Radiology

ORIGINAL RESEARCH • BREAST IMAGING

Breast MRI during Neoadjuvant Chemotherapy: Lack of Background Parenchymal Enhancement Suppression and Inferior Treatment Response

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

See also the editorial by Philpotts in this issue.

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Background: Suppression of background parenchymal enhancement (BPE) is commonly observed after neoadjuvant chemotherapy (NAC) at contrast-enhanced breast MRI. It was hypothesized that nonsuppressed BPE may be associated with inferior response to NAC.

Purpose: To investigate the relationship between lack of BPE suppression and pathologic response.

Materials and Methods: A retrospective review was performed for women with menopausal status data who were treated for breast cancer by one of 10 drug arms (standard NAC with or without experimental agents) between May 2010 and November 2016 in the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2, or I-SPY 2 TRIAL (NCT01042379). Patients underwent MRI at four points: before treatment (T0), early treatment (T1), interregimen (T2), and before surgery (T3). BPE was quantitatively measured by using automated fibroglandular tissue segmentation. To test the hypothesis effectively, a subset of examinations with BPE with high-quality segmentation was selected. BPE change from T0 was defined as suppressed or nonsuppressed for each point. The Fisher exact test and the *Z* tests of proportions with Yates continuity correction were used to examine the relationship between BPE suppression and pathologic complete response (pCR) in hormone receptor (HR)-positive and HR-negative cohorts.

Results: A total of 3528 MRI scans from 882 patients (mean age, 48 years ± 10 [standard deviation]) were reviewed and the subset of patients with high-quality BPE segmentation was determined (T1, 433 patients; T2, 396 patients; T3, 380 patients). In the HR-positive cohort, an association between lack of BPE suppression and lower pCR rate was detected at T2 (nonsuppressed vs suppressed, 11.8% [six of 51] vs 28.9% [50 of 173]; difference, 17.1% [95% CI: 4.7, 29.5]; $P = .02$) and T3 (nonsuppressed vs suppressed, 5.3% [two of 38] vs 27.4% [48 of 175]; difference, 22.2% [95% CI: 10.9, 33.5]; $P = .003$). In the HR-negative cohort, patients with nonsuppressed BPE had lower estimated pCR rate at all points, but the *P* values for the association were all greater than .05.

Conclusions: In hormone receptor–positive breast cancer, lack of background parenchymal enhancement suppression may indicate inferior treatment response.

Online supplemental material is available for this article.

At contrast-enhanced breast MRI, enhancement of normal fibroglandular tissue, known as background parenchymal enhancement (BPE), is described separately from tumor enhancement. Qualitative assessment of BPE with a four-point scale (minimal, mild, moderate, or marked) was incorporated into clinical practice in the Breast Imaging Reporting and Data System, fifth edition (1). In the research arena, various algorithms to quantitatively measure BPE have been investigated in pursuit of less subjective assessment (2–7).

BPE is a dynamic phenomenon and varies between individuals and over time in the same individual. The level of BPE is affected by hormonal status associated with estrogen level (eg, menstrual cycle, lactation, menopause, hormone replacement therapy, and hormone therapy) (8–14). Estrogen stimulates tumor growth of hormone receptor (HR)-positive breast cancers (15). Hormone therapies based on drugs that block estrogen-based signaling for tumor growth or suppress estrogen synthesis have been developed to target HR-positive cancers (16–18) and are known to decrease BPE (12,13).

Abbreviations

BPE = background parenchymal enhancement, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, I-SPY 2 TRIAL = Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2, NAC = neoadjuvant chemotherapy, pCR = pathologic complete response

Summary

Lack of background parenchymal enhancement suppression at breast MRI during neoadjuvant chemotherapy may indicate inferior treatment response in hormone receptor–positive breast cancer.

Key Results

- In hormone receptor (HR)-positive patients enrolled in the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2, or I-SPY 2 TRIAL, lack of background parenchymal enhancement (BPE) suppression was associated with lower pathologic complete response rate at interregimen point (nonsuppressed vs suppressed, 11.8% vs 28.9%, respectively; $P = .02$) and presurgery point (nonsuppressed vs suppressed, 5.3% vs 27.4%, respectively; $P = .003$).
- BPE suppression was observed in both premenopausal patients (82%–90% of the HR-positive cohort and 73%–84% of the HR-negative cohort) and peri- or postmenopausal patients (62%–73% of the HR-positive cohort and 72%–77% of the HR-negative cohort).

Suppression of BPE is commonly observed after neoadjuvant chemotherapy (NAC) (4,6,14,19–22). Although to our knowledge the exact biologic mechanism has not yet been determined, this phenomenon may be explained by the suppression of ovarian function and subsequent reduction in estrogen level during chemotherapy. As well, it could reflect a dampening of proliferative activity and decreased vascularity in the breast tissue (23). Our motivation for this study originated from the observation that some patients exhibit unchanged or stronger BPE after NAC compared with before NAC (nonsuppressed BPE). In a recent comprehensive review summarizing research findings on BPE (24), five separate studies investigating BPE before and after NAC found that BPE could be a predictor of neoadjuvant treatment response (4,6,19–21). Considering the known relationship between BPE and hormonal status and the known treatment efficacy of lowering estrogen levels in patients with HR-positive cancer, we hypothesized that nonsuppressed BPE during NAC may indicate inferior treatment response, especially in HR-positive cancer.

The purpose of our study is to investigate the relationship between lack of BPE suppression and treatment response to NAC in HR-positive and HR-negative cohorts.

Materials and Methods

We conducted our study in compliance with the Health Insurance Portability and Accountability Act and all participating sites received approval from their institutional review boards. All patients provided written informed consent to participate in the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2 TRIAL).

Data Sharing

Our study reports new results from the ongoing I-SPY 2 TRIAL, which has been open to accrual since 2010. There are more than 25 separate papers with partial overlap of cohorts (25). Data generated or analyzed during the study are available from the corresponding author by request.

Study Cohort

We retrospectively reviewed 988 women who underwent NAC between May 2010 and November 2016 in the I-SPY 2 TRIAL. This multicenter trial for patients with breast cancer at high risk for early recurrence is an ongoing, adaptively randomized phase II trial with multiple neoadjuvant therapy arms. Women aged 18 years or older diagnosed with locally advanced breast cancer (tumor size $\geq$ 2.5 cm) without distant metastasis were eligible to enroll in the trial. Patients who were undergoing estrogen replacement therapy were eligible to enroll but had to discontinue therapy before the initiation of NAC. Patients with HR-positive and human epidermal growth factor receptor 2 (HER2)-negative tumors that were assessed as low risk by the 70-gene assay (MammaPrint; Agendia) were screened out from the trial. Participants were administered 12 cycles of weekly paclitaxel (standard of care) and/or a combination of nine experimental agents for 12 weeks, followed by four cycles of anthracycline-cyclophosphamide before the surgical procedure. Patients with HER2-positive cancer were also administered trastuzumab for the first 12 weeks. Each patient had MRI examinations at four points: before treatment (T0), early treatment (3 weeks after treatment initiation, T1), interregimen (T2), and before surgery (T3). The study schema is shown in Figure 1.

Patients without available menopausal status data were not eligible for the current study. Considering the possible influence on the calculation of BPE in the contralateral breast (14), patients with concurrent bilateral breast cancer, with history of contralateral breast cancer, with history of contralateral breast surgery (eg, benign tumor, breast augmentation, breast reduction), or with history of chest radiation (eg, Hodgkin Disease) were not eligible for the study.

