Medicine®

OPEN

Analysis of factors influencing the degree of detectability on diffusion-weighted MRI and diffusion background signals in patients with invasive breast cancer

Soo Yeon Hahn (MD, PhD)[a], Eun Sook Ko (MD, PhD)[a], Boo-Kyung Han (MD, PhD)[a], Yaeji Lim (PhD)[b], Seonhye Gu (MS)[c], Eun Young Ko (MD, PhD)[a,*]

Abstract

To determine the factors influencing the degree of detectability of lesions and diffusion background signals on magnetic resonance diffusion-weighted imaging (DWI) in invasive breast cancer.

Institutional review board approval was obtained and patient consent was waived. Patients with newly diagnosed invasive ductal carcinoma, who underwent preoperative breast magnetic resonance imaging with DWI were included in this study (n = 167). Lesion detectability on DWI and contrast-enhanced subtracted T1-weighted images, the degree of background parenchymal enhancement (BPE), and diffusion background signal were qualitatively rated. Detectability of lesions on DWI was compared with clinicopathological findings including menopausal status, mammographic density, and molecular subtype of breast cancer. Multivariate linear regression analysis was performed to determine variables independently associated with detectability of lesions on DWI and diffusion background signals.

Univariate analysis showed that the detectability of lesions on DWI was significantly associated with lesion size ($P = 0.001$), diffuse background signal ($P < 0.0001$), and higher detectability scores for contrast-enhanced T1-weighted subtraction images ($P = 0.000$). The degree of diffusion background signal was significantly affected by age ($P < 0.0001$), BPE ($P < 0.0001$), mammographic density ($P = 0.002$), and menopausal status ($P < 0.0001$). On multivariate analysis, the diffusion background signal ($P < 0.0001$) and histologic grade ($P < 0.0001$) were correlated with the detectability on DWI of invasive breast cancer. Only BPE was correlated with the amount of diffusion background signal on DWI ($P < 0.0001$).

For invasive breast cancers, detectability on DWI was significantly affected by the diffusion background signal. BPE, menopausal status, menstrual cycle, or mammographic density did not show statistically significant correlation with the diffusion detectability of lesions on DWI.

Abbreviations: ADC = apparent diffusion coefficient, BPE = background parenchymal enhancement, DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging, DWI = diffusion-weighted imaging, ER = estrogen receptor, HER2 = human epidermal growth factor receptor type 2, IDC = invasive ductal carcinoma, LMP = last menstrual period, PR = progesterone receptor, SISH = silver-enhanced in situ hybridization.

Keywords: breast cancer, diffusion background signal, diffusion-weighted imaging, lesion detectability, magnetic resonance imaging

1. Introduction

Magnetic resonance imaging (MRI) is widely used in patients with breast cancer, with several indications because of its high sensitivity.[1,2] The basic principles of breast MRI, as currently used, rely on the difference between enhancement levels for normal and malignant tissue on T1-weighted dynamic contrast-enhanced MRI (DCE-MRI) sequences. Based on these principles, DCE-MRI has been an essential tool for the detection, diagnosis, and monitoring of breast malignancies.[3–6] However, there are 2 major issues with this technique. First, breast MRI is known to have a relatively low specificity because normal tissue and benign lesions are also enhanced.[7,8] However, through the combined use of mammography alongside DCE-MRI, as well as technological advances such as diffusion, perfusion, and spectroscopy, several recent publications have reported an improved specificity.[6,9–11] Second, the requirement for intravenous administration of a gadolinium-based contrast agent increases the associated time,

costs, and potential toxicity of a breast DCE-MRI examination. Recently, several researchers have reported that use of intravenous gadolinium-based contrast agents is associated with neuronal tissue deposition even without renal dysfunction.[12] These factors make it difficult to accept a wider use of contrast-enhanced MRI, especially for screening purposes.

Because of concerns about possible contrast material-related problems, various approaches to breast MRI without contrast agents, both for lesion detection and characterization, have been proposed.[13] Diffusion-weighted imaging (DWI) is one of the most promising MRI techniques with which to improve the diagnostic specificity of breast MRI without the use of contrast material.[2,14,15] Several researchers have reported that combinations of unenhanced MRI including DWI show good diagnostic performance.[13,16,17] Furthermore, DWI provides quantitative information by measuring the apparent diffusion coefficient (ADC), which is significantly lower in breast cancers compared to benign lesions.[18–20] However, to replace the DCE-MRI, detection of lesions on DWI should be preceded. Following this, a quantitative ADC measurement can be performed. Nevertheless, little is known about the factors influencing the degree of detectability of lesions on DWI or the diffusion background signal in patients with invasive breast cancer.[21,22]

The purpose of this study was to identify the factors influencing the degree of detectability of lesions on DWI and diffusion background signal in cases of invasive breast cancer.

2. Materials and methods

2.1. Patients

Institutional review board approval was obtained for this study and informed patient consent was waived due to the retrospective nature of the study.

Between January 2013 and May 2013, 282 patients who had a histological diagnosis of an invasive ductal carcinoma presented as a mass on preoperative MRI by using a 1.5 T scanner were identified. We excluded cases for which MRI was performed after diagnosis by vacuum-assisted biopsy or excisional biopsy (n = 53). Patients treated with neoadjuvant chemotherapy (n = 42), those who had bilateral malignancies (n = 5), and those who had a history of prior breast malignancies (n = 15) were also excluded. Finally, 167 cancers from 167 women age 27 to 77 years (mean, 51 years; range, 27–77 years) were included in this study.

