Sonoelastographic Strain Index for Differentiation of Benign and Malignant Nonpalpable Breast Masses

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Objective. The purpose of this study was to evaluate the diagnostic potential of the sonoelastographic strain index for differentiation of nonpalpable breast masses. Methods. Ninety-nine nonpalpable breast masses (79 benign and 20 malignant) in 94 women (mean age, 45 years; range, 21–68 years) who had been scheduled for a sonographically guided core biopsy were examined with B-mode sonography and sonoelastography. Radiologists who had performed the biopsies analyzed the B-mode sonograms and provided American College of Radiology Breast Imaging Reporting and Data System categories. The strain index (fat to lesion strain ratio) was calculated by dividing the strain value of the subcutaneous fat by that of the mass. The histologic result from the sonographically guided core biopsy was used as a reference standard. The diagnostic performance of the strain index and that of B-mode sonography were compared by receiver operating characteristic (ROC) curve analysis. Results. The mean strain index values ± SD were 6.57 ± 6.62 (range, 1.29–28.69) in malignant masses and 2.63 ± 4.57 (range, 0.54–38.76) in benign masses (P = .019). The area under the ROC curve values were 0.835 (95% confidence interval [CI], 0.747–0.902) for B-mode sonography and 0.879 (95% CI, 0.798–0.936) for the strain index (P = .490). The sensitivity, specificity, positive predictive value, and negative predictive value were 95% (19 of 20), 75% (59 of 79), 48% (19 of 39), and 98% (59 of 60), respectively, when a best cutoff point of 2.24 was used. Conclusions. The strain index based on the fat to lesion strain ratio has diagnostic performance comparable with that of B-mode sonography for differentiation of benign and malignant breast masses. Key words: breast neoplasm diagnosis; breast sonography; sonoelastography; sonographic tissue characterization.

Abbreviations
AUC, area under the receiver operating characteristic curve; BI-RADS, Breast Imaging Reporting and Data System; CI, confidence interval; DCIS, ductal carcinoma in situ; ROC, receiver operating characteristic; ROI, region of interest.

Sonoelastography is an imaging modality that can quantitatively measure tissue elasticity with the use of sonography. There have been 2 types of sonoelastography. The first type is modulus imaging, which estimates the modulus of the tissue by measurement of the shear wavelength. Although modulus imaging is able to estimate an intrinsic tissue parameter, it has lower spatial resolution and higher noise, and the assumptions regarding boundary conditions might lead to biased estimates.1 The second type of sonoelastography shows the relative strain of lesions compared with the surrounding tissue by the use of a freehand compression technique in real time. Strain is defined as the spatial rate of change of displacement when an object is compressed by external force.1 Because the breast is easily

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Compressible, and breast cancers are much stiffer than other breast tissue, sonoelastography has been widely studied for differentiation of breast masses. Krouskop et al. reported that fat, normal glandular tissue, fibrous tissue, ductal carcinoma in situ (DCIS), and infiltrating ductal carcinoma of the breast had different elastic modules according to their strain levels. These investigators also found that infiltrating ductal carcinoma was much stiffer than other breast tissues.

Several clinical studies showed that sonoelastography was useful for differentiation of benign and malignant breast lesions, with sensitivity of 78.0% to 100% and specificity of 21.0% to 98.5%. A discrepancy in lesion sizes between the use of B-mode sonography and sonoelastography was a key factor for the diagnostic criteria in several studies. Other studies used a 5-point scoring system based on visual assessment of the degree and distribution of strain in the hypoechoic mass and surrounding tissue. However, interobserver variability in data acquisition and interpretation has been shown as a limitation of the use of sonoelastography. To overcome this limitation, recent studies suggested that the fat to mass strain ratio could be used as an objective and constant characteristic regardless of data acquisition or interpretation variability. However, one study included palpable masses and did not compare the diagnostic performance of the strain index and B-mode sonography.

The purpose of this study was to evaluate the diagnostic performance of the strain index based on the fat to mass strain ratio compared with that of B-mode sonography for differentiation of benign and malignant nonpalpable breast masses with histologic analysis as a reference standard.

Materials and Methods

Patients and Breast Lesions

The Institutional Review Board of our institution approved the study, and informed consent was obtained from each patient. Between July 2007 and December 2007, 223 consecutive patients who had been scheduled to undergo a sono graphically guided core biopsy based on sonographic findings were examined by sonoelastography. Among these 249 patients with 254 lesions, 155 lesions were later excluded for the following reasons: the patient had a palpable lesion (n = 103); the lesion was greater than 2 cm in diameter (n = 22); and follow-up sono graphy was not performed for at least 1 year in women with benign lesions (n = 30). Palpable and larger lesions were excluded because they were usually confirmed by cytologic analysis or biopsy. In addition, to obtain an adequate strain index, inclusion of sufficient normal tissue around the target mass was needed.

