Measurements of Breast Density: No Ratio for a Ratio

**Gerco Haars, Paulus A.H. van Noord, Carla H. van Gils
Diederick E. Grobbee, and Petra H.M. Peeters**

Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

Abstract

Breast density, as visible on mammograms, is generally assessed as the occupied percentage of the breast and is a risk factor for breast cancer. Various studies have looked into the causation and alteration of relative density but the relation of a determinant with a relative measure does not allow a direct etiologic interpretation. It was our goal to compare the effects of known determinants on relative density and the absolute amounts of dense and nondense tissues. We measured the absolute and relative densities in a population of 418 postmenopausal women participating in a breast cancer screening program. The occupied surface area was calculated after manually tracing the contours of the tissues on digitized mammograms. Information on determinants was available through physical examination and questionnaires. Data were analyzed by multivariate linear regression. Age and parity were found to decrease the amount of dense tissue and the ages at menarche and menopause were found to increase it (R^2 = 13%). The amount of nondense tissue was increased by higher body mass index (BMI), age, and parity (R^2 = 43%). Relative density was affected by a combination of these factors (R^2 = 29%) with directionalities of effects that are comparable to those of dense tissue. However, the magnitudes of these effects were the resultant of the effects on dense and nondense tissues. The influence of BMI on relative density was completely due to an effect on nondense tissue. Although relative density is a relevant prognostic factor, inferences about the etiology of breast density should be made on the basis of absolute measures. (Cancer Epidemiol Biomarkers Prev 2005; 1411(11):2634–40)

Introduction

The mammographic appearance of the female breast, or parenchymal pattern, is determined by the amounts of radiodense and nondense tissues relative to each other. The radiodense tissue, which appears white on X-ray mammograms, has been shown to consist of stromal and epithelial tissues and thereby is assumed to reflect the target tissue for breast cancer (1, 2).

Wolfe (3) was the first to develop a classification of parenchymal patterns consisting of four categories: N, P1, P2, and DY. This classification was based on the overall appearance of the breast combined with the estimated percentage of the breast occupied by dense tissue with N for normal breasts with little or no dense tissue, P1 and P2 for intermediate states, and DY for a breast with predominant dense parenchymal tissue, which was referred to as dysplasia. Other classifications were subsequently developed, all using a ratio or percentage to classify the amount of dense tissue (4, 5) and with current technology the relative density is often measured on a continuous scale (6, 7).

High relative amounts of dense tissue have been consistently found to be related to elevated breast cancer risk by studies that used one or more categorical or continuous approaches (8-10). The currently available continuous measurement of density has been found to be the most informative in this regard (11, 12). Inspired by the established relation between relative density and breast cancer risk, many studies have tried to identify factors that cause and/or influence the parenchymal pattern. In these studies, factors including age, BMI, parity, passing through the menopause, and smoking have been shown to decrease the relative density. Factors including a late age at first birth, use of hormone therapy, and alcohol consumption have been found to increase the relative density (13-21).

Although the modern, continuous techniques determine the absolute amounts of total, dense, and nondense tissues on the mammogram, investigators usually still work with the ratio of dense over total tissue, or in other words, the relative amount of dense tissue (15-18). The absolute amount of density was used in only a small number of studies, and of these, only the studies by Boyd et al. and Heng et al. made an inference about the difference in effects on absolute and relative densities (13, 19-21).

The consequence of a relative measure is that for a given amount of dense tissue in a small breast (i.e., surrounded by little fat or other nondense tissue) compared with a similar amount in a larger breast, a higher relative amount will be measured. This is a general methodologic issue with ratios because they always combine the effects of the constituting measures (22). The relative density therefore does not convey any information about the absolute amount of target tissue whereas, as hypothesized by Albanes and Winick (23) and Trichopoulos and Lipman (24), the actual amount of target cells may be a straightforward and important risk factor for cancer, although this was never conclusively shown.

The use of a ratio or percentage score thus only shows the effect of a determinant on the degree of density but obscures whether a determinant affects the absolute amount of dense tissue, the absolute amount of nondense tissue, or both. The relative density may still be a useful and easily applicable prognostic factor as an indicator of breast cancer risk but would not seem to be the measure of choice in etiologic research into the causes and determinants of breast density. We set out to determine which of the established determinants of relative measurements of density indeed influence the absolute amount of dense tissue. The implications of the findings for breast cancer research are discussed.

Materials and Methods

Subjects. The Diagnostisch Onderzoek Mammacarcinoom (DOM) project is a population based breast cancer screening

Received 11/10/04; revised 9/4/05; accepted 9/13/05.

