Electromagnetic Breast Imaging: Results of a Pilot Study in Women with Abnormal Mammograms

To prospectively assess quantitatively the inherent contrast of electromagnetic (EM) properties that can be imaged by using available technology in women with abnormal findings at conventional breast imaging who underwent subsequent biopsy.

The protocol was HIPAA compliant and approved by the institutional review board. All participants provided informed consent. Fifty-three women with normal (Breast Imaging Reporting and Data System [BI-RADS] category 1) and ninety-seven women with abnormal (BI-RADS category 4 or 5) screening mammograms were imaged with three EM imaging methods: electrical impedance spectroscopy (EIS), microwave imaging spectroscopy (MIS), and near-infrared spectral tomography (NIR). A region-of-interest (ROI) analysis was used to assess the EM image properties for comparison of findings with conventional image findings and correlation with specific pathologic parameters for women with abnormal findings. Statistical analyses were conducted.

One hundred fifty participants (age range, 35–81 years) were included. EM image property contrast ratios of 150%–200% were found in breast abnormality ROIs relative to the ipsilateral breast background. Analysis of variance demonstrated significant differences in ROI image summaries of mammographically normal versus abnormal breasts for EIS, across diagnostic groups for NIR, and for MIS (analysis restricted to lesions larger than 1 cm³). Receiver operating curve (ROC) analysis of the EM properties for cancers among subjects with BI-RADS category 4 or 5, compared with the EM properties for the subjects with normal breasts (BI-RADS category 1), yielded areas under the ROC curve ranging from 0.67 to 0.81. Pathologic correlations with mean vessel density, mean vessel area, and epithelium-to-stroma ratio suggest a biological origin of the EM image properties associated with disease.

Results from EM breast examinations provide statistical evidence of a mean increase in image contrast of 150%–200% between abnormal (benign and malignant) and normal breast tissue.

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Breast imaging can potentially reduce the mortality and morbidity of breast disease in a variety of clinical settings, which include risk assessment, breast cancer screening, differential diagnosis, monitoring of therapy, and treatment outcome. Mammography has an established role in breast cancer screening and diagnosis (1,2) and has been shown to contribute to a reduction in breast cancer–specific mortality (3,4). However, mammography has a low positive predictive value (PPV) and diminished sensitivity in the radiographically dense breast (5,6). Contrast material–enhanced breast magnetic resonance (MR) imaging appears promising in the screening of younger women who are at high risk for breast cancer (7,8). Contrast-enhanced breast MR imaging and positron emission tomography have been used to monitor neoadjuvant chemotherapy, with a mix of positive and negative results in regard to the early identification of treatment response (9–11). Given the association of breast cancer with radiographically dense tissue (12–14), there also may be a role for imaging in risk assessment.

Data exist (15–18) that suggest that the electromagnetic (EM) properties of breast tissue offer high contrast for depiction of malignancy over wide portions of the nonionizing EM spectrum. Proof-of-principle demonstrations of imaging methods that exploit this potential contrast mechanism have been reported (19–22), and in some instances, clinical examinations have even been performed with these methods, although generally in small numbers of subjects and with mixed results (23–26). Thus, the purpose of our study was to prospectively assess quantitatively the inherent contrast of EM properties that can be imaged by using available technology in women with abnormal findings at conventional breast imaging who underwent subsequent biopsy.

**Materials and Methods**

**Recruitment**

All study participants provided informed consent as part of the protocol approved by our institutional review board. The study was Health Insurance Portability and Accountability Act compliant. Participants were recruited into either (a) an abnormal group of women who at presentation had imaging findings that were suspicious for malignancy (Breast Imaging Reporting and Data System [BI-RADS] category 4) or highly suggestive of malignancy (BI-RADS category 5) and were scheduled for breast biopsy or (b) a normal control group of women with negative findings (BI-RADS category 1) at screening mammography. Thirty-nine consecutive women in the abnormal group were initially enrolled, and without a time lapse in recruitment, an interleaved set of 53 normal control subjects and 58 additional subjects in the abnormal group were enrolled. Thus, the total number of women in the abnormal group was 97. Participant characteristics that included age, ethnicity, height, weight, and menopausal status were recorded, and body mass index was calculated. All participants were recruited by study coordinators (C.A.K., S.K.S.). Normal control subjects were enlisted on the basis of a random sampling of women with recent negative findings at screening mammography. Subjects in the abnormal group underwent EM examinations on a mean of 2.5 days (range, 0–15 days) prior to breast biopsy, and normal control subjects were examined within a few months, or on a mean of 78.6 days (range, 7–118 days), after the normal screening mammogram was obtained.

