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BREAST IMAGING

ORIGINAL ARTICLE

Three-dimensional vascular mapping of the breast by using contrast-enhanced MRI: association of unilateral increased vascularity with ipsilateral breast cancer

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PURPOSE
We aimed to retrospectively compare three-dimensional vascular maps of both breasts obtained by dynamic magnetic resonance imaging (MRI) and determine the association of one-sided vascular prominence with ipsilateral breast cancer.

MATERIALS AND METHODS
MRI was performed using gadolinium in 194 cases. Two readers scored vascular density using maximum intensity projections (MIPs). Dynamic fat-saturated T1-weighted gradient-echo MIPs were acquired. Two readers evaluated the MIPs, and vessels greater than 2 mm in diameter and longer than 3 cm were counted. The difference in vessel numbers detected in the two breasts determined the score.

RESULTS
A total of 54 patients had malignant lesions (prevalence, 28%), including invasive ductal carcinoma (n=40), invasive mixed ductal-lobular carcinoma (n=5), invasive lobular carcinoma (n=3), ductal carcinoma *in situ* (n=3), mucinous carcinoma (n=1), medullary carcinoma (n=1), and leukemic metastasis (n=1). In 62 patients, there were benign lesions (fibroadenomas, fibrocysts), and four patients had inflammation (granulomatous mastitis in two patients, breast tuberculosis in two patients). There were 78 normal cases. When a difference of at least two vessels was scored as vascular asymmetry, the sensitivity, specificity, positive likelihood ratio (+LR), and negative (-LR) of unilaterally increased vascularity associated with ipsilateral malignancy were 69%, 92%, 8.72, and 0.34, respectively. When four infection and three post-operative cases with vascular asymmetry were excluded; prevalence, specificity, and +LR increased to 29%, 97%, and 22.8, respectively, with the same sensitivity and -LR. Differences in mean vascularity scores were evaluated with regard to tumor size. T1 and T2 tumors were not significantly different from each other. The mean score of T3 tumors differed significantly from T1 and T2 tumors.

CONCLUSION
MRI vascular mapping is an effective method for determining breast tissue vascularization. Ipsilateral increased vascularity was commonly associated with malignant breast lesions.

Key words: • breast cancer • blood vessels • magnetic resonance imaging • maximum intensity projection

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The role of contrast-enhanced magnetic resonance imaging (MRI) of the breast for breast cancer diagnosis and management is increasing. Defined indications include pre-surgical local tumor staging in dense breasts, surgically treated breasts in which a residual or recurrent tumor is suspected, evaluation of the effects of neoadjuvant chemotherapy, the search for occult breast cancer with known metastases, and screening of women who are at high genetic-familial risk of having breast cancer (1). Currently, breast MRI is considered to have very high (94%–99%) sensitivity for the detection of invasive cancers, but lower (50%–80%) sensitivity for the detection of *in situ* cancers (2–8). Moreover, the specificity of MRI for breast cancer detection is, at best, only moderate (65%–79%), even in interpretation models in which morphological and dynamic criteria are integrated (7, 9).

Angiogenesis is an important process for tumor growth and proliferation. With its high temporal and spatial resolution, MRI is well-suited for use in the assessment of angiogenesis. Magnetic resonance (MR) angiography can be used clinically and experimentally for the identification of tumor-feeding and -draining vessels, tumor characterization, and treatment planning. Using specific contrast agents, the morphological structure of tumor vessels can be investigated in relation to tumor vessel permeability. Non-invasive quantification of angiogenesis may also be possible with MRI. Future directions in tumor imaging may include so-called four-dimensional (4D) MR angiography, in which high-resolution three-dimensional (3D) MR angiography is combined with dynamic contrast-enhanced MRI.

In this study we sought to retrospectively determine the diagnostic value of vascular map asymmetry as a marker for breast tumors, obtained by maximum intensity projection (MIP) images from breast MRI.

Materials and methods

From January 2009 to June 2011, conventional MRI examinations were performed in 194 women. The mean age of the 54 patients with malignant lesions was 46.8±11.0 years and that of the 140 patients with benign lesions was 44.3±10.2 years (range, 18–76 years).

The study had local ethics committee approval. Informed consent was obtained from all patients.

