Using Sonography to Screen Women with Mammographically Dense Breasts

Pavel Crystal[1,2]
Selwyn D. Strano[2,3]
Semyon Shcharynski[2]
Michael J. Koretz[2]

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]

Received October 4, 2002; accepted after revision December 31, 2002.

[1]Department of Radiology, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, P. O. Box 151, Beer Sheba, Israel. Address correspondence to P. Crystal (pcrystal@bgumail.bgu.ac.il).

[2]Comprehensive Breast Center, Soroka University Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheba, Israel.

[3]Present address: The Rachel Nash Jerusalem Comprehensive Breast Clinic, Bet-Ofer, 5 Nachum Heftzadi St., Jerusalem, 95484 Israel.

AJR 2003;181:177–182

0361–803X/03/1811–177

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 examinations were performed by the same radiologist who reviewed the screening mammography. In the remaining 204 women, sonography was performed by a radiologist who was not the initial reviewer of the screening mammography. In these cases, the mammogram was always reviewed before screening sonography.

We evaluated the density of breast parenchyma according to the gradation of the American College of Radiology BI-RADS [14] protocol on a scale of 1–4, with 4 representing extremely dense breast tissue that "could obscure a lesion on mammography"; 3 representing breast tissue that is heterogeneously dense and "may lower the sensitivity of mammography"; 2 representing the presence of scattered fibroglandular densities; and 1 being a breast that "is almost entirely fat."

Patients were eligible for screening sonography if findings on mammography were normal and breast density was defined as grades 2–4. The distribution of the breast density categories in the examined women is presented in Table 1.

The guidelines contained in the Declaration of Helsinki [15] were followed in this study. All patients were given a detailed verbal description of the procedure, the reason for its utility, and the possible risk associated with false-positive findings versus possible benefit with the true-positive early diagnosis of breast cancer. This explanation was provided by the examining breast radiologist to the patient when she received the results of the normal screening mammography. The patients provided verbal consent, and in most patients, screening sonography was performed on the same day.

Before sonography of the breast was performed, all patients underwent a physical examination by the breast radiologist with each breast examined separately with appropriate anatomic positioning. If a palpable abnormality was present, the patient was excluded from the study. Furthermore, patients with carcinomas detected on sonography alone were later reexamined by a breast surgeon who had the mammograms and sonograms available. If a lesion was determined to be palpable by the surgeon, the patient was excluded from the study (one patient in our study).

All sonography of the breast was performed with ATL 3000 or 5000 units (Advanced Technology Laboratories, Bothell, WA) by using electronically focused transducers with a bandwidth of 5–12 MHz. Both breasts were systematically examined with overlapping scans in a radial and antiradial pattern from the nipple to the periphery. The retroareolar region was separately scanned with angled views to ensure the complete coverage of all breast tissue. The procedure time was 4–15 min (mean, 7 min), depending on the size and texture of the breasts.

The sonography findings were categorized as normal (no focal lesions, simple cyst, or ductal ectasia), probably benign (complex cysts or sonographically benign solid lesions), or indeterminate and suspicious for malignancy. Characterization of solid lesions as probably benign or suspicious was based on criteria previously published by Stavros et al. [16] and reviewed by Baker and Soo [17]. For a mass to be classified as benign, we required a combination of at least three of the following findings: ellipsoid shape, two or three gentle lobulations, thin pseudocapsule, intense and uniform hyperechogenecity, and absence of malignant findings. If two of the following malignant signs were present, the mass was assessed as sonographically suspicious for malignancy: spiculation, angular margins, marked hypoechogenecity, shadowing, duct extension, branch pattern, and microlobulation. Lesions that fell between these groups were classified as indeterminate.

Cysts with internal echoes or septations were defined as complex cysts and were recommended for 6-month follow-up imaging according to Venta et al. [18]. Sonographically guided fine-needle aspiration of complex cysts was performed in cases of patient preference or anticipated noncompliance with follow-up recommendations. Clear straw-colored fluid was not sent for cytologic analysis. Cytologic evaluation was requested after sonographically guided fine-needle aspiration of complex cysts if bloody fluid was aspirated or apparent solid material was received. Our policy for sonographically benign solid lesions included sonographically guided biopsy or repeated sonography after 6 months. All indeterminate and suspicious findings underwent sonographically guided core needle biopsy.

Sonographically guided core needle biopsy of 21 solid masses was performed with a disposable automated 14-gauge needle with a 22-mm throw (Monopty, Bard Peripheral Technologies, Covington, GA). We used a standard freehand technique [19] for all sonographically guided biopsies of nonpalpable breast lesions.

