Wolfe's Parenchymal Pattern and Percentage of the Breast with Mammographic Densities: Redundant or Complementary Classifications?

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Abstract

Mammographic breast densities are one of the strongest breast cancer risk factors. The two most frequently used classifications of breast densities are Wolfe's parenchymal pattern and the percentage of the breast with densities. In this analysis, associations of these two classifications with breast cancer risk were compared, and the dose response curve of risk with densities was examined. Three case-control studies were combined totaling 1060 cases with newly diagnosed breast cancer and 2352 controls. A single observer had assessed parenchymal pattern and percent density without any information on subjects. Relative risks (RRs) were estimated with logistic regression and spline functions adjusting for age and body weight. The two classifications were strongly correlated ($r = 0.81$, $P = 0.0001$). Breast cancer risk increased progressively with percent density reaching a 5–6-fold increase for women with 85% or more of the breast with densities compared with women with no density. In contrast, women with P2 or DY patterns had only a 2–3-fold increase in risk compared with women with N1 pattern. More importantly, among women with P2 or DY, RR varied substantially with percent density, whereas, among women with a given percent density, RR varied little with parenchymal pattern. Comparisons of multivariate models reveal that in the presence of parenchymal pattern, inclusion of percent density in the model improved the prediction of breast cancer risk ($\chi^2 = 35.5$, $P = 0.0082$) but not the opposite ($\chi^2 = 1.1$, $P = 0.7662$). These findings show that the percentage of the breast with densities provide more information on breast cancer risk than Wolfe's parenchymal patterns and that, once percent breast density is taken into account, no more information on breast cancer risk is given by assessing parenchymal pattern.

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Introduction

The mammographic image of the female breast is characterized by dense areas occupied by epithelial and stromal tissue and translucent zones occupied by fat. Breast densities vary from one woman to another, and these variations are related to the risk of developing breast cancer. Several approaches have been used to classify/measure breast densities, but there is still no consensus as to the relative value of each approach (1).

Measurements of breast densities can be grouped in two broad categories. First, a classification can attempt to integrate and summarize in four or five categories a variety of mammographic features, including the extent of dense breast tissue on the mammogram, as well as characteristics of densities such as their shape and texture. An early classification of breast densities proposed by Wolfe illustrates this approach (2, 3). Wolfe defined four parenchymal patterns not only on the basis of extent of densities but also on the basis of characteristics of densities seen (prominent ducts and dysplasia). This classification was repeatedly found to be associated with breast cancer risk (4–30). Several other classifications of this type have been used and most of them have some similarities with Wolfe's parenchymal patterns, including the classifications proposed by the American College of Radiology (BI-RADS[2]) (31) and by Tabar (32).

Second, a classification of breast densities may attempt to assess separately the extent of fibroglandular breast densities on the mammogram without taking into account the various types of fibroglandular densities seen (21, 22, 24, 25, 27, 28, 30, 33–35). Extent of densities has usually been expressed as the percentage of the breast showing densities. Risk of breast cancer was repeatedly seen to increase progressively with increasing extent of densities on the mammogram (22, 24, 25, 27, 28, 30, 33–35).

Some authors have examined simultaneously Wolfe's parenchymal pattern and percent density in terms of their association with breast cancer risk (25, 27, 30). These studies have found that variations in breast density were associated with substantial variations of breast cancer risk within P2 and DY parenchymal patterns. One study observed that risk also varied according to parenchymal pattern within categories of percent density (30). Thus, currently, it is still unclear whether these two classifications of breast density provide overlapping or complementary information on breast cancer risk and both classifications continue to be used.

In this analysis, Wolfe's parenchymal pattern and percent density are compared with respect to their relation to breast cancer risk to evaluate the additional contribution of each

[2] The abbreviations used are: BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; RR, relative risk.

Table 1 Attributes of combined case-control studies

	References of studies		
	Ref. 15	Ref. 18	Ref. 22
Cases (*n*)	408	362	290
Controls (*n*)	1021	686	645
Period of selection	1972–1978	1978–1979	1982–1984
Age range (years)	20–95	24–85	40–62
Site	Boston	Boston and Livingston, NJ	Quebec City, Quebec Canada

classification to information on risk of breast cancer. The specific objectives of the analysis are (*a*) to examine the correlation between the two classifications, (*b*) to assess the effects of percent density within N1, P1, P2, and DY patterns, as well as the effects of parenchymal pattern at a given level of percent density, and (*c*) to examine the shape of the dose response relation of percent density to risk.

