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Assessment of Quantitative MRI Background Parenchymal Enhancement Parameters to Improve Determination of Individual Breast Cancer Risk

Diana L. Lam, MD¹, Daniel S. Hippe, MS¹, Averil E. Kitsch, BS¹, Savannah C. Partridge, Ph.D¹, and Habib Rahbar, MD¹

¹Department of Radiology, University of Washington School of Medicine, Seattle Cancer Care Alliance, 825 Eastlake Avenue East, G2-600, Seattle, WA 98109-1023

Abstract

Objectives—To identify optimal quantitative breast MRI background parenchymal enhancement (BPE) parameters associated with breast cancer risk and compare performance to qualitative assessments.

Methods—Using a matched case-control cohort of 46 high-risk women who underwent screening MRI (23 who developed breast cancer matched to 23 who did not), fibroglandular tissue area, BPE area, and intensity metrics (mean, standard deviation, quartiles, skewness, and kurtosis) were quantitatively measured at varying enhancement thresholds. Optimal thresholds for discriminating between cancer and control cohorts were identified for each metric and performance summarized using area under the receiver operating characteristic curve (AUC).

Results—Women who developed breast cancer exhibited greater BPE area (adjusted $p=0.004$) and higher intensity statistics (adjusted $p<0.004$, except skewness and kurtosis with $p>0.99$) than controls, with AUCs ranging from 0.75-0.78 at optimized thresholds.

Conclusions—Elevated quantitative BPE parameters, related to both area and intensity of enhancement, are associated with breast cancer development.

Keywords

breast; magnetic resonance imaging; risk assessment; background parenchymal enhancement; breast cancer

Introduction

Breast cancer is the second leading cause of cancer related deaths in women. Early detection with screening mammography reduces patient mortality [1–4], and its value persists in microsimulation models, even with modern advances in treatment [5]. However, mammography performs less well in some subsets of women, particularly those who are at higher than average lifetime risk [6; 7]. Accordingly, the American Cancer Society

recommends screening breast MRI in addition to mammography in women with >20% lifetime risk of developing breast cancer [8].

Precise determination of an individual's breast cancer risk to inform eligibility for breast MRI and risk-reducing strategies is a challenge. Currently, breast cancer risk assessments are reliant on models that weigh factors common in the general population, such as family history and hormonal exposures [9; 10]. Furthermore, while these clinical models are helpful at predicting risk at the population level, they are less accurate in estimating which individual woman will develop breast cancer.

Imaging markers of breast cancer risk may be capable of augmenting clinical risk assessments. It is well established that mammographic density is associated with elevated breast cancer risk; however, clinical incorporation of this imaging parameter using qualitative systems such as the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) has been challenging due to inter-observer variability [11; 12]. Qualitative background parenchymal enhancement (BPE) assessment, based on visual assessment of the amount and intensity of normal tissue enhancement on dynamic contrast enhanced (DCE) MRI, holds promise as a more accurate imaging feature to refine breast cancer risk assessments [13–15]. However, visual assessments of BPE are subjective and also prone to inter and intra-observer variability. Thus, the development of a robust approach to objectively measure the amount of fibroglandular tissue (FGT), a correlate to mammographic breast density, and BPE levels on MRI could lead to better integration of these markers into individual breast cancer risk assessments [16–19].

With this goal, we developed a semi-automated MR image-processing tool to quantitatively measure a variety of FGT and BPE characteristics [20]. Using a case-control cohort of high-risk patients who underwent screening breast MRI, we aimed to identify and optimize quantitative parameters associated with risk of developing breast cancer. Furthermore, we sought to compare the degree of association of these quantitative parameters with future breast cancer diagnosis versus standard qualitative BPE assessments.