**Conventional Breast Imaging**

All 53 normal control subjects and 55 of 97 subjects in the abnormal group underwent mammography with digital (Selenia; Hologic, Danbury, Conn) or screen-film (Lorad MIV with HTC grids; Hologic) mammographic units. Most (51 of 55, 93%) of these 55 subjects in the abnormal group also underwent ultrasonography (US) (HD1 5000; Philips Medical Systems, Bothell, Wash). The remaining 42 of 97 subjects in the abnormal group were referred for biopsy after screening or diagnostic imaging was performed elsewhere by using variable mammographic and US equipment. The exact nature of the imaging equipment that was used and the frequency of performance of US in this outside referral group cannot be determined. Images obtained in all referred subjects were reinterpretated as part of routine clinical practice.

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**Abbreviations:**

- AUC — area under the ROC curve
- BI-RADS — Breast Imaging Reporting and Data System
- EIS — electrical impedance spectroscopy
- EM — electromagnetic
- MIS — microwave imaging spectroscopy
- NR — near-infrared spectral tomography
- PPV — positive predictive value
- ROC — receiver operating characteristic
- ROI — region of interest

**Author contributions:**

Guarantors of integrity of entire study, S.P.P., K.D.P.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, S.P.P., T.D.T., W.A.W., B.W.P., P.M.M., K.D.P.; clinical studies, S.P.P., T.D.T., W.A.W., B.W.P.; P.M.M., C.A.K., S.K.S., K.D.P.; experimental studies, B.W.P., P.M.M., C.A.K., K.D.P.; statistical analysis, T.D.T., J.J.G.; and manuscript editing, S.P.P., T.D.T., W.A.W., B.W.P., P.M.M., C.A.K., K.D.P.

K.D.P. and P.M.M. founded Microwave Imaging System Technologies, Hanover, NH, and are co-inventors on two patents related to microwave imaging held by the company. P.M.M. is acting president of the company.
Conventional Image Interpretation

Conventional breast imaging (i.e., digital or screen-film mammography and US) findings were reevaluated by the study mammographer (S.P.P.), who had 10 years of breast imaging experience at the inception of the study and who completed a conventional image interpretation form for each participant. There were discordant final assessments between the clinical interpretation and study reinterpretation in five subjects in the abnormal group. In two participants, findings that were highly suggestive of malignancy (BI-RADS category 5) were downgraded to findings suggestive for malignancy (BI-RADS category 4) by the study mammographer. In two participants, findings that were suggestive for malignancy (BI-RADS category 4) were upgraded to findings that were highly suggestive of malignancy (BI-RADS category 5). In one participant, findings were downgraded from suspicious for malignancy (BI-RADS category 4) to findings that were probably benign (BI-RADS category 3), but this participant underwent biopsy per the clinical recommendation. The BI-RADS assessment rendered by the clinical radiologist was used in our study. All other conventional imaging results, which include data in the tables, were derived from the study mammographer’s conventional imaging reinterpretation. There were no disagreements about the negative findings (BI-RADS category 1) at assessment of normal control subjects. The mammographic reinterpretation included information about radiographic density, anteroposterior breast diameter in centimeters, BI-RADS assessment category, abnormality type (e.g., calcifications), maximum abnormality size in millimeters, and depth from the nipple in centimeters. The US interpretation included information about abnormality type (e.g., solid mass), maximum size in millimeters, radial distance from the nipple, and depth from the skin surface. The location of the primary abnormality was depicted according to its clock position on a coronal breast diagram to identify a region of interest (ROI) on the subsequent EM image. Additional imaging abnormalities were also reported and diagrammed, when evident.

