Analysis of Parenchymal Density on Mammograms in 1353 Women 25–79 Years Old

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OBJECTIVE. This study was undertaken to determine the frequency and distribution of dense mammograms. Factors that may affect parenchymal density of breasts among the diverse age groups of women who undergo mammography were also studied.

MATERIALS AND METHODS. Mammograms of 1353 women between 25 and 79 years old who were grouped in 5-year age cohorts were reviewed. Breast density and the presence of benign calcifications were analyzed.

RESULTS. Parenchymal density on mammograms decreased progressively in the patient cohorts 25–29 years old through 75–79 years old (Spearman correlation, $p < .01$). In the cohort of 25- through 29-year-old patients, 38% had predominantly (>50%) fatty breasts. In the cohort of 75- through 79-year-old patients, 76% had predominantly fatty breasts. Increased parenchymal density mammograms were more common in women who had smaller breasts, had had fewer than two pregnancies, and underwent hormone replacement ($p < .01$). Forty-nine percent of women 50–79 years old undergoing hormone replacement had predominantly dense breasts, a percentage similar to that (48%) of the patient cohort of women 40–44 years old. Prevalence of benign calcifications also increased with age, from 8% at ages 25–29 to 86% at ages 75–79 ($p < .01$).

CONCLUSION. In our study, a significant percentage (38%) of women who were 25–39 years old had predominantly fatty breast tissue that should not impede selective mammographic screening or diagnostic efforts in this age group.

The clinical significance of increased parenchymal density on mammograms as a risk factor for the development of breast cancer has been shown to be minimal [1–3]. Increased parenchymal density is, however, of greater clinical significance as a cause of false-negative mammograms [4–6].

In an era of increased use of mammography, including initiation of screening mammography by some younger women at high risk [7], concern is increasing about mammographic parenchymal density and its effect on the sensitivity of mammography for detecting early breast carcinoma [8]. Also, new technologies, including breast MR imaging, are now being evaluated with the hope that one of the newer technologies may complement mammography for evaluating women with mammographically dense breasts [9–13].

The frequency and age distribution of dense tissue seen on mammograms and the factors affecting parenchymal density on modern film-screen mammography have not been well described in the diverse age groups of women who may undergo mammography.

This study was undertaken to establish the frequency and age distribution of breast tissue density and benign calcifications and to study several factors that have been suggested to affect parenchymal density on mammograms.

Materials and Methods

The study population consisted of 1353 women grouped into 5-year age cohorts that ranged from 25–29 to 75–79 years old. These 5-year age cohorts of consecutive patients who underwent film-screen mammography between 1990 and 1995 at one diagnostic and screening mammography center were identified through the hospital radiology information system. The first 100–126 consecutive mammograms in each age cohort of patients who had not undergone surgery or radiation treatment were reviewed by one of two mammographers. During assessment of the mammograms, these mammographers were unaware of the age of the patient. All patients in the study had their mammograms done on a Senographe 600T or DMR mammography unit (General Electric Medical Systems, Milwaukee, WI) using Min-RH film and Min-R cassettes (Eastman Kodak, Rochester, NY).

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Parenchymal density on mammograms was assessed visually on both craniocaudal and mediolateral oblique views and was categorized as follows: less than 10% dense tissue, 10–49% dense tissue, 50–89% dense tissue, and 90% or greater dense tissue. The subcutaneous and retromammary fat regions in each breast were excluded during the determination of dense tissue. In patients with asymmetric tissue, the breast with greater density was categorized. The categorization of mammographic density for a 300-patient subgroup was done independently by the two mammographers. To determine the interobserver agreement rate, the categorization of the first mammographer was used for the study analysis.

For each patient, benign or probably benign calcifications were also recorded. Routine or short-term mammographic follow-up was recommended for these findings.

The size of the breast was determined on the mediolateral oblique view of the largest breast of each patient by measuring the greatest horizontal width of the breast and the vertical dimension of the breast perpendicular to the bisection of the line representing the greatest horizontal width. The products of these dimensions for each patient were then categorized for the purposes of this analysis as small, the lowest third percentile in each age group; intermediate, the middle third percentile; and large, the upper third percentile.

The following clinical information was recorded from the history form completed by each patient and the mammography technologist and reviewed by the radiologist at the time of the mammographic examination: age at first complete pregnancy; parity; use of hormone replacement therapy; and family history of breast carcinoma categorized as none, minor risk factor (any relative other than mother, sister, or daughter), strong risk factor (mother, sister, or daughter with unilateral postmenopausal breast cancer), or very strong risk factor (mother, sister, or daughter with either bilateral or premenopausal breast cancer). This information was not available in all cases. To assess associations between age groups and possible affecting factors, mammographic density was correlated with the fraction of patients in any subgroup who had predominantly fatty breasts (less than 50% dense tissue) or very dense breasts (90% or greater dense tissue). Chi-square tests, chi-square trends, and Spearman correlation tests were done [14] for statistical analysis. *P* values of less than .05 were considered significant.

