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Association of Breast Cancer Odds with Background Parenchymal Enhancement Quantified Using a Fully Automated Method at MRI: The IMAGINE Study

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Conflicts of interest are listed at the end of this article.

See also the editorial by Bokacheva in this issue.

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Background: Background parenchymal enhancement (BPE) at breast MRI has been associated with increased breast cancer risk in several independent studies. However, variability of subjective BPE assessments have precluded its use in clinical practice.

Purpose: To examine the association between fully objective measures of BPE at MRI and odds of breast cancer.

Materials and Methods: This prospective case-control study included patients who underwent a bilateral breast MRI examination and were receiving care at one of three centers in the United States from November 2010 to July 2017. Breast volume, fibroglandular tissue (FGT) volume, and BPE were quantified using fully automated software. Fat volume was defined as breast volume minus FGT volume. BPE extent was defined as the proportion of FGT voxels with enhancement of 20% or more. Spearman rank correlation between quantitative BPE extent and Breast Imaging Reporting and Data System (BI-RADS) BPE categories assigned by an experienced board-certified breast radiologist was estimated. With use of multivariable logistic regression, breast cancer case-control status was regressed on tertiles (low, moderate, and high) of BPE, FGT volume, and fat volume, with adjustment for covariates.

Results: In total, 536 case participants with breast cancer (median age, 48 years [IQR, 43–55 years]) and 940 cancer-free controls (median age, 46 years [IQR, 38–55 years]) were included. BPE extent was positively associated with BI-RADS BPE (r_s = 0.54; P < .001). Compared with low BPE extent (range, 2.9%–34.2%), high BPE extent (range, 50.7%–97.3%) was associated with increased odds of breast cancer (odds ratio [OR], 1.74 [95% CI: 1.23, 2.46]; P for trend = .002) in a multivariable model also including FGT volume (OR, 1.39 [95% CI: 0.97, 1.98]) and fat volume (OR, 1.46 [95% CI: 1.04, 2.06]). The association of high BPE extent with increased odds of breast cancer was similar for premenopausal and postmenopausal women (ORs, 1.75 and 1.83, respectively; interaction P = .73).

Conclusion: Objectively measured BPE at breast MRI is associated with increased breast cancer odds for both premenopausal and postmenopausal women.

Clinical trial registration no. NCT02301767

Supplemental material is available for this article.

The amount of fibroglandular tissue (FGT) in the breast is associated with an increased risk of breast cancer (1–4). The amount of FGT is visualized on mammograms or MRI scans and subjectively classified into one of four categories following the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) (5). For average-risk patients undergoing routine mammography for breast cancer screening, those with the most FGT have between two and four times the risk of future breast cancer relative to those with primarily fatty breasts (1,2). For higher-risk patients undergoing breast MRI, several groups have reported that three-dimensional FGT volume is likewise associated with breast cancer risk (6,7), while others have reported a weaker association with FGT for the population undergoing MRI (8–10).

FGT measurement divides the breast into "non-FGT" and "FGT" compartments, with FGT reflecting both fibrous and glandular tissue. At dynamic contrast-enhanced MRI, the administration of a gadolinium-based contrast agent causes portions of the FGT to enhance to varying degrees, a feature called background parenchymal enhancement (BPE). In clinical practice, the degree of

Abbreviations

BI-RADS = Breast Imaging Reporting and Data System, BMI = body mass index, BPE = background parenchymal enhancement, FGT = fibroglandular tissue, IMAGINE Study = The Imaging and Epidemiology Study, OR = odds ratio

Summary

Background parenchymal enhancement measured quantitatively at breast MRI is associated with increased odds of breast cancer for both premenopausal and postmenopausal women after accounting for breast cancer risk factors.

Key Results

- In this prospective case-control study of 536 breast cancer cases and 940 cancer-free controls, background parenchymal enhancement (BPE) measured using a fully automatic method at MRI was correlated with radiologist-assessed BPE (r_s = 0.54; P < .001).
- Odds of breast cancer were associated with high BPE extent (≥50.7% of FGT enhancing; odds ratio [OR], 1.74) after accounting for covariates.
- The association between high BPE extent and increased breast cancer odds was consistent when participants were stratified by premenopausal and postmenopausal status (OR, 1.8 for both; interaction P = .73).

enhancement is assessed subjectively by radiologists following the BI-RADS scale as minimal, mild, moderate, or marked BPE (5). BPE is hormonally sensitive and is thought to reflect the metabolic activity within the FGT (11,12). We and others have shown that BPE is associated with increased breast cancer risk (6–8,10,13,14). In several of these prior studies, BPE was associated with breast cancer, whereas FGT was not statistically significantly associated (8,10,13). Therefore, BPE is a promising new marker of breast cancer risk that could be used to refine breast cancer risk assessment.

A barrier to the use of BPE for breast cancer risk assessment in clinical practice is the variability of BPE evaluation by radiologists (15). This variability precludes reproducibility, reduces precision, and may introduce bias in studies of breast cancer risk. To enable objective, quantitative measurement of BPE across all MRI devices and clinical settings, a fully automated volumetric method was developed to segment FGT and measure quantitative BPE for both sagittal- and axial-view MRI scans (16).