At the time of performing the MRI, patients were asked questions about their menopausal status, the regularity of their menstrual cycles (if the patient was premenopausal), and the date of their last menstrual period. The menstrual cycle was divided into 4 weeks; Week 1 began on the 1st day of menstruation.

2.2. MRI protocol

MRI was performed using a 1.5-T system (Achieva; Philips Medical Systems, Best, The Netherlands) for 167 lesions with dedicated bilateral phased array breast coils. Images of both breasts were acquired with the patient in the prone position. The backbone MRI sequence consisted of a turbo spin-echo T1- and T2-weighted sequence, a single-shot spin-echo planar diffusion-weighted sequence, and a 3-dimensional DCE sequence. The DCE-MRI parameters included repetition time (TR) = 6.5, echo time (TE) = 2.5, slice thickness = 1.5 mm, flip angle = 10°, matrix size = 376 × 374, and field of view = 320 × 320 mm. Before contrast agent injection, DW images were obtained for both

breasts with diffusion-sensitizing gradients applied along 3 orthogonal directions. These images were used to synthesize isotropic axial DW images under 2 b values (0 and 750 s/mm²).[23] The DWI parameters included TR = 15,000, TE = 66.7, slice thickness = 3 mm, matrix size = 156 × 158, and field of view = 300 × 300 mm.

Axial DCE-MRI included 1 precontrast and 6 postcontrast dynamic series. The first-phase images of postcontrast dynamic series were obtained 30 s after contrast injection, and the rest 5 phases were obtained at 60 s intervals until 330 s. After dynamic series, images were subtracted. A 0.1 mmol/kg bolus of Gadobutrol (Gadovist; Bayer Healthcare Pharmaceutical, Berlin, Germany) was injected for dynamic contrast imaging, after a 20-mL saline flush.

2.3. Image analysis

All MR images were retrospectively reviewed and interpreted by 2 radiologists (ESK and SYH with 10 and 8 years of experience in breast MR images, respectively) in consensus. The reviewers were blinded to the clinicopathological findings including mammographic density, hormonal receptor status, and menopausal status. Tumor size was defined as the maximum diameter of the tumor in the second phase after contrast injection. In the case of multifocal or multicentric disease, only the index lesion was analyzed.

The radiologists evaluated the tumor detectability of DWI, and positive detection was defined as high signal intensity than that of the surrounding parenchyma on DW images with 2 b values. DCE-MR images were referenced to find the target malignant mass. When positive detection was identified on DWI, the detectability was scored on DWI with b value of 750 s/mm² by consensus of 2 radiologists. The score was determined according to the 5-point scale as follows: 1 = not detectable, 2 = slight, 3 = fair, 4 = moderate, and 5 = excellent (Fig. 1). Similarly, detectability on contrast-enhanced subtracted T1-weighted images was also rated using the same 5-point scale. The amount of background parenchymal enhancement (BPE) and diffusion background signals were visually assessed and classified according to a 4-point scale: 1 = minimum, 2 = mild, 3 = moderate, and 4 = marked enhancement (Figs. 2 and 3).[24] Mammographic density of the contralateral breast was scored according to a 4-point scale (1 = a predominantly fatty breast, 2 = a scattered fibroglandular fatty breast, 3 = a heterogeneous dense breast, and 4 = an extremely dense breast).

The 2 radiologists measured ADC values in consensus. Using a dedicated picture archiving and communication system workstation, the ADC values were obtained by placing the region of interest (ROI) within the border of area on the ADC map, corresponding to enhancing solid portion of targeted lesion demonstrated on the first or second phase of DCE-MRI. The ROI was drawn on the slice in which the tumor showed the greatest diameter, excluding the cystic or necrotic parts of the tumor. The mean size of the ROIs was 60.2 mm² (range, 10.8–343.8 mm²).

