# Mammographic Features and Subsequent Risk of Breast Cancer: A Comparison of Qualitative and Quantitative Evaluations in the Guernsey Prospective Studies

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## Abstract

**Mammographic features are known to be associated with breast cancer but the magnitude of the effect differs markedly from study to study. Methods to assess mammographic features range from subjective qualitative classifications to computer-automated quantitative measures. We used data from the UK Guernsey prospective studies to examine the relative value of these methods in predicting breast cancer risk. In all, 3,211 women ages ≥35 years who had a mammogram taken in 1986 to 1989 were followed-up to the end of October 2003, with 111 developing breast cancer during this period. Mammograms were classified using the subjective qualitative Wolfe classification and several quantitative mammographic features measured using computer-based techniques. Breast cancer risk was positively associated with high-grade Wolfe classification, percent breast density and area of dense tissue, and negatively associated with area of lucent tissue, fractal dimension, and lacunarity. Inclusion of the quantitative measures in the same model identified area of dense tissue and lacunarity as the best predictors of breast cancer, with risk increasing by 59% [95% confidence interval (95% CI), 29-94%] per SD increase in total area of dense tissue but declining by 39% (95% CI, 53-22%) per SD increase in lacunarity, after adjusting for each other and for other confounders. Comparison of models that included both the qualitative Wolfe classification and these two quantitative measures to models that included either the qualitative or the two quantitative variables showed that they all made significant contributions to prediction of breast cancer risk. These findings indicate that breast cancer risk is affected not only by the amount of mammographic density but also by the degree of heterogeneity of the parenchymal pattern and, presumably, by other features captured by the Wolfe classification.** (Cancer Epidemiol Biomarkers Prev 2005;14(5):1052–9)

## Introduction

The breast comprises a mixture of epithelial and connective tissues (fibroglandular tissue) together with fatty tissue. Their distribution on the mammogram is referred to as the mammographic parenchymal pattern. Fat is radiographically lucent and appears dark on the image, whereas fibroglandular tissue is radiographically dense and appears brighter.

The Wolfe classification (1) was the earliest method to evaluate mammographic parenchymal patterns and is still one of the most widely used. This subjective visual method classifies mammograms into four categories according to extent of density and other mammographic features. Other subjective qualitative classifications are those proposed by the American College of Radiology (*Breast imaging reporting and data system*; ref. 2) and by Tabar (3). Subjective assessments of the proportion of the breast image occupied by mammographic density on a quantitative scale have also been developed including visual assessment, planimetry (4), and computer-assisted interactive thresholding techniques (5). Subjective appraisal of mammographic patterns can be substantially affected by within- and between-observer variability. To overcome this, quantitative computer-automated measures have recently been proposed as an observer-independent alternative (6).

Mammographic parenchymal patterns are being increasingly used as intermediate markers in studies investigating the etiology of breast cancer (7, 8) and testing new preventive strategies (9, 10). But although it is well established that women with radiologically dense breasts are at substantially higher risk of developing breast cancer than women whose breasts are radiologically lucent (11-16), there is wide variation in the magnitude of the reported risk estimates, partly due to differences in the methods used to classify/measure density. It is also unclear whether mammographic features other than density affect risk.

The relative predictive value for breast cancer risk of the alternative methods used for classifying/measuring mammographic features has never been assessed in a comprehensive way, although some studies have compared Wolfe classification with breast density (12, 14-16). The aim of this study is to compare several quantitative measures of mammographic features (percent breast density, total area of dense tissue, total area of lucent tissue, total area and volume of the breast, fractal dimension, regional skewness, and lacunarity) and the Wolfe classification as breast cancer risk factors within a large prospective study of over 3,000 healthy volunteers living on the island of Guernsey (United Kingdom).

## Materials and Methods

**Study Population.** The Guernsey Breast Cancer Research Project started in 1961 to investigate the role of endogenous hormones in the etiology of female breast cancer (17) and

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consisted of a series of six prospective studies which were conducted at fairly regular intervals in Guernsey, a small island in the English Channel with a relatively stable population. All women resident in the island ages ≥35 years were invited to take part in the third study, Guernsey III (GIII), between 1977 and 1985. Of the target population, 5,104 (31%) volunteered to participate (including 60 women ages 26-34 years who were recruited by mistake). These volunteers were invited a few years later (in 1986-1989) to participate in Guernsey IV (GIV). The response rate to GIV was 75% among women who were still alive and resident in the island (80 died and 150 left the island between GIII and GIV). Thus, a total of 3,679 women who participated in both studies were potentially eligible for the present analyses. At entry to GIII and GIV, women completed a detailed interviewer-administered questionnaire on demographic, lifestyle, and reproductive variables and had anthropometric measurements taken. Follow-up of the cohort is still active and information on cancer incidence is obtained regularly (every 6 months) through pathology reports from the only pathology laboratory in Guernsey, death certificates, and data from the Wessex Cancer Registry. The study was approved by all the relevant ethics committees and women asked to provide written informed consent.

