

## Review

# Mammographic Densities and Breast Cancer Risk<sup>1</sup>

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### Abstract

**The radiological appearance of the female breast varies among individuals because of differences in the relative amounts and X-ray attenuation characteristics of fat and epithelial and stromal tissues. Fat is radiolucent and appears dark on a mammogram, and epithelium and stroma are radiodense and appear light. We review here the evidence that these variations, known as mammographic parenchymal patterns, are related to risk of breast cancer.**

Studies that used quantitative measurement to classify mammographic patterns have consistently found that women with dense tissue in more than 60–75% of the breast are at four to six times greater risk of breast cancer than those with no densities. These risk estimates are independent of the effects of other risk factors and have been shown to persist over at least 10 years of follow up. Estimates of attributable risk suggest that this risk factor may account for as many as 30% of breast cancer cases.

Mammographically dense breast tissue is associated both with epithelial proliferation and with stromal fibrosis. The relationship between these histological features and risk of breast cancer may be explained by the known actions of growth factors that are thought to play important roles in breast development and carcinogenesis.

Mammographically dense tissue differs from most other breast cancer risk factors in the strength of the associated relative and attributable risks for breast cancer, and because it can be changed by hormonal and dietary interventions. This risk factor may be most useful as a means of investigating the etiology of breast cancer and of testing hypotheses about potential preventive strategies.

### Introduction

The radiographic appearance of the female breast varies among individuals because of differences in the relative amounts of fat, connective and epithelial tissue, and the different X-ray attenuation characteristics of these tissues (1). Fat is radiologically lucent and appears dark on a mammogram, and connective and epithelial tissues are radiologically dense and appear light. The different radiological appearances created by variations in the relative amounts of these tissues are referred to as the parenchymal patterns of the breast and examples are shown in Fig. 1.

Although there is now a substantial body of evidence showing that variations in mammographic parenchymal patterns are associated with differences in risk of breast cancer as large or larger than those associated with any other risk factors for the disease (reviewed in Refs. 2 and 3), parenchymal pattern is frequently omitted from discussion of risk factors for breast cancer (4). Even when mammographic parenchymal patterns are recognized as a risk factor for breast cancer, there is uncertainty about the size of the associated cancer risk and the extent to which estimates of risk may be distorted by difficulty in detecting cancer in radiologically dense breast tissue.

The purpose of this report is to review the evidence that mammographic parenchymal patterns are related to risk of breast cancer. Specifically, we examine the strength and consistency of the published estimates of breast cancer risk associated with mammographic parenchymal patterns, emphasizing studies that have used quantitative methods of classification, and the effects that "masking," or difficulties in cancer detection, may have on these estimates. Furthermore, we seek evidence of a dose-response relationship between breast patterns and risk of breast cancer. Finally, we describe the association of parenchymal pattern with other risk factors and consider whether the association of mammographic patterns with breast cancer risk is biologically plausible in light of existing knowledge of the pathogenesis of the disease.

### Literature Review

The literature that forms the subject of this review was identified through searches of Index Medicus for the years 1976–1997 under terms that included mammographic parenchymal patterns, mammographic patterns, mammography, and breast cancer risk. Additional searches of the bibliographies of reports identified in this way were also carried out.

### Mammographic Parenchymal Patterns and Breast Cancer Risk

**Qualitative Assessment of Mammographic Parenchymal Patterns.** An association between the mammographic parenchymal pattern of the breast and risk of breast cancer was first proposed in 1976 by Dr. John Wolfe (5–7). Wolfe used a classification of the breast parenchyma based on four patterns designated N1, P1, P2, and DY. N1 indicates a breast in which the breast parenchyma is radiologically lucent and risk of breast cancer is lowest. DY indicates a breast in which the paren-

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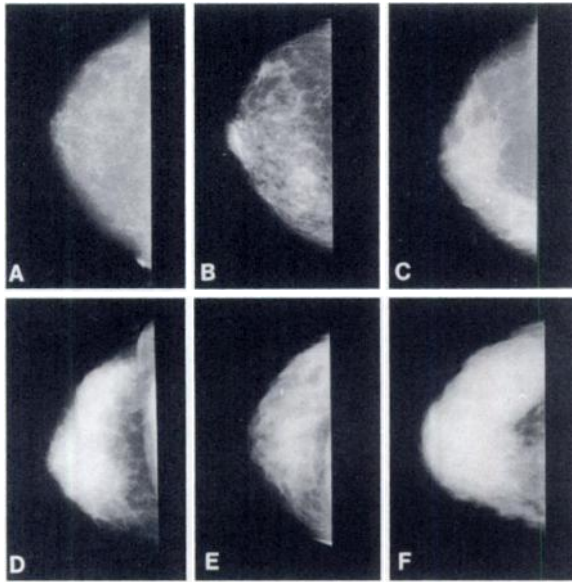


Fig. 1. Six categories of density. A, density = 0%; B, density = 0% to <10%; C, density = 10% to <25%; D, density = 25% to <50%; E, density = 50% to <75%; F, density  $\geq$ 75%.

chyma is radiologically dense and risk of cancer is highest. P1 and P2 patterns are characterized by linear radiological densities called ductal prominence, respectively of lesser and greater extent, and associated with intermediate increases in risk. In the three cohorts of subjects studied by Wolfe, the DY pattern was found to be associated with a higher risk of breast cancer than the N1 pattern. Tabar has also described a method of classifying mammographic patterns that to date has been shown to be associated with some risk factors for breast cancer but not yet with risk of breast cancer (8–10).

Since Wolfe's original descriptions, a total of 34 additional reports containing a total of 40 studies have been published in English that assessed the risk of breast cancer according to Wolfe's classification. Fifteen of these are cohort studies, or case-control studies nested within cohorts (11–25), 19 are case-control studies, and 6 are cross-sectional studies carried out in association with cohort studies (13–15, 17, 26–44). In addition to Wolfe's three cohort studies, 13 of the 15 cohort or nested case-control studies and 15 of the 19 case-control studies found a statistically significant higher risk of breast cancer in the DY or combined P2/DY categories than in the N1 or combined P1/N1 category. Cross-sectional studies have generally failed to find an association between mammographic patterns and risk of breast cancer, possibly because of the effects on this study design of differences in lead time for cancer detection in breast tissue with different patterns (45).

