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Review

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Abbreviations:
BI-RADS = Breast Imaging Reporting and Data System
HRT = hormone replacement therapy

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Quantitative Assessment of Mammographic Breast Density: Relationship with Breast Cancer Risk[1]

Increased mammographic breast density is a moderate independent risk factor for breast cancer, with findings of published studies in which quantitative methods of assessment were used showing a positive association. Breast density may be quantified by using visual assessment or planimetry. Although the category definitions vary, the odds ratio for developing breast cancer for the most dense compared with the least dense breast tissue categories ranges from 1.8 to 6.0, with most studies yielding an odds ratio of 4.0 or greater. Plausible explanations for the association of breast density with increased breast cancer risk may be the development of premalignant lesions such as atypical ductal hyperplasia, elevated growth factors, or increased estrogen production within the breast due to overactive aromatase. The amount of breast density may be due in part to genetic heredity. However, unlike other risk factors, breast density may be influenced. Specifically, breast density is very hormonally responsive and potentially may be influenced by lifestyle factors such as alcohol intake and diet. Assessment of breast density may become useful in risk assessment and prevention decisions.

Breast density is perhaps the most undervalued and underutilized risk factor in studies investigating the causes of breast cancer.

Celia Byrne (1)

In 1976, Wolfe published an article that demonstrated a relationship between breast density and breast cancer risk (2). However, investigators of subsequent studies either did not reproduce the association (3,4) or did not show the association to be as strong as that in the Wolfe original report (5–7). Reader inconsistency issues also caused doubt as to the usefulness of the Wolfe density classification scheme (6,8), which fell into disuse in this country in the 1980s, although it is still commonly used outside of the United States.

Beginning in the early 1980s, more precise quantitative methods of measuring breast density were developed. Since 1982, to our knowledge 12 studies (9–20) in which quantitative methods were used for assessing breast density have been performed; findings of all these studies showed a positive moderate association with breast cancer risk. The risk of breast cancer for women with increased breast density in most of these studies is four to six times that for women with less dense tissue, a relative risk greater than most traditional risk factors such as nulliparity and early menarche. Unlike most other breast cancer risk factors, breast density may be influenced by hormonal agents, alcohol use, and possibly other means.

In this article, we review normal changes in breast composition over time, methods of measuring breast density, the association of breast density measured with quantitative methods to breast cancer risk, alternative explanations for the association, how hormonal and other factors are associated with breast density, and plausible reasons that increased breast density increases breast cancer risk. Last, we examine potential future directions for use of quantitative assessment of breast density in relation to breast cancer risk.

CHANGES IN BREAST COMPOSITION OVER TIME: NORMAL PHYSIOLOGY

Premenopause

The mature breast undergoes cyclic changes during the menstrual cycle. Estrogen increases cell proliferation and progesterone enhances this effect. During the follicular phase, cell proliferation increases and is further enhanced during the luteal phase (21). There is also an increase in breast volume and water content during the luteal phase of the cycle (22). Hypertrophy, or enlargement of individual cells, may also contribute to the increase in breast volume during this portion of the menstrual cycle, although little information exists regarding cellular hypertrophy during the menstrual cycle. Acute deprivation of estrogen and progesterone causes an increase in cell death, or apoptosis, which peaks during the time of menstrual bleeding (23). On mammograms, these changes are reflected by greater breast density during the luteal phase than during the follicular phase (24,25).

As women near menopause, the menstrual cycle shortens. Specifically, the follicular phase shortens, with no significant change in the length of the luteal phase. This continues until the onset of oligomenorrhea. During the perimenopausal years, preovulatory estradiol levels tend to be higher than they are in younger women, while progesterone levels remain similar. Breast cysts are the most common form of breast lumps between ages 40 and 49 years, possibly due to the shortened follicular phase and elevated estrogen levels during this time. The breasts continue to become less dense, with about 50% of women in their 40s and about 65% of women in their 20s having 50% or greater breast density (26).

Menopause

With the reduction of estrogen and progesterone levels after menopause, the cyclic proliferative process becomes quiescent. Lobular tissue regresses, while the more proximal portions of the ductal system remain. The mammographic appearance of the breasts becomes increasingly radiolucent (26), with about 34% of women aged 75–79 years having fat-replaced breasts compared with only 11% of women aged 25–29 years. Likewise, only 30% of women aged 75–79 years have 50% or greater breast density (26).

METHODS OF MEASURING BREAST DENSITY

Wolfe applied a method of classification of parenchymal patterns that used qualitative, as well as quantitative criteria. The following are the descriptions provided by Wolfe (2): N1 category refers to parenchyma composed primarily of fat with, at most, small amounts of dysplasia; no ducts are visible. P1 category refers to parenchyma composed chiefly of fat, with prominent ducts in the anterior portion up to one-fourth the volume of breast; also may be a thin band of ducts extending into a quadrant. P2 category refers to severe involvement, with prominent ductal pattern occupying more than one-fourth the volume of breast. DY category refers to severe involvement with dysplasia, often obscures an underlying prominent ductal pattern.

