Breast Cancer: Diffusion Kurtosis MR Imaging—Diagnostic Accuracy and Correlation with Clinical-Pathologic Factors¹

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Purpose:
To assess diagnostic accuracy with diffusion kurtosis imaging (DKI) in patients with breast lesions and to evaluate the potential association between DKI-derived parameters and breast cancer clinical-pathologic factors.

Materials and Methods:
Institutional review board approval and written informed consent were obtained. Data from 97 patients (mean age ± standard deviation, 45.7 years ± 13.1; range, 19–70 years) with 98 lesions (57 malignant and 41 benign) who were treated between January 2014 and April 2014 were retrospectively analyzed. DKI (with b values of 0–2800 sec/mm²) and conventional diffusion-weighted imaging data were acquired. Kurtosis and diffusion coefficients from DKI and apparent diffusion coefficients from diffusion-weighted imaging were measured by two radiologists. Student t test, Wilcoxon signed-rank test, Jonckheere-Terpstra test, receiver operating characteristic curves, and Spearman correlation were used for statistical analysis.

Results:
Kurtosis coefficients were significantly higher in the malignant lesions than in the benign lesions (1.05 ± 0.22 vs 0.65 ± 0.11, respectively; P < .0001). Diffusivity and apparent diffusion coefficients in the malignant lesions were significantly lower than those in the benign lesions (1.13 ± 0.27 vs 1.97 ± 0.33 and 1.02 ± 0.18 vs 1.48 ± 0.33, respectively; P < .0001). Significantly higher specificity for differentiation of malignant from benign lesions was shown with the use of kurtosis and diffusivity coefficients than with the use of apparent diffusion coefficients (83% [34 of 41] and 83% [34 of 41] vs 76% [31 of 41], respectively; P < .0001) with equal sensitivity (95% [54 of 57]). In patients with invasive breast cancer, kurtosis was positively correlated with tumor histologic grade (r = 0.75) and expression of the Ki-67 protein (r = 0.55). Diffusivity was negatively correlated with tumor histologic grades (r = −0.44) and Ki-67 expression (r = −0.46).

Conclusion:
DKI showed higher specificity than did conventional diffusion-weighted imaging for assessment of benign and malignant breast lesions. Patients with grade 3 breast cancer or tumors with high expression of Ki-67 were associated with higher kurtosis and lower diffusivity coefficients; however, this association must be confirmed in prospective studies.

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Magnetic resonance (MR) imaging is an important technique for risk stratification and treatment planning in patients with breast cancer. Dynamic contrast material–enhanced (DCE) T1-weighted imaging is the most commonly used MR imaging sequence for identification of benign and malignant breast lesions. However, the background parenchymal enhancement and the overlap of the time intensity curves of benign and malignant lesions produce a high false-positive rate with breast DCE imaging, leading to high sensitivity but varied specificity for detection of breast cancer (1,2).

Additional MR imaging methods such as diffusion-weighted imaging (DWI) have been proposed to improve the diagnostic specificity of DCE imaging. DWI of the breast was demonstrated to be a useful adjunct sequence to DCE imaging, improving diagnostic accuracy compared with the accuracy with DCE imaging alone (3,4). Conventional DWI can be used to measure the apparent diffusion coefficient (ADC) in breast lesions. Differences in the ADCs of benign and malignant breast lesions have been reported (4). Although malignant lesions of the breast, on average, demonstrate lower ADCs than do benign lesions, there is also a substantial overlap in values for malignancy and benignancy. A consensus on the ADC threshold to distinguish malignancy from nonmalignancy remains controversial.

The conventional DWI model is based on the assumption that water diffusion follows a Gaussian behavior such that water molecules diffuse without any restriction. Thus, the diffusion-weighted MR signal monoexponentially decreases with increasing b value. While in living tissue, the diffusion is normally restricted by tissue microstructure and shows non-Gaussian phenomena. Jensen et al (3) proposed a non-Gaussian diffusion-weighted model called diffusion kurtosis imaging (DKI) in 2005. This model included calculation of kurtosis and diffusion coefficients. Kurtosis quantifies the deviation of tissue diffusion from a Gaussian pattern; diffusivity is the diffusion coefficient with correction of non-Gaussian bias (6). Authors of previous studies on gliomas (7,8), hepatocellular carcinomas (9), prostate cancers (6,10), and breast lesions (11) found that DKI shows substantially higher sensitivity than that shown with conventional DWI for cancer detection. Results of these studies also suggest that high-grade tumors have more obvious microstructural heterogeneity than do low-grade tumors. To our knowledge, however, no study has included evaluation of the correlation between the DKI-derived parameters and different clinical-pathologic factors of breast cancer. If accurate prediction of histologic malignancy grade and proliferative activity of breast cancer based on DKI-derived parameters is possible, the localization for biopsy can be optimized to achieve an adequate sample for breast cancer, which will improve the confidence of practitioners in clinical decision making. Our study aim was to assess diagnostic accuracy with DKI in patients with breast lesions and to evaluate the potential associations between DKI-derived parameters and breast cancer clinical-pathologic factors.

