Using Sonography to Screen Women with Mammographically Dense Breasts

OBJECTIVE. Mammographically dense breast tissue has been reported both as a cause of false-negative findings on mammography and as an indicator of increased breast cancer risk. We conducted this study to evaluate the role of breast sonography as a second-line screening test in women with mammographically dense breast tissue.

MATERIALS AND METHODS. Between January 2000 and January 2002, 1517 asymptomatic women with dense breasts and normal mammography and physical examination findings underwent physician-performed breast sonography as an adjunct screening test. Within the study group, 318 women had a first-degree family history or personal history of breast cancer. The high-risk subgroup comprised these women. The detection rate of breast cancer in this subgroup was compared with the detection rate in the remaining study population with baseline risk.

RESULTS. Of 1517 women examined, seven breast cancers were diagnosed (cancer-detection rate, 0.46%). Four carcinomas were detected in high-risk women and three in women with baseline risk. The cancer-detection rate in the subgroup of high-risk women was 1.3%, significantly higher (p < 0.04) than the cancer-detection rate of 0.25% in the baseline risk subgroup. All cancers were T1 (range, 4–12 mm; mean, 9.6 mm). Sentinel lymph nodes were negative for cancer in six of seven carcinomas.

CONCLUSION. Screening breast sonography in the population of women with dense breast tissue is useful in detecting small breast cancers that are not detected on mammography or clinical breast examination. The use of sonography as an adjunct to screening mammography in women with increased risk of breast cancer and dense breasts may be especially beneficial.

Mammography has been proven in randomized controlled trials to be a sensitive screening tool for the detection of early breast cancer [1, 2]. The reported sensitivity of screening mammography varies from 65% [3] to 91% [4]. One of the various factors leading to false-negative findings on mammography is the effect of breast density [5, 6]. Furthermore, breast density on mammography is also associated with increased risk of breast cancer [7, 8].

Breast sonography has traditionally been performed to evaluate specific abnormalities discovered either at clinical examination or on mammography [9]. Recent studies have indicated the ability of breast sonography to depict an occult malignancy in women with dense breast tissue [10–13]. Current advances in ultrasound technology and scan head design permit greater spatial and contrast resolution and shortened scan time. Therefore, we decided to assess the role of breast sonography in our practice as a second-level screening test in a population of women with negative findings on mammography and dense breast tissue. Our aims were to determine how often screening breast sonography can detect clinically and mammographically occult breast carcinomas, to assess the rate of interventional procedures resulting from sonographically detected abnormalities, and to describe the features of breast cancers discovered on screening sonography. We also separately analyzed these parameters for the subgroups of women with baseline and high risk for breast cancer.

Materials and Methods

Between January 1, 2000, and January 1, 2002, 1517 asymptomatic women (range, 31–84 years old; mean ± SD, 52.1 ± 8.1 years) with breast tissue designated as Breast Imaging Reporting and Data System (BI-RADS) density categories 2, 3, or 4 [14]...
were examined with high-resolution sonography of the breast as an adjunct to normal mammography and physical examination.

All mammograms were obtained with dedicated mammography units (Glory, Elscint, Haifa, Israel). Dedicated mammography cassettes (Min R-2, Kodak, Rochester, NY) and screens (Min-R, Kodak) were used. Film processing was optimized for the mammography units. The mammography unit was under a national quality control accreditation program for the full duration of this study. All mammograms were interpreted online by radiologists experienced in breast imaging (reviewing volume for radiologists in our center varies from 3500 to 9000 mammograms per year). All sonography of the breast was performed by breast radiologists with experience in breast sonography ranging from 2 to 5 years; 1313 (86.6%) of 1517 screening sonography were normal and almost entirely fat.”

The guidelines contained in the Declaration of Helsinki [15] were followed in this study. All patients were eligible for screening sonography if findings on mammography were normal and the risk associated with false-positive findings versus the true-positive early diagnosis was seen. In sum, 1427 women (94.1%) were diagnosed, and in 35 women (2.3%) ductal ectasia was seen. In sum, 1427 women (94.1%) had a negative screening sonography without any suspicious finding. Complex cysts or solid lesions were identified in the remaining 90 patients (5.9%). Table 2 shows the number of women in each diagnostic category with the corresponding number of interventional procedures and the number of detected cancers.

Six-month follow-up sonography was recommended in 62 patients who had complex cysts...
Cytologic analysis was requested after four graphically guided fine-needle aspirations. Clear fluid was obtained in 13 of 17 sonographically benign lesions. In the remaining seven women, 6-month follow-up results were stable.