**Measurement of Mammographic Features.** Each woman had a mammogram (two views per breast: cranio-caudal and medial-lateral-oblique) taken at entry into both GIII and GIV. Only GIV mammograms were still available for digitization and therefore only the readings obtained from these will be considered here. Mammograms were originally classified according to the Wolfe grade (1) by one of the radiologist involved in the study as follows: N1, parenchyma composed primarily of fat (radiologically lucent) with at most small amounts of dysplasia; P1, parenchyma composed mainly of fat with prominent ducts in anterior portion involving less than a quarter of the breast; P2, severe involvement with prominent duct pattern involving more than a quarter of the breast; and DY, severe involvement with dysplasia, often obscuring an underlying prominent duct pattern. The radiologist was kept blind to the baseline characteristic of the women. The reproducibility of the Wolfe classification was not assessed in GIV but it was shown to be over 0.90 in GIII (18).

Recently, an Astra 2400S scanner with a transparency adapter with the 8-bit (0-255 grey values) output was used to digitize GIV mammograms. The size of each pixel was of 0.1693 $mm^2$ (format 150 × 150 pixels per inch). The scanned images were stored in the computer using the standard Window BMP file format. The images were displayed using a standard VGA monitor with 800 × 600 pixels and 16-bit color pixel resolution (65,535 displayable colors). A computer program was developed to measure several mammographic features. The computer-assisted procedures were based on Byng et al. (5) and adapted from Ursin et al. (19). For each image, the observer selected interactively two threshold grey levels, one to identify the edge of the breast and a second to identify mammographic densities. The first threshold separated the image of the breast itself from the darker background; pixels with a grey value equal to, or greater than, this threshold represented the total area of the breast. The second one distinguished dense areas from lucent ones within the breast gland; pixels with a grey level equal to, or greater than, the selected threshold represented the area of the breast occupied by dense tissue. Percentage breast density was then calculated as the percentage of ''dense'' pixels within the breast area. Breast volume was computed using the method proposed by Katariya et al. (20). These measures, although subjective, were shown highly reproducible as measured within this study in a sample of mammograms from 102 women. The within- and between-person intraclass correlation coefficients for measurement of total area and volume of the breast were all 0.99, whereas the within and between-person intraclass correlation coefficients for percent breast density were 0.94 [95% confidence interval (95% CI), 0.91-0.98] and 0.92 (95% CI, 0.89-0.94), respectively.

In addition to computer-assisted measurements, the computer algorithm provided automated measurements of fractal dimension, regional skewness, and lacunarity. Fractal dimension is a measure of the texture or complexity of the radiological image (21). A digital image can be regarded as a surface or terrain, by treating the brightness of each pixel as a vertical dimension (see Appendix 1). High values of fractal dimension correspond to a coarse texture, typical of low-density mammograms in which there is marked contrast between dense and lucent tissue, whereas low values correspond to a smooth texture as those found in high-density mammograms. The frequency distribution of pixel gray levels (i.e., brightness) in a digitized image is given by a histogram. Skewness measures the asymmetry of this distribution (21). To be more sensitive to regional variations in image brightness, skewness was calculated for individual small square regions of 24 × 24 pixels covering the projection of the breast and averaged over the squares to obtain the final skewness. Positive regional skewness corresponds to low-dense mammograms, whereas negative regional skewness corresponds to high-dense mammograms. Lacunarity, a novel computer-automated variable that has never been used before to assess mammograms, quantifies the degree of heterogeneity or structural variation within the image (ref. 22; see Appendix 1). Low lacunarity values correspond to a homogeneous parenchymal pattern, whereas high values correspond to a heterogeneous (nodular) pattern.

Only one single view of one breast is required to assess mammographic density as strong correlations ($r$ = 0.86-0.96) have been found between readings from views of the right and left breast and from cranio-caudal and medial-lateral-oblique views of the same breast (23). The left cranio-caudal view was used in the present study because it is the most appropriate for estimation of breast volume (20). All computer-based measurements were carried out by a single observer (G.T.M.) without knowledge of the baseline characteristics, the Wolfe grade, or the breast cancer status of the participants.

**Statistical Methods.** Cox proportional hazard models were fitted on the age time scale to estimate hazard ratios (HR) for breast cancer in relation to the various classification/measures of mammographic features. Women's follow-up time was calculated from their entry into GIV to the earliest of date of diagnosis of an *in situ* or invasive breast cancer, date of death, date of emigration, or 31 October 2003. Proportional hazards assumptions were assessed using Nelson-Aalen plots (24, 25). The outcome was defined by the occurrence of an invasive or *in situ* breast cancer. The effect of mammographic features on the risk of invasive breast cancer was also examined by treating *in situ* cases as censoring events. The findings reported here were adjusted for age, age at leaving full-time education, social class, job status, nulliparity/parity, height, body mass index [defined as weight (kg)/height $(m)^2$] at GIII, and changes in body mass index from GIII to GIV. Further adjustment for other available reproductive variables (listed in Table 1) had little or no effect on the strength of the associations. Analyses were done keeping the quantitative mammographic features on their original continuous scale and the results presented as the effect on breast cancer rates per SD increase in these measures. Departures from linearity were checked using the likelihood ratio test on the quadratic term (26). In addition, quantitative mammographic features were categorized into fourths of their overall distribution in the study population and likelihood ratio tests were used to test the significance of linear effects across the ranked categories. Likelihood ratio tests were also used to assess the additional contribution of