A total of 99 lesions in 94 patients (age range, 21–68 years; mean age, 45 years) were included in the final data analysis (Table 1). Eighty-nine patients had 1 lesion, and 5 had 2 lesions. Of the 99 lesions, 20 (20%) were malignant, and 79 (80%) were benign. The malignant masses included infiltrating ductal carcinoma (n = 14), DCIS (n = 4), and invasive lobular carcinoma (n = 2). Of the 14 infiltrating ductal carcinomas, 4 lesions were low histologic grade; 7 were intermediate grade; and 3 were high grade. The benign masses included fibrocystic changes (n = 43), fibroadenoma (n = 30), papilloma (n = 4), and tubular adenoma (n = 2). The duration of imaging follow-up for the lesions with benign biopsy results was 12 to 18 months, and lesion stability was confirmed in all cases. The lesion size defined as the maximal diameter measured on sonography was 3 to 20 mm (mean, 9 mm).

Of the 94 patients, 82 (87%) had no symptoms; 7 (8%) had nipple discharge; and 5 (5%) had pain. One patient did not undergo mammography. Of the 93 patients who underwent mammography, 41 (44%) showed normal findings; 26 (28%) showed the presence of a noncalcified mass; 20 (22%) showed focal asymmetry; 4 (4%) showed the presence of a mass with microcalcifications; and 2 (2%) showed architectural distortion. The histologic diagnosis was confirmed by sono graphically guided 14-gauge automated gun biopsy (n = 62) or by 11- or 8-gauge vacuum-assisted biopsy (n = 10). Surgical excision was performed in 27 masses because of a malignant finding determined after a core biopsy (n = 20), imaging-histologic analysis discordance (n = 3), or a high-risk lesion determined from histologic analysis (n = 4).

Data Acquisition and B-Mode Image Evaluation

The strain index and B-mode sonograms were obtained with the use of a 14–6 MHz linear trans-
ducer and an EUB-8500 scanner (Hitachi Medical Corporation, Tokyo, Japan) by 1 of 5 radiologists before the biopsy. After identification of a target mass on B-mode sonography, the radiologist who performed the biopsy saved representative B-mode sonograms, including transverse and longitudinal scans, to a picture archiving and communications system. Images were then saved as bitmap files on a hard disk for later review.

To obtain the strain index, a rectangular region of interest (ROI) box was first set to include the area from the subcutaneous fat layer to the superficial portion of the pectoralis muscle layer and to focus on the target mass. Next, the target mass was vertically compressed with very light pressure by the transducer to depict the subcutaneous fat layer as mixed red and green and the muscle layer as blue. The sonoelastographic images were displayed with 256 color mapping from red (softest component) to green (intermediate stiffness) to blue (hardest component) according to the level of strain. On a representative static image, relative strain values of the mass and fat were measured. The first ROI (A) for the mass strain was manually drawn and placed to be bounded by the inner margin of a hypoechoic mass. The second ROI (B) for the fat strain was placed in the fat tissue at a depth similar or as close to the depth of the target mass to avoid stress decay with the depth. The second ROI for the fat strain was placed in the fat tissue encoded green because it represented intermediate stiffness in the chosen area. The maximum depth difference between the measurements in the fat tissue and mass was limited to 5 mm. The strain index, defined as the fat to mass strain ratio that indicated mass stiffness, was calculated automatically by an embedded software program in the ultrasound unit. Screen capture images including the measured strain index and areas of the ROI were saved to a picture archiving and communications system for later analysis (Figures 1 and 2). Acquisition of the strain index took approximately 2 minutes per case.

Two experienced breast radiologists who had not performed the sonoelastography or biopsy analyzed the randomly ordered B-mode image files and assigned American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) final assessment categories according to the probability of malignancy in consensus without information from the histologic or sonoelastographic studies. Category 3 indicated a probability of malignancy of 2% or lower; category 4a, higher than 2% to 10%; category 4b, higher than 10% to 50%; category 4c, higher than 50% and lower than 95%; and category 5, 95% or higher.