Material and Methods

Study population

In this institutional review board approved, Health Insurance Portability and Accountability Act-compliant study, we used a case-control matched cohort comprised of 23 women with a breast cancer invasive cancer or ductal carcinoma in situ (DCIS) diagnosed at any time-point after screening MRI and 23 women who did not have breast cancer diagnosed by the time of our tumor-registry query. This 1:1 matched case control was identified from a total of 487 asymptomatic women who underwent high-risk screening breast MRIs from January 2006 through December 2011 at our institution. Women in the cohort were 18 years of age with no personal history of breast cancer but considered high-risk due to having a genetic mutation (or untested 1st degree relative) such as BRCA1 or 2, a genetic syndrome (e.g., Li Fraumeni or Cowden's syndrome), a history of chest irradiation under the age of 30, or a >20% lifetime risk based on a clinical model that incorporates family history (e.g., Tyrer-Cuzick). In the case of a single subject having multiple high-risk screening MRIs during the

study period, only the earliest (index) examination was included. After identifying the 23 women in our case group, potential control cases were identified from the remaining 464 women who did not receive a diagnosis of breast cancer during the study period. The 1:1 case to control matching was achieved by randomly selecting a negative control case, matched both with age and BRCA mutation status, while maximizing MRI follow-up time for the negative controls. In the cancer cohort, time to diagnosis was defined as the time from index MRI to the date of biopsy that led to the cancer diagnosis. In the control cohort, follow-up time was defined as the time of index MRI to the time of tumor-registry inquiry performed September 30, 2013.

MRI Technique

Two MRI scanning protocols were used during our study period: one from January 2006 - January 2010 performed on a 1.5 tesla (T) GE Signa LX scanner (GE Healthcare, Waukesha, WI, USA) and the second from January 2010 - December 2011 performed on a 3T Philips Achieva TX scanner (Philips Healthcare, Best, the Netherlands). Both MRI protocols were in compliance with American College of Radiology breast MRI accreditation program guidelines [21]. For both protocols, imaging was performed in the axial plane and included pre-contrast and at least two post-contrast T1-weighted fat-suppressed 3D fast spoiled gradient recalled acquisitions. Gadolinium contrast material (Omniscan, GE Healthcare) was power injected (0.1 mmol/kg at 2 mL/s) followed by a 20 mL saline flush for all examinations. All exams were processed using a computer-aided evaluation system (CADstream, Merge Healthcare, Chicago, IL) and reviewed on high-resolution picture archiving and communication system monitors.

For the 1.5T protocol, an 8-channel dedicated breast coil (Sentinelle, Invivo) was used and DCE was acquired with the following parameters: repetition time/echo time, 5.5/2.7 msec; flip angle, 10°; field of view, 32-38 cm; 0.85 × 0.85 mm in-plane, slice thickness, 1.6 mm, and matrix size, 420 × 420. For the 3T protocol, a 16-channel dedicated breast coil (Mammotrak, Philips Healthcare) was used and DCE was acquired with the following parameters: repetition time/echo time, 5.9/3.0 msec; flip angle, 10°; field of view, 22-33 cm; 0.5 × 0.5 mm in-plane, slice thickness, 1.3 mm, and matrix size, 440 × 660. Scan time was approximately 180 seconds per acquisition for both 1.5 and 3T, with initial contrast-enhanced acquisition centered between 90 and 110 seconds after contrast material administration.

MRI Quantification

BPE quantification was performed using customized software developed in MATLAB (Mathworks, Natick, MA). On the dynamic contrast enhanced (DCE) series, a single slice of one breast at or near the level of the nipple, felt to be most representative of the patient's fibroglandular tissue (FGT), was selected for analysis by a radiologist (BLINDED FOR REVIEW) with 8 years of radiology experience, blinded to outcomes. In patients who had suspicious findings described on the MRI in one breast, the contralateral breast was used for quantification. A research scientist with 2 years of experience in quantitative breast MR analysis was trained to perform the segmentation. First, whole breast area was calculated by segmenting the breast using a semi-automated edge extraction algorithm with manual

definition of the chest wall, Figure 1a. Next, an automated threshold was applied to the pre-contrast DCE image to segment FGT from adipose tissue within the whole breast area. The FGT boundary was then manually refined to exclude the nipple and large vessels from the FGT calculation, Figure 1b. FGT area was calculated from the segmentation, as well as FGT area to whole breast area ratio.