The Wolfe classification has been applied inconsistently. In a 1993 review, Oza and Boyd (27) found that the Wolfe classification had an interobserver agreement of 52%–97% and an intraobserver agreement of 69%–97%. Authors of case-control and cohort studies have found an association between increased breast cancer risk and the Wolfe P2 and DY categories, although no association was as high as that in the original report by Wolfe (28). Findings of cross-sectional studies have shown a weak association or no association (27).

Attempts to develop a reproducible quantitative method of assessing breast density began in the early 1980s (9). Visual estimation of the percentage of the breast occupied by breast tissue has been used frequently, with the number of categories varying from five (9) to 20 (29), with the most frequently used method as proposed by Boyd et al (10) having six categories. Agreement for visual assessment was very good, with intrareader reliability estimation of 0.82 reported in one 20-category study (30) and κ value of 0.89 (31) and intraclass correlation coefficient of 0.94 (10) reported in the six-category studies.

In the United States, the Breast Imaging Reporting and Data System (BI-RADS) was developed to standardize mammography reporting terminology and the assessment and recommendation categories (32). BI-RADS density classification is included in the report to inform referring physicians of the decline in sensitivity of mammography with increasing breast density. It was not intended to serve as a method of measuring breast density. The four-category system (almost entirely fat; scattered fibroglandular densities; heterogeneously dense, may lower the sensitivity of mammography; extremely dense, which could obscure a lesion on mammography) is based on quantitative assessment, although the categories are not defined by the percentage of density. The lack of well-defined categories likely accounts for the only moderate interobserver agreement seen with the use of BI-RADS density categories, with an overall κ value of 0.43–0.59 (33,34). However, the advantage of the BI-RADS classification is that it is widely used in the United States and allows analysis of large study populations (18).

More consistent computer-assisted measurements of breast density have been developed. All methods use planimetry in some way. Computer-assisted planimetry was used as early as 1987 (11). With this method, an acetate overlay was placed over the mammogram, and the outline of the breast and breast tissue was made by using a wax pencil. A computerized compensating planimeter was then used to obtain the total area of the breast and the total area of the breast tissue (11–13). The percentage of density is then calculated by dividing the area of the breast tissue by the total area of the breast. Agreement with this method is 70%–94% (11,12). More recently, film mammograms have been digitized, and the area of the breast parenchyma and the total area of the breast are outlined by using either a mouse (25) or a digital segmentation of the mammogram (35,36). With the digital segmentation method, the histogram of the digitized mammogram is divided into fatty tissue and parenchyma by using interactive thresholding (35) (Fig 1). Agreement with this method is reported to be 90% or greater (35). Other investigators (37–40) are developing automated calculation of the percentage of density by using segmentation, with promising results, and most recent methods yielded 80%–90% agreement with radiologist assessment of density (38–40).

A limitation of the current planimetry methods is that the pixels are used in a binary fashion (fat or parenchyma) without the actual depth of the pixel being taken into account. Thus, a pixel containing a small amount of breast tissue is considered the same as one with a large amount of breast tissue. Taking pixel depth into account would add some three-dimensional information about the breast. An additional limitation of any method that may be very important when assessing a change in density over time is variation in film exposure factors. Changes in exposure, compression, and processor chemis-