Invasive procedures were performed in 38 (2.5%) of all patients. Seventeen fine-needle aspirations and two core biopsies were performed in sonographically benign lesions. Clear fluid was obtained in 13 of 17 sonographically guided fine-needle aspirations. Cytologic analysis was requested after four fine-needle aspirations. In one of them, malignant cells were found, and subsequent sonographically guided core needle biopsy confirmed the diagnosis of carcinoma. This lesion was assessed prospectively as indeterminate, but initially the patient refused core biopsy. Results of 21 sonographically guided core needle biopsies are presented in Table 3.

The mean age of women who underwent biopsy was 55.8 years, statistically not different (p > 0.2) from the mean age of the overall group. Six invasive ductal carcinomas, not otherwise specified, and one lobular carcinoma were detected on screening sonography. Their size ranged from 4 to 12 mm (mean, 9.6 mm) and was smaller than the size of invasive carcinomas detected on mammographic screening (mean, 13.5 mm) in our breast center during the study period, but this difference was not statistically significant (p > 0.1). Four of seven tumors were high-grade ductal carcinomas. The remaining tumors included one intermediate-grade ductal, one low-grade ductal, and one lobular carcinoma. A ductal carcinoma in situ component was found in two of seven carcinomas. Sentinel lymph node biopsy was positive for cancer in only one of seven patients. No additional metastatic nodes were found at subsequent axillary lymph node dissection.

Of seven sonographically detected cancers, two were in patients with BI-RADS category 4 and five were in patients with BI-RADS category 3 densities. No carcinomas were detected in patients with BI-RADS category 2 density. No statistical difference was found in the number of cancers among a range of breast densities.

The distribution of screening examinations, interventional procedures, and cancer-detection rates among our breast radiologists is presented in Table 4. We did not find any significant difference in the biopsy and cancer-detection rates among our radiologists.

The cancer-detection rate was 0.46% (six carcinomas from 1313 studies) for the patients in whom mammography and sonography were performed by the same radiologist versus 0.49% cancer-detection rate (one cancer from 204 studies) in patients in whom examinations were performed by different radiologists.

In the subgroup of 1199 women with usual risk, 15 core biopsies and 13 fine-needle aspirations were performed. The biopsy rate in this subgroup was 2.3%. Three cancers were diagnosed in this subgroup (detection rate, 0.25%).

In the subgroup of 318 women with high risk, six core biopsies and four fine-needle aspirations were performed. The biopsy rate in this subgroup was 3.1%. Four cancers were diagnosed in the subgroup of high-risk women (cancer-detection rate, 1.3%). The size of cancers detected in the high-risk subgroup was somewhat smaller than that in the baseline risk subgroup, but this difference was not statistically significant (p > 0.3).

An illustration of cancer detected by screening sonography is shown in Figure 1.

The biopsy rate in the total study population was 2.5%, and the cancer-detection rate was 0.46%. No complications were recorded during diagnostic procedures. No patients from the study were referred for diagnostic surgical biopsy.

**Discussion**

Breast cancer is the most common malignancy among women worldwide [20]. In the absence of a known preventable cause of breast cancer, the single most important factor in reducing death from breast cancer and in the extent of treatment required is early detection through screening. Mammography

### Table 2

**Distribution of Detected Lesions in Diagnostic Categories with Corresponding Number of the Performed Biopsies and Detected Cancers**

<table>
<thead>
<tr>
<th>Assessment on Sonography</th>
<th>No. of Lesions</th>
<th>No. of Biopsies</th>
<th>No. of Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>71</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>14</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Malignant</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>38</td>
<td>7</td>
</tr>
</tbody>
</table>