Advances in Knowledge

- Significantly higher specificity for differentiation of malignant from benign lesions was shown with diffusion kurtosis imaging (DKI)–derived kurtosis and diffusion values than with apparent diffusion coefficients (83% [34 of 41] and 83% [34 of 41] vs 76% [31 of 41], respectively; P < .0001, with equal sensitivity (95% [54 of 57]).

- In patients with invasive breast cancer, the kurtosis values calculated from the DKI model were positively correlated with tumor histologic grades (r = 0.75; 95% confidence interval [CI]: 0.56, 0.86) and expression of the Ki-67 protein (r = 0.55; 95% CI: 0.31, 0.76), while the diffusivity values calculated from the DKI model were negatively correlated with tumor histologic grades (r = −0.44; 95% CI: 0.66, 0.17) and Ki-67 expression (r = −0.46; 95% CI: 0.67, 0.18).

Implications for Patient Care

- Non-Gaussian water diffusion with the use of DKI can lead to a substantial improvement in the diagnosis of breast disease compared with the use of conventional diffusion-weighted imaging.

- The kurtosis and diffusivity values derived from the DKI model may be helpful for the preoperative differentiation of histologic grade and proliferative activity of breast cancer.

Materials and Methods

Patients

Institutional review board approval and written informed consent were obtained. Between January 2014 and April 2014, 317 women with breast cancer diagnosed as Breast Imaging Reporting and Data System (BI-RADS) category 4 or higher at mammography or ultrasonography were selected for breast MR imaging. All patients were approached for inclusion in the study, and 184 consented to participate. Conventional DWI was a commonly used

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Abbreviations:
ADC = apparent diffusion coefficient
BI-RADS = Breast Imaging Reporting and Data System
CI = confidence interval
DCE = dynamic contrast material enhanced
DKI = diffusion kurtosis imaging
DWI = diffusion-weighted imaging

Author contributions:
Guarantors of integrity of entire study, K.C., F.Y.; study concepts/design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, K.Sun, C.C., K.F., clinical studies, K.Sun, W.C., X.F., X.Y., K.Shen, F.Y.; statistical analysis, K.Sun, X.C., X.Y., V.Z.; and manuscript editing, K.Sun, W.C., F.Y.

Conflicts of interest are listed at the end of this article.
diagnostic sequence, but DKI was a research protocol that required written informed consent. The exclusion criteria included the following: patients who had undergone prior treatment (n = 3), patients who had not undergone surgery (n = 75), patients who had only undergone fine-needle aspiration biopsy (n = 4), patients who had undergone core-needle biopsy before MR imaging (n = 3), and patients whose MR images had substantial susceptibility artifacts (n = 2); therefore, 97 patients (mean age ± standard deviation: 45.7 years ± 13.1; range, 19–70 years) with positive pathologic results (87 who underwent tumor resection after MR imaging and 10 who underwent core-needle biopsy after MR imaging) were included in our study. Two patients had multiple lesions (one patient with multiple malignant lesions in the ipsilateral breast, and one patient with bilateral lesions, one malignant and one benign). To limit the intracorrelation effect, only the tumor with the highest grade was included in the statistical analysis (n = 96) for the patient who had multiple lesions in the ipsilateral breast. In the per-lesion assessment, for the patients who had more than one lesion, each lesion was evaluated separately.

**MR Imaging Technique**

Two coauthors (X.Y. and C.F.) are employees of Siemens Healthcare (Shenzhen, China). Only authors (K.Sun, W.C., Y.Z., and F.Y.) who are not employees of Siemens Healthcare had control of the data and information submitted for publication.

All MR imaging examinations were performed by using a 1.5-T MR imager (Magnetom Aera; Siemens Healthcare, Erlangen, Germany) with a dedicated four-channel bilateral breast coil in the axial orientation. Two diffusion sequences (ie, single-shot spin-echo echo-planar imaging) were performed with comparable parameters (Table 1) by using a three-image trace mode to determine the diffusion gradient. The field of view was the same for both diffusion sequences. A T2-weighted fast spin-echo sequence and a T1-weighted non-fat-suppressed gradient-echo sequence were executed before diffusion sequences, and dynamic contrast-enhanced MR imaging data were acquired after DWI and DKI by using a three-dimensional TI-weighted volumetric interpolated examination sequence (3).

### Image Analysis

ADC maps were automatically generated from conventional DWI with b values of 50 and 1000 sec/mm² with the software integrated in the MR imager (Syngo; Siemens Healthcare, Erlangen Germany). Kurtosis maps and diffusivity maps were calculated from DKI with b values of 0, 700, 1400, 2100, and 2800 sec/mm² by using an in-house developed software program based on a computing language and interactive environment (MATLAB; Mathworks, Natick, Mass). A Gaussian filter was first applied in the software with a full width at half maximum of 3 mm to suppress diffusion imaging noise data. Then a voxel-by-voxel fitting of DKI data was performed on the basis of the DKI nonlinear equation (3) by using the following equation: $S = S_0 \cdot \exp (- b \cdot D + 1/6 \cdot b^2 \cdot D^2 \cdot K)$, where $S$ is DWI signal at a particular $b$ value, $S_0$ is the baseline signal without diffusion weighting, $D$ is diffusivity, and $K$ is kurtosis, a unitless parameter that allows quantification of the deviation of water motion from the Gaussian distribution. Kurtosis is zero for a perfect Gaussian diffusion, and a large kurtosis value indicates that diffusion considerably deviates from a perfect Gaussian behavior. Diffusivity is a corrected ADC that removes this non-Gaussian bias.