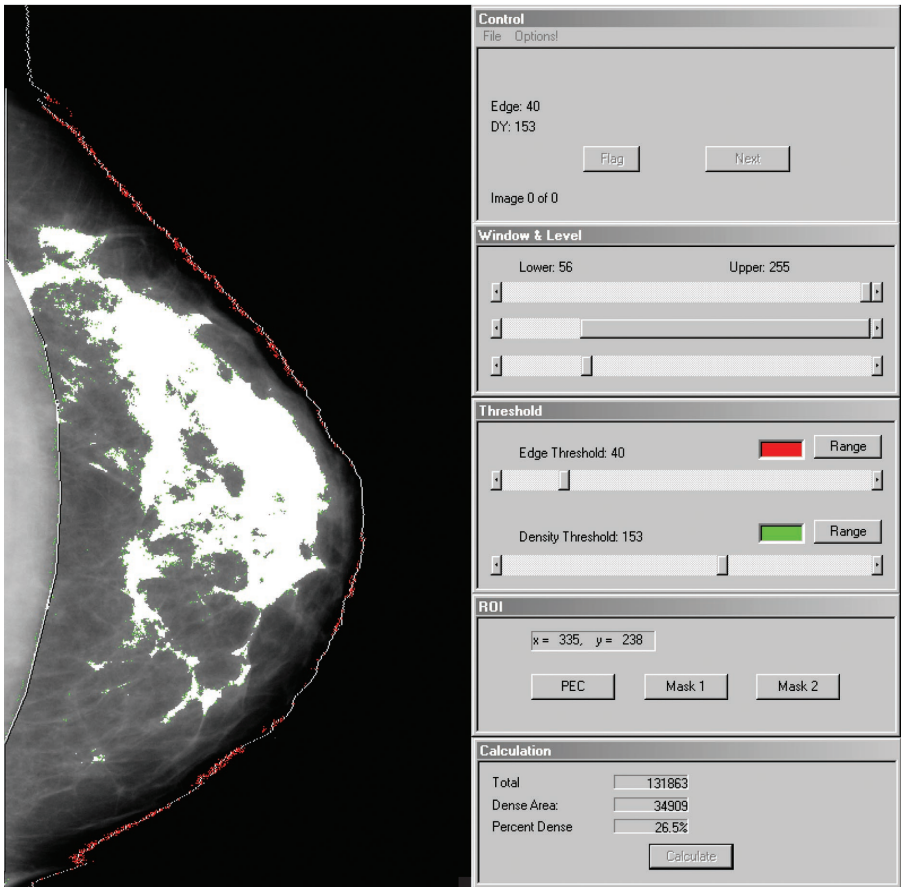

Figure 1. Quantitative assessment of breast density with a computerized thresholding method (35). The computer interface is demonstrated. With this technique, the digitized mammogram is displayed. The red line marks the skin edge and is controlled by the bar labeled "Edge Threshold" in the threshold panel. The green line marks the breast parenchyma and is controlled by the bar labeled "Density Threshold." The user can move either bar to select the appropriate skin line and the area of breast tissue. The user draws a line to denote the boundary of the pectoralis muscle and that area is excluded. Two other masks can be used to exclude markers, et cetera. The total, dense area, and percentage of density are then calculated. In this example, the breast is 26.5% dense. (Image courtesy of Martin Yaffe, University of Toronto).

try may influence the background density of the film and potentially the measured breast density.

Another problem receiving increasing attention is that use of the percentage of mammographic density represents only a two-dimensional representation of a three-dimensional phenomenon. Women with large breasts may have a substantial amount of glandular breast tissue yet have low breast density percentages. On the other hand, women with small breasts and reduced amounts of glandular tissue may have a higher percentage of breast density. A number of investigators are trying to devise a means of determining the total glandular content from three-dimensional reconstruction of breast (Shephard J, oral communication, July 2002). It may be that this parameter would be a better predictor of breast cancer than quantification of density based on current two-dimensional techniques. Further studies are ongoing to address this issue in a meaningful way (Cummings S, oral communication, July 2002).

Other investigators are exploring the use of magnetic resonance imaging (41,42) and ultrasonography (43) for quantifying breast density, although these methods may not prove as useful for widespread use as density information already obtained on the mammogram. Shephard et al (44) are also investigating the use of dual x-ray absorptiometry for measuring breast density.

RELATIONSHIP OF BREAST DENSITY AND BREAST CANCER RISK

In 1976, Wolfe proposed the positive association of qualitatively assessed breast density and breast cancer risk (2). However, subsequent reports primarily showed an association with case-control studies but it was not reproduced in many prevalence studies, and the association was questioned. In 1987, Saftlas and Szklo (28) reviewed the studies that were performed to that date by using the Wolfe criteria and concluded that the most carefully conducted studies supported an association of breast cancer risk and the Wolfe classification, but that lack of consistency in applying the parenchymal pattern classification was a major problem when findings between investigators were compared.

Since 1982, authors of at least 12 studies have reported an association of breast density with breast cancer risk by using quantitative methods (Table) (9–20). Findings of all these studies have shown a moderate to strong positive association of increased breast cancer risk with higher levels of breast density. All were either population-based or clinic-based case-control studies, and several were nested within large cohort populations. All studies were substantial in size, with more than 150 cases, and half of the studies had two or more controls for each case. In all studies, radiologists were blinded to the case or control status.

Findings of all 12 studies in which quantitative methods were used in assessing breast density showed a significant increase in breast cancer risk for women with the highest levels of breast density. Although the category definitions vary, the odds ratio for the most dense compared with the least dense categories ranges from 1.8 to 6.0, with most studies yielding an odds ratio of 4.0 or greater. The Maskarinec and Meng study (20) had the lowest risk and was composed of an ethnically diverse population in Hawaii that included Asian and Native Hawaiian women known to be at lower risk of breast cancer.

Eight of these studies used both the Wolfe classification and quantitative assessment of breast density; in all but the Wolfe et al (11) and Kato et al (13) studies, the quantitative analysis showed a stronger association with breast cancer risk than did the Wolfe classification, which suggests that quantitative methods may be more useful in identifying women at increased risk for developing breast cancer.

Sala et al (45) report a positive association with higher histologic grade tumors and mammographic density assessed by using Wolfe criteria. In this issue of *Radiology*, Roubidoux et al (46) report a

Summary of Studies Evaluating Breast Density by Quantitative Assessment and Breast Cancer Risk