MRI Protocol

MRI was performed at each site by using a 3.0-T or 1.5-T MRI scanner with a dedicated breast coil. As a general requirement of the clinical trial, MRI examinations included a dynamic contrast-enhanced series by using a bilateral, three-dimensional, fat-suppressed, and T1-weighted gradient-echo sequence (repetition time msec/echo time msec, 4–10/minimum; flip angle, 10°–20°; field of view, 26–36 cm; acquired frequency or read matrix, 384–512; acquired phase encoding matrix, $\geq$256; in-plane spatial resolution, $\leq$1.4 $\times$ 1.4 mm; section thickness, $\leq$2.5 mm; temporal resolution, 80–100 seconds; axial orientation; prone position). The standardized contrast agent injection rate was 2 mL/sec with a 20-mL saline flush. Dynamic contrast-enhanced MRI was performed once before and multiple times after contrast agent injection by using identical sequences, with scanning to continue for at least 8 minutes after contrast agent injection. The early contrast-

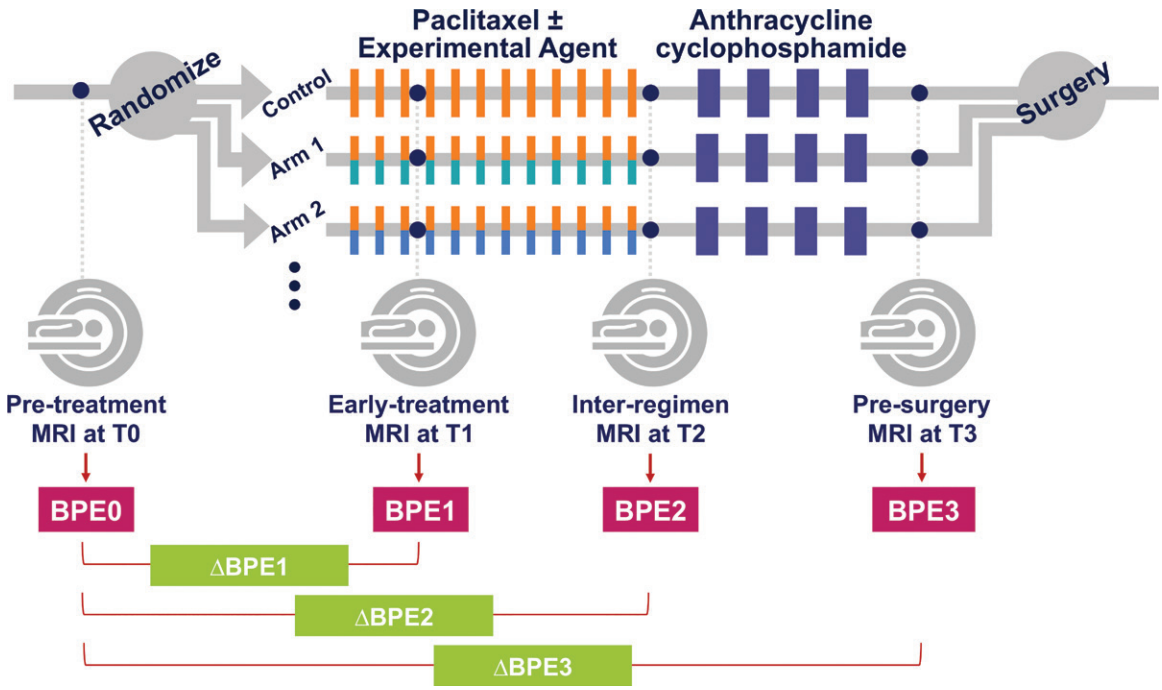

Figure 1: Study schema. Patients were randomized to one of 10 drug arms (nine experimental drug arms and a standard of care control arm). An experimental agent or combination may substitute for part of the standard therapy (paclitaxel). Each patient underwent MRI examinations at four points during neoadjuvant chemotherapy. BPE0 = background parenchymal enhancement at T0, BPE1 = background parenchymal enhancement at T1, BPE2 = background parenchymal enhancement at T2, BPE3 = background parenchymal enhancement at T3, ΔBPE1 = percent change of background parenchymal enhancement relative to T0 at T1, ΔBPE2 = percent change of background parenchymal enhancement relative to T0 at T2, ΔBPE3 = percent change of background parenchymal enhancement relative to T0 at T3.

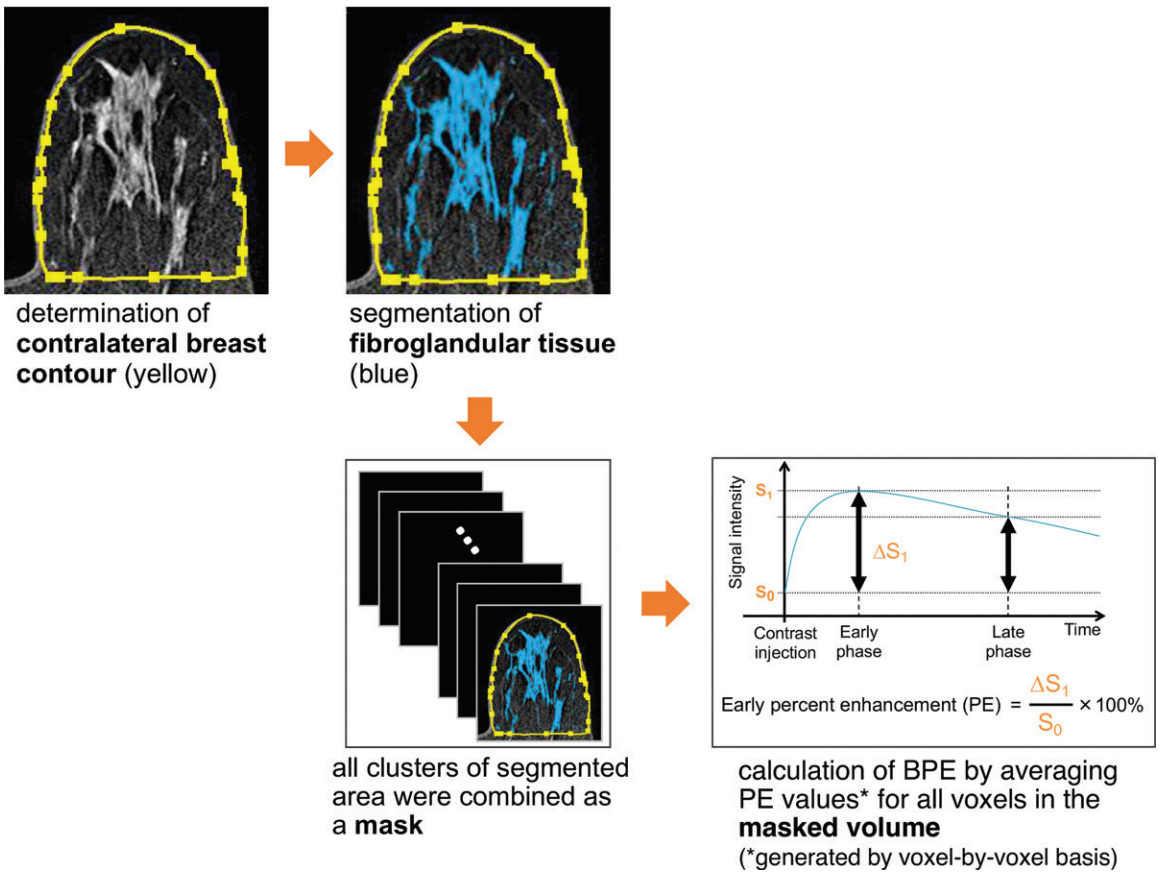

Figure 2: Fully automated background parenchymal enhancement (BPE) measurement. S_0 = signal intensity at contrast-unenhanced phase, S_1 = signal intensity at early contrast-enhanced phase, $\Delta S_1 = S_1 - S_0$.

