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BREAST IMAGING (H OJEDA-FOURNIER, SECTION EDITOR)

Background Parenchymal Enhancement on Breast MRI: Assessment and Clinical Implications

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Abstract
Purpose of Review To present recent literature regarding the assessment and clinical implications of background parenchymal enhancement on breast MRI.
Recent Findings The qualitative assessment of BPE remains variable within the literature, as well as in clinical practice. Several different quantitative approaches have been investigated in recent years, most commonly region of interest-based and segmentation-based assessments. However, quantitative assessment has not become standard in clinical practice to date. Numerous studies have demonstrated a clear association between higher BPE and future breast cancer risk. While higher BPE does not appear to significantly impact cancer detection, it may result in a higher abnormal interpretation rate. BPE is also likely a marker of pathologic complete response after neoadjuvant chemotherapy, with decreases in BPE during and after neoadjuvant chemotherapy correlated with pCR. In contrast, pre-treatment BPE does not appear to be predictive of pCR. The association between BPE and prognosis is less clear, with heterogeneous results in the literature.
Summary Assessment of BPE continues to evolve, with heterogeneity in approaches to both qualitative and quantitative assessment. The level of BPE has important clinical implications, with associations with future breast cancer risk and treatment response. BPE may also be an imaging marker of prognosis, but future research is needed on this topic.

Keywords Background parenchymal enhancement · Breast MRI · Breast cancer · Breast cancer risk · Treatment response · Breast cancer prognosis

Introduction

Although the normal enhancement of breast parenchyma on breast MRI has been appreciated for many years, the clinical implications of this enhancement have only become evident more recently. Reporting of this normal enhancement, termed "background parenchymal enhancement" (BPE), was standardized in 2013 as part of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) Atlas (fifth edition) when the original MRI lexicon was revised. Since that time, there has been a substantial increase in publications related to BPE. The purpose of this review is to update the reader on the literature published in the last five years, with a particular focus on the assessment and clinical implications of BPE.

Overview

BPE refers to the normal enhancement of the breast fibroglandular tissue. According to the fifth edition of the ACR BI-RADS Atlas, it should be assessed on the first post-contrast image at approximately 90 s, as this is the time point at which cancer detection is typically performed. BPE is evaluated with respect to the amount of

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fibroglandular tissue (not breast volume) and is to be reported as minimal, mild, moderate, or marked [1] (Figs. 1, 2).

BPE will most commonly be diffuse and symmetric. More peripheral enhancement, or "picture framing," can also be seen (Fig. 3) and has been attributed to the arterial vascular supply of the breast, which enters the breast peripherally [2]. Asymmetric BPE should be reported when present, as is often seen after breast conservation therapy with radiation therapy [3] (Fig. 4). While different distributions and morphologies of enhancement have been explored in the prior literature [4, 5], BPE assessment currently is based on the volume and intensity of enhancement only and does not account for distribution or morphology [1].

Earlier studies suggested that BPE varied with the menstrual cycle [4, 6, 7], leading to the recommendation that non-urgent breast MRI be performed early in the menstrual cycle (typically the second week) [1]. However, a few recent studies, including studies by Lee et al. (1536 screening MRI examinations) and Dontchos et al. (320 screening MRI examinations), have demonstrated no significant difference in screening MRI BPE by week of the menstrual cycle [8, 9•, 10•]. More importantly, these studies did not demonstrate a difference in performance metrics (such as abnormal interpretation rate, cancer detection rate, sensitivity, specificity) by week of the menstrual cycle. As such, the timing of breast MRI screening studies may not be as relevant as previously thought.

A comprehensive discussion of other patient characteristics influencing BPE is beyond the scope of this review, but a few factors warrant mention, given that they are routinely encountered in clinical practice. Younger age and premenopausal status have both been shown to be associated with higher BPE [11–13], as has a higher body mass index (BMI) [11, 14]. BPE is also affected by exogenous hormone therapies. Hormone replacement therapy has been shown to increase BPE, while the anti-estrogen effects of aromatase inhibitors and selective estrogen receptor modulators used in endocrine therapy for breast cancer have been shown to decrease BPE. The cessation of tamoxifen (a selective estrogen receptor modulator) can result in focal or global "rebound" in BPE [2], which may lead to a diagnostic dilemma if this history is not known. Focal rebound in BPE can be particularly challenging to interpret. Adjuvant chemotherapy has also been shown to decrease BPE [15]. Finally, it has been shown that radiation therapy after breast conservation surgery and prophylactic breast irradiation in high risk populations reduce BPE [16, 17]. However, this reduction may not be seen in all patients with a history of breast radiation exposure, as Zeng et al. reported that patient's with a history of chest radiation for childhood or early adulthood Hodgkin's lymphoma had

