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# Detection of Contralateral Breast Cancer Using Diffusion-Weighted Magnetic Resonance Imaging in Women with Newly Diagnosed Breast Cancer: Comparison with Combined Mammography and Whole-Breast Ultrasound

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**Objective:** To compare the screening performance of diffusion-weighted (DW) MRI and combined mammography and ultrasound (US) in detecting clinically occult contralateral breast cancer in women with newly diagnosed breast cancer.

**Materials and Methods:** Between January 2017 and July 2018, 1148 women (mean age ± standard deviation, 53.2 ± 10.8 years) with unilateral breast cancer and no clinical abnormalities in the contralateral breast underwent 3T MRI, digital mammography, and radiologist-performed whole-breast US. In this retrospective study, three radiologists independently and blindly reviewed all DW MR images (b = 1000 s/mm$^2$ and apparent diffusion coefficient map) of the contralateral breast and assigned a Breast Imaging Reporting and Data System category. For combined mammography and US evaluation, prospectively assessed results were used. Using histopathology or 1-year follow-up as the reference standard, cancer detection rate and the patient percentage with cancers detected among all women recommended for tissue diagnosis (positive predictive value; $PPV_2$) were compared.

**Results:** Of the 30 cases of clinically occult contralateral cancers (13 invasive and 17 ductal carcinoma *in situ* [DCIS]), DW MRI detected 23 (76.7%) cases (11 invasive and 12 DCIS), whereas combined mammography and US detected 12 (40.0%, five invasive and seven DCIS) cases. All cancers detected by combined mammography and US, except two DCIS cases, were detected by DW MRI. The cancer detection rate of DW MRI (2.0%; 95% confidence interval [CI]: 1.3%, 3.0%) was higher than that of combined mammography and US (1.0%; 95% CI: 0.5%, 1.8%; $p$ = 0.009). DW MRI showed higher PPV2 (42.1%; 95% CI: 26.3%, 59.2%) than combined mammography and US (18.5%; 95% CI: 9.9%, 30.0%; $p$ = 0.001).

**Conclusion:** In women with newly diagnosed breast cancer, DW MRI detected significantly more contralateral breast cancers with fewer biopsy recommendations than combined mammography and US.

**Keywords:** *Breast cancer; Diffusion-weighted imaging; Mammography; Screening; Ultrasound; Ultrasonography*

## INTRODUCTION

Women with newly diagnosed breast cancer have a 1.0–4.6% incidence of synchronous contralateral breast cancer [1,2]. During the initial diagnosis of breast cancer, it is important to detect contralateral cancer to avoid the

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second round of cancer therapy. Dynamic contrast enhanced (DCE) MRI can clinically and mammographically detect occult contralateral breast cancer in 1.4–4.1% of women [3-6]. However, the use of preoperative MRI for staging breast cancer, including screening for contralateral breast cancer, is limited not only by high costs but also by high false-positive findings, resulting in more benign biopsies and extensive surgeries [7]. In addition, intravenous (IV) gadolinium-based contrast agent use is contraindicated in pregnancy and women with renal impairment or contrast material allergy [8-10]. Mammography combined with ultrasound (US) can be used to screen for contralateral breast cancer in women who cannot undergo MRI [11,12]. However, US is operator-dependent and time-consuming and has significantly low cancer detection rate and low positive predictive value (PPV) for biopsy recommendation [13-15].

Diffusion-weighted (DW) MRI is a fast, widely available, unenhanced technique that has shown promise for the detection and characterization of breast cancers [16-19]. Due to the restricted or hindered diffusion of water molecules within tissues, breast cancers appear hyperintense on high b-value DW MRI and have lower apparent diffusion coefficient (ADC) values than normal tissue or benign tumors [20]. There is emerging evidence that DW MRI can be part of a multiparametric or non-contrast-enhanced approach for local staging of the affected breast in women with breast cancer [21,22]. In detecting clinically occult breast cancer, the sensitivity of DW MRI is lower than that of DCE MRI, but probably higher than that of mammography or targeted US [23-26]. However, the performance of DW MRI, relative to that of combined mammography and whole-breast US, in the detection of clinically occult breast cancer is unknown [16]. We hypothesized that DW MRI as a stand-alone screening test should be superior to the current state-of-the-art digital mammography plus whole-breast US in detecting clinically occult contralateral cancer in women with breast cancer.

Thus, the purpose of our study was to compare the screening performance of DW MRI at 3T and combined mammography and US in detecting clinically occult contralateral breast cancer in women with newly diagnosed breast cancer.

## MATERIALS AND METHODS

### Study Population

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital, and the requirement for written informed consent was waived (IRB No. H-1906-128-1042).

A retrospective review of the Radiology Department database identified 1931 consecutive women with breast cancer who underwent preoperative breast MRI and radiologist-performed US for local staging between January 2017 and July 2018. During the study period, DW MRI was performed within 2 weeks before surgery as part of the standard clinical breast MRI protocol. The inclusion criteria were women with newly diagnosed unilateral breast cancer and no abnormalities revealed by clinical examination of the contralateral breast. The exclusion criteria were as follows: women who were treated with neoadjuvant chemotherapy before surgery (n = 654), had signs or symptoms of breast disease in the contralateral breast (n = 44), had no available mammography data (n = 46), poor DW MRI image quality (n = 9), missing pathology data on tumor characteristics (n = 14), or had been followed up for less than one year (n = 16). Finally, 1148 women (mean age ± standard deviation, 53.2 ± 10.8 years; range, 26–84 years) were included (Fig. 1). Of them, 1111 were included in a previous study [26] that evaluated the diagnostic performance of DW MRI relative to DCE MRI for detecting contralateral breast cancers, whereas we compare and report the diagnostic performances of DW MRI and combined mammography and US in this study.

### Image Acquisition

All women were examined using two 3T MRI scanners (Ingenia Cx, Philips Medical Systems; Skyra, Siemens Medical Solutions) with a dedicated 16- or 18-channel breast coil. A standardized breast MRI protocol, including axial acquisition of bilateral DW MRI and T1-weighted DCE MRI, was used as described previously [26]. In brief, high-resolution DW MRI was acquired using a single-shot (SENSE, Philips) or multishot (RESOLVE, Siemens) echo-planar imaging sequence with the following parameters: b-values of 0 and 1000 sec/mm$^2$, repetition time/echo time of 9194/93 and 8880/63 ms, field of view of 300 x 300 mm and 360 x 240 mm, section thickness of 3 mm, image matrix of 160 x 160 and 200 x 132, in-plane resolution of 1.9 x 1.9 mm and 1.8 x 1.8 mm, and scanning duration of 2 minutes 46 seconds and 4 minutes 37 seconds, respectively.

