Generalized breast density metrics

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Abstract
Mammograms represent data that can inform future risk of breast cancer. Data from two case-control study populations were analyzed. Population 1 included women (N = 180 age matched case-control pairs) with mammograms acquired with an indirect x-ray conversion mammography unit. Population 2 included women (N = 319 age matched case-control pairs) with mammograms acquired from 6 direct x-ray conversion units. The Fourier domain was decomposed into n concentric rings (radial spatial frequency bands). The power in each ring was summarized giving a set of measures. We investigated images in raw, for presentation (processed) and calibrated representations and made comparison with the percentage of breast density (BD) determined with the operator assisted Cumulus method. Breast cancer associations were evaluated with conditional logistic regression, adjusted for body mass index and ethnicity. Odds ratios (ORs), per standard deviation increase derived from the respective breast density distributions and 95% confidence intervals (CIs) were estimated.

A measure from a lower radial frequency ring, corresponding 0.083–0.166 cycles mm$^{-1}$ and BD had significant associations with risk in both populations. In Population 1, the Fourier measure produced significant associations in each representation: OR = 1.76 (1.33, 2.32) for raw; OR = 1.43 (1.09, 1.87) for processed; and OR = 1.68 (1.26, 2.25) for calibrated. BD also provided significant associations in Population 1: OR = 1.72 (1.27, 2.33). In Population 2, the Fourier measure produced significant associations for each representation as well: OR = 1.47 (1.19, 1.80) for raw; OR = 1.38 (1.15, 1.67) for processed; and OR = 1.42 (1.15, 1.75) for calibrated. BD provided significant associations in Population 2: OR = 1.43 (1.17, 1.76). Other coincident spectral regions were also predictive of case-control status.

In sum, generalized breast density measures were significantly associated with breast cancer in both FFDM technologies.

1. Introduction

Breast density is a strong breast cancer risk factor, typically assessed from mammograms (McCormack and dos Santos Silva 2006, Boyd et al 2011, Huo et al 2014, Pettersson et al 2014, Chen et al 2015, Brandt et al 2016). There are various methods of measuring breast density (Ding et al 2008, Boyd et al 2009, Heine et al 2011a, 2011b, 2011c, Shepherd et al 2011, Huo et al 2014, Chen et al 2015, Gastounioti et al 2016, Destounis et al 2017). Many of these measures capture the degree of bright tissue (mammographic breast density) in a mammogram. The breast cancer risk associated with the percentage of mammographic breast density (BD) estimated by operator assisted methods is robust across studies (Vachon et al 2013, Pettersson et al 2014). Various automated texture measures have also shown to correlate with breast cancer (Gastounioti et al 2016); examples of these metrics
include image domain filtering, co-occurrence measures, and higher order (above one) moments derived from the pixel distribution. We refer to measures of this kind as generalized breast density metrics because they do not capture dense tissue directly. Generalized automated measures may be more sensitive to data representations because their consistency across imaging platforms can be dependent upon the spatial frequency reproduction capabilities of the respective imaging systems.

Although breast density is an accepted risk factor (McCormack and dos Santos Silva 2006, Boyd et al 2011, Huo et al 2014, Pettersson et al 2014, Chen et al 2015, Brandt et al 2016), it has not been integrated into the clinical management for breast care (Susan G. Komen Foundation 2017) and there is no recognized standard for breast density determination clinically (Melnikow et al 2016). Moreover, the relationships between breast density and the underlying biological processes are also not well understood (Pettersson and Tamimi 2014). Texture measures can capture breast structure over varying spatial scales. Metrics capable of capturing relevant spatial scales could be useful for informing studies focused on understanding the related biological processes with breast structure, in addition to risk prediction purposes.

We have shown that variation measured in mammograms is associated with breast cancer whether based on digitized film mammograms (Heine et al 2012) or mammograms acquired with a specific indirect x-ray detection full field digital mammography unit (Heine et al 2011c) (FFDM). We have also shown that measures taken over annular regions in the Fourier domain are associated with breast cancer using digitized film mammograms (Manduca et al 2009). This methodology decomposes the image domain variation into annular regions (rings) in the Fourier domain with well-defined radial spatial frequency bandwidths resulting in a set of measures. The measure from each ring can also be considered as a texture feature when viewed in the image domain. The set cardinality is adjustable depending on the endpoint and detector element or pixel spacing. In this report, we examined the Fourier spectral properties of mammograms acquired with two FFDM technologies using raw, for presentation (processed), and calibrated mammograms to find spectral regions associated with breast cancer and document similarities. We also made comparisons with the percentage of breast density measure (BD) determined with the Cumulus method, considered as the reference standard. Two case-control studies were used to evaluate these metrics.

2. Materials and methods

2.1. Population and imaging

2.1.1. Population 1

Study 1 included 180 individually matched case-control pairs of adult women that attended the breast clinics at the Moffitt Cancer Center (MCC) between 2006 and 2011. Study images were acquired with a General Electric (GE) Senographe 2000D FFDM unit (General Electric Medical Systems, Milwaukee, WI, USA). This unit uses indirect x-ray detection and has $\Delta = 100 \mu m$ pitch. Raw images are in monochrome 1 format with 14 bit per pixel dynamic range and processed images are in monochrome 2 format with 12 bit dynamic range. We used mammograms in cranial caudal (CC) orientation as study images to avoid pectoral muscle interference. Raw images were used for calibration purposes.

2.1.2. Population 2

Study 2 included 319 individually matched case-control pairs of adult women that attended the breast clinics at MCC between 2011 and 2017. Two-dimensional (2D) study mammograms were acquired from one of six Hologic (Hologic, Inc., Bedford, MA) mammography units: three conventional 2D Selenia FFDM units (H units) and three Dimensions digital breast tomosynthesis (DBT) units (D units). The 2D FFDM component from the combo-HD mode was used to supplement the dataset derived from the 2D FFDM units because MCC phased out conventional 2D units in the recent past. These units use direct x-ray detection and have $\Delta = 70 \mu m$ pitch. Raw images are in monochrome 1 format with 14 bit per pixel dynamic range and processed images are in monochrome 2 format with 12 bit dynamic range. We used mammograms in the CC orientation as study images. Raw images were used for calibration purposes.