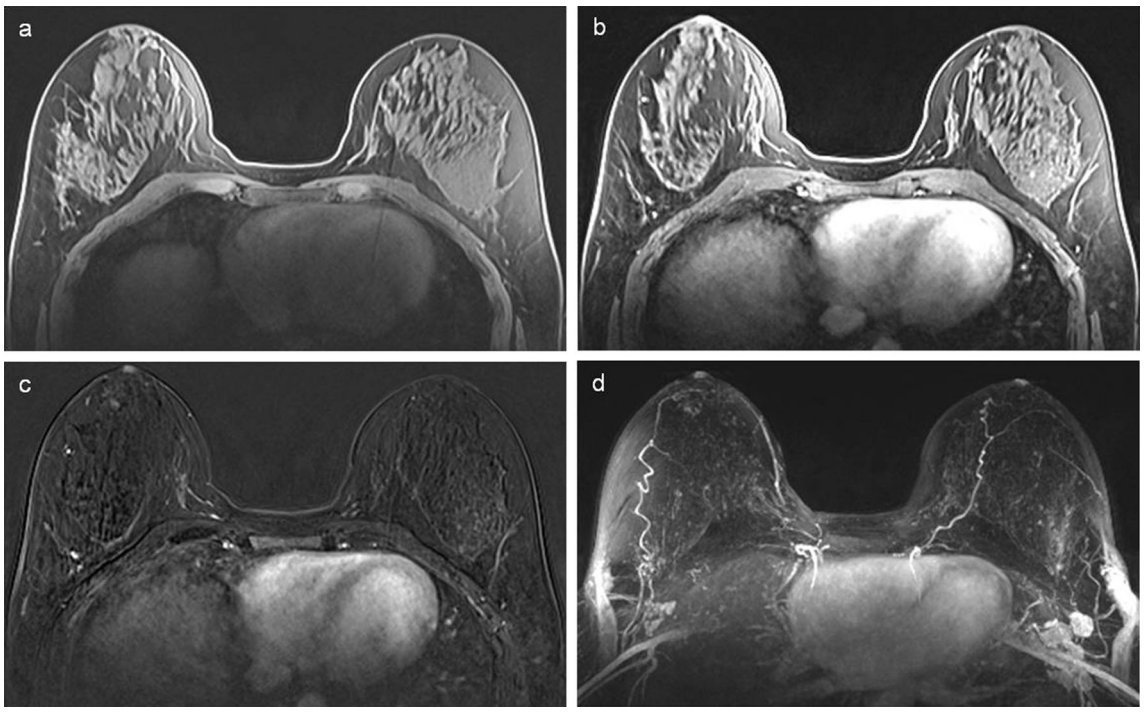

Fig. 1 **a** Axial unenhanced T1-weighted fat-suppressed, **b** axial contrast-enhanced T1-weighted fat-suppressed, **c** axial contrast-enhanced T1-weighted fat-suppressed subtraction, and **d** axial contrast-enhanced T1-weighted fat-suppressed subtraction MIP MR images demonstrating an example of mild BPE