2.4. Pathological data

Pathological reports of either breast-conserving surgery or mastectomy specimens were reviewed to determine estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2) status, as well as tumor type, histological grade, Ki-67 status, lymphovascular invasion, and the presence of extensive intraductal components. The criteria for ER and PR positivity were ≥1% of their nuclei
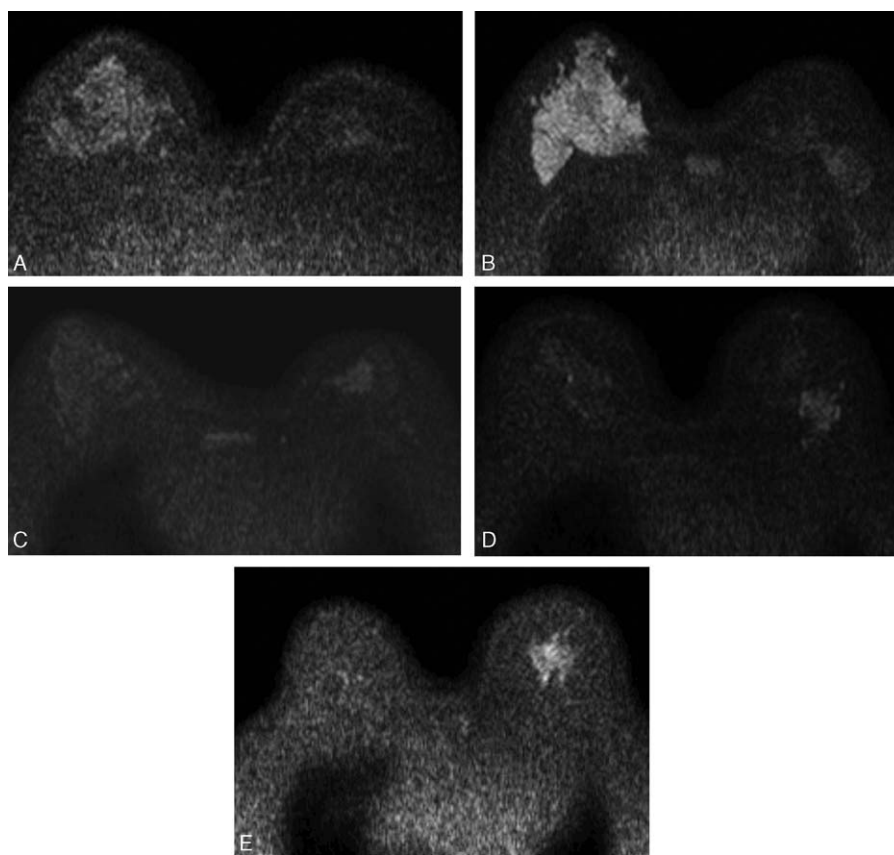
Figure 1. Axial diffusion-weighted magnetic resonance images (b value, 750 s/mm^2) according to the 5-point scale (1: not detectable, 2: slight, 3: fair, 4: moderate, 5: excellent). (A) Score 1. (B) Score 2. (C) Score 3. (D) Score 4. (E) Score 5. All masses were left-sided.

stained. Immunohistochemical HER2 scores of 3+ (i.e., strong homogeneous staining) were interpreted as positive. In cases of 2 + scores (i.e., moderate complete membranous staining in ≥10% of tumor cells), silver-enhanced in situ hybridization (SISH) was used to determine HER2 amplification (gene copy number > 6 or HER2/chromosome 17 ratio > 2.2). Molecular subtypes of breast cancer were classified into luminal A (ER-positive and/or PR-positive, HER2-negative and Ki-67 < 14%), luminal B (ER-positive and/or PR-positive, HER2-negative, and Ki-67 ≥ 14% or ER- and/or PR-positive and HER2-positive, irrespective of Ki-67 expression), HER2-enriched (ER-negative, PR-negative, and HER2-positive), and triple-negative breast cancer (ER-negative, PR-negative, and HER2-negative) based on immuno-histochemistry or SISH findings of ER, PR, HER2, and Ki-67 expression.

2.5. Statistical analysis

Univariate linear regression was used to identify the factors affecting the degree of detectability of lesions on DWI or the diffusion background signal. Multivariate linear regression with stepwise selection was used to select best-fit parameters that were associated with diffusion detectability or diffusion background signals. A stepwise procedure was used such that variables were added if $P < 0.2$ and were removed if $P > 0.2$.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC), and a P value of <0.05 was considered to indicate a statistically significant difference.

3. Results

The mean lesion size was 19.5 mm (range, 6–75 mm). The mean ADC value was 1.023×10^{-3} (range, $0.582–1.914 \times 10^{-3}$). Characteristics of patients included in this study are shown in Table 1. Out of 167 lesions, 20 (12.0%) were not detected on DWI. One hundred sixteen of the patients (69.5%) had mammographically dense breasts. Eighty-nine (53.3%) women were postmenopausal.