Results

Comparison of the categorization of parenchymal density on mammograms of a 300-patient subgroup by each mammographer showed that the two readers were highly consistent with each other (kappa value, .86; 95% confidence interval, 81–91%). The readers agreed in 90% of cases. All disagreements were by one category.

The parenchymal density seen on mammograms of women 25–79 years old is shown in Table 1. The parenchymal density on mammograms decreased progressively from the age cohort of 25- to 29-year-olds, in which 38% of patients had predominantly (≥50%) fatty breasts, through the cohort of 75- to 79-year-olds, in which 76% had predominantly fatty breasts (Spearman correlation, $p < .01$). Thirty-nine percent of patients who were 25–29 years old had mammographic parenchymal density categorized as very (≥90%) dense. Six percent of patients who were 75–79 years old had very dense breast tissue.

The relationship of hormone replacement and parenchymal density on mammograms is shown in Table 2. Of 747 patients who were 50–79 years old, 26% were taking hormones. Fifty-one percent of all women taking hormones had predominantly fatty breasts as compared with 78% of women in the same age group not taking hormones ($p < .01$). As with older women on hormones, 52% of women 40–44 years old had predominantly fatty breasts.

The relationship between parenchymal density on mammograms and breast size is shown in Table 3. Less parenchymal density on mammograms was seen in women with larger breast size for each age cohort ($p < .01$). In the 25–29 age cohort, 61% of women with larger breast size (upper third percentile) had predominantly fatty parenchymal density on mammograms compared with only 11% of women with small breast size (lowest third percentile). In this study population, breast size was independent of patient age, parity, age at first pregnancy, or hormone replacement status.

The relationship between parenchymal density on mammograms and various clinical factors is shown in Table 4. Two or more pregnancies were associated with predominantly fatty breasts in 68% of women compared with nulliparity or one pregnancy (46% and 50%, respectively; $p < .01$). Age at first pregnancy of less than 22 years showed a trend toward predominantly fatty breasts (71%) when compared with age at first pregnancy of 22 years or older (65%) ($p = .07$). The significant associations between parenchymal density on mammograms and breast size and hormone replacement are again shown in Table 4 for comparison with the other factors.

There was no significant difference in the frequency and age distribution of parenchymal density on mammograms in women with no, minor, strong, or very strong family histories of breast cancer.

The frequency and age distribution of benign calcifications are shown in Table 5. The prevalence of benign calcifications increases progressively with age, ranging from 8% at ages 25–29 to 86% at ages 75–79 (chi-square trend, $p < .01$).

Discussion

Although this study shows that younger age is a factor in parenchymal density seen mammographically, a significant percentage (38%) of women 25–39 years old have predominantly fatty tissue on mammograms. Small breast size and fewer than two pregnancies are also signif-

TABLE 1 Parenchymal Density on Mammograms in Women 25–79 Years Old

Age Cohort	Parenchymal Density No. of Patients (%)				
	<10% [a]	10–49% [a]	50–89%	≥90% [b]	Total
25–29	10 (11)	27 (27)	24 (24)	39 (39)	100
30–34	9 (7)	31 (25)	34 (27)	52 (41)	126
35–39	18 (14)	38 (30)	27 (22)	42 (34)	125
40–44	20 (16)	46 (37)	37 (30)	22 (18)	125
45–49	21 (17)	48 (38)	32 (26)	24 (19)	125
50–54	28 (22)	42 (33)	33 (26)	23 (18)	126
55–59	17 (14)	70 (56)	26 (21)	12 (10)	125
60–64	35 (28)	59 (47)	23 (18)	9 (7)	126
65–69	22 (18)	67 (54)	29 (23)	7 (6)	125
70–74	34 (27)	63 (51)	17 (14)	11 (9)	125
75–79	34 (27)	61 (49)	23 (18)	7 (6)	125

[a] Spearman correlation, $p < .01$ ($r = .97$), comparing predominantly fatty (≤49% density) fractions.
[b] Spearman correlation, $p < .01$ ($r = -.94$), comparing very dense (≥90%) fractions.