Mammograms of patients with suspicious lesions detected on screening sonography were reviewed to determine if the lesion was retrospectively visible. All mammograms of patients in whom sonographically guided core needle biopsy revealed carcinoma were later interpreted again by a fellowship-trained breast radiologist who was unaware of the results of mammography and sonography studies. If the lesion on sonography was visible as a mass on mammography retrospectively, the case was excluded from the study.

Our total patient population included 318 women with a first-degree family history or personal history of breast cancer. For women with a previous history of breast cancer, we included screening sonography only for the breast without a history of malignant disease. We compared the results of sonography screening between baseline risk and high-risk patients. The characteristics of cancers detected on screening sonography were compared with those of cancers detected on mammographic screening in our center.

Descriptive statistics were calculated for all study variables. Statistical analysis of the results was performed using either the chi-square or Student's *t* test when appropriate. Statistical significance was assigned a *p* value of less than 0.05.

TABLE 1 **Distribution of the Breast Density Categories in Regard to Breast Cancer Risk and Corresponding Cancers Detected on Sonographic Screening**

Risk	Total No. of Patients	Total No. of Cancers	No. of BI-RADS Category 2[a]		No. of BI-RADS Category 3[b]		No. of BI-RADS Category 4[c]	
			Women	Cancers	Women	Cancers	Women	Cancers
High	318	4	72	0	202	3	44	1
Usual	1199	3	84	0	947	2	168	1
Total study	1517	7	156	0	1149	5	212	2

Note.—BI-RADS = Breast Imaging Reporting and Data System [14].

[a]Presence of scattered fibroglandular densities.

[b]Breast tissue that is heterogeneously dense that "may lower the sensitivity of mammography."

[c]Extremely dense breast tissue that "could obscure a lesion on mammography."

Results

Of the 1517 patients evaluated on screening sonography, 841 (55.4%) had no focal finding. In 551 women (36.3%), simple cysts 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

TABLE 2 Distribution of Detected Lesions in Diagnostic Categories with Corresponding Number of the Performed Biopsies and Detected Cancers

Assessment on Sonography	No. of Lesions	No. of Biopsies	No. of Cancers
Benign	71	19	0
Indeterminate	14	14	2
Malignant	5	5	5
Total	90	38	7

or sonographically benign solid masses. One-year follow-up sonography results were available in 55 patients, and all lesions were stable. 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.

TABLE 3 Results of Sonographically Guided Core Needle Biopsies of Otherwise Occult Lesions in 21 Women

Age (yr)	Risk	Diagnosis	Surgical History	Pathologic Size of Lesion (mm)
63	Baseline	Fibroadenoma		
67	Baseline	Carcinoma	Lobular carcinoma	12
44	Baseline	Fibrocystic changes		
53	Baseline	Fibroadenoma		
54	Baseline	Fibroadenoma		
77	Baseline	Fibrosis		
52	Baseline	Fibroadenoma		
63	Baseline	Carcinoma	Low-grade ductal carcinoma	10
67	High	Carcinoma	High-grade ductal carcinoma	9
62	Baseline	Fibrocystic changes		
57	Baseline	Fibroadenoma		
56	Baseline	Fibroadenoma		
51	Baseline	Fibroadenoma		
48	Baseline	Fibroadenoma		
50	Baseline	Carcinoma	High-grade ductal carcinoma	11
50	High	Fibrosis		
41	Baseline	Fibroadenoma		
41	High	Carcinoma	High-grade ductal carcinoma	4
56	High	Carcinoma	Intermediate-grade ductal carcinoma	12
63	High	Fibrosis		
57	High	Carcinoma	High-grade ductal carcinoma	9

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 4 Distribution of the Screening Sonography Examinations, Interventional Procedures, and Cancer Detection Rate Among Breast Radiologists

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

is currently the sole acceptable technique for mass screening for breast cancer. Despite the reported decline in mortality rates from breast cancer [21], the dispute concerning the effectiveness of screening mammography continues [22, 23]. The sensitivity of mammography in the diagnosis of breast cancer is variable and influenced by age, breast density, family history, and other factors [24].