Mammography was performed using one of two digital mammography systems: Lorad Selenia (Hologic) or Senographe Essential (GE Healthcare). One of eight


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Korean Journal of Radiology
KJR

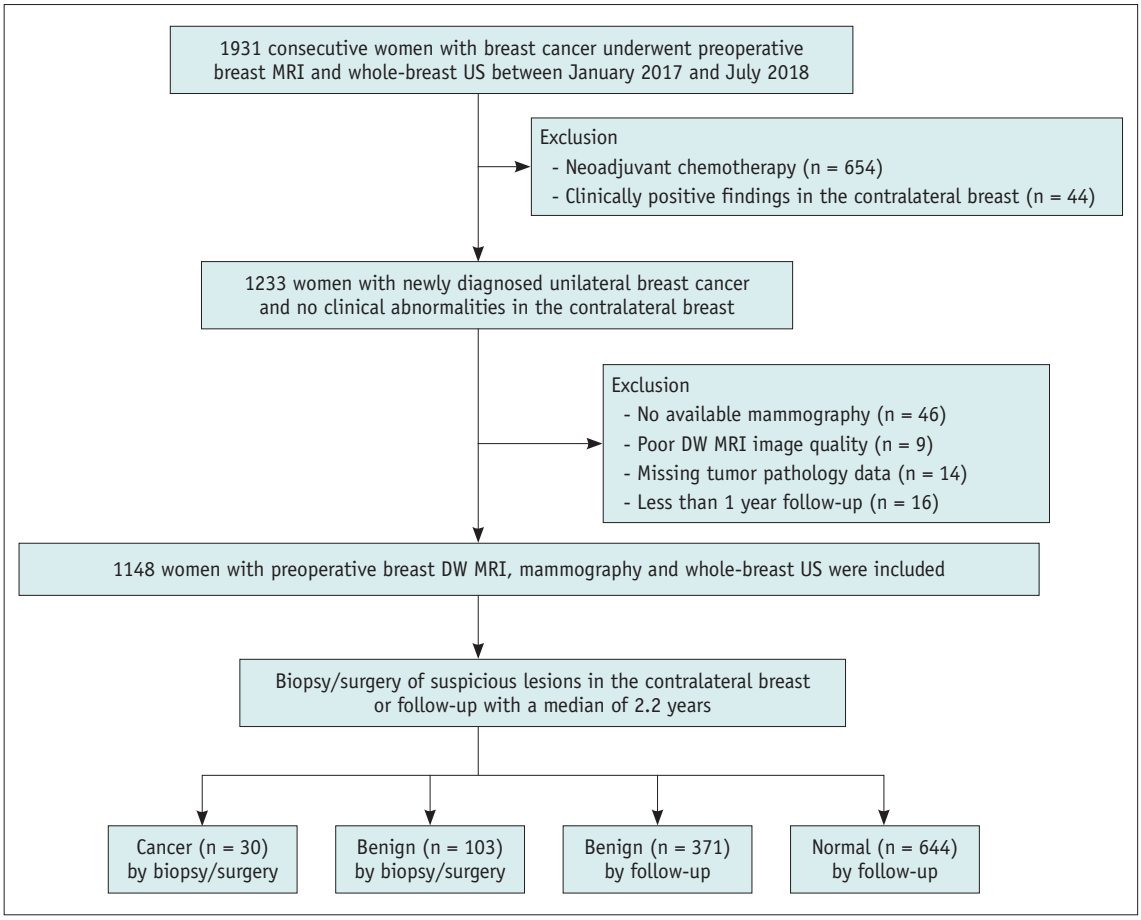


**Fig. 1. Flow chart of the study population and diagnosis of contralateral breast diseases.** DW = diffusion-weighted, US = ultrasound

radiologists with 1–27 years of experience in breast imaging performed bilateral whole-breast US before MRI using one of the following three high-resolution US machines: EUB-8500 (Hitachi Medical Systems America), Aixplorer (SuperSonic Imagine), and iU22 (Philips Medical Systems). Screening whole-breast US of the contralateral breast was the standard of care for all patients diagnosed with breast cancer at our institution, and preoperative US was performed before preoperative MRI acquisition in all but 13 patients. In 13 patients who underwent MRI before preoperative US, the US examination performed at the time of breast cancer diagnosis at the referral hospital was used. Targeted US performed after MRI was not included in this study, and even if a lesion was detected on targeted US after MRI, it was not considered as positive in our analysis.

### Image Interpretation

Three breast radiologists (with 7, 9, and 14 years of experience in breast MRI) independently assessed all DW MRI and unenhanced T1- and T2-weighted images of the contralateral breast in 1148 women. The radiologists were blinded to the DCE MRI, mammographic, or US and histologic findings, except the laterality of the index cancer. Before the reader study, the three readers had a one-month training on the use of the DW MRI interpretation algorithm [26]. First, any unique areas of high signal intensity were identified on DW MRI (b-value of 1000 sec/mm$^2$), and the ADC value was measured in small (6–10 mm$^2$) regions of interest within the darkest part of the lesion's ADC map [27] using PACS software (M-view, INFINITT Healthcare). The radiologist avoided partial volume effects due to the inclusion of normal parenchyma and necrotic tissue by cross-referencing the T2-weighted image. The suspicious DW MRI findings included irregular shape, non-circumscribed margins, rim or heterogeneous internal signal pattern, segmental distribution, and low ADC value ($\leq$ 1.25 x 10$^{-3}$ mm$^2$/sec) [17]. The Breast Imaging Reporting and Data System (BI-RADS) category 1 (negative) or 2 (benign) assessment was used for DW MRI examinations without any hyperintense lesions or hyperintense lesions

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without any suspicious findings, while BI-RADS category 3 (probably benign), 4 (suspicious), and 5 (highly suggestive of malignancy) assessments were used for DW MRI examinations with more than one suspicious finding (Supplementary Fig. 1). In cases of multifocal suspicious lesions in the contralateral breast, the readers recorded the lesions in the most suspicious or high BI-RADS category. A non-blinded breast radiologist who was not involved in the reader study tracked the lesions detected by at least one of the three readers for the correlation of identical lesions on both DW MRI and DCE MRI as well as mammography and US for the final evaluation of identical lesions.