Both populations were developed with the same IRB-approved protocol. Cases (unilateral disease) were either: (i) women attending the breast clinics at MCC diagnosed with breast cancer or (ii) attendees of surrounding area clinics sent to MCC for breast cancer treatment or diagnostic purposes and found to have breast cancer. Cases had pathology verified unilateral (first time) breast cancer. Controls were attendees of MCC with no history of breast cancer. Controls were individually matched to cases on age ($\pm 2$ years), hormone replacement therapy (HRT) usage and current duration, screening history, and mammography unit. The HRT match was based on status of current users or non-users. Non-users included women that have not taken HRT for at least two years. If a case was a current HRT user, the control was matched on this duration ($\pm 2$ years). Controls were matched by screening history using a three category classification. Group 1 included women with prior screening history by any means; the duration between the last screening and the study image date must be no more than 30
months. Group 2 included women with a screening history that does not fit within Group 1 or Group 3. Group 3 included women with no screening history. The unaffected breast was used as the study image for cases (image acquired before treatment) and the matching lateral breast for controls. Population characteristics are provided in Table 1. Women that had breast implants were excluded from this study.

2.2. Breast density measures

The work involved comparing the same Fourier domain spectral measurements taken from raw, processed, and calibrated mammograms (derived from raw mammograms). Two populations were investigated with mammograms acquired from different FFDM technologies. Each technology and unit had its own calibration data described previously (Heine and Behera 2006, Heine and Thomas 2008, Heine et al 2009, 2010, Fowler et al 2013, 2018, Lu et al 2015). Briefly, calibration adjusts for acquisition technique differences, resulting in a normalized intensity scale over this range (0, 100). This Fourier domain approach provided a set of measures that summarize the power of a given mammogram in a radial spatial frequency system, referred to as $P$ (Power), stemming from our earlier work (Heine and Velthuizen 2002). The power spectrum of a given mammogram was decomposed radially into $n$ concentric rings, where $n$ was an adjustable integer parameter. For a given system, $f_c$ applies in both the $f_x$ and $f_y$ directions. Figure 1 shows

![Fourier ring architecture illustration](image)

**Figure 1.** Fourier ring architecture illustration: this shows the ring layout in the two-dimensional Fourier plane. We use a relatively coarse ring-width example with $n = 11$ for illustrative purposes. Cartesian spatial frequency coordinates are referenced as $(f_x, f_y)$. The highest resolvable special frequency, $f_c$, is applicable to both frequency directions. This also shows a radial frequency variable defined as $f_r$. The radial width of a given ring measure is given by $f_r = \frac{f_c}{n}$ cycles mm$^{-1}$. Each ring corresponds to a specific radial frequency band. Ring labeling starts at $r = 0$ (center disk) to $r = n - 1 = 10$ (inner border of the outer ring); rings are gray shaded, where the inner ring is white and regions exterior to the last ring are black. The radial frequency bounds for the $r$th ring are expressed as $r \times \epsilon$ for the inner ring border and $(r + 1) \times \epsilon$ for the outer ring border; in this, example $f_r$ points to the inner boundary of the second ring that is $2 \times \epsilon$ from the origin. This mask is used as an overlay for the frequency spectrum of a given mammogram. Summing over the spectrum within each ring area produces $n = 11$ measures in this example designated as $P_r$. The portion of the spectrum exterior to the last ring (black), where $f_r > n \times \epsilon = 11 \times \epsilon$, is referred to as the corners; the sum over this area produces an additional measure.
the basic ring architecture in the two-dimensional Fourier plane using a coarse illustration (relatively large ring widths) with the relevant quantities labeled. In this example, \( n = 11 \) (integer ring indexing from \( r = 0 \), to \( n - 1 \)) giving ring widths in the radial direction defined as \( \varepsilon = f_c/n = f_c/11 \). The support region for any given ring measure is more easily described by considering a radial frequency variable \( f_r = r \times \varepsilon \) that ranges in radial spatial frequencies over this interval, \([ (r) \times \varepsilon, (r + 1) \times \varepsilon ] \) measured in cycles \( \text{mm}^{-1} \). In this example, summarizing the power in each ring would give 11 different ring measurements with each ring corresponding to a specific radial frequency band noting the center is a disk with diameter \( =2 \times \varepsilon \). The portion of the power spectrum exterior to the rings was considered separately, summarized, and used as another measure. These exterior regions are referred to as the corners. The ring-width lower limit is dependent upon the breast area size. The number of divisions, \( n \), must be less than half of the ROI shorter dimension (i.e. the \( x \)-dimension) to prevent degenerate ring widths, which scales with the breast area. In our work, we ensured that the ring-width was not less than the width of four pixels in the Fourier domain measured along the \( f_x \) coordinate axis. In general, the ring-width is an adjustable experiment parameter. Two measures were derived from the ring analysis. One measure was the summarized power in a given ring referenced as \( P_r \). The other related measure was normalized at the patient level given by \( P_r = P_r / (\text{total power from the rings excluding the center + the power in the corners}) \). Several automated processing steps were required to apply this methodology to mammograms: first, the breast was segmented from the background creating a binary mask; the largest rectangular region that fits within the breast area with trimmed margins was detected (Heine and Velthuizen 2002), discussed in more detail below; a separable two-dimensional

Figure 2. Region of interest algorithm illustration: (a) this shows a typical mammogram; (b) this shows the segmented breast area; (c) this shows six color coded rectangles inscribed with in the breast region selected from approximately 3000 possible rectangles; and (d) this shows the breast area plotted for all possible rectangles as function of their \( x \)-dimension with the six selected color-coded rectangles marked with their respective color-coded dots. The horizontal line marks \( 0.67 \times A_b \) and the vertical line marks the detected rectangle (black point).
Hanning window (Brigham 1988) was applied to this ROI; the ROI mean was removed; 2D Fourier transform (FT) was taken and the power spectrum was formed (the square of the FT magnitude); and the ring analysis was applied. We note, applying a Hanning window reduces spectral leakage with the tradeoff of spreading (blurring) the frequency resolution (Brigham 1988). The breast area segmentation was applied to the corresponding clinical display (for presentation) mammograms rather than the raw images. These Hologic processed images have two non-zero regions: the breast area (large area) and view maker (relatively small area). A simple threshold was used to form a binary image comprised of two separate regions; the smaller region was set to zero leaving the binary breast area mask. For these GE processed images, the breast area is the only non-zero region. The sum over all rings plus the corners is equivalent to the image variance (in our case the largest rectangle). The ring analysis essentially decomposes the image variation. This relationship was an approximation in this situation because of the Hanning window application.

