Comparison Between Qualitative and Quantitative Assessment of Background Parenchymal Enhancement on Breast MRI

Akshat C. Pujara, MD,[1] Artem Mikheev, BS,[1,2] Henry Rusinek, PhD,[1,2] Yiming Gao, MD,[1,3] Chloe Chhor, MD,[1,3] Kristine Pysarenko, MD,[1,3] Harikrishna Rallapalli, BS,[2] Jerzy Walczyk, AMET,[1,2] Melanie Moccaldi, BS,[1,4] James S. Babb, PhD,[1] and Amy N. Melsaether, MD[1,3]*

Background: Potential clinical implications of the level of background parenchymal enhancement (BPE) on breast MRI are increasing. Currently, BPE is typically evaluated subjectively. Tests of concordance between subjective BPE assessment and computer-assisted quantified BPE have not been reported.
Purpose or Hypothesis: To compare subjective radiologist assessment of BPE with objective quantified parenchymal enhancement (QPE).
Study Type: Cross-sectional observational study.
Population: Between 7/24/2015 and 11/27/2015, 104 sequential patients (ages 23 – 81 years, mean 49 years) without breast cancer underwent breast MRI and were included in this study.
Field Strength/Sequence: 3T; fat suppressed axial T2, axial T1, and axial fat suppressed T1 before and after intravenous contrast.
Assessment: Four breast imagers graded BPE at 90 and 180 s after contrast injection on a 4-point scale (a–d). Fibroglandular tissue masks were generated using a phantom-validated segmentation algorithm, and were co-registered to pre- and postcontrast fat suppressed images to define the region of interest. QPE was calculated.
Statistical Tests: Receiver operating characteristic (ROC) analyses and kappa coefficients (k) were used to compare subjective BPE with QPE.
Results: ROC analyses indicated that subjective BPE at 90 s was best predicted by quantified QPE $\leq$20.2 = a, 20.3–25.2 = b, 25.3–50.0 = c, >50.0 = d, and at 180 s by quantified QPE $\leq$ 32.2 = a, 32.3–38.3 = b, 38.4–74.5 = c, >74.5 = d. Agreement between subjective BPE and QPE was slight to fair at 90 s (k = 0.20–0.36) and 180 s (k = 0.19–0.28). At higher levels of QPE, agreement between subjective BPE and QPE significantly decreased for all four radiologists at 90 s ($P \leq 0.004$) and for three of four radiologists at 180 s ($P \leq 0.004$).
Data Conclusion: Radiologists were less consistent with QPE as QPE increased.
Level of Evidence: 3
Technical Efficacy: Stage 3

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Background parenchymal enhancement (BPE) is the volume and intensity of normal breast fibroglandular tissue (FGT) enhancement after contrast administration (BPE).[1,2] Initial studies of BPE described potential for lesion obscuration at high levels of BPE.[3–7] Subsequent studies of BPE focused on changes related to hormonal status, including a decrease after menopause[8] and variation with the menstrual cycle.[1,9] Imaging premenopausal patients during the second week of the menstrual cycle when BPE is typically lowest can mitigate potential diagnostic challenges posed by BPE.[1,9–11]

More recently, there has been growing interest in the potential of BPE as an imaging biomarker of breast cancer risk. One group reported an association between BPE > mild

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*Address reprint requests to: A.M., 160 East 34th Street, 3rd Floor, New York, NY 10016. E-mail: amy.melsaether@nyumc.org

From the [1]Department of Radiology, New York University School of Medicine, New York, New York, USA; [2]Center for Biomedical Imaging, New York University School of Medicine, New York, New York, USA; [3]Breast Imaging Section, New York University School of Medicine, New York, New York, USA; and [4]Perlmutter Cancer Center, New York University School of Medicine, New York, New York, USA

and the presence of a breast cancer,[12] and another group reported an association between BPE > minimal and the development of a breast cancer.[13] In these studies, as in clinical practice, BPE was assessed qualitatively.[12,13] Qualitative BPE assessment is subject to intra- and inter-reader variability, which ranges widely from fair to substantial (k = 0.36 – 0.70).[12,14,15]