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-

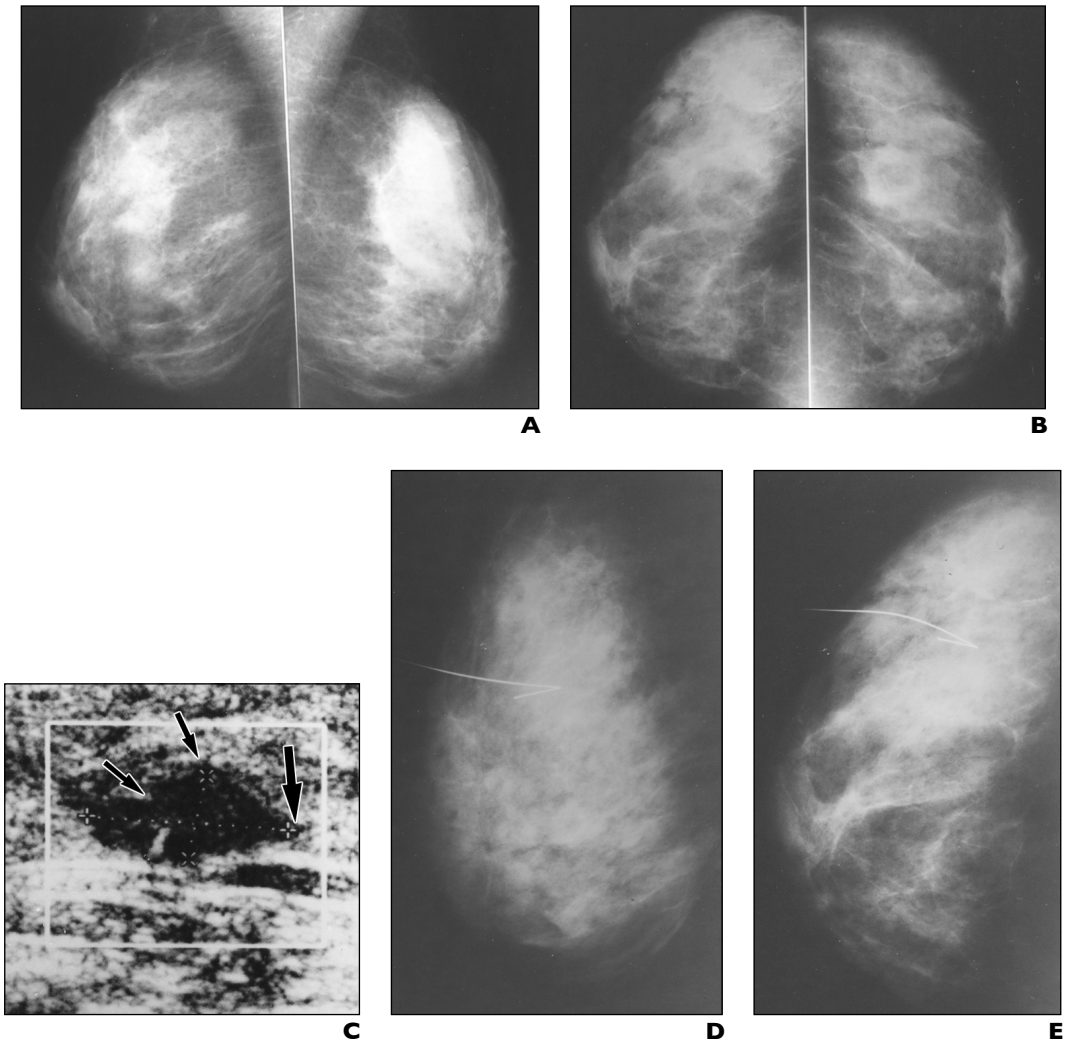

Fig. 1.—67-year-old woman with dense Breast Imaging Reporting and Data System (BI-RADS) [14] category 3 breast tissue.
A and **B,** Mediolateral oblique (**A**) and craniocaudal (**B**) screening mammograms reveal no abnormalities.
C, Screening sonogram shows solid hypoechoic mass that measures 9 mm 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 hyperechoic appearance on sonography. Because most breast cancers are hypoechogenic, 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