3.1. Analysis of factors influencing the degree of detectability of lesions on DWI

The univariate analysis of factors affecting the degree of diffusion detectability of lesions is shown in Table 2. The lesion size, with larger lesions being easier to detect, affected DWI detectability ($P = 0.001$). While BPE and mammographic density did not affect the diffusion detectability score ($P = 0.322$ and 0.191, respectively), the diffusion background signal significantly decreased the diffusion detectability ($P < 0.0001$). Menopausal status and menstrual cycle did not affect the diffusion detectability ($P = 0.433$ and 0.242, respectively). The diffusion detectability score did not show a statistically significant difference according to molecular subtype ($P = 0.281$). The higher the detectability scores for contrast-enhanced T1-weighted subtraction images, the higher the detectability scores were for DWI ($P = 0.000$). On multivariate analysis with stepwise selection, diffusion back-ground signal and histological grade were associated with
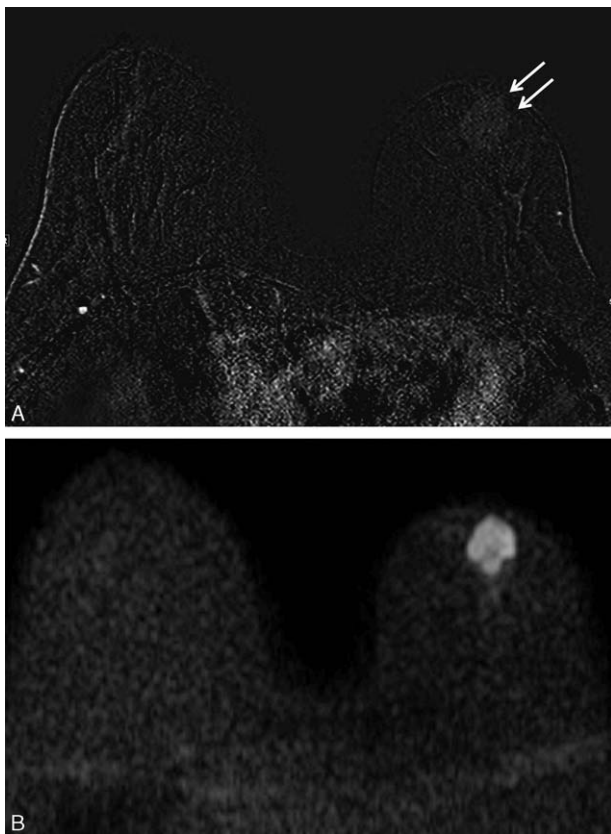
Figure 2. Invasive ductal carcinoma of the left breast in a 55-y-old woman. (A) Axial contrast-enhanced T1-weighted subtraction image shows a 27-mm mass (arrows). Background parenchymal enhancement score of contralateral breast was 1. The detectability score on subtraction image was 2. (B) Axial diffusion-weighted magnetic resonance imaging (b value, 750 s/mm^2) shows a high signal intensity mass (arrows). Diffusion background signal was rated as score 1. Score of diffusion detectability was 5.
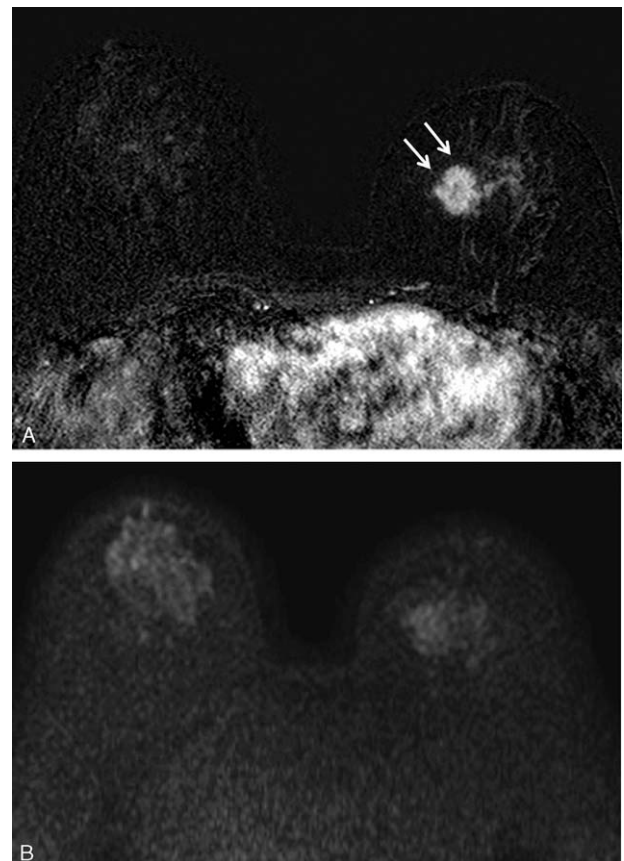

Figure 3. Invasive ductal carcinoma of the left breast in a 60-y-old woman. (A) Axial contrast-enhanced T1-weighted subtraction image shows a 20-mm mass (arrows). Background parenchymal enhancement score of contralateral breast was 2. The detectability score on subtraction image was 5. (B) Axial diffusion-weighted magnetic resonance imaging (b value, 750 s/mm^2) shows subtle high signal intensity mass. Diffusion background signal was rated as score 4. Score of diffusion detectability was 2.

diffusion detectability ($P < 0.0001$ and $P < 0.0001$, respectively) (Table 3).

3.2. Analysis of factors influencing the degree of diffusion background signal

Table 4 shows the univariate analysis of factors affecting the degree of diffusion background signal. The degree of diffusion background signal was statistically significantly affected by age ($P < 0.0001$), BPE ($P < 0.0001$), mammographic density ($P = 0.002$), and menopausal status ($P < 0.0001$). As age increased, the diffusion background signal decreased. Similarly, premenopausal women showed higher scores of diffusion background signal than postmenopausal women. BPE and mammographic density were negatively correlated with diffusion background signal. In a multivariate analysis with stepwise selection, when the other covariates were held constant, BPE was correlated with the degree of diffusion background signals on DWI ($P < 0.0001$) (Table 5).