DWI and DCE imaging datasets were analyzed by two radiologists specializing in breast imaging (reader 1: W.C., with 8 years of experience, and reader 2: Y.Z., with 6 years of experience). DCE imaging features were analyzed by using the BI-RADS MR imaging lexicon (12). Disagreement between the two observers was resolved in consensus. Inter- and intra-reader correlation coefficients were used to test the consistency of ADCs, diffusivity, and kurtosis. In a similar way, intra-reader correlation coefficients were used to test the consistency of the BI-RADS categories. The two sets of BI-RADS classifications were given. One classification was based on DCE imaging data only, the other was based on DCE imaging and DKI data. For our primary calculation of sensitivity and specificity, findings classified as BI-RADS categories 4 or 5 were considered positive; findings classified as BI-RADS categories 1–3 were considered negative. Both readers were blinded to the histopathologic diagnosis. For definition of regions of interest, the readers were able to view

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Conventional DWI</th>
<th>DKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence</td>
<td>Single-shot echo planar</td>
<td>Single-shot echo planar</td>
</tr>
<tr>
<td>Orientation</td>
<td>Axial bilateral</td>
<td>Axial bilateral</td>
</tr>
<tr>
<td>Repetition time (msec)</td>
<td>5900</td>
<td>7300</td>
</tr>
<tr>
<td>Echo time (msec)</td>
<td>80</td>
<td>92</td>
</tr>
<tr>
<td>Voxel size (mm³)</td>
<td>2.0 × 2.0 × 4.0</td>
<td>2.0 × 2.0 × 4.0</td>
</tr>
<tr>
<td>Fat suppression</td>
<td>Spectral adiabatic inversion recovery</td>
<td>Spectral adiabatic inversion recovery</td>
</tr>
<tr>
<td>Field of view (mm²)</td>
<td>384 × 384</td>
<td>384 × 384</td>
</tr>
<tr>
<td>Matrix</td>
<td>192 × 192</td>
<td>192 × 192</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No. of sections</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>No. of signals acquired</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Bandwidth (Hz/pixel)</td>
<td>446</td>
<td>1370</td>
</tr>
<tr>
<td>Imaging time (min)</td>
<td>2:04</td>
<td>4:16</td>
</tr>
<tr>
<td>b values (sec/mm²)</td>
<td>50, 1000</td>
<td>0, 700, 1400, 2100, 2800</td>
</tr>
</tbody>
</table>
diffusion-weighted images, ADC maps, and contrast-enhanced MR images. Regions of interest for each lesion were drawn on ADC maps by avoiding necrotic tissues, vessels, and dominant ducts and were later copied onto diffusion maps and kurtosis maps. The mean region-of-interest size was 150 mm$^2$ (range, 98–420 mm$^2$).

Medical record review was performed to assess results of hematoxylin and eosin staining and immunohistochemical analysis of surgical specimens. These results were used to determine the pathologic types and grades, estrogen receptor, progesterone receptor, c-erb-B2 expression, lesion size and lymph node status (sentinel lymph nodes and axillary lymph nodes), and expression of the Ki-67 protein. We used a cutoff value of 14% to divide Ki-67 into low-expression and high-expression groups according to St Gallen International Expert Consensus (13). Invasive breast cancers were classified into two groups, tumors with diameters larger than or equal to 2 cm and tumors smaller than 2 cm. Expression of estrogen receptor, progesterone receptor, and c-erbB2 was classified as negative or positive. Ki-67 expression was classified as low or high. Histologic grades given were grades 1, 2, or 3.

Statistical Analysis

A goodness-of-fit evaluation was performed for fitting of kurtosis models by using the computer language and interactive environment (MATLAB, Mathworks). The $R^2$ value was calculated. Diffusion parameters were expressed as means ± standard deviation and were tested first with the Kolmogorov-Smirnov test for normality analysis and then with the Levene test for variance homogeneity analysis.

Clinical data, DCE imaging data, and all diffusion features were compared by using the Student t test (comparison of mean values for normally distributed data), the $\chi^2$ test (comparison of percentages for normally distributed data), the Fisher exact test (comparison of percentages for small sample sizes), the Wilcoxon signed-rank test (ordered data), and the Jonckheere-Terpstra test (ordered data). Differences in performance were analyzed by comparing the areas under the receiver operating characteristic curves. Sensitivity and specificity were calculated with a threshold criterion determined as the value that would maximize the average sensitivity and specificity. Areas under the receiver operating characteristic curves were compared by using the method developed by DeLong et al (14). The McNemar test was used to examine differences in sensitivity and specificity between paired groups. The McNemar test also was used for the comparison of specificity, with fixed equal sensitivity of the DKI and DWI models.