BPE-maps were generated by calculating the percent enhancement (PE) for each voxel within the FGT

$$PE = (S_1 - S_0)/S_0 \times 100 \quad (1)$$

where S_0 and S_1 are the signal intensity on the pre-contrast and first post-contrast DCE images, respectively. BPE-maps were generated for varying PE thresholds - specifically, 10%, 20%, 30%, 40%, 50%, 60%, 70% - where only voxels equal to or greater than the minimum threshold were included in the map, Figure 2. Higher thresholds could not be reliably assessed due to the limited number of voxels meeting the enhancement criteria in many of the women. A total of 10 quantitative parameters were calculated for each BPE-map, including BPE area (mm^2), BPE area to FGT area ratio, BPE intensity statistics (25th percentile, median, 75th percentile, mean, standard deviation [SD], skewness, and kurtosis), and integrated intensity (BPE area multiplied by mean BPE intensity [mm^2]). If no voxels met the given threshold, the area and integrated intensity parameters were defined as 0. For the remaining BPE intensity statistics, values were considered missing if there were not at least 5 voxels meeting the given threshold.

Qualitative BPE assessment was performed at the time of the clinical interpretation using the American College of Radiology BI-RADS 4th edition criteria [22]. The four categories of BPE are as follows: 1–minimal, 2–mild, 3–moderate, and 4–marked.

Statistical Analysis

The Wilcoxon signed-rank test was used to compare the quantitative BPE parameters at each PE threshold between the cancer and control cohorts. Matched pairs were excluded from a comparison if the parameter could not be calculated at a given threshold due to an insufficient number of enhancing voxels. Each of the 10 BPE parameters was optimized by selecting the PE threshold that resulted in the largest Wilcoxon signed-rank test statistic (ranging from 0 = no difference to 1 = difference in all pairs) for cancer versus control cohorts, with the smaller threshold chosen in the case of a tie. P-values for each BPE metric were adjusted for multiple comparisons using a two-stage approach: A permutation-based step-down method was first used to account for testing 7 thresholds [23], followed by Holm's method to account for testing 10 parameters.

Receiver operator characteristic curve (ROC) analysis and the area under the ROC curve (AUC) were used to assess performance of the optimized quantitative BPE parameters to discriminate between cancer and control cohorts in comparison with qualitative BPE categorization. The bootstrap was used to adjust AUC estimates to account for optimizing the BPE parameters using the same data set [24] and to compute confidence intervals (CIs)

using the percentile method [25]. Spearman's rank correlation coefficient was used to examine relationships between the qualitative and quantitative BPE parameters. All statistical analyses were performed using R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

The cancer cohort included 23 women who developed breast cancer at any time-point after the screening breast MRI (mean age, 47.7 ± 10 years; six patients with BRCA mutations). The control cohort was comprised of women matched 1:1 for age and BRCA status while maximizing follow-up time (mean= 5.6 ± 1.3 years, range=2.4 to 7.0 years) (Table 1). In five cases the cancer and control subjects were imaged at different field strengths (one cancer subject at 1.5T with control at 3T, 4 cancer subjects at 3T with controls at 1.5T).

Identification of Optimal Enhancement Thresholds for BPE Parameters

First, the identification of optimal enhancement thresholds for each BPE parameter was performed by comparing the quantitative BPE parameters at each threshold between cancer and control cohorts. Performance of the quantitative BPE parameters at each PE threshold is shown in Figure 3 and comparison of each optimized metric between cases and controls is shown in Table 2. Optimal PE thresholds were 50% for BPE area and area ratio, 40% for BPE integrated intensity, and ranged from 10-30% for BPE intensity parameters (other than skew and kurtosis). Based on the optimized thresholds, all quantitative BPE parameters were significantly higher in cancer cases than matched controls after accounting for the number of comparisons except for BPE skewness and kurtosis (adjusted $p > 0.99$ for both). Results were not affected by excluding the 5 case-control pairs imaged using different field strengths.

As shown in Figure 3, each BPE metric tended to have similar performance over a range of PE thresholds, though performance also tended to drop off at low or high thresholds. BPE integrated intensity was relatively less sensitive to the PE threshold as its rank correlation ranged from 0.64 to 0.74 when the enhancement threshold ranged from 10% to 40% ($p=0.13$).

