Mammography and Subsequent Whole-Breast Sonography of Nonpalpable Breast Cancers: The Importance of Radiologic Breast Density

OBJECTIVE. Our purpose was to determine the contribution of mammography followed by sonography for the detection of nonpalpable breast cancers in Breast Imaging Reporting and Data System (BI-RADS) density grades 1–4 breasts, in grades 1 and 2 breasts, and in grades 3 and 4 breasts.

MATERIALS AND METHODS. The results of physical, mammographic, and sonographic examinations performed in 4236 patients were reviewed to determine the sensitivities of mammography and sonography for the detection of nonpalpable breast cancers and to calculate the relative risk for detecting nonpalpable breast cancers using sonography in comparison with mammography in density grades 1–4, grades 1 and 2, and grades 3 and 4 breasts. Sonography was performed after mammographic interpretation.

RESULTS. Sensitivities of mammography and subsequent sonography for the detection of nonpalpable breast cancers were 69% and 88% in grades 1–4, 80% and 88% in grades 1 and 2, and 56% and 88% in grades 3 and 4 breasts, respectively. The relative risk for detecting nonpalpable breast cancers using sonography was statistically significantly greater than that for detecting nonpalpable breast cancers using mammography in grades 1–4 (relative risk, 1.29; \( p = 0.024 \)) and in grades 3 and 4 (relative risk, 1.57; \( p = 0.013 \)) but not in grades 1 and 2 (relative risk, 1.1; \( p = 0.445 \)) breasts.

CONCLUSION. Sonography is a useful adjunct after mammography for the detection of nonpalpable breast cancer, particularly in the dense breast.

Early treatment of nonpalpable breast cancer reduces the breast cancer mortality rate [1], and mammography is routinely used for the detection of breast cancer because of its high sensitivity. However, several conditions, including grades 3 and 4 breasts, may decrease the sensitivity of mammography [2, 3]. Recent studies performed in selected populations, including women with dense breasts on mammography [4, 5], women with known breast cancer [6], women with mammographic abnormalities, and women with physical abnormalities [7–9], showed the ability of sonography to detect clinical and mammographically occult breast cancer. Using both sonography and mammography increases the sensitivity for the detection of cancer from 83% to 91% [2].

In our institution, breast imaging almost systematically includes mammography and sonography, independently from the clinical examination. Except patients in whom only sonography is performed (pregnant and lactating women, women < 30 years old, and follow-up at 6 months for a benign-on-sonography-only lesion) and patients in whom only mammography is performed (women with entirely fatty breasts and follow-up at 6 months of a mammographically benign lesion), patients are routinely screened with whole-breast sonography and mammography.

The purpose of our study was to determine the respective contributions of mammography and sonography for the detection of nonpalpable breast cancer in breasts of different mammographic densities.

Materials and Methods

From April 2000 through March 2001, 5376 women were referred to our institution for breast imaging, and the results of examinations were prospectively recorded. We excluded 1140 patients from the study group, including pregnant women, breast-feeding women, women younger than 30 years old (n = 276) in whom only sonography was performed after mammographic interpretation.

RESULTS. Sensitivities of mammography and subsequent sonography for the detection of nonpalpable breast cancers were 69% and 88% in grades 1–4, 80% and 88% in grades 1 and 2, and 56% and 88% in grades 3 and 4 breasts, respectively. The relative risk for detecting nonpalpable breast cancers using sonography was statistically significantly greater than that for detecting nonpalpable breast cancers using mammography in grades 1–4 (relative risk, 1.29; \( p = 0.024 \)) and in grades 3 and 4 (relative risk, 1.57; \( p = 0.013 \)) but not in grades 1 and 2 (relative risk, 1.1; \( p = 0.445 \)) breasts.

CONCLUSION. Sonography is a useful adjunct after mammography for the detection of nonpalpable breast cancer, particularly in the dense breast.

Early treatment of nonpalpable breast cancer reduces the breast cancer mortality rate [1], and mammography is routinely used for the detection of breast cancer because of its high sensitivity. However, several conditions, including grades 3 and 4 breasts, may decrease the sensitivity of mammography [2, 3]. Recent studies performed in selected populations, including women with dense breasts on mammography [4, 5], women with known breast cancer [6], women with mammographic abnormalities, and women with physical abnormalities [7–9], showed the ability of sonography to detect clinical and mammographically occult breast cancer. Using both sonography and mammography increases the sensitivity for the detection of cancer from 83% to 91% [2].