The Spearman correlation was used to evaluate the association of diffusion parameters with histologic grade and Ki-67 expression. A correlation coefficient ($r$) of 0.75–1.00 was deemed to indicate very good to excellent correlation; 0.50–0.74, moderate to good correlation; 0.25–0.49, fair correlation; and 0.24 or lower, little or no correlation (15).

Intra- and interclass agreement of ADCs, diffusivity, and kurtosis was evaluated. Intraclass correlation coefficients were computed from reader 1’s two measurements. Interclass correlation coefficients were computed from reader 1’s first measurements and from reader 2’s measurements. An interclass correlation coefficient greater than 0.75 was considered indicative of good agreement (16). The average of four measurements (two from reader 1 and two from reader 2) of ADC, diffusivity, and kurtosis were used for subsequent statistical analysis.

Statistical analyses were performed by using software (SPSS version 16.0; SPSS, Chicago, Ill and MedCalc; MedCalc, Mariakerke, Belgium). Given the four variables used in the main analysis of this study, Bonferroni correction was used. A $P$ value of less than .0125 was considered indicative of a significant difference. Post hoc power analysis was performed with software (Power and Precision; BioStat, Englewood, NJ).

Results

Clinical-Pathologic Findings

Of the 98 lesions, 57 were malignant and 41 were benign. For the patient with two lesions, the pathologic results of the lesion in the right breast showed invasive ductal carcinoma, and the lesion in the left breast was fibroadenoma, which was misdiagnosed as breast cancer at MR imaging. The malignant lesions included ductal carcinoma in situ ($n = 5$) and invasive ductal carcinoma ($n = 52$; grade 1 [$n = 9$], grade 2 [$n = 15$], and grade 3 [$n = 28$]). Benign lesions included fibroadenomas ($n = 36$) and other benign changes ($n = 5$; fibrocystic change [$n = 3$], cyst combined chronic infection [$n = 1$], abscess [$n = 1$]). The clinical features, dynamic contrast-enhanced and diffusion parameters between benign and malignant lesions are shown in Table 2. Estrogen receptor, progesterone receptor, and c-erb-B2 expression of invasive breast cancer are shown in Table 3.

Summary of Metrics Included Dynamic Contrast-enhanced Features

The mean $R^2$ value for the kurtosis fit was 0.99 ± 0.01 (range, 0.98–0.99). The software successfully generated parametric maps for the kurtosis metrics in all patients, with sample patients shown in Figures E1 and E2 (online) and Figure 1. Kurtosis was significantly higher in the malignant lesions than in the benign lesions (1.05 ± 0.22 vs 0.65 ± 0.11, respectively; $P < .0001$). Diffusivity and ADC were significantly lower in the malignant lesions than in the benign lesions (1.13 ± 0.27 vs 1.97 ± 0.33 and 1.02 ± 0.18 vs 1.48 ± 0.33, respectively; $P < .0001$, Table 2). The two sets of BI-RADS classification were those only based on DCE imaging data (category 3, $n = 17$; category 4, $n = 54$; category 5, $n = 27$) and those based on DCE imaging and DKI data (category 2, $n = 17$; category 3, $n = 22$; category 4, $n = 19$; category 5, $n = 40$). The combined use of DCE imaging and DKI showed higher specificity (90% [37 of 41]) than did the use of DCE imaging data (37% [15 of 41], $P$
Table 2

