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Background Parenchymal Enhancement of the Contralateral Normal Breast: Association with Tumor Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy[1]

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Abstract

PURPOSE: This study investigated the association between background parenchymal enhancement (BPE) and pathologic response to neoadjuvant chemotherapy (NAC). *METHODS:* A total of 46 patients diagnosed with invasive breast cancer were analyzed. Each patient had three magnetic resonance imaging (MRI) studies, one pre-treatment and two follow-up (F/U) MRI studies. BPE was measured as the averaged enhancement of the whole fibroglandular tissues. The pre-treatment BPE and the changes in the F/U MRI were compared between patients achieving pathologic complete response (pCR) *versus* those not. Subgroup analyses based on age, estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) status of their cancers were also performed. *RESULTS:* The pre-treatment BPE was higher in the pCR group than that in the non-pCR group. Compared to baseline, BPE at F/U-1 was significantly decreased in the pCR group but not in the non-pCR group. In subgroup analysis based on age, these results were seen only in the younger group (<55 years old), not in the older group (≥55 years old). Older patients had a significantly lower pre-treatment BPE than younger patients. In analysis based on molecular biomarkers, a significantly decreased BPE at F/U-1 was only found in the ER-negative pCR group but not in the non-pCR, nor in the ER-positive groups. *CONCLUSIONS:* A higher pre-treatment BPE showing a significant decrease early after starting NAC was related to pCR in pre/peri-menopausal patients.

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Introduction

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is widely used for the diagnosis of breast cancer. The amount of contrast agents that can reach the normal fibroglandular breast tissue is an indicator of blood perfusion to the normal tissue, referred to as background parenchymal enhancement (BPE), which can be evaluated qualitatively [1,2] or measured quantitatively [3]. Previous studies have demonstrated that BPE is affected by age, physiologic hormonal status, and hormonal therapy [4–6]. It was noted that BPE in pre-menopausal women is altered over the women's menstrual cycle [7,8].

Most published studies about BPE focused on the diseased breast harboring breast cancer. It was found that BPE may affect the diagnostic performance of breast MRI [9,10]. Because of its clinical

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impact on the diagnosis, BPE and its descriptors have been added to the recent updates and revision of The Breast Imaging Reporting and Data System (BI-RADS) breast MRI lexicon [11]. Several studies also noted that BPE surrounding primary breast tumors was associated with response to neoadjuvant chemotherapy (NAC) and prognosis [12], as well as with recurrence-free survival in patients with ductal carcinoma *in situ* after breast conservation surgery [13]. However, because of the presence of cancer, the measurement of BPE in the diseased breast will be strongly dependent on the location where the measurement was made from or the placement of region of interest (ROI).

As most DCE-MRI studies were performed bilaterally on breast cancer patients, the BPE in the contralateral normal breast could be measured, and on the basis of breast symmetry, the measured BPE in this way could reflect the normal tissue enhancements in the diseased breast. A recent study comparing the difference of BPE in the normal breasts between pre-menopausal and post-menopausal women found that BPE was higher in pre-menopausal than in post-menopausal women, and a decreased BPE after receiving NAC was found in pre-menopausal, not in post-menopausal, women [14]. These results suggested that the difference was most likely coming from ovarian function and the suppression due to chemotherapy [14]. Since the BPE is related to blood perfusion (thus affecting delivery of therapeutic agent) and likely ovarian function (thus affecting the hormone level), it may also affect the treatment response of breast cancer to NAC. So far, there has been no report to investigate this relationship yet.

In the present study, we measured BPE in the contralateral normal breasts of NAC patients who achieved pathologic complete response (pCR) and those not achieving pCR (non-pCR). The pre-treatment BPE and the changes during NAC between the pCR and non-pCR groups were compared. In addition, we performed subgroup analysis by separating patients based on age, the estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) of their cancers. The BPE between patients with ER-positive and ER-negative cancers and that between patients with HER2-positive and HER2-negative cancers were also compared.