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**Table 1. Baseline characteristics of women by breast cancer status, Guernsey IV study, United Kingdom**

| | Cases ($n$ = 111), median (range)* | Noncases ($n$ = 3,100), median (range)* |
|---|---|---|
| *Demographic characteristics* | | |
| Age at entry (yrs) | 53.2 (40.3-79.9) | 51.8 (34.1-79.8) |
| Age at exit (yrs) | 63.4 (44.2-85.2) | 66.9 (42.9-93.7) |
| Age left full-time education (yrs)† | 15 (11-19) | 15 (11-20) |
| Occupation: manager/supervisor | 6.3% | 8.2% |
| Social class I-II ‡ | 34.2% | 31.2% |
| *Reproductive characteristics* | | |
| Age at menarche (yrs)§ | 13 (10-17) | 13 (9-18) |
| Nulliparity | 18.9% | 12.4% |
| Age at first birth (yrs) (among parous women only)‖ | 24 (18-39) | 24 (16-42) |
| Parity (among parous women only) | 2 (0-5) | 2 (0-12) |
| Still premenopausal at entry | 36.9% | 36.8% |
| Age at natural menopause (yrs) | 49 (39-58) | 50 (36-60) |
| Ever use of OC‡ | 50.9% | 50.8% |
| On OC at GIV | 1.8% | 1.1% |
| Ever use of HRT¶ | 21.6% | 26.7% |
| On HRT at GIV | 5.4% | 6.9% |
| *Anthropometric characteristics at GIII* | | |
| Height (m)‖ | 161 (147-176) | 160 (120-200) |
| BMI‖ | 23.9 (19.1-33.3) | 24.3 (16.0-58.7) |
| Weight gain from GIII to GIV** | 25.5% | 18.4% |
| Weight loss from GIII to GIV** | 5.5% | 9.4% |
| *Mammographic features* | | |
| Qualitative (Wolfe grade) | | |
| N1 | 15.3% | 34.4% |
| P1 | 19.8% | 20.6% |
| P2 | 53.2% | 35.8% |
| DY | 11.7% | 9.3% |
| Quantitative | | |
| Percent breast density (%) | 33.7 (2.9-67.4) | 31.5 (0.28-80.5) |
| Total area of dense tissue ($cm^2$) | 33.0 (2.8-143.5) | 30.0 (0.39-169.9) |
| Total area of lucent tissue ($cm^2$) | 72.2 (19.10-253.3) | 70.7 (6.4-334.9) |
| Total area of the breast ($cm^2$) | 105.0 (35.4-271.4) | 105.9 (19.2-339.4) |
| Total volume of the breast ($cm^3$) | 704.7 (184.2-2133.4) | 717.4 (79.3-3416.6) |
| Fractal dimension†† | 2.45 (2.37-2.53) | 2.45 (2.34-2.62) |
| Regional skewness†† | 0.54 (0.07-2.09) | 0.47 (−0.23 to 5.54) |
| Lacunarity†† | 4.98 (4.44-5.43) | 4.99 (4.16-5.51) |

NOTE: Abbreviations: BMI, body mass index; GIII/IV, Guernsey III/IV; HRT, hormone replacement therapy; OC, oral contraceptives.
*Cases include 94 invasive and 17 *in situ* tumors; median (range) for quantitative variables and percentage for qualitative variables.
† Values missing for 64 women.
‡ Values missing for two women.
§Values missing for 14 women.
‖Value missing for one woman.
¶Values missing for 72 women.
**Values missing for nine women.
†† These measures have no units.

each mammographic measure/classification to breast cancer risk, by comparing models that included several measures with models that included only a subset. All statistical analyses were carried out in STATA (27).

## Results

**Baseline Characteristics.** Of the 3,679 women who participated in both GIII and GIV, 468 were excluded because of unknown menopausal status ($n$ = 84), history of breast cancer at entry into GIV ($n$ = 38), were ages ≥80 years at entry into GIV ($n$ = 29), had breast implants ($n$ = 3), or their GIV mammograms were no longer available for digitization ($n$ = 314), leaving 3,211 women included in the analysis. Women for whom mammograms were no longer available but would have been otherwise eligible had similar baseline characteristics and Wolfe grades to those who participated (data not shown). A total of 111 breast cancer cases (94 invasive and 17 *in situ*) occurred among the participants from entry in GIV to 31 October 2003. The median age at invasive or *in situ* breast cancer incidence was 63 years (range, 44-85). The median age at the end of the follow-up for those women who did not develop breast cancer was 67 years (range, 43-94), reflecting a median follow-up time of 15 years (range, 0.5-17). Cases and noncases had similar baseline characteristics except that higher proportions of cases were of high social class, nulliparous, never users of hormone replacement therapy, and gained weight from GIII to GIV. A higher proportion of cases than noncases had a high-density Wolfe grade (i.e., P2/DY). Relatively to noncases, cases had, on average, higher percent breast density levels and larger areas of the breast occupied by dense and lucent tissues but lower breast volume. Cases had also higher values of regional skewness but similar values of fractal dimension and lacunarity (Table 1).