Breast Biopsy

Percutaneous breast biopsy was performed with mammographic guidance (dedicated prone stereotactic table) or US guidance, depending on lesion visibility, with the units mentioned before by one of two breast imaging specialists with 5 and 10 years (S.P.P.) of breast biopsy experience at the inception of the study. Abnormalities were sampled with 8- or 11-gauge vacuum-assisted probes (Mammatome; Ethicon Endosurgical, Cincinnati, Ohio) or 14-gauge automated cutting devices (CR, Bard, Peripheral Vascular Division, Tempe, Ariz; Interv, Medical Device Technologists, Gainesville, Fla). Participants with benign percutaneous biopsy results underwent follow-up breast imaging at either 6 or 12 months, depending on the specific nature of the pathologic result as per clinical protocol.

Participants who had malignant (n = 31) or atypical (n = 2) needle biopsy results underwent surgical resection as per clinical protocol. In subjects with a diagnosis of malignancy, the pathologic measures from the excisional biopsy material were used in 20 (64%) of 31 of the subjects in whom specimens from both core-needle biopsy and surgical excision were available. No pathologic correlates were measured in two subjects with malignant results (two of 31, 6%) who underwent imaging at the beginning of the study. The original core-needle biopsy material was used to derive pathologic measures in the remaining nine (29%) of 31 subjects with malignant findings: In four (44%) of nine subjects, this procedure was followed because there was no residual lesion in the specimen obtained at surgi-
Radiologic excision; in three (33%) of nine subjects, this procedure was followed because the amount of residual lesion in the specimen obtained at surgical excision was less than that in the specimen obtained at core-needle biopsy; and in two (22%) of nine subjects, this procedure was followed because excisional biopsy was performed at another institution, and the results could not be retrieved. Pathologic measures were derived from the specimens obtained at surgical excision in the two subjects with atypical core-needle biopsy results.

Pathologic Analysis Methods

Biopsy specimens were prepared by using accepted immunohistochemical processing techniques and were evaluated (W.A.W., with 12 years of experience in evaluation of breast pathologic findings) for epithelium-to-stroma ratio, mean vessel density, and mean vessel area by using computer-assisted analysis to generate pathologic correlates for comparison with the EM imaging modality findings. These procedures have been shown to yield reproducible and diagnostically significant markers of breast cancer versus benign abnormalities (27).

EM Imaging Examinations

The technical underpinnings of the three imaging modalities used in this study (Tables 1, 2) have been described in considerable detail elsewhere (28–30), and the imaging machines were developed internally as prototypes. All three of the methods involve prone positioning of the subject during an examination, wherein the imaging array circumscribes the pendant breast. Acquired data are then reconstructed to generate tomographic coronal images of the EM properties of the tissue.

An ROI that corresponds to the location of the abnormality on the conventional imaging diagram (determined by the study mammographer) was identified for each subject in the abnormal group. The mirror-image location served as the ROI in the contralateral breast of subjects in the abnormal group. Pseudo-ROIs were generated for each breast in normal control subjects, on the basis of the location of the most recently imaged density- and age-matched subject in the abnormal group. In the initial 39 subjects in the abnormal group, the clock location and side of involvement (right vs left) were known at the time of EM examination, and the imaging arrays were placed accordingly by one of the study coordinators (S.K.S.), but the cancer status of the ROI was unknown at the time of image analysis. In this series of abnormalities, the ROI size range was 3–40 mm. During the second phase of recruitment, which included all 53 normal control subjects and 58 (60%) of 97 subjects in the abnormal group, symmetric fiducial markings were placed on both breasts at the time of EM imaging by one of the study coordinators (C.A.K.), without disclosure of BI-RADS status or pathologic analysis outcome prior to image analysis. In this series of 58 abnormal lesions, the ROI size range was 3–30 mm.

Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EIS</th>
<th>MIS</th>
<th>NIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examination geometry</td>
<td>Prone, pendant breast</td>
<td>Prone, pendant breast</td>
<td>Prone, pendant breast</td>
</tr>
<tr>
<td>No. of planes</td>
<td>1–3</td>
<td>7</td>
<td>1–3</td>
</tr>
<tr>
<td>No. of images per plane</td>
<td>20*</td>
<td>14†</td>
<td>10‡</td>
</tr>
<tr>
<td>Examination time per breast (min)*</td>
<td>5–7</td>
<td>12–15</td>
<td>10–15</td>
</tr>
<tr>
<td>Reconstruction time (min)§</td>
<td>&lt;30</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Note.—In addition to optical absorption and scattering with NIR, images of total hemoglobin concentration, oxygen saturation, water fraction, scattering amplitude, and scattering power are formed.

