Rationale and Objectives: To investigate the application of computer-added diagnosis (CAD) in dynamic contrast-enhanced (DCE) MRI of the healthy lactating breast, focusing on false-positive rates and background parenchymal enhancement (BPE) coloring patterns in comparison with breast cancer features in non-lactating patients.

Materials and Methods: The study population was composed of 58 healthy lactating patients and control groups of 113 healthy premenopausal non-lactating patients and 55 premenopausal non-lactating patients with newly-diagnosed breast cancer. Patients were scanned on 1.5-T MRI using conventional DCE protocol. A retrospective analysis of DCE-derived CAD properties was conducted using a commercial software that is regularly utilized in our routine radiological work-up. Qualitative morphological characterization and automatically-obtained quantitative parametric measurements of the BPE-induced CAD coloring were categorized and subgroups’ trends and differences between the lactating and cancer cohorts were statistically assessed.

Results: CAD false-positive coloring was found in the majority of lactating cases (87%). Lactation BPE coloring was characteristically non-mass enhancement (NME)-like shaped (87%), bilateral (79%) and symmetric (64%), whereas, unilateral coloring was associated with prior irradiation \( (p < 0.0001) \). Inter-individual variability in CAD appearance of both scoring-grade and kinetic-curve dominance was found among the lactating cohort. When compared with healthy non-lactating controls, CAD false positive probability was significantly increased \([\text{Odds ratio} 40.2, p < 0.0001]\), while in comparison with the breast cancer cohort, CAD features were mostly inconclusive, even though increased size parameters were significantly associated with lactation-BPE \( (p < 0.00001) \).

Conclusion: BPE was identified as a common source for false-positive CAD coloring on breast DCE-MRI among lactating population. Despite several typical characteristics, overlapping features with breast malignancy warrant a careful evaluation and clinical correlation in all cases with suspected lactation induced CAD coloring.

Key Words: BPE; CAD MRI; MRI lactation; PABC; pregnancy-associated breast cancer; DWI.

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INTRODUCTION

Computer-aided diagnosis (CAD) systems of breast dynamic contrast enhanced (DCE) MRI provide automated means of cancer detection and characterization based on color-coded mapping of the enhancement kinetic curves (1). Extensive validation of CAD capabilities in clinical settings (2), has catalyzed its clinical integration as a valuable tool in routine breast MRI radiological workup (3). In particular, CAD systems were found to be effective in improving specificity of breast MRI (4,5). Further
applications of CAD in breast MRI have shown its utility as a prognostic imaging biomarker, owing to CAD’s parametric mapping correlation with pathological markers(6), response to neo-adjuvant chemotherapy (7) and overall survival (8).

Despite its clear diagnostic value, CAD systems have been also prone to discrepancy and limitations due to several drawbacks, such as the effect of signal intensity (SI) threshold on its sensitivity and specificity (9), false negative results induced by movement (10), variability between different software systems (11) and overlapping kinetic patterns between benign and malignant breast lesions, due to biological diversity (12).

The lactating breast is characterized by a rich vasculature network (13) and typically displays a prominent background enhancement (BPE) on DCE MRI (14–17). Lactation-induced BPE may markedly reduce the conspicuity of coexistent tumor (18), therefore imposing a diagnostic complexity in discriminating between physiological and pathological findings, including the often delayed diagnosis of pregnancy-associated breast cancer (PABC) (16). Consequently, the use of DCE MRI during lactation has been debated (19).

Lactation-induced BPE may also create an additional diagnostic challenge for CAD systems; however, the application of CAD in breast-DCE MRI during lactation has yet to be studied. Herein, we investigated the application of CAD in scans of healthy lactating patients, with the aim to examine the rates and patterns of CAD’s false positive detection and to quantify the lactation-induced BPE kinetic features in comparison with those of non-lactating breast cancer controls.

MATERIALS AND METHODS

This study was approved by our institutional review board, and the necessity to obtain informed consent was waived.

Study Population

Using a computational search of our departmental radiological information system (RIS) database, MRI examinations of lactating patients scanned between 2011 and 2020 were tracked and reviewed. Prerequisite inclusion criteria were: no suspicious findings on baseline scan during lactation and at least one year of negative radiological follow-up workup after breastfeeding weaning. Overall, the study included 61 scans of 58 healthy lactating patients (median age: 36 range: 23–46) scanned during lactation (median lactation duration at the time of examination, 7 months; range, 1–36 months), with three patients scanned twice in separate lactation periods. Indications for MRI were as follows: annual follow up (n = 55) and evaluation of palpable mass (n = 3). Most patients were BRCA carriers (n = 42) or at high-risk (n = 13).