Table 1: Patient Characteristics

Parameter	All Eligible Patients (n = 882)	High-Quality Segmentation BPE0		High-Quality Segmentation ΔBPE1		High-Quality Segmentation ΔBPE2		High-Quality Segmentation ΔBPE3	
		No. of Patients (n = 564)	P Value	No. of Patients (n = 433)	P Value	No. of Patients (n = 396)	P Value	No. of Patients (n = 380)	P Value
Mean age (y)*	48 ± 10 (23–73)	48 ± 10 (23–72)	.83	48 ± 10 (24–72)	.60	49 ± 10 (24–71)	.16	48 ± 10 (25–71)	.88
Menopausal status			.07		.66		.93		.60
Premenopausal	457 (52)	300 (53)		229 (53)		202 (51)		205 (54)	
Perimenopausal	31 (4)	18 (3)		15 (3)		13 (3)		11 (3)	
Postmenopausal	273 (31)	160 (28)		126 (29)		124 (31)		112 (29)	
Unclear†	121 (14)	86 (15)		63 (15)		57 (14)		52 (14)	
Race			.34		.17		.02†		.13
White	701 (79)	456 (81)		350 (81)		328 (83)		313 (82)	
Black or African American	105 (12)	57 (10)		41 (9)		33 (8)		34 (9)	
Asian	59 (7)	38 (7)		32 (7)		24 (6)		23 (6)	
American Indian or Alaska Native	4 (0)	3 (1)		2 (0)		2 (1)		2 (1)	
Native Hawaiian or Pacific Islander	5 (1)	4 (1)		2 (0)		3 (1)		3 (1)	
More than one race	8 (1)	6 (1)		6 (1)		6 (2)		5 (1)	
Immunohistochemical subtype			.31		.41		.39		.35
HR-positive HER2-negative	338 (38)	224 (40)		175 (40)		156 (39)		155 (41)	
HR-positive HER2-positive	136 (15)	88 (16)		70 (16)		68 (17)		58 (15)	
HR-negative HER2-positive	80 (9)	44 (8)		36 (8)		33 (8)		28 (7)	
HR-negative HER2-negative	328 (37)	208 (37)		152 (35)		139 (35)		139 (37)	
Assigned chemotherapy			.15		.68		.80		.36
Standard	187 (21)	111 (20)		89 (21)		82 (21)		75 (20)	
Experimental	695 (79)	453 (80)		344 (79)		314 (79)		305 (80)	
Treatment response			>.99		.62		.20		.43
pCR	291 (33)	186 (33)		139 (32)		140 (35)		131 (34)	
NonpCR	591 (67)	378 (67)		294 (68)		256 (65)		249 (66)	

Note.—Unless otherwise specified, data represent the number of patients and data in parentheses are percentages. P values show the results of the comparisons between the high-quality segmentation set versus the excluded patients. The Mann-Whitney U test was used for continuous variable (age), and the Fisher exact test was used for categorical variables. BPE = background parenchymal enhancement, ΔBPE1 = percent change of BPE relative to T1, ΔBPE2 = percent change of BPE relative to T2, ΔBPE3 = percent change of BPE relative to T3, HR = hormone receptor, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, pCR = pathologic complete response.

* Data are ± standard deviation; data in parentheses are range.

† Unclear because of estrogen replacement therapy or prior gynecologic surgery.

enhanced phase was selected from the contrast-enhanced series at the time of analysis on the basis of temporal sampling of the center of k-space closest to 2:30 minutes.

Automated Measurement of Quantitative BPE

Quantitative measurement of BPE was performed by using a previously described fully automated method (2,3,26), which was developed in-house (D.C.N., with 15 years of experience in computational breast imaging research) in the IDL software environment (L3Harris Geospatial). BPE was evaluated in the contralateral breast to avoid the confounding effects of tumor enhancement. First, the contralateral breast contour was automatically determined on contrast-unenhanced images. The central 50% of axial sections in the breast was set as the target volume to avoid over or under segmentation because of artifacts associated with implanted port or distorted shape (26). Second, within the target volume, segmentation of fibroglandular tissue from other components (eg, fat) was performed by using a fuzzy c-means clustering algorithm. All clusters determined to be fibroglandular tissue were combined as a mask. Third, an early

percent enhancement map was generated on a voxel-by-voxel basis by computing as follows: $PE = \frac{S_1 - S_0}{S_0} \times 100\%$, where PE is percent enhancement, S_0 and S_1 are signal intensities at contrast-unenhanced and early contrast-enhanced phase, respectively. Finally, quantitative BPE was calculated by averaging the percent enhancement values for all voxels in the masked volume (Fig 2).

Determination of Analysis Set

To effectively test our hypothesis, this study was restricted to a subset of data with high-quality BPE measurements. Thus, we excluded examinations at which automated determination of the contralateral breast contour failed because of the presence of artifacts, incomplete or failed fat suppression, or signal inhomogeneity (Fig E1 [online]). Then, for examinations with successful determination of the contralateral breast contour, the quality of the fibroglandular tissue segmentation was assessed by using three-point scoring: 2, good; 1, adequate; 0, poor (Fig E2 [online]). These assessments were performed by N.O. (a radiologist with 8 years of experience in breast MRI), who was blinded to BPE values, images of the ipsilateral breast, and all clinical information including treatment response.

We defined BPE at each point (T0, T1, T2, and T3; hereafter referred to as BPE0, BPE1, BPE2, and BPE3, respectively). BPE with segmentation quality score of 2 or 1 was determined as high-quality. Percent change of BPE relative to T0 (hereafter, referred to as ΔBPE1, ΔBPE2, and ΔBPE3) was determined as high quality if both BPE0 and BPE at the given point were high quality. The subset of patients with high-quality BPE0, ΔBPE1, ΔBPE2, and ΔBPE3 were determined as high-quality segmentation set. For the primary analysis, the high-quality segmentation set was split into two cohorts on the basis the hormone receptor status (HR positive or HR negative). Further analyses were performed according to the menopausal status (premenopausal or peri- and postmenopausal), HER2 receptor status (HER2 positive or HER2 negative), or chemotherapy regimen (standard or experimental).

BPE Suppression and Treatment Response

BPE suppression at each point was evaluated by a binary indicator of whether or not BPE was suppressed relative to T0. For example, BPE suppression at T1 was evaluated as suppressed if ΔBPE1 was less than 0, and nonsuppressed if ΔBPE1 was more than or equal to 0.

Treatment response was evaluated by a binary indicator of pathologic complete response (pCR) or nonpCR confirmed in a surgical specimen after completion of NAC. pCR was defined as the absence of residual invasive carcinoma in the breast and axillary lymph nodes after NAC.