In our institution, breast imaging almost systematically includes mammography and sonography, independently from the clinical examination. Except patients in whom only sonography is performed (pregnant and lactating women, women < 30 years old, and follow-up at 6 months for a benign-on-sonography-only lesion) and patients in whom only mammography is performed (women with entirely fatty breasts and follow-up at 6 months of a mammographically benign lesion), patients are routinely screened with whole-breast sonography and mammography.

The purpose of our study was to determine the respective contributions of mammography and sonography for the detection of nonpalpable breast cancer in breasts of different mammographic densities.

Materials and Methods

From April 2000 through March 2001, 5376 women were referred to our institution for breast imaging, and the results of examinations were prospectively recorded. We excluded 1140 patients from the study group, including pregnant women, breast-feeding women, women younger than 30 years old (n = 276) in whom only sonography was performed after mammographic interpretation.
performed, women with entirely fatty breasts and normal findings on mammography (n = 72) in whom no sonography was performed, women referred for follow-up of benign findings at 6 months (n = 540) because mammography on only one side or only sonography was performed, and women referred for a second study after equivocal previous investigations (n = 252) because we did not perform complete mammographic and complete sonographic examinations at our institution.

A total of 4236 patients who had complete mammography and whole-breast sonography in our institution were included in our study. The indications of the examination were screening for 3084 patients (73%); follow-up after breast cancer surgery for 1016 patients (24%) (conservative surgery in 640 patients and mastectomy in 376); and physical abnormality, including a suspicious palpable mass, in 136 patients (3%). Patients with palpable abnormalities were included in the study because they had complete mammographic and sonographic examinations and additional nonpalpable cancers could be found. Palpable abnormalities were excluded from the analysis.

Two radiologists, one with 4 and one with 10 years’ experience in breast imaging, participated in the study. The same radiologist performed the physical, mammographic, and sonographic examinations in each patient. Physical examination of the whole breasts and axillary regions was performed with the patient in the sitting position with arms both lowered and in the supine position with arms raised. Physical findings were drawn on a report and the estimated size of the masses, if any, was noted. Except for the 3% of patients referred for suspicious masses, the remaining patients had negative findings at physical examination.

Mammograms were obtained with dedicated mammography units (CRG 600T, General Electric Medical Systems, Milwaukee, WI; MammoMat II, Siemens, Erlangen, Germany). Cranio-caudal and oblique views were obtained in all patients. Mediolateral views were obtained in particularly dense or heterogeneous breasts. If necessary, magnification views were obtained with focal spots of 0.1 mm. Dedicated mammography cassettes (Minn-R 2000; Kodak, Rochester, NY) and screens (Minn-R 2000; Kodak) were used.

On mammograms, lesions were defined according to standard criteria that included the presence of a mass, distortion, and calcifications. Mammograms were analyzed and the breast density grades were determined according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) [10] on a scale of 1–4, with 4 corresponding to a dense breast, 3 to a heterogeneous breast, 2 to “scattered fibroglandular densities that could obscure a lesion,” and 1 to an “almost entirely fat breast.” All mammograms were interpreted before sonography was performed.

Sonographic examinations were systematically performed by the radiologist who had performed the physical examination and who had interpreted the mammograms of that patient. Sonographic examinations were performed using a high-resolution unit (Elegra; Siemens, Erlangen, Germany) with a linear array probe centered at 7.5 MHz. Tissue harmonic imaging, which is commercially available, was used in all cases. The incident frequency was 4.8 MHz and the received frequency was 9.6 MHz. One focalization was used according to the depth of the breast. All sonographic examinations were performed with the patient in a supine position for the medial parts of the breast and in a contralateral posterior oblique position with arms raised for the lateral parts of the breast. Mild compression was applied. The whole breasts were scanned. Pectoralis muscle had to be seen on all images to be sure that the entire breast was examined.