Materials and Methods

Subjects

The study is a retrospective analysis of prospectively enrolled breast cancer patients who were elected to receive NAC treatment before surgery from 2002 to 2006. The study was approved by the Institutional Review Board and was The Health Insurance Portability and Accountability Act (HIPAA) compliant. All participants gave written informed consent. A total of 52 subjects who had one pre-treatment baseline MRI and at least two follow-up (F/U) MRIs while undergoing NAC regimen and received surgery after NAC were identified. Six patients were excluded from the analysis because of the following reasons: patients with contralateral breast lesions, patients with extremely fatty breast (< 5% breast density as measured in MRI), and patients with poor MR image quality in any of their three MRIs. Of remaining 46 subjects, 40 had invasive ductal cancer (IDC), 5 had infiltrating lobular cancer (ILC), and one had mixed IDC and ILC. The age of patients at the start of study ranged from 31 to 77 years old [50 ± 11 (mean ± SD), median 49 years]. The one-dimensional tumor size in baseline MRI ranged from 0.5 to 9.9 cm [4.1±2.3cm (mean ± SD), median 3.4 cm].

The pathologic response was determined based on the examination of surgical specimen after completing NAC. pCR was defined as the absence of malignant cancer cells. Non-pCR was defined as the presence of residual cancer cells in pathology. For subgroup analysis based on age, patients were separated into pre/peri-menopausal (< 55 years old, $N = 32$) and post-menopausal groups (≥ 55 years old, $N = 14$). For the whole group, and each age and biomarker subgroup (ER-positive cancer, ER-negative cancer, HER2 receptor–positive cancer, and HER2 receptor–negative cancer), BPE in patients of the pCR and non-pCR groups were compared.

NAC Treatment Protocol

The chemo-regimen used at our institution from 2002 to 2006 consisted of two to four cycles of dose-dense AC (doxorubicin and cyclophosphamide, one cycle every 2 weeks) followed by taxane regimen (TCa ± H, paclitaxel and carboplatin with Herceptin for HER2/neu-positive patients). After the patient received two cycles of AC, based on clinical examination and ultrasound findings, the oncologist determined the response and decided whether she should go on to receive additional two cycles of AC (if responding well) or be switched to the second regimen (if not). The first F/U-MRI was performed after one cycle ($N = 19$) or two cycles ($N = 27$) of AC. The second F/U-MRI was performed after receiving four cycles of AC ($N = 25$) or after receiving two cycles AC plus three weekly second-line taxane-based regimen ($N = 21$).

MRI Study Protocol

All MRI studies were performed on a 1.5-T Philips Eclipse MR scanner (Philips Medical System, Best, Netherlands) using a dedicated bilateral breast coil with the patient in the prone position. The DCE-MRI was acquired using a three dimensional (3D) gradient echo pulse sequence (RF-FAST) with repetition time (TR)/echo time (TE) = 10/3.6 milliseconds, flip-angle = 20°, 32 bilateral-axial partitions covering both breasts with 4-mm thickness each, field of view (FOV) = 32 to 38 cm, and acquisition matrix = 256 × 128. Sixteen dynamic frames (repetitions) were prescribed for the DCE-MRI, each of which was acquired in 42 seconds. The contrast agent [Omniscan (0.1 mmol/kg); Nycomed-Amersham, Princeton, NJ] was injected manually at start of the fifth frame acquisition and then followed by 10-ml saline flush. All MR images were transferred to a personal computer for post-processing.