4. Discussion

Until now, most studies of DWI with quantitative measurement of ADC have focused on the differentiation between benign and malignant lesions or on correlations with pathological findings.[19,25,26] One strong advantage of DWI is its quite high sensitivity for breast cancer detection without the need for a contrast material injection. One recent meta-analysis calculated an overall sensitivity of 0.84 (0.82–0.87) and a specificity of 0.79 (0.75–0.82) for DWI of the breast.[27]

Due to increasing interest in breast MRI as a screening method, Kuhl et al[28] suggested using abbreviated breast MRI, which consists of a first postcontrast subtracted image and a maximum-intensity projection, as a novel approach to breast cancer screening. This protocol needs just 3 min for imaging acquisition and shows good diagnostic accuracy. However, because of various drawbacks related to DCE-MRI, including the use of a contrast agent, several studies have evaluated the diagnostic performance of unenhanced MRI including DWI.[13,16,17] Trimboli et al[17] evaluated the diagnostic performance of unenhanced MRI in detecting breast cancer. In their study, DWI played a crucial role in cancer detection, increasing the sensitivity from 59–62% to 70–76% when adding DWI to T1-weighted imaging. According to Baltzer et al,[13] the sensitivity of unenhanced MRI was 86% to 93% while that of contrast-enhanced MRI was 96.5% to 98.3%; the respective specificities were 85.2% and 92.6%. Partridge et al showed 89% of mammographically and clinically occult malignancies were hyperintense on b=600 s/mm^2 DWI. However, this feature was not restricted to malignancies, with 81% of benign lesions

Table 1

Patients' characteristics.

	Number of patients (%)
Diffusion detectability (n = 167)	
1	20 (12.0%)
2	19 (11.4%)
3	24 (14.4%)
4	40 (24.0%)
5	64 (38.3%)
Diffusion background (n = 167)	
1	61 (36.5%)
2	46 (37.5%)
3	31 (18.6%)
4	29 (17.4%)
BPE (n = 167)	
1	86 (51.5%)
2	42 (25.2%)
3	17 (10.2%)
4	22 (13.2%)
Subtraction detectability (n = 167)	
1	4 (2.4%)
2	8 (4.8%)
3	23 (13.8%)
4	42 (25.2%)
5	90 (53.9%)
Mammographic density (n = 167)	
1	4 (2.4%)
2	47 (28.1%)
3	86 (51.5%)
4	30 (18.0%)
Molecular subtype (n = 167)	
Luminal A	116 (69.5%)
Luminal B	20 (12.0%)
HER2-enriched	11 (6.6%)
Triple-negative	20 (12.0%)
Menopausal status (n = 167)	
Premenopausal	78 (46.7%)
Postmenopausal	89 (53.3%)
Menstrual cycle (n = 78)	
1	24 (30.8%)
2	17 (21.8%)
3	18 (23.1%)
4	19 (24.4%)
Histologic grade (n = 167)	
1	44 (26.4%)
2	72 (43.1%)
3	51 (30.5%)
Lymphovascular invasion (n = 167)	
Absent	110 (65.9%)
Present	57 (34.1%)
EIC (n = 167)	
Absent	128 (76.7%)
Present	39 (23.4%)

BPE = background parenchymal enhancement, EIC = extensive intraductal component, HER2 = human epidermal growth factor receptor type 2.

Table 2

Univariate linear regression analysis for factors affecting the diffusion detectability.

	β	Standard error	P value
ADC ($\times 10^{-3}$ mm^2/s)	−0.917	0.551	0.098
Size	0.038	0.011	0.001
Menopausal status			
Postmenopausal	Reference	0.217	0.433
Premenopausal	0.171	0.217	
Lymphovascular invasion			
Absent	Reference		0.004
Present	0.660	0.223	
EIC			
Absent	Reference		0.217
Present	−0.316	0.2550	
Diffusion background			
1	Reference		<0.0001
2	−0.426	0.243	
3	−1.231	0.275	
4	−1.709	0.281	
Mammographic density			
1	1.6	0.739	0.191
2	0.238	0.325	
3	0.286	0.295	
4	Reference		
BPE			
1	0.394	0.333	0.322
2	−0.026	0.367	
3	0.016	0.450	
4	Reference		
Subtraction detectability			
1	−0.739	0.678	0.000
2	−1.489	0.489	
3	−1.206	0.310	
4	−0.322	0.248	
5	Reference		
Histologic grade			
1	Reference		<0.0001
2	1.098	0.251	
3	1.182	0.270	
Menstrual cycle			
1	Reference		0.242
2	−0.461		
3	−0.3611		
4	−0.746		
Molecular subtype			
Luminal A	0.245	0.337	0.281
Luminal B	0.700	0.441	
HER2-enriched	0.741	0.523	
Triple-negative	Reference		

ADC = apparent diffusion coefficient, BPE = background parenchymal enhancement, EIC = extensive intraductal component, HER2 = human epidermal growth factor receptor type 2.

also demonstrating hyperintensity.[29] In another study by Partridge et al,[30] they concluded that, when looking into the differentiation of breast masses, there is 10% improvement in the positive predictive value when combining DWI with DCE-MRI. Several reports have also demonstrated that ADC values of DWI allowed for the differentiation between malignant and benign breast lesions by demonstrating significant differences, with malignancy yielding a low ADC value and benignity yielding a high value.[20,31–33] According to these results, they suggested that many mammographically and clinically occult breast cancers

can be detected on DWI, and benign and malignant lesions can be separated by using an ADC threshold.