Grant support: World Cancer Research Fund grant 1999/69 (P.A.H. van Noord).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Gerco Haars, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Stratenum, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. Phone: 31-30-253-8097; Fax: 31-30-253-9028. E-mail: G.Haars@umcutrecht.nl

doi:10.1158/1055-9965.EPI-04-0824

program in Utrecht, the Netherlands (25). It was initiated in 1974 and up until 1986, the screening progressed in four sequential subcohorts, which were all of an experimental nature. At that time, 55,519 women had been recruited into the DOM study cohort. Apart from having their mammograms taken, all participants had anthropometric information collected by trained technicians and completed questionnaires on demographics, family-related information, history of disease, and reproductive history. To ensure uniformity and completeness of the follow-up, we chose only to include participants from the first subcohort (known as DOM-I, recruitment: 1974-1981) that had attended all screening rounds. For the final population for this study, we took a random sample of 500 women from which we excluded participants that were not definitively postmenopausal (82 women). This resulted in a population of 418 postmenopausal women for whom, at random, the right (n = 209) or left (n = 209) craniocaudal xero-print mammogram from the first screening round was retrieved. The first screening round was selected because most of the relevant other data were supplied at this point and because it again ensured the best uniformity. Xero-print mammograms preceded the currently applied X-ray film mammograms and differs by being a positive image. Although the contrast of current-film mammograms is higher than that of the older xero-print mammograms, the latter show a great deal of detail and can easily be evaluated on the amount of radiodense tissue in a similar way as film mammograms are currently evaluated.

Measurement and Baseline Data. All xeromammograms were digitized at 100 dpi using a flatbed scanner (HP5300C Scanjet, Hewlett Packard, Palo Alto, CA). Digitized images were evaluated on the total breast size and amount of dense tissue by a trained observer (G.H.) who manually traced the edges of the areas by setting mouse clicks (Fig. 1). The surface of the selected area was calculated by the program Image-Xplorer (Image Sciences Institute, University Medical Center, Utrecht, the Netherlands). The calculated amounts of pixels were transformed into square centimeters on the basis of the pixel density (100 dots per inch = 10,000 dots on 6.45 cm^2). The absolute amount of nondense tissue, which predominantly consists of fat, was calculated by subtracting the dense tissue from the total breast size. The percentage of the breast occupied by dense tissue, or relative density, was calculated by dividing the absolute amount of dense tissue by the total breast size. Intrareader reliability was determined by a 10% retest sample.

A number of characteristics known from the literature to be related to the relative amount of density or to breast cancer were examined for their relation with absolute and relative measures of breast density. These included anthropometric measures such as height, weight and BMI, lifestyle factors such as hormone therapy and smoking, and characteristics such as age, parity, and age at menopause. Data on some known determinants of breast density, such as race/ethnicity and insulin-like growth factor I levels, were not available in our cohort.

Statistical Analysis. Geometric group means of dense tissue, nondense tissue, and percent density were calculated in classes of determinants. Dichotome classes applied to all Yes/No variables, such as family history and use of hormone therapy. Parity was used as an ordinal class, truncated at >3, and continuous variables were classified into tertiles, except for BMI, which was classified according to the generally accepted classes of underweight (<20), normal weight (20 to <25), overweight (25 to <30), and obesity (≥30). A test for linear trends was done on the geometric data through ANOVA with an F test for linearity.

For use in multivariate regression analyses, the amount of dense tissue, nondense tissue, and the percentage of dense tissue were transformed to normalize the data by taking the square root. Variables for which two or more of the measures under investigation had a clear trend over the classes were then simultaneously entered in multivariate regression models. Mathematically related variables, such as weight and BMI or height, were never modeled simultaneously. The same applies to the age at examination and the combinations of the age at menopause and the time since the menopause and nulliparity (yes/no) and the number of children.

The decision on which variables to use for multivariate modeling was made on the basis of the P for trend and the magnitude of effect that was visible in the group means. In the multivariate analyses, variables were entered and removed on the basis of the combination of β's, P values, and overall model-fit in explained variance (R^2), but finally the models with the best fit were those with $P < 0.10$ and matching, relevant β's. The results of the final model were transformed back to the normal units.

Results

Participants selected had a mean age at the time of examination of 56.4 years (range, 49.2-65.8 years) and were all postmenopausal at the time of examination. General characteristics of the study population are given in Table 1.