<table>
<thead>
<tr>
<th>Characteristics of Patients and Lesions</th>
<th>Benign Lesion Group</th>
<th>Malignant Lesion Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient age (y)*</td>
<td>36.9 ± 12.2 (19–68)</td>
<td>51.6 ± 10.1 (29–70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Menstrual status†</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Premenopausal (n = 55)</td>
<td>33 (60)</td>
<td>22 (40)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal (n = 42)</td>
<td>7 (17)</td>
<td>35 (83)</td>
<td></td>
</tr>
<tr>
<td><strong>Lesion characteristic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size (cm)*</td>
<td>1.9 ± 1.0 (0.7–5.0)</td>
<td>2.4 ± 1.0 (0.8–5.0)</td>
<td>.017</td>
</tr>
<tr>
<td>Masses</td>
<td>34/41 (83)</td>
<td>44/57 (77)</td>
<td>.614</td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Round</td>
<td>9/34 (26)</td>
<td>3/44 (7)</td>
<td></td>
</tr>
<tr>
<td>Oval</td>
<td>18/34 (53)</td>
<td>11/44 (25)</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>7/34 (21)</td>
<td>30/44 (68)</td>
<td></td>
</tr>
<tr>
<td>Margin</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Circumscribed</td>
<td>30/34 (88)</td>
<td>18/44 (41)</td>
<td></td>
</tr>
<tr>
<td>Not circumscribed</td>
<td>4/34 (12)</td>
<td>26/44 (59)</td>
<td></td>
</tr>
<tr>
<td>Internal enhancement</td>
<td></td>
<td></td>
<td>.835</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>15/34 (44)</td>
<td>24/44 (55)</td>
<td></td>
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<tr>
<td>Heterogeneous</td>
<td>16/34 (47)</td>
<td>13/44 (30)</td>
<td></td>
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<tr>
<td>Rim</td>
<td>3/34 (9)</td>
<td>7/44 (16)</td>
<td></td>
</tr>
<tr>
<td>Nonmass enhancement</td>
<td>7/41 (17)</td>
<td>13/57 (23)</td>
<td>.614</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
<td></td>
<td>.057</td>
</tr>
<tr>
<td>Focal</td>
<td>6/7 (86)</td>
<td>4/13 (31)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>1/7 (14)</td>
<td>9/13 (69)</td>
<td></td>
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<tr>
<td>Internal enhancement</td>
<td></td>
<td></td>
<td>.417</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>1/7 (14)</td>
<td>1/13 (8)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>6/7 (86)</td>
<td>7/13 (54)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0/7</td>
<td>5/13 (39)</td>
<td></td>
</tr>
<tr>
<td>Dynamic imaging peak</td>
<td>81.4 ± 28.0 (48–170)</td>
<td>90.6 ± 23.5 (40–144)</td>
<td>.081</td>
</tr>
<tr>
<td>percentage of enhancement*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kinetic curve type</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Persistent enhancement</td>
<td>24/41 (69)</td>
<td>9/57 (16)</td>
<td></td>
</tr>
<tr>
<td>Plateau</td>
<td>11/41 (27)</td>
<td>13/57 (23)</td>
<td></td>
</tr>
<tr>
<td>Washout</td>
<td>6/41 (14)</td>
<td>35/57 (61)</td>
<td></td>
</tr>
<tr>
<td>Diffusion parameters*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DWI kurtosis</td>
<td>0.65 ± 0.11 (0.41–0.95)</td>
<td>1.05 ± 0.22 (0.71–1.93)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DWI diffusivity</td>
<td>1.97 ± 0.33 (1.21–2.94)</td>
<td>1.13 ± 0.27 (0.45–1.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DWI ADC</td>
<td>1.48 ± 0.33 (0.86–2.30)</td>
<td>1.02 ± 0.18 (0.74–1.60)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are proportion of lesions, with percentage in parentheses.

* Data are means ± standard deviation, with the range in parentheses.
† Data are number of patients (n = 98), with percentages in parentheses.

< .0001), with equal sensitivity (97% [55 of 57], Table 4).

The areas under the curve for three parameters were 0.974 for kurtosis, 0.973 for diffusivity, and 0.895 for ADC. For ADC versus diffusivity, Z = 2.17 (P = .03); ADC versus kurtosis, Z = 2.17 (P = .03); diffusivity versus kurtosis, Z = 0.07 (P = .95; Table 5, Fig 2). Kurtosis and diffusivity showed significantly higher specificity for differentiation of malignant from benign lesions than did ADC (83% [34 of 41] and 83% [34 of 41] vs 76% [31 of 41], respectively, P < .0001), with equal sensitivity (95% [54 of 57]).

In patients with invasive breast cancer, kurtosis was positively correlated with tumor histologic grades (r = 0.75, [95% CI: 0.56, 0.86]) and Ki-67 expression (r = 0.55, [95% CI: 0.31, 0.76]). Diffusivity was negatively correlated with tumor histologic grades (r = −0.44, [95% CI: 0.66, 0.17]) and Ki-67 expression (r = −0.46, [95% CI: 0.67, 0.18]). ADC showed no relation with histologic grades (r = 0.05, [95% CI: 0.22, 0.35]) and Ki-67 expression (r = 0.16, [95% CI: 0.12, 0.44]).

There were no significant differences among all diffusion parameters in estrogen receptor, progesterone receptor, C-erb-B2 expression–positive and –negative lesions (P > .05). There were no significant differences in diffusion parameters between tumors with diameters of 2 cm or larger and tumors smaller than 2 cm (P > .05, Table 3).

Results of Post Hoc Power Analysis

The power of the Wilcoxon signed-rank test with a sample size of 52 to allow detection of a significant difference among estrogen receptor, progesterone receptor, Cer-bB2 expression, and lymph node positive and negative lesions was 5%. The power of the Wilcoxon signed-rank test between tumor diameter larger than or equal to 2 cm and smaller than 2 cm was 5%. The power of the Wilcoxon signed-rank test with a sample size of 52 to allow detection of significant differences between lymph node positive and negative lesions was 5%.