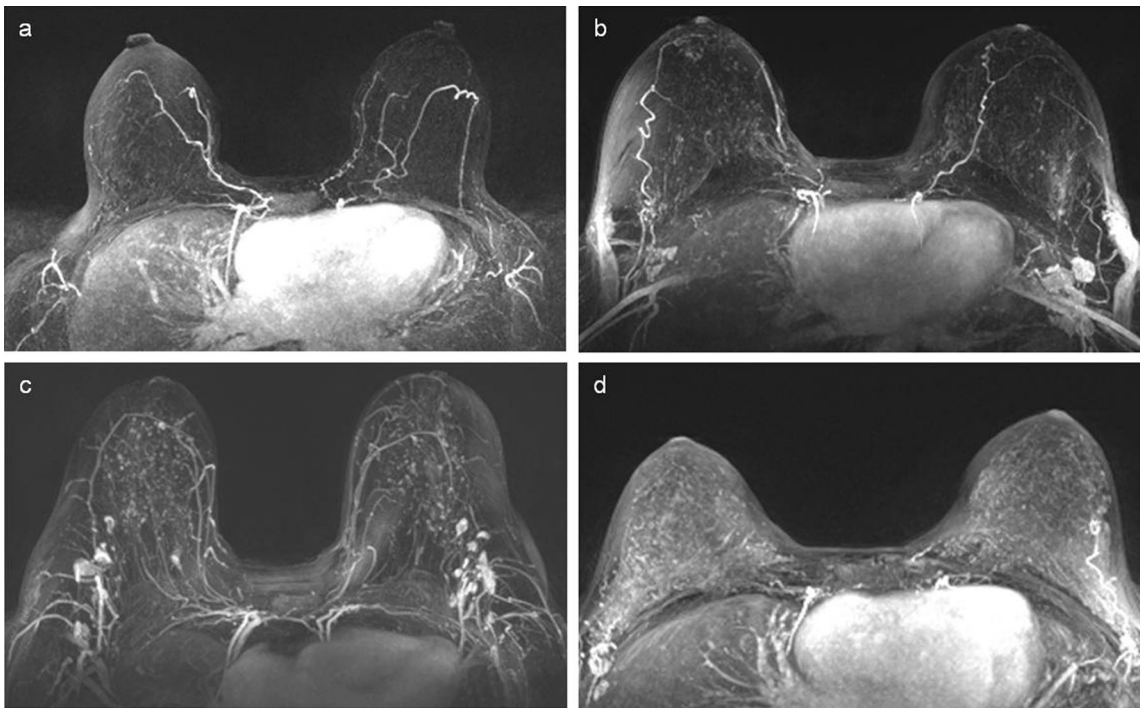

Fig. 2 **a** Minimal, **b** mild, **c** moderate, and **d** marked BPE on axial contrast-enhanced T1-weighted fat-suppressed subtraction MIP MR images

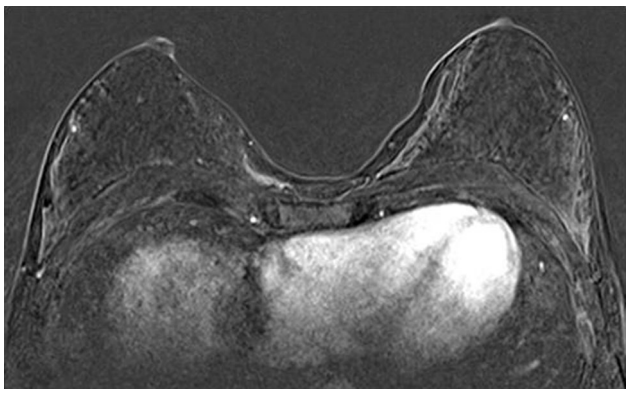

Fig. 3 Axial contrast-enhanced T1-weighted fat-suppressed subtraction MR image demonstrating a peripheral "picture framing" BPE pattern

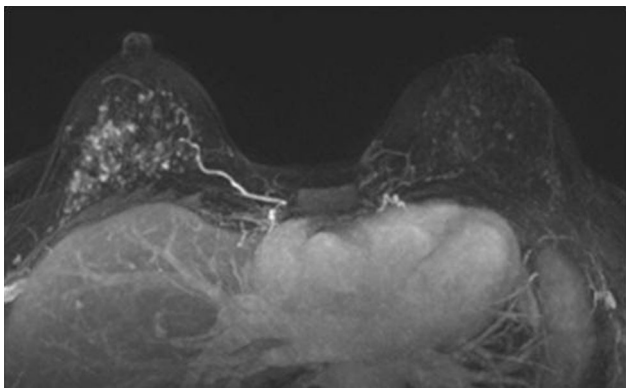

Fig. 4 Axial contrast-enhanced T1-weighted fat-suppressed subtraction MIP MR image demonstrating asymmetric BPE in a patient with history of breast conservation surgery status post radiation therapy

higher BPE than age-matched controls when undergoing screening breast MRI years later [18].