Fibroglandular Tissue Segmentation

To avoid the bias coming from the arbitrary ROI selection, we applied a computer-based segmentation algorithm to segment the entire fibroglandular tissues contained in the normal breast using the pre-contrast images of DCE-MRI [15]. Briefly, the segmentation procedures consisted of the following steps: 1) an initial segmentation of the breast region based on V-shape cut using three user-entered anatomic landmarks (thoracic spine and bilateral pectoral muscles); 2) a fuzzy c-means (FCM)–based segmentation algorithm with the B-spline curve fitting to obtain the chest wall boundary; 3) exclusion of skin along the breast boundary by dynamic searching algorithm; 4) removal of non-uniformity in image intensity through bias field correction based on the adaptive FCM; 5) differentiation of the fibroglandular tissue from the surrounding fatty tissue using an FCM-based clustering method. An experienced operator performed the segmentation for all subjects included in this study.

Measurement of BPE

BPE was defined as the average of the contrast enhancements measured from all pixels contained with the segmented fibroglandular tissue. BPE indicated a percent (%) increase of enhancement after

contrast injection ($BPE_i = ((S_{enh,i} - S_{non\text{-}enh})/S_{non\text{-}enh}) \times 100\%$, where $S_{enh,i}$ denoted the fibro-pixel–averaged signal intensity from the ith enhanced image and $S_{non\text{-}enh}$ denoted the averaged signal intensity of the same fibro-pixels from the four pre-contrast imaging sets). The calculation was done for each of the 12 post-contrast frames acquired during the 7-minute DCE period, and a mean BPE for each MRI study was obtained by averaging over all 12 time points for subsequent analysis (i.e., $BPE = \sum BPE_i/12$).

Statistical Analyses

Two-tailed t test was used to assess the statistical significance of observed group differences. The significance level in all statistical tests was set at $P < .05$. The statistical analyses were carried out using the Matlab Statistics Toolbox.

Results

Clinicopathologic Characteristics

The clinicopathologic characteristics of pCR and non-pCR groups were listed in Table 1. Twenty-four patients achieved pCR, and 22 patients had residual disease (non-pCR). Of the 46 patients, 25 had (ER) positive cancer and 21 had ER-negative cancer; 25 had HER2 receptor–positive cancer and 20 had HER2 receptor–negative cancer. The HER2 information was not available for one patient. It was noted that all the six patients with lobular component had residual cancer following the therapy.

BPE in pCR and Non-pCR Groups

Of the 46 patients, 24 (52%) achieved pCR. This very high pCR response rate was similar to the previous literature reports [16]. The BPEs in the contralateral normal breast measured in the baseline, F/U-1, and F/U-2 MRI studies in the pCR and non-pCR groups are listed in Table 2. In the pCR group, compared to the baseline BPE value (mean 19.4%), the BPE at F/U-1 after 2 to 4 weeks of chemotherapy was decreased (15.6%, $P = .02$) and further decreased at F/U-2 (12.5%, $P = .006$). In the non-pCR group, the BPE was not decreased at F/U-1 but became significantly decreased at F/U-2 (only marginally with $P = .04$). When comparing the baseline BPE, it was higher in the pCR group than in the non-pCR group (19.4% *vs* 15.8%, $P = .31$) but not reaching the significance level. If the contralateral normal breast is considered the mirror of the diseased breast without cancer, the results suggest that a higher normal tissue BPE before treatment that shows reduction after chemotherapy is more likely to achieve pCR.