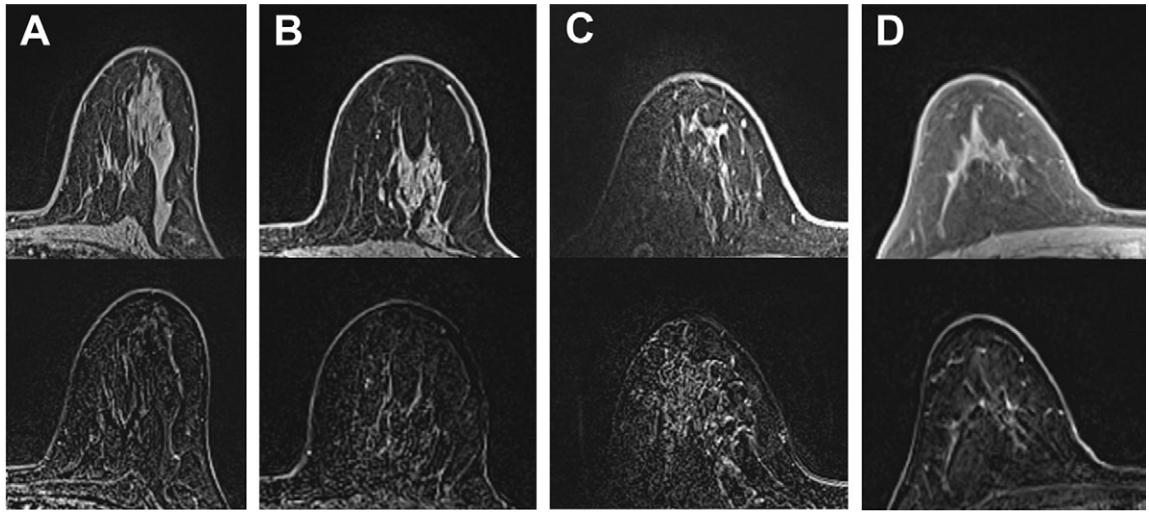
This large multisite study examines the association of fully automated quantitative measures of BPE at MRI with odds of breast cancer in patients undergoing breast MRI in the United States.

Materials and Methods

The Imaging and Epidemiology (IMAGINE) Study (ClinicalTrials.gov identifier NCT02301767) is a multicenter, hospital-based, prospective, case-control study approved by the institutional review boards at each study site. Eligible participants provided written informed consent to participate in the study.

Study Sample

Patients who received care from November 2010 to July 2017 at Memorial Sloan Kettering Cancer Center, Perelman Cancer



BI-RADS BPE	Minimal	Mild	Moderate	Marked
Age at MRI, years	42	61	46	41
Case-control status	Case	Control	Control	Case
Menopausal status	History of oophorectomy	Postmenopausal	Postmenopausal	Postmenopausal
BI-RADS FGT	Heterogeneous FGT	Heterogeneous FGT	Heterogeneous FGT	Heterogeneous FGT
BPE Extent	37.9%	39.8%	59.1%	69.4%
FGT Volume, cm^3 (%)	111 cm^3 (15.9%)	93 cm^3 (15.2%)	64 cm^3 (6.3%)	48 cm^3 (10.1%)

Figure 1: Examples of preanalysis MRI series show **(A)** minimal, **(B)** mild, **(C)** moderate, and **(D)** marked background parenchymal enhancement (BPE) according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) criteria assessed by a board-certified breast radiologist blinded to case-control status and all clinical characteristics. The top row shows a single image from the precontrast non–fat-saturated series, and the bottom row shows a single image from the subtraction series. The study radiologist assessed each non–fat-saturated image along with the postcontrast and subtraction series to determine BPE. The corresponding BI-RADS fibroglandular tissue (FGT) and quantitative BPE and FGT measures are provided in the text below each image.