The median breast size in this population was 123.7 cm^2 (interquartile range, 94.7-162.6 cm^2). The median area of the breast occupied by dense breast tissue was 26.4 cm^2 (interquartile range, 15.2-46.6 cm^2) and the median area of the breast occupied by nondense tissue was 87.8 cm^2 (interquartile range, 55.6-130.6 cm^2). The median percentage of dense tissue in the breast was 23.2% (interquartile range, 11.6-43.6%). Intrareader reliability, as measured by the intraclass correlation coefficient, for relative density was 93%. For

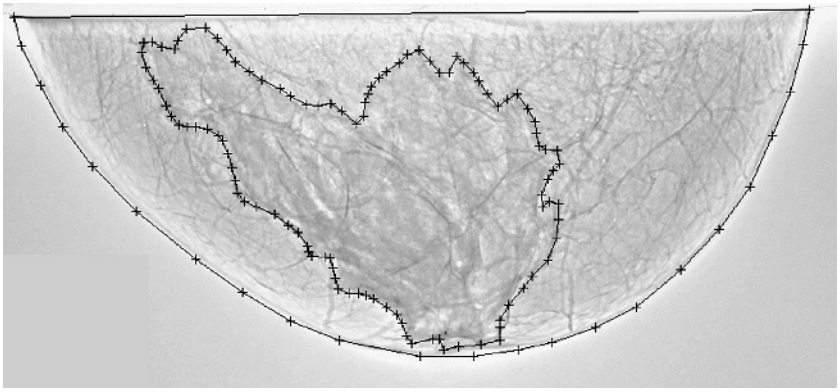

Figure 1. Manually traced contours of total breast size (*outer contour*) and dense tissue (*inner contour*) on a digitized xero-film mammogram.

Table 1. Distribution of density and/or breast cancer risk factors in study population

	Mean (SD)	Range
Age at examination, y	56.4 (4.16)	49.2-65.8
Weight, kg	67.7 (9.83)	43.5-105.0
Height, m	1.63 (0.06)	1.46-1.87
BMI, kg/m^2	25.6 (3.41)	17.8-42.8
Age at menarche,* y	13.5 (1.57)	11.0-18.3
Age at menopause,† y	49.6 (3.78)	32.0-60.0
Time since menopause,† y	7.5 (5.36)	0.1-28.5
Parity (no. children)	2.4 (1.91)	0-9
Age at first childbirth,‡ y	27.3 (4.11)	18.1-39.9
	n (proportion)	
Parous (yes)	332 (79%)	
Current oral contraceptive use (yes)	8 (2%)	
Ever used oral contraceptives (yes)	43 (10%)	
Used hormone therapy in the last 12 mo (yes)	47 (11%)	
Ever smoked (yes)	116 (28%)	
Family history of breast cancer (yes)§	26 (6%)	
	Median (interquartile range)	Range
Breast size, cm^2	123.7 (94.7-162.6)	29.1-345.3
Absolute amount dense tissue, cm^2	26.4 (15.2-46.4)	0.3-138.0
Absolute amount nondense tissue, cm^2	87.8	55.6-130.6
Percent dense	23.2	11.6-43.6

*Data available for 416 women.
† Data available for 361 women.
‡ Including only parous women; $n = 332$.
§Data available for 408 women.

absolute amount of dense tissue, this was 82% and for nondense tissue, 97%.

BMI, weight, age at the time of examination, the time since the menopause, and the number of children that a woman has had showed a positive univariate trend with the amount of dense tissue ($P < 0.10$). The age at which menopause occurred and having ever smoked showed a negative univariate trend with dense tissue ($P < 0.10$). Height and the age at menarche also showed a negative univariate trend in the group means, but with $P > 0.10$ (Table 2). The best multivariate fit for the absolute amount of dense tissue ($R^2 = 13\%$, Table 3) was obtained with a model that contained the ages at time of examination ($\beta = -1.38$ cm^2/y), occurrence of menarche ($\beta = 1.55$ cm^2/y), occurrence of the menopause ($\beta = 0.84$ cm^2/y), and the number of children ($\beta = -2.94$ cm^2/child). The other factors with a univariate relationship were not found to contribute to the multivariate model.

For nondense tissue, a positive univariate trend with $P < 0.10$ was found with the age at examination, weight, BMI, the time since the menopause, and the number of children (Table 2). A negative univariate trend in group means was found in the age at occurrence of the menarche and having ever smoked ($P < 0.10$). The age at occurrence of the menopause and height were also included in the multivariate analyses based on the involvement with the other two measures. The final multivariate model ($R^2 = 43\%$, Table 3) was composed only of BMI ($\beta = 10.08$ cm^2/kg/m^2), the age at the time of examination ($\beta = 1.74$ cm^2/y), and the number of children ($\beta = 3.81$ cm^2/child).