Study and Year	Study Type	Study Population*	No. of Cases/ Controls	Time between Density Measure and Case Ascertainment	Wolfe Odds Ratio†	Quantitative Odds Ratio	95% CI	Quantitative Method	Threshold (%)	Adjustments
Boyd et al, 1982 (9)	Case-control	Women's College Hospital, Toronto, Canada	183/183	Simultaneous	1.9–3.7‡	2.8–6.0‡	1.4, 5.6 2.5, 14.1	Visual	<10 vs ≥75	Age at first birth, parity, family history
Brisson et al, 1982 (14)	Case-control	Two Boston hospitals (1972–1978)	408/1,021	0–12 mo	4.0	3.8–5.4§	1.6, 8.7 2.5, 11.4	Visual	0 vs ≥60	Parity, age at first birth, family history, age at menopause, hormone use
Brisson et al, 1984 (15)	Case-control	Three Boston hospitals (1978–1982)	362/686	0–12 mo	2.7	2.0–4.4§	2.5, 7.9	Visual	0 vs ≥60	Weight, height
Wolfe et al, 1987 (11)	Case-control	Hutzel Hospital, Detroit, Mich (1979–1982)	160/160	Simultaneous	12.2	4.3	1.8, 10.4	Manual planimetry	<25 vs ≥70	Parity
Brisson et al, 1989 (16)	Case-control	Quebec City (1982–1984)	290/645	Simultaneous	3.7	5.5§	2.3, 13.2	Visual	0 vs ≥60	Age, parity, education, weight, height
Saftas et al, 1991 (12)	Case-control nested in cohort	BCDDP (1973–1975)	260/301	5 y	2.6	4.3	2.1, 8.8	Manual planimetry	<5 vs ≥65	Age, weight, parity
Boyd et al, 1995 (10)	Case-control nested in cohort	NBSS	354/354	1–5 y	NA NA	6.0 4.0	2.8, 13.0 2.1, 7.7	Visual Computerized (thresholding)	0 vs ≥75	Age, parity, age at first birth, weight, height, age at menarche, family history
Kato et al, 1995 (13)	Case-control nested in cohort	NYU Women's Health Study (1985–1991)	197/521	0–5.5 y	10.5 (premenopausal) 0.7 (postmenopausal)	3.6 (premenopausal) 2.1 (postmenopausal)	1.7, 7.9 1.1, 3.8	Manual planimetry	<48 vs ≥65 (premenopausal) <28 vs ≥44 (postmenopausal)	Body mass index, parity, menopausal status
Byrne et al, 1995 (17)	Case-control nested in cohort	BCDDP (1973–1980)	1,880/2,152	1–16 y	2.7	4.3	3.1, 6.1	Computerized planimetry	0 vs ≥75	Weight, age at first birth, family history, education, alcohol use, prior biopsies, reproductive years
Lam et al, 2000 (18)	Case-control nested in cohort	VBCSS (1996–1997)	529/2,116	6 mo to 2 y	NA	4.5	1.9, 10.6	BIRADS	Entirely fatty vs extremely dense	Weight
Van Gils et al, 1999 (19)	Case-control nested in cohort	Nijmegen Breast Cancer Screening Program (1985–1994)	108/400	10 y	NA	3.3	1.5, 7.2	Computerized (automated)	<5 vs >25	Menopausal status, Quetelet index
Maskarinec and Meng, 2000 (20)	Case-control	Kaiser Permenente Hawaii (1991–1997)	647/647	85% within 1 y (mean, 6 mo)	NA	1.8	1.1, 3.0	Computerized (thresholding)	<10 vs ≥50	Age at menarche, menopausal status, parity, age at first birth, family history, hormone use, previous breast problems

* BCDDP = Breast Cancer Detection Demonstration Project, NBSS = Canadian National Breast Cancer Screening Study, NYU = New York University, VBCSS = Vermont Breast Cancer Surveillance System.
† NA = not applicable.
‡ Range of three reading radiologists.
§ Percentage of nodular or ductal tissue occupying the breast.

higher incidence of invasive breast cancers that are estrogen-receptor negative, are of higher histologic grade, and are of larger size in women with dense breast tissue that had negative clinical and mammographic screening findings within 17 months of diagnosis. However, authors of the study found that only tumor size was independent of age. The authors postulate that the association between larger tumor size and dense tissue at mammography may be due to either more rapid growth in glandular breasts or increased difficulty in detection due to the dense tissue.

Attributable Risk

Higher levels of breast density are fairly common, since 50% of women between the age of 40 and 49 years and 30% of women aged 70–79 years have breasts that are at least 50% dense (26). If breast density is a moderate risk factor and the risk factor is fairly common, breast cancers attributable to increased breast density could potentially account for an important percentage of total breast cancer cases. In two studies, attributable risk from increased breast density was 28%–30% for 50% or greater density and 40%–44% for any breast density (10,17). In comparison, less than 5% of breast cancers are attributable to breast cancer gene (*BRCA1* and *BRCA2*) mutations.

Breast cancers attributable to dense breast tissue may become more prevalent in the future. Blane et al (47) have found that for women aged 50–59 years, breast density on screening mammograms obtained in the 1990s did not decline with age as rapidly as that seen in the 1980s, even in those women not undergoing hormone replacement therapy (HRT). Authors of that study did not control for such factors as parity, age at first birth, or weight; therefore, slower involution of the breast may be due to these or other causes. Regardless of the cause, findings of the study suggest that if breast density is a moderate risk factor for developing breast cancer, then the attributable risk due to density may become more significant in our population.

Dose Response

If high breast density is a risk factor for breast cancer compared to fat-replaced breasts, then increasing density should be associated monotonically with increasing risk. Boyd et al (48) reviewed the earliest nine of the 12 studies cited in the Table and found a positive trend in all but the Wolfe study (11). In four studies (10,12,13,17), statistical evaluation for trend was significant ($P < .001$ to $P < .0001$). This implies that the breast cancer risk increases in proportion to the degree of breast density.