Statistical Analysis

Statistical analyses were performed by N.O. and J.K. (with 20 years of experience in medical imaging statistics research) by using software (R version 3.5.1; R Foundation for Statistical Computing). In this study, nominal P values without adjustment for multiple testing were reported and P values less than .05 were considered to indicate statistical significance. For the comparisons of patient characteristics (the high-quality segmentation set vs the excluded patients), the Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables were used. BPE at pretreatment point (ie, BPE0) was compared between the HR-positive and HR-negative cohorts by using the Mann-Whitney U test. At each point (T1, T2, and T3) in each of the HR-positive and HR-negative cohorts, the association between BPE suppression and pCR was tested by using the Fisher exact test (to generate the P value) and the Z-test of proportions with Yates continuity correction was used to estimate the 95% CIs for the difference in pCR rates between patients with suppressed and nonsuppressed BPE (the primary analyses). The subcohort analyses were performed in the same manner.

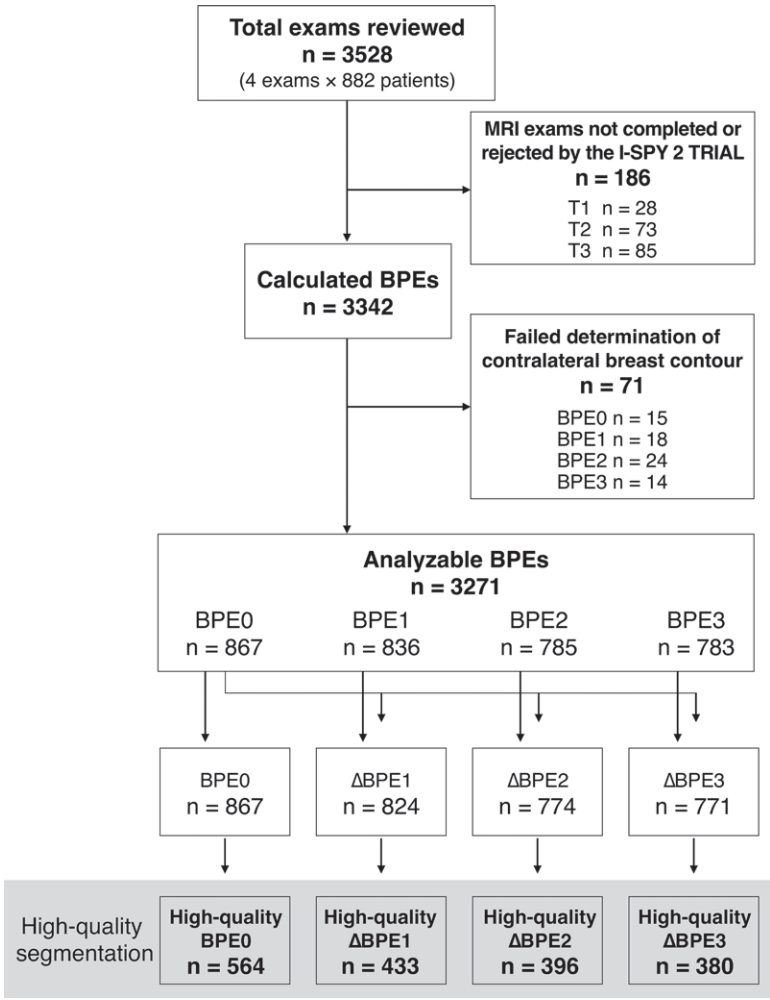

Figure 3: Study flowchart. BPE = background parenchymal enhancement, BPE0 = background parenchymal enhancement at T0, BPE1 = BPE at T1, BPE2 = BPE at T2, BPE3 = BPEt at T3, ΔBPE1 = percent change of BPE relative to T0 at T1, ΔBPE2 = percent change of BPE relative to T0 at T2, ΔBPE3 = percent change of BPE relative to T0 at T3.

Table 2: Association between Background Parenchymal Enhancement Suppression and Pathologic Complete Response in Hormone Receptor–positive and Hormone Receptor–negative Cohort

Primary Analysis	No. of Patients with pCR*	No. of Patients without pCR*	Total No. of Patients*	pCR Rate	Difference in pCR Rates†	*P* Value‡
HR-positive cohort						
ΔBPE1						
Suppressed	43 (78)	138 (73)	181 (74)	23.8	5.0 (−7.4, 17.5)	.49
Nonsuppressed	12 (22)	52 (27)	64 (26)	18.8		
ΔBPE2						
Suppressed	50 (89)	123 (73)	173 (77)	28.9	17.1 (4.7, 29.5)	.02
Nonsuppressed	6 (11)	45 (27)	51 (23)	11.8		
ΔBPE3						
Suppressed	48 (96)	127 (78)	175 (82)	27.4	22.2 (10.9, 33.5)	.003
Nonsuppressed	2 (4)	36 (22)	38 (18)	5.3		
HR-negative cohort						
ΔBPE1						
Suppressed	64 (76)	74 (71)	138 (73)	46.4	6.4 (−10.9, 23.7)	.51
Nonsuppressed	20 (24)	30 (29)	50 (27)	40.0		
ΔBPE2						
Suppressed	70 (83)	63 (72)	133 (77)	52.6	16.7 (−2.2, 35.7)	.07
Nonsuppressed	14 (17)	25 (28)	39 (23)	35.9		
ΔBPE3						
Suppressed	65 (80)	64 (74)	129 (77)	50.4	8.3 (−11.3, 27.9)	.46
Nonsuppressed	16 (20)	22 (26)	38 (23)	42.1		

Note.—BPE = background parenchymal enhancement, ΔBPE1 = percent change of BPE relative to T1, ΔBPE2 = percent change of BPE relative to T2, ΔBPE3 = percent change of BPE relative to T3, HR = hormone receptor, pCR = pathologic complete response.

* Data are the number of patients and data in parentheses are percentages.

† pCR rate for patients with suppressed BPE minus that for patients with nonsuppressed BPE estimated by the *Z*-test of proportions with Yates continuity correction; data in parentheses are 95% CIs.

‡ Nominal *P* values without adjustment for multiple testing on the basis of the Fisher exact test.

Results

Patient Data Set

Of the 988 patients reviewed, 106 patients (38 patients with no menopausal status data, 31 patients with concurrent bilateral breast cancer, six patients with a history of contralateral breast cancer, 30 patients with a history of contralateral surgery, and one patient with a history of chest radiation) were not eligible for this study. There were 882 eligible patients (HR positive, 474 patients; HR negative, 408 patients; mean age, 48 years ± 10 [standard deviation]). Patient characteristics including age, menopausal status, race, immunohistochemical subtype, assigned chemotherapy and treatment response for all eligible patients, and the high-quality segmentation set are listed in Table 1. Patient characteristics of the high-quality segmentation set were comparable to those of the excluded patients except for race in ΔBPE2. In I-SPY 2, menstrual cycle data at the time of MRI were not controlled for premenopausal patients, and the data were not available. Menopausal status was unclear for 121 patients because of estrogen replacement therapy or previous gynecologic surgery. There were 71 patients who were undergoing estrogen replacement therapy at the time of trial enrollment (49 postmenopausal patients, two premenopausal patients, and 20 patients in whom it was unclear). In the subanalyses regarding menopausal status, patients who were undergoing estrogen replacement therapy were excluded and the other patients with unclear menopausal status were considered to be premenopausal if their age at trial enrollment was younger than 50 years (n = 32) and to be peri- or postmenopausal if their age was 50 years or older (n = 69).