We used conventional breast MRI with a 1.5 Tesla MRI machine (Signa HDx, General Electric, Milwaukee, Wisconsin, USA) and a dedicated eight-channel high-definition breast coil. All patients were examined in the prone position. The breasts were compressed slightly from the lateral sides using compression paddles, taking care not to apply too much pressure on the tissue.

The routine sequences were axial short TI inversion recovery, sagittal fast spin echo fat-saturated T2W, and sagittal 3D VIBRANT (post-contrast fat-saturated T1-weighted gradient echo sequence), which were optimized for imaging breast tissue. For the dynamic series, two pre-contrast and six post-contrast series with a temporal resolution of about 1 min (depending on the size of the breast and the number of images per sequence) were taken. Standard imaging parameters were as follows: a field of view of about 19 cm (depending on the size of the breast); a matrix of 256×190 (ZIP 512); TE, minimum 2.5 ms, maximum 12 ms; flip angle 10°; and NEX 1. This covered both sides of the breast tissue simultaneously with 3D thin slices (slice thickness, 2.8 mm; ZIP×2 effective slice thickness, 1.4 mm) with no gap. The total imaging time for the dynamic series was about 7 min, 42 s. A standard dose of commercially available contrast material (0.1 mmol/kg gadolinium) was administered using an automated injector (a bolus at a rate of 2 mL/s, followed by a 20 mL saline flush).

The images were transferred to the Advantage Windows 4.4 workstation. Following the MRI examination, post-processing applications were used, and MIP images were obtained for all patients. We chose either the first or second post-contrast series, depending on which showed the better "angiographic effect," for both arteries and veins. Sagittal and axial images were prepared from the fat-suppressed, non-subtracted VIBRANT MR images by the same radiologist (S.O.). Sagittal MIPs were used for assessment because they were superior to the axial MIPs, with optimal spatial and contrast resolution. Two readers (S.O. and I.B.) evaluated the MIP images. The score for each patient was determined by consensus. The numbers of vessels per breast that were 3 cm or greater in length and 2 mm or greater in maximal transverse diameter were counted. The difference in the number of these vessels between the two breasts (number of vessels in the ipsilateral breast minus the number of vessels in the contralateral breast) determined the vascular score. The vascularity of a breast with at least two more vessels as compared with the other breast was considered to be increased. The presence and size of enhancing lesions were also considered during these evaluations. Lesions were categorized according to the maximum diameter of the lesion in accordance with the TNM classification of breast tumors: small (less than or equal to 20 mm), moderate (21–49 mm), or large (greater than 50 mm). When more than one lesion per breast was detected, the one with the largest diameter was considered.

Results

On histopathological examination, 54 malignant lesions were identified including invasive ductal carcinoma (n=40), invasive ductal+lobular carcinoma (n=5), lobular carcinoma (n=3), ductal carcinoma *in situ*, (n=3), malignant phyllodes tumor (n=1), mucinous carcinoma (n=1), medullary carcinoma (n=1), and metastatic leukemia (n=1). The mean size of the malignant lesions was 37.7 mm (range, 5–130 mm).

In total, 62 benign lesions were included. They were either histopathologically demonstrated to be benign, stable on follow-up, or had typical benign findings (BIRADS 2) on imaging. The distribution of benign lesions was as follows: fibroadenoma (n=30), papilloma (n=1), simple cysts (n=17), hemorrhagical cyst (n=3), post-operative seroma (n=2), post-operative infection (n=1), tuberculosis abscess (n=2), granulomatous mastitis (n=2), phyllodes tumor (n=1), atypical ductal hyperplasia (n=1), and fat necrosis (n=1). The mean size of the benign lesions was 18.3 mm (range, 6–50 mm). In 78 cases, MRI studies showed no significant findings, and they were reported as normal.

Results were evaluated statistically using a commercially available software (Statistical Package for Social Sciences, version 16, SPSS Inc., Chicago, Illinois, USA). Sensitivity, specificity, and positive and negative likelihood ratios for unilaterally increased vascularity in association with an ipsilateral malignancy were determined for the 54 histopathologically confirmed lesions using gadolinium-enhanced MRI. When a difference of at least two vessels was deemed as vascular asymmetry, the presence of unilaterally increased vascularity was observed in 48 of the 194 patients. In 37 (77%) of these 48 patients, the increased vascularity was associated with ipsilateral breast cancer. These were considered to be true positive cases. Five cases of the malignant lesions had symmetrical vascular maps, 11 cases had a score of one on the ipsilateral, and one case had a score of one on the contralateral side. These 17 cases were considered to be false-negative cases. None of the tumors in the false-negative cases was greater than 5 cm (11 cases, ≤20 mm; 6 cases, 21–50 mm).