As the potential role of BPE in breast cancer risk stratification has gained interest, attempts to quantify BPE and thereby remove the currently subjective nature of its evaluation have been made. Ranges of quantified parenchymal enhancement (QPE) corresponding to radiologist assessment have been described.[16] However, tests of concordance between subjective radiologist BPE assessment and QPE (hereafter referred to as subjective-quantified agreement) is needed. Quantification of BPE requires that the region of interest, specifically FGT, be accurately defined. Thus, the objective of this study was to assess subjective-quantified agreement for BPE using a phantom-validated segmentation algorithm for generation of FGT masks. We hypothesized that individual radiologists would show variable agreement with QPE, and that the level of BPE would affect subjective-quantified agreement.

Materials and Methods

This cross-sectional observational study was approved by the Institutional Review Board and compliant with the Health Insurance Portability and Accountability Act. Patients were retrospectively selected for inclusion and written informed consent was waived by the institutional review board.

Patients

Between July 24, 2015, and November 27, 2015, a total of 369 consecutive, unique patients (ages 23–83 years, mean 53 years) underwent breast MRI; July 24, 2015 marks the first day of axial breast MRI scanning at our institution and thus the initial date of this study. Of these 369 patients, 253 (68.6%) had a prior history of breast cancer or suspicious enhancement on breast MRI and were excluded due to possible associated changes in BPE.[17,18] The remaining 116 (31.4%) patients were read as without abnormal enhancement and were included in this study; all 116 were imaged during the second week of the menstrual cycle. Twelve patients in whom BPE quantification was technically unsuccessful were excluded before statistical analysis.

MRI Examination

MR images were acquired using a dedicated seven-element surface breast coil (Sentinelle, Invivo, Gainesville, FL) on a 3T magnet (MAGNETOM Trio, A Tim System, Siemens Medical Solutions, Erlangen, Germany) with the patient in the prone position. Both breasts were imaged with a fat suppressed axial T2 weighted sequence (repetition time / echo time = 5180 ms / 81 ms, field-of-view 320 mm^2, matrix 384 × 250, slice thickness 3.00 mm). An axial T1-weighted three-dimensional (3D) volumetric scan, and an axial 3D volumetric fat suppressed T1-weighted scan that was obtained once before and three times after the intravenous injection of 0.1 mmol/L gadolinium chelate/kg body weight were also acquired (repetition time / echo time = 4.74 ms / 1.79 ms, field-of-view 320 mm^2, matrix 448 × 358, slice thickness 1.10 mm). These three axial postcontrast image sets were completed at 90, 180, and 270 s postinjection. Axial postcontrast subtraction images were generated.

Radiologist Assessment

To minimize bias from an individual radiologist's estimation of BPE, four subspecialty-trained breast imagers (R1–R4) with 2–8 years of experience (Y.G. 2, K.P. 6, A.M. 7, and C.C. 8 years) independently and qualitatively graded BPE on the first two postcontrast image sets for each breast on a 4-point scale (up to 25% = a; 26–50% = b; 51–75% = c; >75% = d) as per the Breast Imaging Reporting and Data System (BI-RADS) lexicon.[2] BPE was assessed in each breast at both 90 and 180 s postcontrast injection on postcontrast T1-weighted images as it is not yet clear which timepoint will be most useful for breast cancer risk stratification and predicting response to treatment.[19]

To convert QPE to radiologist scoring of a–d and assess subjective-quantified agreement, receiver operating characteristic (ROC) analyses were performed and required a single assessment of BPE at each time in each breast. Thus for the ROC analyses, the BPE category chosen by the majority of the four radiologists was used. When there was no majority, the radiologists together assessed and decided the BPE assessment in consensus.