At sonographic examination, a lesion was defined by the presence of a mass, of an acoustic shadow, or of an architectural distortion of the breast. A mass was considered to be a typical cyst if it was entirely anechoic, had smooth walls, and had posterior enhancement. Lesions that did not show all features of a typical cyst were measured in three planes on the screen during the sonographic examination. Images and measurements of lesions were printed on films, and topography and size of the lesions were drawn on a report. The patient was informed immediately of the results of the sonographic examination.

When a lesion was found, sonographically guided fine-needle aspiration biopsy with a 22-gauge needle was performed by the radiologist who did the physical, mammographic, and sonographic examinations immediately after the patient gave oral consent. Fine-needle aspiration biopsy was performed in cases of not-previously-documented or enlarging nontypical cystic masses. Results of fine-needle aspiration biopsy were available in less than 24 hr. In cases of insufficient diagnosis with fine-needle aspiration biopsy, core biopsy with a 14-gauge needle was performed with sonographic guidance (n = 6). A mean of 4.5 tissue samples were obtained and placed in a formalin solution.

For lesions visible only with mammography, stereotactic core biopsies were performed with a 14-gauge needle. A mean of 7.6 tissue samples were obtained.

Reports sent to the referring physician included the results of fine-needle aspiration biopsy and the results of biopsy, when performed.

All patients with positive findings on fine-needle aspiration biopsy or on biopsy underwent surgery, and histopathologic type and size were available in all cases.

For the assessment of interobserver reproducibility in determining BI-RADS grades, the mammograms of each patient were interpreted by the radiologist who had not been involved in the patient’s workup. All mammograms of patients with cancers diagnosed only at sonography were reviewed in retrospect.

Sensitivities of mammography and sonography for the detection of nonpalpable breast cancers were determined in density grades 1–4, grades 1 and 2, and grades 3 and 4 breasts. When the findings of physical examination, mammography, and sonography were negative, they were considered to be true-negative.

Data were analyzed using the relative risk calculation at a confidence interval (CI) of 95%, using the Mantel-Haenszel method to evaluate the statistical difference between sonography and mammography for the detection of nonpalpable breast cancers in grades 1–4 breasts and separately in grades 1 and 2 and grades 3 and 4 breasts. Relative risks directly expressed the amount of cancers detected by sonography compared with mammography (e.g., if relative risk = 2, sonography detected twice as many nonpalpable breast cancers as mammography did). Findings with a p value of less than 0.05 were considered statistically significant [11]. Kappa statistics were calculated to evaluate interobserver variability for breast density grading.

Results

Contributions of Mammography and Sonography in the Entire Population

In the entire population, cancer was diagnosed in 161 patients. Fifty nonpalpable breast cancers were diagnosed in 47 patients. The mean patient age was 60.7 years (median age, 60 years; range, 41–87 years). Sonographic sizes and histologic sizes and types are listed in Table 1.

Twenty-eight (56%) nonpalpable breast cancers were detected on both mammography and sonography, six (12%) on mammography only, and 16 (32%) on sonography only (Table 2) (Figs. 1 and 2). All mammograms were interpreted before sonographic examinations were performed. Sensitivities of mammography and sonography for the detection of nonpalpable breast cancers were 69% and 88%, respectively.

In grades 1–4 breasts, the relative risk of sonography for detecting nonpalpable breast cancers compared with mammography was 1.29 (95% CI, 1.04–1.61), and this difference was statistically significant (p = 0.024).

A retrospective review of mammograms of patients with cancers diagnosed only at sonography showed no specific mammographic findings of malignancy.

Contributions of Sonography and Mammography in Breasts of Density Grades 1 and 2 and Grades 3 and 4

Our study found 25 nonpalpable breast cancers (24 patients) in grades 1 and 2 breasts and 25 nonpalpable breast cancers (23 patients) in grades 3 and 4 breasts (Table 3). The distribution of patients in tissue density groups is given in Table 4.

In grades 3 and 4 breasts, sensitivities of mammography and sonography for the de-
Mammography and Whole-Breast Sonography of Breast Cancers

TABLE I Mammographic and Histologic Findings

<table>
<thead>
<tr>
<th>Finding</th>
<th>Mammography and Sonography</th>
<th>Mammography Only</th>
<th>Sonography Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiculated mass</td>
<td>8 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ill-defined mass</td>
<td>6 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass with irregular margins</td>
<td>6 (6)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mass with microcalcifications</td>
<td>2 (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcalcifications</td>
<td>4 (4)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>16</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>4</td>
<td>5^a</td>
<td>2</td>
</tr>
<tr>
<td>Tubular carcinoma</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colloid carcinoma</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Note.—Above double rule, data are numbers of patients; numbers in parentheses are numbers of lesions.