Eleven patients without malignancy had asymmetrical vascular maps. When four cases with inflammatory conditions and three post-operative cases were excluded, only four patients with unilaterally increased vascularity who had benign lesions (n=1) or no lesion (n=3) in the ipsilateral breast were considered to be false-positive cases.

The 129 cases with no lesion (n=75) or benign findings (n=54) constituted the true negative cases. A bar graph representation of the asymmetrical vascularity, determined as the difference in vessels between the two sides on sagittal MIPs obtained from post-contrast 3D dynamic breast images is shown in Fig. 1. Representative cases are presented in Figs. 2–6. The overall sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) of one-sided increased vascularity associated with ipsilateral malignancy were 69%, 92%, 8.72, and 0.34, respectively. However, when the four cases of infection and three post-operative cases with vascular asymmetry were excluded, the prevalence, specificity, and +LR increased to 29%, 97%, and 22.8, respectively, with no significant change in sensitivity or -LR. Results of the statistical analyses are summarized in Table 1.

There were 20 cases of T1, 20 cases of T2, and 14 cases of T3 malignant tumors in the study group; 45% of the T1 (9/20), 70% of the T2 (14/20), and all of the T3 (14/14) tumors were associated with ipsilateral increased vascularity, with a minimum score of two.

The results of the mean vascularity scores of the ipsilateral breast were also evaluated in comparison with the size of the lesions. These results are summarized in Table 2.

The mean vascularity scores of the ipsilateral breast with malignant lesions (mean, 2.34±1.45; range, 1–8) were higher than those of the benign lesions (mean, 1.47±1.04; range, 1–5; $P < 0.001$, Kruskal-Wallis analysis of variance [ANOVA]).

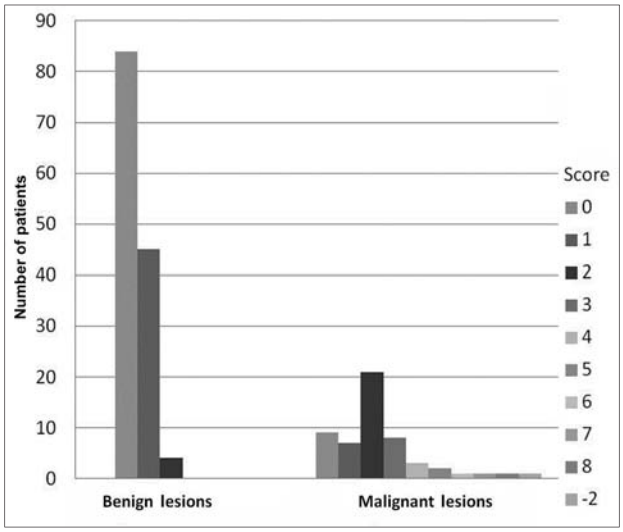

Figure 1. Bar graph representation of the asymmetrical vascularity, determined as the difference in vessels between the two breasts (the score, ranging from -2 to 8, is represented by different shades of gray) for the benign and malignant groups. The score was determined using sagittal MIPs obtained from post-contrast 3D dynamic breast images.