QPE Determination

Independent of radiologist assessment, we performed an objective, computer-assisted measurement of QPE for each breast, beginning with whole breast and FGT segmentation. Locally developed software (FireVoxel, New York University School of Medicine, New York, NY) was used to segment both breasts from the chest wall using a semi-automated contour-based approach as described in previous studies.[16,20–23] Briefly, a single radiologist contoured both breasts every fifteenth slice on the axial T1-weighted precontrast sequence. The contours were automatically filled and interpolated to yield whole breast masks, with subsequent partial volume reduction and skin removal using a 1.5 mm erosion operator within our in-house software (FireVoxel). Compound images of both breasts containing MR sequences of interest were divided in the midline to allow quantification of parenchymal enhancement within individual breasts and assessment of symmetry.

FGT segmentation of individual breasts was performed using a phantom-validated, modified BiCal (Bias Calculation) nonuniformity correction technique.[24] Briefly, four pairs of breast phantoms with variable composition were assembled using 0.1 mM manganese chloride to represent FGT and canola oil (Crisco, The J.M. Smucker Company, Orrville, OH) to represent adipose tissue. Each phantom pair was scanned in three different positions using the same dedicated breast coil, 3 Tesla magnet, and T1-weighted parameters used for patient imaging. Two hundred forty paired regions of interest were placed in four phantom breast training volumes; each pair consisted of a 6-mm region of interest on FGT and another on nearby fat.

The BiCal algorithm represents the multiplicative bias field as a slowly varying function. Regions of rapid signal transition were excluded and constrained smoothing of the remaining areas

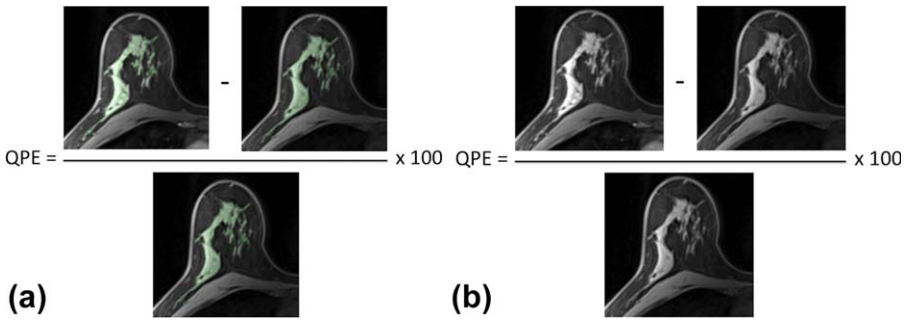

FIGURE 1: A 33-year-old *BRCA1* mutation-positive woman, screening breast MRI. MR images show calculation of QPE. (A) FGT masks (shaded in green) were co-registered to postcontrast (top left) and precontrast fat suppressed (top right, bottom center) images. QPE was calculated as the percent increase in mean voxelwise signal intensity within the FGT masks after contrast administration. (B) Corresponding images without FGT masks are provided for reference.

was performed. Nonuniformity correction parameters, namely smoothing radius and degree of Legendre polynomials, were tested until signal variability was minimized while preserving tissue contrast. Optimal nonuniformity correction parameters (smoothing radius = 45 mm, degree of Legendre polynomials = 10) were validated on all phantom breast volumes and then applied to patient MRI exams to generate FGT masks. The utility of BiCal-based nonuniformity correction for FGT segmentation on routine T1-weighted breast MRI has been described previously.[23]

To quantify parenchymal enhancement, FGT masks were co-registered to T1-weighted pre- and postcontrast fat suppressed images to define the region of interest and images were reviewed for misregistration. QPE at 90 and 180 s postcontrast was calculated as [(mean voxelwise SI within FGT mask on postcontrast images – mean voxelwise SI within FGT mask on precontrast images) / mean voxelwise SI within FGT mask on precontrast images)] × 100, where SI = signal intensity. Quantification of parenchymal enhancement is illustrated in Figure 1.