Table 1. Patient Ages, Lesion Sizes, and Final Assessment Categories for the 99 Lesions

<table>
<thead>
<tr>
<th>Feature</th>
<th>Benign Lesions (n = 79)</th>
<th>Malignant Lesions (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age, y</td>
<td>44.3 ± 9.6</td>
<td>47.7 ± 7.3</td>
</tr>
<tr>
<td>Lesion size, mm</td>
<td>9.4 ± 3.8</td>
<td>10.5 ± 5.2</td>
</tr>
<tr>
<td>Lesion size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–10 mm</td>
<td>58 (73.4)</td>
<td>11 (55.0)</td>
</tr>
<tr>
<td>11–20 mm</td>
<td>21 (26.6)</td>
<td>9 (45.0)</td>
</tr>
<tr>
<td>BI-RADS final assessment category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10 (12.7)</td>
<td>0</td>
</tr>
<tr>
<td>4a</td>
<td>66 (83.5)</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>4b</td>
<td>3 (3.8)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td>4c</td>
<td>0 (0)</td>
<td>5 (25.0)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
<td>2 (10.0)</td>
</tr>
</tbody>
</table>

Data are means ± SD and numbers of lesions (percentages). Percentages have been rounded.
Data Analysis
The mean strain indices were compared between the benign and malignant masses and between low, intermediate, and high grades of infiltrating ductal carcinoma by the Student t test using SPSS version 12.0 for Windows (SPSS Inc, Chicago, IL). Two-tailed \( P < .05 \) was considered statistically significant. The strain index was divided into 5 groups according to range: range 1, 0.51 to 1.50; range 2, 1.51 to 2.50; range 3, 2.51 to 3.50; range 4, 3.51 to 4.50; and range 5, 4.51 and greater. To evaluate the performance of the strain index for differentiation of benign and malignant masses, the malignancy rate according to the strain index range and the area under the receiver operating characteristic (ROC) curve (\( A_z \)) were analyzed. To suggest optimal quantitative strain index criteria for differentiation of benign and malignant masses, the best cutoff point to achieve the maximal sum of the sensitivity and specificity was analyzed. The sensitivity, specificity, positive predictive value, and negative predictive value of the strain index as determined with the use of sonoelastography were calculated when the best strain index cutoff point was used.

The diagnostic performance of the strain index was compared with that of B-mode sonography by ROC analysis with MedCalc version 9.3.1 for Windows (MedCalc Software, Mariakerke, Belgium).

Results
The mean strain index value ± SD for malignant masses (6.57 ± 6.62; range, 1.29–28.69) was significantly higher than that for benign masses (2.63 ± 4.57; range, 0.54–38.76; \( P = .019 \); Figures 1 and 2). No difference was found in the mean strain indices between benign low- to intermediate-grade (7.4 ± 7.6) and high-grade (9.7 ± 8.8) infiltrating ductal carcinomas (\( P = .664 \)). The rates of malignancy according to the strain index ranges were as follows: 3% (1 of 31) for range 1, 6% (2 of 35) for range 2, 33% (4 of 12) for range 3, 40% (2 of 5) for range 4, and 69% (11 of 116) for range 5 (Table 2). The best strain index cutoff point to achieve the maximal sum of the sensitivity and specificity was 2.24. The sensitivity, specificity, positive predictive value, and negative predictive value were 95% (19 of 20), 75% (59 of 79), 48% (19 of 39), and 98% (59 of 60), respectively, when the best cutoff point of 2.24 was used. The 1 false-negative result obtained with this criterion was a 9-mm DCIS with a strain index of 1.29 (Table 2). The \( A_z \) values were 0.879 (95% confidence interval [CI], 0.798–0.936) for the strain index determined with the use of sonoelastography and 0.835 (95% CI, 0.747–0.902) for B-mode sonography (\( P = .490 \); Figure 3).

The final assessment categories according to the BI-RADS classification were as follows: category 3 (probably benign), 10 lesions; category C4a (low suspicion of malignancy), 73 lesions; category C4b (intermediate suspicion of malignancy), 9 lesions; category C4c (moderate suspicion of malignancy), 5 lesions; and category 5 (highly suggestive of malignancy), 2 lesions (Table 1). Malignancy rates for the strain index ranges according to the BI-RADS categories from the B-mode images are shown in Table 3.

Discussion
Our study results showed that there was a significant difference in the mean strain indices between nonpalpable benign and malignant breast masses: 2.63 ± 4.57 (range, 0.54–38.76) for
benign masses versus 6.57 ± 6.62 (range, 1.29–28.69) for malignant masses (P = .019). A strain index cutoff value of 2.24 enabled the best distinction between benign and malignant masses. Most (95% [19 of 20]) of the malignant masses were more than 2.24 times stiffer than the surrounding fat tissue; however, 75% (59 of 79) of the benign masses were less than 2.24 times stiffer than the surrounding fat tissue (P < .001). This result is concordant with that of an initial in vitro study using breast specimens. That study showed that the elastic moduli of malignancy were greater than those of benign masses, and the elastic moduli of benign masses were greater than those of fat tissues.2 Our result suggests that sonoelastography using a strain index can be helpful for differentiation of breast masses that should be examined by the use of a percutaneous biopsy, which is in concordance with previous studies, in which sonoelastography was shown to be able to differentiate between benign and malignant breast lesions.3–9 Quantitative measurement of the relative stiffness by comparison of the strain values of background tissue and the target lesion has also been reported in another study regarding cervical lymph nodes, in which the strain index was calculated by computer postprocessing of sonoelastographic images.10 The investigators reported that the strain index was helpful for differentiation of benign and metastatic cervical lymph nodes. However, the computer postprocessing procedure makes the use of this method difficult in clinical practice. Obtaining the strain index from a static image during real-time sonoelastography, as in our study, is a simple and fast method for estimating the relative lesion stiffness.