In order to compare the incidence of false positive CAD coloring among lactating and non-lactating healthy patients, a control group of 113 age-matched (median age: 37 range: 25–42) subjects was constituted. The healthy premenopausal non-lactating control group was composed of BRCA carriers (n = 81) and high-risk patients (n = 32) who underwent surveillance between 2018 –2019, with negative examination and 2 years of follow up.

In addition, in order to compare lactation-related with breast cancer related CAD’s features, a second control group was constituted. The cancer control group included young (age 25–45), non-lactating patients with newly diagnosed breast cancer, scanned with pretreatment MRI, including CAD analysis, between January 2019 and June 2020. Overall, the control cohort included 55 patients (median ± SD age: 38±6) with 55 pathologically-confirmed tumors [43 invasive ductal carcinoma (IDC), 5 ductal carcinoma in-situ (DCIS), 5 unspecified invasive carcinoma and two invasive lobular carcinoma (ILC), with median ± standard deviation (SD) lesion diameter of 26±19 mm, range: 6–80 mm].

MRI Protocol

MRI was performed on 1.5-T MRI (Signa Excite HDX, GE Healthcare) using a dedicated double breast coil equipped with eight channels. DCE-MRI protocol was obtained via axial vibrant multiphase 3D DCE T1-weighted sequence with the following parameters: echo time (TE)/ repetition time (TR) of 2.6/5.4 ms, flip angle 15°, bandwidth 83.3 kHz, matrix 512 × 364; field of view (FOV) 340 mm and slice thickness of 2 mm. DCE was acquired prior to and four times after an automated injection of contrast agent bolus [0.1 ml/kg at 2 ml/sec Dotarem, (gadoterate meglumine, Guerbet)] followed by a 20-ml saline flush. Post-contrast images were acquired, with the first acquisition centered at 1:25 minutes after injection and the delayed acquisition centered at 7:35 minutes after injection. Diffusion-weighted imaging (DWI) was not routinely acquired in our MRI protocol during the study timespan. Yet, in examinations in which it was acquired, DWI was performed using echo-planar imaging sequence, using fat suppression, with the following parameters: three orthogonal directions, b-values 0, 600 sec/mm² with five averages, TE/TR of 74/9700 ms.

CAD Software

A commercial CAD software (Merge CADstream, version 6.0; Merge Healthcare - IBM, New-York) was employed to process and analyze the DCE-MRI datasets. The software incorporates the dynamic images to generate CAD mapping as follows: initially, a pixel-by-pixel based comparison between pre-contrast and the first post-contrast datasets dictates which pixels, if any, will be colored by CAD. Colored pixels are those which exceed the enhancement SI threshold, which is usually 50% – 100% (2). In this study, our routine default threshold of 50% increase in enhancement was applied, in accordance with previous publications (20–22). In pixels enhancing above the established threshold, a comparison between the SI values of the first and the delayed post-contrast datasets is generated for determining the exact coloring: blue, yellow and red which represents kinetic curve patterns of persistent wash-in (increase by more than 10%),
plateau (less than 10% change in SI values, in either direction) and wash-out (decrease by more than 10%), respectively. The software algorithm connects colored pixels to constitute a lesion and ultimately a color-coded map is displayed on each slice, as well as on the maximal intensity projection (MIP) image. Parametric measurements are automatically generated for each colored region: the lesion’s total volume and size in 3 dimensions, peak enhancement value, calculated as the highest percent enhancement in the pixel with the most suspicious curve type (wash-out, followed by plateau, followed by persistent), an initial phase classified as medium (50% –100%), or rapid (>100%) enhancement, determined by the SI change between the pre-contrast and first post-contrast datasets, and the distribution of each color fraction from the total lesion volume, in percentages.