The 882 patients underwent MRI at one of the 22 participating sites. Detailed information about each institution and MRI systems are shown in Table E1 (online). Figure 3 shows the study flowchart. Of a possible total of 3528 MRI examinations (four examinations × 882 patients), 5.3% (186 of 3528) of examinations were not completed or were rejected by I-SPY 2 because of patient's withdrawal of treatment consent (n = 66), early surgical procedure after early discontinuation of NAC (n = 8), patient illness (n = 20), missed patient appointments for unknown reasons (n = 88), or MRI scanner or contrast agent injection issues (n = 4). BPE calculation was performed for the rest of the examinations (94.7%; 3342 of 3528). Of those, 71 examinations with BPE (BPE0, 15; BPE1, 18; BPE2, 24; BPE3, 14) with failed determination of the contralateral breast contour were excluded from the analyses. For the 3271 examinations with BPE that were able to be analyzed, quality scores of the automated segmentation of fibroglandular tissue were assessed (Table E2

[online]): BPE0 (score 2, 96 of 867 [11.1%]; score 1, 468 of 867 [54.0%]; score 0, 303 of 867 [34.9%]), BPE1 (score 2, 74 of 836 [8.9%]; score 1, 422 of 836 [50.5%]; score 0, 340 of 836 [40.7%]), BPE2 (score 2, 71 of 785 [9.0%]; score 1, 392 of 785 [49.9%]; score 0, 322 of 785 [41.0%]), and BPE3 (score 2, 61 of 783 [7.8%]; score 1, 392 of 783 [50.1%]; score 0, 330 of 783 [42.1%]). Finally, the high-quality segmentation set was determined: BPE0, 564 patients; ΔBPE1, 433 patients; ΔBPE2, 396 patients; ΔBPE3, 380 patients. The high-quality segmentation set was split into two cohorts on the basis of hormone receptor status (Table E3 [online]).

BPE and BPE Change

Both BPE and BPE change appeared to display a positively skewed distribution and therefore median and 1st and 3rd quartiles were used to describe location and variation of these quantities: The quartiles are in parentheses after the median value. The median of BPE0, BPE1, BPE2, and BPE3 were 24.2% (interquartile range, 17.1%–34.7%), 20.7% (interquartile range, 15.0%–28.6%), 18.9% (interquartile range, 13.8%–25.7%), and 17.8% (interquartile range, 13.0%–23.1%), respectively. The median values of ΔBPE1, ΔBPE2, and ΔBPE3 were −15.1% (interquartile range, −31.4% to 3.1%), −19.9% (interquartile range, −39.0% to −1.4%), and −25.7% (interquartile range, −43.3% to −5.1%), respectively. No evidence for an important difference was found in BPE0 between the HR-positive and HR-negative cohorts (P = .43), as follows: HR positive, 24.1% (interquartile range, 16.8%–35.2%); HR negative, 24.4% (17.9%–33.8%).

BPE Suppression and pCR

BPE suppression was shown in 73%–82% of patients (HR positive at T1, 74% [181 of 245]; HR positive at T2, 77% [173 of 224]; HR positive at T3, 82% [175 of 213]; HR negative at T1, 73% [138 of 188]; HR negative at T2, 77% [133 of 172]; HR negative at T3, 77% [129 of 167]), and lack of BPE suppression was shown in 18%–27% of patients (HR positive at T1, 26% [64 of 245]; HR positive at T2, 23% [51 of 224]; HR positive at T3, 18% [38 of 213]; HR negative at T1, 27% [50 of 188]; HR negative at T2, 23% [39 of 172]; HR negative at T3, 23% [38 of 167]), as shown in Table 2. In the HR-positive cohort, patients with nonsuppressed BPE had a lower estimated pCR rate than those with suppressed BPE at every point: T1, 18.8% versus 23.8% (12 of 64 vs 43 of 181 [difference, 5.0%; 95% CI: −7.4, 17.5]); T2, 11.8% versus 28.9% (six of 51 vs 50 of 173 [difference, 17.1%; 95% CI: 4.7, 29.5]); and T3, 5.3% versus 27.4% (two of 38 vs 48 of 175 [difference, 22.2%; 95% CI: 10.9, 33.5]). The association between lack of BPE suppression and

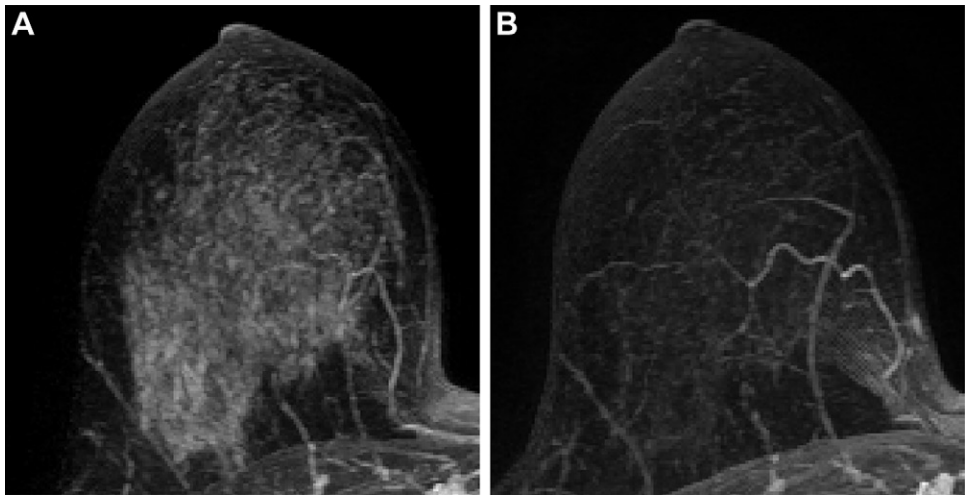

Figure 4: Axial maximum intensity projection of subtracted early contrast-enhanced phase MRI in right breast of a 47-year-old perimenopausal woman with left hormone receptor–positive human epidermal growth factor 2–negative invasive breast cancer at **(A)** T0 and **(B)** T2. The calculated background parenchymal enhancement (BPE) values were **(A)** 46.3% and **(B)** 15.9%, and the BPE change was evaluated as suppressed (percent change of BPE at T2, <0). The patient was confirmed at pathologic analysis as having complete response in the surgical specimen after neoadjuvant chemotherapy.

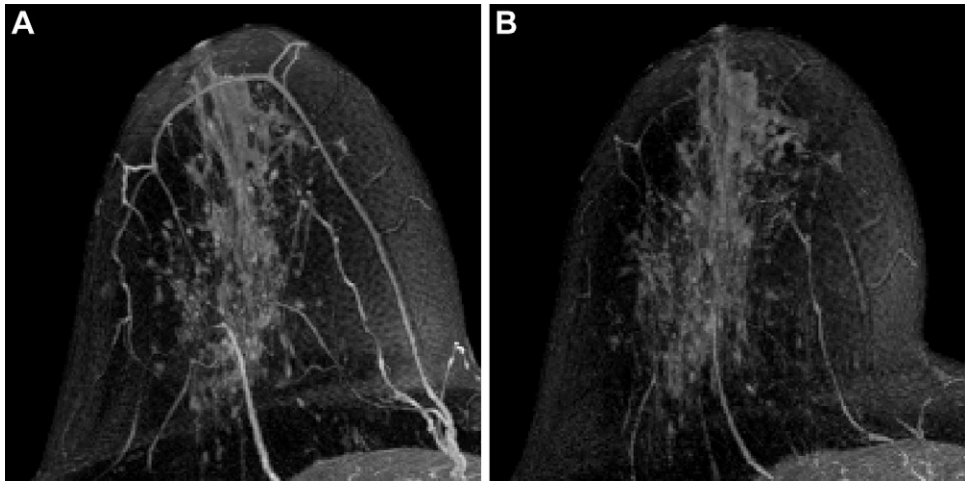

Figure 5: Axial maximum intensity projection of subtracted early contrast-enhanced phase MRI in right breast of a 55-year-old postmenopausal woman with left hormone receptor–positive human epidermal growth factor 2–negative invasive breast cancer at **(A)** T0 and **(B)** T2. The calculated background parenchymal enhancement (BPE) values were **(A)** 32.3% and **(B)** 35.0%, and the BPE change was evaluated as nonsuppressed (percent change of BPE at T2, ≥0). The patient was confirmed at pathologic analysis as having noncomplete response in the surgical specimen after neoadjuvant chemotherapy.