For replication purposes, we have provided details for the algorithm used to locate the inscribed rectangular ROI that was developed previously. This method is a general approach that applies to both digitized film and FFDM images. This algorithm determines the rectangle with approximately the largest area that fits within a given breast area and then reduces this area by preset margins; this applies to rectangles that have sides paralleling the image borders. We defined $A_L$ as the area of the largest rectangle that can be inscribed within a given breast area. As discussed above, the number of rings was limited by the $x$-direction spatial extent of a given breast area. To mitigate this limitation, we preferred ROIs with larger $x$-dimensions. This was achieved by first finding the area for all rectangles that can be inscribed within a given breast area. Figure 2 provides a graphical illustration of the steps: (a) a typical mammogram; (b) segmented binary mask; (c) the binary mask with representative color-coded rectangles inscribed selected from approximately 3000 rectangles; (d) plot of all possible areas as a function of their $x$-dimension. The area curves were smoothed with a box car averaging filter of length 21. The color coded points in figure 2 correspond to the areas of the selected rectangles shown in (c). The area-curve for a given mammogram in (d) was searched starting at the $0.67 \times A_L$ intersection on the right portion of the plot for a derivative sign change. The search was performed in the $x$-direction. The reverse search order preferred regions with larger $x$-dimensions, and initiating the search at this intersection rather than finding $A_L$ directly is an empirical correction that accounts for poor breast area segmentation (i.e. most often with digitized film) where the area curve may not be smooth or have a clear maximum. In previous applications with similar FFDM images, the search found a rectangle within 5% of $A_L$ in 100% of the samples (i.e. the curves were very smooth), which was also the case for the mammograms used in this study. Figure 3 shows the detected region (black border) and the region with the trimmed margins (white border) for this example. In anatomical positions for CC mammograms, the trimmed region was determined by removing these margins (see figure 3 caption for more detail):
0.10 \times y\)-dimension from both the left and right sides (i.e. 0.20 in total), 0.10 \times x\)-dimension from the anterior side, and 0.01 \times x\)-dimension from the posterior side. The right, left, and anterior reductions removed breast area corresponding to where the breast may not have been uniformly compressed.

The ring analysis can be adjusted, producing many measurements per patient. Based on our earlier findings (Manduca et al. 2009), we initially performed a constrained low frequency search over (0.0, 1.0) cycles mm\(^{-1}\) using raw images from Population 1 to determine rings associated with breast cancer. We let the number or rings vary within this spectral range and found that $\varepsilon = 0.083$ produced two inner ring measures that were associated with breast cancer by comparisons across cases and controls with a paired $t$-test. In the more general spectral analysis, we used $\varepsilon = 0.083$ giving $n = 61$ for Population 1 and $n = 86$ for Population 2. This choice kept $\varepsilon$ constant across populations and was within the $x$-dimension width limitation discussed above. In both populations, we appended the power in the corners as an additional last point ($r = 61$ and $r = 86$, respectively). The goal was to find common spectral regions related to breast cancer status. This comparison analysis was applied to both raw and processed images. For each ring set, we performed a paired $t$-test at each ring across the case and controls (e.g. $P_i$ from the cases was compared with $P_i$ from the controls for all $r$) giving a set of comparisons internal to each population. Plotting the $p$-values for a given ring set provided a graphical technique to determine important regions in the Fourier spectra within a given population and note similar regions across populations. From experience in developing breast density measures, we used $p$-value $\leq 0.02$ as the upper threshold. When comparing these spectral measures across populations with $t$-test, findings with $p$-values greater than this threshold were not discussed.

The Cumulus (version 3, University of Toronto) application was implemented by an experienced operator in the batch mode to label processed mammograms only. Cases and controls were randomly mixed and the operator was blinded to all patient information and case-control status to ensure objectivity. This measure provided a performance metric for comparison because it has been investigated and validated on a wide-variety of datasets over extended timeframes (Harvey and Bovbjerg 2004, McCormack and dos Santos Silva 2006, Boyd et al. 2011, Boyd 2013, Eng et al. 2014, Pettersson et al. 2014) and it does not require data processing expertise.

Conditional logistic regression modeling was used to estimate breast cancer associations. Associations were developed for the same images in the raw, processed, and calibrated formats. Breast density distributions were log-transformed. Odds ratios (ORs) from both continuous and quartile models were used as the association metrics with 95% confidence intervals (CIs). Continuous ORs were estimated as per standard deviation (SD) increase determined from the respective breast density measurement distribution. In the quartile models, cut points were determined from the breast density distributions of the controls. We also considered the area under the receiver operating characteristic curve (Az) for each model with 95% CIs. Models will be presented as unadjusted and adjusted for body mass index (BMI) and ethnicity. When comparing proportions, we used the McNe- mar’s (exact) test for within population comparisons. When comparing continuous measures, we used the $t$-test. Image processing was performed in the IDL environment (Version 8.6, Exelis Visual Information Solutions, Inc., Jersey City, NJ) and regression analyses in the SAS environment (V9.4, SAS Institute Inc., Cary, NC).

3. Results

Patient characteristics for Population 1 are provided in table 1(a). Race varied across cases and controls to some degree. Caucasians ($p = 0.74$) and Asians ($p = 0.16$) were represented similarly, whereas African Americans had a greater representation in the control group (7.2%) compared with the case group (3.9%) ($p < 0.001$). Ethnicity was similar across cases and controls: Hispanics (0.84) and non-Hispanics (0.70). Cases had higher mean BMI ($p = 0.011$) than controls, but menopausal status was similar ($p = 0.076$). Cases had higher mean levels of breast density than controls for all measures except $P_1$-processed ($p = 0.075$); BD ($p = 0.017$); $P_1$-raw ($p = 0.001$); $P_1$-calibrated ($p = 0.022$); $P_1$-raw ($p = 0.002$); $P_1$-processed ($p = 0.001$); and $P_1$-calibrated ($p = 0.001$).

Patient characteristics for Population 2 are provided in table 1(b). Both Caucasian ($p = 0.91$) and African American ($p = 0.25$) women were represented similarly across cases and controls. Controls had a greater proportion of Hispanics compared with the cases ($p < 0.001$), whereas differences in BMI ($p = 0.07$) and menopausal status ($p = 0.46$) were not statistically significant. Cases had higher mean levels of breast density than controls for all measures except $P_1$-processed ($p = 0.11$); BD ($p = 0.023$); $P_1$-raw ($p = 0.002$); $P_1$-calibrated ($p = 0.008$); $P_1$-raw ($p = 0.003$); $P_1$-processed ($p = 0.003$); and $P_1$-calibrated ($p = 0.008$).