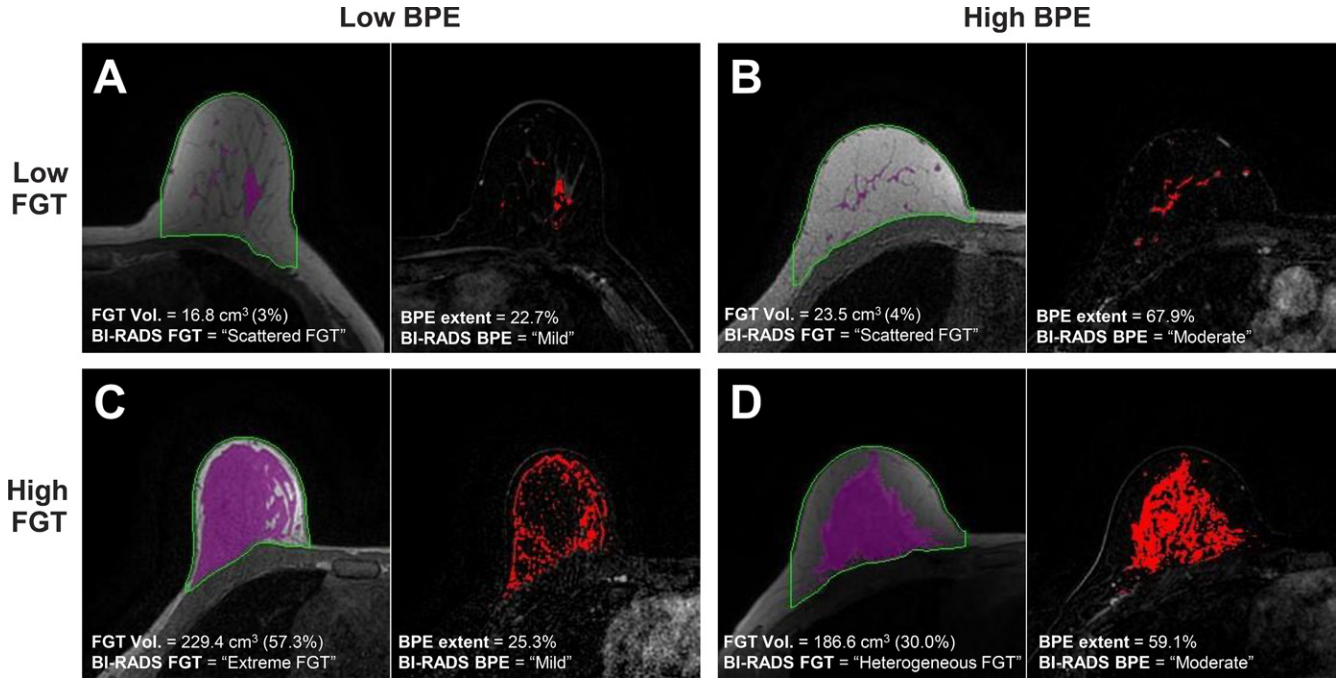


Figure 2: Examples of automatic fibroglandular tissue (FGT) segmentations on the precontrast (T1) non–fat-saturated series and background parenchymal enhancement (BPE) extent on the postcontrast (T2) series for four control participants. For each participant, the left image shows the automated whole-breast segmentation (green line) and FGT segmentation (purple shading). The right image shows the areas of enhancement (red shading) within the FGT, defined as all voxels with 20% or more enhancement from the precontrast to postcontrast series. For each series, the middle section is presented. Example images were selected randomly within four categories defined by quantitative FGT volume (Vol) and BPE extent, where "low" refers to participants with measures in the bottom tertile and "high" refers to participants with measures in the top tertile. **(A)** Low FGT volume and low BPE extent in a 50-year-old premenopausal control participant. **(B)** Low FGT volume and high BPE extent in a 50-year-old control participant with a history of bilateral oophorectomy. **(C)** High FGT volume and low BPE extent in a 39-year-old premenopausal control participant. **(D)** High FGT volume and high BPE extent in a 44-year-old premenopausal control participant. BI-RADS = Breast Imaging Reporting and Data System.

Center at the University of Pennsylvania School of Medicine, or Huntsman Cancer Institute at the University of Utah and who underwent bilateral breast MRI during or before the recruitment period (2015–2018) were potentially eligible for this study. The study sample includes both high-risk patients undergoing routine breast cancer screening and patients undergoing whole-breast MRI as part of a recall or diagnostic work-up. Those with a diagnosis of unilateral invasive breast cancer and/or ductal carcinoma in situ who underwent bilateral breast MRI before radiation therapy or systemic therapy were included as cases. Patients who underwent an MRI examination and had no breast cancer diagnosis at the time of or within 6 months after their examination were included as controls. Controls were individually matched to cases 1:1 on age at time of MRI (5-year age groups), menopausal status at time of MRI, self-reported race or ethnicity, and year of MRI (2-year groups). Additional study design details are given in a prior IMAGINE Study publication (13).

Image Evaluation and Qualitative FGT and BPE Assessment

MRI scans were obtained using standard clinical protocols at the site where the patient underwent MRI. A single breast laterality was selected for analysis: the unaffected breast for cases and the corresponding laterality for matched controls. In a prior publication, we evaluated the association between breast cancer odds and BI-RADS BPE in the IMAGINE Study (13). An experienced board-certified radiologist (J.S.S., with 12 years of experience) blinded to case-control status and clinical data assessed the images of the selected breast for FGT and BPE for matched cases and controls. With use of the BI-RADS guidelines (5), FGT was classified as "almost entirely fat," "scattered FGT," "heterogeneous FGT," or "extreme FGT"; BPE was classified as minimal, mild, moderate, or marked. Figure 1 shows example MRI series with each category of BI-RADS BPE. The intrareader agreement (Cohen weighted κ) of the BI-RADS BPE measures based on 130 repeated readings was 0.73 for BPE and 0.83 for FGT (13).

Quantitative FGT and BPE Measurement

With use of a fully automated computational method described previously (16), FGT and BPE were measured in the selected breast (Fig 2). If the postcontrast series was not available, the subtraction series was used. BPE extent was defined as the proportion of FGT voxels enhancing 20% or more, based on the finding in a prior study (16) that this threshold had the strongest correlation with BI-RADS BPE. BPE intensity was defined as the median percentage enhancement across all FGT voxels.

Statistical Analysis

The IMAGINE Study was powered to detect odds ratios (ORs) for adjusted associations between breast cancer odds and BI-RADS BPE of 1.5 overall and 1.8 within strata defined by menopausal status. In the absence of a priori categorizations for the quantitative imaging measures, each imaging measure was

