of case–control pairs twice to assess interobserver (evaluated by two readers once) and intraobserver (evaluated by one reader twice) replicability. For parenchymal pattern assessment, the interobserver exact agreement ranged from 67.1% to 76.3%, and the intraobserver exact agreement ranged from 72.6% to 81.5%. For the five-category measure of percent density, the interobserver exact agreement ranged from 64.6% to 75.0%, and the intraobserver exact agreement ranged from 68.6% to 80.8%. The correlation between repeated evaluations for the continuous measure of percent density ranged from .86 to .93 for interobserver comparisons and from .85 to .94 for intraobserver comparisons. The interobserver and intraobserver percent agreements did not vary by subsequent case status or by age of the woman at the time of the mammographic examination.

Statistical Methods

To assess the relative risk of breast cancer associated with mammographic features, conditional logistic regression was used to provide maximum likelihood estimates of the odds ratios (ORs) with 95% confidence intervals (CIs) as point and interval measures of the incidence density rate ratios (PECAN) (27). Analyses conducted among the subjects with no missing data provided similar results to analyses that included subjects where a separate missing value code was created for variables in the dataset, including the mammographic variables. Thus, to reduce loss of covariate information and matched pairs, women with missing data were included in the analyses. To understand the association between mammographic density and other nonmammographic risk factors, we adjusted the effects of other breast cancer risk factors for percent density. We then evaluated the age-adjusted distribution of control subjects across the categories of percent density. To assess the degree to which the effects from mammographic features were explained by known breast cancer risk factors, conditional analyses included the following: 1) an initial model controlling only for the matching factors; 2) a model controlling only for weight—the strongest potential confounder known a priori; and 3) a model controlling for weight, age at birth of first child, first-degree relatives with breast cancer, years of education, alcohol use, number of prior biopsies reported as benign, and reproductive years.

Results

Table 1 presents the effects of nonmammographic risk factors adjusted for the categorical variable percent of the breast area with dense mammographic appearance (percent breast density). Breast cancer risk increased for women with a first-degree family history of breast cancer and was highest for those with both an affected mother and sister. In addition, breast cancer risk rose with the number of reproductive years (i.e., the range of years from the age at menarche to the age at menopause). Compared with women with a first birth before the age of 20 years, nulliparous women and women with a first birth at age 30 years or older had an increased risk of breast cancer. Also at increased breast cancer risk were women who completed 17 or more years of education, had two or more benign breast biopsy specimens prior to their mammographic examination, drank alcoholic beverages, were heavy, or were tall.

The proportion of control subjects with extensive mammographic density (≥50% breast density) was inversely related to age. Thus, to present how other nonmammographic breast cancer risk factors were associated with mammographic density, the far right column of Table 1 shows the proportion of the control subjects in this study with 50% or more mammographic density across each category of other risk factors. After age adjustment, being in higher-risk categories of the recognized breast cancer risk factors tended to be associated with increased mammographic density for all risk factors except height and weight. Half of the control subjects who weighed less than 122 lbs or were in the lowest quartile of Quetelet's index had a breast density of 50% or more, while only 16% of the control subjects who weighed 150 lbs or more and 11% of those women in the highest quartile of Quetelet's index had a breast density of 50% or more.

Of the four parenchymal patterns, most women had either the P2 or P1 pattern (42.5% and 29.8% of the control subjects, respectively), while only 11.7% of control subjects had a Dy pattern. Compared with women with the N1 pattern, women with the P1, P2, and Dy patterns had an increased risk of breast cancer; women who had the P2 and Dy patterns had the highest risk (Table 2). Of the other breast cancer risk factors, adjustment for weight minimally increased the ORs associated with each parenchymal pattern because heavier women, who were at increased risk, were less likely to have the P2 or Dy patterns. Since adjustment for the other breast cancer risk factors slightly decreased the ORs, multivariate adjustment for weight with age at first birth, first-degree family history of breast cancer, years of education, alcohol use, number of prior breast biopsies reported as benign, and number of reproductive years produced ORs similar in magnitude to those obtained from the analysis controlling only for the matching factors.