The Fourier ring analysis comparisons were performed with raw and processed images. In the comparison figures (figures 4–7) the upper plots show $p$-values for each ring. The dashed lines mark significance levels at 0.05 and 0.02 for reference in each plot. The lower plots show the corresponding $t$-statistics, where the dashed line marks $t$-statistic $= 0$ in each lower plot. Points above this line show where a given measure from the case group exhibited stochastic dominance and vice versa.
Table 1. (a) Population 1 characteristics: this table provides population 1 characteristics by either distribution mean for a given measure or percentages of the population. Where applicable, the standard deviation of the respective distribution is provided parenthetically. This population has images acquired with a General Electric Senographe 2000D unit. Breast density quantities were derived from log-transformed data for modeling. (b) Population 2 characteristics: this table provides population 2 characteristics by either distribution mean for a given measure or percentages of the population. When applicable, the standard deviation of the respective distribution is provided parenthetically. Breast density quantities were derived from log-transformed data for data modeling. This population has two-dimensional (2D) images from both conventional 2D Selenia and Dimensions digital breast tomosynthesis Hologic units.

(a) Population 1

| Measure     | p-values | Case N | Case mean standard deviation or percentage | Control N | Control mean standard deviation or percentage | Total N | Total mean standard deviation or percentage |
|-------------|----------|--------|------------------------------------------|-----------|-----------------------------------------------|---------|---------------------------------------------|
| Age         | 0.25     | 180    | 58.6 (10.5)                              | 180       | 58.5 (10.4)                                   | 360     | 58.6 (10.4)                                 |
| Race        |          |        |                                          |           |                                               |         |                                             |
| Caucasian   | 0.74     | 159    | 88.3%                                    | 162       | 90.0%                                         | 321     | 89.2%                                       |
| African-American | <0.0001 | 7      | 3.9%                                     | 13        | 7.2%                                          | 20      | 5.6%                                        |
| Asian       | 0.16     | 7      | 3.9%                                     | 3         | 1.7%                                          | 10      | 2.8%                                        |
| More than one | N/A | 2      | 1.1%                                     | 0         | 0.0%                                          | 2       | 0.6%                                        |
| Other       | N/A      | 4      | 2.2%                                     | 0         | 0.0%                                          | 4       | 1.1%                                        |
| Unknown     | <0.0001  | 1      | 0.6%                                     | 2         | 1.1%                                          | 3       | 0.8%                                        |
| Ethnicity   |          |        |                                          |           |                                               |         |                                             |
| Non-hispanic| 0.70     | 165    | 91.7%                                    | 162       | 90.0%                                         | 327     | 90.8%                                       |
| Hispanic    | 0.84     | 14     | 7.8%                                     | 16        | 8.9%                                          | 30      | 8.3%                                        |
| Unknown     | <0.0001  | 1      | 0.6%                                     | 2         | 1.1%                                          | 3       | 0.8%                                        |
| BMI         | 0.011    | 179    | 26.6 (4.6)                               | 180       | 25.3 (4.3)                                   | 359     | 25.9 (4.5)                                 |
| Screening group |      |        |                                          |           |                                               |         |                                             |
| Group 1     | N/A      | 162    | 90.0%                                    | 162       | 90.0%                                         | 324     | 90.0%                                       |
| Group 2     | N/A      | 13     | 7.2%                                     | 13        | 7.2%                                          | 26      | 7.2%                                        |
| Group 3     | N/A      | 5      | 2.8%                                     | 5         | 2.8%                                          | 10      | 2.8%                                        |
| HRT usage   |          |        |                                          |           |                                               |         |                                             |
| Current     | N/A      | 36     | 20.0%                                    | 36        | 20.0%                                         | 72      | 20.0%                                       |
| Not currently | N/A | 144   | 80.0%                                    | 144       | 80.0%                                         | 288     | 80.0%                                       |
| MS          | 0.08     |        |                                          |           |                                               |         |                                             |
| Pre-menopausal |      | 38     | 21.1%                                    | 48        | 26.7%                                         | 86      | 23.9%                                       |
| Menopausal  | 142      | 78.9%  |                                          | 132       | 73.3%                                         | 274     | 76.1%                                       |
| BD          | 0.017    | 180    | 2.9 (0.7)                                | 180       | 2.7 (0.8)                                     | 360     | 2.8 (0.8)                                   |
| P (raw)     | 0.0010   | 180    | 4.3 (0.8)                                | 180       | 4.0 (0.8)                                     | 360     | 4.1 (0.8)                                   |
| P (processed) |       | 0.075  | 5.5 (0.8)                                | 180       | 5.3 (0.8)                                     | 360     | 5.4 (0.8)                                   |
| P (calibrated) |    | 0.022  | -1.5 (1.1)                               | 180       | -1.7 (1.2)                                    | 360     | -1.6 (1.2)                                  |
| p (raw)     | 0.0017   | 180    | -0.9 (0.3)                               | 180       | -1.0 (0.3)                                    | 360     | -0.9 (0.3)                                  |
| p (processed) |       | 0.0010 | -0.9 (0.3)                               | 180       | -1.0 (0.3)                                    | 360     | -0.9 (0.3)                                  |
| p (calibrated) |     | 0.0005 | -0.9 (0.3)                               | 180       | -1.0 (0.3)                                    | 360     | -0.9 (0.3)                                  |

(b) Population 2

| Measure     | p-values | Case N | Case mean standard deviation or percentage | Control N | Control mean standard deviation or percentage | Total N | Total mean standard deviation or percentage |
|-------------|----------|--------|------------------------------------------|-----------|-----------------------------------------------|---------|---------------------------------------------|
| Age         | 0.13     | 319    | 58.8 (11.3)                              | 319       | 58.7 (11.3)                                   | 638     | 58.8 (11.3)                                 |
| Race        |          |        |                                          |           |                                               |         |                                             |
| Caucasian   | 0.91     | 273    | 85.6%                                    | 271       | 85.0%                                         | 544     | 85.3%                                       |
| African-American | 0.25 | 26    | 8.2%                                     | 36        | 11.3%                                         | 62      | 9.7%                                        |
| Asian       | 1.00     | 8      | 2.5%                                     | 8         | 2.5%                                          | 16      | 2.5%                                        |
| More than one | 0.63 | 3      | 1.0%                                     | 1         | 0.3%                                          | 4       | 0.6%                                        |
| Other       | N/A      | 3      | 1.0%                                     | 0         | 0.0%                                          | 3       | 0.5%                                        |
| Unknown     | 0.51     | 6      | 1.9%                                     | 3         | 0.9%                                          | 9       | 1.4%                                        |

(Continued)
Comparisons
When comparing across populations, rings 0–60 were comparable. Rings above this correspond to spatial frequencies beyond 5 cycles mm\(^{-1}\) (in a rectangular spatial frequency coordinate system) and do not exist in 100 \(\mu\)m images (Population 1). For raw P, the first ring (\(f_r = 0.083–0.166\) cycles mm\(^{-1}\)) and rings 16–61 (\(f_r = 1.66–7.07\) cycles mm\(^{-1}\)) were predictive of case status in Population 1; for processed P, the first ring was predictive, whereas rings 43–45 and 47–61 were predictive of control status. For raw P in Population 2, rings 1–34 (\(f_r = 0.083–2.91\) cycle mm\(^{-1}\)) were in predictive of case status; in contrast, the processed data showed no preference. In sum, rings 1 and 16–34 (\(f_r = 1.33–2.91\) cycles mm\(^{-1}\)) were coincident across populations in the raw data and predictive of case status.