Image Analysis

Qualitative analysis of CAD results was performed by two radiologists [NN and MSK] with 10 and 22 years of experience in breast MRI, respectively, who read the studies together and reached agreement by consensus. False positive rates of CAD software among the healthy lactating group, were determined based on analysis of axial MIP images. For each case, the two breast radiologists read the CAD sequence and determined whether the software has colored a suspected region in the breast parenchyma with enhancement which exceeds the threshold. Colored regions that were recognized by the two readers were defined as false-positive cases. Positive CAD cases were further classified as uni- or bilateral, depending on whether CAD coloring was apparent in both breasts and then, as appearing symmetric or asymmetric. Coloring pattern was also classified as central or peripheral, focal or non-mass enhancing (NME)-like and heterogeneous or specific-color dominant. Finally, in order to grade the lactating induced BPE coloring we divided the exams into four scoring categories: minimal, mild, moderate and marked, based on the extent of the coloring, similarly to the BI-RADS BPE grading (23). In cases with unilateral or asymmetric CAD coloring grade between the two breasts, each breast received its own grade, though per case, the higher grade of the two was accounted.

For quantitative assessment, parametric measurements of the largest automatically-detected region were served for representing each breast of the healthy lactating patients separately. In breast cancer controls, the largest automatically-detected tumor region was analyzed. In both analyzes, MIP CAD images were used for analysis, in order to include a maximal amount of pixels and a whole-volume assessment.

For further characterization of the lactating breast MRI properties, we also investigated the diffusivity measurements among the lactating cohort with available DWI datasets. DWI datasets were analyzed using GE working station toolbox. ROIs were manually delineated by a single reader (NN, with 10 years’ experience in breast DWI) on apparent diffusion coefficient (ADC) maps of a single central slice at the height of the nipple. Breast tissue was sub-classified to the anterior-central region, and the posterior peripheral region, and ADC values between these two regions was compared.

Statistical Analysis

The relationship between unilateral coloring and history of prior breast cancer and irradiation was examined using the Chi square test. Pearson’s correlation test was applied to measure association between CAD scoring grade with patient’s age and lactation duration. The difference in probability of false positive CAD coloring between healthy lactating and non-lactating patients was examined using Odds ratio test (Medcalc, New-York). Unpaired two-tailed Student’s t-test (Excel 2010, Microsoft) was applied for evaluating differences in CAD scoring grade between groups of lactating and non-lactating healthy patients, as well as among lactating patients who were nursing for short and long period (cut-off was defined as five months of lactation). Paired two-tailed Student’s t-test was applied for evaluating differences in ADC values between the anterior and the posterior regions of the breast, among the healthy lactating patients. Unpaired two-tailed Student’s t-test was also applied for evaluating differences in CAD’s automatic quantitative parametric properties between the coloring of lactation-induced BPE and breast cancer of non-lactating premenopausal controls. Histogram analysis of CAD’s parametric measurements yielded box and whiskers plots (GraphPad Prism 5.03, California). Statistical significance was defined as p < 0.05.

RESULTS

False-Positive Rates and Qualitative CAD Coloring Patterns Among Healthy Lactating Women

Overall, 53 out of 61 scans (87%) included at least one false-positive coloring region of CAD. CAD’s coloring was characteristically bilateral (79%) and symmetric in appearance (64%). Unilateral coloring was strongly associated with personal history of ipsilateral breast cancer and irradiation (8/11, 73%, p < 0.0001). CAD grading was defined as minimal in 11 cases (including 8 without any coloring and three with foci smaller than 25% of the breast), mild in 11 cases, moderate in 23 cases and marked in 16 cases, of them only 8 with bilateral marked coloring. The distribution of CAD’s grading is further demonstrated in (Fig 1).

CAD coloring has typically presented with non-mass enhancement (NME)-like appearance (83/95 breasts with CAD coloring, 87%), ranging from scattered to full breast coloring. Distribution was mostly in the central breast (67%) rather than peripherally located (33%). In terms of kinetic curve dominance, pronounced persistent wash-in pattern was the most common (36%), followed by plateau (21%) and wash-out (11%). Heterogeneous lesion with nonspecific coloring dominance were apparent in a third of cases. The many faces of CAD coloring during lactation are further illustrated in (Fig 2).
Neither age nor lactation duration were strongly correlated with CAD grade ($r = 0.18$, $r = -0.09$, respectively), however, when dividing the lactating patients based on duration, those who were breastfeeding for a shorter period had statistically significant higher CAD grades, as compared with patients who were breast-feeding for a longer period (1.62±0.98 vs 1.02±1.09, $p < 0.05$).