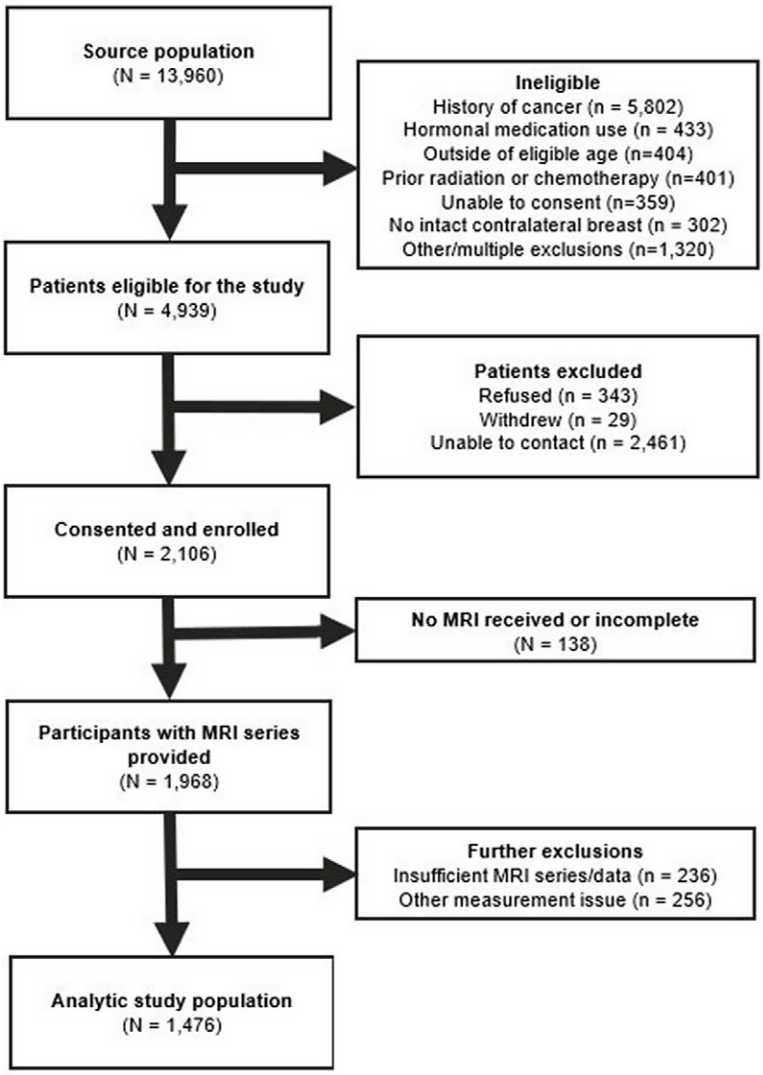


Figure 3: Study sample selection diagram. Participants were recruited from women receiving care at one of three centers who had undergone a bilateral breast MRI from 2010 to 2017. Case participants underwent their MRI examination at the time of or after the diagnosis of a unilateral breast cancer; control participants underwent MRI as part of a high-risk screening program or other clinical workup and were not diagnosed with breast cancer for at least 6 months after the breast MRI examination.

divided into tertiles calculated based on the distribution in the cancer-free control group, corresponding to low, moderate, and high categories. Defining quantiles based on the control group is common for studies of risk markers, allowing a comparison of the distribution of the new marker relative to a cancer-free reference population (17,18). Breast cancer case-control status was regressed on tertiles of BPE, FGT volume, and fat volume with use of unconditional logistic regression without interaction terms, adjusted for the factors used to match controls to cases: parity (nulliparous, one live birth, or more than one live birth); MRI view (axial or sagittal); history of lobular carcinoma in situ; history of benign breast disease; and history and results of testing for *BRCA1* and *BRCA2* pathogenic variants (negative, positive, or not tested). We calculated *P* values for trend across the BPE tertiles, defined as a Wald test with one degree of freedom for the significance of the quantitative measures tertiles modeled as a numeric variable (1 to 3). Participants missing covariate values were excluded from multivariable models.

In sensitivity analyses, the models were refit with quantitative imaging measures expressed as *(a)* continuous values and *(b)* quartiles. The continuous values were square root–transformed and standardized following the odds per adjusted standard deviation, or OPERA, concept to enable direct comparisons of the magnitude of association for the quantitative imaging measures (19).

The multivariable logistic regressions were also performed with stratification by menopausal status; body mass index (BMI) (calculated as patient weight in kilograms divided by patient height in meters squared and stratified as less than 30 and 30 or higher); and FGT volume (dichotomized at the median value for the controls). The menopause strata were prespecified, and the BMI and FGT strata were specified post hoc. Differences in the associations of breast cancer odds with quantitative BPE, FGT volume, and fat volume were tested across strata by using a likelihood ratio test comparing the model with and without interaction terms.

Statistical analyses were carried out by an author (G.P.W., with 9 years of experience conducting statistical analyses) using R, version 4.1.2 (The R Foundation), with functions from the Tidyverse (20), Hmisc (21), and gtsummary (22) packages. The type I error rate for CIs and statistical tests was .05.

Results

A total of 13 960 patients receiving care at one of the recruitment centers were identified as potential participants (Fig 3). At least one exclusion criterion was identified for 9021 patients, leaving 4939 potential participants, of whom 343 chose not to participate, 29 withdrew, 2461 were unable to be contacted, and 138 had no MRI scans available. From 2106 consented and enrolled participants, there were 1968 eligible participants with complete MRI studies provided to the IMAGINE Study team. Twelve percent of the images (236 of 1968) had missing or corrupted image series and could not be analyzed. An additional 256 patients were excluded due to issues with image metadata or other program failure. The final study sample included 1476 participants with quantitative imaging measures, comprising 536 breast cancer cases (526 invasive cancers, 10 ductal carcinomas in situ; median participant age, 48 years [IQR, 43–55 years]) and 940 cancer-free controls (median age, 46 years [IQR, 38–55 years]). Most participants (n = 1343) had BI-RADS assessments from a prior study (14). There were 133 additional participants who did not have BI-RADS assessments but had quantitative MRI measurements completed for this study.

The characteristics of the participants in the analytic study population are given in Table 1. Sixty-three percent of controls

(595 of 940) and 63% of cases (338 of 536) were premenopausal at the time of MRI. *BRCA1*/*BRCA2* pathogenic variants, family history of breast cancer, history of bilateral oophorectomy, and history of lobular carcinoma in situ and benign breast disease were more common for the controls (all χ^2 test *P* values <.001).