Despite the large number of studies that have confirmed that Wolfe's classification of mammographic pattern is associated with variations in risk of breast cancer, there is great heterogeneity in the risk estimates generated. For example, estimates of the risk of breast cancer in the DY compared with the N1 pattern vary from 0.5 to 40 in cohort studies and from 0.06 to 12 in case-control studies. This heterogeneity seems likely to be due, at least in part, to the substantial methodological differences and variations in quality that exist between studies (46). One source of variation between studies is the

methods used to classify mammograms. Because Wolfe's classification is subjective, its use may vary between different observers, and observer variation in the use of Wolfe's classification has been reported to be both satisfactory and unsatisfactory (47, 48). Wolfe's nomenclature classifies qualitatively variations in the proportion of the mammographic image occupied by radiologically dense breast tissue, and these variations might be better described quantitatively. We next consider approaches to the classification of mammographic densities that are based on measurement.

**Quantitative Assessment of Mammographic Densities.** The approaches that have been taken to measurement of mammographic parenchymal densities include visual estimation of the proportion of the breast area occupied by densities, measurement by planimetry of the area of density, and the measurement of densities in digitized images with computer-assisted methods.

Table 1 gives a summary of the principal features and results of all studies published to date that have used one or more of these quantitative approaches. A total of nine studies has been published, five conventional case-control studies (26–29, 49) in which the mammograms at diagnosis in cases were compared with those of controls and four nested case-control studies carried out within defined cohorts that analyzed the risk of developing breast cancer during follow-up in relation to the characteristics of the mammogram taken at entry to the cohort (22, 23, 50, 51). Two of the nested case-control studies were performed within the Breast Cancer Detection and Demonstration Projects (52), one in the Canadian National Breast Screening Study, a randomized trial of screening with mammography (53–55), and one in the cohort of the New York Women's Health Study (22). All nine studies have been of substantial size, only three had fewer than 200 cases and, in toto, the studies have examined a total of 4221 cases and 5872 controls.

In all studies, those classifying mammograms were "blinded" to the identity of cases by selecting for measurement the mammogram from the breast contralateral to the cancer. Mammographic densities were measured in five studies by visual estimation of the proportion of the breast area occupied by radiologically dense tissue. In one study, densities were further classified according to their nodular or homogeneous appearance. Four studies used planimetry, in which the edges of the breast and area of density are traced by an operator and the areas delineated were calculated by a computer. One study used both visual estimation of the extent of density and measurements in digitized images of the areas of the breast and dense tissue. In this procedure, illustrated in Fig. 2, an operator establishes "thresholds" for the edge of the breast and the edge of dense tissue. A computer then records the number of pixels in the digitized image that lie within the defined areas. This method of measurement has been shown to give highly reproducible results, and details have been given elsewhere (56, 57). Ursin *et al.* (58) have also described a method of classifying change in mammographic features, but this approach has not yet been used to assess risk of breast cancer.

Although definitions of the categories of density compared vary, all of the studies included in Table 1 found significantly elevated summary odds ratios between extremes of the categories of the classification used. Odds ratios vary between 2.1 and 6.0 for different observers, types of density, and menopausal status, but most found odds ratios of 4.0 or greater. Similar odds

Table 1 Quantitative studies of breast density and cancer risk: Summary of methods and results

Author (Ref.)	Design	Age	Sample size	Measurement	Blinded <sup>a</sup>	Partition <sup>b</sup>	Odds ratio	95% CI	Trend <sup>c</sup>	Adjustments <sup>d</sup>
Boyd <i>et al.</i> (29)	Case-control	40–65	183 pairs	Estimation <sup>e</sup>	Yes	<10% vs. ≥75%	a. 6.0 <sup>f</sup> b. 2.8 <sup>g</sup> c. 3.7 <sup>h</sup>	2.5–14.1 1.4–5.6 1.7–4.1	Yes } No } Yes }	Age at first birth, parity, family history (subset)
Brisson <i>et al.</i> (26)	Case-control	20–69	408 cases 1021 controls	Estimation <sup>e</sup>	Yes	0% vs. ≥60%	a. 5.4 <sup>g</sup> b. 3.8 <sup>h</sup>	2.5–11.4 1.6–8.7	Yes } Yes }	Parity, age at first birth, family history, age at menopause, hormone use
Brisson <i>et al.</i> (27)	Case-control	Not stated	362 cases 686 controls	Estimation <sup>e</sup>	Yes	0% vs. ≥60%	4.4	(2.5–7.9)	Yes	Weight and height
Brisson <i>et al.</i> (28)	Case-control	40–67	290 cases 645 controls	Estimation <sup>e</sup>	Yes	0% vs. ≥60%	a. 4.6 <sup>g</sup> b. 3.2 <sup>h</sup> c. 5.5 <sup>i</sup>	2.4–8.5 1.6–6.5 2.3–13.2	Yes	Age, parity, education, weight, and height
Wolfe <i>et al.</i> (49)	Case-control	30–85	160 pairs	Planimetry	Yes	<20% vs. ≥70%	4.3	1.8–10.4	No	Parity
Saftlas <i>et al.</i> (50)	Nested case-control in cohort	35–74	266 cases 301 controls	Planimetry	Yes	<5% vs. ≥65%	4.3	2.1–8.8	Yes	Age, weight, parity
Boyd <i>et al.</i> (51)	Nested case-control in cohort	40–59	354 pairs	1. Estimation <sup>e</sup> 2. Computer assisted	Yes Yes	0% vs. ≥75%	a. 6.0 <sup>f</sup> b. 4.0 <sup>g</sup>	2.8–13.0 2.1–7.7	Yes } Yes }	Age, parity, age at first birth, weight, height, no. of births, age at menarche, family history
Kato <i>et al.</i> (22)	Nested case-control in cohort	35–65	197 cases 521 controls	Planimetry	Yes	Lower 1/3 vs. upper 1/3	a. 3.6 <sup>j</sup> b. 2.1 <sup>k</sup>	1.7–7.9 1.1–3.8	Yes } Yes }	BMI, parity, menopause
Byrne <i>et al.</i> (23)	Nested case-control in cohort	Not stated	1880 cases 2152 controls	Planimetry	Yes	0% vs. ≥75%	4.3	3.1–6.1	Yes	Weight, age at first birth, family history, years of education, alcohol use, previous benign biopsies, reproductive years

<sup>a</sup> Blinded, measurement made without knowledge of the identity of cases and controls.