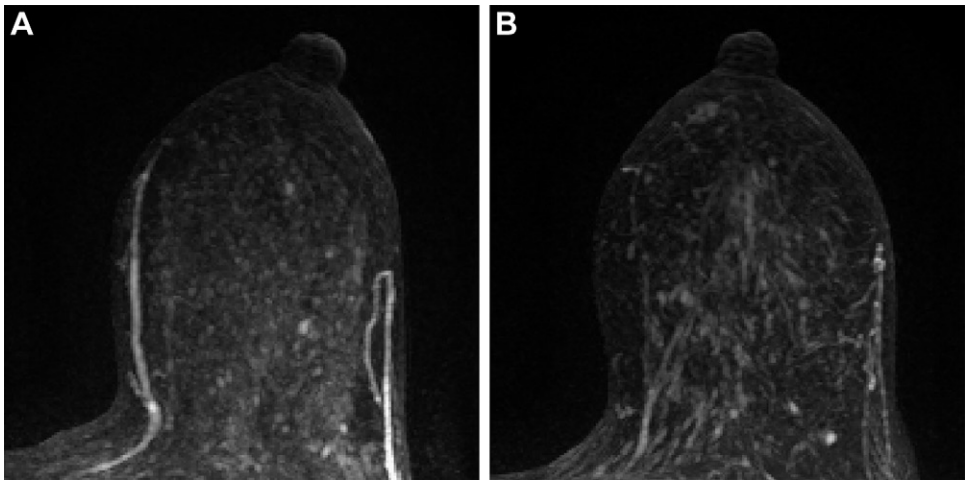

Figure 6: Axial maximum intensity projection of subtracted early contrast-enhanced phase MRI in left breast of a 50-year-old premenopausal woman with right hormone receptor–positive human epidermal growth factor 2–negative invasive breast cancer at **(A)** T0 and **(B)** T3. The calculated background parenchymal enhancement (BPE) values were **(A)** 20.5% and **(B)** 22.0%, and the BPE change was evaluated as nonsuppressed BPE (percent change of BPE at T3, ≥0). The patient was confirmed at pathologic analysis as having noncomplete response in the surgical specimen after neoadjuvant chemotherapy.

lower pCR rate was detected at T2 (P = .02) and T3 (P = .003) but not at T1 (P = .49). The representative three patients with suppressed or nonsuppressed BPE are shown in Figures 4–6. In the HR-negative cohort, patients with nonsuppressed BPE had lower estimated pCR rate than those with suppressed BPE at every point: T1, 40.0% versus 46.4% (20 of 50 vs 64 of 138 [difference, 6.4%; 95% CI: −10.9, 23.7]); T2, 35.9% versus 52.6% (14 of 39 vs 70 of 133 [difference, 16.7% [95% CI: −2.2, 35.7]); T3, 42.1% versus 50.4% (16 of 38 vs 65 of 129 [difference, 8.3%; 95% CI: −11.3, 27.9]). However,

Table 3: Association between Background Parenchymal Enhancement Suppression and Pathologic Complete Response in Hormone Receptor–positive Subcohorts

Subcohort Analyses in HR-positive Cohort	No. of Patients with pCR*	No. of Patients without pCR*	Total No. of Patients*	pCR Rate	Difference in pCR Rates†	*P* Value‡
Menopausal status and hormone replacement therapy						
Premenopausal subcohort						
ΔBPE1						
Suppressed	26 (84)	87 (81)	113 (82)	23.0	3.0 (−16.9, 22.9)	>.99
Nonsuppressed	5 (16)	20 (19)	25 (18)	20.0		
ΔBPE2						
Suppressed	32 (94)	79 (88)	111 (90)	28.8	13.4 (−12.2, 39.1)	.51
Nonsuppressed	2 (6)	11 (12)	13 (10)	15.4		
ΔBPE3						
Suppressed	31 (97)	77 (83)	108 (86)	28.7	22.8 (5.3, 40.3)§	.07
Nonsuppressed	1 (3)	16 (17)	17 (14)	5.9		
Peri- and postmenopausal subcohort						
ΔBPE1						
Suppressed	15 (71)	36 (59)	51 (62)	29.4	10.1 (−11.2, 31.4)	.44
Nonsuppressed	6 (29)	25 (41)	31 (38)	19.4		
ΔBPE2						
Suppressed	15 (79)	34 (59)	49 (64)	30.6	16.3 (−4.8, 37.4)	.17
Nonsuppressed	4 (21)	24 (41)	28 (36)	14.3		
ΔBPE3						
Suppressed	15 (94)	32 (67)	47 (73)	31.9	26.0 (4.6, 47.4)	.048
Nonsuppressed	1 (6)	16 (33)	17 (27)	5.9		
HER2 receptor status						
HER2-positive subcohort						
ΔBPE1						
Suppressed	19 (79)	32 (70)	51 (73)	37.3	10.9 (−16.5, 38.4)	.57
Nonsuppressed	5 (21)	14 (30)	19 (27)	26.3		
ΔBPE2						

Table 3 *(continues)*

the *P* values for the association were greater than .05 (T1, *P* = .51; T2, *P* = .07; and T3, *P* = .46).

In the subanalyses of the HR-positive cohort (Table 3), premenopausal patients showed BPE suppression in 82% (113 of 138) at T1, 90% (111 of 124) at T2, and 86% (108 of 125) at T3. Peri- and postmenopausal patients showed BPE suppression in 62% (51 of 82) at T1, 64% (49 of 77) at T2, and 73% (47 of 64) at T3. An association between lack of BPE suppression and lower pCR rate was detected at T3 in the peri- and postmenopausal subcohort, HER2-positive

Table 3 (*continued*): Association between Background Parenchymal Enhancement Suppression and Pathologic Complete Response in Hormone Receptor–positive Subcohorts