TABLE 2 Hormone Replacement Status[a] and Parenchymal Density on Mammograms in Women 50–79 Years Old

Age Cohort	Parenchymal Density No. of Patients (%)				
	<10%	10–49%	50–89%	≥90%	Total
50–54	28 (22)	42 (33)	33 (26)	23 (18)	126
Hormone replacement	12 (24)	8 (16)	20 (39)	11 (22)	51
No hormones	16 (21)	34 (45)	13 (17)	12 (16)	75
55–59	17 (14)	70 (56)	26 (21)	12 (10)	125
Hormone replacement	1 (2)	26 (57)	11 (24)	8 (17)	46
No hormones	16 (21)	44 (56)	15 (19)	4 (5)	79
60–64	35 (28)	59 (47)	22 (18)	9 (7)	125
Hormone replacement	7 (22)	13 (41)	9 (28)	3 (9)	32
No hormones	28 (30)	46 (49)	13 (14)	6 (6)	93
65–69	22 (18)	67 (54)	29 (23)	7 (6)	125
Hormone replacement	2 (7)	12 (13)	11 (11)	4 (4)	29
No hormones	20 (21)	55 (57)	18 (19)	3 (3)	96
70–74	34 (27)	63 (51)	17 (14)	11 (9)	125
Hormone replacement	1 (5)	10 (50)	3 (15)	6 (30)	20
No hormones	33 (31)	53 (50)	14 (13)	5 (5)	105
75–79	34 (28)	58 (48)	22 (18)	7 (6)	121
Hormone replacement	2 (14)	4 (29)	6 (43)	2 (14)	14
No hormones	32 (30)	54 (50)	16 (15)	5 (5)	107
50–79	170 (23)	359 (48)	149 (20)	69 (9)	747
Hormone replacement	25 (13)	73 (38)	60 (31)	34 (18)	192
No hormones	145 (26)	286 (52)	89 (16)	35 (6)	555

[a]For the number of patients in each subgroup for whom this information was available.

TABLE 3 Effects of Breast Size on Parenchymal Density on Mammograms

Age Cohort and Size	Parenchymal Density No. of Patients (%)				
	<10%	10–49%	50–89%	≥90%	Total
25–29					
Small	0 (0)	4	10 (27)	22 (61)	36
Medium	3 (8)	11 (36)	8 (22)	12 (33)	36
Large	7 (25)	10 (36)	6 (21)	5 (18)	28
50–54					
Small	3 (7)	16 (39)	11 (27)	11 (27)	41
Medium	6 (14)	17 (39)	15 (34)	6 (14)	44
Large	19 (46)	9 (22)	7 (17)	6 (15)	41
75–79					
Small	4 (10)	24 (59)	10 (24)	3 (7)	41
Medium	8 (19)	25 (60)	8 (19)	1 (2)	42
Large	22 (52)	12 (29)	5 (12)	3 (7)	42
25–79					
Small	37 (8)	157 (35)	118 (26)	141 (31)	453
Medium	54 (12)	207 (46)	113 (25)	79 (17)	453
Large	157 (35)	188 (42)	74 (17)	28 (6)	447

icant factors associated with increased breast tissue density in all age groups. Among women 25–29 years old with small breasts, 11% had predominantly fatty breasts and 61% had very dense breasts, compared with 61% predominantly fatty breasts and 18% very dense breasts among women with large breasts in the same age group. However, none of these factors was highly predictive of breast tissue density on mammograms.

These data may be helpful when considering the use of mammography and new imaging techniques to detect and diagnose breast cancer in younger women. Approximately 50% of mammographically detected carcinomas are noncalcified soft-tissue abnormalities [15]. These soft-tissue abnormalities may be mammographically inapparent if they are present within and obscured by dense parenchymal tissue. Dense parenchyma is comprised of fibrous and glandular tissue [16]. The frequency of histologic atypia or hyperplasia and cellular proliferative activity measured by DNA S-phase percentage has been shown to be similar in fatty and dense tissue in excised specimens [17, 18]. Physical examination and degree of compressibility have been shown to be inaccurate predictors of parenchymal density on mammograms [19].

An increased rate of false-negative mammograms has been reported in premenopausal women compared with postmenopausal women. For example, in the Breast Cancer Detection Demonstration Project (BCDDP), 13% of breast carcinomas in premenopausal women were not detected mammographically but were found on clinical examination as compared with 7% for postmenopausal women [20]. In the BCDDP study, however, most breast cancers in premenopausal and postmenopausal women, 87% and 93%, respectively, were detected mammographically. The mammographic appearances of breast carcinoma in women less than 35 years old have been described by Meyer et al. and others [21–23]. The lower sensitivity of mammography reported in younger women may be related not only to dense breasts on mammograms but also to faster tumor growth rates in younger as compared with older women [6].