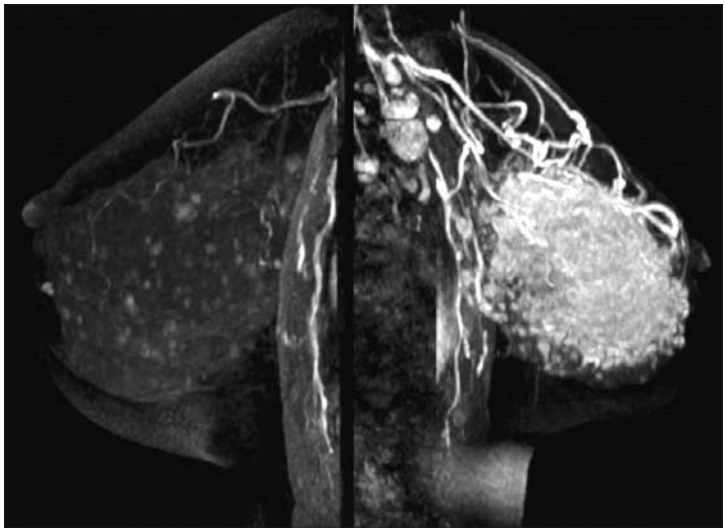

Figure 2. Sagittal MIP reconstructions of both breasts in a 45-year-old female patient, showing increased vascularity in the left breast compared to the right breast, which was associated with a large invasive ductal carcinoma and multiple enlarged axillary lymph nodes.

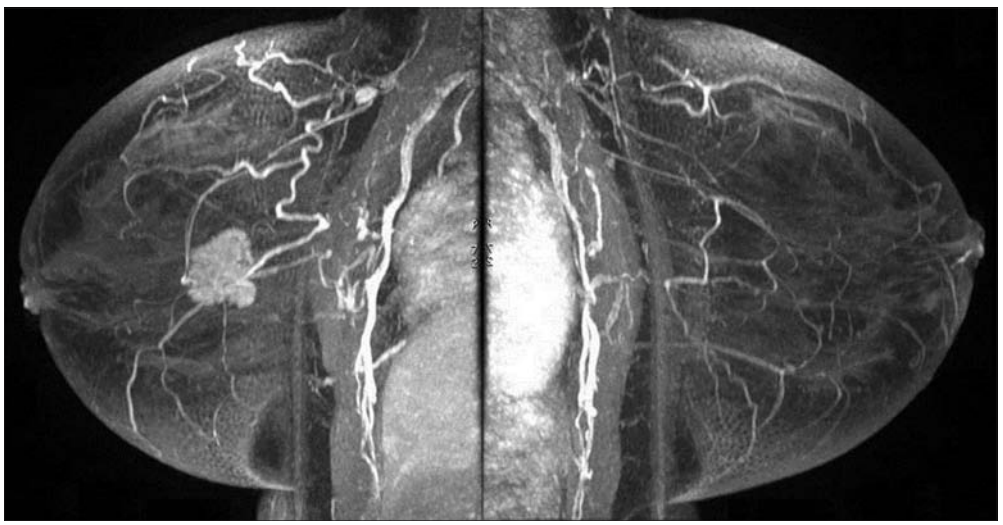

Figure 3. A 55-year-old female patient. Sagittal MIPs obtained from post-contrast dynamic breast MRI revealed increased vascularity in the right breast associated with an enhancing mass lesion 3 cm in diameter (invasive ductal carcinoma) in the central region and a lymph node at the axillary tail.

In terms of the difference in the number of vessels, there was no statistically significant difference between benign lesions sized 0–20 mm (mean, 1.42±0.96; range, 1–4) and 20–50 mm (mean, 1.55±1.21; range, 1–5; $P = 0.7$, Mann-Whitney U test). No benign lesion was larger than 5 cm in diameter.

Table 1. Sensitivity, specificity, positive and negative likelihood ratios (+LR and –LR) of vascular asymmetry in 3D dynamic breast MRI as an indicator of breast cancer

Parameter	Value	95% confidence interval
Sensitivity	69%	54%–80%
Specificity	97%	92%–99%
+LR	22.8	8.5–60.8
-LR	0.32	0.22–0.48

When the difference in the number of vessels was evaluated in comparison with the size of the lesion, T1 tumors (0–20 mm) had a mean vascularity score of 1.61 (standard deviation, 0.77; range, 1–3). The scores were 1.94 (standard deviation, 0.64; range, 1–3) for T2 tumors (21–50 mm) and 3.79 (standard deviation, 1.87; range, 1–8) for T3 tumors (>51 mm). The difference in mean vascularity scores between T1 and T2 tumors was not statistically significant ($P = 0.1$). However, the mean score of T3 tumors differed significantly from both T1 and T2 tumors ($P = 0.001$, Mann-Whitney U test).