Association of Optimized Quantitative MRI Parameters with Breast Cancer Risk

A comparison of the matched cancer and control cohorts was then performed using the optimized thresholds for the quantitative BPE parameters. Among the BPE area parameters, BPE area (AUC=0.78) had the highest estimated AUC, though the AUC for BPE area ratio was similar (AUC=0.76, Table 2). The 25th percentile of BPE intensity (AUC=0.77) had the highest AUC among BPE intensity parameters, though most of these parameters had comparable AUCs between 0.75 and 0.77. BPE integrated intensity, a combination of area and mean BPE, had an AUC of 0.78, similar to the best area-based and intensity-based parameters.

Whole breast area ($p=0.89$), FGT area ($p=0.29$), and FGT area to whole breast area ratio ($p=0.39$) were not significantly different between cancer cases and controls (Table 2). The qualitative assessment of BPE had an AUC of 0.70 (95% CI: 0.57-0.83; Table 2), as reported in a prior study [13]. Though numerically higher, the AUCs for quantitative BPE parameters

of BPE area, 25th percentile, and integrated intensity were not significantly higher than that of qualitative BPE assessment ($p=0.10$, $p=0.62$, and $p=0.08$, respectively). ROC curves for each are shown in Figure 4.

Correlation Between Quantitative and Qualitative BPE Parameters

Correlation of each quantitative BPE parameter at the optimized threshold with qualitative assessments was then performed. At their optimized PE thresholds, most of the quantitative BPE parameters were significantly correlated with the qualitative BPE categorization (Table 3). BPE integrated intensity ($\rho=0.72$, $p<0.001$) and area ($\rho=0.71$, $p<0.001$) had the highest correlation with the qualitative BPE category while the other BPE intensity parameters had more moderate correlation coefficients between 0.58 and 0.64 ($p<0.001$ for each).

Substantial correlation was observed between the different threshold-optimized quantitative BPE parameters. BPE area, BPE to FGT area ratio, and integrated intensity were highly inter-correlated (ρ : 0.92 to 1.0). BPE skewness had relatively low correlation with all other quantitative parameters (ρ : -0.12 to 0.17) while BPE kurtosis was more correlated with the other parameters (ρ : 0.60 to 0.63 for all except SD [0.35] and skewness [-0.12]). The other BPE intensity parameters were correlated both with each other (ρ : 0.86 to 0.99) and with the BPE area and integrated intensity parameters (ρ : 0.80 to 0.97).

Discussion

We examined a wide range of quantitative breast MRI BPE parameters in women undergoing high-risk screening, and found that increased BPE area, BPE to FGT area ratio, and BPE intensity were each significantly associated with the development of breast cancer, while quantitative pre-contrast breast tissue MRI parameters, including FGT area and whole breast area, were not. This suggests that the optimized BPE parameters identified may allow for more sophisticated risk models that combine clinical features with quantitative breast MRI metrics. While these quantitative BPE parameters demonstrated numerically larger AUCs for association of breast cancer diagnosis than qualitatively assessed BPE, the AUC differences were not found to be statistically significant. This suggests that qualitative BPE parameters may provide a reasonable stratification of breast cancer risk in clinical practice, despite their subjective nature, though a larger study is needed to more definitively compare the performance of qualitative and quantitative BPE parameters. Previous studies regarding inter-observer variability in qualitative BPE assessment showed fair agreement overall. With training (2 hour presentation), there was sustained improvement in inter-observer variability to moderate agreement [18].

Our study further builds on prior studies validating semi- and fully-automated software in quantitatively evaluating BPE compared to qualitative assessment [17; 26]. Tagliafico *et al.* used a manually-selected threshold value to separate enhancing from non-enhancing breast tissue, and showed that the semi-automated software they used had better intra- and inter-observer correlation in quantifying BPE than qualitative assessments [17]. With a semi-automated 3D tool, Ha *et al.* found statistically significant positive correlation between quantitative and qualitative BPE assessments at different BPE threshold values [26]. In

addition to validation of our semi-automated quantification tool, our study found additional BPE measures which were correlated to qualitative BPE assessments and associated with increased breast cancer risk. These tools hold promise in incorporating quantitative assessment of BPE into future breast cancer risk-assessment models due to the non-subjective assessment and potential for integration into existing software for interpreting breast MRI such as computer aided diagnosis systems.