The relative amount of density showed a positive univariate relation ($P < 0.10$) with the age at examination, weight, BMI, the time since menopause, and the number of children (Table 2). There was a negative univariate relation ($P < 0.10$) with the ages at which menarche and menopause occurred and having ever smoked. There was also an apparent negative trend in grouped mean relative density with height, but with $P > 0.10$. The age at examination ($\beta = -1.16$ cm^2/y), BMI ($\beta = -2.12$ cm^2/kg/m^2), the age at occurrence of the menarche ($\beta = 1.00$ cm^2/y), the age at which the menopause occurred ($\beta = 0.80$ cm^2/y), and the number of children ($\beta = -2.49$ cm^2/child) together provided the best multivariate fit ($R^2 = 29\%$, Table 3).

Whereas 43% of the variance in nondense tissue is explained by BMI, age at examination, and the number of children together, a model with BMI alone already has an explained variance of 40%. Addition of the other factors therefore only raises the explained variance by 3%. In contrast, absolute breast density was not related to BMI. Yet, for the relative amount of density, a univariate regression model of BMI has an explained variance of 17%, which is only raised to 29% after addition of the four other determinants.

Table 4 lists a cross-tabulation of quartiles of the absolute amount of dense tissue by the relative density to compare these two measures. There is a one-class shift in 144 of 418 women and a two-class shift in 12 of 418, resulting in a total level of agreement of $\kappa = 0.50$ ($P < 0.000$). Women in the lowest quartile of absolute amount of density had a relative density anywhere from near 0% to 33%. This was 6% to 60% for women in the second quartile, 11% to 90% in the third quartile, and 20% to 88% in the upper quartile of absolute density.

Vice versa, the lowest quartile of relative density translated to an absolute amount of density ranging from 0.28 to 32.3 cm^2. The second and third quartiles of relative density both had a lower bound of 8.5 cm^2 with an upper bound of 65.2 cm^2 for quartile 2 and 91.5 cm^2 for quartile 3. The highest quartile of relative density had an upper bound as high as 138 cm^2 of absolute amount of dense tissue, but the lower bound of 17.9 cm^2 shows that the range in corresponding absolute amount of density of quartile 4 still overlaps the range of quartile 1.

Discussion

This study shows that the effects of determinants on the relative density are not an accurate representation of the actual relation that exists between these determinants and the dense tissue, which is considered to represent the target tissue for breast cancer. This disturbance is due to the relation that a determinant may also have with the amount of nondense tissue. As the effect on the amounts of dense and nondense tissues is measured in square centimeters and that on the relative density in percent, the magnitudes cannot be compared directly. However, in the case of age at examination and parity, the inverse relation of dense and nondense tissues intuitively leads to an effect on the relative density which is an overestimation of the direct effect on dense tissue.

We can best support this by an example. If we take the ''median woman'' with median amounts of dense (26.4 cm^2) and nondense tissues (87.8 cm^2), the relative density will be 23.1%. If we then consider a second woman who is exactly identical but 1 year older, the subsequent decrease in dense tissue of 1.38 cm^2 and increase in nondense tissue of 1.74 cm^2 will indeed decrease the relative density by ~1.16%. If we now assume that there was no effect of age on the nondense tissue, the change in relative density due to the decrease in dense tissue of 1.38 cm^2 would have only been 0.92%.

This effect is most clearly seen in BMI, which is found to influence the relative density but has no actual effect on the amount of dense tissue. Aside from the additional effect of BMI itself, the extra variable may also affect the estimates of the other variables. The relative density thus also comprises the effects on the nontarget tissue, which prevents a direct, and therefore correct, etiologic interpretation of the influences.

Table 2. Geometric means of absolute density, absolute nondensity and relative density and trend tests over groups of characteristics