Risk of breast cancer rose significantly with increasing percent of the breast area with mammographic density (test for trend: $P<.0001$) as presented in Table 3. Risk rose almost fivefold among the small number of women (10.5% of case subjects and 6.4% of control subjects) with 75% or more breast density compared with those with no density. As with parenchymal patterns, adjustment for weight slightly increased the effects associated with higher percent breast density, while multivariate adjustment did not change the ORs materially from those of the univariate-matched analysis. The relative risks calculated from the regression coefficient (beta = .0142) for the continuous variable were fairly consistent with the ORs from the categorical analysis with estimates of 1.6, 2.0, 2.7, and 3.6, respectively, for 30%, 50%, 70%, and 90% breast density compared with none.

To understand the effects of increasing percent density within categories of parenchymal patterns, we selected a common reference category. Within each parenchymal pattern category, risk rose with increasing percent density. Compared with the ORs for women with the N1 pattern and no mammographic density, the ORs for women with the P2 pattern increased from 2.55 (95% CI = 2.0-3.3) to 2.83 (95% CI = 2.2-3.6) to 4.54 (95% CI = 3.2-6.4) for breast densities of 25%-49%, 50%-74%, and 75% or more, respectively. For women with the Dy pattern, the comparable increases were from 2.52 (95% CI = 1.7-3.8) to 2.55 (95% CI = 1.8-3.6) to 4.10 (95% CI = 2.4-6.9) for breast densities of 25%-49%, 50%-74%, and 75% or more, respectively. Thus, the increased risk for women with Wolfe's two high-density parenchymal patterns, P2 (OR = 3.2; 95% CI = 2.5-4.0) and Dy (OR = 2.9; 95% CI = 2.2-3.9), was explained primarily by measured percent of the breast with dense mammographic appearance.

In addition to percent breast density, breast cancer risk was also evaluated in relation to total breast size and absolute area of the breast with mammographic density. Increasing total breast size was not associated with higher breast cancer risk in this study. The ORs for each quintile of increasing breast size adjusted for mammographic features were 1.00, 0.96 (95% CI = 0.8-1.2), 1.07 (95% CI = 0.9-1.3), 1.01 (95% CI = 0.8-1.3), and 1.16 (95% CI = 0.9-1.4). As the absolute area of the breast with mammographic density increased, the breast cancer risk rose, although not quite to the same extent as with the percent breast density measure. Because no a priori categories existed for absolute percent density, cut points were selected that divided the control subjects into six approximately equal groups. Compared with women with no breast density, women with an absolute area of breast density of 1-13.9 cm^2, 14-22.9 cm^2, 23-33.9 cm^2, 34-52.9 cm^2, and 53 cm^2 or more had ORs of 1.48 (95% CI =

Table 1. Nonmammographic breast cancer risk factors

Risk factor	Cases*	Controls*	Odds ratio†	95% confidence interval	Proportion of women with high breast density‡
First-degree family history					
None	1344	1757	1.00	—	.31
Any	473	327	1.79	1.6-2.1	.40
Mother only	230	178	1.75	1.5-2.1	.38
Sister only	190	123	1.75	1.4-2.1	.52
Mother and sister	48	18	2.66	1.7-4.3	.39
Reproductive years§					
<25	52	92	1.00	—	.26
25-29	147	221	1.30	0.9-1.8	.27
30-34	414	463	1.65	1.2-2.3	.32
35-39	881	984	1.80	1.3-2.5	.36
≥40	334	339	1.99	1.4-2.8	.29
Age at first birth, y					
<20	166	242	1.00	—	.23
20-24	648	859	1.17	1.0-1.4	.29
25-29	474	490	1.48	1.2-1.8	.34
≥30	239	210	1.58	1.2-2.0	.40
Nulliparous	191	185	1.63	1.3-2.1	.42
Years of education‖					
<12	192	264	1.00	—	.27
12	669	872	0.99	0.8-1.2	.31
12-14	403	443	1.18	1.0-1.4	.32
15-16	347	351	1.19	1.0-1.5	.35
≥17	233	186	1.26	1.0-1.6	.42
No. of benign breast biopsy specimens before mammographic examination					
None	1631	1904	1.00	—	.31
1	134	153	1.23	1.0-1.5	.44
≥2	84	63	1.68	1.3-2.1	.48
Drinks alcohol					
No	557	750	1.00	—	.29
Yes	1086	1201	1.29	1.2-1.5	.34
Weight, lbs					
<122	351	422	1.00	—	.50
122-134	454	506	1.21	1.0-1.4	.40
135-149	457	523	1.27	1.1-1.5	.32
150-300	561	645	1.42	1.2-1.6	.16
Quetelet's index (body mass index)					
<21.16	389	476	1.00	—	.52
21.16-23.14	522	540	1.17	1.0-1.4	.38
23.15-25.76	435	519	1.08	0.9-1.3	.32
≥25.77	476	558	1.32	1.1-1.5	.11
Height, in					
<62	209	272	1.00	—	.30
62-63.9	465	551	1.08	0.9-1.3	.35
64-65.9	548	615	1.27	1.1-1.5	.33
≥66	600	655	1.31	1.1-1.6	.32