Our study did not find any statistically significant associations between MRI measurements of FGT, the MRI correlate to mammographic breast density, and breast cancer development. These findings agree with other studies that qualitative MRI assessments of amount of FGT do not correlate with breast cancer development in this high-risk group of women [13; 27]. Given the previously established correlation of breast density with breast cancer development, it is interesting that neither qualitative nor quantitative MRI correlates of breast density were significant associated with breast cancer in this population, suggesting that mammographic density/FGT is a relatively weak risk factor for breast cancer development in women already determined to be at higher risk than the average population. This limited relationship with breast cancer risk in the high-risk population is supported by a previously published study, which showed that in women with a BRCA gene mutation, mammographic breast density did not improve breast cancer risk assessment [28].

With the optimized thresholds for each parameter, both BPE area and intensity parameters had comparable performance to qualitative assessment in predicting breast cancer risk. However, the performance of most parameters varied with enhancement threshold (Figure 3), and BPE intensity parameters performed substantially worse at higher thresholds while area parameters performed worse at lower thresholds. Enhancement thresholds in this study were optimized for the scanning protocol(s) used at our institution, and different optimal enhancement thresholds may be identified for varying acquisition protocols.

There are several important limitations. First, our patient population only included women who were at high-risk for developing breast cancer. Since women who are at average-risk are not generally screened with breast MRI, it is unknown whether or not BPE assessment can be extended to this population of women. A single, cross-sectional study assessing qualitative FGT and BPE assessments of average-risk women who may have had a breast MRI for a variety of reasons, including newly diagnosed cancer, did not show any association of amount of FGT or BPE with breast cancer [29]. However, in that study, there was no long-term follow up to see if those patients with more FGT or BPE had a higher risk of developing breast cancer. Secondly, we used the same population as a prior study evaluating qualitative BPE assessments; as a result, this study cannot be seen as a validation of previous findings correlating BPE with breast cancer risk. In addition, our sample size was likely insufficient to determine whether optimized quantitative BPE parameters could improve diagnostic performance compared with the qualitative BPE assessment. Thirdly, our semi-automated tool used to measure BPE characteristics was based off a single representative slice of the breast at the level of the nipple, chosen by an experienced, fellowship-trained radiologist. A 3D tool, such as one developed by Ha *et al.* [26] may better quantify BPE parameters throughout the entire breast as a single slice at the level of the nipple may not be the best representation of breast parenchyma for all women. A single,

trained, research scientist performed the semi-automated segmentation, which prevented inter-observer variability; however, smaller vessels could have been included the quantification and counted as background between different cases.

In conclusion, our study identified several readily measurable quantitative BPE measurements that correlate with basic clinical qualitative BPE assessments and are associated with breast cancer development in our small sample of high-risk women. These quantitative BPE measurements hold promise for providing a less subjective imaging marker of risk that could be integrated into current clinical risk models.