* The number was calculated on the basis of 10 frequencies multiplied by two imaged properties.
† The number was calculated on the basis of seven frequencies multiplied by two imaged properties.
‡ The number was calculated on the basis of five wavelengths multiplied by two imaged properties.
§ The examination time included time for positioning.

Table 3

| Summary of Clinical Characteristics of Subjects |
|----------------|------------------|------------------|
| Variable | Subjects in Abnormal Group (n = 97) | Normal Control Subjects (n = 53) |
| Age (y)* | 56.2 ± 11.6 | 57.2 ± 10.4 |
| Body mass index (kg/m²)* | 27.2 ± 6.3 | 25.2 ± 4.1 |
| Breast density† | | |
| BI-RADS category 1 | 6 (6) | 4 (8) |
| BI-RADS category 2 | 51 (52) | 26 (49) |
| BI-RADS category 3 | 28 (29) | 19 (36) |
| BI-RADS category 4 | 12 (12) | 4 (8) |

* Values are the mean ± standard deviation.
† Values are the number of subjects, and numbers in parentheses are percentages.
the analysis was completed plane by plane in an independent manner. The contralateral breast of subjects in the abnormal group and both breasts of normal control subjects were treated similarly.

Ratios of \((a)\) ROIs to the background in the abnormal breast and \((b)\) ROIs in the abnormal ipsilateral breast to ROIs in the contralateral breast were formed. Paired Wilcoxon tests were used to compare the ROI with background and to compare the ROI in the ipsilateral breast with the ROI in the contralateral breast. An analysis of covariance was conducted to compare the means and ratios, according to pathologic diagnostic category, that were calculated for both unadjusted models and models adjusted for the subject’s body mass index and age, with \(P\) values that were based on an \(F\) test. The Proc Mixed procedure from the statistical package (SAS; SAS, Cary, NC) was used for these analyses. Correlation coefficients were calculated to examine the associations between the image property data and histologic assays.

A multimodal index was also formed by using weighting coefficients derived from logistic regressions to predict BI-RADS categories and final diagnostic categories. To make the best use of the available examination findings, missing data were imputed on the basis of a multivariate normal assumption to generate 60 complete data sets in which missing values for the modality properties were predicted from the properties available for that subject. By using multiple logistic regressions for each imputed data set, index values were calculated. The resulting 60 indices were averaged for each individual and used to form estimates of receiver operating characteristic (ROC) curves, and normal control subjects (BI-RADS category 1) were compared with subjects in the abnormal group (BI-RADS category 4 or 5) who had cancer outcomes. The calculations were performed with Proc Mi and Proc Logist by using the statistical package mentioned before. The results of this analysis were intended to explore the potential utility of combining the

**Table 4**

<table>
<thead>
<tr>
<th>Pathologic Diagnosis</th>
<th>No. of Subjects with Masses*</th>
<th>No. of Subjects with Calcifications*</th>
<th>No. of Subjects with Asymmetry or Architectural Distortion*</th>
<th>Mean Size of Lesion (mm)</th>
<th>Mean Epithelium-to-Stroma Ratio†</th>
<th>Mean Vessel Density†</th>
<th>Mean Vessel Area (mm²)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (11/21)</td>
<td>21 (68)</td>
<td>8 (26)</td>
<td>2 (6)</td>
<td>12.5</td>
<td>0.12 (0.01)</td>
<td>0.68 (0.03)</td>
<td>93.0 (7.1)</td>
</tr>
<tr>
<td>Fibrocystic disease (11/49)</td>
<td>12 (24)</td>
<td>31 (63)</td>
<td>6 (12)</td>
<td>11.2</td>
<td>0.03 (0)</td>
<td>0.39 (0.02)</td>
<td>122.4 (5.1)</td>
</tr>
<tr>
<td>Fibroadenoma (11/11)</td>
<td>8 (73)</td>
<td>2 (18)</td>
<td>1 (9)</td>
<td>13.1</td>
<td>0.05 (0.01)</td>
<td>0.47 (0.03)</td>
<td>247.7 (10.9)</td>
</tr>
<tr>
<td>Other benign abnormalities (6/4)</td>
<td>4 (67)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>9.5</td>
<td>0.01 (0.01)</td>
<td>0.95 (0.27)</td>
<td>135.3 (21.9)</td>
</tr>
<tr>
<td>All (97)</td>
<td>45 (46)</td>
<td>42 (43)</td>
<td>13 (11)</td>
<td>11.7</td>
<td>0.06 (0.01)</td>
<td>0.53 (0.03)</td>
<td>128.0 (3.4)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are percentages.
† Numbers in parentheses are the standard error.