<sup>b</sup> Partition, the definition of categories of most and least extensive categories of density from which odds ratios were calculated.

<sup>c</sup> Trend, a statistically significant increasing risk of breast cancer across all the categories of density analyzed in each study.

<sup>d</sup> Adjustments, other factors included in the analysis of risk associated with mammographic density.

<sup>e</sup> Estimation, visual estimation by an observer.

<sup>f</sup> Odds ratio shown for each of three radiologists who estimated density.

<sup>g</sup> Odds ratio for homogeneous density.

<sup>h</sup> Odds ratio for nodular density.

<sup>i</sup> Odds ratio for total density.

<sup>j</sup> Odds ratio for estimation of area of density by radiologist.

<sup>k</sup> Odds ratio for computer-assisted measurement of area of density.

<sup>l</sup> Results shown for: (a) premenopausal; and (b) postmenopausal subjects.

ratios (or RRs<sup>3</sup>) are seen in case-control and nested case-control studies based upon cohorts. In one case-control study, the elevated odds ratio associated with extensive breast density was seen with each of three radiologists who independently classified images, although the magnitude of the odds ratio varied considerably between radiologists (29). In another case-control study, both homogeneous and nodular densities were found to be associated with a substantial increase in risk of breast cancer (26). In one nested case-control study, both radiologist's classification of density and measurement of density using a computer-assisted method found elevations in risk of breast cancer associated with extensive breast densities (51). Assessment of density by planimetry in another large nested case-control study found estimates of risk that were very similar to those found in the study that used computer-assisted measurement (23).

Despite the consistency among these studies in their esti-

mates of overall risk of breast cancer associated with mammographic densities, there are some differences between studies in the reported potential modifying effects of age. Some case-control studies found larger differences in risk associated with density in younger women. Two large case-control studies nested within cohorts, however, found larger differences in older women. In the study of Byrne *et al.* (23), the largest published cohort study to date, the point estimate of risk for density in more than 75% of the breast relative to no density was 3.8 (95% CI, 2.3–6.2) for premenopausal women and 5.8 (95% CI, 3.0–11.3) for postmenopausal women. Radiologists' classification in the study of Boyd *et al.* (51) also showed somewhat higher estimates of risk associated with dense breast tissue in women aged 50–59 years (RR, 7.1; 95% CI, 2.0–25.5) than in women aged 40–49 (RR, 6.1; 95% CI, 1.5–24.2). The smaller nested case-control study of Kato *et al.* (22) found a smaller gradient in risk between the highest and lowest tertiles of a quantitative classification of density among postmenopausal women (RR, 2.1; 95% CI, 1.1–3.8) than among premenopausal women (RR, 3.8; 95% CI, 1.7–7.9).

All of the studies summarized in Table 1 used mammo-

<sup>3</sup> The abbreviations used are: CI, confidence interval; RR, relative risk; BCDDP, Breast Cancer Detection Demonstration Project; NBSS, Canadian National Breast Screening Study; MDA, mammography.

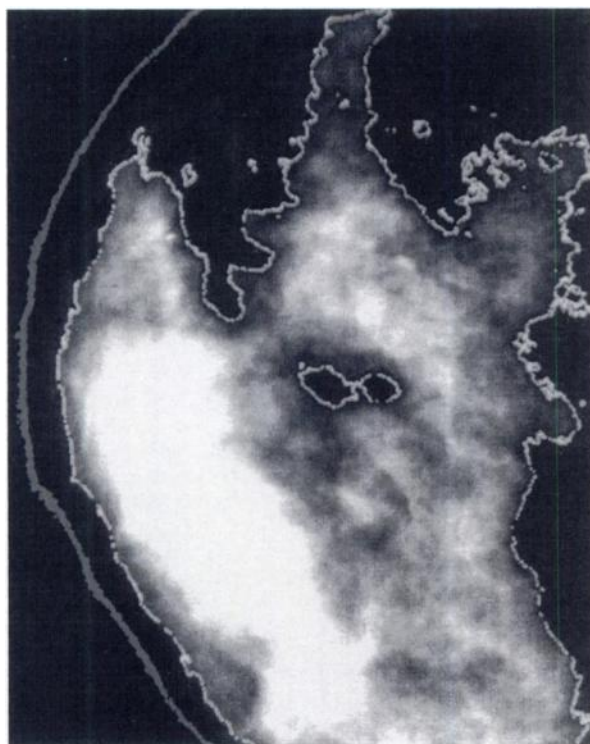


Fig. 2. Method used to measure mammographic features. Dark gray line, edge of the breast; light gray line, edge of dense tissue.

grams taken in a variety of clinical settings in the 1970s and 80s. Some variation among mammograms generated in these settings is expected, due to differences in breast compression, mammography equipment, and film exposure and processing. However, mammographic density is a relatively coarse feature of the mammogram and is not influenced by moderate variations in exposure and processing (59). Although it is unlikely that density is substantially affected by changes in image production in the past decade, no study has yet been published examining breast cancer risk in relation to features of modern mammograms.

**Comparison of Qualitative and Quantitative Methods of Classification of Parenchymal Patterns.** Wolfe's qualitative method of classification and quantitative methods were applied to the same population in five case-control studies and two nested case-control studies, allowing a direct comparison of the two approaches. The results obtained are shown in Table 2. In three of these studies, classification of mammographic pattern was made by Dr. Wolfe (23, 49, 50). In all of these studies, Wolfe's classification was associated with statistically significant differences in the RR of breast cancer between DY and N1 categories. However, when the same set of mammograms was classified quantitatively, the odds ratios for the RR of breast cancer, in the most extensive category of density compared with the least extensive category, were larger than with Wolfe's classification in five of the studies. Furthermore, in the study of Brisson *et al.* (26), the association between Wolfe's classification of parenchymal pattern and breast cancer risk was completely explained when adjustment in analysis was made for the percentage of the breast occupied by nodular and homogeneous density. The study of Byrne *et al.* (23) showed that gradients in risk of breast cancer were created within Wolfe's categories by

Table 2 Mammographic pattern and risk of breast cancer: a comparison of methods of classification