For mammography and combined mammography and US evaluation, prospectively assessed results by attending breast radiologists were used, and the BI-RADS [28] final category was determined after each examination. In our institution, radiologists usually perform whole-breast US while looking at mammograms obtained the same day or earlier, and they report the mammography findings separately as well as the combined assessment of the mammographic and US findings. We avoided the use of BI-RADS category 0 in the mammography reading for the preoperative setting and used BI-RADS final assessment categories 3, 4, or 5.

### Reference Standard and Histopathologic Analysis

We defined the reference standard, which could be cancer or not, based on the results of the image-guided biopsy, surgery, and clinical or imaging follow-up of at least 1 year. Malignancy was defined as invasive cancer or ductal carcinoma *in situ* (DCIS). We recorded the pathologic size and histologic features of benign and malignant lesions. For invasive cancer, lymph node status and histological grade were recorded. The nuclear grade was recorded for the DCIS. The expression levels of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2) were determined for all cancers. Any high-risk lesions diagnosed were confirmed by the final surgical pathology.

### Statistical Analysis

The categorical data, such as age, menopausal status, family history of breast cancer, and mammographic breast density, of women with and without contralateral cancer were compared using the $\chi^2$ test or Fisher's exact test. To compute the performance of mammography, combined mammography and US, and DW MRI, the BI-RADS categories were dichotomized as follows: negative (including BI-RADS categories 1 and 2) or positive (including BI-RADS categories 3, 4, and 5). The results of the combined mammography and US were considered positive when the lesion was positive on either mammography or US. We defined the DW MRI examination as positive when two or more radiologists considered the lesion to be BI-RADS category 3 or higher. For subgroup analysis, the cancer detection rates of each imaging modality according to the characteristics of the women and the contralateral breast cancers were compared. The cancer detection rate, sensitivity, specificity, abnormal interpretation rate (AIR), and PPV were determined as simple proportions with an exact 95% confidence interval (CI) (Clopper-Pearson). AIR was defined as the proportion of women classified as BI-RADS category 3, 4, or 5. $PPV_1$ was defined as the percentage of women with detected cancer who had positive imaging results. $PPV_2$ was defined as the percentage of women with cancers detected among all the women recommended for tissue diagnosis. The *p* values for the differences in PPV were calculated using generalized estimating equations, and the *p* values for the other comparisons were determined using McNemar's test. Bonferroni correction was used for multiple comparisons. The inter-reader agreement for the BI-RADS assessment was evaluated using the $\kappa$ statistic. The threshold for statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS (version 14.0, SPSS Inc.).

## RESULTS

### Patient and Tumor Characteristics

After breast cancer surgery (including lumpectomy [n = 19, 63.3%] and mastectomy [n = 11, 36.7%]) and follow-up with a median of 2.2 years (interquartile range, 1.9–2.7 years; 818 [71.2%] with over 2-year follow-up), 30 (2.6% [30/1148]) breast cancers in 30 women (mean age ± standard deviation, 53.2 ± 9.9 years; range, 31-77 years) and 474 benign lesions in 474 women were found in the contralateral breast (Fig. 1). Of the 30 contralateral breast cancers, 20 were diagnosed preoperatively using US-guided biopsy (n = 19) or MRI-guided biopsy (n = 1), and 10 were diagnosed using US-guided (n = 7) or mammography-guided (n = 3) localization and surgery. All 30 contralateral breast cancers were visible on preoperative DCE MRI. The contralateral breast cancers included invasive ductal carcinoma in 43.3% (13/30) with a median size of 1.0 cm


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Korean Journal of Radiology
KJR

(interquartile range, 0.3–2.0 cm; mean, 1.3 cm) and DCIS in 56.7% (17/30) with a median size of 2.4 cm (interquartile range, 1.1–3.7 cm; mean, 2.5 cm). None of the cancers was associated with lymph node metastasis. The characteristics of the women with 30 contralateral breast cancers are summarized in Tables 1 and 2.

### Detection of Contralateral Cancers by DW MRI vs. Combined Mammography and US

Of the 30 contralateral breast cancers, DW MRI detected 23 (76.7%) (11 invasive and 12 DCIS), whereas mammography combined with US detected 12 (40.0%) (five invasive and seven DCIS) ($p$ = 0.009) (Fig. 2). Of the 23 contralateral breast cancers detected by DW MRI, 10 (33.3%, five invasive and five DCIS) were also detected by combined mammography and US, while 13 (43.3%, six invasive and seven DCIS) were missed by combined mammography and US (Figs. 3, 4). All invasive cancers detected by combined mammography and US were also detected using DW MRI. Two cancers (6.6%) manifesting as calcifications detected by combined mammography and US but missed by DW MRI were both DCIS (one low grade, pathologic size, 1.2 cm) and one intermediate grade (pathologic size, 6.6 cm) (Fig. 5). Five cancers (16.6%) missed by all imaging modalities were invasive ductal carcinomas (pathologic size, 0.1 cm and 0.4 cm) and three DCIS (pathologic size, 1.0, 2.0, and 2.5 cm) (Table 2). Of the seven cancers missed by DW MRI during the reader study, four cancers were not visible in retrospect, and three cancers were visible but misclassified as benign. Among the cancers missed on DW MRI, two low-grade and intermediate invasive cancers measured as less than 0.5 cm in size on DCE MRI were missed by all readers; they were assessed as BI-RADS category 1, negative. Another 2.0 cm papillary DCIS with cystic change on pathological evaluation, rim enhancement on DCE MRI, and a corresponding high ADC value was misclassified and assessed as BI-RADS category 2, benign. The BI-RADS categories of the contralateral breast based on mammography, combined mammography and US, and DW MRI for the 1148 women are summarized in Supplementary Table 1, and 30 benign lesions classified as probably benign (n = 16) or suspicious (n = 14) by DW MRI are summarized in Supplementary Table 2.