**Figure 1**

Corresponding craniocaudal mammographic views (top row) and coronal EM images (bottom row) of three invasive ductal cancers (arrows) in three subjects. Left: An 11-mm invasive ductal cancer seen as a 1-cm oval mass on the right craniocaudal mammogram and as a white focus (with a peak conductivity value of 1.5 siemens per meter) in the upper outer quadrant on the corresponding coronal EIS conductivity image of the right breast. Middle: An 8-mm invasive ductal cancer identified as focal asymmetry on the left craniocaudal mammogram and as a lighter gray focus (with a peak conductivity of 0.8 siemens per meter) in the upper outer quadrant on the corresponding coronal MIS conductivity image of the left breast. Right: A 35-mm invasive ductal cancer seen as bilobed asymmetry with architectural distortion on the left craniocaudal mammogram and as a black focus (with a peak hemoglobin value of 40 μmol/L) in the lower central left breast on the corresponding coronal NIR hemoglobin image.
modalities. More formal inference procedures (32) that are used to adjust confidence intervals appropriately for the amount of missing data were not implemented, given the mainly descriptive purpose of this portion of the study.

ROC curves were generated both empirically and with a binormal fit, and the 95% confidence intervals were included (33,34). In addition, an estimate of the PPV in combination with mammography was determined, on the basis of the BI-RADS category 4 and 5 group, as a function of the cutoff value of the contrast ratio used to determine a cancer designation from each EM examination.

Results

Clinical and Pathologic Characteristics

Approximately one-third (31 of 97, 32%) of the subjects in the abnormal group had breast cancer; nine of these women had ductal carcinoma in situ. Two women with a diagnosis of atypical ductal hyperplasia at core-needle biopsy were included in the group of 49 women with fibrocystic disease, because subsequent surgical excision of the biopsy site showed fibrocystic disease with variable amounts of bland ductal hyperplasia, cysts, and adenosin, but no residual atypia (Tables 3, 4). The six women in the category for other benign abnormalities had pathologic diagnoses of complex cysts (n = 2), which completely resolved with fine-needle aspiration; intramammary lymph nodes (n = 2); granulomatous mastitis (n = 1); and hematoma with granulation tissue (n = 1). The lesions depicted at mammography were relatively small, with mean and median sizes of 11.7 mm and 10 mm, respectively, for all subjects; for malignant lesions, the mean and median sizes were 12.5 mm and 11 mm, respectively. Pairs of representative mammographic and EM correlative images are shown for three participants (Fig 1). Because of space limitations, only the craniocaudal mammogram is displayed; however, in each example, the conventional image was localized to the quadrant in which the EM image was abnormal.

Examination Completion

EM examination completion and analysis rates varied among modalities. Images from examinations were excluded when they were not delivered or examinations were not completed or when the data collected from the examinations could not be analyzed. The most common reasons for missed or incomplete examinations were technical difficulties (eg, data acquisition failure from faulty software control) with the equipment (15 with EIS, five with MIS, five with NIR) and breast size (four with EIS, none with MIS, 11 with NIR) from restrictions on the maximum array diameters. The most common reasons for an-
alytic failures were data calibration (33 with EIS, 15 with MIS, none with NIR) and insufficient power or wavelengths caused by technical limitations of the equipment during an examination (none with EIS and MIS, 34 with NIR).

**EM Modality Findings**

**EIS imaging results.**—A total of 62 subjects in the abnormal group (BI-RADS category 4 or 5) and 36 normal control subjects (BI-RADS category 1) were included in this analysis for EIS. Among the examinations in the 62 subjects in the abnormal group, findings were classified as malignancies in 16, fibrocystic disease sites in 32, fibroadenomas in nine, and other benign abnormalities in five. The mean conductivity and permittivity ratios of ROI to background according to diagnostic category, with the 95% confidence intervals and the P values for the analysis of covariance for the groups being compared, are summarized in Figure 2.