Qualitative Assessment

Despite standardization of BPE reporting in the BI-RADS lexicon, there is variability in the methods used by radiologists to qualitatively assess BPE. In a 2017 systematic review by Bignotti et al., 16 of 39 studies qualitatively assessed BPE using a combination of unenhanced and contrast-enhanced fat-suppressed T1-weighted and subtraction images, 5 of 39 added maximum intensity projection (MIP) images to this assessment, 14 of 39 used a combination of post-contrast fat-suppressed T1 weighted and/or subtraction images, and 1 of 39 used only MIP images (3 of 39 did not clearly state the assessment technique used) [19].

Separately, one study demonstrated that the combination of the initial contrast-enhanced fat-suppressed T1-weighted images, initial contrast-enhanced subtraction images, and initial contrast-enhanced MIP image has the highest reliability for assessing BPE (Gwet's AC1 value 0.80 [95% confidence interval 0.77–0.84] and absolute agreement of 91.8% among three readers) (62). However, using the MIP image alone showed similar reliability (Gwet's AC1 value

0.80 [95% confidence interval 0.76–0.83] and absolute agreement of 92.4%) and lower reading time (4 s for MIP alone versus 38 s) [20]. Despite being an uncommon methodology in the literature, using the MIP image alone for BPE assessment may be a useful time-saving step in clinical practice.

The subjective nature of qualitative assessment also results in intra-reader and inter-reader variability. Kappa values for intra-reader agreement range from moderate to almost perfect in prior literature, while Kappa values for inter-reader agreement range from fair to almost perfect [19].

Quantitative Assessment

The fifth edition of the BI-RADS Atlas recommends a visual estimation of BPE, stating "categorizing based on percentages (and specifically into quartiles) is not recommended. Quantification of BPE volume and intensity on MRI may be feasible in the future, but we await publication of robust data on that topic before endorsing percentage recommendations" [1]. Several different quantitative approaches have been investigated since the publication of the fifth edition of the BI-RADS Atlas, with numerous studies in the past five years [21–34].

Region of interest-based and segmentation-based assessments are the two most common approaches in the recent literature. Generally, region of interest-based approaches still rely on user input, leading to potential reader variability. Segmentation-based assessments attempt to address this issue by isolating the fibroglandular tissue from the remaining tissues and assessing the entire fibroglandular volume rather than a region of interest. Various semi-automated and automated segmentation models have been created [27–30]. BPE assessment tools using machine learning have also been developed [31–34]. Overall, many of these approaches have correlated well with qualitative BPE assessment. However, despite this progress, quantitative assessment has not become standard in clinical practice to date.

BPE on Emerging MRI Protocols

Ultrafast MRI protocols consist of multiple high temporal resolution images after contrast injection, acquiring enhancement data prior to the first post-contrast sequence in standard protocols. One of the potential benefits of ultrafast MRI protocols is less prominent BPE at these early time points. Tomida et al. showed that there is almost no BPE during the "super early phase" (20 s after contrast injection) [35]. Honda et al. found that BPE was lower on the twelfth and twentieth phases of a 75 s ultrafast protocol compared to the first post-contrast phase of conventional dynamic contrast-enhanced MRI, with higher lesion detectability at the ultrafast protocol time points in patients with higher BPE at the conventional MRI time point [36]. Other studies have also demonstrated higher lesion conspicuity in cases with moderate or marked BPE [37, 38].

Abbreviated protocol MRIs have also been a focus in recent years due to their potential benefits of lower acquisition time, interpretation time, and cost. Abbreviated protocols vary but usually include at least an unenhanced and first post-contrast sequence, providing only morphologic information without kinetic assessment. While these protocols are promising, one study showed moderate or marked BPE lowered the rate of concordance between MRI measurements and pathology measurements for the maximum extent of ductal carcinoma in situ (DCIS) [39]. More research is needed to determine the impact of BPE on abbreviated protocols.