Author (Ref.)	Method of classification <sup>a</sup>	
	Wolfe <sup>b</sup>	Quantitative <sup>c</sup>
Boyd <sup>d</sup> <i>et al.</i> (29)	3.3 (1.8–6.0)	6.0 (2.5–14.1)
	1.9 (1.1–3.3)	2.8 (1.4–5.6)
	3.7 (2.0–6.8)	3.7 (1.7–4.1)
Brisson <i>et al.</i> (26)	4.0 (1.1–3.3)	5.4 (2.5–11.4) <sup>e</sup>
		3.8 (1.6–8.7) <sup>f</sup>
Brisson <i>et al.</i> (27)	3.7 (1.8–7.4)	4.6 (2.4–8.5) <sup>g</sup>
		3.2 (1.6–6.5) <sup>h</sup>
		5.5 (2.3–13.2) <sup>i</sup>
		4.3 (1.8–10.4)
Wolfe <sup>b</sup> <i>et al.</i> (49)	12.2 (42.1–3.5)	4.3 (1.8–10.4)
Saftlas <sup>b</sup> <i>et al.</i> (50)	2.6 (1.3–5.4)	4.3 (2.1–8.8)
Kato <sup>c</sup> <i>et al.</i> (22)	a) 10.5 (2.0–55.4)	a) 3.6 (1.7–7.9)
	b) 0.7 (0.1–4.0)	b) 2.1 (1.1–3.8)
Byrne <sup>b</sup> <i>et al.</i> (23)	2.7 (2.0–3.7)	4.3 (3.1–6.1)

<sup>a</sup> Numbers shown are point estimates of risk and 95% CIs.

<sup>b</sup> Odds ratio, or RR, between N1 and DY categories of classification.

<sup>c</sup> Odds ratio, or RR, between most and least extensive category of classification.

<sup>d</sup> Results shown are for each of three radiologists who classified films.

<sup>e</sup> Nodular densities.

<sup>f</sup> Homogeneous densities.

<sup>g</sup> Total densities.

<sup>h</sup> Classification of Wolfe categories made by Dr. John Wolfe.

<sup>i</sup> Compared N1 and P1 versus DY; results shown separately for: (a) pre- and (b) postmenopausal subjects.

the quantitative classification of the extent of density. For example, compared with the N1 category, the RR of breast cancer within the DY category varied from 2.5 for women with breast density of 25–49%, to 4.1 for women with breast density of 75% or more. Similar gradients in risk according to density were found within the P2 pattern.

Studies that have measured the proportion of the mammographic image occupied by radiologically dense tissue have, without exception, found a strong association between increasing densities and increasing risk of breast cancer, and it appears that the risk of breast cancer associated with Wolfe's classification can be explained by variations in the amount of radiologically dense breast tissue present in the mammogram.

Radiologically dense breast tissue is not only associated with a large increase in the RR of breast cancer but also is present in a substantial proportion of subjects with the disease. For example, dense breast tissue in >75% of the breast area was present in 18.6% of cases in the study based on the NBSS (51), and 10% of cases in the study based on the BCDDP (23). Byrne *et al.* (23) calculated the attributable risk associated with breast density, from the observed RR and the prevalence of density in the BCDDP population, and found that 8% of cases could be attributed to density of >75%, of the breast area and 28% to density in more than 50% of the breast. Applying the same calculations to the data of Boyd *et al.* (51) gave estimates of 15% and 33% of breast cancer attributable to the same categories of density (see the "Appendix" for details of the calculation).

**Dose-Response Relationship.** For a quantitative trait that is related to risk of disease, it is expected that increasing levels of the risk factor will be associated with increasing risk of disease. Statistical tests for trend were used in all of the studies included in Table 1 to find out whether the increasing extent of mammographic densities was associated with increasing risk of breast cancer. In eight of the nine studies in Table 1, the test for trend was statistically significant. In the study of Boyd *et al.* (29), a statistically significant trend was found for two of the

three radiologists who classified films. In the study of Brisson *et al.* (26), increasing homogeneous and nodular densities were both associated with a significant trend in risk. In the nested case-control study of Boyd *et al.* (51), both radiological classification and computer-assisted measurement gave a significant test for trend. The computer-assisted method generated a continuous measurement of the proportion of the breast occupied by radiologically dense tissue, and the model fitted to the observed relationship between density and risk of breast cancer predicts that for every 1% increase in density, there will be a 2% increase in the RR of breast cancer. The total area of dense breast tissue was also associated with risk, with a 3% change in RR for every 406-mm<sup>2</sup> change in area of breast density. The total area of the breast was not related to risk of breast cancer. Byrne *et al.* (23) also found with planimetry that the area of radiologically dense tissue and the percentage of the breast area occupied by densities were related to risk of breast cancer but that breast area was not.

The results of these studies thus provide strong evidence for a dose-response relationship between increasing mammographic densities and increasing risk of breast cancer.

**The Masking Hypothesis.** Egan and Mosteller (12) first proposed what has become known as the “masking hypothesis” to explain Wolfe’s early reports that the radiologically dense DY and P2 patterns were associated with an increased risk of breast cancer. Egan and Mosteller proposed that, because breast cancer is easiest to detect by mammography in breasts with radiolucent parenchyma and most difficult to detect in breasts with dense parenchyma, more cancers will be missed at the first examination in subjects with dense breast tissue and will be detected subsequently. In the absence of any real difference in risk, the apparent excess of cancers in this group of subjects during follow-up will make subjects with dense breast tissue appear to be at higher risk than those with radiolucent breast tissue.

Masking of breast cancer by radiologically dense tissue could affect any cohort study in which the mammogram taken at the time of entry is related to risk of breast cancer occurring during follow-up and lead to overestimation of the risk of breast cancer associated with dense breast tissue. The same considerations apply to case-control studies nested within cohorts. However, as Whitehead *et al.* (60) has pointed out, in a cohort of subjects that is regularly examined over an extended period of time, any effect of masking on risk estimates will be small and short lived because cancers missed on one examination will eventually be detected at a later examination. Both empirical data and a model show that the effects of masking are likely to be seen only after examinations with mammography cease and that even then the magnitude of the effect of masking on estimates of risk is small (60). All of the nested case-control studies shown in Table 1 were carried out in screening programs for breast cancer in which regular reexamination was performed over several years. These cohorts have shown that the increased risk of breast cancer in those with dense breast tissue persisted for a substantial period of time. Two of the nested case-control studies shown in Table 1, one in the population that took part in the BCDDP and the other in the cohort that comprised the mammography arm of the NBSS, have shown that subjects with extensive areas of dense breast tissue in the mammogram taken at entry have a marked increase in risk of breast cancer, relative to those without densities, that persisted for at least 5 years of follow-up (50, 51); and the study of Byrne *et al.* (also based on the BCDDP) found an elevated risk of breast cancer associated with dense breast parenchyma

that persisted for at least 10 years after the initial mammogram (23).