Materials and Methods

This is a reanalysis of existing data. The cases and controls have been gathered from three different studies (Refs. 15, 18, 22; Table 1). See Refs. 15, 18, 22 for details concerning each study. In brief, the 1060 cases were women with newly diagnosed unilateral breast cancer confirmed histologically. The 2352 controls were women without breast cancer who had had mammograms as part of a routine or screening examination.

In each of the three combined studies, mammograms showing the lateral (or mediolateral) and craniocaudal views of the unaffected breast of cases and of a randomly chosen breast of controls had been reviewed. This review had been made by one of the authors (J. B.) who was trained in the assessment of mammographic features. The percentage of the breast showing epithelial or stromal densities had been estimated visually using category scores (score 0 for 0%, score 5 for 1–9%, score 10 for 10–14%, . . . , score 90 for 90–94%, and score 95 for 95–100% of the breast with densities). Wolfe's classification had been assessed using the original four categories as follows (2): N1, parenchyma composed primarily of fat with at most small amounts of dysplasia. No ducts visible; P1, parenchyma chiefly fat with prominent ducts in anterior portion up to one-fourth of volume of breast. Also, may be a thin band of ducts extending into a quadrant; P2, severe involvement with prominent duct pattern occupying more than one-fourth of volume of breast; and DY, severe involvement with dysplasia. Often obscures an underlying prominent duct pattern.

The assessment of parenchymal pattern and percent density was done without knowledge of case-control status and without any interview data or other information on women. Intraobserver agreement for this reviewer has been shown to be good (15, 36). For parenchymal pattern assessment, the weighted κ ranged from 0.82 to 0.83, and the Pearson correlation between repeated evaluations for the assessment of the percent density ranged from 0.89 to 0.92.

Analysis was made on a total of 1060 cases and 2352 controls. When otherwise, the number of subjects is indicated in context. The correlation between five categories of percent density (0, 1–24, 25–49, 50–74, and ≥75%) and the four categories of parenchymal patterns was evaluated by calculating the Spearman correlation coefficient. All RRs and their 95% CIs were obtained by logistic regression for each of the above categories of breast densities and adjusted for age and body weight, which were entered in the model as continuous variables. The lack of information concerning body weight in one (15) of the three original studies required the addition of an indicator variable in the models, which was coded 0 if weight was known and 1 otherwise. In counterpart, the continuous variable represented by body weight was assigned the value 0 when the information on weight was missing.

The curve representing the relation of breast densities to breast cancer risk were obtained by cubic-smoothing splines (37). To obtain this curve, mutually comparable RRs were first estimated by unconditional logistic regression for each of 18 categories of percent density (1–9, 10–14, . . . , 80–84, 85–89, or 90–100%) using women with no density as reference. RRs were adjusted for age and also for body weight using the approach mentioned above. Then, adjusted RRs were entered in a weighted cubic-smoothing spline regression function using the inverse of the variance of RRs as weights. The 95% CIs were calculated for expected RRs obtained by smoothing spline regression. Curves representing the combined effect of percent density and parenchymal pattern were estimated using the same approach, but the reference group was women with no density and a N1 parenchymal pattern (details about the modeling is provided in the legend of each figure).

The Wald χ^2 tests were used to evaluate the additional contributions of each classification to information on breast cancer risk. For the first test, the complete model, which contained indicator variables for 18 categories of the percent density (1–9, 10–14, . . . , 80–84, 85–89, and 90–100%), indicator variables for parenchymal patterns (P1, P2, and DY), age, and body weight, was compared with a model that included only parenchymal patterns, age, and body weight. For the second test, the complete model was compared with another model containing the 18 categories of the percent density, age, and body weight.

Additional adjustments for other factors (age at first birth, parity, family history of breast cancer, history of breast biopsy, use of oral contraceptives, use of hormone replacement therapy, and study population) had little or no effect on the strength or shape of relations of mammographic features to risk and therefore were not added in the models. All statistical analyses were carried out using the Statistical Analysis System (SAS Institute, Inc., Cary, NC) and S-PLUS (MathSoft, Inc., Seattle, WA) software systems.

Results

Wolfe's parenchymal pattern classification is strongly related to the percentage of the breast with densities demonstrating the substantial overlap between the two classification systems (Table 2). For instance, among the controls, 71.5% of women with N1 pattern had no density, 74.9% of women with P1 pattern had 1–24% densities, 86.2% of women with P2 pattern had 25–74% densities, and 74.0% of women with DY had ≥50% densities.