**Quantitative Measures of Mammographic Features and Subsequent Risk of Breast Cancer.** There was a strong statistically significant trend between Wolfe categories and subsequent risk of breast cancer, with DY women being approximately four times (HR, 3.90; 95% CI, 1.76-8.62) more likely to develop breast cancer later in life than N1 women after adjustment for age and other potential confounding variables (Table 2). Strong positive associations with breast cancer risk were also found with percent breast density and


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**Table 2. Separate effect of mammographic features on subsequent risk of breast cancer, Guernsey IV study, United Kingdom**

| Mammographic feature | Category* | | | | $P^{\dagger}$ |
|---|---|---|---|---|---|
| *Wolfe's grade* | *N1* | *P1* | *P2* | *DY* | |
| $D^{\ddagger}$ | 17 | 21 | 58 | 12 | <0.001 |
| HR[§] (95% CI) | 1.00 | 2.06 (1.08-3.94) | 3.50 (1.98-6.21) | 3.90 (1.76-8.62) | |
| *Percent breast density* | *0.50-* | *18.7-* | *31.7-* | *45.9-80.5* | |
| $D^{\ddagger}$ | 13 | 32 | 33 | 30 | 0.001 |
| HR[§] (95% CI) | 1.00 | 2.71 (1.40-5.24) | 3.11 (1.59-6.12) | 3.49 (1.69-7.18) | |
| HR[§] per 1 SD increase | 1.40 (1.12, 1.75) | | | | 0.003 |
| *Total area of dense tissue ($cm^2$)* | *0.39-* | *18.8-* | *30.2-* | *45.4-169.9* | |
| $D^{\ddagger}$ | 14 | 29 | 34 | 31 | 0.003 |
| HR[§] (95% CI) | 1.00 | 2.21 (1.16-4.22) | 2.68 (1.42-5.04) | 2.69 (1.40-5.16) | |
| HR[§] per 1 SD increase | 1.27 (1.07-1.51) | | | | 0.05 |
| *Total area of lucent tissue ($cm^2$)* | *6.4-* | *45.4-* | *70.6-* | *103.8-334.9* | |
| $D^{\ddagger}$ | 33 | 21 | 30 | 24 | 0.179 |
| HR[§] (95% CI) | 1.00 | 0.56 (0.32-0.98) | 0.74 (0.42-1.29) | 0.56 (0.29-1.11) | |
| HR[§] per 1 SD increase | 0.76 (0.57-1.02) | | | | 0.064 |
| *Total area of the breast ($cm^2$)* | *19.2-* | *78.6-* | *105.4-* | *140.6-339.4* | |
| $D^{\ddagger}$ | 28 | 28 | 22 | 30 | 0.874 |
| HR[§] (95% CI) | 1.00 | 0.96 (0.56-1.64) | 0.77 (0.43-1.40) | 1.03 (0.54-1.96) | |
| HR[§] per 1 SD increase | 0.98 (0.76-1.26) | | | | 0.855 |
| *Breast volume ($cm^3$)* | *79.3-* | *496.8-* | *715.7-* | *1,009.0-3,416.6* | |
| $D^{\ddagger}$ | 33 | 24 | 24 | 27 | 0.310 |
| HR[§] (95% CI) | 1.00 | 0.67 (0.39-1.15) | 0.65 (0.36-1.15) | 0.73 (0.38-1.40) | |
| HR[§] per 1 SD increase | 0.98 (0.75-1.29) | | | | 0.823 |
| *Fractal dimension* | *2.68-* | *2.85-* | *2.90-* | *2.96-3.24* | |
| $D^{\ddagger}$ | 25 | 37 | 27 | 19 | 0.174 |
| HR[§] (95% CI) | 1.00 | 1.52 (0.91-2.54) | 1.02 (0.58-1.80) | 0.70 (0.36-1.34) | |
| HR[§] per 1 SD increase | 0.80 (0.64-1.00) | | | | 0.046 |
| *Lacunarity* | *4.16-* | *4.88-* | *4.99-* | *5.10-5.51* | |
| $D^{\ddagger}$ | 33 | 28 | 21 | 26 | 0.207 |
| HR[§] (95% CI) | 1.00 | 0.79 (0.47-1.31) | 0.60 (0.34-1.07) | 0.74 (0.41-1.32) | |
| HR[§] per 1 SD increase | 0.80 (0.65-1.00) | | | | 0.046 |
| *Regional skewness* | *−0.228-* | *0.267-* | *0.475-* | *0.776-5.539* | |
| $D^{\ddagger}$ | 27 | 22 | 33 | 29 | 0.562 |
| HR[§] (95% CI) | 1.00 | 0.85 (0.48-1.49) | 1.21 (0.72-2.03) | 1.05 (0.62-1.80) | |
| HR[§] per 1 SD increase | 1.02 (0.84-1.24) | | | | 0.823 |

*Fourths of the distribution in the whole cohort, except for Wolfe grade.
† *P* for linear trend.
‡ Number of breast cancer cases (three excluded due to missing data on potential confounding variables).
§ HRs (and 95% CIs) adjusted for age, age at leaving full time education, social class, job status, parity, height, BMI at GIII, and BMI change from GII to GIV.

total area of dense tissue (Table 2). Women in the top fourth of percent breast density (i.e., ≥45.9%) were about 3.5 times (HR, 3.49; 95% CI, 1.69-7.18) more likely to develop breast cancer than those in the bottom fourth (i.e., <18.7%). Similarly, women in the top fourth of total area of dense tissue (i.e., ≥45.4 $cm^2$) had a 2.7-fold (HR, 2.69; 95% CI, 1.40-5.16) increase in breast cancer risk relative to those in the bottom one (i.e., <18.8 $cm^2$). These corresponded to increases in the risk of