For \(p\) (normalized), the first ring was predictive of case status (raw and processed) and rings 5–61 (raw and processed) were predictive of control status in Population 1. For Population 2, the normalized measure from the first ring (raw) was also predictive of case status, whereas rings 25–86 (\(f_r = 2.1–10.1\) cycles mm\(^{-1}\)) for raw data and rings 18–60 (\(f_r = 1.49–5.56\) cycles mm\(^{-1}\)) for processed data were coincident across populations and predictive of control status (the 61st ring in Population 1 captured the corners, whereas the 61st ring in Population 2 is a one ring-band measure indicating the two are not directly comparable). In sum, it is interesting to note that the normalized raw plots for both populations appear similar across populations.

In the following breast cancer association comparisons, ORs and Azs are provided with 95% confidence intervals parenthetically. To limit the presentation, we compared continuous and quartile adjusted models. For continuous models, ORs are cited as per standard deviation increases determined from the log-transformed distributions. For quartile models, ORs are cited as per quartile adjustments determined from the log-transformed distributions. For the quartile models, we compared the fourth quartile.

Breast cancer associations for BD are shown in Table 2. These were used for standard reference comparisons. BD provided significant ORs in the continuous models: OR = 1.72 (1.27, 2.33) with Az = 0.64 (0.57, 0.71) for Population 1; and OR = 1.43 (1.17, 1.76) with Az = 0.62 (0.56, 0.67) for Population 2. In the quartile models, BD provided significant fourth quartile associations: OR = 3.25 (1.53, 6.88) with Az = 0.63 (0.56, 0.70) and OR = 2.27 (1.29, 4.00) with Az = 0.65 (0.59, 0.70) for Population 1 and 2, respectively.

### Table 1. (Continued)

| Measure | Population 2 |
|---------|--------------|
|         | p-values | Case N | Case mean standard deviation or percentage | Control N | Control mean standard deviation or percentage | Total N | Total mean standard deviation or percentage |
| Ethnicity | Non-Hispanic | 0.0008 | 287 | 90.0% | 258 | 80.9% | 545 | 85.4% |
| | Hispanic | 0.0003 | 29 | 9.1% | 59 | 18.5% | 88 | 13.8% |
| | Unknown | 1.00 | 3 | 0.9% | 2 | 0.6% | 5 | 0.8% |
| BMI | 0.07 | 319 | 28.7 (6.0) | 314 | 27.8 (6.6) | 632 | 28.3 (6.3) |
| Screening group | Group 1 | N/A | 224 | 70.2% | 224 | 70.22% | 448 | 70.22% |
| | Group 2 | N/A | 58 | 18.9% | 58 | 18.2% | 116 | 18.2% |
| | Group 3 | N/A | 37 | 11.6% | 37 | 11.6% | 74 | 11.6% |
| HRT usage | Current | N/A | 18 | 5.6% | 18 | 5.6% | 36 | 5.6% |
| | Not currently | N/A | 301 | 94.4% | 301 | 94.4% | 602 | 94.4% |
| MS | 0.46 |
| Pre-menopausal | 79 | 24.8% | 73 | 22.9% | 152 | 23.8% |
| Menopausal | 240 | 75.2% | 246 | 77.1% | 486 | 76.9% |
| BD | 0.023 | 319 | 3.1 (0.5) | 319 | 3.0 (0.5) | 638 | 3.1 (0.5) |
| \(P_1\) (raw) | 0.0023 | 319 | 2.6 (1.0) | 319 | 2.4 (1.0) | 638 | 2.5 (1.0) |
| \(P_1\) (processed) | 0.11 | 319 | 8.5 (0.7) | 319 | 8.3 (0.8) | 638 | 8.4 (0.8) |
| \(P_1\) (calibrated) | 0.0085 | 319 | -1.2 (1.1) | 319 | -1.4 (1.3) | 638 | -1.3 (1.2) |
| \(p_1\) (raw) | 0.0027 | 319 | -1.2 (0.4) | 319 | -1.3 (0.4) | 638 | -1.2 (0.4) |
| \(p_1\) (processed) | 0.0035 | 319 | -1.2 (0.4) | 319 | -1.3 (0.4) | 638 | -1.2 (0.4) |
| \(p_1\) (calibrated) | 0.0080 | 319 | -1.1 (0.4) | 319 | -1.2 (0.4) | 638 | -1.2 (0.4) |
The ring comparison indicated that the first ring was similar across populations. We examined the \( P_1 \) and \( p_1 \) measures. Population 1 results for the ring analysis are provided in table 3. Note that associations for \( P_1 \) as a continuous variable were statistically significant for all representations and the magnitude of the ORs were nearly identical. Results based on quartiles revealed that \( p_1 \) associations with risk were stronger for calibrated images (OR = 5.25) than processed (OR = 3.74) or raw images (OR = 3.64), although the Az values were nearly identical. In total, the associations provided by these measures were at least equivalent to those produced by BD.

Population 2 results are provided in table 4. The associations and Az for \( P_1 \) as a continuous variable were statistically significant for all representations and the magnitude of the ORs were similar. The fourth quartile associations were also statistically significant for all representations with similar magnitude and Az. The associations and Az for \( p_1 \) were also similar to those produced by \( P_1 \) in this population. The associations provided both measurement variants for all representations were at least equivalent to those produced by BD.

We briefly discuss other coincident rings. Rings 16–34 were similar in the raw format across populations. We summed the power in these rings producing one measure referred to as \( P_{16-34} \). As a continuous measure from raw data, \( P_{16-34} \) produced significant associations in the adjusted models: OR = 1.52 (1.11, 1.97) with Az = 0.62 (0.55, 0.69) in Population 1; and OR = 1.48 (1.09, 2.01) with Az = 0.62 (0.56, 0.67) for Population 2. We performed a similar investigation for the normalized measure by summing rings 25–60 for both populations producing \( p_{25-60} \) where the control measure (raw data) showed stochastic dominance (inverse relationship). As a continuous variable, this measure produced significant associations in the adjusted model: OR = 0.64 (0.50, 0.83) with Az = 0.64 (0.57, 0.71) for Population 1; and OR = 0.74 (0.61, 0.89) with Az = 0.63 (0.57, 0.68) for Population 2.