### Quantitative CAD Features Among Healthy Lactating Women

Among the healthy lactating patients with false-positive CAD coloring, the program output of the largest automatically detected BPE region per breast was as follows: mean±SD largest diameter 8.4±5.2 cm (range: 0.4−26.5), mean±SD region volume 45.0±83.9 cm$^3$ (range: 0.03−477.3), mean±SD peak curve 987.9±1190.9 (range: 124−7262), mean rapid uptake 79.7 % (range: 1−100) and mean medium uptake 20.3 % (range: 0−99). When summarizing the distribution of kinetic curve patterns, most pixels exhibited persistent wash-in (42.4%), followed by plateau (36.5%) and wash-out coloring (21%). Yet, per breast, plateau pattern was the most frequently leading pattern (43%), followed by persistent wash-in (41%) and wash-out (16%). The most dangerous curve pattern was wash-out (87%), followed by plateau (8%), whereas BPE containing only blue pixels of persistent wash-in, was apparent in only 5% of the cases.

![Figure 1](image1.png)

**Figure 1.** CAD maps grading and distribution. CAD images of four healthy lactating patients representing the four grades of coloring: Grade 0 - minimal (a), Grade 1 - mild (b), Grade 2 - moderate (c) and Grade 3 - marked (d). A relatively even CAD grade distribution was found except for slight Grade 2 predominance. Percentages of each grade portion from the total lactating cohort is indicated. Axial MIP CAD maps are presented overlaid on MIP subtraction images of the first post-contrast and pre-contrast T1-weighted images. (Color version of figure is available online.)

![Figure 2](image2.png)

**Figure 2.** Variations in CAD mapping among different lactating patients. A collage of CAD images of six healthy lactating patients exhibiting representative different features of coloring. Note: Bilateral marked heterogeneous pattern (a), symmetric focal coloring of nipples (b), marked unilateral with washout-dominance (c), bilateral symmetric NME with central wash-in dominance (d) bilateral symmetric NME with peripheral plateau dominance (e) bilateral asymmetric heterogeneous NME (f). (Color version of figure is available online.)
Comparison of CAD Features with Non-Lactating Control Groups

When comparing the incidence of CAD’s false positive coloring among lactating and non-lactating healthy patients, it appears that CAD’s false positive rates among the latter were only 14.1% (16/113), significantly lower than the probability among healthy lactating patients (Odds ratio 40.2, [95% CI 16.1 – 100.0], p <0.0001). Moreover, the CAD grading score among non-lactating patients (n = 16) with false positive coloring (1.13±0.35) was significantly lower in comparison with the CAD grading score among healthy lactating patients (n = 50) (2.12±0.73, p <0.0001).

When comparing CAD’s measurements of lactation-related BPE with those of the premenopausal non-lactating breast cancer control group, several parameters showed a statistically significant difference. Size parameters, including largest diameter and the total volume of the automatically detected region were 2.7 and 11 times larger in lactation BPE than in cancer, respectively (p <0.00001 for both). Nevertheless, several breast cancer lesions exhibited diffuse CAD coloring and even marked non-lactation BPE coloring on the contralateral breast, thus resembling a lactation BPE appearance. Therefore, despite the striking difference, due to overlapping measurements, a complete separation between the groups was impossible to reach based on size parameters only (see representative cases and plots in Fig 3). Other discriminators were the change in the first post contrast enhancement uptake slope; Medium uptake of between 50% – 100 %, was more common in lactation BPE than in cancer, while rapid uptake of more than 100%, was more commonly a characteristic of cancer (p <0.00001 for both). Interestingly, the remaining kinetic curve measurements, in terms of both peak enhancement and curve pattern distribution, were comparable between the 2 groups. The statistical comparison between the lactating cohort and breast cancer controls is summarized in (Table 1).

Follow-up Assessment of CAD Features Among Healthy Lactating Women

A follow-up annual MRI scan, performed upon weaning, was available for 30 patients with false-positive CAD flagging during lactation. In all of those cases (100%), a complete vanishing of CAD’s findings was found in the consecutive exam, confirming the transient, lactation-dependent CAD coloring (p <0.00001). The gradual decrease in BPE along the lactation period is demonstrated by a single case of patient who was scanned in two occasions during the same lactation period, and exhibited a decrease in the CAD coloring grade of the second scan (Fig 4). Furthermore, three different patients were scanned twice in different lactation periods, exhibiting intra-individual variations between the two scans, as shown in (Fig 5).