An ROC curve (Fig 3) was constructed from data in subjects in the abnormal group (BI-RADS category 4 or 5) with outcomes of cancer and normal control subjects (BI-RADS category 1) by calculating the sensitivity and specificity for diagnostic decisions, with cutoffs that were based on conductivity ratios to background. The AUC is estimated at 0.78 (95% confidence interval: 0.66, 0.91). AUCs for cancer–noncancer and cancer–benign lesion groupings (not shown) were 0.66 and 0.59, respectively. Given our study design, these ROC curves do not directly yield an estimate of sensitivity and specificity in the screening population because we did not include subjects whose findings were classified as BI-RADS category 2 or 3 with verification. An estimate of the PPV in combination with mammography is shown (Fig 3) that is based on the pathologic outcome of the subjects in the abnormal group as a function of the cutoff used for the conductivity contrast ratio.

**MIS imaging results.**—A total of 80 subjects in the abnormal group and 50 normal control subjects were examined with MIS. Among the examinations in these 80 subjects in the abnormal group, findings were classified as malignancies in 28, fibrocystic disease sites in 32, fibroadenomas in 15, and other benign abnormalities in five. The mean conductivity and permittivity ratios of ROI to background according to diagnostic category, with the 95% confidence intervals and the P values for the analysis of covariance for the groups being compared, are summarized in Figure 2.

An ROC curve (Fig 3) was constructed from data in subjects in the abnormal group (BI-RADS category 4 or 5) with outcomes of cancer and normal control subjects (BI-RADS category 1) by calculating the sensitivity and specificity for diagnostic decisions, with cutoffs that were based on conductivity ratios to background. The AUC is estimated at 0.78 (95% confidence interval: 0.66, 0.91). AUCs for cancer–noncancer and cancer–benign lesion groupings (not shown) were 0.66 and 0.59, respectively. Given our study design, these ROC curves do not directly yield an estimate of sensitivity and specificity in the screening population because we did not include subjects whose findings were classified as BI-RADS category 2 or 3 with verification. An estimate of the PPV in combination with mammography is shown (Fig 3) that is based on the pathologic outcome of the subjects in the abnormal group as a function of the cutoff used for the conductivity contrast ratio.

**Figure 3:** ROC (top row) and PPV plots (bottom row) for the EM modalities for EIS conductivity (far left), MIS conductivity (left), NIR total hemoglobin (right) contrast ratios, and those for all three modalities combined (far right). Comparison groups for the ROC analyses were based on cancers in BI-RADS category 4 or 5 for subjects in the abnormal group versus the normal control subjects (BI-RADS category 1). Dotted horizontal lines in each PPV plot show the percentage of cancers among the subjects with BI-RADS 4 or 5 classification in the examination sets analyzed for each modality. EIS shows good sensitivity to breast abnormality but relatively poor specificity, whereas MIS and NIR are more diagnostically specific and improve the PPV of mammography considerably in the subjects in the abnormal group pool. The multimodal index shows some diagnostic improvement over the best single-modality performance. Numbers in parentheses after AUC values are the 95% confidence intervals, AUC = area under the ROC curve, HbT = total hemoglobin, σ = conductivity.
nancies in 26, fibrocystic disease sites in 41, fibroadenomas in eight, and other benign abnormalities in five. Mean conductivity and permittivity ratios of ROI to background are summarized according to diagnostic groups (Fig 2), groups that included all participants and a subset of participants with larger (>1-cm) abnormalities. For lesions with a mammographic abnormality that was greater than 1 cm, differences in the mean conductivity contrast were highly significant (P < .001 [unadjusted], P < .002 [adjusted]) in group comparisons for the diagnostic categories.

An ROC curve that was based on the mean conductivity values for subjects in the abnormal group with cancers larger than 1 cm and for normal control subjects, with the AUC estimated to be 0.80 (95% confidence interval: 0.68, 0.92), was constructed (Fig 3). AUCs for cancer–noncancer and cancer–benign lesion groupings (curves not shown) were 0.83 and 0.89, respectively. The ROI ratios for larger lesions (ie, >1 cm) were used to plot the PPV (Fig 3) for women with positive mammograms and ROI ratios greater than a given cutoff. In this subgroup, the addition of MIS more than doubled the PPV and provided a meaningful statistical inference.