In case-control studies, the predicted effects of masking are different from cohort studies because the mammogram taken at the time of diagnosis of breast cancer is used to determine breast density in a group of cases and compared with a control group who are free of breast cancer. The subjects included as cases in a case-control study are, by definition, those in whom breast cancer has been diagnosed, and thus are those in whom any barriers to diagnosis created by masking have been overcome. If masking of cancer by breast density leads to the under diagnosis of breast cancer, dense breast tissue will be underrepresented among diagnosed cases. Furthermore, misclassification of a control subject with undetected cancer is more likely in those with dense than with lucent breast tissue, which might lead to the overrepresentation of dense breast tissue among controls. Under the assumptions of the masking hypothesis, the risk of breast cancer associated with mammographic density should be underestimated by case-control studies.

The masking hypothesis is plausible, and dense breast parenchyma is known to increase the probability of failing to detect breast cancer by mammography (61). However, as Table 1 shows, very similar estimates of breast cancer risk in mammographically dense breast tissue have been obtained by conventional case-control studies, in which masking should lead to underestimation of risk, and in studies that have been nested within cohorts, which the masking hypothesis predicts should be inflated. These findings, combined with the persistence of risk over extended follow-up observed in cohort studies, do not support the hypothesis that the masking of cancer by dense breast tissue is responsible for the estimates of increased risk of breast cancer associated with mammographic densities, or that masking has created any important distortion of these estimates.

#### ***Mammographic Densities and Other Risk Factors for Breast Cancer***

Mammographic densities have consistently been found to be associated with some other risk factors for breast cancer, particularly age, menopausal status, parity, and body weight. Less frequently, associations have been described with alcohol consumption, nutritional variables, a family history of breast cancer, and race. The evidence for these associations is described briefly in the sections that follow. Most of the literature on this subject to date has been based on Wolfe’s classification. The relationship of mammographic densities to histological features of the breast is described in the section on biological plausibility.

**Age and Menopause.** The prevalence of mammographically dense breast tissue declines with increasing age (11, 13, 26, 62, 63), and dense breast tissue is more common before than after the menopause (5, 63–66). Regression analyses applied to data from a cross-sectional study of subjects of different ages suggest that menopausal status, rather than age, is the stronger determinant of breast density (62). These relationships between mammographic densities, age, and the menopause appear at first to be paradoxical, because breast cancer incidence increases with age and is higher in postmenopausal than in premenopausal women. This apparent paradox may, however, be explained by the relationship of mammographic densities to the rate at which breast cancer develops in the population, as shown by the slope of the incidence curve.

As Key and Pike (67) have noted, a log-log plot of breast cancer incidence and age for the United States shows two



distinct slopes, a more rapid increase in incidence up to about age 50, and a less rapid increase in incidence after age 50. These differences in the slope of the breast cancer incidence curve before and after age 50 have been interpreted as indicating an effect of ovarian function on the development and progression of breast cancer before and after the menopause. The more rapid increase in breast cancer incidence before age 50 suggests an effect of ovarian hormones on the development of the disease that ceases at the menopause, after which the age-incidence curve rises less steeply.

The prevalence of mammographic densities in the population also changes at the menopause. The steeper, premenopausal component of the age-incidence curve is associated with a higher prevalence of mammographic densities, and the less steep postmenopausal component is associated with a lower prevalence of densities. Direct evidence of a striking reduction in the proportion of the breast occupied by radiological densities at the menopause has now been observed in a cohort of women examined by mammography before and after the cessation of menstrual activity (68). The prevalence of radiologically dense breast tissue in the population is thus not related directly to the incidence of breast cancer but does appear to be related to the rate at which breast cancer incidence changes in the population and to the slope of the age-incidence curve. This relationship is consistent with the suggestion that ovarian sex hormones influence both the rate of development of breast cancer in the population and the mammographic pattern of the breast. The decline in the prevalence of mammographic density with increasing age means that it is density at a given age, rather than density *per se*, that is the relevant measure with respect to risk of breast cancer. Studies of density as a risk factor must therefore compare women of the same age.

Further evidence that ovarian function influences breast density comes from the association described between early menarche and more extensive mammographic densities (69), the observation that hormone replacement therapy increases breast densities (70–76), and the findings of Spicer *et al.* (77) that the administration for 1 year of a hormonal contraceptive regimen that minimizes exposure of the breast epithelium to estrogen and progesterone reduces mammographic densities. Preliminary data also suggest that the anti-estrogen tamoxifen may reduce breast density (78). Few studies to date have examined the relationship of breast density to levels of endogenous hormones, but one study found women with the N1 and P1 patterns to have higher levels of estrogen and prolactin and lower levels of progesterone than women with the P2 and DY patterns (79).

**Reproductive Variables.** Parity has been found in several studies to be related to mammographic density (10, 34, 35, 62, 63, 65, 66, 80–83). Nulliparous women are at higher risk for breast cancer than parous women (84) and have denser breast tissue. Density decreases further with increasing number of children (83). Among parous women, later age at first birth and fewer live births have been associated with greater risk of breast cancer and with a higher proportion of dense breast tissue (10, 38, 81, 83).

**Body Weight and Height.** Weight and the Quetelet Index of obesity have repeatedly been shown to be inversely associated with breast density, expressed as a percentage of the breast area (27, 30, 44, 62, 63, 65, 66, 81, 85, 86). This is consistent with other data that show leanness to be associated with increased risk of premenopausal breast cancer but not with the observation that obesity is a risk factor for breast cancer after the menopause (87). The inverse association between obesity and

mammographic density suggests that the increased risk of breast cancer associated with obesity after the menopause, which may be due to increased levels of estrogen (88), is not mediated through density. Height has been shown to be positively associated with mammographic density (27, 81) and with an increased risk of breast cancer (89, 90). Higher birth weight has been found to be associated in adult life with a greater risk of breast cancer (91) and possibly with a higher prevalence of the P2 and DY mammographic patterns of Wolfe's classification (92).