^a With 2-mm invasive ductal carcinoma in one patient.

Size on sonography (mm)

<table>
<thead>
<tr>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.7</td>
<td>7</td>
<td>4–15</td>
</tr>
</tbody>
</table>

Size at histology (mm)

<table>
<thead>
<tr>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.9</td>
<td>9.5</td>
<td>4–22</td>
</tr>
</tbody>
</table>

Table 2 Cancers Diagnosed with Mammography or Sonography or Both

<table>
<thead>
<tr>
<th>Mammography</th>
<th>Sonography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>No Cancer</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses are percentages.

 Detection of nonpalpable breast cancers were 56% and 88%, respectively. The relative risk of sonography for detecting nonpalpable breast cancers compared with mammography was 1.57 (95% CI: 1.08–1.4), and this difference was statistically significant (p = 0.013).

In grades 1 and 2 breasts, sensitivities of mammography and sonography for the detection of nonpalpable breast cancers were 80% and 88%, respectively. The relative risk of sonography for detecting nonpalpable breast cancers was 1.1 (95% CI: 0.86–1.4) without a statistically significant difference (p = 0.445).

The interobserver agreement for the evaluation of breast density was excellent (κ = 0.91).

Discussion

The results of our study are threefold. First, in the entire study population, sensitivities of mammography and sonography for the detection of nonpalpable breast cancers were 69% and 88%, respectively, with a 1.29 higher risk for detecting nonpalpable breast cancers by means of sonography than by means of mammography. Comparison between the current and previous studies is limited because of the use of tissue harmonic sonography and the analysis of nonpalpable breast cancers. First, we studied a radiographically unselected population with consecutive patients, including patients referred for screening. Second, we selected nonpalpable breast cancers; and third, we used exclusively tissue harmonic imaging. To our knowledge, the overall comparison of mammography and tissue harmonic sonography for detecting breast cancer has not yet been assessed. Therefore, the relatively poor sensitivity of mammography for detecting nonpalpable breast cancers could be related to the fact that sonography largely contributed to the detection of nonpalpable breast cancers.

Second, in density grades 3 and 4 breasts, our study showed that sensitivities of mammography and sonography for the detection of nonpalpable breast cancers were 56% and 88%, respectively, with a 1.57 significantly greater risk for the detection of nonpalpable breast cancers by means of sonography than by means of mammography. Similar to findings in prior studies [5–7], these results corroborate the finding of the increased sensitivity of sonography for detecting nonpalpable breast cancers in grades 3 and 4 breasts. Most likely, the added value of sonography derives partially from the reduced value of mammography in dense breasts [2]. Bird et al. [12] reported that cancers missed at mammography were more frequent in dense breasts. Of the 50 nonpalpable breast cancers detected in our study, 16 (32%) were detected only at sonography. Of these 16 nonpalpable breast cancers, 11 (69%) were detected in dense breasts.

Finally, in grades 1 and 2 breasts, the sensitivities of mammography and sonography for the detection of nonpalpable breast cancers were 80% and 88%, respectively, with no significant superiority for sonography. Five nonpalpable breast cancers were detected in grades 1 and 2 breasts, which represent 31% of nonpalpable breast cancer detected only at sonography in our series.

The major limits of sonography are cancers seen only on mammography, which were detected in six patients (12%) in our series. Among these cancers, five were clustered microcalcifications, of which four were found to be ductal carcinomas in situ on histologic examination and one was a 2-mm infiltrating carcinoma. Microcalcifications are generally not visible on sonography. In our series, four nonpalpable breast cancers visible as microcalcifications with mass on mammography were seen at sonography (three invasive ductal carcinoma and one ductal carcinomas in situ), and two clustered microcalcifications (ductal carcinomas in situ) detected on mammography were seen at sonography. In the sixth case, the cancer missed at sonography was a posterior mass located in a fatty area in a voluminous breast (histologic type was infiltrating ductal carcinoma).