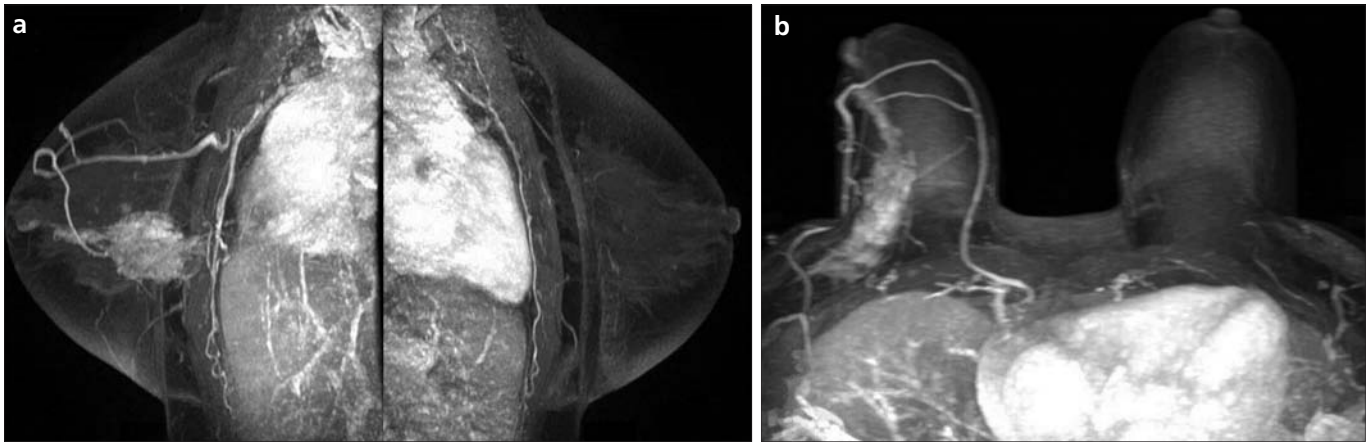

Figure 4. a, b. Sagittal **(a)** and axial **(b)** MIP images of both breasts demonstrated a ductal carcinoma *in situ* in a 53-year-old female patient with cable-stone enhancement at the middle-outer quadrant of the right breast in a segmental distribution, from the nipple deep to the glandular tissue. Ipsilateral increased vascularity associated with the axillary and internal mammary arteries can be observed.

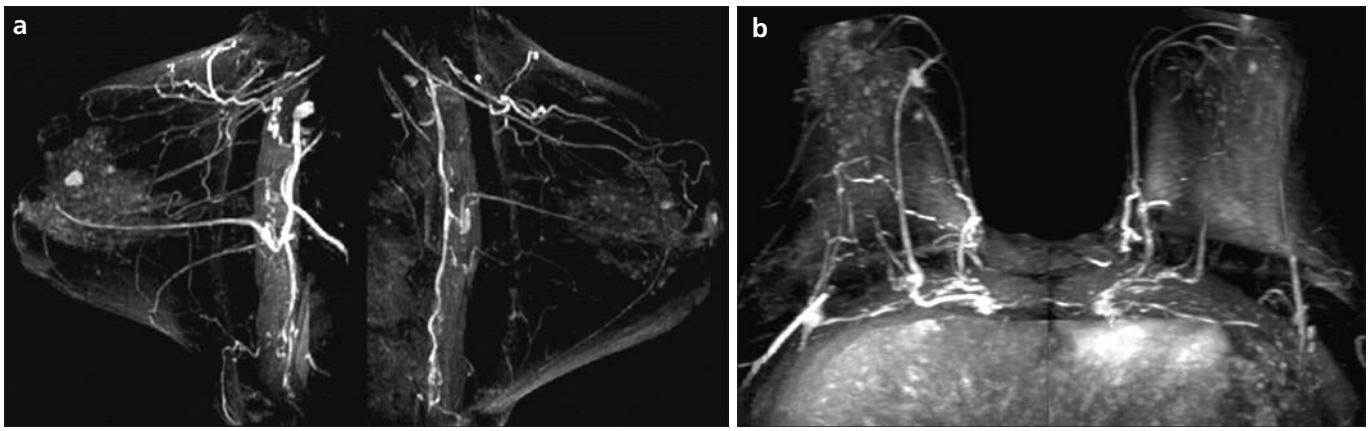

Figure 5. a, b. Sagittal **(a)** and axial **(b)** MIP images of both breasts of a 64-year-old female patient. A dilated vessel associated with the internal mammary vessels accompanies an invasive ductal carcinoma (9 mm in diameter) located in the upper-inner quadrant of the right breast.