Table 2 Distribution of breast cancer cases and controls and relative risks[a] according to parenchymal pattern by percentage of the breast showing densities[b]

Percent density (%)	Parenchymal pattern												Total		
	N1			P1			P2			DY					
	Cases/ Controls	RR	95% CI	Cases/ Controls	RR	95% CI	Cases/ Controls	RR	95% CI	Cases/ Controls	RR	95% CI	Cases/Controls	RR	95% CI
0	67/191	1.0[c]											67/191	1.0[d]	
1–24	29/76	1.2	0.7–2.1	240/551	1.4	1.0–2.0				4/22	0.8	0.3–2.5	273/649	1.4	1.0–1.9
25–49				75/185	1.5	1.0–2.2	217/378	2.5	1.7–3.5	33/97	1.8	1.1–3.0	325/660	2.1	1.5–2.9
50–74							187/378	2.7	1.8–3.8	65/191	2.5	1.6–3.9	252/569	2.6	1.8–3.7
≥75							74/121	4.1	2.7–6.4	65/148	4.4	2.8–6.9	139/269	4.2	2.8–6.3
Total	96/267	1.0[e]		315/736	1.3	1.0–1.8	478/877	2.5	1.9–3.3	167/458	2.4	1.7–3.3	1056/2338		

[a] All RRs are adjusted for age and body weight (see "Materials and Methods"). RRs were estimated from three separate models: one for RRs in the right margin, one for RRs in the bottom margin, and one for RRs in the body of the table.
[b] The cells including less than or equal to one case or control were removed.
[c] Reference group for RRs in the body of the table (excluding the right and bottom margins).
[d] Reference group for RRs in the right margin.
[e] Reference group for RRs in the bottom margin.

A correlation coefficient of 0.81 ($P = 0.0001$) was found between the two classifications.

Taken separately, percent density and Wolfe's parenchymal patterns were both associated with breast cancer risk (Table 2). RR increased progressively with percent density from 1.0 for women with no breast density to 4.2 (95% CI = 2.8–6.3) for those with ≥75% of the breast with densities. Moreover, we observed for women with P1, P2, or DY patterns RRs of 1.3 (95% CI = 1.0–1.8), 2.5 (95% CI = 1.9–3.3), and 2.4 (95% CI = 1.7–3.3), respectively, when compared with a RR of 1.0 for women with N1 pattern.

Examination of the joint association of the two classifications with breast cancer risk reveals that RR varied more with percent density than with parenchymal pattern (Table 2). Among women with a given parenchymal pattern, RR tended to increase with the percentage of the breast with densities but not the opposite. For instance, the RRs for women with P2 pattern rose from 2.5 (95% CI = 1.7–3.5) to 4.1 (95% CI = 2.7–6.4) depending on the amount of breast densities compared with women with N1 pattern and no breast density. Similarly, we observed for women with DY pattern an increase in RR from 0.8 (95% CI = 0.3–2.5) to 4.4 (95% CI = 2.8–6.9) with increasing percent density. In contrast, in any given category of percent density, RRs varied little with parenchymal pattern.

The smoothing spline curve revealed that breast cancer risk increased strongly and progressively with percent density (Fig. 1). According to these data, the increase in RR was more pronounced in the ranges from 0 to 39 and 70 to 100% of the breast with densities, but RR seemed stable between 40–69%. The spline curve suggested that women with >85% of the breast with densities have a >5-fold increase in risk compared with women with no density of the same age and body weight.

Fig. 2 shows trends in RR of breast cancer with breast densities for women with different parenchymal patterns. At any given level of breast density, estimated RRs appear similar whether women had the N1 or P1 pattern and whether women had the P2 or DY pattern. In contrast, among women with either a P2 or DY pattern, RR varies substantially. For instance, compared with women with no breast density, those with a P2 or DY pattern can have either a <2-fold increase in RR or a >5-fold increase according to whether the percentage of the breast with densities is 25 or 85%.

When parenchymal pattern was given, percent density improved the prediction of breast cancer risk but not the opposite. Comparing a complete logistic regression model (percent density, parenchymal patterns, age, and body weight as described in "Materials and Methods") to a model that included only parenchymal patterns, age, and body weight, percent density improved substantially the prediction of breast cancer risk ($\chi^2 = 35.5$, $P = 0.0082$). In contrast, parenchymal pattern added little to the prediction of breast cancer risk once percent density was taken into account ($\chi^2 = 1.1$, $P = 0.7662$). This result was obtained by comparing the complete model as previously defined to another model containing only percent density, age, and body weight.