BPE in Pre-Menopausal and Post-Menopausal Groups

The summary results are listed in Table 3. The younger group (<55 years old) had 32 patients, 19 achieving pCR and 13 not. The older group (≥55 years old) had 14 patients, including 5 patients with pCR and 9 patients with non-PCR. Younger patients had a higher pCR rate (59% *vs* 36%). Similar to a study reported before [14], the younger patient group had a significantly higher BPE compared to the older patient group (20.2% *vs* 12.0%, $P = .007$). As the whole group, the younger patients showed a slightly decreased BPE after the start of chemotherapy at F/U-1 (18.0%) compared to the baseline value (20.2%, $P = .19$, not significant), and the BPE was further decreased at F/U-2 (12.9%, $P = .0001$). After stratifying patients to the pCR and non-pCR groups, it was seen that pCR patients had a higher baseline BPE (21.1%), which decreased significantly at F/U-1 (16.0%, $P = .01$) and further decreased at F/U-2 (12.4%, $P = .003$). In the non-pCR group, there was no significant change in BPE at F/U-1 (in fact, it increased from 18.8% at baseline to 20.9% at F/U-1), but after more chemotherapy sessions, the BPE was decreased to 13.6% at F/U-2 ($P = .01$). In contrast, in the older patient group, there was no significant change at F/U-1 or F/U-2 compared to the baseline value in any group comparison. This finding in the post-menopausal women may be related to small patient number as well as the low BPE at baseline, which leaves no room for further decrease.

BPE in ER-Positive and ER-Negative Groups

We had 25 ER-positive and 21 ER-negative patients. The summary results are listed in Table 4. In ER-positive group, 9 achieved pCR (36%) and 16 not; in the ER-negative group, 15 achieved pCR (71%) and 6 not. The pCR rate result was consistent with the general knowledge that ER-negative patients have a better response to chemotherapy. The baseline BPE in the ER-negative group was 19.2%, which was higher compared to the baseline BPE in the ER-positive group (16.4%, $P = .45$, not significant). The BPE was significantly decreased at F/U-1 and F/U-2 only in the pCR group of ER-negative patients. The mean BPE of this subgroup was 20.3% at baseline, which decreased to 16.5% ($P = .03$) and further decreased to 12.5% at F/U-2 ($P = .01$). Figure 1 shows a pre-menopausal woman with ER-negative cancer achieving pCR

Table 1. Clinicopathologic Information of the pCR and Non-pCR Groups

	pCR ($N = 24$)	Non-pCR ($N = 22$)
Mean age (years old)	47.4	52.9
IDC	24	16
ILC	0	5
IDC/ILC	0	1
Baseline tumor size (cm)	4.3	3.9
ER-positive	9	16
ER-negative	15	6
HER2-positive	16	9
HER2-negative	8	12

Table 2. BPE (Mean ± SD, %) Stratified Based on pCR and Non-pCR

	Baseline MRI	F/U-1 MRI	F/U-2 MRI
pCR ($N = 24$)	19.4±13.4	15.6±9.0 †	12.5±7.0 *
Non-pCR ($N = 22$)	15.8±10.9	16.2±15.7	12.9±9.3 *

† Significantly lower at F/U-1 compared to the baseline value ($P = .02$).
* Significantly lower at F/U-2 compared to the baseline value ($P = .006$ in the pCR group and $P = .04$ in the non-pCR group).

Table 3. BPE (Mean ± SD, %) Stratified Based on Age (<55 years old and ≥55 years old) and the pCR and Non-pCR Cases in Each Age Group

	Baseline MRI	F/U-1 MRI	F/U-2 MRI
Younger than 55 years old ($N = 32$)	20.2±13.5 #	18.0±14.0 #	12.9±8.9 *
pCR ($N = 19$)	21.1 ± 14.4	16.0 ± 10.0 †	12.4 ± 7.1 *
Non-pCR ($N = 13$)	18.8 ± 12.4	20.9 ± 18.5	13.6 ± 11.3 *
Older or equal to 55 years old ($N = 14$)	12.0±6.2	11.0±6.0	12.1±6.1
pCR ($N = 5$)	13.2 ± 6.3	14.0 ± 3.3	12.7 ± 7.5
Non-pCR ($N = 9$)	11.4 ± 6.4	9.4 ± 6.6	11.8 ± 5.7

† Significantly lower at F/U-1 compared to the baseline value ($P = .01$ for the <55 year old pCR group).
* Significantly lower at F/U-2 compared to the baseline value ($P = .0001$ for patients <55 years old, $P = .003$ for the <55 year old pCR group, and $P = .01$ for the <55 year old non-pCR group).
# Significant difference between the <55 year old and ≥55 year old groups ($P = .007$ for baseline MRI and $P = .02$ for F/U-1 MRI).