Statistical Analysis

Within-subject correlations were accounted for in each aspect of statistical analysis. Inter-reader agreement was assessed using the linear weighted kappa coefficient (k) with 95% confidence intervals (CIs). $k < 0.0$ was interpreted as poor agreement, $0.0 \leq k \leq 0.20$ as slight agreement, $0.20 < k \leq 0.40$ as fair agreement, $0.40 < k \leq 0.60$ as moderate agreement, and $k > 0.60$ as substantial agreement.[25] ROC analyses at each timepoint were used to determine values of QPE that best discriminated reader BPE = a from BPE > a, BPE = b from BPE > b, and BPE = c from BPE = d, at both 90 s and 180 s postcontrast injection. Subjective-quantified agreement was assessed using the linear weighted kappa coefficient (k) as above. Mann-Whitney tests were performed to assess subjective-quantified agreement as a function of QPE.

All statistical tests were conducted at the two-sided 5% significance level using SAS 9.3 software (SAS Institute, Cary, NC).

Results

Technical Success

FGT segmentation required approximately 7 min per case and was successful in both breasts for all 116 patients upon visual inspection. QPE results for both breasts at both postcontrast timepoints in 104/116 (89.7%) patients (ages, 23–81 years; mean, 49 years) were included in statistical analysis. Visual inspection of co-registration steps revealed misregistration of FGT masks due to patient motion in 10/116 (8.6%) patients. QPE values for 2/116 (1.7%) additional patients were excluded due to poor fat suppression. Indications for MRI in the final study population of 104 patients included screening in 93/104 (89.4%; BRCA1 positive in 13, BRCA2 positive in 16, family history of breast cancer in 57, history of atypia in 5, and history of lobular carcinoma in situ in 2 patients) and problem solving in 11/104 (10.6%) patients.

Radiologist BPE Assessment

Inter-reader agreement across all radiologist pairs was moderate at both timepoints (k = 0.51 [0.48, 0.55] and 0.48 [0.44, 0.51], respectively). The distribution of individual radiologist BPE assessment at each timepoint is shown in Table 1. Radiologist assignment of asymmetric BPE among 104 patients was variable at 90 and 180 s postcontrast injection (R1: 0 and 0; R2: 16 and 13; R3: 15 and 21; R4: 24 and 33). Substituting 1–4 for a–d, mean radiologist BPE assessment for 208 breasts significantly increased between 90 and 180 s postcontrast injection for all 4 radiologists (R1: 1.62 ± 0.95 versus 1.93 ± 1.02, $P = 0.001$; R2: 1.95 ± 1.01 versus 2.34 ± 1.05, $P < 0.001$; R3: 1.55 ± 0.86 versus 1.88 ± 0.93, $P < 0.001$; R4: 1.63 ± 0.65 versus 1.80 ± 0.69, $P = 0.007$).

Quantified Parenchymal Enhancement

The distribution of QPE as a function of individual radiologist assessment on both postcontrast image sets is shown in Figure 2. Mean QPE significantly increased between 90 and 180 s postcontrast injection (23.2 ± 15.4 versus 42.8 ± 32.9, $P < 0.001$). At 180 s, mean QPE was asymmetric (left breasts 44.2 ± 34.8 versus right breasts 41.4 ± 31.0, $P = 0.002$); mean QPE was not asymmetric at 90 s (left breasts 23.0 ± 15.1 versus right breasts 23.2 ± 15.7, $P = 0.4$).

ROC analyses indicated that radiologist BPE at 90 s was best predicted by QPE ≤20.2 = a, 20.3–25.2 = b, 25.3–50.0 = c, >50.0 = d, and at 180 s by QPE ≤ 32.2 = a, 32.3–38.3 = b, 38.4–74.5 = c, >74.5 = d.

TABLE 1. Distribution of Radiologist BPE Stratified by Postcontrast Time[a]

	Radiologist BPE at 90 s (n = 208 breasts)				Radiologist BPE at 180 s (n = 208 breasts)			
Radiologist	**a**	**b**	**c**	**d**	**a**	**b**	**c**	**d**
R1	132 (63.5)	42 (20.2)	16 (7.7)	18 (8.6)	96 (46.2)	50 (24.0)	42 (20.2)	20 (9.6)
R2	90 (43.3)	58 (27.9)	40 (19.2)	20 (9.6)	54 (26.0)	67 (32.2)	50 (24.0)	37 (17.8)
R3	137 (65.9)	35 (16.8)	29 (13.9)	7 (3.4)	92 (44.2)	62 (29.8)	42 (20.2)	12 (5.8)
R4	97 (46.6)	93 (44.7)	17 (5.5)	1 (0.5)	71 (34.1)	110 (52.9)	24 (11.5)	3 (1.4)

[a]Numbers in parentheses are percentages.