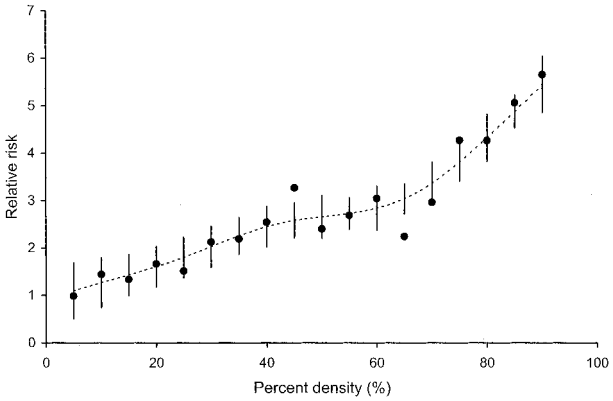

Fig. 1. RR of breast cancer by percentage of the breast showing mammographic densities. Each ● represents a RR for women in 18 categories of percent density (1–9, 10–14, . . . , 80–84, 85–89, and 90–100%) compared with women with no density. RRs were obtained by logistic regression adjusting for age and body weight. The *dotted curve* is a weighted cubic smoothing spline function that models the adjusted RRs. The *vertical lines* represent the 95% CIs around each RR predicted by the spline function.

Discussion

In these data, Wolfe's parenchymal pattern and the percentage of the breast with densities were each related to breast cancer risk. However, the two classifications are not independent but instead substantially overlap and are highly correlated. The dose response curves revealed strong increasing RR of breast cancer with increasing breast densities for women with P2 or DY pattern, as well as for all women. In our data, the parenchymal pattern classification provided little additional informa-

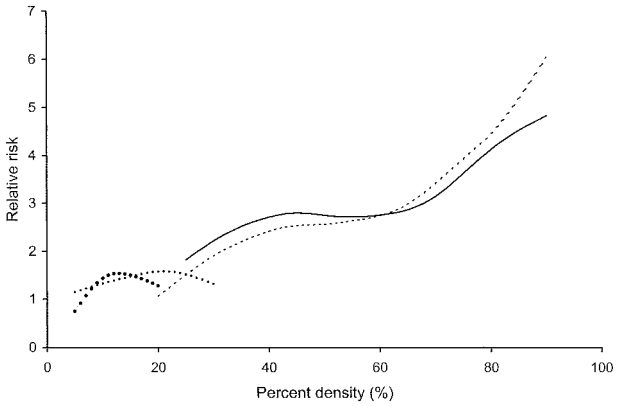

Fig. 2. RR of breast cancer by percentage of the breast showing densities for women with N1 pattern (•••), P1 pattern (···), P2 pattern (—), and DY pattern (---). To obtain these curves, subjects were cross-classified according to both percent density categories (0, 1–9, 10–14, . . . , 80–84, 85–89, and 90–100%) and parenchymal pattern (N1, P1, P2, and DY). Groups with ≤5 subjects (cases plus controls) were removed leaving 1053 cases and 2326 controls in the analysis. Indicator variables for the remaining percent density/parenchymal pattern categories were created. RRs were then estimated simultaneously by logistic regression for all categories relative to women with no density and a N1 pattern adjusting for age and body weight. Curves of RRs by percent density are assessed for each parenchymal pattern separately by use of a weighted cubic-smoothing spline function.