Table 4. BPE (Mean ± SD, %) Stratified Based on ER Status and the pCR and Non-pCR Cases in Each ER Group

	Baseline MRI	F/U-1 MRI	F/U-2 MRI
ER-positive (N = 25)	16.4 ± 11.7	15.5 ± 13.7	12.9 ± 9.4
pCR (N = 9)	18.1 ± 10.1	13.9 ± 4.8	12.4 ± 7.0
Non-pCR (N = 16)	15.5 ± 12.4	16.4 ± 16.8	13.1 ± 10.6
ER-negative (N = 21)	19.2 ± 13.1	16.2 ± 11.3	12.4 ± 6.4*
pCR (N = 15)	20.3 ± 15.1	16.5 ± 10.7†	12.5 ± 7.0*
Non-pCR (N = 6)	16.5 ± 5.7	15.5 ± 13.6	12.2 ± 4.8

† Significantly lower at F/U-1 compared to the baseline value (P = .03 in ER-negative pCR group).
* Significantly lower at F/U-2 compared to the baseline value (P = .004 for the entire ER-negative group and P = .01 for the ER-negative pCR group).

after NAC. A strong BPE is seen in the baseline MRI, and it is decreased in the F/U-1 and further decreased in the F/U-2. In contrast to Figure 1, Figure 2 shows a post-menopausal woman with non-pCR after NAC. Since BPE is low in all three studies of pre-treatment and post-treatment MRIs, the decrease of BPE in the F/U-1 and the F/U-2 was not obvious.

BPE in HER2-Positive and HER2-Negative Groups

The summary results are listed in Table 5. Of 25 HER2-positive patients, 16 achieved pCR (64%) and 9 not; of 20 HER2-negative patients, 8 achieved pCR (40%) and 12 not. Since HER2-positive patients received the targeted therapy trastuzumab, it is well known that they have a higher pCR rate. The baseline BPE in HER2-positive group was 19.7%, which was higher than that in the HER2-negative group (15.2%, P = .24, not significant). The BPEs in both HER2-positive and HER2-negative groups were not significantly decreased at F/U-1 but became significant at F/U-2. Interestingly, in either HER2-positive or HER2-negative group, the BPE was decreased at F/U-1 in both pCR groups and remained at a comparable baseline level in both non-pCR groups. Therefore, the

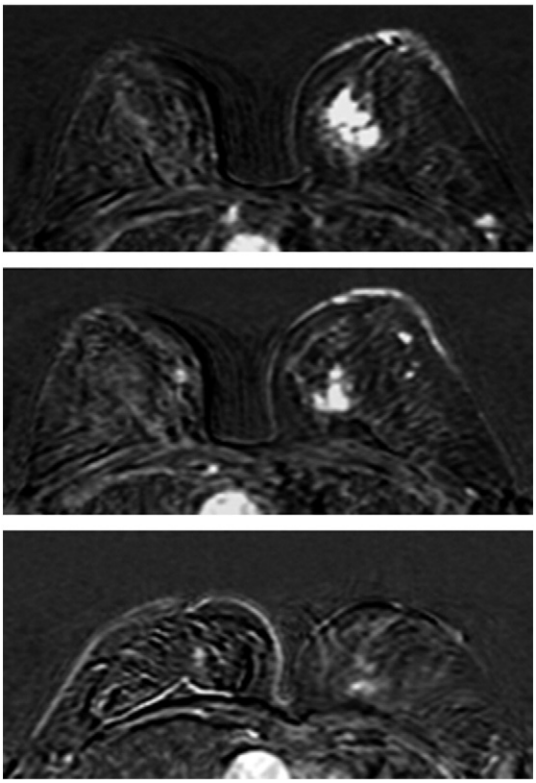

Figure 2. Contrast-enhanced subtraction images of a 56-year-old woman with non-pCR after NAC. Before NAC, a 3-cm ER-positive and HER2-negative IDC in the left breast was noted. Upper panel: baseline MRI; middle panel: FU-1 MRI (after two AC); lower panel: FU-2 MRI (after two AC plus three AbCaH). Note that the background enhancement in the fibroglandular tissue of the right breast throughout the three MRI studies was scarce.