Clinical Implications

Breast Cancer Risk

Numerous studies have now identified an association between BPE and breast cancer risk. The Imaging and Epidemiology (IMAGINE) case–control study with 835 breast cancer cases and 963 controls demonstrated an association between moderate or marked BPE and premenopausal cancer after adjusting for breast density and other risk factors and confounders (OR 1.49); a similar but non-significant association was seen between mild, moderate, or marked BPE and postmenopausal cancer (OR 1.45) [40•]. A retrospective study by Arasu et al. assessed 4247 women imaged at one of 46 radiology facilities within the Breast Cancer Surveillance Consortium. 176 developed breast cancer, with increasing BPE levels associated with increased cancer risk. This association was independent of breast density. Mild, moderate, or marked BPE also demonstrated a significant increased risk of invasive cancer (hazard ratio 2.73) [41•]. These results are corroborated by a recent meta-analysis of 13 studies (13,788 patients with 4,046 breast cancer cases) showing that moderate BPE and marked BPE were associated with an elevated risk of breast cancer (OR 2.66 and 2.51, respectively) [42]; a separate meta-analysis of 12 studies (9541 patients with 3870 breast cancer cases) showed similar results (moderate BPE OR 2.93 and marked BPE OR 2.89) [43]. Studies have demonstrated this association using both qualitative and quantitative BPE assessments. Saha et al. demonstrated that quantitative BPE assessment using machine learning models can be predictive of the

subsequent development of breast cancer independent of qualitative BPE assessment [44].

In addition, a meta-analysis by Thompson et al. analyzing 18 studies (1910 breast cancer cases and 2541 controls) found that higher levels of BPE were associated with the presence of breast cancer in women with an elevated lifetime risk of breast cancer, but not in women with average lifetime risk of breast cancer [45•]. It is important to note that data on women considered to be at average lifetime risk is somewhat limited, as screening MRI is not typically performed in this patient population (and therefore most available data is in the setting of symptoms, suspicious imaging findings, or known malignancy). For women with an elevated lifetime risk, this increased risk may be present even for mild BPE [45, 46]. This future risk of breast cancer relative to lower BPE levels has also been shown to persist in women with elevated lifetime risk after risk-reducing salpingo-oophorectomy, suggesting BPE is not merely a surrogate marker for endogenous hormone levels [47, 48]. Moderate to marked BPE has also been associated with the development of interval cancers in patients with a personal history of breast cancer [49].

Further evidence of the association between BPE and breast cancer may come from its link to obesity. There is evidence that higher BMI is a risk factor for at least postmenopausal breast cancer [50], and, as discussed earlier, higher BMI has been shown to be associated with higher BPE [11, 14]. More specifically, visceral adipose tissue has been identified as a risk factor for numerous disease processes, including breast cancer, and has had many of its endocrine functions and pro-inflammatory roles linked to disease pathogenesis [51]. Brown et al. demonstrated that, while several body composition measures including BMI correlated with BPE prior to an exercise intervention, only reductions in visceral adipose tissue correlated with a decrease in BPE after exercise intervention [52]. This association between visceral adipose tissue and BPE further supports the available data suggesting BPE may serve as an imaging marker of future breast cancer risk.

BPE has also been associated with breast metabolic activity, correlating with FDG uptake on PET [53–56]. Mema et al. hypothesized that the increased breast cancer risk associated with higher BPE could be due to this elevated basal metabolic activity, resulting in an environment for tumor growth [54].

Cancer Detection, Extent of Disease Assessment, and Margin Status

Several recent studies have shown that BPE does not influence cancer detection rate [57•, 58, 59•], although moderate or marked BPE may be associated with higher abnormal interpretation rates [57•, 59•]. Higher biopsy rates and lower specificity have also been noted [59•, 60]. Similarly, studies have shown that BPE in the lactating breast, which is often moderate or marked, does not prevent cancer detection [61, 62].

Recent data regarding the impact of BPE on extent of disease measurements and margin status is more heterogeneous. Two studies have shown no association between BPE and positive margins or need for repeat surgeries for invasive lobular carcinoma [63, 64]. However, other studies have reported an association between higher BPE and positive or close (<2 mm) margins in breast conserving surgeries for invasive ductal carcinoma [65, 66]. BPE also has been reported to negatively influence diagnostic performance in the evaluation for residual malignancy after excisional biopsy for microcalcifications [67]. In addition, two recent studies have shown that tumor size measurement may be more accurate in cases with minimal or mild BPE [68, 69], although a third study assessing pure DCIS cases found that BPE did not influence size measurements [58]. Further research is needed to determine whether BPE does in fact impact tumor size measurements in a clinically significant way.