Based on these prior studies, we designed this study to evaluate the factors affecting the degree of lesion detectability on DWI. In our study, detectability was not influenced by molecular subtype, menopausal status, menstrual cycle, mammographic density, BPE, or lesion size. In general, our results agreed with existing published studies. Youk et al[25] reported ADC values changed according to molecular subtype but detectability scores did not. In terms of BPE, Iacconi et al found that the visibility of breast lesions on DWI was not influenced by the amount of breast tissue and BPE,[34] although the amount of breast tissue affected the

Table 3

Multivariate linear regression analysis for factors affecting diffusion detectability.

	β	Standard error	P value
Diffusion background			
1	Reference		<0.0001
2	−0.309	0.223	
3	−1.038	0.258	
4	−1.667	0.262	
Histologic grade			
1	Reference		<0.0001
2	0.995	0.224	
3	1.139	0.241	

Table 4

Univariate linear regression analysis for factors affecting diffusion background signal.

	β	Standard error	P value
Age	−0.041	0.008	<0.0001
Size	0.010	0.009	0.293
Menopausal status			
Premenopausal	0.696	0.163	<0.0001
Postmenopausal	Reference		
Lymphovascular invasion			
Absent	Reference		0.344
Present	0.172	0.181	
EIC			
Absent	Reference		0.368
Present	0.183	0.203	
Menstrual cycle			
1	Reference		0.153
2	−0.157	0.351	
3	0.556	0.345	
4	0.456	0.340	
Histologic grade			
1	Reference		0.607
2	−0.212	0.212	
3	−0.119	0.228	
BPE			
1	−1.395	0.220	<0.0001
2	−0.528	0.242	
3	0.235	0.297	
4	Reference		
Mammographic density			
1	−1.533	0.568	<0.0001
2	−0.746	0.249	
3	−0.231	0.226	
4	Reference		
Molecular subtype			
Luminal A	0.231	0.269	0.712
Luminal B	0.400	0.352	
HER2-enriched	0.141	0.418	
Triple-negative	Reference		
Subtraction detectability			
1	0.739	0.565	0.347
2	0.364	0.408	
3	0.293	0.258	
4	0.322	0.206	
5	Reference		

BPE = background parenchymal enhancement, EIC = extensive intraductal component, HER2 = human epidermal growth factor receptor type 2.

Table 5

Multivariate linear regression analysis for factors affecting diffusion background signal.

	β	Standard error	P value
Lymphovascular invasion			
Absent	Reference		0.290
Present	0.160	0.150	
BPE			
1	−1.256	0.226	<0.0001
2	−0.480	0.242	
3	0.312	0.296	
4	Reference		

BPE = background parenchymal enhancement.

quantitative measurement of ADC. Several studies researched the effect of the menstrual cycle or menopausal status on DWI. Most of them found that quantitative measurement of DWI in normal premenopausal breast was different according to the menstrual cycle phase; however, there was no statistical significance.[34–36] These findings supported the impression of insignificance to DWI of menopausal status, menstrual cycle, and BPE, which is usually supposed regarding menstrual cycle timing in young women[24,37] and is known to be a weakness of DCE-MRI. Further, mammographic density did not make a significant difference on DWI. Interestingly, although detectability scores on DWI were worse than those on contrast-enhanced T1-weighted subtraction images in the present study and in previous studies,[13] 104 (62.3%) of 167 lesions were scored as a 4 or 5. Therefore, our results suggest that DWI could be a potential breast cancer detection method, without using contrast material, which gives consistent results regardless of menstrual cycle, menopausal status, or mammographically dense breasts. However, at this point, additional technical advances or adjunctive imaging modality, such as mammography, are still needed to reduce the amount of false positive and false negative results due to the low spatial resolution of DWI. Recently, Bickelhaupt et al reported that DWI with background suppression and unenhanced morphological sequences may be useful as a fast and noninvasive approach to assess the likelihood of malignancy for suspicious lesions detected on screening X-ray mammograms and to reduce the number of unnecessary biopsies.[38]

Diffusion background signal is a concept that corresponds to mammographic density or BPE on MRI. We proposed this concept because we realized that increased diffusion background signal diminished the detectability score. The diffusion background signal was independently associated with diffusion detectability on both univariate and multivariate analyses ($P <$ 0.0001). Unlike diffusion detectability, BPE was the most important factor affecting the diffusion background signal on multivariate analysis ($P < 0.0001$).

Our results about the diffusion background signal are quite similar to those found for ^{99m}Tc-methoxyisobutylisonitrile (MIBI) on breast-specific gamma imaging (BSGI). A recent study by Yoon et al showed that high background MIBI uptake on BSGI was significantly correlated with a younger age ($P < 0.001$), premenopausal status ($P = 0.003$), dense breast ($P < 0.001$), and marked BPE ($P < 0.001$). However, on multivariate analysis, only BPE remained a significant factor affecting background MIBI uptake ($P < 0.001$).[39] In our univariate analysis, younger age ($P < 0.0001$), premenopausal status ($P < 0.0001$), dense breast ($P < 0.0001$), and high BPE ($P < 0.0001$) were correlated with an increased diffusion background signal. On multivariate analysis,

only BPE was significantly correlated with the diffusion background signal ($P < 0.0001$). The actual mechanism whereby BPE affects diffusion background signals is unclear. We suspect that hormonal changes could be involved in this process.