Subjective-Quantified Agreement

At 90 s postcontrast injection, subjective-quantified agreement was slight to fair [k with 95% CI: R1 = 0.36 (0.26, 0.46); R2 = 0.20 (0.11, 0.29); R3 = 0.33 (0.23, 0.43); R4 = 0.26 (0.14, 0.37)]. At 180 s postcontrast injection, subjective-quantified agreement decreased for 3 of the 4 radiologists and was slight to fair [k with 95% CI: R1 = 0.28 (0.19, 0.36); R2 = 0.25 (0.16, 0.34); R3 = 0.27 (0.18, 0.34); R4 = 0.19 (0.10, 0.28)]. Higher levels of QPE were significantly associated with subjective-quantified discordance for all 4 radiologists at 90 s ($P \leq 0.004$) and for 3 of 4 radiologists at 180 s ($P \leq 0.004$) (Table 2; Fig. 3).

Discussion

Quantified BPE has not previously been compared with radiologist assessed BPE using ROC-based analysis. In this study, radiologists showed only slight to fair agreement with QPE and subjective-quantified concordance decreased at higher levels of QPE. These inconsistencies at higher levels of QPE are important as potential clinical applications of higher levels of BPE continue to grow. To date, higher levels of BPE have been associated with higher estrogenic states,[26–31] higher amounts of visceral adipose tissue,[32] a history of chest radiation for childhood lymphoma,[33] increased metabolic activity,[34] the presence of a breast cancer,[12] and the development of a breast cancer,[13] Higher pretreatment BPE in the contralateral breast has also been associated with a better response to neoadjuvant therapy in patients with unilateral breast cancer.[35,36] These findings underscore the potential utility of BPE as an imaging biomarker for stratifying breast cancer risk and assessing response to therapy. Accurate assessment of BPE is, therefore, important, especially at higher levels of BPE.

In our study, the variable assignment of asymmetric BPE by four radiologists indicates the subjective nature of qualitative BPE assessment. Inter-reader agreement for BPE among the four radiologists was slightly lower at 180 s postcontrast injection when QPE was higher compared with 90 s, similar to subjective-quantified agreement. Reports of inter-reader agreement for BPE range from fair to substantial (k = 0.36–0.70) in three prior studies.[12,14,15] In one of these studies, two radiologists with moderate (k = 0.47) agreement for BPE demonstrated a greater than threefold difference in odds ratios (10.1 and 3.3) for the association between BPE > mild and the presence of a breast cancer.[12] These results indicate the variable degree of association between BPE and breast cancer risk when qualitatively assessing BPE.