As noted, the Fourier ring measures can equivalently be viewed as texture measures in the image domain. Specifically, examples are provided illustrating textures (structure). Figure 8 shows a mammogram from Popu-
To illustrate texture captured by both an isolated ring and a range of rings, we used the respective rings(s) as a filter by taking the FT of the rectangular region (without the Hanning window application), multiplying by the ring(s), followed by Fourier inversion. Figure 9 (top-left) illustrates the structure captured by the first ring. If we consider a radial spatial frequency variable, \( f_r \), the inner radial boundary for the first ring is given by \( f_r = \Delta = 0.083 \text{ cycles mm}^{-1} \) for both \( P_1 \) and \( p_1 \). Likewise, the first ring outer radial boundary is given by \( f_r = 2 \times \Delta = 0.166 \text{ cycles mm}^{-1} \). The radial spatial frequency components within this band have radial spatial periodicities (i.e. \( 1/f_r \)) between 6–12 mm. Figure 9 (top-middle) shows the structure captured by rings 16–34, where cases exhibited stochastic dominance across the populations (\( P_{16-34} \)). This band range equates with radial spatial periodicities between 0.34–0.75 mm. Figure 9 (top-right) shows the structure captured by rings 25–60, where the controls exhibited dominance for the normalized measure (i.e. \( p_{25-60} \)). The associated band range equates with radial spatial periodicities between 0.20–0.48 mm. The associated bands are illustrated in the bottom row with color coding. Figure 9 also demonstrates the multiresolution aspects of the ring analysis. The lower spatial frequency rings account for the more coarse structure, whereas the higher spatial frequencies tend to account for finer detail.

4. Discussion

Fourier power spectra of mammograms were decomposed with the ring analyses in a radial spatial frequency coordinate system and comparisons were made across FFDM technologies. The data representation influenced...
the relationships of the spectral components with breast cancer status. This is illustrated in both populations when comparing the raw and processed data representations (see top plots in figures 4 and 5). Common regions in the Fourier domain predictive of breast cancer across technologies were isolated. The primary regions predictive of case status were related to lower radial spatial frequencies captured by both the $P_1$ and $p_1$ metrics and more mid-bands captured by $P_{16-34}$. The normalized comparisons showed that $p_{25-60}$, a wider band region, was predictive of control status. In comparison with BD, these measures provided at least equivalent associations with breast cancer within populations. For Population 1, this applied to $P_1$ from raw and calibrated data and to $p_1$ for all representations. For Population 2 and ring $= 1$, all Fourier measures considered were at least equivalent to BD. We note our findings for continuous BD in this report are in agreement with a recent meta-analysis that examined percentage of breast density measures including BD (Petterson et al 2014).

There has been considerable work in relating textures to breast cancer risk (He et al 2015, Gastounioti et al 2016). There is a duality between applying filters in the image domain and spectral analyses in the Fourier domain. The Fourier domain view is normally not the focus of cancer epidemiologic studies. In contrast, our approach considered both views. Our approach can be considered as a multiresolution analysis measured in a radial direction, consistent across varying conditions. We found both a specific lower radial frequency band (i.e. $P_1$) corresponding to specific spatial periodicities and a multiple band region ($P_{16-34}$) corresponding to a wider range of spatial periodicities were predictive of case status. The normalized measures are relative (relative scale) to each woman and isolated two important spectral regions; one very narrow band related to case status ($p_1$) and a wide-band ($P_{25-60}$) related to control status. In contrast, often the focus of texture work is multivariate in

Figure 6. Ring analyses for population 2: this shows the ring analysis for $P$ applied to images acquired with the Hologic units for the raw on the left and for processed (proc) images on the right. The spectrum was divided into 86 rings (bands) and the corners. Top plots give the $p$-values for each band; dashed lines mark the 0.05 and 0.02 significance levels for reference in each plot. The bottom plots show the associated $t$-statistics. The dashed line marks the $t$-statistic $= 0$; points above this line indicate the case group measure exhibited stochastic dominance.
Figure 7. Normalized ring analyses for population 2. This shows the ring analysis for \( p \) (normalized) applied to images acquired with the Hologic units for the raw on the left and processed (proc) images on the right. The spectrum was divided into 86 rings (bands) and the corners. Top plots give the \( p \)-values for each band; dashed lines mark 0.05 and 0.02 significance levels for reference in each plot. The bottom plots show the associated \( t \)-statistics. The dashed line marks where the \( t \)-statistic = 0; points above this line indicate the measure from the case group exhibited stochastic dominance.

Table 2. Percentage of breast density: this table gives the percentage of breast density (BD) associations from the Cumulus method for population 1 (left) and population 2 (right). Breast density distributions were log-transformed. Continuous ORs are provided in per standard deviation (SD) increase. Models are provided in both unadjusted and adjusted for BMI and ethnicity. The area under the receiver operating characteristic curve (Az) is also provided for each model.
Table 3. Population 1 Breast Cancer Associations for the \( P_1 \) and \( p_1 \): this table gives quartile (Qrt) and continuous (Con) odds ratios (ORs) for \( P_1 \) (top) and normalized \( p_1 \) (bottom) for population 1. The three data formats from left to right are raw, processed and calibrated. The area under the receiver operating character curve (Az) is also provided for each model. Breast density distributions were log-transformed. Continuous ORs are provided in per standard deviation (SD) increase. Models are provided in both unadjusted and adjusted for BMI and ethnicity.