### Table 3

**Results of Sonographically Guided Core Needle Biopsies of Otherwise Occult Lesions in 21 Women**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Risk</th>
<th>Diagnosis</th>
<th>Surgical History</th>
<th>Pathologic Size of Lesion (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>63</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td>Lobular carcinoma</td>
<td>12</td>
</tr>
<tr>
<td>67</td>
<td>Baseline</td>
<td>Carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Baseline</td>
<td>Fibrocystic changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td>Low-grade ductal carcinoma</td>
<td>10</td>
</tr>
<tr>
<td>77</td>
<td>Baseline</td>
<td>Fibrosis</td>
<td>High-grade ductal carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>52</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>63</td>
<td>Baseline</td>
<td>Carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>High</td>
<td>Carcinoma</td>
<td>Low-grade ductal carcinoma</td>
<td>10</td>
</tr>
<tr>
<td>62</td>
<td>Baseline</td>
<td>Fibrocystic changes</td>
<td>High-grade ductal carcinoma</td>
<td>9</td>
</tr>
<tr>
<td>57</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Baseline</td>
<td>Carcinoma</td>
<td>High-grade ductal carcinoma</td>
<td>11</td>
</tr>
<tr>
<td>50</td>
<td>High</td>
<td>Fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>Baseline</td>
<td>Fibroadenoma</td>
<td>High-grade ductal carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>41</td>
<td>High</td>
<td>Carcinoma</td>
<td>Intermediate-grade ductal carcinoma</td>
<td>12</td>
</tr>
<tr>
<td>56</td>
<td>High</td>
<td>Carcinoma</td>
<td></td>
<td></td>
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<tr>
<td>63</td>
<td>High</td>
<td>Fibrosis</td>
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<td></td>
</tr>
<tr>
<td>57</td>
<td>High</td>
<td>Carcinoma</td>
<td>High-grade ductal carcinoma</td>
<td>9</td>
</tr>
</tbody>
</table>
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Dense fibroglandular tissue is the most important inherent limitation of mammography in the diagnosis of breast cancer. Furthermore, dense breast tissue is a reported risk factor in the subsequent development of breast cancer, particularly in women with a first-degree family history of this malignancy [6, 7, 25]. The biologic basis for the excess risk associated with increased mammographic density remains unknown. The increasing use of hormone replacement therapy amplifies the problem of breast density. Rutter et al. [26] reported that breast density is modified by hormone replacement therapy, increasing with initiation and decreasing with discontinuation. Estrogen in-

<table>
<thead>
<tr>
<th>Radiologist</th>
<th>No. of Patients</th>
<th>Fine-Needle Aspiration</th>
<th>Core Needle Biopsy</th>
<th>Total Biopsies</th>
<th>Biopsy Rate (%)</th>
<th>Cancers Detected</th>
<th>Detection Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1187</td>
<td>16</td>
<td>12</td>
<td>28</td>
<td>2.4</td>
<td>4</td>
<td>0.34</td>
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<tr>
<td>2</td>
<td>266</td>
<td>1</td>
<td>8</td>
<td>9</td>
<td>3.4</td>
<td>2</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.6</td>
<td>1</td>
<td>1.56</td>
</tr>
</tbody>
</table>

Fig. 1.—67-year-old woman with dense Breast Imaging Reporting and Data System (BI-RADS) [14] category 3 breast tissue. A and B, Mediolateral oblique (A) and craniocaudal (B) screening mammograms reveal no abnormalities. C, Screening sonogram shows solid hypoechoic mass that measures 9 mm wide by 5 mm high. Angular margins (arrows) between mass and surrounding tissues are suspicious for malignancy. Sonographically guided biopsy (not shown) revealed invasive ductal carcinoma. D and E, Right mediolateral (D) and right craniocaudal (E) mammograms obtained after sonographically guided wire localization show uniformly dense breast tissue with no evidence of mass in hookwire area.
creases cell proliferation indexes, a potential pathway to both increased breast density and increased risk of breast cancer [27].

Dense glandular tissue usually has a hypoechoic appearance on sonography. Because most breast cancers are hypechoic, carcinomas in this setting are easily detected on sonography.

Our results indicate that sonography can be effective as a second-line screening test in the evaluation of women with dense breast tissue on mammography. We detected breast cancers in seven women in our study of 1517 patients. The resulting 0.46% cancer-detection rate is slightly lower than screening mammography results in centers of excellence [28, 29] but is similar to results of other screening mammography programs as cited in the peer-reviewed literature [30, 31]. Our cancer-detection rate is also somewhat higher than that in previous studies [12, 13] in which screening sonography was performed in women with dense breast tissue. This difference may be explained by the use of modern equipment and the higher percentage of high-risk women in our study.

Assuming that sonography is an operator-dependent examination, we analyzed the biopsy rate and cancer-detection rate for our breast radiologists (Table 4). We did not find a significant difference among performing radiologists. This finding may be explained by the small number of cancers in our study. Kaplan [13] reported comparable cancer-detection rate (0.3%), although in his study, screening breast sonography was performed by a trained technologist.

Characteristics of breast cancers detected in our study are well within the parameters of mammography screening. Tabar et al. [32] have suggested that 50% of invasive cancers detected on screening mammography should be less than 15 mm in diameter to achieve a substantial reduction in mortality rates. In our study, all cancers were less than 15 mm in diameter. An audit of screening mammography by Dee and Sickles [28] found that 50% of invasive cancers were 10 mm or less, whereas in our series 67% of cancers were 10 mm or less.

Our current sensitivity for screening sonography in women with mammographically dense tissue is 100%. No interval carcinomas have to date been detected in the study group. However, our follow-up period is in part short, ranging from 8 to 30 months.