Intra- and Interclass Agreement of ADC, Diffusivity, Kurtosis, and BI-RADS Classification

The intraclass correlation coefficient calculated on the basis of reader 1’s two measurements of ADC was 0.996 (95% CI: 0.994, 0.997). The interclass correlation coefficient between reader 1’s first measurements and reader 2’s measurements was 0.907 (95% CI: 0.862, 0.938). The intraclass correlation coefficient calculated on the basis of reader 1’s two measurements of diffusivity was 0.980 (95% CI: 0.971, 0.987). The interclass correlation coefficient between reader 1’s first measurements and reader 2’s measurements was 0.876 (95% CI: 0.812, 0.915). The intraclass correlation coefficient calculated on the basis of reader 1’s two measurements...
Table 3

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of Patients</th>
<th>Mean Kurtosis</th>
<th>Median Kurtosis*</th>
<th>P Value</th>
<th>Mean Diffusivity</th>
<th>Median Diffusivity*</th>
<th>P Value</th>
<th>Mean ADC</th>
<th>Median ADC*</th>
<th>P Value</th>
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<tr>
<td>Estrogen receptor</td>
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<tr>
<td>Positive</td>
<td>35</td>
<td>1.04 ± 0.17 (0.74–1.54)</td>
<td>1.02 (0.22)</td>
<td>.477</td>
<td>1.09 ± 0.22 (0.67–1.70)</td>
<td>1.03 (0.32)</td>
<td>.774</td>
<td>0.96 ± 0.16 (0.74–1.50)</td>
<td>0.93 (0.20)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>17</td>
<td>1.14 ± 0.28 (0.86–1.98)</td>
<td>1.05 (0.23)</td>
<td></td>
<td>1.06 ± 0.22 (0.45–1.53)</td>
<td>1.09 (0.22)</td>
<td></td>
<td>1.07 ± 0.12 (0.86–1.25)</td>
<td>1.02 (0.25)</td>
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<tr>
<td>Progesterone receptor</td>
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<td>.190</td>
<td></td>
<td>1.08 (0.22)</td>
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<td>0.97 ± 0.20 (0.74–1.50)</td>
<td>0.93 (0.21)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
<td>1.01 ± 0.14 (0.74–1.25)</td>
<td>1.02 (0.27)</td>
<td></td>
<td>1.11 ± 0.23 (0.77–1.70)</td>
<td>1.07 (0.35)</td>
<td></td>
<td>1.07 ± 0.20 (0.74–1.50)</td>
<td>0.93 (0.21)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>33</td>
<td>1.11 ± 0.24 (0.86–1.98)</td>
<td>1.05 (0.23)</td>
<td></td>
<td>1.06 ± 0.22 (0.45–1.54)</td>
<td>1.06 (0.26)</td>
<td></td>
<td>1.01 ± 0.13 (0.81–1.25)</td>
<td>0.98 (0.22)</td>
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</tr>
<tr>
<td>C-erb-B2</td>
<td></td>
<td></td>
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<td>.341</td>
<td></td>
<td>1.13 (0.22)</td>
<td></td>
<td>0.98 ± 0.18 (0.74–1.50)</td>
<td>0.93 (0.24)</td>
<td></td>
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<tr>
<td>Positive</td>
<td>18</td>
<td>1.14 ± 0.30 (0.82–1.93)</td>
<td>1.04 (0.33)</td>
<td></td>
<td>1.05 ± 0.24 (0.45–1.53)</td>
<td>1.10 (0.37)</td>
<td></td>
<td>1.03 ± 0.10 (0.89–1.23)</td>
<td>1.00 (0.22)</td>
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<tr>
<td>Negative</td>
<td>34</td>
<td>1.03 ± 0.14 (0.74–1.40)</td>
<td>1.03 (0.21)</td>
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<td>1.09 ± 0.21 (0.67–1.70)</td>
<td>1.05 (0.27)</td>
<td></td>
<td>0.98 ± 0.18 (0.74–1.50)</td>
<td>0.93 (0.24)</td>
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<tr>
<td>Ki-67</td>
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<td></td>
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<td>.008</td>
<td></td>
<td>1.12 (0.22)</td>
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<td>1.09 ± 0.21 (0.67–1.40)</td>
<td>1.05 (0.27)</td>
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</tr>
<tr>
<td>&lt;14%</td>
<td>20</td>
<td>0.96 ± 0.14 (0.74–1.27)</td>
<td>0.95 (0.21)</td>
<td>.001</td>
<td>1.18 ± 0.22 (0.89–1.70)</td>
<td>1.17 (0.29)</td>
<td></td>
<td>0.97 ± 0.20 (0.74–1.50)</td>
<td>0.95 (0.22)</td>
<td></td>
</tr>
<tr>
<td>≥14%</td>
<td>32</td>
<td>1.14 ± 0.23 (0.90–1.93)</td>
<td>1.08 (0.15)</td>
<td></td>
<td>1.02 ± 0.20 (0.45–1.53)</td>
<td>1.03 (0.22)</td>
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<td>1.02 ± 0.13 (0.81–1.25)</td>
<td>0.99 (0.20)</td>
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<tr>
<td>Tumor diameter</td>
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<td></td>
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<td>.173</td>
<td></td>
<td>1.12 (0.22)</td>
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<td>0.98 ± 0.18 (0.74–1.50)</td>
<td>0.93 (0.24)</td>
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<tr>
<td>&lt;2 cm</td>
<td>21</td>
<td>1.09 ± 0.26 (0.82–1.93)</td>
<td>1.04 (0.26)</td>
<td></td>
<td>1.11 ± 0.28 (0.45–1.53)</td>
<td>1.07 (0.28)</td>
<td></td>
<td>0.96 ± 0.13 (0.81–1.23)</td>
<td>0.93 (0.19)</td>
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<tr>
<td>≥2 cm</td>
<td>31</td>
<td>1.06 ± 0.18 (0.74–1.68)</td>
<td>1.04 (0.18)</td>
<td></td>
<td>1.06 ± 0.17 (0.67–1.46)</td>
<td>1.06 (0.24)</td>
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<td>1.11 ± 0.28 (0.74–1.50)</td>
<td>0.98 (0.20)</td>
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<td>Lymph node status</td>
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<td>.970</td>
<td></td>
<td>1.10 (0.22)</td>
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<td>0.99 ± 0.15 (0.74–1.40)</td>
<td>0.98 (0.23)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>20</td>
<td>1.11 ± 0.22 (0.82–1.68)</td>
<td>1.06 (0.24)</td>
<td></td>
<td>1.05 ± 0.22 (0.67–1.54)</td>
<td>1.00 (0.29)</td>
<td></td>
<td>1.01 ± 0.17 (0.81–1.50)</td>
<td>0.96 (0.24)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>32</td>
<td>1.05 ± 0.20 (0.74–1.93)</td>
<td>1.04 (0.21)</td>
<td></td>
<td>1.10 ± 0.22 (0.45–1.70)</td>
<td>1.10 (0.18)</td>
<td></td>
<td>0.99 ± 0.15 (0.74–1.40)</td>
<td>0.98 (0.23)</td>
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<tr>
<td>Histologic grades</td>
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<td>&lt;.001</td>
<td></td>
<td>1.10 (0.22)</td>
<td></td>
<td>0.99 ± 0.20 (0.45–1.53)</td>
<td>1.01 (0.22)</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>9</td>
<td>0.86 ± 0.06 (0.74–0.96)</td>
<td>0.86 (0.08)</td>
<td>.001</td>
<td>1.26 ± 0.25 (0.89–1.70)</td>
<td>1.26 (0.34)</td>
<td></td>
<td>1.09 ± 0.22 (0.84–1.50)</td>
<td>1.03 (0.33)</td>
<td></td>
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<tr>
<td>Grade 2</td>
<td>15</td>
<td>1.00 ± 0.08 (0.91–1.14)</td>
<td>0.98 (0.16)</td>
<td></td>
<td>1.13 ± 0.17 (0.92–1.54)</td>
<td>1.09 (0.15)</td>
<td></td>
<td>0.93 ± 0.15 (0.74–1.21)</td>
<td>0.88 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>28</td>
<td>1.18 ± 0.22 (0.90–1.93)</td>
<td>1.12 (0.22)</td>
<td></td>
<td>0.99 ± 0.20 (0.45–1.53)</td>
<td>1.01 (0.22)</td>
<td></td>
<td>1.01 ± 0.12 (0.81–1.24)</td>
<td>0.98 (0.16)</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are means ± standard deviations, with the range in parentheses.