Correlation of Quantitative BPE with Other Participant Characteristics

MRI scans were obtained using devices manufactured by GE Medical Systems (*n* = 925; six different models) and Siemens (*n* = 545; five different models) (Table 2). There were 1343 participants with both BI-RADS and quantitative BPE assessments, of whom 365 (27%) had minimal BPE, 600 (45%) had mild BPE, 273 (20%) had moderate BPE, and 105 (7.8%) had marked BPE (Table 2; examples of each category shown in Fig 1). BI-RADS BPE was positively associated with BI-RADS FGT categories (χ^2 = 25.1; *P* = .003). The median quantitative BPE extent observed for each BI-RADS BPE category was 32.1% (IQR, 22.4%–43.2%), 41.9% (IQR, 31.7%–52.1%), 57.4% (IQR, 45.8%–65.8%), and 68.6% (IQR, 59.0%–80.0%) for minimal, mild, moderate, and marked BPE, respectively (Fig 2). For BPE intensity, the median values were 9.3% (IQR, 5.71%–15.4%), 15.1% (IQR, 10.1%–21.5%), 25.2% (IQR, 17.4%–33.3%), and 37.5% (IQR, 26.4%–52.1%) for minimal, mild, moderate, and marked BPE, respectively. Each quantitative BPE measure had a Spearman correlation of 0.54 (*P* < .001) with BI-RADS BPE (Fig 4). There were 20 participants with BPE intensity of 0, indicating that more than 50% of the voxels had no increase in intensity from the precontrast to postcontrast series. The correlation between BPE extent and BPE intensity was 0.92 (*P* < .001).

Quantitative FGT volume explained less than 1% of the variance in BPE extent (R^2 = 0.7%). Age at MRI was negatively associated with BPE extent (β = −0.17; *P* < .001) but explained less than 1% of the variance (R^2 = 0.9%). BPE extent was greatest for premenopausal women (median, 44.8% [IQR, 32.4%–59.2%]) and lower for postmenopausal women (41.3% [IQR, 29.6%–53.5%]) and those who had undergone bilateral oophorectomy (42.6% [IQR, 29.7%–56.2%]; *F* test for difference between groups, *P* < .001). Quantitative fat volume was associated with BMI (β = 0.06 per 10 cm^3 fat volume; *P* < .001), explaining 65% of the variance in BMI (R^2 = 0.65).

Multivariable Models of the Association between Breast Cancer Odds and BPE

The multivariable analysis excluded 116 observations with missing responses for one or more

Table 1: Demographic and Clinical Characteristics of the IMAGINE Study Sample

Characteristic	Controls (*n* = 940)	Cases (*n* = 536)
Age at MRI (y)*	46 (38–55)	48 (43–55)
Year of MRI		
2010–2013	25 (2.7)	43 (8.0)
2014–2015	499 (53)	261 (49)
2016–2017	416 (44)	232 (43)
Recruitment site		
NY	650 (69)	274 (51)
PA	117 (12)	101 (19)
UT	173 (18)	161 (30)
Menopausal category		
Premenopausal	595 (63)	338 (63)
Postmenopausal	282 (30)	183 (34)
History of bilateral oophorectomy	63 (6.7)	15 (2.8)
Self-reported race or ethnicity†		
Asian or Pacific Islander (non-Hispanic)	29 (3.1)	27 (5.0)
Black (non-Hispanic)	38 (4.0)	42 (7.8)
Indigenous American (non-Hispanic)	0 (0)	1 (0.2)
Hispanic (any race)	54 (5.7)	33 (6.2)
Multiple races or other race† (non-Hispanic)	22 (2.3)	10 (1.9)
White (non-Hispanic)	797 (85)	423 (79)
Family history of breast cancer‡		
No	304 (32)	370 (69)
Yes	622 (66)	131 (24)
Unknown	14 (1.5)	35 (6.5)
Tests for pathogenic variants in *BRCA1* or *BRCA2*§		
Negative	195 (21)	228 (43)
Positive	238 (25)	27 (5.0)
Not tested	481 (51)	245 (46)
Unknown	26 (2.8)	36 (6.7)
History of lobular carcinoma in situ		
No	873 (93)	527 (98)
Yes	67 (7.1)	9 (1.7)
History of benign breast disease		
No	478 (51)	425 (79)
Yes	462 (49)	111 (21)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. IMAGINE Study = The Imaging and Epidemiology Study; NY = Memorial Sloan Kettering Cancer Center, New York, NY; PA = University of Pennsylvania Perelman School of Medicine; UT = University of Utah Huntsman Cancer Institute.

* Data are medians, with IQRs in parentheses.

† Self-reported race was collected in compliance with funder requirements. Participants were asked to choose the race category that best defined them ("White or Caucasian"; "Black or African American"; "Asian or Pacific Islander"; "other race"; or "don't know") and respond to the question of ethnicity, "Do you consider yourself to be of Latino or Hispanic origin?" Those responding "other race" or "don't know" who responded "no" to the ethnicity question were categorized as "other (non-Hispanic)."

‡ First-degree female family history or first- or second-degree male family history.

§ *BRCA1* and *BRCA2* pathogenic variants and testing history were self-reported.