In addition, if the relationship between breast density and risk is proportional, then changing density should change risk. Investigators of one study have found a trend of changes in risk with changes in density (19). In that study, women with 5%–25% density initially had an odds ratio of 5.7 (95% CI: 2.2, 15.2) for developing breast cancer if their density did not change over an 8-year interval. However, if their breast density decreased to less than 5% during the interval, then the odds ratio for developing breast cancer was only 1.9 (95% CI: 0.6, 6.1), while those with an increase in density to 25% or greater had an odds ratio of 6.9 (95% CI: 2.1, 22.9) (19). This was a small study with wide CIs, and the findings should be confirmed in larger studies.

ALTERNATIVE EXPLANATIONS FOR THE LINK BETWEEN BREAST DENSITY AND CANCER RISK

Density Is a Marker but Not an Independent Risk Factor

Breast density may reflect increased risk due to other causes or it may be an independent risk factor. While weight, body mass index, age, menopausal status, age at first birth, nulliparity, family history, hormone use, and previous breast biopsy may all influence breast density, breast density is identified consistently as an independent risk factor after adjustment for other variables associated with both density and breast cancer risk (17,18). Regardless of the ultimate cause of breast density and its association with risk, if density is a moderate predictor of risk, it may be a useful marker for disease risk even if it is only a more proximal link in a longer chain of causality.

"Masking" Explains the Apparent Association of Density to Increased Risk

Egan and Mosteller (49) proposed the masking hypothesis to explain the apparent relationship of breast density and breast cancer risk. Because cancers are more difficult to detect in dense breast tissue, prevalent cancers may be more likely to be missed at the first screening among women with dense tissue. When the tumors are detected later as apparent incident cancers, a spurious association may arise between the breast cancer risk and tissue density. Evaluation of a relationship between density and breast cancer risk from mammograms obtained in the 1st year or 2 years after initial screening may artificially suggest that density is a risk factor for breast cancer. However, if breast density was not a risk factor for breast cancer, then at some future point after the initial screening, cancer incidence in women with dense and in those with fatty breasts should become similar. In addition, findings in studies in which cancer diagnosis is evaluated at the time of the initial screening examination should show fewer cancers in women with dense breast tissue than in women who have fat-replaced breast tissue.

A small study (50) was performed examining the possible effect of masking on the relationship of breast density and cancer risk. Authors of the study found that increased density defined as more than 25% of the breast occupied by fibroglandular tissue was associated with a relative risk of 1.4 at the initial screening examination, 1.2 at 1–2 years, 3.3 at 3–4 years, and 1.2 at 5–6 years (50). These findings are consistent with the hypothesis that masking of cancers in dense breast tissue does occur, although the effect is small and peaks 3–4 years after the initial screening examination. Masking, however, does not explain the increased relative risk of breast cancer for women with dense breast tissue at study entry, since cancers that are masked within the dense tissue should result in a lower detection and therefore lower apparent relative risk. Of note, the study (50) used mammograms obtained in the 1970s, which were much lower in contrast than are those obtained by using more modern techniques.

Masking bias was less likely to occur in studies that had an initial period during which tumors were excluded from the study (10,17) or had a longer period between initial screening and case status ascertainment (12,19). Studies performed on the basis of cohorts with long-term follow-up that examine density and risk using mammograms obtained in a regularly screened population should also be less affected by masking (10–13,17,19). Findings of three nested case-control studies (10,12,17) have shown that risk remains elevated for at least 5–10 years of follow-up. Byrne et al (17) reported findings for women with 10 or more years between density assessment and case-

control determination; among women with 0% density, there were 17 cases and 42 controls, while among women with density greater than 75%, there were 45 cases and 29 controls. Therefore, 45 (73%) of 62 cases had dense tissue and only 29 (40%) of 71 controls had dense tissue. For masking of prevalent cancers to account for this large difference at 10 years after initial screening, the effect would have to be substantial and long-lived. We estimate that about 75% of prevalent cancers in women with dense breasts would have been missed and subsequently diagnosed 10 or more years later to account for this difference, which is highly unlikely.

Masking has been shown to introduce some bias in the detection of breast cancer in dense tissue in one small study in which older mammograms were used (50). However, the association between breast cancer risk and increased breast density was consistent in every quantitative study reviewed, from those in which density and disease were ascertained nearly simultaneously (9,11,16) to those with up to a decade between density and disease ascertainment (17,19). Given the findings of these studies, masking bias does appear to occur but likely has only a small and short-lived effect.

Current but Not Past Density Is Associated with Increased Risk

In an editorial about breast density, White stated that "disagreement also exists over whether current or past breast density serves as the better risk predictor" (51). Since the effect of breast density on cancer risk persists for at least 5–10 years after assessment (10,12,17), past breast density appears to be important. On the other hand, findings of one study suggest that changes in density change risk (19). In that study, reduction of breast density over time lowered breast cancer risk but not to the extent as in women with comparable density at baseline. This implies that increased density has some persistent effect. Their data also suggest that during the 8 years of follow-up, striking changes in density were relatively uncommon in both cases and controls. The studies reviewed here have widely varying times between disease detection and density determination (Table), and all show associations between density and breast cancer risk. It appears likely that both past and current breast density are associated with risk.