	n	Absolute dense, cm^2	Absolute nondense, cm^2	Percent dense, %
Age at examination, y				
<54	139	31.3	72.0	26.1
54-58	140	22.2	80.1	18.9
>58	139	18.2	92.3	14.3
P for trend	418	<0.01	<0.01	<0.01
Weight, kg				
<63	140	26.2	53.0	29.0
63-70	143	22.6	91.3	17.6
>70	135	21.2	114.6	13.8
P for trend	418	0.06	<0.01	<0.01
Height, m				
<1.60	133	21.3	84.7	17.5
1.60-1.65	151	23.6	81.0	19.4
>1.65	134	25.2	80.2	20.8
P for trend	418	0.15	0.51	0.18
BMI, kg/m^2				
<20	12	28.3	21.7	52.0
20 to <25	187	26.6	62.0	26.4
25 to <30	171	21.6	101.1	15.8
<30	41	17.3	156.1	8.9
P for trend	418	0.07	<0.01	<0.01
Age at menarche, y				
<13	122	21.4	96.6	16.1
13-14	178	23.4	72.3	21.1
>14	116	25.5	82.8	20.5
P for trend	416	0.16	0.07	0.08
Age at menopause, y				
<49	107	19.5	83.1	16.8
49-51	139	19.9	90.9	15.8
>51	115	27.0	77.7	22.5
P for trend	361	0.01	0.42	0.04
Time since menopause, y				
<4	120	28.3	74.4	23.7
4-9	121	21.1	81.5	18.1
>9	120	17.4	98.5	13.5
P for trend	361	<0.01	<0.01	<0.01
Parous				
Yes	332	22.2	87.8	17.7
No	86	28.1	62.5	26.3
P	418	0.04	<0.01	<0.01
Age at first childbirth, y				
<25	110	20.8	92.6	16.2
25-28	111	22.6	81.7	19.1
>28	111	23.1	89.6	17.9
P for trend	332	0.42	0.70	0.50
Parity (no. children)				
0	86	28.1	62.5	26.3
1	53	26.9	82.3	21.3
2	93	28.5	77.3	23.6
3	89	20.2	92.4	15.8
>3	97	17.2	98.2	13.5
P for trend	418	<0.01	<0.01	<0.01
Current oral contraceptive use				
Yes	8	31.3	66.2	28.8
No	410	23.2	82.2	19.1
P	418	0.87	0.36	0.29
Ever used oral contraceptives				
Yes	43	28.0	78.3	23.5
No	375	22.8	82.3	18.8
P	418	0.18	0.64	0.19
Used hormone therapy in the last 12 mo				
Yes	47	27.8	75.9	23.9
No	371	22.8	82.7	18.7
P	418	0.18	0.41	0.14
Ever smoked				
Yes	116	27.4	67.5	25.1
No	302	21.9	88.3	17.3
P	418	0.03	<0.01	<0.01
Family history of breast cancer*				
Yes	26	23.6	77.4	20.7
No	382	23.2	82.7	19.0
P	408	0.92	0.62	0.71

NOTE: Geometric means were calculated in tertiles of continuous variables or binary groups of dichotomous variables. For BMI, standard classes were used and for parity, nominal classes were used, with a truncation at >3. Tests for linear trends were done through ANOVA with an *F* test on the geometric data.
*Defined as one or more affected mother and/or sister.

Table 3. Multivariate determinants of absolute density, absolute nondensity and relative density

	Absolute dense	Absolute nondense	Relative dense
	β* (95% confidence interval), cm^2	β*− (95% confidence interval), cm^2	β*− (95% confidence interval), %
BMI, kg/m^2		10.08 (8.80 to 11.35)	−2.12 (−1.55 to −2.59)
Age at examination, y	−1.38 (−0.83 to −1.90)	1.74 (0.74 to 2.73)	−1.16 (−0.78 to −1.55)
Age at menarche, y	1.55 (0.09 to 3.04)		1.00 (−0.19 to 2.22)
Age at menopause, y	0.84 (0.23 to 1.46)		0.80 (0.30 to 1.30)
Parity (no. children)	−2.94 (−1.80 to −4.05)	3.81 (1.63 to 6.04)	−2.49 (−1.55 to −3.32)
Adjusted R^2	0.13	0.43	0.29

*Back-transformed β's from analyses based on square root–transformed measurements of density.

The determinants of the relative amount of density found in our study and the explained variance (29%) are quite similar to results previously reported (13, 20, 21). Our reliability results and the average tissue amounts are also similar to those reported in other studies. Thus, although the xeromammograms in this study prevented us from using the widely used, computer-assisted method for evaluating mammograms, we believe that our method gives equally reliable and comparable results.

The use of oral contraceptives (current and ever), use of hormone therapy in the last 12 months, and smoking were not found to significantly affect either the absolute or relative amount of density in the multivariate models. This may in part be due to the low prevalence of these factors in this population, which can be explained by the time period in which the participants were accrued (1974-1977) and their age at that time (>50 years). The use of oral contraceptives by postmenopausal women at the time of examination can also be ascribed to the accrual period as oral contraceptives were applied as a form of hormone therapy at the time. Despite the fact that these factors were not found to significantly contribute to the multivariate model (data not shown), the univariate influences showed an increase in the absolute amount of dense tissue and a decrease in nondense tissue if oral contraception or hormone therapy was used (Table 2). The combined effect on the relative density is thereby amplified as the amounts of dense and nondense tissues are negatively correlated. This makes more likely the finding of a significant effect of these factors on relative density as was done in some previous reports (26-28).