Table 2: Characteristics of MRI Scan Acquisition and Subjective BI-RADS Evaluations of FGT and BPE for the IMAGINE Study Sample

Characteristic	Controls (n = 940)	Cases (n = 536)
MRI scanner manufacturer		
GE	650 (69)	275 (51)
Siemens	285 (30)	260 (49)
Unknown	5 (0.5)	1 (0.2)
MRI view used for quantitative imaging measures		
Axial	893 (95)	489 (91)
Sagittal	47 (5.0)	47 (8.8)
MRI field strength		
1.5 T	432 (46)	344 (64)
3.0 T	503 (54)	189 (35)
Unknown	5 (0.5)	3 (0.6)
BI-RADS FGT*		
Almost entirely fat	63 (6.7)	38 (7.1)
Scattered	206 (22)	165 (31)
Heterogeneous	380 (40)	240 (45)
Extreme	178 (19)	73 (14)
Unknown†	113 (12)	20 (3.7)
BI-RADS BPE*		
Minimal	247 (26)	118 (22)
Mild	367 (39)	233 (43)
Moderate	154 (16)	119 (22)
Marked	59 (6.3)	46 (8.6)
Unknown†	113 (12)	20 (3.7)

Note.—Data are numbers of participants, with percentages in parentheses. BI-RADS = Breast Imaging Reporting and Data System, BPE = background parenchymal enhancement, FGT = fibroglandular tissue, IMAGINE = Imaging and Epidemiology.

* BI-RADS measures were assessed by an experienced board-certified breast radiologist for a single unaffected breast laterality with blinding to case-control status and all patient information. BI-RADS FGT was assessed using the precontrast non–fat-saturated series. BI-RADS BPE was measured using the subtraction series together with the pre- and postcontrast series.

† BI-RADS assessments were completed in a prior study. Participants who were not successfully matched were not assessed for BI-RADS BPE and FGT but were eligible to have quantitative FGT and BPE assessment for the present study.

covariates. Thus, a total of 465 cases and 895 controls were included, with 184 cases (40%) and 298 controls (33%) with high BPE extent (≥50.7% of FGT enhancing). Relative to participants with low BPE extent (range, 2.9%–34.2% of FGT enhancing), participants with moderate BPE extent (34.3%–50.6%) and high BPE extent (≥50.7%) had 1.39 times (95% CI: 0.99, 1.96) and 1.74 times (95% CI: 1.23, 2.46) increased odds of breast cancer, respectively (Table 3). Odds of breast cancer were also associated with FGT volume (OR for moderate vs low, 1.49 [95% CI: 1.06, 2.09]) and fat volume (OR for high vs low, 1.46 [95% CI: 1.04, 2.06]). Breast cancer odds increased monotonically across BPE extent categories (P for trend = .002). When BPE extent was modeled as a continuous variable, a 1-SD increase in BPE extent was associated with a 1.28 times increased odds of breast cancer (95% CI: 1.10, 1.48) (Table S1).

In the multivariable model of BPE intensity (Table S2), relative to participants with low BPE intensity (range, 0%–10.5%), participants with high BPE intensity (range, 20.7%–111.0%) had 1.85 times increased odds of breast cancer (95% CI: 1.30, 2.64). Because BPE extent and BPE intensity are highly correlated and have similar associations with breast cancer odds, the remaining results focus on BPE extent as the preferred measure of the amount of BPE as defined by BI-RADS.

When the association of breast cancer odds with BPE extent expressed were modeled as quartiles (Table S3) rather than tertiles, participants with BPE extent in quartile 4 had 1.76 times increased odds (95% CI: 1.18, 2.63) of breast cancer relative to participants in quartile 1. The odds of breast cancer increased monotonically across the quartiles (P for trend = .009).

No statistical difference was detected between pre- and postmenopausal participants for the association of breast cancer odds with BPE extent or FGT volume (interaction P = .73 and .36, respectively) (Table 4). In contrast, the association of breast cancer odds with high fat volume (range, 895.9–4438.4 cm^3) was greater for postmenopausal participants (OR, 2.90 [95% CI: 1.58, 5.49]) than premenopausal participants (OR, 1.02 [95% CI: 0.65, 1.59]; interaction P = .02).

The association between breast cancer odds and BPE extent was not modified by BMI at time of MRI (<30 vs ≥30; interaction P = .48) (Table S4) or median quantitative FGT amount (<95.0 cm^3 vs ≥95.0 cm^3; P = .64) (Table S5).

Discussion

In this study, we used fully automated objective measures of background parenchymal enhancement (BPE) to evaluate the association with breast cancer odds in a multisite case-control study of patients undergoing breast MRI. Participants with high BPE extent had 74% increased odds of breast cancer (odds ratio, 1.74 [95% CI: 1.23, 2.46]) relative to participants with low BPE extent in a multivariable model adjusting for fibroglandular tissue volume, breast fat volume, reproductive factors, and other confounders. We did not detect a difference in the association between premenopausal and postmenopausal participants (interaction P = .73).

Quantitative methods for measuring BPE for the whole breast have been proposed previously. Hu et al (23) segmented FGT and used a statistical approach to threshold enhancing from nonenhancing FGT on subtraction MRI scans but did not compare the quantitative measure with BI-RADS BPE. Nam et al (24) classified BPE into four categories with use of a model trained on BI-RADS BPE assessments for 594 MRI series. In a holdout set of 200 images, the model-classified BPE showed moderate agreement (κ = 0.50) with radiologist-classified BI-RADS BPE. Ha et al (25) developed a quantitative measure of BPE by using convolutional neural networks trained on 1114 breast volumes in 137 patients. In a holdout set, the model achieved considerable overlap with the ground truth (Dice coefficient = 0.83) but was implemented only for sagittal-view MRI scans. Our approach measured quantitative FGT and BPE for both axial and sagittal MRI scans obtained using