**Nutrition, Alcohol, and Exercise.** There is controversy about the relationship of both nutrition and alcohol consumption to breast cancer risk (87, 93, 94), and to date, few studies have examined their relationship to mammographic densities. In one observational study, intake of both total fat and saturated fat were found to be positively associated with breast density, and fiber to be inversely associated (28). Intake of saturated fat has also been found to be associated with a higher prevalence of dense breast patterns at the time of diagnosis in a group of subjects with breast cancer (95). In a randomized trial of intervention for 2 years with a low-fat, high-carbohydrate diet, change in mammographic density was assessed in 817 subjects using the computer-assisted image analysis technique described above. The total area of density was reduced by an average of 6.1% in the intervention group and 2.1% in controls ( $P = 0.02$ ), a difference that was not explained by weight loss, menopausal status, age at entry to the trial, or hormone use. These results suggest that diet has a causal role in the etiology of mammographic density (68).

Two studies to date have found alcohol consumption to be positively associated with mammographic density (86, 96), and another study found no association (97). Physical exercise has been found in one study to be associated with a lower prevalence of densities (98).

**Family History.** A family history of breast cancer in first-degree relatives has been reported in one study to have an additive or greater effect on the risk of breast cancer associated with mammographic densities (25). However, at present it is not clear whether a family history of breast cancer influences breast density. Some studies have found that women with a family history of breast cancer have more dense breast tissue than women without such a history (30, 35), but other studies have failed to find this association (34, 49, 65, 83, 99, 100). There is evidence that mammographically dense breast tissue may be inherited (101). Sister-sister correlations in breast density, unadjusted or after adjustment for age, body mass index, and other variables, were found to be between 0.16 and 0.27 and statistically significant, and segregation analysis suggested that a major autosomal gene influences breast density.

**Race.** There are few data describing differences in breast parenchymal patterns in different ethnic or racial groups or in groups in different geographical locations. One study that compared parenchymal patterns in women of Japanese ancestry and white women living in Hawaii showed no significant differences between the two groups (62). However, a forensic necropsy study using radiological and histological examination of whole-breast sections found significantly fewer American Indian women (a group at lower risk of breast cancer) had the denser P2/DY pattern of Wolfe's classification than Hispanic and non-Hispanic white women of the same age (64, 66). A study of Japanese and British women reported that the lower risk Japanese had one-half the prevalence of the P2 pattern and a 4-fold higher prevalence of the low risk, radiologically lucent, N1 pattern compared with British women (102). A comparison

Table 3 Summary of studies of histology and mammographic patterns

Author (Ref.)	Population <sup>a</sup>			Material	Radiology classification	Results <sup>b</sup>		Comments
	Design	Source	Size			Epithelium	Stroma	
Fisher <i>et al.</i> (104)	Cross-sectional	Hospital series	50 CA 50 FCD	Mastectomy	Wolfe	No association of proliferative fibrocystic disease and mammographic pattern	Fibrous mazoplasia more frequent in DY pattern	
Bartow <i>et al.</i> (105)	Cross-sectional	Forensic autopsy series	519	Mastectomy	Wolfe	Epithelial hyperplasia and intralobular calcification more frequent in P2/DY patterns	No comment	
Wellings and Wolfe (108)	Cross-sectional	Hospital series	143	Biopsies	Wolfe	Atypical lobules more frequent in DY pattern	Parenchymal fibrosis greater in DY than NI pattern	
Bright <i>et al.</i> (106)	Cross-sectional	Hospital series	320	Biopsies	Wolfe	Epithelial hyperplasia association with P2 and DY patterns	Fibrosis associated with mammographic density	
Urbanski <i>et al.</i> (107)	Cross-sectional	Hospital series	160	Biopsies	Quantitative (estimation)	Epithelial hyperplasia with atypia associated with extensive densities	No comment	
Bland <i>et al.</i> (109)	Cohort (P + I)	BCDDP	863	Biopsies	Wolfe	Nonproliferative and proliferative FCD associated with P2 and DY patterns	No comment	
Moskowitz <i>et al.</i> (16)	Cohort (I)	BCDDP	8,033	Biopsies	Modified Wolfe	No association of proliferative fibrocystic disease and mammographic pattern	No comment	No pathology review
Arthur <i>et al.</i> (110)	Cohort (P + I)	Screening trial	162	Biopsies + mastectomy	Wolfe	No association of epithelial hyperplasia or CIS and Wolfe pattern	Fibrosis associated with P2 and DY patterns	DY pattern in 53% of screened population
Boyd <i>et al.</i> (111)	Cohort (P + I)	NBSS	400 B 400 C	Biopsies	Quantitative (estimation)	Extensive density (>75% area), 9.7 greater risk of CIS or AH, 12 times greater risk of hyperplasia than no density	Increasing collagen and decreasing fat as biopsy associated with increasing radiological density	
Lee <i>et al.</i> (112)	Cross-sectional	Referral clinic	588	Cytology on nipple aspirate fluid	High vs. low density	Atypical cells noncommon in women with high density, 4.4 ( $P = 0.08$ )	Not applicable	Results only after BMI adjusted for analysis

<sup>a</sup> CA, cancer; FCD, fibrocystic disease; P, prevalent; I, incident; B, biopsied subjects; C, control subjects.

<sup>b</sup> FCD, fibrocystic disease; CIS, carcinoma *in situ*; AH, atypical hyperplasia; BMI, body mass index.

of the breast parenchymal patterns, according to Wolfe's classification, of Asian and Caucasian women attending a screening program in the United Kingdom showed that 68% of Asians had breast patterns in the NI and P1 categories compared with 45% of Caucasians, and that 32% of Asians had the P2 or DY pattern compared with 55% of Caucasians (103).

**Mammographic Densities as an Independent Risk Factor for Breast Cancer.** Although several risk factors for breast cancer are associated with mammographic densities, these associations do not account for the relationship of densities to risk of breast cancer. Nonmammographic risk factors in general have much weaker associations with risk than mammographic densities. As is summarized in Table 1, mammographic densities remain associated with risk of breast cancer after adjustment for the effects of other risk factors. However, all risk factors for breast cancer must ultimately exert their influence on risk, either directly or indirectly, through an effect on breast tissue, and it may be through an effect that is seen as radiological densities that these risk factors influence risk. Potential mechanisms for such an effect are discussed below in the section on biological plausibility.