No data were available at all in our cohort on the ethnicity of the participants whereas ethnicity has long been an established determinant of breast patterns. However, the general population at the time of recruitment into the original DOM cohort was predominantly Caucasian. The results presented here should therefore be seen to reflect the situation in Caucasians and may differ to some extent in other ethnic groups.

Previously, Boyd et al. (13) and Mascarinec et al. (20, 21) reported the effects of similar determinants on the absolute amount of density in premenopausal women and a combined cohort of pre- and postmenopausal women, respectively. In contrast to our results, they reported that the absolute amount of dense tissue was also inversely influenced by BMI. In this study, the effect of BMI on the relative amount of density is entirely due to the relation between BMI and nondense tissue. When BMI was added to the final multivariate model for the absolute amount of density described in Table 3, the R^2 remained the same and the β for BMI was $-0.47\ cm^2/kg/m^2$ (95% confidence interval, 0.20 to −1.14). The absence of an effect of BMI in our study in postmenopausal women may reflect the findings of a study on the role of diet on breast tissue (29). Adherence to a 2-year low-fat, high-carbohydrate diet was shown to lower both the absolute and relative densities in premenopausal women, but in postmenopausal women the effect was negligible. Those results may indicate that the menopause causes changes in the dense tissue, which decrease the susceptibility to dietary and BMI-related influences.

BMI itself has been shown to be a risk factor for breast cancer and independent roles for breast density and BMI as risk factors for breast cancer have been shown (30-32). Den Tonkelaar et al. (33) found that one in five women experiences an increase in breast size after menopause, which is mainly due to weight gain and a subsequent increase in BMI. In view of the present study, one may argue that changes in risk that are ascribed to a difference in the relative amount of density are as likely to be attributable to differences in BMI as they are to actual changes in the dense tissue.

In the mathematical structure of a ratio, BMI would deflate the influence of the absolute density on breast cancer risk in the estimated influence on breast cancer risk by the relative density. However, because BMI itself influences breast cancer risk, the elevated risk attributed to the relative density will be a resultant of the two influences and may therefore be higher than, lower than, or equal to the influence of the absolute density. Each of these options has indeed been shown in one or more studies that did calculate the breast cancer risk attributable to both the absolute and relative densities (3, 34-36). This implies that the relative density may be a better prognostic value as the indicator of overall breast cancer risk associated to a certain parenchymal pattern but it is not necessarily the best etiologic value as the indicator of the risk that can be ascribed to the dense tissue.

Table 4. Cross-tabulation of quartiles of absolute amount of density by quartiles of relative amount of density

		Absolute amount of density					
		Range*	Q1	Q2	Q3	Q4	Total
Relative amount of density	Q1 (0-12%)	0.3-32.3	86	19	1	0	106
	Q2 (12-24%)	8.5-65.2	15	63	27	2	107
	Q3 (25-42%)	8.5-91.5	3	20	43	31	97
	Q4 (43-90%)	17.9-138	0	6	32	70	108
	Total		104	108	103	103	418
Range within quartile†, cm^2			0.3-15.2	15.2-26.5	26.7-46.4	46.5-138	
Corresponding range‡, %			0-33	6-60	11-90	20-88	

*Range of the absolute amount of dense tissue (in cm^2) corresponding to the quartile of relative density.
† Range of the absolute amount of density (in cm^2) within each quartile.
‡ Range of the relative amount of density (in %) corresponding to the quartile of absolute amount of density.

Apart from the mathematical conflict between density and BMI, other factors may make the relations between BMI, absolute dense tissue, and breast cancer risk quite complex. One could argue that women with the same amount of dense tissue surrounded by more fatty tissue are at a higher risk due to increased aromatization of androgens into estrogens in the surrounding fatty tissue. Higher circulating levels of endogenous estrogens translate into higher risk and these levels may be elevated even more locally in the breast in relation to the amount of fat (37). Similarly, higher local lipid peroxidation has been suggested to influence the dense tissue and thereby cancer risk (38). Consequently, there may be nonlinear relations between the absolute amount of dense tissue and breast cancer risk as it is modified by the presence of fat tissue.

The comparison of quartiles of absolute density with quartiles of relative density showed that 37% (156 of 418) of the women in our study are classified differently for these measures. More importantly, however, the ranges of the relative amounts of density that correspond with each quartile of absolute amount of density show that quite similar absolute amounts merit a substantial range in relative amount and vice versa, depending on the absence or presence of fat. This shows that the relative density is not a good indicator of the absolute amount of density and that a low amount of relative density may still be associated with a large amount of high-risk, dense target tissue, simply surrounded by an even larger amount of nondense tissue. This implies that within a category of relative density, there may still be a substantial range in risk, depending on the absolute amounts of dense and nondense tissues constituting the percentage.