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References

1. Shapiro S, Venet W, Strax P, Venet L, Roeser R. 1985; Selection, follow-up, and analysis in the Health Insurance Plan Study: a randomized trial with breast cancer screening. *Natl Cancer Inst Monogr.* 67:65–74. [PubMed: 4047153]
2. Strax P, Venet L, Shapiro S. 1973; Value of mammography in reduction of mortality from breast cancer in mass screening. *Am J Roentgenol Radium Ther Nucl Med.* 117:686–689.
3. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. 2009; Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med.* 151:727–737. w237–742. [PubMed: 19920273]
4. Tabar L, Vitak B, Chen TH, et al. 2011; Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology.* 260:658–663. [PubMed: 21712474]
5. Birnbaum J, Gadi VK, Markowitz E, Etzioni R. 2016; The Effect of Treatment Advances on the Mortality Results of Breast Cancer Screening Trials: A Microsimulation Model. *Ann Intern Med.* 164:236–243. [PubMed: 26756332]
6. Chiarelli AM, Prummel MV, Muradali D, et al. 2014; Effectiveness of screening with annual magnetic resonance imaging and mammography: results of the initial screen from the ontario high risk breast screening program. *J Clin Oncol.* 32:2224–2230. [PubMed: 24934793]
7. Weinstein SP, Localio AR, Conant EF, Rosen M, Thomas KM, Schnall MD. 2009; Multimodality Screening of High-Risk Women: A Prospective Cohort Study. *Journal of Clinical Oncology.* 27:6124–6128. [PubMed: 19884532]
8. Saslow D, Boetes C, Burke W, et al. 2007; American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography. *CA: A Cancer Journal for Clinicians.* 57:75–89. [PubMed: 17392385]
9. Gail MH, Brinton LA, Byar DP, et al. 1989; Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst.* 81:1879–1886. [PubMed: 2593165]
10. Claus EB, Risch N, Thompson WD. 1991; Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet.* 48:232–242. [PubMed: 1990835]
11. Boyd NF, Martin LJ, Yaffe MJ, Minkin S. 2011; Mammographic density and breast cancer risk: current understanding and future prospects. *Breast Cancer Research.* 13:223. [PubMed: 22114898]
12. McCormack VA, Santos SI. 2006 Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* :15.
13. Dontchos BN, Rahbar H, Partridge SC, et al. 2015; Are Qualitative Assessments of Background Parenchymal Enhancement, Amount of Fibroglandular Tissue on MR Images, and Mammographic Density Associated with Breast Cancer Risk? *Radiology.* 276:371–380. [PubMed: 25965809]

14. King V, Brooks JD, Bernstein JL, Reiner AS, Pike MC, Morris EA. 2011; Background parenchymal enhancement at breast MR imaging and breast cancer risk. *Radiology*. 260:50–60. [PubMed: 21493794]
15. Telegrafo M, Rella L, Stabile Ianora AA, Angelelli G, Moschetta M. 2016; Breast MRI background parenchymal enhancement (BPE) correlates with the risk of breast cancer. *Magnetic Resonance Imaging*. 34:173–176. [PubMed: 26597834]
16. Grimm LJ, Anderson AL, Baker JA, et al. 2015; Interobserver Variability Between Breast Imagers Using the Fifth Edition of the BI-RADS MRI Lexicon. *American Journal of Roentgenology*. 204:1120–1124. [PubMed: 25905951]
17. Tagliafico A, Bignotti B, Tagliafico G, Tosto S, Signori A, Calabrese M. 2015; Quantitative evaluation of background parenchymal enhancement (BPE) on breast MRI. A feasibility study with a semi-automatic and automatic software compared to observer-based scores. *Br J Radiol*. 88:20150417. [PubMed: 26462852]
18. Melsaether A, McDermott M, Gupta D, Pysarenko K, Shaylor SD, Moy L. 2014; Inter- and Intrareader Agreement for Categorization of Background Parenchymal Enhancement at Baseline and After Training. *American Journal of Roentgenology*. 203:209–215. [PubMed: 24951217]
19. Pujara AC, Mikheev A, Rusinek H, et al. 2017; Comparison between qualitative and quantitative assessment of background parenchymal enhancement on breast MRI. *J Magn Reson Imaging*. doi: 10.1002/jmri.25895
20. Rahbar H, Kurland BF, Olson ML, et al. 2016; Diffusion-Weighted Breast Magnetic Resonance Imaging: A Semiautomated Voxel Selection Technique Improves Interreader Reproducibility of Apparent Diffusion Coefficient Measurements. *J Comput Assist Tomogr*. 40:428–435. [PubMed: 27192501]
21. American College of Radiology. ACR Breast Accreditation Program. Available via <http://www.acr.org/Quality-Safety/Accreditation/BreastMRI>. Accessed July 14, 2014
22. D'Orsi, CJME, Ikeda, DM. , et al. Breast Imaging Reporting and Data System: ACR BI-RADS - Breast imaging atlas. 4th. Reston, VA: American College of Radiology; 2003.
23. Westfall, PH, Young, S. Resampling-based multiple testing: Examples and methods for p-value adjustment. John Wiley & Sons, Inc; New York NY: 1993.
24. Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. 2001; Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol*. 54:774–781. [PubMed: 11470385]
25. Davison, AC, Hinkley, DV. Bootstrap methods and their application. Cambridge University Press; Cambridge, United Kingdom: 1997.
26. Ha R, Mema E, Guo X, et al. 2016; Three-Dimensional Quantitative Validation of Breast Magnetic Resonance Imaging Background Parenchymal Enhancement Assessments. *Curr Probl Diagn Radiol*. doi: 10.1067/j.cpradiol.2016.02.003
27. Wu S, Zuley ML, Berg WA, et al. 2017; DCE-MRI Background Parenchymal Enhancement Quantified from an Early versus Delayed Post-contrast Sequence: Association with Breast Cancer Presence. *Scientific Reports*. 7:2115. [PubMed: 28522877]
28. Passaperuma K, Warner E, Hill KA, Gunasekara A, Yaffe MJ. 2010; Is mammographic breast density a breast cancer risk factor in women with BRCA mutations? *J Clin Oncol*. 28:3779–3783. [PubMed: 20625126]
29. Bennani-Baiti B, Dietzel M, Baltzer PA. 2016; MRI Background Parenchymal Enhancement Is Not Associated with Breast Cancer. *PLOS ONE*. 11:e0158573. [PubMed: 27379395]