RELATIONSHIP BETWEEN NONHORMONAL FACTORS AND BREAST DENSITY AND BREAST CANCER RISK

Age and Menopausal Status

The association of breast density and breast cancer risk may be greater for older women. Byrne et al (17) found a greater effect of breast density on breast cancer risk in postmenopausal women (odds ratio, 5.8; 95% CI: 3.0, 11.3) compared with that in premenopausal women (odds ratio, 3.8; 95% CI: 2.3, 6.2). Boyd et al (10) also found a higher risk, with women aged 50–59 years having a relative risk of 7.1 (95% CI: 2.0, 25.5) compared with women aged 40–49 years having a relative risk of 6.1 (95% CI: 1.5, 24.2). Findings of both studies, however, show significant overlap in the CIs, which indicates that neither study findings show a strong association between increased breast density and cancer risk according to menopausal status. Kato et al (13) found the opposite effect, although their study was smaller.

The association of breast density with cancer risk seems counterintuitive given that breast cancer risk increases with advancing age at the same time that breast density decreases. However, other age-associated factors besides breast density are likely driving the age-associated increase in breast cancer risk. A parallel situation may be seen with smoking and the incidence of heart disease. As people age, they are more likely to quit smoking (52). However, an 80-year-old nonsmoker is more likely to die of heart disease than a 40-year-old smoker. This does not imply that smoking does not increase the risk of heart disease, only that other factors besides smoking increase the risk of heart disease. Likewise, other factors besides breast density contribute to breast cancer risk. The association between decreasing breast density and increasing breast cancer risk with aging does not negate the association between increased breast density and breast cancer risk.

Weight and Body Mass Index

Obesity is a known risk factor for breast cancer. Lam et al (18) specifically examined the relationship between weight and body mass index on the association of breast density and breast cancer risk. They found that women with higher body weight and body mass index were less likely to have dense breasts. The unadjusted odds ratio for developing breast cancer for women who weighed more than 81 kg compared with those weighing less than 63 kg was 1.7 (95% CI: 1.2, 2.6). However, after adjusting for density, the odds ratio increased to 2.1 (95% CI: 1.3, 3.2). This increase indicates that density is an independent risk factor and that women who are obese and have dense breasts are at higher risk. Likewise, the unadjusted odds ratio for women with extremely dense breasts was 3.2 compared with that in women with predominantly fatty breasts. However, when adjusted for weight and body mass index, the odds ratio increased to 4.5 (95% CI: 1.9, 10.6). Sala et al (53) found similar findings and noted that "this negative confounding of two positive risk factors means that the effect of parenchymal patterns on risk will tend to be underestimated when not adjusted for body mass index and waist hip ratio and vice versa."

Parity

Increased breast density is associated with nulliparity and late age at first birth (54). van Gils et al (55) examined the relationship of parity and breast density with breast cancer risk. In that study, nulliparous women with fatty breasts were not at increased risk compared with parous women. However, women who were nulliparous with greater than 25% density were 6.6 times more likely (95% CI: 2.6, 16.5) to develop breast cancer, while parous women with greater than 25% density were only 3.6 times (95% CI: 1.7, 7.7) more likely develop breast cancer.

Family History

Boyd et al (56) performed a subanalysis within the Canadian National Breast Screening Study by examining breast density and the influence of family history on breast cancer risk. For women with at least one affected first-degree relative, the relative risk of breast cancer was 11.1 (95% CI: 1.5, 80.4) for women with dense breasts compared with those with less than 10% density. The authors concluded that mammographic density may be strongly associated with the risk of breast cancer in women with a family history of the disease. Likewise, Ziv et al (57) have found that women with extremely dense breast tissue were more likely to have first-degree relatives with breast cancer.

Benign Breast Disease

Women with benign breast disease have a greater risk of breast cancer if they also have dense breast tissue than if they

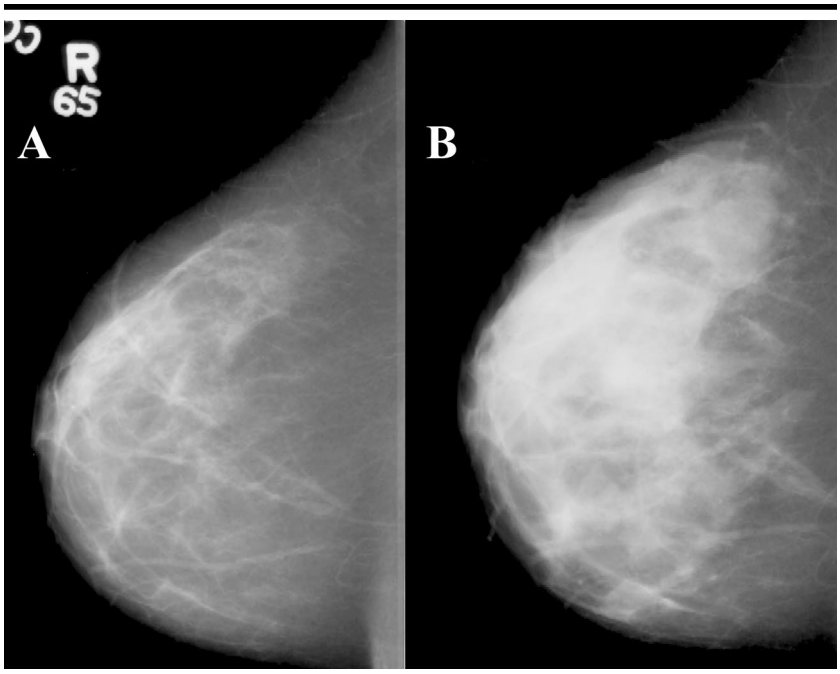

Figure 2. Mammograms demonstrate marked increase in density with HRT. *A,* Prior to HRT use, the breast is minimally dense. *B,* After 1 year, the breast is extremely dense and has increased in size.