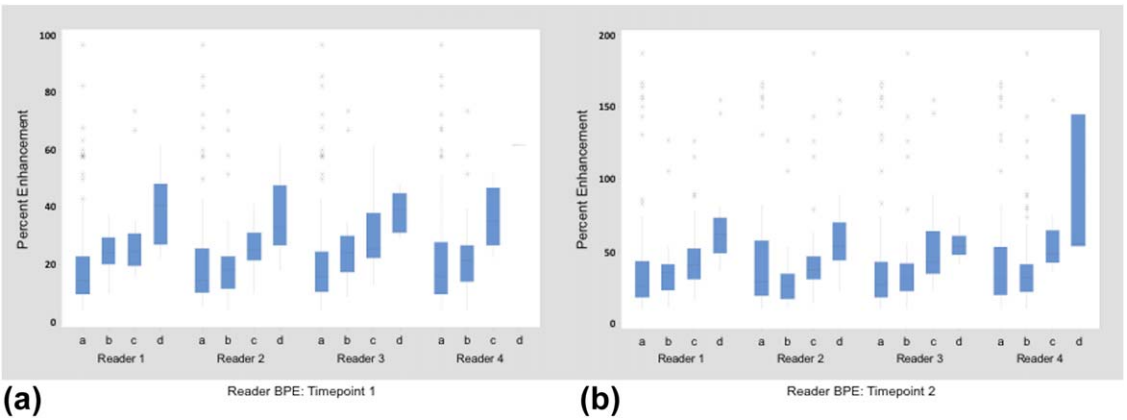

FIGURE 2: Box and whisker plots show distribution of QPE as a function of individual radiologist assessment of BPE. Each box indicates the median QPE and interquartile range (IQR). Whiskers extend 1.5 × IQR above and below. (A) Distribution of QPE at postcontrast timepoint 1. (B) Distribution of QPE at postcontrast timepoint 2. Overlapping ranges of QPE corresponding to each level of radiologist BPE assessment (a–d) indicate intra- and inter-reader variability at both postcontrast timepoints.

TABLE 2. Effect of Level of QPE on Subjective-Quantified Agreement for BPE*

		Concordant		Discordant		
Time (s)	**Radiologist**	**n[a] (%)**	**Mean QPE ± /- SD[b]**	**n[a] (%)**	**Mean QPE ± /- SD[b]**	***P***
90	R1	127 (61.1)	16.6 ± 10.3	81 (38.9)	33.4 ± 16.4	< 0.001
90	R2	87 (41.8)	16.1 ± 8.3	121 (58.2)	28.6 ± 18.0	< 0.001
90	R3	123 (59.1)	17.1 ± 10.8	85 (40.9)	32.3 ± 17.8	< 0.001
90	R4	114 (54.8)	19.7 ± 10.9	94 (45.2)	27.8 ± 19.6	0.004
180	R1	82 (39.4)	32.3 ± 24.2	126 (60.6)	49.6 ± 36.0	< 0.001
180	R2	73 (35.1)	36.5 ± 25.6	135 (64.9)	45.9 ± 35.7	0.08
180	R3	84 (40.4)	29.8 ± 15.7	124 (59.6)	51.3 ± 38.1	< 0.001
180	R4	93 (44.7)	33.2 ± 18.1	115 (55.3)	50.2 ± 39.4	0.004

*Numbers in parentheses are percentages.
[a]n = 208 breasts per radiologist per timepoint.
[b]Mean quantified parenchymal enhancement.
SD = standard deviation.