Figure 1.

Representative image of a semi-automated region of interest drawn around the whole breast area (a) and FGT area (b). For FGT area calculation, the nipple and large vessels were manually omitted.

Figure 2.

(a-j): Image of a fat-saturated, T1-weighted pre-contrast (a), post-contrast (b) image of the breast with the region of interest drawn around the fibroglandular tissue (c). Representative BPE maps created at varying enhancement thresholds used for optimization (h-j). Notice that there are very few areas of “BPE” at the >70% threshold, and therefore the maximum threshold evaluated for our study was >70%.

Figure 3.

Rank correlation (Wilcoxon signed-rank test statistic) for each threshold of each BPE metric. The points indicate the threshold selected for each metric. Parameters were grouped as area-based (blue curves), intensity-based (red curves), and mixed (black curve). BPE skewness and kurtosis were not significantly different between the cancer and control cohorts at any threshold and are not included to simplify this figure. The two metrics had rank correlations ranging from 0.01 (20% and 10% thresholds, respectively) to 0.43 (70% threshold) and 0.36 (70% threshold), respectively. Solid circle, dotted line – BPE area; solid triangle, dashed line – BPE area ratio; open circle, solid line – Mean BPE; open triangle, dashed line – Standard deviation BPE intensity; Plus sign, dotted line – 25th percentile BPE intensity; “x”, dot-dash line – Median BPE intensity; open diamond, dashed line – 75th percentile BPE intensity; solid square, solid line – Integrated intensity.

Figure 4.

Receiver operating characteristic curves comparing the qualitative BPE category with an AUC of 0.70 (dot-dash line) and selected quantitative BPE parameters (solid line – BPE area [AUC=0.78]; dashed line – 25th percentile BPE intensity [AUC=0.77]; dotted line – BPE integrated intensity [AUC=0.78]).

Table 1

Patient characteristics of the cancer cohort and matched negative controls *

Variable	Cancer (<i>n</i> = 23)	No Cancer (<i>n</i> = 23)
Age (years) [†]	47.7 ± 10 (31-70)	47.6 ± 9.7 (31-70)
Follow-up Interval (years) [‡]	2.1 ± 1.6 (0.01-5.1)	5.1 ± 1.3 (2.4-7.0)
Screening MRI Indication		
BRCA mutation	6 (26)	6 (26)
Family and/or Genetic History	17 (74)	17 (74)
MR Imaging Protocol		
1.5 Tesla (prior to Feb 2010)	19 (83)	22 (96)
3 Tesla (after Feb 2010)	4 (17)	1 (4)
DCIS	11 (48)	n/a
Invasive Breast Cancer	12 (52)	n/a

Unless otherwise indicated, data are numbers of patients and data in parenthesis are percentages. All patients were matched for age and BRCA mutation status, maximizing follow-up time in the control cohort.

* Table is adapted from [BLINDED FOR REVIEW].

[†] Mean ± standard deviation with range in parenthesis.

[‡] Data are time to cancer diagnosis in the cancer cohort and follow-up time in the control cohort.