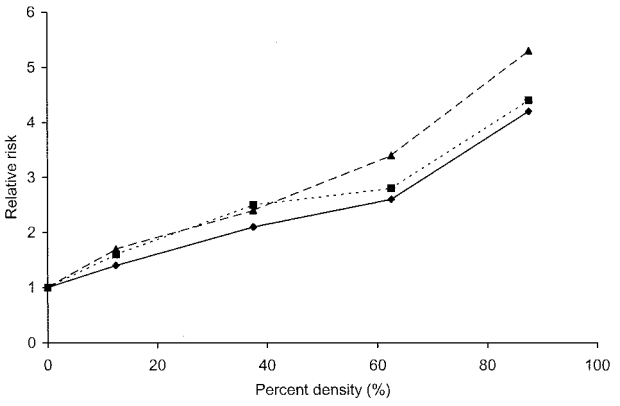

Fig. 3. RR of breast cancer by percentage of the breast showing densities for women in the present (♦), Byrne *et al.* (Ref. 27; ■), and Boyd *et al.* (Ref. 33; ▲) studies. Each symbol represents the RR for women at the middle point of four categories of percent density (1–24, 25–49, 50–74, and ≥75%) compared with women with no density. Linear interpolations between RRs have been drawn to simulate dose response relationships. Only studies that classified percent density using the same categories were considered to facilitate comparison of dose response relations. To include Boyd *et al.* (33) study in this analysis, an average of RRs (1.2 and 2.2) for the categories 1–9 and 10–24%, respectively, has been estimated using the inverse of the variance of RRs as weights.

tion on risk of breast cancer when percentage of the breast with densities was given.

Three other studies compared Wolfe's parenchymal pattern classification and relatively wide categories of percent density in terms of their association with breast cancer risk (25, 27, 30). Among women with P2 pattern, the RR of breast cancer increased with increasing breast densities in these three studies. Increasing RR with increasing density was also observed among women with the DY pattern in two of the analyses (25, 27). By contrast, at a given level of breast density, Byrne *et al.* (27) observed little or no variation in RR of breast cancer whether women had a P2 or DY pattern. However, Thomas *et al.* (30) have found that RRs increased from a P1 to a P2 pattern for women with 26.8–50.1% densities and from a P2 to a DY pattern for women with >70.2% densities. The remaining effect of parenchymal pattern may be attributable to variability of breast density within these relatively broad categories of percent density. The study reported by Saftlas *et al.* (25) included fewer subjects and presented results only for broad categories of breast density, which impeded examination of this issue in this article.

Because the association of Wolfe's parenchymal pattern to risk appears to be largely explained by percent density, the same may be true for the other classifications that use the same approach as Wolfe. In particular, the BI-RADS classification and the Tabar classification of mammographic breast features should also be compared with percent density in terms of their association to breast cancer risk (31, 32). This comparison would clarify whether the BI-RADS or the Tabar classifications contribute supplementary information on a woman's risk of breast cancer beyond that already obtained through assessment of percent density.

Previous studies provide some information on the dose response curve of increasing risk with increasing breast density, but these studies used only broad categories of percent density. In Fig. 3, we show our findings and those of Boyd *et al.* (33) and Byrne *et al.* (27). These studies were selected because they presented results using categorization of breast density similar to the ones we used. Boyd *et al.* (33) observed a steady increase in RR with increase in density (Fig. 3). However, in our study as well as that of Byrne *et al.* (27), RR was only slightly higher in women with 50–74 percent density compared with those with 25–49% and CIs overlapped substantially. When we used a finer categorization of density, increase in RR showed almost a plateau for values of breast density around 40 to 69 percent. Thus, our data and those of Byrne *et al.* (27) suggest that within this range of values, breast density may have a more limited ability to discriminate between women at different levels of risk of breast cancer. In our controls, about one-quarter of women were within this 40–69 percent density range. Although the plateau could be a chance finding in the two datasets, in our experience, relying on one or two two-dimensional views to assess extent of fibroglandular tissue in a three-dimensional organ poses greater challenges in this range than at lower or higher values of percent density. The possibility that the observed plateau in RR could be attributable to limitations of the current approaches used to measure extent of fibroglandular tissue in these women should be considered. If this hypothesis is correct, development of methods to assess densities taking into account the volume of the breast may result in a different shape of the dose response curve.

Although the distinction between N1 and P1 or between P2 and DY does not appear to be helpful in discriminating between women at high and low risk of breast cancer, some mammographic features other than simply percent density may improve characterization of a woman's risk of breast cancer. For instance, at a given percent density, Boyd *et al.* (14) have observed a higher risk of breast cancer for women showing dysplasia as compared with women showing ductal prominence. Moreover, Brisson *et al.* (15, 18, 22) have observed that women with nodular densities are more at risk of breast cancer than women with homogeneous densities at any given percent density. Finally, for a given percent density or Wolfe's parenchymal pattern, Thomas *et al.* (30) have noted a higher risk of breast cancer for women with calcifications as compared with

women with no calcification, although Byrne *et al.* (27) have not observed such effects. These observations suggest that mammograms might provide more information on breast cancer risk than what is already provided by measuring simply percent density.

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Wolfe's Parenchymal Pattern and Percentage of the Breast with Mammographic Densities: Redundant or Complementary Classifications?

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