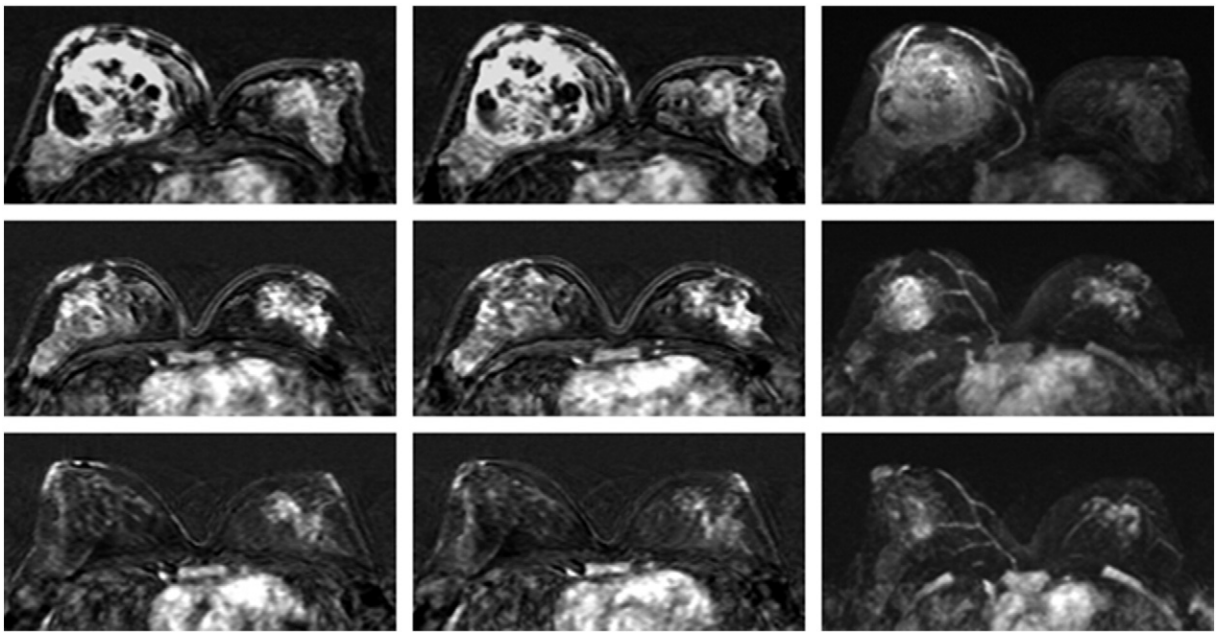

Figure 1. A 32-year-old woman with pCR after NAC. Before NAC, a 9.1-cm triple negative IDC in the right breast was noted. Upper panel: baseline MRI; middle panel: FU-1 MRI (after two AC); lower panel: FU-2 MRI (after four AC). The left and middle columns are two continuous subtraction images. The right column is the maximal intensity projection image. Note the strong background enhancement in the fibroglandular tissue of the left breast in the baseline MRI. The enhancement decreases in the FU-1 MRI and further decreases remarkably in the FU-2 MRI. The BPE was 60.0%, 46.3%, and 30.0% in baseline, F/U-I, and F/U-2 MRI, respectively.

results between HER2-positive and HER2-negative groups were quite similar, different from those reported above in age comparison or ER status comparison.