*Case and control subject distribution among those subjects with density measure. Differences in totals are due to missing category.

†Adjusted for percent of breast area with dense mammographic appearance.

‡Age-adjusted proportion of controls with 50% or more of the breast area with dense mammographic appearance.

§Defined as the number of years between menarche and menopause. Women who had a bilateral oophorectomy prior to menopause were assumed to be menopausal as of the date of surgery. Women with a surgical menopause with one or more ovaries retained were assumed to be postmenopausal at age 50, the age at which 58% of the control subjects in this study who had a natural menopause were menopausal.

‖Additionally adjusted for age at first birth.

1.1-1.9), 1.99 (95% CI = 1.5-2.6), 2.08 (95% CI = 1.6-2.7), 3.24 (95% CI = 2.5-4.2), and 3.35 (95% CI = 2.6-4.3), respectively.

Women with mammographic calcifications also had a slightly increased risk of breast cancer, with an OR of 1.69 (95% CI = 1.5-1.9) after adjustment for percent breast density. The presence of calcifications was associated with both the presence of either the P2 or the Dy pattern or having increased percent density among the control subjects in this study. Adjustment for the presence of calcifications, however, did not change the effects associated with parenchymal patterns or percent breast density.

Further analyses focused on effects from percent of the breast area with density stratified by time (time between the date of the initial mammographic examination and cancer diagnosis for each case subject and her matched control subject), age at the time of the mammographic examination, and menopause status

Table 2. Parenchymal pattern effects

Parenchymal pattern	No. of case subjects	No. of control subjects	Odds ratio* (95% confidence interval)	Odds ratio*,† (95% confidence interval)	Odds ratio*,‡ (95% confidence interval)
N1	158	344	1.00 (—)	1.00 (—)	1.00 (—)
P1	471	642	1.71 (1.4-2.2)	1.76 (1.4-2.2)	1.68 (1.3-2.1)
P2	1032	915	2.93 (2.3-3.7)	3.15 (2.5-4.0)	2.83 (2.2-3.6)
Dy	219	251	2.65 (2.0-3.5)	2.89 (2.2-3.9)	2.73 (2.0-3.7)

*Matched analysis. Control subjects were matched to screening cases on study center, race, year of birth, date of entry, and number of screening visits, and follow-up case subjects on study center, race, year of birth, and follow-up group.

†Additionally adjusted for weight.

‡Additionally adjusted for weight, age at first birth, first-degree relatives with history of breast cancer, years of education, alcohol use, number of prior benign breast biopsy specimens, and reproductive years.

during the study (Table 4). The breast cancer risk for women with a breast density of 75% or more was highest for those diagnosed within 2 years after the mammographic examination, with an OR of 7.58 (95% CI = 3.2-17.9), but the risk was still elevated more than fourfold for women whose mammographic examination was 10 or more years prior to diagnosis for cases. Regardless of the age of the women at the time of the mammographic examination, breast cancer risk rose with increasing percent density. The relative magnitude of this increase, however, was somewhat greater for older women. Mammographic density measured from either premenopausal or postmenopausal mammograms was associated with an increased risk of breast cancer. These effects were seen in women who were premenopausal at the time of the mammographic examination and at diagnosis, in women who were postmenopausal at the time of the mammographic examination and at diagnosis, and in women who were premenopausal at the time of the mammographic examination and postmenopausal at diagnosis.