### Detection of Contralateral Cancers according to Patient and Tumor Characteristics

DW MRI (90.9% [10/11]) detected more contralateral

**Table 1. Characteristics of the Women with 30 Contralateral Cancers**

| Variables | n (%) |
|---|---|
| Age, years | |
| < 50 | 11 (36.7) |
| ≥ 50 | 19 (63.3) |
| Menopausal status | |
| Premenopausal | 13 (43.3) |
| Postmenopausal | 17 (56.7) |
| Family history of breast cancer | |
| No | 28 (93.3) |
| Yes | 2 (6.7) |
| Mammographic breast density | |
| Fatty or scattered fibroglandular | 3 (10.0) |
| Heterogeneously or extremely dense | 27 (90.0) |
| Histologic type | |
| Invasive | 13 (43.3) |
| DCIS | 17 (56.7) |
| Tumor size, median [IQR], cm | |
| All | 1.7 [1.0–2.5] |
| Invasive | 1.0 [0.3–2.0] |
| DCIS | 2.4 [1.1–3.7] |
| Tumor stage (pT) | |
| pTis | 17 (56.7) |
| pT1 | 11 (36.7) |
| MIC and 1a (≤ 0.5 cm) | 4 (13.3) |
| 1b (> 0.5–1.0 cm) | 3 (10.0) |
| 1c (> 1.0–2.0 cm) | 4 (13.3) |
| pT2 | 2 (6.7) |
| Lymph node metastasis | |
| No | 30 (100.0) |
| Yes | 0 (0) |
| Invasive cancer, histologic grade | |
| Low | 4 (30.8) |
| Intermediate | 9 (69.2) |
| High | 0 (0) |
| DCIS, nuclear grade | |
| Low | 6 (35.3) |
| Intermediate | 8 (47.1) |
| High | 3 (17.6) |
| Receptor status | |
| ER+ and/or PR+/HER2- | 26 (86.7) |
| ER+ and/or PR+/HER2+ | 2 (6.7) |
| ER-/PR-/HER2+ | 1 (3.3) |
| ER-/PR-/HER2- | 1 (3.3) |
| Surgery | |
| Breast conservation | 19 (63.3) |
| Mastectomy | 11 (36.7) |

Unless otherwise indicated, data are numbers of patients and data in parenthesis are percentages. DCIS = ductal carcinoma *in situ*, ER = estrogen receptor, HER2 = human epidermal growth factor receptor type 2, IQR = interquartile range, MIC = microinvasive, PR = progesterone receptor


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**Table 2. Clinical, Pathologic and Imaging Characteristics of 30 Cancers Detected in the Contralateral Breast**

| Patient No. | Age (Year) | Mammographic Breast Density | Tumor Size on Pathology (cm) | Cancer Type | Tumor Grade | ER/PR/HER2 Receptor Status | Lymph Node Status | MG BI-RADS | MG + US BI-RADS | DW MRI BI-RADS | DCE Finding |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 52 | D | 0.1 | IDC | II | -/-/+ | Negative | 1 | 1 | 1* | Nonmass |
| 2 | 56 | D | 0.4 | IDC | I | +/+/- | Negative | 1 | 1 | 1* | Mass |
| 3 | 44 | C | 0.2 | IDC | II | +/+/- | Negative | 1 | 1 | 3 | Mass |
| 4 | 58 | C | 1.1 | IDC | II | +/+/- | Negative | 1 | 4 | 4 | Mass |
| 5 | 45 | C | 0.7 | IDC | I | +/+/- | Negative | 1 | 1 | 4 | Mass |
| 6 | 60 | B | 1.0 | IDC | II | +/-/- | Negative | 4 | 4 | 4 | Mass |
| 7 | 49 | C | 1.0 | IDC | I | +/-/- | Negative | 1 | 2 | 3 | Mass |
| 8 | 64 | B | 0.2 | IDC | I | +/+/- | Negative | 2 | 2 | 4 | Mass |
| 9 | 56 | C | 2.0 | IDC | II | +/-/- | Negative | 5 | 5 | 4 | Mass |
| 10 | 59 | C | 2.2 | IDC | II | +/-/- | Negative | 4 | 4 | 4 | Mass |
| 11 | 64 | C | 4.5 | IDC | II | +/+/+ | Negative | 5 | 5 | 4 | Mass |
| 12 | 49 | C | 2.0 | IDC | II | +/+/- | Negative | 1 | 2 | 3 | Mass |
| 13 | 64 | D | 1.4 | IDC | II | +/+/- | Negative | 1 | 2 | 4 | Mass |
| 14 | 77 | C | 1.0 | DCIS | 3 | +/+/- | Negative | 1 | 1 | 2* | Nonmass |
| 15 | 42 | C | 2.0 | DCIS | 2 | +/+/- | Negative | 1 | 2 | 2* | Mass |
| 16 | 52 | C | 2.5 | DCIS | 3 | -/-/- | Negative | 1 | 1 | 1* | Nonmass |
| 17 | 50 | C | 6.6 | DCIS | 2 | +/+/- | Negative | 4 | 4 | 1† | Nonmass |
| 18 | 51 | C | 1.2 | DCIS | 1 | +/+/- | Negative | 4 | 4 | 2† | Mass |
| 19 | 65 | C | 2.5 | DCIS | 1 | +/+/- | Negative | 1 | 2 | 3 | Nonmass |
| 20 | 36 | D | 2.4 | DCIS | 2 | +/-/- | Negative | 1 | 1 | 4 | Mass |
| 21 | 42 | D | 3.0 | DCIS | 2 | +/+/- | Negative | 1 | 1 | 4 | Nonmass |
| 22 | 62 | C | 1.0 | DCIS | 2 | +/+/- | Negative | 4 | 4 | 4 | Mass |
| 23 | 48 | D | 2.5 | DCIS | 3 | +/-/+ | Negative | 4 | 4 | 4 | Nonmass |
| 24 | 57 | D | 4.5 | DCIS | 1 | +/+/- | Negative | 1 | 2 | 3 | Nonmass |
| 25 | 62 | C | 2.0 | DCIS | 1 | +/+/- | Negative | 1 | 1 | 4 | Mass |
| 26 | 31 | C | 1.2 | DCIS | 1 | +/+/- | Negative | 1 | 1 | 4 | Mass |
| 27 | 46 | B | 4.7 | DCIS | 2 | +/+/- | Negative | 5 | 5 | 3 | Mass |
| 28 | 43 | D | 1.0 | DCIS | 1 | +/+/- | Negative | 1 | 1 | 4 | Mass |
| 29 | 62 | C | 0.2 | DCIS | 2 | +/+/- | Negative | 1 | 4 | 3 | Mass |
| 30 | 52 | C | 5.4 | DCIS | 2 | +/+/- | Negative | 1 | 4 | 4 | Nonmass |