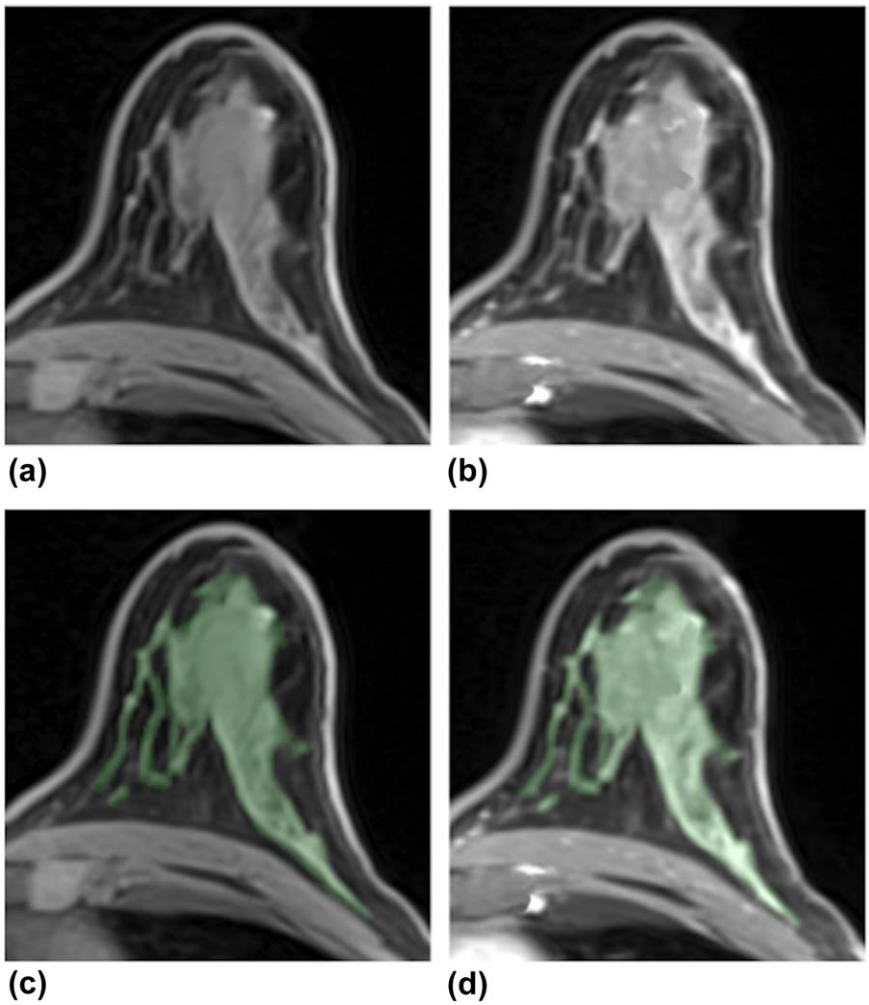

FIGURE 3: A 40-year-old *BRCA2* mutation-positive woman, screening MRI. MR images show divergent radiologist estimation of BPE compared with QPE at high level of PE. (A) T1-weighted precontrast fat suppressed image without FGT mask. (B) Corresponding postcontrast image (90 s) without co-registered FGT mask. (C) T1-weighted precontrast fat suppressed image with FGT mask. (D) Corresponding postcontrast image (90 s) with co-registered FGT mask. QPE = 29.9%, corresponding to radiologist score of c after ROC-based conversion. Two radiologists assigned BPE of b, one radiologist assigned BPE of c, and one radiologist assigned BPE of d.

The quantitative component of our study further highlights the limitations of qualitative BPE assessment. Specifically, the overlapping ranges of QPE corresponding to each level of radiologist BPE assessment (a–d) indicates intra-reader variability; our radiologists did not discriminate levels of QPE into discrete groups, similar to Klifa et al.[16] The sets of overlapping ranges also varied between radiologists, indicating inter-reader variability. Furthermore, subjective-quantified agreement for BPE varied with the level of QPE, showing lower agreement at higher levels of PE that may be associated with increased risk of breast cancer. A reference for comparison of these results was not found in the literature, yet the variations of radiologist BPE assessment relative to computer-assisted quantification of BPE in this study suggest a need for standardized quantification of BPE.

The technical differences between quantification of BPE in the current study and other reports are noteworthy. Phantom validation of FGT segmentation parameters was not reported in prior studies of quantified BPE.[32,33,35–37] In two prior studies,[32,37] voxelwise enhancement was considered a binary variable. Thus, the total volume of enhancing voxels was accounted for, but not the intensity of enhancement as prescribed by the 2013 BI-RADS lexicon.[2] In the current study, percent increase in mean voxelwise signal intensity was calculated accounting for both the volume and intensity of background enhancement after contrast administration.

The current study has several limitations. First, the initial step of isolating the breasts from the chest wall was semi-automated, as in other prior studies.[16,20–22] Second, determination of QPE was based on the MR protocols and postprocessing algorithms of a single institution. Third, 12/116 (10.3%) patients were excluded due to erroneous calculation of QPE related to patient motion or poor fat suppression. Fourth, conversion of QPE to radiologist scoring of a–d to assess subjective-quantified agreement was based on ROC-derived thresholds set by majority and consensus among four radiologists at a single institution; potential institutional bias in grading BPE is difficult to entirely exclude. Lastly, the current study was a comparison of subjective-quantified agreement for BPE during a single imaging exam; the longitudinal impact of subjective-quantified disagreement was not assessed.

In conclusion, radiologists were less consistent with QPE as QPE increased. Integration of a standardized technique for quantification of BPE into clinical workflows warrants further investigation, as BPE may be a useful imaging biomarker for breast cancer risk stratification, assessing response to therapy, and predicting outcomes.

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