Discussion

Perhaps the least appreciated and least used risk factor for breast cancer is the extent of mammographic density within the breast. This lack of recognition seems particularly unfortunate because attention to this risk factor could have profound implications for both breast cancer screening and etiology. In our study, we compared the mammographic features for almost 2000 case subjects with more than 2000 control subjects compared with women who had no mammographic density. For women with any mammographic density, the breast cancer risk rose twofold. For those women with breast density of 75% or more, the breast cancer risk rose more than fourfold. The highest category of percent breast density was associated with the greatest increase in the ORs in this study population, exceeding the OR of 2.7 for women with a family history of breast cancer in both mother and sister and the ORs of 1.6 for nulliparous women and those women with a late age at first birth compared with those having a first live birth under age 20 years. In contrast to these other recognized risk factors (*28*) in which substantially elevated risks apply to a relatively small segment of the population, a large segment of the population has sufficient mammographic density to place it in categories with markedly elevated risk. Only 0.8% of the control subjects and 2.6% of the case subjects were women with a known family history of breast cancer in both a mother and a sister, although 15.7% of the control subjects and 26.0% of the case subjects had any first-degree family history. Furthermore, only 10.6% of the control subjects and 13.9% of the case subjects had their first live birth at age 30 years or older. On the other hand, 85.4% of the control subjects and 92.4% of the case subjects were women who had any mammographic density (OR = 2.0, compared with none), 32.5% of the control subjects and 41.7% of the case subjects had breast density of 50% or more (OR = 3.1), and 6.4% of the control subjects and 10.5% of the case subjects had 75% or more of the breast area involved with density (OR = 4.4). The implications of the high prevalence of mammographic density to the attributable risk or etiologic fraction are obvious. Assuming that density is involved in a causal manner with breast cancer risk,

Table 3. Percent density effects

Percent density*	No. of case subjects	No. of control subjects	Odds ratio† (95% confidence interval)	Odds ratio†,‡ (95% confidence interval)	Odds ratio†,§ (95% confidence interval)
0	141	309	1.00 (—)	1.00 (—)	1.00 (—)
1-24	445	632	1.62 (1.3-2.1)	1.68 (1.3-2.1)	1.57 (1.2-2.0)
25-49	490	489	2.53 (2.0-3.2)	2.69 (2.1-3.5)	2.47 (1.9-3.2)
50-74	576	554	2.85 (2.2-3.6)	3.13 (2.4-4.0)	2.77 (2.1-3.6)
≥75	194	136	4.54 (3.3-6.3)	5.08 (3.6-7.1)	4.35 (3.1-6.1)

*Percent density is the measured percent of the total breast area with dense mammographic appearance from the cranio-caudal image.

†Matched analysis. Test for trend $P < .0001$.

‡Additionally adjusted for weight.

§Additionally adjusted for weight, age at first birth, first-degree relatives with history of breast cancer, years of education, alcohol use, number of prior breast biopsies reported as benign, and reproductive years.

Table 4. Percentage of breast density and breast cancer risk, stratified by time, age, and menopausal status

	Percent density*				
	0	1-24	25-49	50-74	≥75
Time, y†					
1-1.9	1.00 (—) 28/84	1.78 (1.0-3.2) 86/171	2.88 (1.6-5.2) 81/108	3.25 (1.8-5.8) 93/107	7.58 (3.2-17.9) 29/15
2-4.9	1.00 (—) 60/100	1.25 (0.7-2.3) 160/212	2.03 (1.1-3.7) 169/143	2.46 (1.3-4.5) 110/128	3.24 (1.5-6.8) 46/31
5-9.9	1.00 (—) 34/82	2.20 (1.2-4.1) 116/142	3.10 (1.7-5.7) 126/117	2.48 (1.4-4.5) 159/188	3.56 (1.8-7.0) 70/61
≥10	1.00 (—) 17/42	1.88 (1.0-3.6) 74/105	2.44 (1.3-4.6) 105/115	3.10 (1.7-5.8) 145/127	4.47 (2.1-9.6) 45/29
Age at mammographic examination, y‡					
<50	1.00 (—) 54/107	1.27 (0.8-1.9) 115/192	2.04 (1.4-3.1) 173/199	2.52 (1.7-3.7) 322/324	3.78 (2.4-5.9) 138/104
50-59	1.00 (—) 47/103	1.54 (1.0-2.4) 185/280	2.61 (1.7-4.1) 194/186	2.90 (1.9-4.5) 177/160	4.16 (2.2-7.8) 41/29
≥60	1.00 (—) 38/98	2.53 (1.6-4.1) 136/158	3.45 (2.1-5.7) 114/98	3.24 (1.9-5.6) 68/66	13.78 (3.6-53.4) 11/3
Menopausal status§					
Premenopausal	1.00 (—) 66/163	1.47 (0.95-2.3) 244/346	1.69 (1.1-2.6) 253/237	2.31 (1.6-3.4) 174/185	3.79 (2.3-6.2) 31/18
Premenopausal/ postmenopausal‖	1.00 (—) 35/62	1.31 (0.89-1.9) 82/103	2.39 (1.6-3.5) 89/105	2.78 (1.9-4.0) 176/164	3.49 (2.2-5.6) 82/57
Postmenopausal	1.00 (—) 37/70	1.79 (1.3-2.5) 108/164	2.82 (2.0-4.0) 141/138	2.68 (1.9-3.9) 215/196	5.82 (3.0-11.3) 78/61