Mammographic density A is fatty, B is scattered fibroglandular, C is heterogeneously dense, and D is extremely dense. Tumor grade I is low, grade II is intermediate, and grade III is high. *False negative cases on both DW MRI and MG + US, †False negative cases on DW MRI only. BI-RADS = Breast Imaging Reporting and Data System, DCE = dynamic contrast enhanced, DCIS = ductal carcinoma *in situ*, DW = diffusion-weighted, ER = estrogen receptor, HER2 = human epidermal growth factor receptor type 2, IDC = invasive ductal carcinoma, MG = mammography, PR = progesterone receptor, US = ultrasound

Korean Journal of Radiology
KJR

breast cancers than combined mammography and US (18.2% [2/11]) ($p$ = 0.009) in women aged < 50 years, whereas there was no difference in the women aged ≥ 50 years (Supplementary Table 3). In women with dense breast tissue, DW MRI (74.1% [20/27]) detected more contralateral breast cancers than combined mammography and US (37.0% [10/27]; $p$ = 0.015), whereas there was no difference in women with non-dense breast tissue. In women with invasive cancer histology or lesions with a pathologic tumor size of > 1 cm, DW MRI (84.6% [11/13], 75.0% [18/24]) detected more contralateral breast cancers than combined mammography and US (38.5% [5/13]; $p$ = 0.028, 41.7% [10/24]; $p$ = 0.041, respectively), whereas there was no difference in women with DCIS histology or lesions with pathologic tumor size ≤ 1 cm.

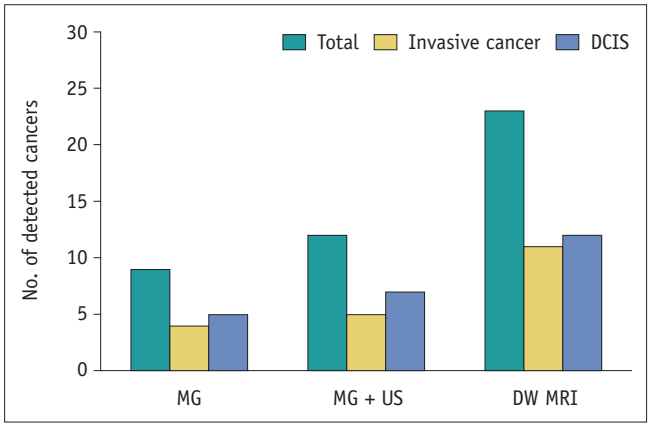


**Fig. 2. The bar graph shows the number of clinically occult contralateral cancers detected by each imaging modality.**
DCIS = ductal carcinoma *in situ*, DW = diffusion-weighted, MG = mammography, US = ultrasound

## Comparison of Performance Metrics

The cancer detection rate of DW MRI (2.0%; 95% CI: 1.3%, 3.0%) was higher than that of combined mammography and US (1.0%; 95% CI: 0.5%, 1.8%) (Table 3). The differences between DW MRI and combined mammography and US were significant ($p$ = 0.009). For invasive cancer only, the cancer detection rates of DW

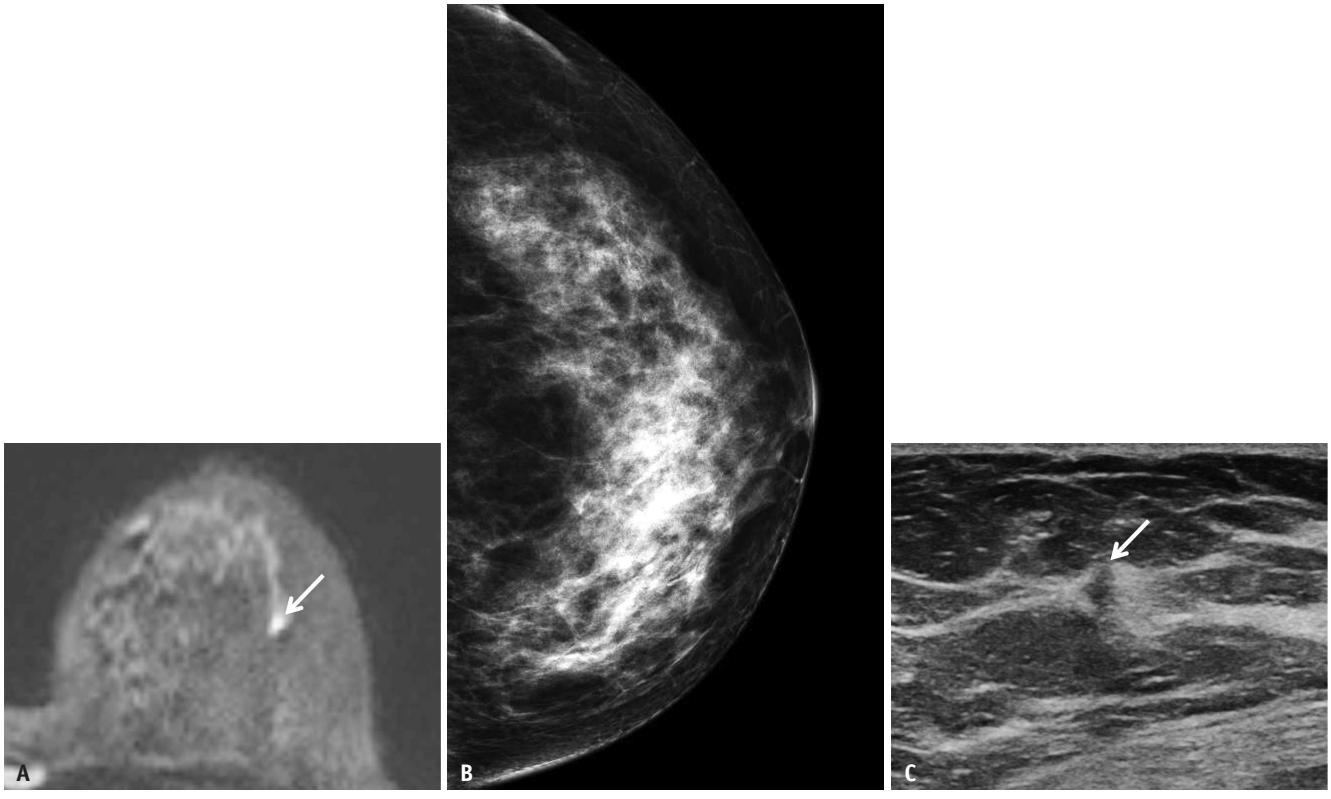


**Fig. 3. Images of a 45-year-old woman with a 0.7-cm invasive ductal carcinoma in the left breast (patient no. 5 in Table 2).**
**A.** Axial image from DW MRI (b = 1000 sec/mm$^2$) showing an irregular mass (arrow) with high signal intensity in the outer breast. The mass showed a low mean apparent diffusion coefficient value (1.06 x 10$^{-3}$ mm$^2$/sec) and was assessed as BI-RADS category 4, suspicious on DW MRI. **B.** Craniocaudal view mammography shows a heterogeneously dense breast with no suspicious findings. The lesion was also negative on US (not shown), and combined mammography and whole-breast US showed that it was BI-RADS category 1, negative. **C.** Targeted US after MRI shows an irregular hypoechoic mass (arrow) with nonparallel orientation in the corresponding area to DW MRI. US-guided biopsy and surgery revealed a low-grade node-negative invasive ductal carcinoma. BI-RADS = Breast Imaging Reporting and Data System, DW = diffusion-weighted, US = ultrasound