1. Shapiro S, Venet W, Strax P, Venet L, Roeser R. Ten-to fourteen-year effect of screening on breast cancer mortality. *J Natl Cancer Inst* 1982;69:349–355
2. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomized trials. *Lancet* 2002; 359:909–919
3. Yankaskas BC, Cleveland RJ, Schell MJ, Kozar R. Association of recall rates with sensitivity and positive predictive values of screening mammography. *AJR* 2001;177:543–549
4. Robertson CL. A private breast imaging practice: medical audit of 25,788 screening and 1077 diagnostic examinations. *Radiology* 1993;187:75–79
5. Ma L, Fishell F, Wright B, Hanna W, Allan S, Boyd NF. Case-control study of factors associated with failure to detect breast cancer by mammography. *J Natl Cancer Inst* 1992;84:781–785
6. Saarenmaa I, Salminen T, Geiger U, et al. The effect of age and density of the breast on the sensitivity of breast cancer diagnostic by mammography and ultrasonography. *Breast Cancer Res Treat* 2001;67: 117–123
7. Oza AM, Boyd NF. Mammographic parenchymal patterns: a marker of breast cancer risk. *Epidemiol Rev* 1993;15:196–208
8. Boyd NF, Lockwood GA, Martin LJ, et al. Mammographic densities and risk of breast cancer among subjects with a family history of this disease. *J Natl Cancer Inst* 1999;91: 1404–1408
9. Bassett LW, Kimme-Smith C. Breast sonography. *AJR* 1991;156:449–455
10. Gordon PB, Goldenberg SL. Malignant breast masses detected only by ultrasound: a retrospective review. *Cancer* 1995;76:626–630
11. Kolb TM, Lichy J, Newhouse JH. Occult cancer in women with dense breasts: detection with screening US—diagnostic yield and tumor characteristics. *Radiology* 1998;207:191–199
12. Buchberger W, DeKoekkoek-Doll P, Springer P, Obrist P, Düsner M. Incidental findings on sonography of the breast: clinical significance and diagnostic workup. *AJR* 1999;173:921–927
13. Kaplan SS. Clinical utility of bilateral whole-breast US in the evaluation of women with dense breast tissue. *Radiology* 2001;221:641–649
14. American College of Radiology. *Breast imaging reporting and data system* (*BI-RADS*), 3rd ed. Reston, VA: American College of Radiology, 1998
15. World Medical Association. *Declaration of Helsinki: ethical principles for medical research involving human subjects,* revised. Edinburgh: World Medical Association, 2000
16. Stavros TA, Thickman D, Rapp CL, Dennis MA, Parker SH, Sisney GA. Solid breast nodules: use of sonography to distinguish between benign and malignant lesions. *Radiology* 1995;196:123–134
17. Baker JA, Soo MS. The evolving role of sonography in evaluating solid breast masses. *Semin Ultrasound CT MR* 2000;21:286–296
18. Venta LA, Kim JP, Pelloski CE, Morrow M. Management of complex breast cysts. *AJR* 1999; 173:1331–1336
19. Fornage BD. Sonographically guided needle biopsy of nonpalpable breast lesions. *J Clin Ultrasound* 1999;27:385–398
20. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999;80:827–841
21. Tabar L, Vitak B, Chen HH, Yen MF, Duffy SW, Smith RA. Beyond randomized controlled trials: organized mammographic screening substantially reduces breast carcinoma mortality. *Cancer* 2001; 91:1724–1731
22. Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet* 2000;355:129–134
23. Olsen O, Gotzsche PC. Cochrane review on screening for breast cancer with mammography. *Lancet* 2001;358:1340–1342
24. Kerlikowske K, Grady D, Barclay J, Sickles EA, Ernster V. Effect of age, breast density, and family history on the sensitivity of first screening mammography. *JAMA* 1996;276:33–38
25. Saftlas AF, Wolfe JN, Hoover RN, et al. Mammographic parenchymal patterns as indicators of breast cancer risk. *Am J Epidemiol* 1989;129: 518–526
26. Rutter CM, Mandelson MT, Laya MB, Seger DJ, Talpin S. Changes in breast density associated with initiation, discontinuation, and continuing use of hormone replacement therapy. *JAMA* 2001;285:171–176
27. Clemons M, Goss P. Estrogen and the risk of breast cancer. *N Engl J Med* 2001;344:276–285
28. Dee KE, Sickles EA. Medical audit of diagnostic mammography examinations: comparison with screening outcomes obtained concurrently. *AJR* 2001;176:729–733
29. Kopans DB. Imaging analysis of breast lesions. In: Harris JR, ed. *Disease of the breast*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:126–127
30. Vizcaino I, Salas D, Vilar JS, Ruiz-Perales F, Herranz C, Ibanez J. Breast cancer screening: first round in the population-based program in Valencia, Spain—collaborative group of readers of the Breast Cancer Screening Program of the Valencia community. *Radiology* 1998;206:253–260
31. Olivotto IA, Kan L, d'Yachkova Y, et al. Ten years of breast screening in the Screening Mammography Program of British Columbia, 1988-97. *J Med Screen* 2000;7:152–159
32. Tabar L, Fagerberg G, Duffy SW, Day NE, Gad A, Grontoff O. Update of the Swedish Two-County Program of Mammographic Screening for Breast Cancer. *Radiol Clin North Am* 1992; 30:187–210
33. Teh W, Wilson AR. The role of ultrasound in breast cancer screening: a consensus statement by the European Group for Breast Cancer Screening. *Eur J Cancer* 1998;34:449–450
34. Liberman L, Feng TL, Dershaw DD, Morris EA, Abramson AF. US-guided core breast biopsy: use and cost-effectiveness. *Radiology* 1998;208:717–723
35. Gilliland FD, Joste N, Stauber PM, et al. Biologic characteristics of interval and screen-detected breast cancers. *J Natl Cancer Inst* 2000;92:743–749