### \( P_1 \) (raw)

| Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) |
|-----|--------------|------------------------|-------------------------------------|-----|--------------|------------------------|-------------------------------------|-----|--------------|------------------------|-------------------------------------|
| 1   | 24           | 1.00 (Ref.)            | 1.00 (Ref.)                         | 1   | 35           | 1.00 (Ref.)            | 1.00 (Ref.)                         | 1   | 32           | 1.00 (Ref.)            | 1.00 (Ref.)                         |
| 2   | 51           | 2.20 (1.15, 4.21)      | 3.00 (1.46, 6.14)                   | 2   | 38           | 1.08 (0.57, 2.04)      | 1.28 (0.66, 2.47)                   | 2   | 32           | 1.58 (0.86, 2.91)      | 2.12 (1.10, 4.11)                  |
| 3   | 42           | 1.89 (0.93, 3.83)      | 2.96 (1.33, 6.60)                   | 3   | 48           | 1.53 (0.80, 2.93)      | 2.05 (1.01, 4.15)                   | 3   | 34           | 1.17 (0.59, 2.32)      | 1.86 (0.87, 3.99)                  |
| 4   | 63           | 2.96 (1.48, 5.89)      | 5.34 (2.37, 12.0)                   | 4   | 59           | 1.77 (0.96, 3.26)      | 2.53 (1.28, 4.98)                   | 4   | 62           | 1.93 (1.03, 3.61)      | 3.29 (1.57, 6.89)                  |
| Az  | 0.60 (0.52, 0.67) | 0.66 (0.59, 0.73) | Az | 0.57 (0.50, 0.64) | 0.64 (0.57, 0.71) | Az | 0.58 (0.50, 0.65) | 0.66 (0.59, 0.72) |

### \( P_1 \) (processed)

| Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) |
|-----|--------------|------------------------|-------------------------------------|-----|--------------|------------------------|-------------------------------------|-----|--------------|------------------------|-------------------------------------|
| 1   | 32           | 1.00 (Ref.)            | 1.00 (Ref.)                         | 1   | 30           | 1.00 (Ref.)            | 1.00 (Ref.)                         | 1   | 27           | 1.00 (Ref.)            | 1.00 (Ref.)                         |
| 2   | 44           | 1.43 (0.75, 2.74)      | 1.68 (0.85, 3.32)                   | 2   | 43           | 1.53 (0.79, 2.97)      | 1.69 (0.84, 3.40)                   | 2   | 42           | 1.88 (0.92, 3.84)      | 1.97 (0.93, 4.19)                  |
| 3   | 38           | 1.20 (0.61, 2.38)      | 1.66 (0.80, 3.45)                   | 3   | 40           | 1.43 (0.73, 2.79)      | 1.92 (0.93, 3.94)                   | 3   | 38           | 1.68 (0.84, 3.36)      | 2.18 (1.04, 4.60)                  |
| 4   | 66           | 2.29 (1.20, 4.36)      | 3.64 (1.75, 7.56)                   | 4   | 67           | 2.51 (1.30, 4.84)      | 3.74 (1.81, 7.72)                   | 4   | 73           | 3.49 (1.71, 7.13)      | 5.25 (2.39, 11.5)                  |
| Az  | 0.58 (0.50, 0.65) | 0.67 (0.60, 0.74) | Az | 0.57 (0.50, 0.64) | 0.65 (0.58, 0.72) | Az | 0.61 (0.53, 0.68) | 0.66 (0.59, 0.73) |

### \( P_1 \) (calibrated)

| Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Qrt | Case N = 180 | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) |
|-----|--------------|------------------------|-------------------------------------|-----|--------------|------------------------|-------------------------------------|-----|--------------|------------------------|-------------------------------------|
| 1   | 32           | 1.00 (Ref.)            | 1.00 (Ref.)                         | 1   | 30           | 1.00 (Ref.)            | 1.00 (Ref.)                         | 1   | 27           | 1.00 (Ref.)            | 1.00 (Ref.)                         |
| 2   | 44           | 1.43 (0.75, 2.74)      | 1.68 (0.85, 3.32)                   | 2   | 43           | 1.53 (0.79, 2.97)      | 1.69 (0.84, 3.40)                   | 2   | 42           | 1.88 (0.92, 3.84)      | 1.97 (0.93, 4.19)                  |
| 3   | 38           | 1.20 (0.61, 2.38)      | 1.66 (0.80, 3.45)                   | 3   | 40           | 1.43 (0.73, 2.79)      | 1.92 (0.93, 3.94)                   | 3   | 38           | 1.68 (0.84, 3.36)      | 2.18 (1.04, 4.60)                  |
| 4   | 66           | 2.29 (1.20, 4.36)      | 3.64 (1.75, 7.56)                   | 4   | 67           | 2.51 (1.30, 4.84)      | 3.74 (1.81, 7.72)                   | 4   | 73           | 3.49 (1.71, 7.13)      | 5.25 (2.39, 11.5)                  |
| Az  | 0.58 (0.50, 0.65) | 0.67 (0.60, 0.74) | Az | 0.57 (0.50, 0.64) | 0.65 (0.58, 0.72) | Az | 0.61 (0.53, 0.68) | 0.66 (0.59, 0.73) |
Table 4. Population 2 Breast Cancer Associations for $P_1$ and $p_1$: this table gives quartile (Qrt) and continuous (Con) odds ratios (ORs) for $P_1$ (top) and normalized $p_1$ (bottom) for population 2. The three data formats from left to right are raw, processed and calibrated. The area under the receiver operating character curve (Az) is also provided for each model. Breast density distributions were log-transformed. Continuous ORs are provided in per standard deviation (SD) increase. Models are provided in both unadjusted and adjusted for BMI and ethnicity.

|           | $P_1$ (raw) |           | $P_1$ (processed) |           | $P_1$ (calibrated) |
|-----------|-------------|-----------|-------------------|-----------|-------------------|
|           | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) |
| Qrt       | Case N = 319 |           | Qrt              | Case N = 319 |           | Qrt               | Case N = 319 |           | Qrt               | Case N = 319 |           | Qrt               | Case N = 319 |           |
| 1         | 62          | 1.00 (Ref.) | 1.00 (Ref.)      | 1           | 47          | 1.00 (Ref.)      | 1            | 52          | 1.00 (Ref.)      |
| 2         | 77          | 1.28 (0.81, 2.02) | 1.47 (0.91, 2.37) | 2           | 89          | 1.86 (1.17, 2.95) | 2           | 81          | 1.59 (0.99, 2.57) |
| 3         | 77          | 1.34 (0.83, 2.17) | 1.69 (1.01, 2.81) | 3           | 99          | 2.15 (1.33, 3.50) | 3           | 97          | 1.93 (1.19, 3.11) |
| 4         | 103         | 1.91 (1.15, 3.18) | 2.36 (1.36, 4.08) | 4           | 84          | 1.85 (1.13, 3.01) | 4           | 89          | 1.75 (1.09, 2.83) |
| Az        | 0.56 (0.31, 0.62) | 0.63 (0.58, 0.69) | Az              | 0.54 (0.49, 0.59) | 0.66 (0.61, 0.71) | Az               | 0.57 (0.51, 0.62) | 0.63 (0.58, 0.69) |
| Log Con   | SD          | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Log Con | SD          | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Log Con | SD          | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) |
|           | 1.0361      | 1.33 (1.10, 1.60) | 1.47 (1.19, 1.80) | 0.7668     | 1.23 (1.05, 1.44) | 1.38 (1.15, 1.67) | 1.1856     | 1.25 (1.05, 1.48) | 1.42 (1.15, 1.75) |
| Az        | 0.59 (0.54, 0.62) | 0.63 (0.58, 0.69) | Az              | 0.57 (0.52, 0.62) | 0.61 (0.56, 0.66) | Az               | 0.59 (0.54, 0.64) | 0.61 (0.56, 0.66) |