NIR imaging results.—NIR hemoglobin (total hemoglobin) contrast ratios have been summarized (Fig 2). A total of 58 subjects in the abnormal group and 42 normal control subjects were included in this analysis. Among the examinations in the 58 subjects in the abnormal group, the findings were malignancies in 18, fibrocystic disease sites in 31, fibroadenomas in seven, and other benign abnormalities in two. Among the diagnostic groups, on the basis of a comparison with analysis of covariance, ratios of the ROI in the ipsilateral breast to the ROI in the contralateral breast for total hemoglobin were statistically significant in both evaluations (P = .013 [adjusted], P = .017 [unadjusted]).

The ROC and PPV plots as applied to the NIR mean total hemoglobin contrast ratio relative to the ROI in the contralateral breast are shown (Fig 3). When lesions smaller than 6 mm were excluded, the mean total hemoglobin contrast ratio in the ipsilateral breast increased to 1.5, which is greater than the contrast ratios for all other benign abnormalities and the normal control subjects. A difference with P < .05 was significant. For this subgroup, the AUC (not shown) also increased significantly to 0.88 (from 0.67 in Fig 3) in the cancer–normal control subject group, and is 0.82 and 0.76 for the cancer–noncancer and cancer–benign lesion groupings, respectively.

Quantitative Pathologic Findings

Statistically valid differences were observed across the diagnostic categories with unadjusted and adjusted P values less than .001, except for mean vessel area, for which the unadjusted and adjusted P values were .004 and .016, respectively. These findings are similar to the results reported in the study of Wells et al (27) for archived specimens.

In additional analyses, we compared EM properties obtained from the ROI with the quantitative morphometric measures. The results for EIS showed a nearly significant (P = .06) correlation coefficient of 0.41 for the correlation of permittivity with pathologic size and a highly significant (P = .005) coefficient of −0.38 for the correlation of permittivity with mean vessel area. For MIS conductivity, significant correlation coefficients of 0.76 and −0.69 were found for the epithelium-to-stroma ratio (P = .03) and mean vessel area (P = .05), respectively, in the large-lesion (>1 cm) group. In addition, the ratio of the ROI of the ipsilateral breast to the ROI of the contralateral breast for conductivity showed a significant (P = .01) correlation coefficient of 0.81 for a correlation with mean vessel density. In NIR, the total hemoglobin concentration was correlated significantly with mean vessel density in abnormalities larger than 6 mm, with a correlation coefficient of 0.75 (P < .05); also, a decrease in scattering power was correlated significantly with an increase in epithelium-to-stroma ratio, with a correlation coefficient of 0.69 (P < .05).

Treatment of Subjects and Follow-up

Seventy-seven of the subjects in the abnormal group underwent subsequent imaging for a mean time of 22 months, with a range of 4–61 months. The remaining 20 subjects in the abnormal group were lost to follow-up because they had moved out of state (n = 3), were referred from an outside institution that reported that no further imaging had been performed (n = 6), or were internal recruitments who had not undergone subsequent imaging (n = 11). Eight subjects in the abnormal group underwent subsequent tissue sampling, and all of them had benign pathologic results. In five of these subjects in the abnormal group, biopsy was performed at a different site in the same breast or the contralateral breast. In the other three subjects, biopsy of the same site at which EM imaging had been performed was conducted. Two of these three subjects received breast-conserving treatment, and later they had clinical (one case) or mammographic (one case) prominence of the lumpectomy site, 26 months and 21 months after diagnosis, respectively. One of these subjects underwent US-guided biopsy, which showed a benign postsurgical change, whereas the other underwent US-guided fine-needle aspiration of a hematoma. The remaining subject had progression of the initial abnormality (ie, increasing asymmetry). Subsequent biopsy showed focal fibrosis. Follow-up imaging was performed in 43 of 53 nor-
On the basis of results from the ROI analysis in our study, the EM property indicators with the highest contrast ratios for cancer (Fig 2) appear to be electrical permittivity at EIS (mean contrast ratio, 1.6), electrical conductivity at MIS (mean contrast ratio for lesions >1 cm in size, 2.0), and total hemoglobin concentration at NIR (mean contrast ratio for lesions >6 mm in size, 1.5). Furthermore, the pathologic correlative data suggest that the biological origins of the EM image properties are probably associated with the extent of vascular activity and cellular proliferation within the abnormality.