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MRI and combined mammography and US were 1.0% (95% CI: 0.5%, 1.7%) and 0.4% (95% CI: 1.4%, 10.1%), respectively, and the differences were statistically significant ($p$ = 0.028). The sensitivity of DW MRI (76.7% [23/30]; 95% CI: 57.8%, 90.1%) was significantly higher than that of combined mammography and US (40.0% [12/30]; 95% CI: 22.7%, 59.4%; $p$ = 0.009), while the specificity of DW MRI (87.4 % [977/1118]; 95% CI: 85.3%, 89.3%) was not different from that of combined mammography and US (88.0% [984/1118]; 95% CI: 86.0%, 89.9%; $p$ > 0.999) (Table 3). The AIR of DW MRI (14.3% [164/1148]; 95% CI: 12.3%, 16.4%) was not significantly

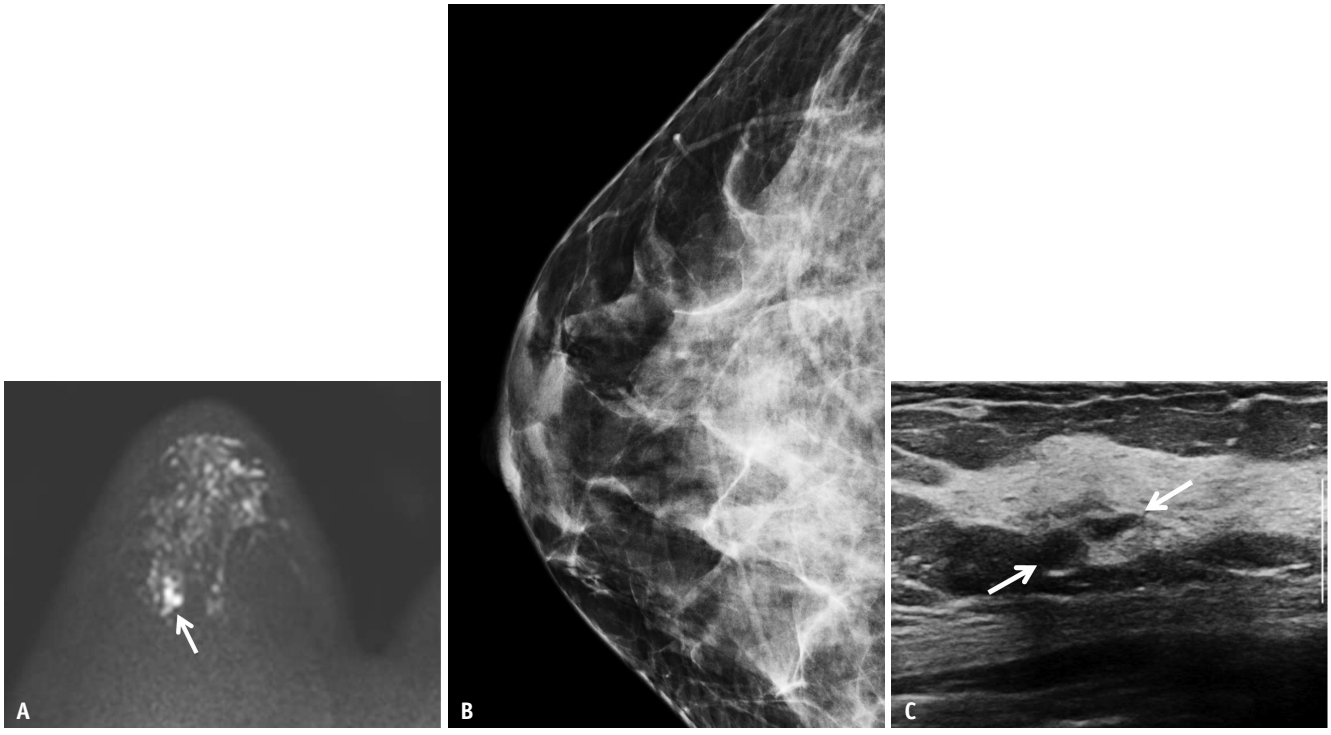


**Fig. 4. Images of a 31-year-old woman with a 1.2-cm ductal carcinoma *in situ* in the right breast (patient no. 26 in Table 2).**
**A.** Axial image from DW MRI (b = 1000 sec/mm$^2$) showing an irregular mass (arrow) with high signal intensity at the glandular-fat junction of the posterior breast. The mass shows a low mean apparent diffusion coefficient value (0.89 x 10$^{-3}$ mm$^2$/sec) and was assessed as BI-RADS category 4, suspicious on DW MRI. **B.** Craniocaudal view mammography shows a heterogeneously dense breast with no suspicious findings. The lesion was also negative on US (not shown), and combined mammography and whole-breast US showed BI-RADS category 1, negative. **C.** Targeted US after MRI shows a subtle indistinct hypoechoic mass (arrows) in the corresponding area on DW MRI. US-guided needle localization and surgery revealed a low-grade ductal carcinoma *in situ*. BI-RADS = Breast Imaging Reporting and Data System, DW = diffusion-weighted, US = ultrasound