Discussion

In this study, we measured the pre-treatment BPE, as well as the changes shortly after the start of chemotherapy (2 to 4 weeks) and at mid time point during the course of NAC (after 8 weeks). For the comparison of BPE, the qualitative assessment of mild, moderate, or severe BPE using visual inspection was not applicable [1,2,5,9,10]. In addition, to facilitate a fair comparison, the assessment of BPE from an arbitrarily defined ROI or a hot spot was not optimal. Since a computer algorithm–based method to segment the entire fibroglandular tissue within the whole breast has been developed [15], this method could be used to well define the ROI for measuring the mean BPE in a breast by averaging the contrast enhancements from all fibroglandular tissue voxels. It has been reported that the contrast enhancement in normal tissues surrounding the cancer was associated with treatment response and prognosis [12,13], but since the value will be strongly dependent on where the measurement is taken from, it cannot serve as a reliable prognostic predictor. The BPE measured from the normal tissue of the contralateral breast, especially using a computer algorithm–based segmentation software, can provide an unbiased method allowing us to investigate the relationship between normal tissue enhancements and pathologic response of breast cancer to NAC.

Table 1 summarizes the major findings in this work. Patients achieving pCR had a higher pre-treatment BPE than that in the non-pCR group. In the pCR group, BPE showed a significant decrease at F/U-1 and further decrease at F/U-2. In contrast, in the non-pCR group, BPE in F/U-1 increased slightly and then showed a significant decrease at F/U-2. These results suggested that patients with a higher pre-treatment BPE that showed a significant decrease at early times after starting NAC were more likely to achieve pCR. This finding obtained in normal tissues is consistent with results found in tumors. Studies have shown that tumors with a higher pretreatment enhancement [17] or having a greater decrease of enhancement after chemotherapy [17–20] tend to have a better response to the treatment. One possible explanation is that since chemotherapy agents are delivered through blood perfusion, a higher BPE in normal breast tissues may allow more delivery of therapeutic agents into the breast leading to a better response. Since chemotherapy exerts effects on tumor vasculature by loss of pro-angiogenic support secondary to tumor cell kill and also directly on endothelial cell function [21], a higher delivery of chemotherapy agents into the normal tissue will lead to more severe damage of vessels and a greater decrease in BPE.

Table 5. BPE (mean ± SD, %) Stratified Based on HER2 Status and the pCR and Non-pCR Cases in Each HER2 Group

	Baseline MRI	F/U-1 MRI	F/U-2 MRI
HER2-positive (N = 25)	19.7 ± 12.3	17.1 ± 14.1	13.9 ± 9.3
pCR (N = 16)	19.5 ± 11.7	15.3 ± 6.6	13.0 ± 6.5
Non-pCR (N = 9)	20.0 ± 14.2	20.4 ± 22.3	15.4 ± 13.3
HER2-negative (N = 20)	15.2 ± 12.4	14.0 ± 10.6	10.9 ± 6.3
pCR (N = 8)	19.4 ± 17.4	16.1 ± 13.1	11.4 ± 8.3
Non-pCR (N = 12)	12.4 ± 7.1	12.6 ± 8.9	10.6 ± 5.0

* Significantly lower at F/U-2 compared to the baseline value (P = .007 for the HER2-positive group, P = .04 for the HER2-positive pCR group, P = .04 for the HER2-positive non-pCR group, and P = .05 for the HER2-negative group).

We also performed subgroup analyses by separating patients based on the age and the ER and HER2 biomarker of their cancers. Previous studies have shown that BPE is affected by the menopausal status [1,4,5,7,8]. We used the cutoff age of 55 to ensure that women ≥ 55 years old were indeed post-menopausal. As expected, the pre-treatment baseline BPE was significantly higher in the younger group compared to the older group (20.2% *vs* 12.0%, P = .007). In previous studies analyzing the change of breast density and BPE after NAC with age, a significant decrease was only found in the pre-menopausal, not in the post-menopausal, women [14]; therefore, one possible explanation was attributed to chemotherapy-induced ovarian suppression [22]. Comparing with Table 2, it can be found that the major findings in Table 1 were mainly driven by the results in pre-menopausal women. In addition to the direct damage of vessels in normal tissues by chemotherapy, another possible reason explaining the decreased BPE after NAC is the loss of tissue proliferation due to decreased hormones coming from ovarian suppression. This side effect of chemotherapy (i.e., ovarian suppression) is known to have a positive prognostic value in the pre-menopausal women [22–24].