Our observation that little difference exists in the proportion of fatty to dense breast tissue in women 40–44, 45–49, and 50–54 years old is noteworthy when considering the age at which mammographic screening begins in the general population. Our data show no significant change in parenchymal density on mammograms at age 50 that would support initiating screening at age 50 rather than age 40.

The association of postmenopausal hormone replacement therapy and increased parenchymal density on mammograms and the reversibility of this process in some patients has been documented in the litera-

TABLE 4 Effects of Various Factors on Parenchymal Density on Mammograms in Women 25–79 Years Old[a]

Factor	Parenchymal Density			
	Total No.	No. of Patients (%)		
		0–49%	50–89%	≥90%
Breast size				
Small	453	194 (43)	118 (26)	141 (31)
Medium	453	261 (58)	113 (25)	79 (17)
Large	447	345 (77)[b]	74 (17)	28 (6)[c]
Postmenopausal hormone replacement				
Hormone replacement	192	98 (51)	60 (31)	34 (18)
No hormones	555	431 (78)[b]	89 (16)	35 (6)[c]
Parity				
Nulliparity	120	55 (46)	32 (27)	33 (28)
One pregnancy	95	47 (50)	28 (30)	20 (21)
Two or more pregnancies	823	560 (68)[d]	170 (21)	93 (11)[e]
Age at first pregnancy				
22 years old or older	496	319 (65)	102 (21)	75 (15)
Less than 22 years old	409	287 (71)	87 (21)	35 (9)
Family history of breast cancer				
None	475	253 (53)	117 (25)	105 (22)
Minor risk	494	315 (64)	98 (20)	81 (16)
Strong risk	197	119 (61)	51 (26)	27 (14)
Very strong risk	147	86 (58)	32 (22)	29 (20)

Note.—*P* values of less than .05 were considered significant.
[a]For the number of patients in each subgroup for whom this information was available.
[b]$p < .01$ comparing 0–49% fractions.
[c]$p < .01$ comparing ≥90% fractions.
[d]$p < .01$ comparing 0–49% fraction with that of one or no pregnancy.
[e]$p < .01$ comparing ≥90% fraction with that of one or no pregnancy.

TABLE 5 Frequency of Benign Calcifications on Mammograms in Women 25–79 Years Old

Age Cohort	Total No. of Patients	No. (%) of Patients with Benign Calcification[a]
25–29	100	8 (8)
30–34	126	10 (8)
35–39	125	22 (18)
40–44	125	37 (30)
45–49	125	36 (29)
50–54	126	43 (34)
55–59	125	54 (43)
60–64	126	63 (50)
65–69	125	75 (60)
70–74	125	78 (62)
75–79	125	108 (86)

[a]Chi-square trend, $p < .01$.

ture [24, 25]. Our data add the observation that the percentage of postmenopausal women taking hormones who have predominantly dense tissue on mammograms (49%) is similar to that of women 40–44 years old not taking hormones.

The association of decreased parenchymal density on mammograms with parity reported was also shown in a BCDDP study analysis [26]. A biologic mechanism for this observation has not been established. The lack of association between parenchymal density and age at birth of the first child was also reported by the BCDDP study analysis [26]. An understanding of the biologic factors associated with the development and regression of parenchymal density on mammograms may lead to the development of therapeutic methods that decrease breast density and unmask carcinomas obscured by dense tissue on mammograms.

The frequency of benign calcifications seen on mammograms is a consideration with regard to additional mammographic projections that may be required at the time of the baseline and possibly one or several follow-up examinations. The knowledge of age-specific frequency of benign calcifications may be important in educating women and health care providers who need to understand reports with these findings [27]. Anxious patients often require explanations and reassurances that some mammographic patterns of calcification suggest malignancy and require biopsy whereas benign calcifications are recognized often on mammograms in women of the same age and increase in frequency with age. In our data, the frequency of benign calcifications on mammograms ranged from 8% in women 25–29 years old to 86% in women 75–79 years old. A corollary statement is that benign calcification can develop on screening mammograms at any age. Also, the presence of new calcifications on a screening mammogram does not by itself raise suspicion for malignancy and does not require biopsy without further characterization. New calcifications should be evaluated like any other calcifications. If clearly benign, no further workup is needed. If indeterminate, magnification projections and prudent interpretive criteria are required.

We conclude that younger age, small breast size, fewer than two pregnancies, and—for postmenopausal women—hormone replacement therapy, are significantly associated with, but not highly predictive of, increased parenchymal density on mammograms. We also conclude that a significant percentage (38%) of women 25–39 years old have predominantly fatty breast tissue on mammograms that should not impede selective mammographic screening or diagnostic efforts in this age group.

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