have less dense breast tissue. In patients participating in the Breast Cancer Detection Demonstration Project, an increased relative risk of breast cancer was seen with nonproliferative (relative risk, 5.8; 95% CI: 1.8, 18.6) and proliferative (relative risk, 3.2; 95% CI: 1.6, 6.6) benign breast disease in women with greater than 75% density than in women with less than 50% density (58). However, atypical hyperplasia had a higher relative risk in women with lower breast density (relative risk, 4.1; 95% CI: 2.1, 8.0) than in women with dense breasts (relative risk, 2.1; 95% CI: 0.6, 7.0). Therefore, the risk associated with benign breast disease is not explained by density alone and vice versa.

Race and Ethnicity

There are little data regarding the differences in breast density between different races and ethnic groups. Maskarinec and Meng (20) have found that the association between density and breast cancer risk for Asian women is similar to that of Caucasian women.

Diet

The relationship between diet and breast density is not well defined. Findings of two studies (16,59) have shown that high intake of saturated fat is associated with greater breast density, but findings of another study (60) showed lower density. High intakes of vitamins C and E have been associated with increased density (60), while high intake of vitamin A has been associated with lower density (16). Findings of a 2-year study (61) in which women were randomly assigned to no intervention or a low-fat high-carbohydrate diet did not show a change in density.

Intake of both soy protein and soy isoflavones has shown an inverse association with breast density in Chinese women in Singapore (62). Breast cancer rates are lower in Asian countries than they are in the United States and Western Europe (63), and dietary differences, including soy intake, have been hypothesized to contribute to a lowered risk. Soy products are high in phytoestrogens, which may displace endogenous estrogens at hormone-binding sites, decreasing the stimulatory effect of endogenous estrogens in the breast (62).

Alcohol

High alcohol intake is associated with increased breast density (60). However, while white wine intake was associated with increased density in postmenopausal women, red wine intake was associated with lower breast density (60). No difference was noted for premenopausal women and the type of alcoholic beverage.

Exercise

Only two studies, to our knowledge, have addressed the relationship between exercise and breast density. Authors of one study found no relationship (60), and authors of the other study found a weak inverse relationship between moderate exercise and breast density (64).

RELATIONSHIP BETWEEN HORMONAL FACTORS AND BREAST DENSITY AND BREAST CANCER RISK

HRT

HRT slows normal breast involution (65–67) and causes an increase in mammographic density in 17%–73% of women (67–72) (Fig 2). The increase in density is most commonly diffuse but may be focal or multifocal (68,69).

Mammographic changes vary with different HRT regimens. Estrogen combined with progestin has a greater association with increase in density than the use of estrogen alone (70–73). An increase in breast density is also more commonly observed with continuous use of combined HRT, where both estrogen and progesterone are taken daily, than with a cycled HRT, where estrogen is used daily but progesterone is only used during part of the month (70,73). In one study, 28% of women undergoing continuous combined therapy had an increase in density compared with 10% of women using cyclic therapy, 5% of women using estradiol alone, and 3% of controls (71). Similar results were found in women participating in the Postmenopausal Estrogen/Progestin Interventions, or PEPI, trial (73). Use of androgenic norprogestins, which is common in Europe, has effects similar to those of medroxyprogestrone acetate, which is commonly used in the United States (74,75).

Breast density appears to be very responsive to HRT. Investigators of the PEPI trial have found that the greatest change in density occurs during the 1st year of use (73). The breast responds rapidly to hormonal manipulation, with a decrease in density seen after just 2 weeks after HRT cessation (Fig 3) (76). Colacurci et al (77) have found that women who stopped HRT for 3 weeks prior to their annual mammography had no significant change from baseline, whereas