The age at menarche and the age at menopause only affect the absolute amount of density and do not influence the absolute amount of nondense tissue. Consequently, the relative amount of density is also affected by these characteristics but the effect on relative density is diluted in comparison with the direct effect on the amount of dense tissue. Previous studies that included the age at menarche in the analyses show a large diversity in the effects that were found. Whereas our findings are quite similar to those reported by McCormack et al. (18), Maskarinec et al. (20) found an inverse relation. Other studies did not find any relation (15, 16, 19). This high variability in findings on the role of the age at menarche indicates that this early effect on breast density may be obscured or negated by other influences later in life and needs further investigation.

The age at examination and parity are inversely related to the absolute amount of density and the absolute amount of nondense tissue. The influence of both determinants on the relative amount of density is therefore a mix of the effects on the two absolute amounts. Although the direction of the relations between the absolute and the relative amount of density with both age and parity is similar, the effect of the relative density gives an overestimation of the direct effect on dense tissue.

The results presented here underline the notion that the relative density score is reflected by the amount of dense tissue as much as by the amount of surrounding tissue. The surrounding tissue largely constitutes of fat and BMI is its main determinant (39). The implication is that when relative measurements of dense tissues are the (intermediate) end point in studies, effects on and of BMI are also being studied and the effect of a determinant on the relative density therefore does not represent the actual effects on dense tissue. Consequently, the use of the relative amount of breast density is warranted when assessing risk in prognostic research because it is a measure that combines several pathways and is likely to yield the best, total estimate of risk associated with a certain breast. If, however, etiologic inferences are to be made in a study, absolute measures should be the measure of choice and should therefore be at least included.

Acknowledgments

We thank all the women who participated in the DOM project, the ''Friends of the DOM Project'', all people who were involved in the mammography screening, and those who helped in the retrieval and digitization of the mammograms.

References

1. Boyd NF, Jensen HM, Cooke G, Han HL. Relationship between mammographic and histological risk factors for breast cancer. J Natl Cancer Inst 1992;84:1170–9.
2. Bright RA, Morrison AS, Brisson J, et al. Relationship between mammographic and histologic features of breast tissue in women with benign biopsies. Cancer 1988;61:266–71.
3. Wolfe JN. Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol 1976;126:1130–7.
4. Gram IT, Funkhouser E, Nordgard L, Tabar L, Ursin G. Oral contraceptive use and mammographic patterns. Eur J Cancer Prev 2002;11:265–70.
5. Geller BM, Barlow WE, Ballard-Barbash R, et al. Use of the American College of Radiology BI-RADS to report on the mammographic evaluation of women with signs and symptoms of breast disease. Radiology 2002;222:536–42.
6. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. Automated analysis of mammographic densities. Phys Med Biol 1996;41:909–23.
7. Yaffe MJ, Boyd NF, Byng JW, et al. Breast cancer risk and measured mammographic density. Eur J Cancer Prev 1998;7 Suppl 1:S47–55.
8. Boyd NF, Byng JW, Jong RA, et al. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. J Natl Cancer Inst 19953; 87:670–5.
9. Byrne C, Schairer C, Wolfe J, et al. Mammographic features and breast cancer risk: effects with time, age, and menopause status. J Natl Cancer Inst 1995;87:1622–9.
10. Wolfe JN. Risk for breast cancer development determined by mammographic parenchymal pattern. Cancer 1976;37:2486–92.
11. Brisson J, Diorio C, Masse B. Wolfe's parenchymal pattern and percentage of the breast with mammographic densities: redundant or complementary classifications? Cancer Epidemiol Biomarkers Prev 2003;12:728–32.
12. Warner E, Lockwood G, Tritchler D, Boyd NF. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. Cancer Detect Prev 1992;16:67–72.
13. Boyd NF, Lockwood GA, Byng JW, Little LE, Yaffe MJ, Tritchler DL. The relationship of anthropometric measures to radiological features of the breast in premenopausal women. Br J Cancer 1998;78:1233–8.
14. Vachon CM, Kuni CC, Anderson K, Anderson VE, Sellers TA. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). Cancer Causes Control 2000; 11:653–62.
15. Jeffreys M, Warren R, Gunnell D, McCarron P, Smith GD. Life course breast cancer risk factors and adult breast density (United Kingdom). Cancer Causes Control 2004;15:947–55.
16. Riza E, dos Santos Silva I, De Stavola B, et al. Correlates of high-density mammographic parenchymal patterns by menopausal status in a rural population in Northern Greece. Eur J Cancer 2005;41:590–600.
17. Gapstur SM, Lopez P, Colangelo LA, Wolfman J, Van Horn L, Hendrick RE. Associations of breast cancer risk factors with breast density in Hispanic women. Cancer Epidemiol Biomarkers Prev 2003;12:1074–80.
18. McCormack VA, dos Santos Silva I, de Stavola BL, et al. Life-course body size and perimenopausal mammographic parenchymal patterns in the MRC 1946 British birth cohort. Br J Cancer 2003;89:852–9.
19. Heng D, Gao F, Jong R, et al. Risk factors for breast cancer associated with mammographic features in Singaporean Chinese women. Cancer Epidemiol Biomarkers Prev 2004;13:1751–8.
20. Maskarinec G, Lyu LC, Meng L, Theriault A, Ursin G. Determinants of mammographic densities among women of Asian, Native Hawaiian, and Caucasian ancestry. Ethn Dis 2001;11:44–50.
21. Maskarinec G, Nagata C, Shimizu H, Kashiki Y. Comparison of mammographic densities and their determinants in women from Japan and Hawaii. Int J Cancer 2002;102:29–33.
22. Jasienski M, Bazzaz FA. The fallacy of ratios and the testability of models in biology. Oikos 1999;84:321–6.
23. Albanes D, Winick M. Are cell number and cell proliferation risk factors for cancer? J Natl Cancer Inst 1988;80:772–4.
24. Trichopoulos D, Lipman RD. Mammary gland mass and breast cancer risk. Epidemiology 1992;3:523–6.
25. Collette HJ, Day NE, Rombach JJ, de Waard F. Evaluation of screening for breast cancer in a non-randomised study (the DOM project) by means of a case-control study. Lancet 1984;1:1224–6.
26. Vachon CM, Sellers TA, Vierkant RA, Wu FF, Brandt KR. Case-control study of increased mammographic breast density response to hormone replacement therapy. Cancer Epidemiol Biomarkers Prev 2002;11:1382–8.
27. Greendale GA, Reboussin BA, Slone S, Wasilauskas C, Pike MC, Ursin G. Postmenopausal hormone therapy and change in mammographic density. J Natl Cancer Inst 2003;95:30–7.