**Table 3. Pearson correlations coefficients among quantitative mammographic measurements, Guernsey IV study, United Kingdom**

| | Percent breast density | Total area of dense tissue ($cm^2$) | Total area of lucent tissue ($cm^2$) | Total area of the breast ($cm^2$) | Total volume of the breast ($cm^3$) | Fractal dimension | Regional skewness | Lacunarity indicator |
|---|---|---|---|---|---|---|---|---|
| Percent breast density | 1.0 | | | | | | | |
| Total area of dense tissue ($cm^2$) | 0.71* | 1.0 | | | | | | |
| Total area of lucent tissue ($cm^2$) | −0.70* | −0.17* | 1.0 | | | | | |
| Total area of the breast ($cm^2$) | −0.37* | 0.28* | 0.90* | 1.0 | | | | |
| Total volume of the breast ($cm^3$) | −0.38* | 0.25* | 0.90* | 0.99* | 1.0 | | | |
| Fractal dimension | −0.64* | −0.40* | 0.61* | 0.42* | 0.43* | 1.0 | | |
| Regional skewness | 0.06* | 0.007 | −0.13* | −0.12* | −0.11* | −0.007 | 1.0 | |
| Lacunarity | −0.21* | 0.39* | 0.66* | 0.82* | 0.79* | 0.17* | −0.03 | 1.0 |

*$P < 0.001$.


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**Table 4. Estimated joint effects of quantitative mammographic features identified as independent predictors of subsequent risk of breast cancer, Guernsey IV study, United Kingdom**

| | HR* (95% CI) | *P* |
|---|---|---|
| A. Model specification with the explanatory variables on the original continuous scale | | |
| *Total area of dense tissue ($cm^2$)* | | |
| HR* per 1 SD increase | 1.59 (1.29-1.94) | <0.001 |
| *Lacunarity* | | |
| HR* per 1 SD increase | 0.61 (0.47-0.78) | <0.001 |
| B. Model specification with the explanatory variables grouped into categories | | |
| *Total area of dense tissue ($cm^2$), fourths* | | |
| 0.39 | 1.00 (baseline) | |
| 18.8 | 2.23 (1.17-4.26) | |
| 30.2 | 3.14 (1.65-5.97) | |
| 45.4 | 3.73 (1.85-7.51) | <0.001† |
| *Lacunarity (fourths)* | | |
| 4.16 | 1.00 (baseline) | |
| 4.88 | 0.62 (0.36-1.05) | |
| 4.99 | 0.43 (0.23-0.79) | |
| 5.10 | 0.46 (0.24-0.89) | 0.006† |

*HRs and 95% CI adjusted for age, age at leaving full time education, social class, job status, parity, height, BMI at GIII, BMI change from GIII to GIV, and the other variable in the table.
† *P* value for likelihood ratio test for linear trend.

subsequent breast cancer of 40% per SD increase in percent breast density and of 27% per SD increase in total area of dense tissue (Table 2).

In contrast, there were negative trends between the risk of developing breast cancer and total area of lucent tissue, fractal dimension and lacunarity, albeit these reached borderline statistical significance only when the data were analyzed on the original continuous scale (Table 2). Each of these measures was associated with a ~20% decrease in breast cancer risk per SD increase in magnitude after adjustment for age and other potential confounding factors. No clear associations were found between breast cancer risk and regional skewness, total area, or volume of the breast.

Most quantitative measures of mammographic features were strongly correlated (Table 3). For instance, percent breast density was positively correlated with total area of dense tissue and regional skewness and negatively correlated with total area of lucent tissue, total area and volume of the breast, fractal dimension, and lacunarity. To identify which features were independently associated with subsequent risk of breast cancer, they were all included simultaneously in the same model except for volume and total area of the breast. Volume was highly correlated with total area ($r = 0.99$; Table 3) and the latter was simply the sum of the areas occupied by the dense and the lucent tissues. Total area of dense tissue and lacunarity emerged as the two best predictors of breast cancer risk (Table 4). For any given level of lacunarity, the risk of developing breast cancer increased by about 60% per SD increase in total area of dense tissue after adjustment for potential confounders. In contrast, for any given level of total area of dense tissue, the risk of breast cancer declined by about 40% per SD increase in lacunarity. Inspection of the Nelson-Aalen plots revealed that the effects of total area of dense tissue and lacunarity on subsequent risk of breast cancer remained constant over the age time scale (test to assess the validity of the proportional hazards assumption: $P = 0.69$ for total area of dense tissue and $P = 0.65$ for lacunarity). Similar results were obtained when these variables were categorized into fourths. There was evidence of a possible interaction between total area of dense tissue and lacunarity ($P = 0.02$), the protective effect of lacunarity being stronger (HR per SD increase in lacunarity, 0.49; 95% CI, 0.35-0.68) in women with total area of dense tissue below the median (i.e., <30.2 $cm^2$) than in those with area of dense tissue equal or above the median (HR per SD increase in lacunarity, 0.91; 95% CI, 0.66-1.25).