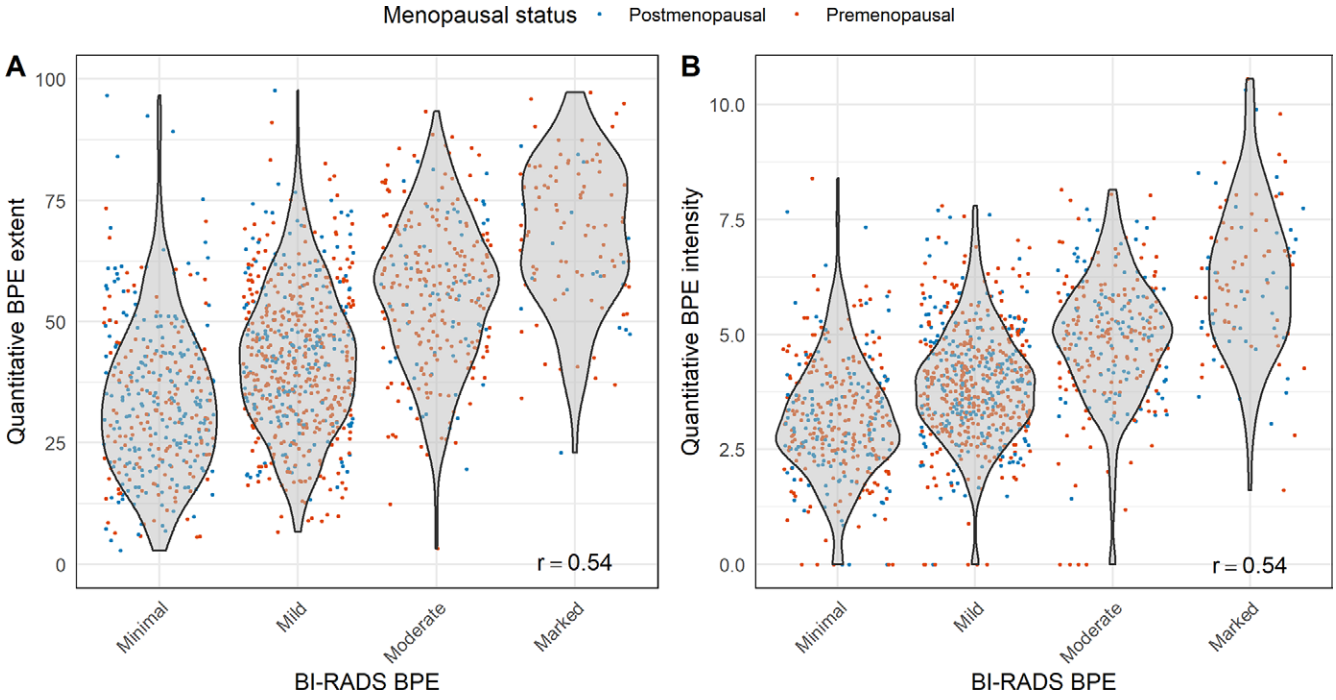


Figure 4: Violin plots show distribution of **(A)** quantitative background parenchymal enhancement (BPE) extent and **(B)** quantitative BPE intensity (square root–transformed) within categories of subjective Breast Imaging Reporting and Data System (BI-RADS) BPE assessed by an experienced board-certified breast radiologist with complete blinding to case-control status and all clinical characteristics. Spearman rank correlation (r_s) of BI-RADS BPE with both quantitative BPE measures was 0.54.

Table 3: Adjusted Multivariable Logistic Regression Evaluating the Associations between Quantitative Measures at Breast MRI and Breast Cancer Case-Control Status

Characteristic	Controls (n = 895)	Cases (n = 465)	OR*	P for trend
BPE extent†				
Tertile 1 (2.9%–34.2%)	299 (33)	123 (26)	1.00	.002
Tertile 2 (34.3%–50.6%)	298 (33)	158 (34)	1.39 (0.99, 1.96)	
Tertile 3 (50.7%–97.3%)	298 (33)	184 (40)	1.74 (1.23, 2.46)	
FGT volume				
Tertile 1 (0.7–60.4 cm^3)	299 (33)	139 (30)	1.00	.09
Tertile 2 (60.5–145.8 cm^3)	298 (33)	177 (38)	1.49 (1.06, 2.09)	
Tertile 3 (145.9–2062.2 cm^3)	298 (33)	149 (32)	1.39 (0.97, 1.98)	
Fat volume				
Tertile 1 (33.5–430.1 cm^3)	299 (33)	121 (26)	1.00	.03
Tertile 2 (430.2–895.8 cm^3)	299 (33)	148 (32)	1.17 (0.83, 1.64)	
Tertile 3 (895.9–4438.4 cm^3)	297 (33)	196 (42)	1.46 (1.04, 2.06)	

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. Tertiles were calculated based on the distribution of quantitative measurements for women in the control group. BPE = background parenchymal enhancement, FGT = fibroglandular tissue, OR = odds ratio.

* Data in parentheses are 95% CIs. ORs were estimated using the logistic model of breast cancer odds regressed on measures in the table with adjustment for variables used to match controls to cases: age at time of MRI, menopausal status at time of MRI (premenopausal, postmenopausal, or a history of bilateral oophorectomy), self-reported race or ethnicity (non-Hispanic White vs other), and year of MRI. The models were further adjusted for parity (nulliparous, one or more full-term births), history of lobular carcinoma in situ, history of benign breast disease, history of testing for and presence of pathogenic variants in *BRCA1/BRCA2*, and MRI view (axial vs sagittal).

† BPE extent is defined as the proportion of FGT volume that enhanced 20% or more on the postcontrast series relative to the precontrast series.

multiple device models in distinct clinical settings. In addition, we evaluated distinct definitions of quantitative BPE, capturing both the extent and intensity of enhancement across the FGT voxels, and provided benchmarking against BI-RADS BPE.