Subcohort Analyses in HR-positive Cohort	No. of Patients with pCR*	No. of Patients without pCR*	Total No. of Patients*	pCR Rate	Difference in pCR Rates†	*P* Value‡
Suppressed	23 (88)	30 (71)	53 (78)	43.4	23.4 (−5.1, 51.9)	.14
Nonsuppressed	3 (12)	12 (29)	15 (22)	20.0		
ΔBPE3						
Suppressed	20 (100)	28 (74)	48 (83)	41.7	41.7 (21.7, 61.7)	.01
Nonsuppressed	0 (0)	10 (26)	10 (17)	0.0		
HER2-negative subcohort						
ΔBPE1						
Suppressed	24 (77)	106 (74)	130 (74)	18.5	2.9 (−11.1, 16.9)	.82
Nonsuppressed	7 (23)	38 (26)	45 (26)	15.6		
ΔBPE2						
Suppressed	27 (90)	93 (74)	120 (77)	22.5	14.2 (0.6, 27.7)§	.09
Nonsuppressed	3 (10)	33 (26)	36 (23)	8.3		
ΔBPE3						
Suppressed	28 (93)	99 (79)	127 (82)	22.0	14.9 (0.8, 29.0)§	.11
Nonsuppressed	2 (7)	26 (21)	28 (18)	7.1		
Chemotherapy regimen						
Standard chemotherapy subcohort						
ΔBPE1						
Suppressed	6 (60)	26 (70)	32 (68)	18.8	−7.9 (−39.0, 23.1)	.70
Nonsuppressed	4 (40)	11 (30)	15 (32)	26.7		
ΔBPE2						
Suppressed	9 (100)	23 (70)	32 (76)	28.1	28.1 (6.0, 50.3)§	.09
Nonsuppressed	0 (0)	10 (30)	10 (24)	0.0		
ΔBPE3						
Suppressed	7 (100)	26 (79)	33 (82)	21.2	21.2 (−1.4, 43.8)	.32
Nonsuppressed	0 (0)	7 (21)	7 (18)	0.0		
Experimental chemotherapy subcohort						
ΔBPE1						
Suppressed	37 (82)	112 (73)	149 (75)	24.8	8.5 (−5.3, 22.3)	.25
Nonsuppressed	8 (18)	41 (27)	49 (25)	16.3		
ΔBPE2						
Suppressed	41 (87)	100 (74)	141 (77)	29.1	14.4 (−0.3, 29.2)	.07
Nonsuppressed	6 (13)	35 (26)	41 (23)	14.6		
ΔBPE3						
Suppressed	41 (95)	101 (78)	142 (82)	28.9	22.4 (9.0, 35.8)	.01
Nonsuppressed	2 (5)	29 (22)	31 (18)	6.5		

Note.—BPE = background parenchymal enhancement, ΔBPE1 = percent change of BPE relative to T1, ΔBPE2 = percent change of BPE relative to T2, ΔBPE3 = percent change of BPE relative to T3, HR = hormone receptor, pCR = pathologic complete response.

* Data are the number of patients and data in parentheses are percentages.

† pCR rate for patients with suppressed BPE minus that for patients with nonsuppressed BPE estimated by the *Z*-test of proportions with Yates continuity correction; data in parentheses are 95% CIs.

‡ Nominal *P* values without adjustment for multiple testing on the basis of the Fisher exact test.

§ The 95% CIs of the difference in the pCR rates were estimated to all be greater than 0, although *P* values were greater than .05. This contradiction occurred because Fisher is an exact test whereas the CIs are on the basis of the Z-test of proportions with Yates continuity correction and use an asymptotic approximation.

Table 4: Association between Background Parenchymal Enhancement Suppression and Pathologic Complete Response in Hormone Receptor–negative Subcohorts

Subcohort Analyses in HR-negative Cohort	No. of Patients with pCR*	No. of Patients without pCR*	Total No. of Patients*	pCR Rate	Difference in pCR Rates†	*P* Value‡
Menopausal status and hormone replacement therapy						
Premenopausal subcohort						
ΔBPE1						
Suppressed	31 (74)	47 (72)	78 (73)	39.7	1.8 (−20.7, 24.4)	>.99
Nonsuppressed	11 (26)	18 (28)	29 (27)	37.9		
ΔBPE2						
Suppressed	33 (82)	39 (80)	72 (81)	45.8	4.7 (−25.1, 34.4)	.79
Nonsuppressed	7 (18)	10 (20)	17 (19)	41.2		
ΔBPE3						
Suppressed	36 (88)	40 (80)	76 (84)	47.4	14.0 (−16.3, 44.4)	.40
Nonsuppressed	5 (12)	10 (20)	15 (16)	33.3		
Peri- and postmenopausal subcohort						
ΔBPE1						
Suppressed	29 (83)	22 (71)	51 (77)	56.9	16.9 (−15.7, 49.5)	.38
Nonsuppressed	6 (17)	9 (29)	15 (23)	40.0		
ΔBPE2						
Suppressed	31 (86)	17 (55)	48 (72)	64.6	38.3 (10.6, 65.9)	.01
Nonsuppressed	5 (14)	14 (45)	19 (28)	26.3		
ΔBPE3						
Suppressed	25 (78)	20 (74)	45 (76)	55.6	5.6 (−29.1, 40.2)	.77
Nonsuppressed	7 (22)	7 (26)	14 (24)	50.0		
HER2 receptor status						
HER2-positive subcohort						
ΔBPE1						
Suppressed	23 (82)	7 (88)	30 (83)	76.7	−6.7 (−46.8, 33.4)	>.99
Nonsuppressed	5 (18)	1 (12)	6 (17)	83.3		
ΔBPE2						
Suppressed	20 (74)	3 (50)	23 (70)	87.0	17.0 (−21.8, 55.7)	.34
Nonsuppressed	7 (26)	3 (50)	10 (30)	70.0		
ΔBPE3						
Suppressed	16 (70)	5 (100)	21 (75)	76.2	−23.8 (−51.5, 3.9)	.29
Nonsuppressed	7 (30)	0 (0)	7 (25)	100.0		
HER2-negative subcohort						
ΔBPE1						
Suppressed	41 (73)	67 (70)	108 (71)	38.0	3.9 (−14.5, 22.2)	.71
Nonsuppressed	15 (27)	29 (30)	44 (29)	34.1		
ΔBPE2						
Suppressed	50 (88)	60 (73)	110 (79)	45.5	21.3 (1.0, 41.6)§	.06
Nonsuppressed	7 (12)	22 (27)	29 (21)	24.1		
ΔBPE3						
Suppressed	49 (84)	59 (73)	108 (78)	45.4	16.3 (−4.3, 36.9)	.15
Nonsuppressed	9 (16)	22 (27)	31 (22)	29.0		
Chemotherapy regimen						
Standard chemotherapy subcohort						
ΔBPE1						
Suppressed	7 (70)	22 (69)	29 (69)	24.1	1.1 (−27.7, 29.8)	>.99
Nonsuppressed	3 (30)	10 (31)	13 (31)	23.1		

Table 4 *(continues)*

Table 4 *(continued)*: Association between Background Parenchymal Enhancement Suppression and Pathologic Complete Response in Hormone Receptor–negative Subcohorts

Subcohort Analyses in HR-negative Cohort	No. of Patients with pCR*	No. of Patients without pCR*	Total No. of Patients*	pCR Rate	Difference in pCR Rates†	*P* Value‡
ΔBPE2						
Suppressed	9 (100)	26 (84)	35 (88)	25.7	25.7 (−0.2, 51.6)	.57
Nonsuppressed	0 (0)	5 (16)	5 (12)	0.0		
ΔBPE3						
Suppressed	8 (89)	21 (81)	29 (83)	27.6	10.9 (−33.1, 54.9)	>.99
Nonsuppressed	1 (11)	5 (19)	6 (17)	16.7		
Experimental chemotherapy subcohort						
ΔBPE1						
Suppressed	57 (77)	52 (72)	109 (75)	52.3	6.3 (−14.1, 26.8)	.57
Nonsuppressed	17 (23)	20 (28)	37 (25)	45.9		
ΔBPE2						
Suppressed	61 (81)	37 (65)	98 (74)	62.2	21.1 (0, 42.2)	.04
Nonsuppressed	14 (19)	20 (35)	34 (26)	41.2		
ΔBPE3						
Suppressed	57 (79)	43 (72)	100 (76)	57.0	10.1 (−11.8, 32.0)	.42
Nonsuppressed	15 (21)	17 (28)	32 (24)	46.9		

Note.—BPE = background parenchymal enhancement, ΔBPE1 = percent change of BPE relative to T1, ΔBPE2 = percent change of BPE relative to T2, ΔBPE3 = percent change of BPE relative to T3, HR = hormone receptor, pCR = pathologic complete response.