Table 2

Comparison of matched cancer and control cohorts using optimized thresholds for the quantitative BPE parameters

Variable	Cohort [*]			
	PE Threshold	Cancer (N=23)	Control (N=23)	P-value [†] AUC [‡] (95% CI)
Qualitative BPE category [§] [13]	n/a	2 (1 - 4)	1 (1 - 4)	0.029 0.70 (0.57, 0.83)
Whole breast area (mm ²)	n/a	11651 (2728 - 25918)	8991 (3761 - 25739)	0.89 0.52 (0.35, 0.69)
FCT area (mm ²)	n/a	1983 (360 - 4404)	1339 (35 - 5891)	0.29 0.64 (0.47, 0.78)
FCT area : whole breast area ratio (%)	n/a	22.4 (4.0 - 45.5)	22.4 (0.2 - 49.5)	0.39 0.59 (0.41, 0.76)
BPE area parameters				
BPE area (mm ²)	50%	94 (6 - 1842)	19 (0 - 252)	0.004 0.78 (0.66, 0.90)
BPE area : FCT area ratio (%)	50%	6.1 (0.6 - 45.3)	1.3 (0.0 - 9.9)	0.004 0.76 (0.64, 0.88)
BPE intensity parameters				
Mean (%)	10%	33.7 (20.4 - 82.0)	24.1 (16.2 - 41.8)	0.004 0.77 (0.64, 0.88)
SD (%)	10%	22.5 (11.8 - 42.5)	13.0 (6.6 - 32.6)	0.013 0.76 (0.63, 0.88)
25 th percentile (%)	30%	36.8 (33.3 - 61.3)	33.8 (31.6 - 39.3)	<0.001 0.77 (0.64, 0.87)
Median (%)	20%	35.3 (26.3 - 86.0)	29.0 (24.1 - 43.3)	0.002 0.75 (0.63, 0.87)
75 th percentile (%)	10%	42.2 (23.5 - 112.2)	29.9 (18.4 - 54.5)	0.002 0.76 (0.64, 0.87)
Skewness	30%	1.8 (0.6 - 3.3)	1.5 (-0.3 - 3.7)	>0.99 0.59 (0.47, 0.81)
Kurtosis	70%	2.7 (-1.8 - 19.4)	0.5 (-1.4 - 16.4)	>0.99 0.57 (0.46, 0.79)
BPE Integrated intensity (mm ²) (area × BPE mean)	40%	92.9 (8.4 - 1939.4)	24.4 (0.4 - 245.9)	0.006 0.78 (0.65, 0.90)

AUC = area under the ROC curve; CI = confidence interval; ROC = receiver operating characteristic curve.

^{*} Values are median (range).[†] Wilcoxon signed-rank test comparing those who developed cancer and matched control who did not; p-values for comparisons of quantitative BPE parameters were adjusted to account for the number of PE thresholds and number of quantitative BPE parameters tested.[‡] The AUC estimates for the optimized BPE parameters were optimism-adjusted using the bootstrap.[§] 1 – minimal amount of BPE, 2 – mild amount of BPE, 3 – moderate amount of BPE, and 4 – marked amount of BPE.

Table 3

Correlation of each quantitative parameter with qualitative assessments

Variable	Threshold	Spearman's rho	P-value
Whole breast area (mm ²)	n/a	-0.06	0.68
FGT area (mm ²)	n/a	0.40	0.006
FGT area : whole breast area ratio (%)	n/a	0.37	0.010
BPE area metrics			
BPE area (mm ²)	50%	0.71	<0.001
BPE area : FGT area ratio (%)	50%	0.61	<0.001
BPE intensity metrics			
Mean (%)	10%	0.60	<0.001
SD (%)	10%	0.58	<0.001
25 th percentile (%)	30%	0.64	<0.001
Median (%)	20%	0.62	<0.001
75 th percentile (%)	10%	0.61	<0.001
Skewness	30%	0.02	0.92
Kurtosis	70%	0.29	0.084
BPE integrated intensity (mm ²) (area × mean BPE)	40%	0.72	<0.001

Note: Cases and controls were pooled together for calculations (i.e., n=46).