**Wolfe Grade, Quantitative Measures of Mammographic Features, and Breast Cancer Risk.** The distribution of quantitative measures of mammographic features differed by Wolfe grade (Table 5). As expected, and on average, percent breast density and total area of dense tissue increased progressively with higher Wolfe grade (i.e., from N1 to DY), whereas the opposite trend was observed for total area of lucent tissue, total area of the breast, and volume. The higher the Wolfe grade the higher, on average, the value for regional skewness but the lower the values for fractal dimension and lacunarity. The observed negative trend between lacunarity and Wolfe grade reflected an increase, on average, in the homogeneity of the breast parenchyma from N1 to DY.

To assess whether Wolfe classification captured any risk information not captured by the two quantitative measures identified above, all three measures were included simultaneously in the same model. The strength of the associations of total area of dense tissue and lacunarity (on their original continuous scale) with breast cancer risk was slightly attenuated after inclusion of Wolfe grade in the model; similarly, the category-specific relative risk estimates for Wolfe grade became closer to one after adjustment for total area of dense tissue and lacunarity (Table 6). Comparing the model that included the Wolfe classification and the two quantitative measures (as well as potential confounders) to models that included only the two quantitative measures showed that the Wolfe classification significantly improved the prediction of breast cancer risk ($P = 0.034$). Comparison of the full model with a model containing only Wolfe grade showed that the two quantitative measures also made a significant additional contribution to prediction of breast cancer risk ($P = 0.018$).

**Table 5. Distribution of quantitative mammographic features by Wolfe categories, Guernsey IV study, United Kingdom**

| Quantitative mammographic feature | Wolfe grade | | | | |
|---|---|---|---|---|---|
| Median (interquartile range) | N1 | P1 | P2 | DY | $P_{trend}$* |
| Percent breast density | 15.2 (17.2) | 27.8 (14.2) | 43.3 (17.9) | 56.2 (16.2) | <0.001 |
| Total area of dense tissue ($cm^2$) | 17.2 (17.0) | 29.7 (19.7) | 40.0 (26.3) | 43.9 (24.9) | <0.001 |
| Total area of lucent tissue ($cm^2$) | 100.0 (68.6) | 78.8 (48.6) | 52.9 (37.8) | 35.5 (24.5) | <0.001 |
| Total area of the breast ($cm^2$) | 120.9 (67.3) | 109.9 (55.6) | 96.3 (56.3) | 79.3 (40.9) | <0.001 |
| Total volume of the breast ($cm^3$) | 850.0 (577.2) | 755.8 (466.1) | 644.5 (454.4) | 486.3 (320.9) | <0.001 |
| Fractal dimension | 2.96 (0.10) | 2.91 (0.08) | 2.86 (0.09) | 2.87 (0.08) | <0.001 |
| Regional skewness | 0.41 (0.42) | 0.48 (0.49) | 0.52 (0.53) | 0.58 (0.59) | <0.001 |
| Lacunarity | 5.03 (0.22) | 5.00 (0.20) | 4.98 (0.25) | 4.88 (0.21) | <0.001 |

*Nonparametric test for linear trend across ordered categories.


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**Table 6. Joint estimates of the effects of total area of dense tissue, lacunarity, and Wolfe grade on subsequent risk of breast cancer, Guernsey IV study, United Kingdom**

| | Quantitative measures of mammographic features only | Wolfe qualitative classification only | Quantitative measures of mammographic features and Wolfe classification |
|---|---|---|---|
| | HR* (95% CI) | HR* (95% CI) | HR* (95% CI) |
| *Total area of dense tissue ($cm^2$)* | | | |
| HR per 1 SD increase | 1.59 (1.29-1.94) | — | 1.30 (1.01-1.69) |
| *Lacunarity* | | | |
| HR per 1 SD increase | 0.61 (0.47-0.78) | — | 0.70 (0.53-0.92) |
| *Wolfe grade* | | | |
| N1 | — | 1.00 | 1.00 |
| P1 | — | 2.06 (1.08-3.94) | 1.80 (0.93-3.48) |
| P2 | — | 3.50 (1.98-6.21) | 2.60 (1.37-4.92) |
| DY | — | 3.90 (1.76-8.62) | 2.31 (0.95-5.62) |
| $P_{\text{linear trend}}$ | | <0.001 | 0.005 |

*Hazard ratios (HR) and 95% confidence interval (CI) adjusted for the effect of age, age at leaving full time education, social class, job status, parity, height, BMI at G III, BMI change from GIII to GIV and the other variables in the column.

To examine whether the effect of total area of dense tissue and lacunarity on breast cancer incidence was modified by the Wolfe grade, analyses were stratified according to a binary reclassification of Wolfe grade (N1/P1 and P2/DY; Table 7). They identified a statistically significant interaction ($P$ = 0.007) between total area of dense tissue and binary Wolfe grade, with the effect of area of dense tissue being stronger in women with N1/P1 patterns than in those with P2/DY. There was also some evidence of an interaction in the opposite direction for lacunarity, with its effect being stronger in P2/DY women, but the test for interaction was not statistically significant.

Similar findings to those reported above were observed when the analysis was restricted to breast cancers diagnosed at least 1 year after entry into the study (three cases excluded) or to invasive cases (17 cases excluded).

## Discussion

**Main Findings.** This study identified total area of dense tissue and lacunarity as the two best predictors of breast cancer risk among the computer-based quantitative measures of mammographic features. Greater area of dense tissue was statistically significantly associated with an increased risk of developing breast cancer, whereas higher lacunarity was associated with a decline in risk.