Treatment Response

Several studies have investigated BPE as a potential predictor of neoadjuvant chemotherapy (NAC) response. A systemic review of 22 articles found that a greater decrease in BPE in the disease-free contralateral breast during and after NAC was associated with pathologic complete response (pCR) [70•]. In individual studies, a low lesion-to-background parenchymal signal enhancement ratio (SER) post-NAC has also been associated with pCR [71, 72]. This association between a reduction in BPE and pCR has been seen for both human epidermal growth factor receptor 2 (HER2) positive and HER2 negative cancers [73–75]. You et al. assessed BPE at multiple treatment time points (after the second, fourth, and sixth cycles of NAC) and showed that the decrease in BPE from baseline after the second cycle of NAC had the most diagnostic value in predicting pCR [75].

Identifying imaging markers predictive of treatment response prior to the start of therapy would be even more beneficial. Unfortunately, most studies have found no correlation between pre-treatment BPE and pCR [74, 76–78], with a minority suggesting a link between pre-treatment BPE and pCR [79].

Prognosis

There is some heterogeneity in the recent literature with respect to the relationship between BPE and prognosis.

BPE in the contralateral breast has been associated with the tumor Oncotype Dx recurrence score [80]. BPE has been correlated with locoregional recurrence [81], and moderate or marked BPE correlated with late recurrence (>2.5 years after surgery) [82]. Lesion peak SER and mean BPE have also been correlated with DCIS recurrence [83]. In addition, Choi et al. showed moderate or marked BPE on pre-NAC MRI was independently associated with worse recurrence-free survival [84], while Lim et al. showed an association between non-minimal BPE and worse recurrence-free survival in postmenopausal women [66]. In contrast, two recent studies have shown no correlation with recurrence [85, 86]. Another study evaluated BPE qualitatively and quantitatively before and after NAC and found that only post-therapeutic quantitative BPE predicted recurrence [77]. In a systemic review by Rella et al., no significant association was found between BPE and invasiveness, histological cancer type, T- and N-stage, multifocality, lymphatic and vascular invasion, and histological tumor grade [70•].

This variability in the literature may in part be explained by the heterogeneous nature of breast cancer. Molecular subtypes of breast cancer play an important role in prognosis [87], but the interrelationships between BPE, molecular subtype, and prognosis are unclear. Studies have suggested that moderate or marked BPE is associated with an increased rate of estrogen receptor (ER) positive and progesterone receptor (PR) positive cancers [88, 89], while minimal or mild BPE may be more frequently associated with triple negative breast cancers [90]. Quantitative image features of BPE have also shown some promise in differentiating molecular subtypes [91]. One recent study by Xu et al. demonstrated that, while pre-operative BPE in the disease-free contralateral breast did not correlate with overall survival or invasive disease-free survival for the overall cohort of 467 patients, moderate or marked BPE correlated with overall survival and invasive disease-free survival in a subset of 127 triple negative breast cancer cases who received adjuvant chemotherapy [92]. Park et al. demonstrated that higher SER around the tumor on pre-operative MRI independently predicted recurrence in triple negative breast cancer patients [93]. With respect to ER positive HER2 negative invasive cancers, one study showed no association with survival outcome in 289 patients with ER positive HER2 negative node negative invasive cancers [94], while another including 398 patients ER positive HER2 negative invasive cancers showed improved overall survival [95].

Conclusions

There has been considerable interest in BPE in the recent literature, and it is now evident that BPE has diverse clinical implications. Numerous studies have demonstrated a clear association between higher BPE and future breast cancer risk, and BPE may be an important imaging marker for risk stratification in the era of personalized medicine. While higher BPE does not appear to significantly impact cancer detection, it may result in a higher abnormal interpretation rate. BPE is also likely predictive of treatment response, with reductions in BPE during and after NAC correlated with pCR. However, most studies have found no correlation between BPE before NAC and pCR. The association between BPE and prognosis is less clear. Given the heterogeneous nature of breast cancer, BPE is unlikely to be a one-size-fits-all prognostic imaging marker. As such, further research is needed on BPE in breast cancer subtypes and population subsets, including women who are otherwise considered to be at average lifetime risk of breast cancer.

Progress has been made in the quantitative assessment of BPE, a topic specifically mentioned as one for further research in the fifth edition of the BI-RADS Atlas, although this has yet to make its way into routine clinical practice. However, although the BPE lexicon is standardized in the BI-RADS Atlas, variability remains in the approaches to both qualitative and quantitative BPE assessment, hampering the comparison of studies. Future research would benefit from standardized methodologies.

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Code availability Not applicable.

Declarations

Conflict of interest The authors have no conflicts of interest.

Animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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