Assessing Improvement in Detection of Breast Cancer with Three-dimensional Automated Breast US in Women with Dense Breast Tissue: The SomoInsight Study[1]

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Purpose: To determine improvement in breast cancer detection by using supplemental three-dimensional (3D) automated breast (AB) ultrasonography (US) with screening mammography versus screening mammography alone in asymptomatic women with dense breasts.

Materials and Methods: Institutional review board approval and written informed consent were obtained for this HIPAA-compliant study. The SomoInsight Study was an observational, multicenter study conducted between 2009 and 2011. A total of 15318 women (mean age, 53.3 years ± 10 [standard deviation]; range, 25–94 years) presenting for screening mammography alone with heterogeneously (50%–75%) or extremely (>75%) dense breasts were included, regardless of further risk characterization, and were followed up for 1 year. Participants underwent screening mammography alone followed by an AB US examination; results were interpreted sequentially. McNemar test was used to assess differences in cancer detection.

Results: Breast cancer was diagnosed at screening in 112 women: 82 with screening mammography and an additional 30 with AB US. Addition of AB US to screening mammography yielded an additional 1.9 detected cancers per 1000 women screened (95% confidence interval [CI]: 1.2, 2.7; $P < .001$). Of cancers detected with screening mammography, 62.2% (51 of 82) were invasive versus 93.3% (28 of 30) of additional cancers detected with AB US ($P = .001$). Of the 82 cancers detected with either screening mammography alone or the combined read, 17 were detected with screening mammography alone. Of these, 64.7% (11 of 17) were ductal carcinoma in situ versus 6.7% (two of 30) of cancers detected with AB US alone. Sensitivity for the combined read increased by 26.7% (95% CI: 18.3%, 35.1%); the increase in the recall rate per 1000 women screened was 284.9 (95% CI: 278.0, 292.2; $P < .001$).

Conclusion: Addition of AB US to screening mammography in a generalizable cohort of women with dense breasts increased the cancer detection yield of clinically important cancers, but it also increased the number of false-positive results.

Breast cancer is a leading cause of death for women in the United States (1). Screening for breast cancer with mammography has reduced breast cancer mortality up to 45% (2), and while mammography is an effective screening tool for most women, its sensitivity is limited in women with dense breasts. The sensitivity of mammography for the detection of breast cancer is reported to be 85% (3), but is as low as 48% in women with extremely dense breasts (> 75% breast density) (4). Mammographic breast density itself is an independent risk factor for developing breast cancer, with estimates of relative lifetime risk ranging from 2.8 to 6.0 (5–11), and risk increases in proportion with percentage breast density as the sensitivity of mammography declines (10). More than one-half of women younger than 50 years old and approximately one-third of women 50 years or older have breasts that are more than 50% dense (12); it has been estimated that 28%–30% of breast cancers are associated with breast density (6,7) in comparison with approximately 5%–10% attributed to mutations in the *BRCA1* or *BRCA2* gene (13). Screening modalities that are effective for this large population of women are, thus, crucial for optimal diagnosis of early, and thereby, curable breast cancers.

Supplemental screening with magnetic resonance (MR) imaging or ultrasonography (US) after mammography increases the rate of early detection of breast cancer in women with dense breasts (14). However, the proposed use of MR imaging has been limited to high-risk women. Breast US is most commonly used as an adjunct to mammography and, like MR, is not limited by breast density (15). Handheld screening breast US significantly increases detection of small, node-negative breast cancers in women with dense breasts (16). However, most of the studies to date have focused primarily on high-risk women with additional risk factors for breast cancer, thus limiting the generalizability of findings. In addition, the reliability of handheld US as a screening tool remains controversial, as the technology has been criticized for its false-positive rate, variability between operators, and the considerable physician time required for image acquisition (15).

Three-dimensional (3D) automated breast (AB) US is being investigated as a solution for intermediate-risk women with dense breasts. With AB US, the entirety of each breast is imaged in sections with an automated 15.4-cm 14–6-MHz linear-array transducer. Images are reconstructed coronally and viewed at a dedicated workstation, requiring an average of 2.9 minutes for the radiologist to interpret all images from each case (16). The purpose of this study was to determine the improvement in breast cancer detection when AB US is used with screening mammography versus when screening mammography alone is used for the population of asymptomatic women with dense breasts.

Advances in Knowledge

- In this large, real-world, observational study conducted between 2009 and 2011 in 15 318 women who presented consecutively for screening mammography with heterogeneously (>50%) or extremely (>75%) dense breasts and with no further risk characterization, the addition of automated breast (AB) US to screening mammography yielded an additional 1.9 detected cancers per 1000 women screened (95% confidence interval [CI]: 1.2, 2.7; $P < .001$).
- Among the 82 cancers detected by using either screening mammography alone or the combined read, 17 were detected with screening mammography alone, 30 were detected with AB US alone, and 65 were detected with both screening mammography and AB US.
- The corresponding recall rate per 1000 women screened was 150.2 (95% CI: 144.1, 155.7; $P < .001$) for screening mammography alone and 284.9 (95% CI: 278.0, 292.2; $P < .001$) for the combined imaging approach.
- Of cancers detected with screening mammography, 62.2% (51 of 82) were invasive versus 93.3% (28 of 30) of additional cancers detected with AB US ($P = .001$).
- Of the 17 cancers detected with screening mammography alone, 64.7% (11 of 17) were ductal carcinoma in situ versus 6.7% (two of 30) of cancers detected with AB US alone.