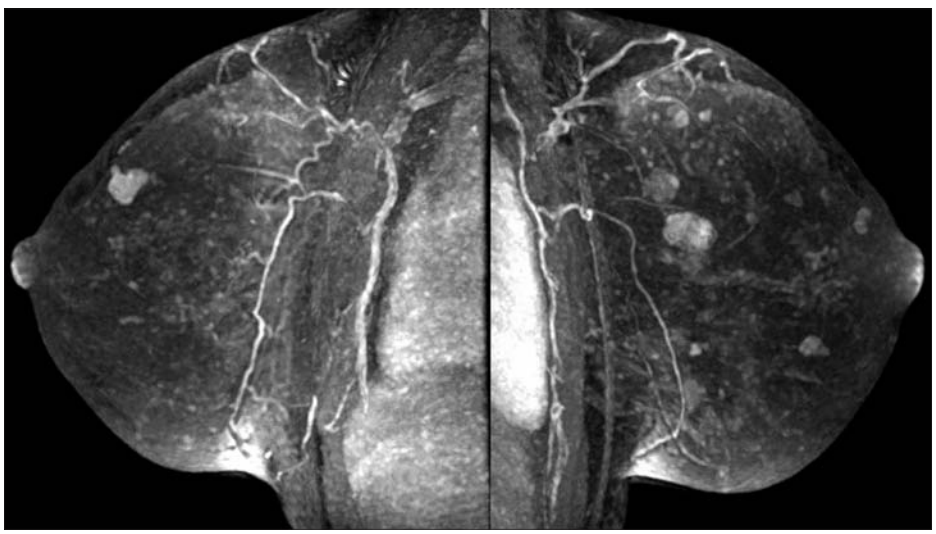

Figure 6. Sagittal MIP reconstructions of both breasts in a 30-year-old female patient with bilateral fibroadenomatosis showing no prominent asymmetry in breast vascularity.

Table 2. The vascularity scores of the ipsilateral breast determined by the vascular maps obtained from dynamic post-contrast MRI images for different tumor sizes, both for benign and malignant groups (cases with a score of 0 were not included)

	Small (0–20 mm)		Moderate (21–50 mm)		Large (>50 mm)		Total	
Vascularity score	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
Mean	1.42	1.61	1.55	1.94	-	3.79	1.47	2.34
Standard deviation	0.96	0.77	1.21	0.64	-	1.87	1.04	1.45
Range	1–4	1–3	1–5	1–3	-	1–8	1–5	1–8

The lesions were categorized according to the maximum diameter in accordance with the TNM classification of breast tumors.

Discussion

Sufficient oxygen and nutrient supplies are essential for the proliferation and survival of cells. In the first stages, cells take up nutrients and oxygen simply by diffusion. It has been shown that tumors do not grow beyond 2 mm^3 in size without the development of new capillaries from surrounding blood vessels, a process called angiogenesis (10). In angiogenesis, new vessels develop from pre-existing vessels by spouting and intussusception; vasculogenesis does not happen. *De novo* generation of blood vessels from endothelial precursors occurs during embryogenesis. Angiogenesis can be seen in physiological settings, such as in the uterus and during wound healing. In some pathological conditions, such as diabetic retinopathy, tumor growth, and synovial proliferation, angiogenesis is the basic factor of new vessel development. In malignancies, tumor growth and metastasis occur as a result of angiogenesis. Angiogenesis is controlled by a balance of circulating proangiogenic and antiangiogenic factors, sometimes referred to as the "angiogenic switch" (11). When there is equilibrium between pro- and antiangiogenic factors, the switch is off. The switch is turned on when there is a surplus of proangiogenic factors, a condition that triggers new vessel formation, allowing a tumor to grow. Proangiogenic factors, such as vascular endothelial growth factor, activate endothelial cells in vessels near the tumor. In tumors, angiogenesis is active continuously, and this activity leads to a relatively high fraction of immature blood vessels. As a result, tumor vessels are structurally and functionally distinct (12). Abnormalities in various components of the vessel wall have also been described. These include changes in the hierarchy of arterioles, capillaries, and venules, as well as other structural changes that result in the hyperpermeability of tumor vessels. Tumor vessels are tortuous, vary in diameter, and tend towards excessive branching and shunt formation.