* Data are medians, with interquartile deviation in parentheses.
**Figure 1**

Images in a 38-year-old woman show two breast cancer lesions in the right breast. Interior tumor near chest wall (arrowheads) is invasive ductal carcinoma grade 3 (estrogen receptor positive, 70%; progesterone receptor positive, 50%; C-erb-B2 positive, Ki-67 positive, 60%); other lateral tumor (arrows) is invasive ductal carcinoma grade 2 (estrogen receptor positive, 30%; progesterone receptor positive, 90%; C-erb-B2 positive, Ki-67 positive, 3%). (a) Axial T2-weighted image shows two irregular isointense lesions. (b, c) ADC and diffusivity maps, respectively, show decreased signal intensity compared with surrounding glandular tissue. Signal intensity of interior lesions on diffusivity map was lower than that on ADC map (interior tumor: ADC, $0.88 \times 10^{-3}$ mm$^2$/sec $\pm 0.16$; diffusivity, $0.77 \times 10^{-3}$ mm$^2$/sec $\pm 0.16$; lateral tumor: ADC, $0.99 \times 10^{-3}$ mm$^2$/sec $\pm 0.16$; diffusivity, $1.00 \times 10^{-3}$ mm$^2$/sec $\pm 0.37$). (d) Kurtosis map shows increased signal intensity compared with surrounding glandular tissue. Interior lesion (kurtosis, $1.26 \pm 0.31$) had considerably higher signal intensity than the lateral lesion (kurtosis, $1.14 \pm 0.30$).

**Discussion**

The findings in this study show that quantitative analysis of DKI-derived parameters can be used to distinguish malignant from benign breast lesions. Furthermore, DKI-derived parameters, in comparison with the ADC from a DWI model, significantly improved diagnostic specificity for characterization of benign versus malignant lesions. We observed diagnostic improvement when diffusivity and kurtosis were added to DCE imaging data. Our study results also showed that kurtosis was positively correlated with histologic grade and Ki-67 expression in patients with invasive breast cancer, while diffusivity was inversely correlated with histologic grade and Ki-67 expression. These results all suggest an added value of the DKI model in the diagnostic performance of breast MR imaging and in yielding functional measures of the tumor microstructure.