Tables 3 and 4 show the subgroup analysis results stratified based on the ER and HER2 status of patient's cancer. The pCR rate was higher in ER-negative than in ER-positive and higher in HER2-postive than in HER2-negative groups in our study, which was consistent with literature reports, e.g., results from seven prospective randomized trials consisting of 6377 patients [25]. The measurement of BPE from the contralateral normal breast was assumed to reflect the enhancement in normal breast tissues surrounding the cancer in the diseased breast. The contralateral BPE was higher in ER-negative (19.2%) than in ER-positive patients (16.4%), and higher in HER2-positive (19.7%) than in HER2-negative (15.2%) patients but both did not reach the significant level. Since we have approximately the same number of pre-menopausal and post-menopausal patients in each subgroup, the observed result was not mediated through age. The contrast enhancements were known to be higher in ER-negative than in ER-positive cancers [26–28], also higher in HER2-positive than in HER2-negative cancers [28,29], and interestingly in our study, we found a similar trend in normal tissues. There has been no study yet to compare the BPE with the type of cancer that was developed, and this warrants further investigation. Such results may provide useful information for chemoprevention.

Table 3 also shows the comparison between pCR and non-pCR patients in the respective ER-positive and ER-negative groups. Patients with ER-negative cancer who achieved pCR had a significant reduction of BPE at F/U-1 compared to the baseline value, while the effect was not noted in the non-pCR patients or in the ER-positive patient group. It was also noted that the ER-negative pCR group had the highest averaged baseline BPE (20.3%) compared to other subgroups. The high BPE may facilitate more delivery of chemotherapy agents into the breast resulting in the early significant reduction of BPE at F/U-1 and subsequently leading to a better response and achieving pCR. Table 4 shows that the BPE results in HER2-positive and HER2-negative groups are pretty similar, both showing a significant decrease at F/U-2 and no difference between pCR and non-pCR patients.

This study had limitations. The number of subjects included in this study was small. The protocol of the MR images acquired in this study was done using a 1.5 T-MR scanner, which was designed to have a high temporal resolution and had to sacrifice the spatial resolution a bit. The spatial resolution (matrix size = 256 × 128) thus was lower, compared to the current standard emphasizing on high spatial resolution. In this study, we defined women < 55 years old as the pre/peri-menopausal group and

women ≥ 55 years old as the post-menopausal group. This is based on the general observation that natural menopause may start from the age of 45 years old and may possibly last for years. Thus, we used 55 years old as the cutoff to ensure that women older than 55 years old should have reached their stable menopause stage. Nevertheless, the division is arbitrary and thus was not 100% correct.

In summary, we have demonstrated the potential value of BPE measured from the contralateral normal breast for predicting NAC response. Using the contrast enhancement averaged over all fibroglandular tissues segmented in the whole breast could reflect the normal tissues surrounding the cancer in the diseased breast and provide an unbiased parameter to serve as a predictive or prognostic indicator. We found that patients with a higher pre-treatment BPE who showed a significant decrease at early times after the start of chemotherapy were more likely to achieve pCR. In subgroup analysis, we further showed that this finding was mainly applicable to younger patients and to patients with ER-negative breast cancer. A higher BPE to normal tissues would allow more delivery of therapeutic agents into the breast, which was a possible reason leading to a better response. These findings and the role of normal breast BPE in the management of breast cancer patients will need to be further investigated in larger studies.

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