Our results are supportive of the idea that DWI may have potential as an alternative noncontrast MRI technique. However, breast DWI is still a challenging technique because of its intrinsic low spatial resolution. Scanning at higher field strength may enable a DWI acquisition with thinner slices that can better demonstrate small or diffuse lesions.[40–42] Using more advanced DWI sequences, such as the readout-segmented echo planar imaging, improves the signal to noise ratio of DWI.[41] Optimization of acquisition parameters and technical developments, such as advanced breast coil hardware with 16 and 32 channels,[43] could improve contrast and spatial resolution, allowing for a higher diagnostic performance of DWI. However, because contrast-enhanced MRI can give many critical pieces of information, such as the kinetic pattern or local staging of the tumor, it could not be entirely replaced in most cases.

There were several limitations to this study. First, all lesions included in this study were biopsy-confirmed malignancies. Also, we often referenced contrast-enhanced MR images to find a target lesion. Thus, we could not evaluate the actual diagnostic performance of DWI. However, the goal of our study was not to investigate the actual diagnostic performance of DWI but to find the factors affecting the degree of detectability. Second, we restricted the included lesions with strict criteria to evaluate DWI under homogenous condition. Therefore, our results might be less robust to generalization to all lesions or all machines. Third, we did not calculate intra- or inter-observer variability for diffusion detectability or diffusion background signal score. Fourth, we did not include information about hormone-related therapy, which might affect mammographic breast density and BPE on MRI. Because this study was retrospective in nature, the available medical records about hormonal replacement therapy were not reliable. Finally, DWI detectability was evaluated using 5-point scale by 2 reviewers in consensus. Although earlier studies have also analyzed data by using this 5-point scale system, this method of data evaluation could still be subjectively biased.[25,36]

In conclusion, diffusion detectability was not influenced by BPE, mammographic density, menopausal status, or menstrual cycle. The diffusion background signal affected the detectability on DWI. BPE on MRI was the most important factor affecting the diffusion background signal on DWI.

References

[1] Kuhl C. The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. Radiology 2007;244:356–78.
[2] Kuhl CK. Current status of breast MR imaging. Part 2. Clin Appl Radiol 2007;244:672–91.
[3] Schnall MD. Breast MR imaging. Radiol Clin North Am 2003;41:43–50.
[4] Morris EA. Breast cancer imaging with MRI. Radiol Clin North Am 2002;40:443–66.
[5] Chang YC, Huang CS, Liu YJ, et al. Angiogenic response of locally advanced breast cancer to neoadjuvant chemotherapy evaluated with parametric histogram from dynamic contrast-enhanced MRI. Phys Med Biol 2004;49:3593–602.
[6] Sinha S, Sinha U. Recent advances in breast MRI and MRS. NMR Biomed 2009;22:3–16.
[7] Peters NH, Rinkes IHB, Zuithoff NP, et al. Meta-analysis of MR imaging in the diagnosis of breast lesions. Radiology 2008;246:116–24.
[8] Sardanelli F, Podo F, Santoro F, et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk Italian 1 study): final results. Invest Radiol 2011;46:94–105.
[9] Kuhl CK, Schrading S, Weigel S, et al. The "EVA" trial: evaluation of the efficacy of diagnostic methods (mammography, ultrasound, MRI) in the secondary and tertiary prevention of familial breast cancer. Preliminary results after the first half of the study period. Rofo 2005;177:818–27.
[10] Leach MO, Boggis CR, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). Lancet 2005;365:1769–78.
[11] Pinker K, Bogner W, Baltzer P, et al. Improved diagnostic accuracy with multiparametric magnetic resonance imaging of the breast using dynamic contrast-enhanced magnetic resonance imaging, diffusion-weighted imaging, and 3-dimensional proton magnetic resonance spectroscopic imaging. Invest Radiol 2014;49:421–30.
[12] McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. Radiology 2015;275:772–82.
[13] Baltzer PA, Benndorf M, Dietzel M, et al. Sensitivity and specificity of unenhanced MR mammography (DWI combined with T2-weighted TSE imaging, ueMRM) for the differentiation of mass lesions. Eur Radiol 2010;20:1101–10.
[14] Pinker K, Stadlbauer A, Bogner W, et al. Molecular imaging of cancer: MR spectroscopy and beyond. Eur J Radiol 2012;81:566–77.
[15] Schnall MD, Blume J, Bluemke DA, et al. Diagnostic architectural and dynamic features at breast MR imaging: multicenter study. Radiology 2006;238:42–53.
[16] Yabuuchi H, Matsuo Y, Sunami S, et al. Detection of non-palpable breast cancer in asymptomatic women by using unenhanced diffusion-weighted and T2-weighted MR imaging: comparison with mammography and dynamic contrast-enhanced MR imaging. Eur Radiol 2011;21:11–7.
[17] Trimboli RM, Verardi N, Cartia F, et al. Breast cancer detection using double reading of unenhanced MRI including T1-weighted, T2-weighted STIR, and diffusion-weighted imaging: a proof of concept study. AJR Am J Roentgenol 2014;203:674–81.
[18] Marini C, Iacconi C, Giannelli M, et al. Quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesion. Eur Radiol 2007;17:2646–55.
[19] Sinha S, Lucas-Quesada FA, Sinha U, et al. In vivo diffusion-weighted MRI of the breast: potential for lesion characterization. J Magn Reson Imaging 2002;15:693–704.
[20] Woodhams R, Matsunaga K, Kan S, et al. ADC mapping of benign and malignant breast tumors. Magn Reson Med Sci 2005;4:35–42.
[21] Woodhams R, Matsunaga K, Iwabuchi K, et al. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. J Comput Assist Tomogr 2005;29:644–9.
[22] Thomassin-Naggara I, De Bazelaire C, Chopier J, et al. Diffusion-weighted MR imaging of the breast: advantages and pitfalls. Eur J Radiol 2013;82:435–43.
[23] Padhani AR, Liu G, Koh DM, et al. Diffusion-weighted magnetic resonance imaging as a cancer biomarker: consensus and recommendations. Neoplasia 2009;11:102–25.
[24] Hambly NM, Liberman L, Dershaw DD, et al. Background parenchymal enhancement on baseline screening breast MRI: impact on biopsy rate and short-interval follow-up. AJR Am J Roentgenol 2011;196:218–24.
[25] Youk JH, Son EJ, Chung J, et al. Triple-negative invasive breast cancer on dynamic contrast-enhanced and diffusion-weighted MR imaging: comparison with other breast cancer subtypes. Eur Radiol 2012;22:1724–34.
[26] Ko ES, Han BK, Kim RB, et al. Apparent diffusion coefficient in estrogen receptor-positive invasive ductal breast carcinoma: correlations with tumor-stroma ratio. Radiology 2014;271:30–7.
[27] Chen X, Li WL, Zhang YL, et al. Meta-analysis of quantitative diffusion-weighted MR imaging in the differential diagnosis of breast lesions. BMC Cancer 2010;10:693.
[28] Kuhl CK, Schrading S, Strobel K, et al. Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection-a novel approach to breast cancer screening with MRI. J Clin Oncol 2014;32:2304–10.
[29] Partridge SC, Demartini WB, Kurland BF, et al. Differential diagnosis of mammographically and clinically occult breast lesions on diffusion-weighted MRI. J Magn Reson Imaging 2010;31:562–70.
[30] Partridge SC, DeMartini WB, Kurland BF, et al. Quantitative diffusion-weighted imaging as an adjunct to conventional breast MRI for improved positive predictive value. AJR Am J Roentgenol 2009;193:1716–22.
[31] Hatakenaka M, Soeda H, Yabuuchi H, et al. Apparent diffusion coefficients of breast tumors: clinical application. Magn Reson Med Sci 2008;7:23–9.