Characterization of the Lactating Breast by DWI

In addition to the DCE-derived characterization of the lactating breast, we further performed DWI analysis of the ADC measurements of the lactating breast (n = 21), in all cases with available DWI datasets. The mean ADC values of the breast among the lactating group was 1.73±0.21, comparable with previous publications of diffusion-based MRI studies among healthy lactating examinees, as provided in (Table 2). Moreover, we further divided the breast tissue to anterior-central.

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Figure 3. Overlapping CAD features between lactating BPE and breast cancer. CAD images of two breast cancer patients with overlapping features with lactation-induced BPE are present: 38 year old patient with newly-diagnosed large invasive ductal carcinoma of the left breast and marked non-lactation induced BPE in the contralateral breast (a), and 30 year old patient with newly-diagnosed unilateral disseminated inflammatory breast carcinoma (b). The bilateral marked BPE appearance of the first case and peripheral persistent wash-in dominance appearance of the second case, resemble some of the lactation-related BPE coloring variations described above. Box plots showing the median ± interquartile range (IQR) and whiskers (±1.5 IQR) of CAD parameters coloring volume (c) and largest diameter (d) measured in healthy lactating patients and breast cancer controls. The plots highlight the most significant discriminators between the groups, albeit with overlapping values, therefore creating a challenge in ruling out cancer based on CAD’s size parameters solely. (Color version of figure is available online.)
The ADC values of the anterior-central region 2.12 ±0.30 were substantially increased as compared with the respective measurements in the posterior-peripheral 1.62 ±0.19 (p < 0.0001).

**DISCUSSION**

In this study, we report on the incidence and characteristics of DCE-derived CAD coloring of the healthy lactating breast. The CAD system is programmed to assist the radiologist by enabling automatic lesion detection, while also delivering useful diagnostic and prognostic information (2,3). The main finding of this study is that the CAD color-coded alert system is non-specific in MRI of healthy lactating patients, since CAD coloring is extremely common among this population. Hence, lactation-induced BPE has now been proven to be an anticipated cause of false-positive CAD coloring on breast DCE-MRI.

Evaluation of the breast during pregnancy and lactation is among the field's current challenges (24). During this period, the breast undergoes physiological changes which affects both clinical and radiological assessment. Physical examination of the breast becomes difficult due to physiologic changes, including increased breast size, firmness, and nodularity (25). In terms of imaging, the breast exhibits increased fibro-glandular density which limits the utility of mammography and places ultrasound (US) as the first-line modality (26). DCE-MRI which is contra-indicated during pregnancy, is considered safe during lactation (27); However, its clinical utility remains in question (19). The characteristic marked lactation-induced BPE on DCE-MRI, stemmed by the temporal increased vascular supply and permeability (25), causes diagnostic challenge in distinguishing between lactation-related changes and suspicious findings (14–17). Instead, unenhanced diffusion-based MRI approaches that were gaining success as alternative for DCE (28,29), were also attempted for characterization of the healthy lactating breast parenchyma (30–34), as well as for preliminary inquiries among PABC patients (16,35).

Substantial past scientific work has validated the diagnostic capabilities of CAD kinetic parameters. Enhancement rate and wash-out behavior were indicated as key features that are correlated with malignancy, while altogether, a certain level of overlap was identified between the enhancement curve types of benign and malignant tumors (12). Therefore, neither CAD coloring alone nor its kinetic parameters are