The case-control associations observed in our study are consistent with prior single-institution studies (reviewed in the article by Thompson et al [14]). Hu et al (23) reported an increased odds of breast cancer associated with dichotomized quantitative BPE categories for 101 cases and controls (unadjusted premenopausal OR, 4.1; unadjusted postmenopausal OR, 4.6). Wu et al (26) observed an adjusted OR of 3.5 comparing BPE on images of the unaffected breast in 51 patients with invasive cancer with that of 51 controls with biopsy-proven benign breast disease. In our study, we fit BPE extent, FGT volume, and fat volume in a single model, observing that all three were independently associated with breast cancer odds. Further, we accounted for variables used to match cases and controls, as well as confounders. Importantly, this study was powered for subgroup analyses, which showed that the association of breast cancer odds with BPE extent did not differ statistically by

Table 4: Adjusted Multivariable Logistic Regression Evaluating Associations between Quantitative Measures at Breast MRI and Breast Cancer Odds in Participants Stratified by Menopausal Status

	Premenopausal			Postmenopausal*			
Imaging Measure	Controls (n = 568)	Cases (n = 286)	OR[†]	Controls (n = 327)	Cases (n = 179)	OR[†]	Interaction P Value[‡]
BPE extent[§]							
Tertile 1 (2.9%–34.2%)	173	71	…	126	52	1.00	.73
Tertile 2 (34.3%–50.6%)	183	93	1.38 (0.87, 2.19)	115	65	1.33 (0.79, 2.27)	
Tertile 3 (50.7%–97.3%)	212	122	1.75 (1.11, 2.79)	86	62	1.83 (1.04, 3.23)	
FGT volume							
Tertile 1 (0.7–60.4 cm^3)	141	58	…	158	81	1.00	.36
Tertile 2 (60.5–145.8 cm^3)	206	116	1.50 (0.94, 2.43)	92	61	1.62 (0.98, 2.69)	
Tertile 3 (145.9–2062.2 cm^3)	221	112	1.62 (0.99, 2.65)	77	37	0.97 (0.56, 1.69)	
Fat volume							
Tertile 1 (33.5–430.1 cm^3)	224	99	…	75	22	1.00	.02
Tertile 2 (430.2–895.8 cm^3)	188	92	0.99 (0.65, 1.50)	111	56	1.94 (1.03, 3.77)	
Tertile 3 (895.9–4438.4 cm^3)	156	95	1.02 (0.65, 1.59)	141	101	2.90 (1.58, 5.49)	

Note.—Unless otherwise specified, data are numbers of participants. Tertiles were calculated based on the distribution of quantitative measurements for women in the control group. BPE = background parenchymal enhancement, FGT = fibroglandular tissue, OR = odds ratio.

* Postmenopausal includes patients who experienced natural menopause and those who had a history of bilateral oophorectomy.

[†] Data in parentheses are 95% CIs. ORs were estimated using a single stratified logistic model of breast cancer odds regressed on measures in the table with adjustment for variables used to match controls to cases: age at time of MRI, self-reported race or ethnicity (non-Hispanic White vs other), and year of MRI. The models were further adjusted for parity (nulliparous, one or more full-term births), history of lobular carcinoma in situ, history of benign breast disease, history of testing for and presence of pathogenic variants in *BRCA1*/*BRCA2*, and MRI view (axial vs sagittal).

[‡] Interaction P value is based on a likelihood ratio test comparing the model with the interaction effect to a model without the interaction effect.

[§] BPE extent is defined as the percentage of FGT volume that enhanced 20% or more on the postcontrast series relative to the precontrast series.

clinically relevant subgroups defined by menopausal status, FGT volume (breast density), or BMI. Notably, we observed a significant interaction of menopausal status with fat volume on breast cancer odds, confirming that greater adiposity is a risk factor for breast cancer for postmenopausal women (27).

Quantitative BPE, whether expressed as extent or intensity, was uncorrelated with the volume of FGT. Prior studies using subjective BI-RADS BPE and FGT measurements have reported significant positive correlations between the two measures (7,11,28–30). Indeed, we observed an association between BI-RADS BPE and BI-RADS FGT in our study. The correlation between visually estimated BI-RADS BPE and FGT is expected given the BI-RADS definitions (5). The quantitative measurement of FGT and BPE thus eliminates bias due to confounding introduced by the correlated BI-RADS measures.

Our study has several limitations. First, participants in the control group frequently underwent MRI for high-risk screening and thus had a greater burden of known breast cancer risk factors than the case participants did. Further, the study included only patients of 70 years of age or younger, and the study sample may differ from the general population undergoing MRI. While we adjusted for high-risk factors, age, FGT, and fat volume in our statistical models, bias may still exist, and additional studies that include a sample more representative of the general population are warranted. Second, quantitative FGT and BPE could not be measured on 492 images, particularly for MRI examinations carried out before 2014 that had incomplete image series or image data. This reflects challenges of collecting standardized biomedical imaging data from diverse clinical settings over many years, but with continued development of our automated software, we expect to achieve better results in the future. Third, the BI-RADS BPE assessments completed previously were performed by one radiologist, which did not permit estimates of interreader variability.

In conclusion, quantitative background parenchymal enhancement (BPE) measured using a fully automated method at MRI is associated with increased breast cancer odds for pre- and postmenopausal women after accounting for fibroglandular tissue, fat volume, reproductive factors, and breast cancer risk factors. Future longitudinal studies are needed to assess the added value of objective measurement of BPE for prospective breast cancer risk prediction beyond established risk prediction models. In the long term, BPE could be used with breast density and other breast cancer risk factors to improve assessment of breast cancer risk and personalize breast cancer screening plans.

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Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

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