In analyses that examined the separate effect of each mammographic feature on subsequent breast cancer risk, there was a positive association between percent breast density and the risk of subsequent breast cancer. Studies that have examined the effect of percent breast density have consistently found that women with percent breast density of >60% to 75% have a 4- to 6-fold increase in breast cancer risk relative to those with low density (12, 13, 15, 28, 29). When we examined percent breast density jointly with other computer-based measures of mammographic features in this study, total area of dense tissue emerged as a better predictor of breast cancer risk than percent breast density. This is of relevance as percent breast density has been the quantitative mammographic feature examined in most published studies. Our results, however, agree with Heine and Malhotra's (30) remark: ''It is our belief, that it is the total density, as opposed to the proportion, that is the true measure of risk.'' Total area of dense tissue is likely to be a better marker of the total amount of fibroglandular tissue in the breast and therefore of the number of cells that are at risk of suffering a malignant transformation (31). Stronger associations of breast cancer risk with total area of dense tissue than with percent breast density have been reported by some researchers (29) but not all (12). However, few studies have presented their results in terms of absolute area of dense tissue, partly because relative measures such as percent breast density are less likely to be affected by technical conditions such as the degree of breast compression.

We found that the level of heterogeneity of the mammographic parenchymal pattern, as measured by lacunarity, was an important and independent determinant of subsequent risk of breast cancer. This is the first time that lacunarity, a new automatically generated computer measure, was assessed in this field. Low lacunarity, corresponding to a homogenous mammographic parenchymal pattern, was associated with higher risk of breast cancer. In contrast, Brisson et al. (32) found that a stronger and steeper increase in breast cancer risk was observed with nodular than with homogeneous density

**Table 7. Effect of total area of dense tissue and lacunarity on subsequent risk of breast cancer by Wolfe grade, Guernsey IV study, United Kingdom**

| Quantitative mammographic feature | Wolfe grade | | Test for interaction* |
|---|---|---|---|
| | N1/P1 ($D$ = 38)†, HR‡ (95% CI) | P2/DY ($D$ = 70)†, HR‡ (95% CI) | |
| *Total area of dense tissue ($cm^2$)* | | | |
| Per 1 SD increase | 2.09 (0.99-4.44) | 1.41 (0.82-2.41) | 0.007 |
| *Lacunarity* | | | |
| Per 1 SD increase | 0.61 (0.33-1.13) | 0.47 (0.31-0.72) | 0.102 |

*Test for interaction between each quantitative measure and binary Wolfe grade.
† $D$ = number of breast cancer cases (three cases excluded due to missing information on potential confounding variables).
‡ HRs and 95% CIs adjusted for age, age at leaving full time education, social class, job status, parity, height, BMI at GIII, and BMI change from GIII to GIV.


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(as assessed by visual inspection). However, among women with a given percentage of nodular densities an increase in the average size of these nodular densities, particularly if they were very large (average size, >4 mm), were associated with an increased risk (32). This would agree with our results as the larger the nodular densities the lower would be lacunarity.

Thurfjell et al. (33) suggested that small breast size was associated with increasing risk of breast cancer through its association with high-risk parenchymal patterns: women with small breasts tended to have higher prevalence of high-density parenchymal patterns (11). We found no associations between breast cancer risk and total area, or volume, of the breast although our study showed that P2/DY women had, on average, smaller breasts than N1/P1 women.

The associations of fractal dimension and regional skewness with risk of breast cancer have been examined only in one previous study by Byng et al. (6). Consistently with their study (6), we found a negative association between fractal dimension, a measure of the texture of the image, and breast cancer risk; however, this association disappeared after adjustment for other quantitative mammographic measures. Byng et al. (6) reported a negative association between regional skewness and breast cancer risk and suggested that this may be due to the strong negative correlation of this variable with percent breast density. In the present study, there was only a very weak correlation between regional skewness and percent breast density and no association between regional skewness and breast cancer risk.

We found a positive association between higher Wolfe grade and breast cancer risk, which persisted after adjustment for total area of dense tissue and lacunarity, probably because Wolfe grade includes mammographic features that are associated with breast cancer risk but are not captured by the computer-based measures. Brisson et al. (14) found that the effect of Wolfe classification was fully explained by its correlation with percent breast density. However, their percent breast density was estimated visually, and by the same observer who did the Wolfe grading, leading presumably to a high correlation between the results obtained by these two methods. In our study, the computer-assisted measurement of percent breast density and the Wolfe grade were carried out independently by different observers.

**Strengths and Limitations.** Our results are from a population-based study, as opposed to a hospital-based one, and thus they are unlikely to have been affected by referral bias. Although the study participants were volunteers and thus may not be fully representative of the whole female population of Guernsey, the internal validity of the mammographic measures should not have been affected. Selection bias due to losses to follow-up is rather unlikely because information on cohort members was obtained regularly and consistently from all available sources (e.g., pathologist reports, cancer registrations, and death certificates). Misclassification of mammographic features might have occurred as some of the assessments were subjective; however, the reliability of the Wolfe grade (assuming it was similar to that observed in GIII) and of the computer-assisted measurements were all very high (above 90%) within this study. Moreover, any misclassification is unlikely to have been differential as mammographic assessments were done in a blind manner (i.e., without knowledge of the baseline characteristics or of the breast cancer status of the participants). The findings cannot be explained by the masking of cancer by radiologically dense breast tissue, as suggested by Egan and Mosteller (34), as similar results were obtained when the analysis was restricted to cases diagnosed at least 1 year from entry into the study. In contrast to many previously conducted studies, analysis accounted for the effects of age (and changes in age during follow-up), changes in body mass index, and other potential confounding factors.