[32] Yoshikawa MI, Ohsumi S, Sugata S, et al. Comparison of breast cancer detection by diffusion-weighted magnetic resonance imaging and mammography. Radiat Med 2007;25:218–23.

[33] Kuroki Y, Nasu K, Kuroki S, et al. Diffusion-weighted imaging of breast cancer with the sensitivity encoding technique: analysis of the apparent diffusion coefficient value. Magn Reson Med Sci 2004;3: 79–85.

[34] Iacconi C, Thakur SB, Dershaw DD, et al. Impact of fibroglandular tissue and background parenchymal enhancement on diffusion weighted imaging of breast lesions. Eur J Radiol 2014;83:2137–43.

[35] Englander SA, Ulug AM, Brem R, et al. Diffusion imaging of human breast. NMR Biomed 1997;10:348–52.

[36] Shin S, Ko ES, Kim RB, et al. Effect of menstrual cycle and menopausal status on apparent diffusion coefficient values and detectability of invasive ductal carcinoma on diffusion-weighted MRI. Breast Cancer Res Treat 2015;149:751–9.

[37] Kuhl CK, Bieling HB, Gieseke J, et al. Healthy premenopausal breast parenchyma in dynamic contrast-enhanced MR imaging of the breast: normal contrast medium enhancement and cyclical-phase dependency. Radiology 1997;203:137–44.

[38] Bickelhaupt S, Laun FB, Tesdorff J, et al. Fast and noninvasive characterization of suspicious lesions detected at breast cancer X-ray screening: capability of diffusion-weighted MR imaging with MIPs. Radiology 2016;278:689–97.

[39] Yoon HJ, Kim Y, Lee JE, et al. Background 99mTc-methoxyisobutyl-lisonitrile uptake of breast-specific gamma imaging in relation to background parenchymal enhancement in magnetic resonance imaging. Eur Radiol 2015;25:32–40.

[40] Matsuoka A, Minato M, Harada M, et al. Comparison of 3.0-and 1.5-tesla diffusion-weighted imaging in the visibility of breast cancer. Radiat Med 2008;26:15–20.

[41] Bogner W, Pinker K, Zaric O, et al. Bilateral diffusion-weighted MR imaging of breast tumors with submillimeter resolution using readout-segmented echo-planar imaging at 7 T. Radiology 2015;274:74–84.

[42] Rahbar H, Partridge SC, DeMartini WB, et al. Clinical and technical considerations for high quality breast MRI at 3 Tesla. J Magn Reson Imaging 2013;37:778–90.

[43] Reiss-Zimmermann M, Gutberlet M, Kostler H, et al. Improvement of SNR and acquisition acceleration using a 32-channel head coil compared to a 12-channel head coil at 3T. Acta Radiol 2013;54:702–8.