Opponents of screening sonography claim that not only low sensitivity, but also a high false-positive rate and a low specificity prevent the use of this tool as a cost-effective clinically acceptable screening method [33]. Buchberger et al. [12] took samples from 7.4% (450/6113) of women screened on sonography, whereas in a screening mammography program, the acceptable biopsy rate is 1–3% [27–30]. Kaplan [13] has recommended fine-needle aspiration or biopsy in 5.2% (97/1862) of sonographically screened women. Kolb et al. [11] reported that 3.7% of women underwent fine-needle aspiration. In our study, the rate of interventional procedures was lower (2.5%) than those in the previously mentioned reports. This low biopsy rate may be explained by our rigorous approach in applying the criteria of Stavros et al. [16] for the characterization of solid masses and our follow-up policy for probably benign solid and complex cyst lesions.

If one assumes that our negative results are true-negative and that findings in patients recommended for short follow-up or with benign biopsy results are false-positive, then the specificity of sonography screening was 94.4%, a figure acceptable for a screening test.

In our practice, breast sonography for women with dense breasts was performed in most patients immediately after the mammography in the sonography suite directly adjacent to the screening mammography reporting area. Thus, adverse psychologic consequences of recalling women for further investigation after screening mammography were prevented. Additionally, fear of breast compression and radiation exposure, both associated with mammography, is absent in breast sonography. A meticulous cost analysis of sonography screening is outside the scope of this report. The charges for sonography and mammography in Israel are similar.

Sonographically guided breast biopsy is less expensive than stereotactic guidance or surgical biopsy [34]. The cost of a radiologist’s time in the United States is greater with sonography screening than with mammography and may be an obstacle for the implementation of screening sonography. A possible solution may be the use of trained technologists as shown by Kaplan [13], who achieved a 0.3% cancer-detection rate.

Screening mammography is associated with a 5–10% initial interpretation rate of abnormal findings [28, 29] that leads to additional imaging and clinical workup and consequently added expense. In our study, screening sonography was associated with a 5.9% interpretation rate of abnormal findings. The cost of breast cancers detected on screening sonography is comparable to the cost of cancers diagnosed on screening mammography in our center. Sonography as a second-level screening test is unquestionably significantly cheaper than MR imaging.

We emphasize the importance of recommendation for screening sonography only in women with dense breast tissue. The similarity in cancer-detection rates between screening mammography and screening sonography established in this study would probably not hold true if women with fat-replaced breasts were also included and if they underwent screening sonography. The rationale is that most malignancies that are undetected on screening mammography are missed because they are obscured by dense tissue [5]. The number of cancers detected on screening sonography in women with fatty-replaced breasts would most likely be markedly fewer than the number in women with dense breasts. Therefore, performing screening sonography in all women who undergo screening mammography would not be cost-effective.

We found a significant difference in the results of the screening sonography in high-risk women compared with the baseline risk subgroup (cancer-detection rates, 1.3% versus 0.25%; p < 0.04; two-tailed Fisher’s exact probability test). The same trend, although statistically nonsignificant (p = 0.09), was reported by Kolb et al. [11]. We indicate that the high-risk women may benefit more from screening sonography. The possible explanation for this hypothesis is the fact that women with a family history of breast cancer have more dense mammographic tissue than controls [8]. In fact, the 1.3% cancer-detection rate in high-risk women is double that anticipated from screening mammography.

A critical issue in the controversy concerning sonography screening of breast cancer is whether it will reduce mortality. The true independent contribution of sonography to breast cancer screening cannot be determined other than by the performance of a randomized controlled trial using death as the end point. It is unlikely that a clinical trial of sufficient magnitude could be performed to assess the potential benefit of sonography screening. We can only speculate that some of the cancers detected on sonography screening would have been detected as interval carcinomas in the usual mammography screening program. If one takes into consideration that interval breast carcinomas tend to be more lethal [35], then their early detection may substantially reduce mortality rates. This possibility is especially true in high-grade and node-positive tumors. In our study, one intermediate-grade tumor was sentinel-lymph-node positive and four tumors were high-grade.
The preclinical detection in these five patients was especially important, and in 71% of cancers detected in our study, vital lead time was gained by screening sonography.

In conclusion, we show that screening sonography in cases of mammographically dense breast tissue permits the effective detection of otherwise occult small breast cancers. Our results particularly point to a potential benefit in high-risk women. In this group, the 1.3% cancer-detection rate was significantly higher than that in women with baseline risk, and it was also higher than the acceptable detection rate for screening mammography. Additional studies to examine issues of reproducibility and cost-effectiveness are needed. We therefore recommend implementation of sonography for breast cancer screening in high-risk women with mammographically dense breast tissue.

References

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