* Data are the number of patients and data in parentheses are percentages.

† pCR rate for patients with suppressed BPE minus that for patients with nonsuppressed BPE estimated by the *Z*-test of proportions with Yates continuity correction; data in parentheses are 95% CIs.

‡ Nominal *P* values without adjustment for multiple testing on the basis of the Fisher exact test.

§ The 95% CIs of the difference in the pCR rates was estimated to all be greater than 0, although *P* values were greater than .05. This contradiction occurred because Fisher is an exact test whereas the CIs are on the basis of the *Z*-test of proportions with Yates continuity correction and use an asymptotic approximation.

subcohort, and experimental chemotherapy subcohort. Although the *P* values were all greater than .05 in the other HR-positive subcohorts and points, lower estimated pCR rates for the patients with nonsuppressed BPE were estimated for all subcohorts and points except in the standard chemotherapy subcohort at T1.

In the subanalyses of the HR-negative cohort (Table 4), premenopausal patients showed BPE suppression in 73% (78 of 107) at T1, 81% (72 of 89) at T2, and 84% (76 of 91) at T3. Peri- and postmenopausal patients showed BPE suppression in 77% (51 of 66) at T1, 72% (48 of 67) at T2, and 76% (45 of 59) at T3. An association between lack of BPE suppression and lower pCR rate was detected at T2 in the peri- and postmenopausal subcohort and experimental chemotherapy subcohort. Although the *P* values were all greater than .05 in the other HR-negative subcohorts and points, lower estimated pCR rates for the patients with nonsuppressed BPE were estimated for all subcohorts and points except in the HER2-positive subcohort at T1 and T3.

There was an apparent contradiction between *P* value (≥.05) and the 95% CIs (all above 0) in some subanalysis results. Because Fisher is an exact test whereas the CIs are on the basis of a different approach with the *Z*-test of proportions with Yates continuity correction, they can sometimes disagree. CIs for differences cannot be generated from Fisher exact test because it is on the basis of relative rates, not differences.

We repeated the primary analysis by using all examinations with analyzable BPE including those with poor-quality segmentation (ie, quality score of 0) and found that the results were broadly in line with those in the high-quality segmentation set (Table E4 [online]). This indicates that the pattern of results is not sensitive to this choice of data set specification.

Discussion

This study demonstrated the association between lack of background parenchymal enhancement (BPE) suppression and inferior response to neoadjuvant chemotherapy (NAC) in a hormone receptor–positive cohort after completion of NAC (presurgery point, T3) and after only 12 weeks of treatment (interregimen point, T2). The association at T2 is noteworthy because nonsuppressed BPE could indicate patients who eventually show inferior response and allow personalized redirection of treatment.

Our results align with previous studies demonstrating the association between BPE and treatment response (4,6,19–21). Strengths of the current study include the objective quantitative measurement of BPE and the controlled cohort with large sample size. We focused on whether BPE was suppressed at the individual patient level rather than how much BPE increased or decreased on average across patients. This approach differs from other studies.

Because BPE was measured only in the contralateral breast in this study, the BPE suppression may indirectly reflect a chemotherapy-induced physiologic change in normal breast tissue. Specifically, the demonstrated association between lack of BPE suppression and lower pCR rate in the HR-positive cohort might be explained by less chemotherapy-induced ovarian suppression and related less decrease in estrogen level, although it is not possible to show this directly in this retrospective study. The contrasting results observed between the HR-positive and the HR-negative cohorts may support this explanation. Lack of BPE suppression might also be explained by less suppression of breast vascularity (14,23,27). Whereas ovarian suppression by cyclophosphamides is known (28), the influence of paclitaxel on ovaries is uncertain: Conflicting results show increase (29–31) or no increase (32,33) of ovarian suppression by adding taxane to anthracycline-cyclophosphamide. Weekly paclitaxel, with both antiangiogenic and antimitotic effects (34,35), may decrease normal breast vascularity and result in BPE suppression. This was suggested by a previous study (22) in which taxane-containing NAC induced the suppression of contrast enhancement of breast cancers, benign lesions, and normal fibroglandular tissue to a similar extent. This might also be supported by the observed BPE suppression in both premenopausal and peri- and postmenopausal patients.

For the subanalyses, it is possible that the difference in pCR rates did not reach statistical significance either because of the smaller sample sizes when splitting the data or because there was genuinely no effect. However, some results had greater than 10% estimated lower pCR rates for the nonsuppressed BPE group, which (if correct) would suggest a potentially clinically important effect, coupled with the 95% CIs providing clear evidence against a clinically meaningful effect in the opposite direction (ie, the 95% CI indicates at most 1% higher pCR rate for the nonsuppressed BPE group). This may suggest the potential benefit of BPE as a noninvasive indicator of inferior response. These thresholds are on the basis of our subjective judgements of clinical importance rather than established cutoffs, and therefore these estimates and CIs are open to different interpretations. We found potentially clinically important effects at T2 in the HR-positive subcohorts (HER2 negative, and standard and experimental chemotherapy), T3 in the HR-positive subcohorts (premenopausal and HER2 negative), and T2 in the HR-negative subcohorts (HER2 negative and standard chemotherapy).

The HR-positive cohort showed an association between BPE suppression and pCR at T2 and T3, however, it was not detected at T2 in any HR-positive subcohort. For the HR-negative cohort, wherein no association was detected at any point, an association at T2 was detected in some subcohorts. These apparent discrepancies may illustrate possible influence of menopausal status, HER2 receptor status, and chemotherapy regimen. However, another simple explanation is smaller sample size in particular subcohorts, which generally requires a larger effect to observe statistical significance. Within the HR-positive subcohorts, some differences were detected. At T2, the association between BPE suppression and pCR was not detected in menopausal status subcohorts, but potentially clinically important effects were detected in HER2-negative, standard chemotherapy, and experimental chemotherapy subcohorts. At T3, the association was detected in the experimental chemotherapy subcohort but not in the standard chemotherapy subcohort. Unknown effects of experimental agents and/or the addition of trastuzumab could potentially bias the results. The effect of a specific drug on the association between BPE suppression and pCR might be assessed further when drugs become available in clinical neoadjuvant settings in the future, allowing for evaluation of more substantial sized data sets.

Our study had limitations. First, it was a retrospective analysis of a prospective clinical trial, wherein the menstrual cycle at time of MRI was not controlled for premenopausal patients. Second, we used the subset of examinations with BPE with high-quality fibroglandular tissue segmentation for the analyses because of varying quality levels in the fully automated segmentations. Also, contralateral BPE segmentation may have included benign tumors such as fibroadenomas. Further technical improvement is crucial for more precise analysis and is a focus of current studies.

In conclusion, lack of background parenchymal enhancement suppression may be an early indicator of inferior response to neoadjuvant chemotherapy especially in hormone receptor–positive breast cancer, enabling discontinuation of ineffective treatment and initiation of a more promising alternative. Improved automated segmentation methods may enable the development of background parenchymal enhancement as a reliable biomarker of treatment response. This will be tested prospectively in the ongoing I-SPY 2 TRIAL.

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