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Lactating Parenchyma</th>
<th>Non-Lactating Breast Cancer</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (cm)</td>
<td>8.4±5.2</td>
<td>4.1±10.2</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Volume (cm³)</td>
<td>45±84</td>
<td>3.1±2.3</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Rapid uptake</td>
<td>79.7±29.4</td>
<td>96±5.9</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Medium uptake</td>
<td>20.3±29.4</td>
<td>3.6±5.7</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Curve peak</td>
<td>987±1191</td>
<td>846±1030</td>
<td>0.46</td>
</tr>
<tr>
<td>Persistent (%)</td>
<td>42±31</td>
<td>39±30</td>
<td>0.47</td>
</tr>
<tr>
<td>Plateau (%)</td>
<td>37±21</td>
<td>32±19</td>
<td>0.30</td>
</tr>
<tr>
<td>Washout (%)</td>
<td>21±25</td>
<td>29±28</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Specific for breast cancer diagnosis. In order to improve specificity without significantly compromising CAD’s sensitivity, an additional morphological consideration is necessary (6). Morphology-wise, our qualitative assessment showed that typical lactation BPE appearance on CAD is bilateral, often symmetric, NME-like coloring. Further characterization of lactation CAD qualities, was afforded by semi-quantitative CAD scoring grade and distribution of color dominance, though neither could offer a distinct representative pattern due to high degree of variance between subjects. Likewise, interindividual variations in imaging appearance of the lactating breast were also described by radionuclide investigation, in which iodine tracer uptake patterns were distributed in full, focal, crescent, and irregular patterns (36). Moreover, our

### TABLE 2. Literature Summary of ADC Values of the Healthy Lactating Breast

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>b-Values</th>
<th>Cases (n)</th>
<th>Mean ADC Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sah et al. (2015)</td>
<td>DWI</td>
<td>0, 500, 1000</td>
<td>12</td>
<td>1.62 ± 0.22</td>
</tr>
<tr>
<td>Nissan et al. (2014)</td>
<td>DTI</td>
<td>0, 700</td>
<td>10</td>
<td>1.66 ± 0.06</td>
</tr>
<tr>
<td>Iima et al. (2018)</td>
<td>DWI-IVIM</td>
<td>0, 5, 10, 20, 30, 50, 70, 100, 200, 400, 600, 800, 1000, 1500, 2000, 2500</td>
<td>12</td>
<td>1.72 ± 0.44</td>
</tr>
<tr>
<td>Current study</td>
<td>DWI</td>
<td>0, 600</td>
<td>21</td>
<td>1.73 ± 0.21</td>
</tr>
</tbody>
</table>

Figure 5. CAD lactation mapping on separated pregnancies. CAD images of three healthy lactating patients: 31 (a), 35 (b) and 35 (c) year old BRCA carriers, each scanned twice during lactation of separated pregnancies, with approximately two years of gap between the scans. Note the morphological pattern remain between the consecutive scans, despite changes in coloring: from wash-out dominance to wash-in dominance (a), from mild to moderate grade (b) and from wash-out dominance to plateau dominance (c). (Color version of figure is available online.)

Figure 6. DWI analysis of healthy lactating breast. Representative analysis of DWI datasets (n = 21) of the healthy lactating breast, as divided to anterior-center (blue) and posterior-peripheral (red) regions, as demonstrated on T2-weighted and ADC maps. Box plots showing the median ± interquartile range (IQR) and whiskers (±1.5 IQR) of the two breast ROIs reveal statistically significant increased ADC values on the anterior-center region, as compared with the posterior-peripheral region. (Color version of figure is available online.)
results showed that unilateral CAD coloring was found to correlate with a past history of cancer and treatment. Indeed, despite being possible, lactation competence (37), as well as BPE occurrence (38), are both known to be markedly reduced in the irradiated breast, and therefore, an ipsilateral absence of CAD coloring may be intuitively anticipated. On the other hand, although rare, lactation BPE cannot be ruled out based on unilateral coloring, in agreement with a recent report on the lactating breast parenchymal $^{18}$F-Fu (FDG) uptake on PET/CT, which typically, but not exclusively, manifests bilaterally (39). Overall, further laboratory and behavioral factors, such as hormonal levels and breastfeeding habits (eg, amount, frequency, dominant breast) are necessary to achieve better clustering and recognition of lactation BPE patterns, though they are likely impractical to maintain in real-life clinical practice, as was the settings of the present study.

Our findings suggest that false-positive CAD coloring is significantly more common and intense, in terms of CAD grading, in healthy lactating patients than in healthy non-lactating patients. Among the lactating group, intense CAD coloring was also found among patients who were breastfeeding for a shorter period, as compared with patients who were breast feeding for a longer period of time. Indeed, the lactating breast blood flow is likely to be reduced when milk production meets minimal threshold production (40). Moreover, our results show that lactation BPE induced false-positive CAD coloring is a transient phenomenon, likely to be dissipated upon nursing weaning, as was confirmed in all cases with available follow-up MRI exams.