The factors described above that are known to be associated with mammographic pattern do not account fully for the variations in pattern seen in the population. This was assessed in a study of risk factors for breast cancer in premenopausal women with different degrees of density of the breast parenchyma on mammography (86). Mammographic densities were measured using the computer-assisted method described above. The proportion of the breast occupied by mammographic den-

sities was found, after controlling for the effects of age and the Quetelet Index of obesity, to be significantly associated with plasma levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, apoprotein B, and urinary excretion of MDA. A multivariate model comprised of the Quetelet Index of obesity, alcohol consumption, apoprotein B, parity, daily MDA excretion, and the skinfolds thickness sum accounted for 36% of the variation in breast density. Studies are in progress to identify factors, including diet, endogenous hormones, and inheritance, that might account for the large proportion of the variance in mammographic density in the population that is presently unexplained.

#### **Biological Plausibility of the Association of Mammographic Densities with Breast Cancer Risk**

We consider here the biological plausibility of mammographic densities as a risk factor for breast cancer by first describing the tissue features of the breast that are associated with mammographic densities and then the manner in which these features might be related to risk of breast cancer. Emphasis is given in these sections to the relationship between epithelium, stroma, and fat, because variations in these tissues are responsible for variations in mammographic densities.

**Histological Basis for Mammographic Densities.** The relationship between histological and radiological features of the breast has been examined in several studies whose principal features and findings are summarized in Table 3. These studies are grouped according to the approach adopted by them. Some

examined the relationship between histological and radiological findings in whole-breast sections from mastectomy specimens. Others examined the histological features of excised breast tissue and related these to the radiological features of the entire breast from which the tissue had been removed. One study estimated the risk of histological lesions of various types developing in subjects according to the radiological features of the mammogram. Only two of the studies included in Table 3 used quantitative methods to classify mammographic density. The others used Wolfe's classification or variants thereof.

Fisher *et al.* (104) examined histological sections from mastectomy specimens from patients treated for breast cancer or fibrocystic disease. The areas examined were selected according to their radiological characteristics on specimen mammography and classified using Wolfe's nomenclature. No association was found between proliferative fibrocystic disease and any mammographic category. However areas of the breast that were radiologically dense on mammography were more likely to contain fibrous tissue ("mazoplasia") than were radiolucent areas.

The study of Bartow *et al.* (105) was based on whole-breast sections obtained from *s.c.* mastectomies performed at forensic autopsy. In contrast to the study of Fisher, the material studied was not selected for the presence of clinical breast disease. Bartow *et al.* (105) found that marked epithelial hyperplasia and lobular microcalcification were at all ages more frequent in subjects with the P2 and DY patterns than the P1 or N1 pattern, and that increasing density in the mammogram was associated histologically with dense fibrous tissue.

Each of the three cross-sectional studies in which the histological findings in breast biopsies were examined in association with radiological classification of the whole breast found that increasing radiological density was associated with epithelial proliferation (106–108). Two commented on the stroma and found that the DY mammographic pattern was associated with stromal fibrosis (106, 108).

The histological features of the breast associated with mammographic pattern have been examined in four cohort studies. Bland *et al.* (109) found in the population of one BCDDP center that fibrocystic disease, both proliferative and nonproliferative, was more frequent in women with the P2 and DY mammographic patterns. Moskowitz *et al.* (16), also studying a BCDDP population, found no association between any histological feature and mammographic pattern. However, that report contains no mention of review of the pathology of biopsy material. Arthur *et al.* (110) found no association between epithelial hyperplasia and Wolfe's patterns in women attending a breast screening center, but the high prevalence of the DY pattern in the population studied (53% compared with 11% in the BCDDP) may indicate radiological misclassification or an unusual population.

The risks of benign breast disease of various types developing in women with different mammographic characteristics were estimated in one study (111). Women with parenchymal densities occupying >75% of the breast area had a RR (estimated by the odds ratio calculated with reference to women with no breast densities) of 9.7 (95% CI, 1.8–54.0) for developing carcinoma *in situ* or atypical hyperplasia and a RR of 12.2 (95% CI, 3.0–50.1) for developing hyperplasia without atypia. This study also showed that increasing density in the mammogram was associated with increasing collagen and decreasing fat in the stroma of breast tissue on biopsy.

One study (112) compared the cytological features of cells in fluid obtained by nipple aspiration with the radiological characteristics of the breast and found that atypical cells occur

four times more frequently in women with marked breast density than in those with less density, a result that was statistically significant after adjustment for body mass index.

In summary, all but one of the nine studies based on histology shown in Table 3 reported an association between mammographic density and proliferation of either stroma or epithelium, the two types of tissue in the breast with X-ray attenuation characteristics that might give rise to mammographic densities. All nine studies report on the relationship between mammographic features and the appearance of the epithelium, and six of the nine found epithelial proliferation, with or without atypia, to be associated with radiological densities, and a further study found cytological atypia associated with densities. All of the six studies that reported specifically on the stroma described an association between stromal fibrosis and mammographic densities.

Of the tissues present in the breast with characteristics that might cause radiological density (*i.e.*, epithelium or stroma), stroma is present in much larger quantities than epithelium and seems likely to account for most radiological densities. A classification of the amounts of epithelium, fat, and collagen in breast tissue obtained by biopsy showed that epithelium comprised an average of 5% of the biopsied tissue, and fat or collagen comprised the remaining 95% (111). The proportions of fat and collagen were related inversely to each other, and an increasing proportion of collagen in the biopsy was associated with increasing radiological density. Direct sampling and histological examination of radiologically dense breast tissue has shown fibrosis in the tissue sampled.

**Potential Biological Mechanisms.** In a framework adapted from a general model of carcinogenesis described by Shigenaga and Ames (113), we have proposed that the risk of breast cancer associated with mammographically dense breast tissue is due to the combined effects of two processes: cell proliferation (mitogenesis); and damage to the DNA of dividing cells (mutagenesis; Ref. 114). We propose that mammographically dense breast tissue reflects proliferation of the breast epithelium and stroma, in response to growth factors induced by circulating levels of sex hormones (mitogenesis). Other factors associated with mammographic densities, such as parity, the menopause, and diet, may influence densities by modulating one or more of these processes.