*Values in columns = odds ratio (95% confidence interval) and number of cases/controls.

†Time is the number of years between the date of the initial screening mammographic examination and the date of diagnosis. Control subjects were given an artificial date of diagnosis based on the date of their matched case subject. All comparisons were restricted to those within the same time category.

‡Comparisons were restricted to women within the same age category at the time of the mammographic examination.

§Comparisons were restricted to women within the same category of menopause status during the study period. Women who had a bilateral oophorectomy prior to menopause were assumed to be menopausal as of date of surgery. Women with a surgical menopause with one or more ovaries retained were assumed to be postmenopausal at age 50, the age at which 58% of the control subjects in this study who had a natural menopause were menopausal.

‖These women were premenopausal at the time of the mammographic examination and postmenopausal at the time of diagnosis.

then in our study the presence of any density was responsible for 46.2% of all breast cancers, breast density of 50% or more accounted for 28.2%, and breast density of 75% or more explained 8.2% of all breast cancers.

While the human breast is a heterogeneous composition of adipose tissue, epithelial cells (parenchyma), and fibrous connective tissue (stroma), most breast cancers arise from the ductal epithelial cells (*29*). Because fat appears translucent on a mammogram, the epithelial cells and fibrous tissue create the area of dense mammographic appearance. Several proposed theories may explain the association of percent breast density with increased breast cancer risk. Trichopoulos and Lipman (*30*) described how increased mammary gland mass and therefore the total number of ductal stem cells should be related to increased breast cancer risk. Thus, if the percent breast density measures epithelial structures, it may reflect the total number of ductal stem cells. In keeping with this theory, mammographic features have been associated with histological and epithelial changes in some (*6*) but not all (*31*) studies. The mammographic features may also reflect the breast tissue response to exogenous or endogenous estrogens, progestogens, or growth hormones (*6,32,33*). Boyd et al. (*34*) proposed that increased density reflected an increased proportion of connective stromal tissue. In addition to the influence stromal cells may have on the growth of epithelial cells, Basset et al. (*35*) reported identifying a stroma-derived gene that may be linked to breast cancer progression.

As a woman ages, breast tissue undergoes a process of involution, which is characterized by a reduction in glandular tissue and an increase in the proportional amount of fat and connective tissue (*36,37*). Both glandular tissue and connective tissue have a dense mammographic appearance. Therefore, some younger women whose breasts appear mammographically dense may not retain this mammographic appearance as they age. Older women, with a high percent of the breast with mammographic density, may have either a delayed involution process and still have a large proportion of glandular tissue or an involution process in which the glandular tissue is replaced primarily with connective tissue and only a small proportion of fat.

Mammographic density does not identify all women who will develop subsequent breast cancers. Nevertheless, because the proportion of the breast occupied by mammographic density is one risk factor that may identify a group at high risk for breast cancer, the implications of the findings of this study for intervention, both for screening strategies and prevention trials, should be considered (*33,38*). While using mammographic features to identify high-risk women has been suggested for screening criteria before, this idea has not been widely accepted because many cancers also are found in women with low-density breasts. Thus, to exclude women, particularly those aged 50 years and older, from screening if they had low-density breasts would deny them the benefits of mammographic screening. Instead of influencing whether a woman receives screening, knowledge of a woman's breast density may be useful in determining frequency of screening. Women with high-density breasts who are at increased risk of developing breast cancer may benefit from annual as opposed to biennial screening. Apart from screening issues, mammographic features should potentially be considered part of eligibility criteria for breast cancer prevention trials (*38*). Currently, the two major primary intervention efforts under way in the United States, i.e., the dietary intervention in the Women's Health Initiative and the randomized trial of tamoxifen in the Breast Cancer Prevention Trial, do not use mammographic density as part of their eligibility criteria.