To obtain the correct strain index indicating the real stiffness of objects, selection of an adequate reference is paramount. A previous study that evaluated the diagnostic performance of the fat to lesion strain ratio found that 4.8 was the best cutoff value for differentiating benign and malignant masses,a a ratio that was higher than determined in our study. This difference was probably due to the different depth of the reference. In the previous study, the ROI for the reference was placed in the superficial fat tissue adjacent to the skin layer. However, in our study, the ROI for the reference was placed in the fat tissue at a depth similar to or as close to the target mass as possible to avoid stress decay, which is dependent on the depth of an object. The superficial layer under the transducer displaces more than the deep layer, so the strain value of an object in the superficial layer would be higher than that in the deep layer. A recent study suggested that a reference ROI placed in the glandular tissue at the same depth as the lesion would indicate the lesion stiffness correctly.11 However, glandular tissue shows various moduli depending on the compression level, whereas fat tissue shows a constant modulus over various compression loading.2 Therefore, fat tissue located at the same depth as the target lesion would be the most adequate reference point.

Table 2. Malignancy Rates According to the Strain Index Range

<table>
<thead>
<tr>
<th>Strain Index Range</th>
<th>Benign (n = 79)</th>
<th>Malignant (n = 20)</th>
<th>Malignancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.51–1.50</td>
<td>30</td>
<td>1</td>
<td>1/31 (3)</td>
</tr>
<tr>
<td>1.51–2.50</td>
<td>33</td>
<td>2</td>
<td>2/35 (6)</td>
</tr>
<tr>
<td>2.51–3.50</td>
<td>8</td>
<td>4</td>
<td>4/12 (33)</td>
</tr>
<tr>
<td>3.51–4.50</td>
<td>3</td>
<td>2</td>
<td>2/5 (40)</td>
</tr>
<tr>
<td>≥4.51</td>
<td>5</td>
<td>11</td>
<td>11/16 (69)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages.

aSurgical histologic analysis revealed a 0.9-cm high-grade DCIS.
bThe strain indices of these lesions were 2.25 and 2.38, respectively. The lesions were categorized as BI-RADS 4a.

Figure 3. Receiver operating characteristic curves for the sonoelastographic strain index and B-mode sonography. The Az values were not statistically different for the strain index (solid line; 0.879; 95% CI, 0.798–0.936) and B-mode sonography (dashed line; 0.835; 95% CI, 0.747–0.902; P = .490).
In terms of comparison of the strain index determined with the use of sonoelastography and B-mode sonography, the diagnostic performance with respect to differentiation of benign and malignant breast masses was similar for both methods. The $A_z$ values were 0.879 (95% CI, 0.798–0.936) for the strain index and 0.835 (95% CI, 0.747–0.902) for B-mode sonography ($P = .490$).

However, because there was a wide range of overlap of strain index values for benign and malignant masses (Table 2), the importance of the strain index can be attributed to a high negative predictive value, which was 98% (59 of 60) in our study. Notably, for BI-RADS category 4a lesions ($n = 73$) with a strain index range of 0.51 to 1.50, only 1 of 23 lesions (4%) showed malignant histologic findings; it was a 0.9-cm high-grade DCIS. Considering this finding, the need for a biopsy may be averted when lesions with low suspicion have a low strain index.

There were some limitations to this study. First, although 1 of 5 radiologists evaluated the sonoelastographic images, we did not evaluate intraobserver and interobserver variability for acquisition of the strain index. Second, we only compared the diagnostic performance of the strain index and B-mode sonography. Comparison of the strain index and visual assessment using the 5-point scoring system would be necessary to assess the usefulness of the strain index in clinical practice. Further studies with larger numbers may be important to have other radiologists perform the procedure and see whether it can be performed easily and quickly during busy clinical practice.

In conclusion, the strain index based on the fat to mass strain ratio determined with the use of sonoelastography showed diagnostic performance comparable with that of B-mode sonography for differentiation of benign and malignant nonpalpable breast masses. Therefore, the sonoelastographic strain index can be used as a supplementary measure for differentiation of benign and malignant breast masses.

### References