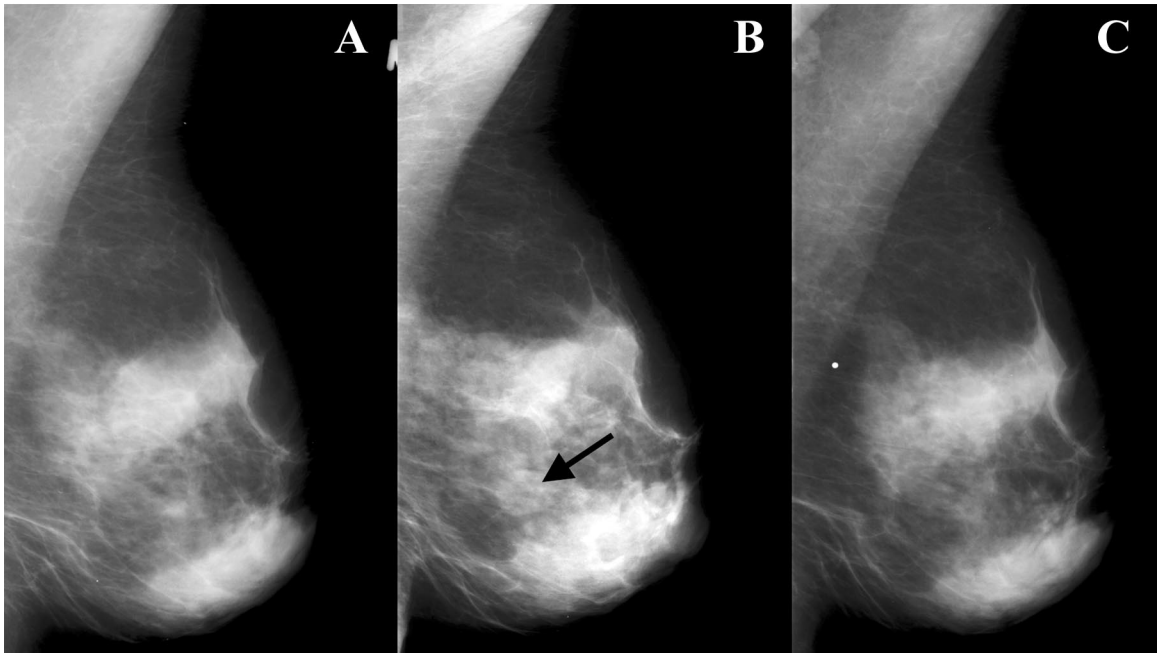

Figure 3. Mammograms obtained in a 65-year-old woman taking 1 mg estradiol daily. *A,* Right mediolateral oblique view from a baseline mammogram shows heterogeneously moderate breast density. *B,* One year later, the right mediolateral oblique view from a screening mammogram shows that the breast density has undergone mild diffuse increase with development of a focal density (arrow). *C,* Right mediolateral oblique view from a diagnostic mammogram obtained after stopping estrogen for 2 weeks shows that the focal density has resolved and the appearance is similar to that at baseline. Metallic marker identifies an incidental skin lesion.

women who continued HRT had an increase in density.

Authors of three large cohort studies have demonstrated a greater breast cancer risk with use of estrogen and progesterone than with use of estrogen alone (78–80). The estrogen-plus-progesterone arm of the Women's Health Initiative trial was halted before study completion because of an increased breast cancer risk (81). The estrogen-only arm of the study continues, because breast cancer risk was only slightly elevated in that group.

At histologic examination, benign breast biopsies performed in women using estrogen plus progestin had significantly higher proliferation indices compared with biopsies performed in women either using estrogen alone or not undergoing HRT (82). In addition, the proliferation noted in women using estrogen with progestin in that study was localized to the terminal duct lobular unit, which is the site of the development of most breast cancers (82).

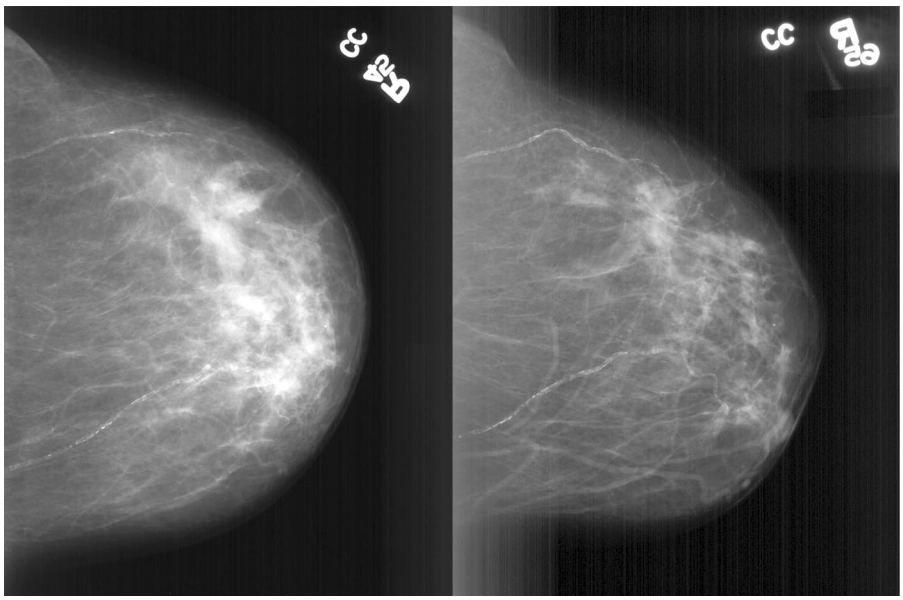

Figure 4. Right craniocaudal mammographic views show a marked decrease in breast density at baseline (left) and 2 years (right) after beginning treatment with tamoxifen for contralateral breast cancer.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators decrease mammographic density presumably due to the antiestrogen effect on the breast (Fig 4). In a breast cancer prevention trial, 44% of women using tamoxifen experienced a reduction in breast density compared with 15% of women randomly assigned to a placebo (83). Raloxifene is another selective estrogen receptor modulator that is approved by the U.S. Food and Drug Administration for treatment of osteoporosis. In the Multiple Outcomes of Raloxifene Evalua-

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