28. Spicer DV, Ursin G, Parisky YR, et al. Changes in mammographic densities induced by a hormonal contraceptive designed to reduce breast cancer risk. J Natl Cancer Inst 1994;86:431–6.
29. Boyd NF, Greenberg C, Lockwood G, et al. Effects at two years of a low-fat, high-carbohydrate diet on radiologic features of the breast: results from a randomized trial. Canadian Diet and Breast Cancer Prevention Study Group. J Natl Cancer Inst 1997;89:488–96.
30. Adami HO, Trichopoulos D. Obesity and mortality from cancer. N Engl J Med 2003;348:1623–4.
31. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U S. adults. N Engl J Med 2003;348:1625–38.
32. Lam PB, Vacek PM, Geller BM, Muss HB. The association of increased weight, body mass index, and tissue density with the risk of breast carcinoma in Vermont. Cancer 2000;89:369–75.
33. Den Tonkelaar I, Peeters PH, van Noord PA. Increase in breast size after menopause: prevalence and determinants. Maturitas 2004;48: 51–7.
34. Chen Z, Wu AH, Gauderman WJ, et al. Does mammographic density reflect ethnic differences in breast cancer incidence rates? Am J Epidemiol 2004; 159:140–7.
35. Maskarinec G, Meng L. A case-control study of mammographic densities in Hawaii. Breast Cancer Res Treat 2000;63:153–61.
36. Ursin G, Ma H, Wu AH, et al. Mammographic density and breast cancer in three ethnic groups. Cancer Epidemiol Biomarkers Prev 2003;12:332–8.
37. Boyd NF, Stone J, Martin LJ, et al. The association of breast mitogens with mammographic densities. Br J Cancer 2002;87:876–82.
38. Boyd NF, McGuire V. Evidence of lipid peroxidation in premenopausal women with mammographic dysplasia. Cancer Lett 1990;50:31–7.
39. Beijerinck D, van Noord PA, Kemmeren JM, Seidell JC. Breast size as a determinant of breast cancer. Int J Obes Relat Metab Disord 1995; 19:202–5.

Measurements of Breast Density: No Ratio for a Ratio

Gerco Haars, Paulus A.H. van Noord, Carla H. van Gils, et al.

Cancer Epidemiol Biomarkers Prev 2005;14:2634-2640.