Tumor size is a mean prognostic factor [1]. In our series, the mean histologic size of tumors detected only at sonography was 10.9 mm (median size, 8.5 mm; range, 2–30 mm). The mean sonographic size of these cancers
was 7 mm (median size, 7 mm; range, 4–17 mm). All lesions but one were 10 mm or smaller. The mean sonographic size was also 7 mm in patients with cancers that were visible on mammography. The advances in sonographic technology, particularly the use of tissue harmonic imaging, improve the detection of small lesions. In our experience, cysts of 1–2 mm in diameter can be detected.

The repartition of nonpalpable breast cancers with respect to breast density grades in our series between grades 1 and 2 breasts and grades 3 and 4 breasts was the same (n = 25 in each category). Apparently the sensitivity of sonography for detecting nonpalpable breast cancers is independent of the BI-RADS grades, with a sensitivity of 88% in grades 1 and 2 and grades 3 and 4 breasts.

Several hypotheses might account for the value of sonography for the detection of nonpalpable breast cancers.

First, we used dedicated sonographic equipment with tissue harmonic imaging. Several studies have shown that tissue harmonic imaging increases contrast and spatial resolution by avoiding many of the artifacts that limit conventional sonography [13, 14]. Rosen and Soo [15] reported that images obtained in breast tissue with tissue harmonic imaging showed significantly increased conspicuity of lesions and improved depiction of lesion margins compared with conventional sonography. Tissue harmonic imaging is particularly interesting for detecting hypoechoic lesions in fatty breast tissue located in extreme parts of the breast.

Second, all sonographic examinations were performed by radiologists who are highly experienced in breast imaging.

Third, the fact that our study population was heterogeneous, including 24% who were patients referred for follow-up after breast cancer surgery and 3% who were patients referred for a suspicious palpable mass, may have decreased the contributions of clinical and radiologic examinations. The physical examination of patients with a previous history of breast cancer surgery may be difficult, especially after radiation therapy. Furthermore, mammograms may be difficult to interpret, essentially because of the scar that creates focal variation of density and architectural distortion.

Our study had several limitations. First, we excluded all women who did not have both complete mammography and whole-breast sonography performed in our institution. We wanted to study the performance of sonography with the systematic use of tissue harmonic imaging. Women with entirely fatty breasts on mammography and at physical examination with normal findings were excluded because of the high confidence in that situation in eliminating the presence of a breast mass.

Fig. 1.—49-year-old woman with nonpalpable breast cancer. A and B, Craniocaudal (A) and oblique (B) mammograms of right breast reveal heterogenous breast with no mammographic finding of malignancy. C, Sonogram reveals irregular 4-mm-diameter, hypoechoic mass (calipers) at union of medial quadrants of right breast.

Fig. 2.—52-year-old woman with nonpalpable breast cancer. A and B, Craniocaudal (A) and oblique (B) mammograms of right breast reveal almost entirely fat breast with no mammographic finding of malignancy. C, Sonogram reveals spiculated 6-mm-diameter hypoechoic mass (arrow) in upper lateral quadrant of right breast.
Second, our study population was heterogeneous because patients were referred for screening in 73% of cases, follow-up after surgery in 24%, and workup of clinically suspicious lesion in 3%; however, we wanted to determine sonographic sensitivity in unselected consecutive patients.

Third, sonography was performed by experienced radiologists who had performed physical examinations and had interpreted the mammograms. Obviously, this expertise in performing sonography and the knowledge of mammographic findings may have altered the value of sonography in the detection of nonpalpable breast cancers. That the sensitivity of sonography may have been artificially increased by the mammographic results is our major limitation; however, 32% of nonpalpable breast cancers in our series were detected only at sonography.

Fourth, our study focused on the detection of nonpalpable breast cancers, and the specificity of sonography was not determined. A prior study showed that sonography can be used to classify some solid lesions as benign, with a negative predictive value of 99.5% [9]. For all these reasons, our study does not aim at validating sonography as a screening tool.

In summary, the use of sonography, particularly in dense breasts, is of value in the detection of nonpalpable breast cancers.

References


Note.—Data are numbers of cancers.

Note.—Data are numbers of patients.