While the basic findings reported here are consistent with those of previous investigations, the reasons for mammographic density not being accepted in the past are possibly related to some of the concerns raised about previous studies. As noted, these concerns included the following: 1) Mammographic density may simply reflect other known risk factors (*13,14*); 2) the findings may not apply to older or postmenopausal women (*7,8,21,22*); and 3) the density may only have masked existing malignancies, precluding a long-lasting predictive capacity of mammographic features (*15*). The sample size and design of the current investigation allowed us to address these issues. First, while mammographic density is associated inversely with age and the anthropometric measures of risk and correlated positively with most of the other identified risk factors, controlling for these exposures did not substantially alter the mammographic feature effects. Second, stratification by age and menopausal status indicated that the association with mammographic features was present in young and old women as well as in premenopausal and postmenopausal women. Finally, the long-term follow-up of BCDDP participants indicated that the increase in breast cancer risk with high mammographic density persisted more than a decade after the mammographic examination was performed. The higher magnitude of the relative risk for women with breast densities of 75% or more diagnosed between 1 and 1.9 years after the mammographic examination may partly reflect the effects of a masking bias for the first 2 years following the mammographic examination. A masking bias, however, seems unlikely to explain the higher risk 10 or more years after the mammographic examination for women with increased percent density.

While the mammographic images reviewed in this study were obtained in the mid-1970s and were not of as high a quality as those in current use, this study was still able to measure a fivefold gradient in breast cancer risk. Analyses in this study restricted to those mammographic examinations rated of good or excellent quality were associated with a greater gradient in risk associated with increased percent density. Thus, because of the advancements in mammographic imaging since the 1970s, mammographic techniques in current use will allow for improved assessment of percent mammographic density and thereby better identify women at increased risk.

In the past, there were many concerns regarding the subjective nature of classifying mammographic patterns according to the Wolfe (*2*) criteria, particularly with regard to the ability of others to replicate these classifications reliably. Therefore, it is important that we, as well as others, found the highest gradients in risk with simple ordinal estimates or quantitative measurements of the percent of the breast area with mammographic density, a measure which does not require a qualitative assessment regarding the appearance of the density (*8-10,12*). When cross-tabulated with the classification of parenchymal patterns, most of the predictive capacity of the patterns appeared to be derived from the estimated proportion of the breast area with mammographic density, the nonqualitative component of the pattern classification. Both intraobserver and interobserver correlations for repeated evaluations of the continuous measure of percent density were about 0.9, indicating the high reliability of this measure. Indeed, such measurement capacity may be relatively easy to automate and incorporate as part of the mammographic image production process itself. In a study of 354 case subjects and 354 control subjects identified over 5 years of the Canadian National Breast Cancer Screening Study (CNBSS), Boyd et al. (*12*) reported on a comparison between radiologists visually classifying each mammographic image into six categories of percent density (0%, <10%, 10%-24%, 25%-49%, 50%-74%, and ≥75%) and a computerized method using a digitized image of the mammogram to measure the percent density. In the CNBSS study, classification by the radiologists better identified those at risk with a sixfold gradient in risk compared with a fourfold gradient from the computerized measurement (*12*). Whether some of the clarity of the image was lost when the mammographic images were digitized into a computer image or whether the skill and training of the radiologists add an unmeasured parameter is not known. Further development of these and other techniques is needed to provide an accessible and reliable measure of mammographic density.

This study, with information from 16 years of the BCDDP, has demonstrated that an easily measured feature from a screening mammographic examination—the percent breast density—had a greater effect on breast cancer risk than most other breast cancer risk factors and could not be explained by these other factors. In addition, percent breast density was not an artifact of a masking bias and applied to women of all ages. Thus, in efforts either to prevent breast cancers or to detect breast cancers earlier, the impact of the percent breast density on breast cancer risk can no longer be ignored.

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Notes

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This study is dedicated to the memory of Dr. John Wolfe who died in September 1993. Dr. Wolfe pioneered the use of mammography for screening, diagnosis, and research. Throughout his life's work, he combined his skills as an observant clinician and dedicated researcher working toward a better understanding of breast cancer etiology.

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