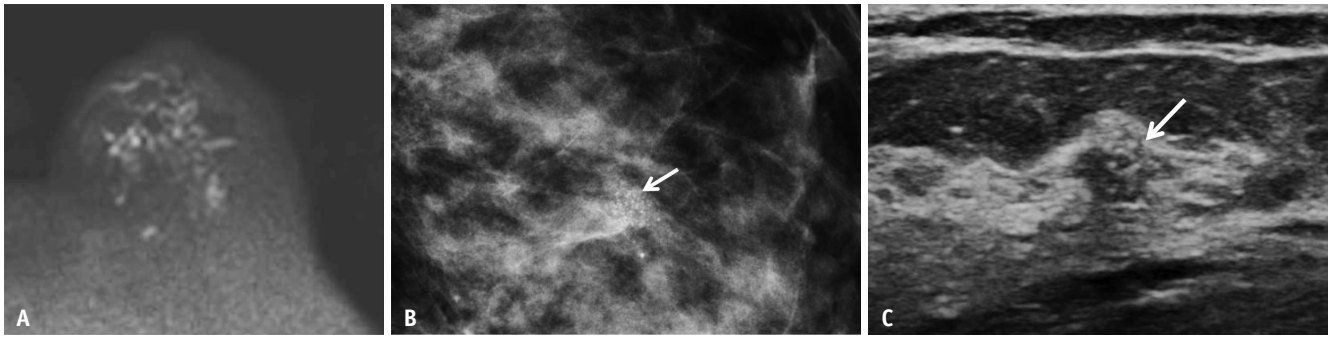


**Fig. 5. Images of a 50-year-old woman with a 6.6-cm ductal carcinoma *in situ* in the left breast (patient no. 17 in Table 2).**
**A.** Axial image from DW MRI (b = 1000 sec/mm$^2$) showed no suspicious focal hyperintensity in the breast, which was assigned a BI-RADS category 1, negative. **B.** Craniocaudal view mammography shows a 1.0-cm group of pleomorphic calcifications (arrow) in the outer breast, which was assessed as BI-RADS category 4, suspicious. **C.** US shows an indistinct hypoechoic mass with calcifications (arrow) in the area corresponding to mammography. The combined mammography and US assessment showed BI-RADS category 4, suspicious. US-guided needle localization and surgery revealed an intermediate-grade ductal carcinoma *in situ*. BI-RADS = Breast Imaging Reporting and Data System, DW = diffusion-weighted, US = ultrasound


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Korean Journal of Radiology
KJR

**Table 3. Performance Metrics of MG, MG + US, and DW MRI in Contralateral Breast Cancer Detection**

| Parameter | MG | MG + US | DW MRI | *P** | *P*† |
|---|---|---|---|---|---|
| Cancer detection rate | 0.8 (0.4, 1.5) [9/1148] | 1.0 (0.5, 1.8) [12/1148] | 2.0 (1.3, 3.0) [23/1148] | 0.002 | 0.009 |
| Invasive cancer detection rate | 0.3 (0.1, 0.9) [4/1148] | 0.4 (1.4, 10.1) [5/1148] | 1.0 (0.5, 1.7) [11/1148] | 0.016 | 0.028 |
| DCIS detection rate | 0.4 (0.1, 1.0) [5/1148] | 0.6 (0.2, 1.3) [7/1148] | 1.0 (0.5, 1.8) [12/1148] | 0.069 | 0.191 |
| Sensitivity | 30.0 (14.7, 49.4) [9/30] | 40.0 (22.7, 59.4) [12/30] | 76.7 (57.8, 90.1) [23/30] | 0.001 | 0.009 |
| Specificity | 97.5 (96.4, 98.3) [1090/1118] | 88.0 (86.0, 89.9) [984/1118] | 87.4 (85.3, 89.3) [977/1118] | < 0.001 | > 0.999 |
| Abnormal interpretation rate‡ | 3.2 (2.3, 4.4) [37/1148] | 12.7 (10.8, 14.8) [146/1148] | 14.3 (12.3, 16.4) [164/1148] | < 0.001 | 0.458 |
| $PPV_1$§ | 24.3 (11.8, 41.2) [9/37] | 8.2 (4.3, 13.9) [12/146] | 14.0 (9.1, 20.3) [23/164] | 0.108 | 0.038 |
| $PPV_2$‖ | 64.3 (35.1, 87.2) [9/14] | 18.5 (9.9, 30.0) [12/65] | 42.1 (26.3, 59.2) [16/38] | 0.216 | 0.001 |

Data are percentages with 95% CI in parentheses. Data in brackets are numbers of patients. *$p$ value between DW MRI vs. MG, †$p$ value between DW MRI vs. MG + US, ‡Abnormal interpretation as classified by Breast Imaging Reporting and Data System category 3, 4 or 5, §$PPV_1$ was defined as the percentage of women with cancers detected among all the women who had positive imaging results, ‖$PPV_2$ was defined as the percentage of women with cancers detected among all the women recommended for tissue diagnosis. CI = confidence interval, DCIS = ductal carcinoma *in situ*, DW = diffusion-weighted, MG = mammography, PPV = positive predictive value, US = ultrasound

higher than that of combined mammography and US (12.7% [146/1148]; 95% CI: 10.8%, 14.8%; $p$ = 0.458). The $PPV_1$ of DW MRI (14.0% [23/164]; 95% CI: 9.1%, 20.3%) was significantly higher than that of combined mammography and US (8.2% [12/146]; 95% CI: 4.3%, 13.9%; $p$ = 0.038). The $PPV_2$ of DW MRI (42.1% [16/38]; 95% CI: 26.3%, 59.2%) was also significantly higher than that of combined mammography and US (18.5% [12/65]; 95% CI: 9.9%, 30.0%; $p$ = 0.001).

The performance metrics of each reader for DW MRI are summarized in Table 4. There was moderate agreement among the three readers on the BI-RADS assessment category for DW MRI ($\kappa$ = 0.57). The performance metrics of US and DW MRI for 1111 women with mammographically negative findings are provided in Supplementary Table 4.

## DISCUSSION

This study compared the screening performance of DW MRI at 3T and combined mammography and US in detecting breast cancer in the asymptomatic contralateral breast of 1148 patients with known malignancy. Our results show that DW MRI detected twice as many cancers and was more sensitive than combined mammography and US without compromising the specificity or $PPV_2$. However, DW MRI has a higher AIR than combined mammography and US. To our knowledge, this is the first study to investigate the performance of DW MRI as a stand-alone screening test for breast cancer detection compared with combined mammography and US. Our findings demonstrate the potential of 3T DW MRI using standardized interpretation as a stand-alone screening tool for breast cancer.