|           | $p_1$ (raw) |           | $p_1$ (processed) |           | $p_1$ (calibrated) |
|-----------|-------------|-----------|-------------------|-----------|-------------------|
|           | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) |
| Qrt       | Case N = 319 |           | Qrt              | Case N = 319 |           | Qrt               | Case N = 319 |           | Qrt               | Case N = 319 |           | Qrt               | Case N = 319 |           |
| 1         | 51          | 1.00 (Ref.) | 1.00 (Ref.)      | 1           | 53          | 1.00 (Ref.)      | 1            | 49          | 1.00 (Ref.)      |
| 2         | 80          | 1.55 (0.99, 2.43) | 1.74 (1.08, 2.80) | 2           | 83          | 1.57 (0.99, 2.48) | 2           | 92          | 1.78 (1.14, 2.78) |
| 3         | 103         | 2.09 (1.30, 3.37) | 2.54 (1.52, 4.24) | 3           | 87          | 1.68 (1.05, 2.67) | 3           | 91          | 1.87 (1.16, 3.03) |
| 4         | 85          | 1.73 (1.07, 2.80) | 2.34 (1.35, 4.03) | 4           | 96          | 1.93 (1.18, 3.15) | 4           | 87          | 1.80 (1.11, 2.93) |
| Az        | 0.59 (0.54, 0.64) | 0.62 (0.57, 0.68) | Az              | 0.56 (0.51, 0.62) | 0.61 (0.56, 0.66) | Az               | 0.57 (0.52, 0.62) | 0.64 (0.59, 0.70) |
| Log Con   | SD          | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Log Con | SD          | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) | Log Con | SD          | Unadjusted OR (95% CI) | BMI and ethnicity adjusted OR (95% CI) |
|           | 0.4062      | 1.29 (1.09, 1.52) | 1.46 (1.20, 1.77) | 0.3799     | 1.28 (1.08, 1.52) | 1.44 (1.19, 1.75) | 0.3996     | 1.25 (1.06, 1.47) | 1.40 (1.16, 1.69) |
| Az        | 0.58 (0.53, 0.64) | 0.63 (0.57, 0.68) | Az              | 0.57 (0.51, 0.62) | 0.63 (0.57, 0.67) | Az               | 0.57 (0.52, 0.62) | 0.61 (0.56, 0.66) |
character (Nielsen et al 2014, Zheng et al 2015, Wang et al 2017, Wanders et al 2018) where the precise description of a given feature is not the primary interest.

The results for the inner ring also agree with our previous work that analyzed digitized film mammograms derived from a screening practice, where associations were also compared with BD (Manduca et al 2009). Our findings, past and present, are an indication that the structure captured from this inner band is robust across mammographic imaging platforms and data representations. This lower band similarity is consistent with characteristics common to imaging systems. The modulation transfer function is often unity at very low spatial frequencies for mammography systems and decreases as frequency increases (Bick and Diekmann 2010). We also found measures from multiple band regions were consistent across platforms indicating these may also be robust metrics, noting that the MTFs generally vary across FFDM systems and screen-film over the spatial frequency domain (Bick and Diekmann 2010). The normalized ring analysis may be the preferred approach when merging data from different sources because it accounts for scaling differences between data sources. Our findings also show that calibration is not required when using these Fourier metrics because the other data representations provided similar magnitudes of breast cancer risk associations. We note, the associations for Population 1 were stronger than Population 2. This may be due to population attributes. Population 1 does not include women with the full spectrum of breast sizes due to the limited detector field of view for the specific mammography unit. This variation could also be due to the sample size of Population 1 relative to Population 2.

We made comparisons with BD. In one context, our approach could provide another way of measuring risk from mammograms because the automated algorithm is relatively simple and does not require thresholds. In another context, these Fourier measures emphasize certain spatial scales within the mammographic structure. These metrics may provide additional information associated with risk because our analysis removed the mean intensity, which is more related to average breast density. The biological mechanisms relating breast density (or breast structure) and breast cancer are largely unknown (Boyd et al 2011, Pettersson and Tamimi 2014, Sherratt et al 2016). A more analytical description of breast structure has the potential to better inform future studies in understanding the biology of risk.
There are several limitations with our study. Sampling of cases and controls was not population-based, but rather a mixture of cases ascertained at an NCI-designated comprehensive cancer center inclusive of referrals from the community. There is no evidence that the cases are not representative, but the current findings should be replicated in a population-based study. The analysis was also restricted to relatively large rectangular regions, indicating a portion of the breast area was excluded from the analyses. Mammograms are three-dimensional volumes projected onto two-dimensions producing overlapping structures or anatomical noise, which is a fundamental limitation for clinical purposes. In our analysis, it is not clear if this is a limitation. It may be that the strength of our signal (bands associated with breast cancer) is dependent upon anatomical noise. Using BD as a control reference indicates these artifacts have negligible impact on the findings. The ring analysis results in metrics with excellent radial spatial frequency resolution due to the well-defined and infinity steep boundaries between each ring. The price for this spatial frequency localization is poor spatial localization in the image domain. This tradeoff is not relevant for our current work because the interest is a global breast measurement rather than a localized one. The ring measures consider radial symmetry implying the image structure lacks directionality. This is only a limitation in this study because the ring analysis can be easily modified to consider radial arcs corresponding to directionality in the image domain.

5. Conclusion

There is a critical need to measure breast density accurately because it is instrumental for various clinical applications. These applications include dictating the BI-RADS tissue composition reporting and for risk prediction purposes. Evidence indicates that many women may experience shifts in their composition classification due to operator variability (Melnikow et al 2016). Although there are many studies assessing various breast density methods for risk prediction, currently there is no clinical standard (Destounis et al 2017), and it is not included routinely in clinical risk assessments (S G K Foundation). An accepted standardized measure of breast density is required to fully actualize the benefits of personalized breast screening and interventions. Future
work includes evaluating these Fourier metrics in other study populations, including population-based samples, to enhance generalizability.

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Conflicts of interest

The authors have patents and pending patent applications in related work.

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