Vascular maps of the breast can be integrated into the standard breast MRI when a dynamic 3D contrast-enhanced imaging sequence is used. We preferred to use non-subtracted fat-saturated images, which produced excellent anatomical landmarks in both the sagittal and transverse planes, comparable to mammograms obtained in lateral and cranio-caudal positions, respectively. Angiographic vascular maps of vessels were reconstructed usually using the first or the second post-contrast series by the MIP technique. Because each phase of the dynamic series had a scan time of about 60 s, depending on the volume of the breast tissue and thus the number of slices obtained per phase, both permitted the detection of arteries and veins of the breast, including internal mammary vessels, as well as the enhancing breast lesions.

Vascular prominence in the breast is a classical finding of breast cancer in physical examinations. Previously, the presence of increased blood flow in breast tumors has also been demonstrated using positron emission tomography (13), temporally-resolved contrast-enhanced MRI (14–17), and color Doppler ultrasonography (18). Furthermore, an ipsilateral association between cancer and increased breast vascularity has been demonstrated using conventional MRI (19, 20).

The presence of ipsilateral vascular prominence in association with cancer may be secondary to reduced flow resistance in the tumor vessels, the tumor's higher metabolism, angiogenic stimulation of the whole breast, or any combination of these factors. When the cancer is relatively large, the first two possibilities are more likely. However, when the tumor is small, angiogenic stimulation of the whole breast seems more probable. The role of neoangiogenic peptides in the prognosis of breast cancer remains an area of active research (21, 22). Ipsilateral vascular prevalence in association with cancer was reported previously. Mahfouz et al. (19) studied 106 randomly selected patients—85 had unilateral malignant lesions and 21 had unilateral benign lesions—and obtained sensitivity, specificity, accuracy, positive predictive, and negative predictive values of 77%, 57%, 73%, 88%, and 38%, respectively. Carriero et al. (20) studied 101 patients—78 with unilateral malignant lesions and 23 with unilateral benign lesions—and obtained sensitivity, specificity, accuracy, positive predictive, and negative predictive values of 72%, 100%, 78%, 100%, and 51%, respectively. Sardenelli et al. (23) reported the overall sensitivity, specificity, accuracy, positive predictive, and negative predictive values of one-sided increased vascularity associated with ipsilateral malignancy as 88%, 82%, 87%, 94%, and 70%, respectively.

The number of cases with inflammatory processes involving the breast, and post-operative cases, all of which showed prominent vascular asymmetry, was higher in our series. When they were excluded, the prevalence, specificity, and +LR increased to 29%, 97%, and 22.8, respectively.

Although they are known to have reduced angiogenesis as compared with invasive carcinomas, two of the three cases with *in situ* carcinomas showed increased vascularity.

Tumor size was an important determinant of vascularity in malignant

breast lesions in our series. All T3 tumors in our series were associated with asymmetrical vascular maps. The number of true-positive cases and the percentage decreased with tumor size (70% for T2, and 45% for T1 tumors). Additionally, the mean vascular score for T3 tumors was larger than those for T1 and T2 tumors ($P < 0.001$). In contrast, Sardenelli et al. (23) reported that the dimensions of the cancer were probably not a key factor in the ipsilateral prevalence of increased breast vascularity, but they had only a small number of false-negative cases.

One limitation of our study was the evaluation of vascular maps without masking the enhancing lesions, which may bias the assessment of vascular asymmetry when the difference between the two sides was small. A further limitation was the absence of follow-up information on unilateral increased vascularity to confirm the false-positive cases of vascular asymmetry.

Nevertheless, the high accuracy of breast MRI based on dynamic and morphological criteria is well-established. Our findings suggest that vascular map asymmetry is a corollary MRI finding that is frequently associated with ipsilateral invasive breast cancer. Thus, standard dynamic contrast-enhanced breast MRI should be evaluated for conspicuity and symmetry on a routine basis.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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