One of the main limitations of the study is the relatively small number of breast cancer cases accrued by the end of the follow-up period and hence its limited power to deal with multivariable models. However, the strength of most of the associations reported here was high. In particular, the effects of total area of dense tissue and lacunarity on the risk of breast cancer were observed regardless of whether the analysis was conducted on a quantitative or on a categorical scale. Because of the small number of cases, we could not estimate separate effects for different age or menopausal status strata, despite the broad age range of the women in the study (range: 34-80 years at mammography) with a median of 15.2 years (range: 0.5-16.7) of follow-up. However, graphical and formal tests supported the assumption that the effects of the various mammographic features on breast cancer risk remained constant over the ages examined.

## Conclusions

To our knowledge, this is the first study to have evaluated prospectively and in the same study population the value of alternative methods of classifying and measuring mammographic features as predictors of subsequent risk of breast cancer. The findings showed that the absolute amount of breast dense tissue is a better predictor of subsequent risk than the more widely used percent density. In addition, breast cancer risk seems to be determined not only by the absolute amount of radiologically dense tissue but also by the degree of heterogeneity of the parenchymal pattern and, presumably, by other mammographic features additionally captured by the Wolfe classification.

## Appendix A

### Appendix 1. Fractal dimension and lacunarity

Fractal dimension is a measure of the texture or complexity of the digitized image. To estimate fractal dimension one needs to calculate the fractal area. With the digitized mammogram represented by a plane with axes $x$ and $y$, each pixel can be regarded as a column, with height $i$ corresponding to its brightness (see Fig. 1). The fractal area for a mammogram, $A(\varepsilon_1)$, $A(\varepsilon_1)$, is defined by the area occupied by the top side of each column ($\varepsilon_1$) plus the ''visible'' areas of the vertical sides of each column (areas $A_1$ and $A_2$ in the example shown in Fig. 1). The ''visible'' vertical areas correspond to the differences in height (or brightness) between neighboring pixels (22).

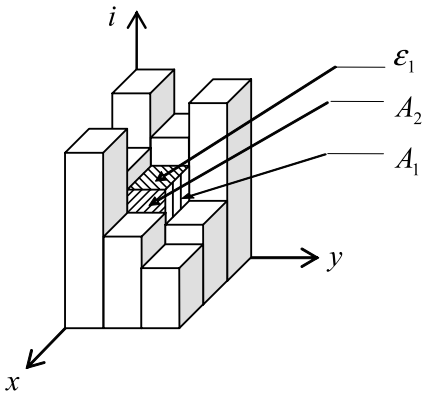


**Figure 1.** Diagramatic representation of pixels in a digitized mammogram.


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Fractal area can also be computed after aggregating different numbers, say ($a \times a$), adjacent pixels, in which case fractal area is denoted by $A(\varepsilon_a)$. Mandelbrot (22) showed that for fractal images there is a power law relationship between $A(\varepsilon_a)$ and $\varepsilon_a$:

$$A(\varepsilon_a) = \lambda \varepsilon_a^{2-D} \quad \text{(A)}$$

where the exponent $D$ and the variable $\lambda$ correspond, respectively, to fractal dimension and lacunarity. The higher the fractal dimension, $D$, the higher the complexity of an image. High values of fractal dimension correspond to a coarse texture, typical of low-density mammograms in which there is marked contrast between dense and lucent tissue, whereas low values correspond to a smooth texture as those found in high-density mammograms.

Two digitized images with the same fractal dimension may, however, look very different depending on whether they have uniformly or nonuniformly distributed densities. Lacunarity (from the Latin *lacuna* for gap or hole) is a measure of the degree of heterogeneity or structural variation within a digitized image. Roughly speaking, the higher the lacunarity the greater the ''clumping'' or ''clustering'' of densities within the image (i.e., the greater the number of conglomerates or nodular densities in the parenchyma). Although Mandelbrot provided a clear interpretation of the variable $\lambda$ in his book (22), lacunarity has never been used before in the analysis of digitized mammographic images.

By taking logarithms, Eq. A can be rewritten as a linear equation:

$$\log A(\varepsilon_a) = \log\lambda + (2 - D)\log\varepsilon_a \quad \text{(B)}$$

with slope $(2 - D)$ and intercept $\log\lambda$. In practice, these variables can be estimated by aggregating adjacent pixels using different combinations (e.g., $1 \times 1$, $2 \times 2$, $3 \times 3$, or $4 \times 4$) to obtain different values of $\varepsilon_a$ with corresponding average intensity and fractal area $A(\varepsilon_a)$ that are then used to estimate the linear regression model defined in Eq. B. The estimated value for the intercept, $\log\lambda$, and D from the slope, $(2 - D)$, were the lacunarity and fractal dimension variables used in the analyses.

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