With regard to the individual EM modalities, EIS as used in this study appears to help in the discrimination between normal and abnormal breast tissue but may not aid in the differentiation of cancer from other abnormal pathologic findings. There is image contrast in both permittivity and conductivity, with statistically significant separation in the conductivity measure from the normal control subjects. The smaller difference in permittivity contrast may be caused by a bias toward a fibroglandular location of the ROI in the normal control subjects because breast permittivity increases with breast density (31).

It is important to recognize that our results have not taken advantage of the multidimensional (ie, three-dimensional) and multispectral character of the examination data, nor have they exploited the high temporal resolution that is possible with the technique.

Our MIS results indicate that both of the image parameters, conductivity and permittivity, provide contrast, although conductivity appears to provide better discrimination. However, the capability of MIS signals to differentiate breast cancer from normal or benign breast conditions may be size dependent. Future technologic improvements are expected to improve image resolution by extending the frequency range of data acquisition and the collection of three-dimensional data.

The NIR data are encouraging but also indicate a possible resolution threshold level below which NIR is unable to recover contrast ratios sufficiently accurately to serve as a quantitative index for cancer discrimination. As with MIS, our NIR results reveal AUC values that approach those recently reported for breast MR imaging (35), in the setting of an enrollment group with screening-detected abnormalities with lesion sizes of greater than 6 mm.

These analyses represent our initial attempt to exploit a multimodality framework for enhancing breast cancer diagnosis. The combined multimodality data appear to add at least some diagnostic value above and beyond the individual EM modality assessments, but the differences appear incremental and have not been evaluated for statistical significance or clinical relevance. At present, the individual examination times are too long to be used in practice for multimodality assessment in a high-throughput clinical setting. However, the lengths of the examinations are predominantly determined by the data acquisition rates available with the respective imaging platforms, which do not represent fundamental technology limits, and could be made much faster in future realizations of the imaging systems. Nonetheless, both the individual and multimodality indices are encouraging, given the early stage of EM imaging technology development. The cancers in our study were small (mean size, approximately 12 mm) relative to the mean size (approximately 16 mm) of screening-detected malignancies in our region (36), and this finding further increases the challenges of detection and diagnostic characterization in this cohort.

Although our initial experience with the EM modalities has been positive, the approximate nature of the spatial colocalization of abnormalities between conventional and EM examinations because of different acquisition geometries is a limitation. In addition, EM results may have been improved by the ROI methods, because the EM modalities have not been evaluated without the aid of a preselected ROI. It is also important to recognize that, although we report our initial experience with these modalities in terms of the standard clinical metrics of AUC, PPV, and other factors, enrollment in this study did not include women with mammographic findings that were classified as BI-RADS category 2 or 3 and women with negative screening mammographic findings (BI-RADS category 1) as representative of the normal population. The overall number of diagnoses of cancer in the enrollment pool is also relatively small; hence, AUCs associated with the cancer–noncancer and cancer–benign lesion comparisons are weaker statistically.

Our initial experience with EM breast imaging methods provides statistical evidence of a mean increase in image contrast of 150%–200% between abnormal (benign and malignant) and normal breast tissue. Both MIS and NIR also show the potential to help in the discrimination between breast cancer and benign breast conditions following a positive screening mammogram. Furthermore, statistically significant correlations of EM image properties with specific pathologic measures—particularly mean vessel density, mean vessel area, and epithelium-to-stroma ratio—point to the biological origins of the EM properties. Although these initial data are encouraging, the influence of various selection biases (eg, subject pool, ROI location, and other factors), lesion size, coregistration accuracy, normal tissue heterogeneity, and other technical factors such as volume averaging require additional study. Further, the examination failure rates experienced in this study are too high for routine clinical use, although they are primarily associated with technical limitations in the
present installations that would be expected to be overcome in future generations of the prototypes used here. These and other important issues need to be analyzed to assess the practical clinical utility of the EM imaging modalities.

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References