In our study, the prevalence of cancer in the contralateral breast was 2.6% (30/1148), which was higher than the prevalence of the cancer detection rate of 1.7% in the general screening population with breast MRI [29]. However, the sensitivity (76.7%) and specificity (87.4%) of DW MRI obtained in our study were comparable to the reported range of sensitivity (45.0–94.0%; mean, 72.0%) and specificity (79.0–95.0%; mean, 90.0%) when using DW MRI or unenhanced MRI protocols for screening women with various cancer prevalence. The sensitivity (40.0%), specificity (88.0%), and $PPV_2$ (18.5%) of combined mammography and US for the detection of contralateral cancer in our study were also not different from those reported in the literature [3,13,15]. In contrast with our study, one research group [22] investigated the usefulness of DW MRI as a complement to DCE MRI in preoperative breast cancer staging. The results showed that the overall diagnostic accuracy and specificity significantly improved

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**Table 4. Performance of Three Readers with Stand-Alone Diffusion-Weighted MRI in Contralateral Breast Cancer Detection**

| Parameters | Reader 1 | Reader 2 | Reader 3 |
|---|---|---|---|
| Total no. cancer detected | 24 | 22 | 25 |
| Cancer detection rate | 2.1 (1.3, 3.1) [24/1148] | 1.9 (1.2, 2.9) [22/1148] | 2.2 (1.4, 3.2) [25/1148] |
| Invasive cancer detection rate | 1.0 (0.5, 1.7) [11/1148] | 1.0 (0.5, 1.8) [12/1148] | 1.0 (0.5, 1.7) [11/1148] |
| DCIS detection rate | 1.1 (0.6, 1.9) [13/1148] | 0.9 (0.4, 1.6) [10/1148] | 1.2 (0.7, 2.0) [14/1148] |
| Sensitivity | 80.0 (61.4, 92.3) [24/30] | 73.3 (54.1, 87.7) [22/30] | 83.3 (65.3, 94.4) [25/30] |
| Specificity | 87.9 (85.9, 89.8) [983/1118] | 87.7 (85.7, 89.6) [981/1118] | 84.3 (82.0, 86.3) [942/1118] |
| Abnormal interpretation rate* | 13.9 (11.9, 16.0) [159/1148] | 13.9 (11.9, 16.0) [159/1148] | 17.5 (15.4, 19.8) [201/1148] |
| $PPV_1$† | 15.1 (9.9, 21.6) [24/159] | 13.8 (8.9, 20.2) [22/159] | 12.4 (8.2, 17.8) [25/201] |
| $PPV_2$‡ | 28.8 (17.8, 42.1) [17/59] | 39.0 (24.2, 55.5) [16/41] | 36.5 (23.6, 51.0) [19/52] |

Data are percentages with 95% CI in parentheses unless specified otherwise. Data in brackets are numbers of patients. *Abnormal interpretation as classified by Breast Imaging Reporting and Data System category 3, 4 or 5, †$PPV_1$ was defined as the percentage of women with cancers detected among all the women who had positive imaging results, ‡$PPV_2$ was defined as the percentage of women with cancers detected among all the women recommended for tissue diagnosis. CI = confidence interval, DCIS = ductal carcinoma *in situ*, PPV = positive predictive value

and unnecessary benign biopsies were decreased when additional breast lesions detected with DCE MRI were assessed using DW MRI with ADC values [22].

The literature suggests that lesions with sizes less than 1 cm and DCIS manifesting as calcifications may be more difficult to detect on DW MRI [16,23-25,30]. The lower detection rate for smaller cancers (≤ 0.5 cm) in our study was expected, given that our DW MRI axial in-plane spatial resolution (1.9 x 1.9 $mm^2$) and section thickness (3 mm) could result in a partial volume effect for small lesions. DCIS exhibits less diffusion restriction as reflected by higher ADC measurements and tends to be less conspicuous than invasive cancer on DW MRI [31]. The false-negative results of DW MRI are problematic for screening. However, the use of advanced acquisition techniques may improve the DW MRI detection of smaller invasive cancers and DCIS through better image quality, spatial resolution, and lesion contrast [32,33].

Our study had several limitations. First, the retrospective nature of the study was the main limitation. The performance of screening US alone could not be analyzed because the radiologist who performed breast US was not blinded to mammography. However, very few published studies have tested the real-world performance of DW MRI in a screening setting to date. Thus, we performed a blinded reader study of a large cohort of consecutive patients. In addition, DW MRI detected suspicious lesions without DCE MRI or US correlates that were not pathologically confirmed. Therefore, $PPV_2$ (results of biopsy recommendations), instead of $PPV_3$ (results of biopsies performed), was provided in this study. The challenge with MRI-guided biopsy of lesions detected only by DW MRI can be problematic for the clinical use of DW MRI for screening [34]. However, targeted US after MRI may detect suspicious findings. Second, the detected cancers in the contralateral breast were few, even though we included a large number of women with unilateral breast cancer. Thus, the results of the subgroup analysis according to age, breast density, and cancer histology or tumor size should be interpreted with caution. Third, with a relatively short-term follow-up period of at least 1 year in our study, we cannot exclude the possibility that a longer follow-up period could reveal additional malignant lesions. Fourth, the inter-observer agreement of the DW MRI was found to be moderate. In addition, DW MRI has a higher AIR than combined mammography and US. However, false-positive readings can be drastically reduced with more training on standardized DW MRI interpretation algorithms and readings combined


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Korean Journal of Radiology
KJR

with pre-contrast T1- and T2-weighted images [20,24,26]. A recently published review article provided an updated DW MRI interpretation algorithm for breast cancer screening [20]. Lastly, two 3T scanners with dedicated 16- or 18-channel breast coils and different echo-planar imaging sequences with b-values of 1000 sec/mm$^2$ were used for DW MRI acquisition in our study. Thus, image quality and ADC value measurement may not be the same as those in previous studies using 1.5T scanners and different DW MRI sequences [35].

In conclusion, DW MRI at 3T detected significantly more contralateral breast cancers with fewer biopsy recommendations than the current state-of-the-art digital mammography plus radiologist-performed whole-breast US. Our results suggest that DW MRI has the potential as a screening tool for breast cancer detection, especially in women who are contraindicated to gadolinium-based contrast agents and cannot tolerate long MRI scan times. To better determine the role of DW MRI as a screening tool, multicenter prospective trials using standardized acquisition and interpretation protocols are needed in women with various breast cancer risk levels [16,20]. Currently, ongoing prospective clinical trials are investigating the role of DW MRI in screening high-risk women (NCT03835897, NCT04619186) or women with dense breasts (NCT03607552).

## Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1183.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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### Author Contributions

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