Although the mechanisms responsible for cell proliferation associated with mammographic densities have not yet been identified, it is likely that they are related to the processes that control cell division in the breast in general. There is a large body of biological data describing interactions between breast stroma and epithelium that potentially could account for both the tissue proliferation that is responsible for radiologically dense breast tissue and the associated risk of developing breast cancer. Interactions between the breast epithelium and stroma, which communicate by means of paracrine growth factors, are important for the embryogenesis and for the normal maturation and development of the mammary gland (115–117). The effects of steroid hormones on the development and maturation of the mammary gland are mediated, at least in part, through interactions between stroma and epithelium (115).

The evidence that the tissue responsible for mammographic densities is hormonally responsive comes from the consistent associations found with age, the menopause, and from the observed effects of exogenous hormones on the radiology of the breast referred to above (78). Few studies to date have examined the relationship of breast density to levels of endogenous hormones, but one study found women with the N1



and P1 patterns to have higher levels of estrogen and prolactin and lower levels of progesterone than women with the P2 and DY patterns (118). We have proposed that the stromal proliferation that contributes to mammographically dense breast tissue may indicate the activity of growth factors operating on the stroma, under the influence of female sex hormones, and either directly or indirectly influencing the epithelium as well (3, 111).

There is presently less extensive evidence for the component of the model concerned with mutagenesis and is limited to observations that mutagenic products of lipid peroxidation are associated both with risk of breast cancer and with mammographic densities.

Dietary fatty acids can be readily oxidized, leading to the production of reactive oxygen species that can then oxidize DNA bases, and this process is thought to be involved in the development of cancer (113, 119). Lipid peroxides and their products can cause damage to membrane-bound enzymes and other macromolecules, including DNA (120). MDA, resulting from the oxidation of polyunsaturated fatty acids (121), is considered the major mutagenic and carcinogenic product of lipid peroxidation (122–124). MDA appears to be an indicator of the rate of lipid peroxidation in the diet or tissues (125, 126). MDA-DNA adducts have been proposed as markers of DNA damage resulting from endogenous oxidative processes (120, 127).

We have now reported two studies showing that urinary MDA excretion is positively related to the amount of breast density in premenopausal women (86, 128), suggesting that lipid peroxidation is also associated with breast tissue at increased risk for breast cancer. Other evidence also suggests that oxidative DNA damage is related to breast cancer. Levels of MDA-DNA adducts were significantly higher in the normal breast tissue of cancer patients than in the breast tissue of controls without cancer, independent of age, smoking status, and body mass index (127). The DNA adduct, 8-hydroxy-2-deoxyguanosine, was significantly greater in tissue from subjects with malignant breast tumors than in benign tumors or tissue from reduction mammoplasty (129, 130). Dietary antioxidants, including vitamins E, A, and carotenoids, reduce the extent of lipid peroxidation, and this may be the mechanism underlying the epidemiological data showing that fruits and vegetables protect against breast cancer (131).

The relative importance of the processes of mitogenesis and mutagenesis in influencing mammographic densities and breast cancer risk remains to be determined. However, these processes are not distinct. Influences in the model described in the context of mitogenesis can influence mutagenesis and *vice versa*. For example, estradiol can influence lipid peroxidation (132). Lipid peroxidation, by causing cell death may increase cell proliferation, and increased cell proliferation can increase lipid peroxidation (133).

### Summary and Conclusions

Mammographic densities, when classified quantitatively, have consistently been found to be strongly associated with risk of breast cancer and, as shown by several direct comparisons of the two approaches, create larger gradients in risk of breast cancer than does Wolfe's classification. The risk of breast cancer associated with mammographic densities is similar in conventional case-control studies and in studies nested within cohorts, persists over long periods of time, and cannot be explained by the masking of cancer by radiologically dense breast tissue.

Although mammographic densities are associated with several other risk factors for breast cancer, the influence of density on risk persists after adjustment for these factors. The estimates of the RR of breast cancer risk associated with mammographic density are substantial and stronger than those associated with any other nongenetic risk factor for breast cancer except age. Mammographic densities are common in the population, and estimates of attributable risk from two large case-control studies nested in cohorts show that 8–15% of cases may be attributable to density in >75% of the breast area and 28–33% of cases to density in >50% of the breast.

The histological feature in the breast that appears to be most responsible for densities is stromal fibrosis. A relationship between stromal fibrosis and risk of breast cancer is biologically plausible and may be explained by the known actions of a variety of growth factors that are thought to play a role in a number of aspects of breast development and carcinogenesis. Further research is needed to determine whether differences in the activity of growth factors in breast tissue can be found in association with radiological and other risk factors for breast cancer. Research is also needed to identify the dietary and hormonal factors that influence mammographic density and to determine whether density is an inherited characteristic.

Because breast cancer develops in a large number of women who do not have radiological changes indicating increased risk, it does not seem appropriate to use mammographic densities to select women for mammographic screening. However, because mammographic densities are associated with an increased risk of breast cancer and affect the ease with which breast cancer can be detected radiologically, the radiological characteristics of the breast might be used to determine the length of the interval between screening examinations.

Mammographic densities differ from most other risk factors for breast cancer in being present in the tissue from which cancer arises, in the strength of their association with risk, in being present in a substantial proportion of cases of breast cancer and, as shown by the effects of interventions with hormones and diet, in being capable of change. For the immediate future, mammographic densities may be most useful as a means of investigating the etiology of breast cancer and of testing hypotheses about potential preventive strategies (134).

### Appendix

**Calculation of Attributable Risk.** The attributable risks of breast cancer associated with mammographic densities of different extents were calculated using the formula: Attributable risk =  $(RR - 1)P_c/RR$ , where  $RR$  is the RR of breast cancer associated with a given category of mammographic density and  $P_c$  is the prevalence of that category in cases (135).

Attributable risks from Byrne *et al.* (23) are quoted from their report. The data used in the calculation of attributable risk from the report of Boyd *et al.* (51) are summarized in Table A1.

Table A1 Attributable risks

Density category	Prevalence of category in cases	RR	Attributable risk
>75%	19%	5.3	15%
>50%	44%	3.4	33%
0%	8%	1.0	Referent

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