Authors of a recent study of the breast (11) have included limited numbers of subjects, and/or have included patients with lesions who had undergone biopsy before MR imaging. Because of the microstructural changes after biopsy, the kurtosis and diffusivity values may have been inaccurate. The 98 lesions in our study were subjected to MR imaging before biopsy. Our results showed that kurtosis and diffusivity showed higher specificity for differentiation of malignant from benign lesions than did the ADC. The higher specificity with the DKI model than that with the DWI model can be attributed to the following reasons. First, the DWI model includes the assumption that water diffusion follows Gaussian behavior, whereas the DKI model incorporates an attempt to

<table>
<thead>
<tr>
<th>Methods</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCE</td>
<td>97 (55/57)</td>
<td>37 (15/41)</td>
<td>68 (55/81)</td>
<td>88 (15/17)</td>
<td>71 (70/98)</td>
</tr>
<tr>
<td>DCE with DKI</td>
<td>97 (55/57)</td>
<td>90 (37/41)</td>
<td>93 (55/59)</td>
<td>95 (37/39)</td>
<td>94 (92/98)</td>
</tr>
</tbody>
</table>

Note.—Data are percentages, with numerators and denominators in parentheses.
BREAST IMAGING: Diffusion Kurtosis MR Imaging in Patients with Breast Cancer

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Table 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Area under the Curve*</th>
<th>Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
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<tr>
<td>Kurtosis</td>
<td>0.974 (0.920, 0.996)</td>
<td>&gt;0.80</td>
<td>95 (54/57) [85, 99]</td>
<td>93 (38/41) [80, 99]</td>
</tr>
<tr>
<td>Diffusivity</td>
<td>0.973 (0.918, 0.995)</td>
<td>≤1.67</td>
<td>97 (55/57) [88, 100]</td>
<td>88 (36/41) [74, 96]</td>
</tr>
<tr>
<td>ADC (×10⁻³ mm²/sec)</td>
<td>0.895 (0.817, 0.948)</td>
<td>≤1.211</td>
<td>86 (49/57) [74, 94]</td>
<td>83 (34/41) [68, 93]</td>
</tr>
</tbody>
</table>

Note.—Unless otherwise indicated, data are percentages, with numerators and denominators in parentheses and 95% confidence intervals (CIs) in brackets.

* Data in parentheses are 95% CIs.

In our study, kurtosis was higher in grade 3 tumors than in grades 1 and 2 tumors. Kurtosis was positively correlated with histologic grade in patients with invasive breast cancer. Diffusivity was lower in grade 3 tumors than in grades 1 and 2 tumors. Diffusivity was inversely correlated with histologic grade in patients with invasive breast cancer. High-grade tumors are characterized by the absence of tubule and gland formation, marked variation of nuclear pleomorphism, and high mitotic counts. These changes represent the increasing tissue complexity at the

depict water diffusion as a non-Gaussian phenomenon. Second, the cellular microstructure is more complex and heterogeneous in malignant lesions than in benign lesions. Third, vigorous cell mitosis and strong proliferative

ability in malignancy can increase the cell density in each voxel and then affect water diffusion.

Figure 2: (a–c) Boxplots show ADC, diffusivity (D), and kurtosis (K) in benign and malignant lesions. (d) Graph shows receiver operating characteristic curves to assess utility of three metrics for discriminating malignant and benign lesions.
Our study had the following limitations. First, the sample size was low, the number of patients with ductal carcinoma in situ was low, and there were no patients with invasive lobular carcinoma and other types of breast cancer. Second, the patients in our study had predominately large lesions. Third, the ADC, diffusivity, and kurtosis cutoffs were derived from our own population, which may have allowed overestimation of the effect. Fourth, we used a monoexponential model with two b values for our ADC assessment, because this was the most commonly used method in clinical studies (3,11,22,25–28); however, monoexponential decay of only two b values may be suboptimal for characterization of breast lesions. Since DWI data with b values less than 200 sec/mm² were not acquired in our study, we could not perform the comparison between the biexponential model and the DKI model. Finally, our estimation algorithm of the DKI model and monoexponential models does not take into consideration Rician noise. The noise in magnitude MR images acquired at high b values is likely to be Rician rather than Gaussian, causing bias in the fit when this simple approach is used (29–33).

In summary, the kurtosis and diffusivity values calculated by using the DKI model demonstrated significantly higher specificity compared with ADCs for differentiation of benign from malignant breast lesions. In addition, the kurtosis values were significantly higher in grade 3 cancers and in high–Ki-67-expression breast tumors than in grades 1 and 2 and in low–Ki-67-expression breast tumors. If our results are substantiated in prospective studies, DKI may be a noninvasive method to evaluate the effects of neoadjuvant chemotherapy.

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References