In theory, part of the high incidence of false positive CAD coloring among lactating patients, that was found in our study, might have been attributed to the relative low threshold (50%) of increased SI post injection, which is used in our institute. Indeed, the two most conventional thresholds used in clinical practice are 50% - 100% [2], yet many institutes favor using 50% (20-22), with the aim of preserving high sensitivity over specificity (9). Nevertheless, when taking into account the prominent peak curve of lactating patients, which reaches >987% on average, it becomes clear that increasing the threshold from 50% to 100% would not have changed the high incidence of false positive coloring in this population.

Our results also propose a high degree of overlap of CAD kinetic and dynamic parameters between lactation BPE and breast cancer in non-lactating controls, though a comparison with lactating patients with breast cancer would have been more direct. Even archetypal malignant features such as increased peak uptake and wash-out curve were as common among CAD's output of lactating exams. The main discriminators between lactation BPE and breast cancer were size parameters of CAD coloring, and in particular, the coloring volume. This may arise from the fact that unlike a localized lesion, lactation involves the entire fibro-glandular tissue. However, we have also encountered several extensive malignant lesions with overlapping coloring size measurements. Thus, as was already described before, the size of NME-like lesions could not differ between benign and malignant cause (41).

In view of the challenges to differentiate between lactation derived changes and breast cancer based on their CAD quantitative properties, the role of other unenhanced sequences, although not fully investigated in this study, should be considered (42,43). T2-weighted imaging without fat suppression allows better depiction of lesion morphology and may increase the specificity for differentiation of benign and malignant lesions (44). In addition, there is a growing evidence supporting the utility of diffusion weighted imaging (DWI) sequences in breast cancer diagnosis (29). To emphasis this, a recent publication reported that unenhanced MRI was equal or better than digital breast tomosynthesis in the preoperative assessment of breast cancer (45). In particular, DWI was suggested to be instrumental in the evaluation of lactating breast, since the diffusivity of the lactating tissue was found to be significantly higher than of breast cancer, among non-lactating patients (30). Indeed, our results of the normal lactating breast ADC values are in agreement with previous publications, and more importantly, are substantially increased in comparison with the recommended ADC threshold, of $1.00 \times 10^{-3}$ mm$^2$/s for breast cancer diagnosis, as suggest by a recent meta-analysis (46).

From a clinical standpoint, breast radiologists should be aware of CAD's shortcoming in analyzing DCE-MRI datasets of lactating patients, in view of the physiological variations that arise from hormonal changes. The nonspecific BPE-induced coloring may therefore reduce the possible role of CAD as a detection tool and help to highlight the challenge of breast MRI interpretation in lactating patients. Additional studies with pathological findings are warranted in order to further evaluate CAD's diagnostic and prognostic capabilities in this unique population (47), as well as the optimal timing upon lactation weaning in the setting of screening among high risk patients (48).

Several limitations of this study should be stated. Firstly, the lactating cohort was limited to healthy lactating examinees. Concurrent benign or malignant lesions are projected to be colored by CAD as well, and although interesting, they were beyond the scope of this research, which focused on unfolding this physiological mimicker of CAD coloring. Moreover, the lactating group was determined based on retrospective identification of lactation status in the radiological reports. Therefore, some un-identified examinees with mild BPE of whom lactation status was neither reported in history nor suggested by the radiologist may have been omitted. Finally, due to the retrospective nature of this study, the groups were not standardized and in-depth information about the breastfeeding habits were missing, resulting in heterogeneous study population grouped together under 'lactating' status, thereby limiting the efficacy of the applied correlation tests.

In conclusion, physiologic BPE-induced false positive CAD coloring is extremely common during lactation and usually presents with a bilateral, symmetrical and NME-like appearance. Lactation CAD coloring exhibited variable inter-individual manifestations and parametric measurements, which were increased among patients who were...
breastfeeding for a shorter period and disappeared in all follow-up MRIs post-weaning. In comparison with the CAD features of breast cancer in non-lactation patients, larger color-diameter and volume were suggestive of lactation BPE. Albeit, in view of the overlapping physiologic and malignant features, breast radiologists should interpret DCE-MRI datasets of lactating patients, and CAD analysis in particular, with extra caution, assisting with further modalities, including unenhanced MRI.

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