Implications for Patient Care

- Clinically important cancers are detected with the addition of AB US compared with screening mammography alone in women with dense breasts.
- Improved detection through the use of AB US supplemented to screening mammography alone has the potential to lead to earlier treatment and better prognosis in patients with dense breasts.

Materials and Methods

The SomoInsight Study was funded by U-Systems, Sunnyvale, Calif. Some

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Abbreviations:
AB = automated breast
BI-RADS = Breast Imaging Reporting and Data System
CI = confidence interval
PPV = positive predictive value
PPV_1 = PPV among cases that have positive results requiring immediate management at screening
PPV_2 = PPV of all biopsy recommendations
PPV_3 = PPV of all biopsies performed
3D = three-dimensional

Author contributions:
Guarantors of integrity of entire study, R.F.B., J.A.R., S.R., B.A.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, R.F.B., J.A.G., J.T., D.P.M.; clinical studies, R.F.B., L.T., M.F.I., J.A.G., B.E.H., M.R.L., R.L.L., M.K.P., J.A.R., S.R., B.A.S., J.T., R.T.W., D.P.M.; statistical analysis, R.F.B., S.W.D., D.P.M.; and manuscript editing, R.F.B., L.T., S.W.D., J.A.G., B.E.H., M.K.P., J.A.R., S.R., J.T., D.P.M.

Conflicts of interest are listed at the end of this article.

authors were consultants to U-Systems during the time of the study (R.F.B., M.F.I., M.R.L., S.R., L.T., and S.W.D.). Some authors had stock in U-Systems (L.T., S.R., M.R.L.). Local control of the data was entered by investigators at the clinical sites where some authors (R.F.B., M.F.I., S.R.) were consultants for U-Systems. Once data were entered at the clinical sites, all data were centrally held and managed by the clinical research organization (Medidata, New York, NY). All data were transferred from the clinical research organization for statistical analysis to another place (ICON Clinical Research, San Francisco, Calif). Central control of the data and data analysis were performed by an author (D.P.M.) who was not a consultant and who did not have stock in U-Systems. All sites had the same AB US device, and most were loaned by U-Systems to the sites for the purpose of the study. This multi-institutional study took place at 13 facilities across the United States from 2009 to 2011. The study was compliant with the Health Insurance Portability and Accountability Act and received central approval from the Western Institutional Review Board, as well as approval from the institutional review board of participating facilities that required local approval. Each participant provided written informed consent.

Study Population

Women who were 25 years old and older who were asymptomatic and determined by a technologist or research coordinator trained in breast density assessment to have heterogeneously (50%–75% dense) or extremely (> 75% dense) dense breast parenchyma were included. Women were excluded if they had signs or symptoms of breast cancer, had undergone surgical or percutaneous breast procedures in the past year, or received a diagnosis of or treatment for any cancer in the prior 12 months. Women who were currently pregnant, breast-feeding, or planning to become pregnant in the following 15 months were also ineligible. Women with a history of lumpectomy, contralateral mastectomy, breast augmentation, or implants were included.

Imaging

Each participant underwent digital screening mammography in the standard craniocaudal and mediolateral oblique views according to routine protocol. A trained technician then performed an examination by using an AB US system (somo·v; U-Systems). Each breast was imaged in three views with an automated 15.4-cm 14–6-MHz linear-array transducer, which acquires up to 1000 two-dimensional images in the transverse plane, imaging the breast in three parts: the central (anteroposterior), lateral, and medial portions of the breast. To ensure inclusion of all breast tissue, particularly in participants with very large breasts, additional views were obtained as deemed necessary by the technician to cover the entirety of the breast. The standardized review process involves the use of the coronal plane for quick navigation through the breast, as well the use of "survey mode," which is similar to cine and allows rapid review of many images. The acquisition time for each view was approximately 60 seconds, with a total examination time of about 15 minutes. Images were reconstructed in the coronal plane and were 3D for the radiologist to interpret.

Image Interpretation

Screening mammograms were interpreted prospectively by one of 39 radiologists at 11 clinical sites (two sites had two AB US systems at two different locations) by using the Breast Imaging Reporting and Data System (BI-RADS) classification (17). The categories for evaluating results of screening mammography alone and AB US alone were BI-RADS category 0, 1, or 2, although the BI-RADS category 3 rating was also assigned in a small number of patients (19 patients, 0.1%). None of these 19 patients had a cancer. Breast density was also reassessed by the radiologist and classified by using BI-RADS density type 1 ("almost entirely fat"), type 2 ("scattered fibroglandular densities"), type 3 ("heterogeneously dense"), or type 4 ("extremely dense"). Patients whose breasts were assessed by the technologist to be dense but were classified as not dense by the radiologist were excluded.

To assess potential malignancies and the need for recall, the radiologist reviewed a participant's screening mammographic images first, without the AB US images. The screening mammographic images were assigned a BI-RADS risk assessment, and once the interpretation from the screening mammographic assessment was recorded, it was locked. With the screening mammographic images still visible, the same investigator interpreted the AB US images. That investigator assigned a BI-RADS risk assessment category to the AB US images; provided a final combined impression on the basis of the findings on the screening mammographic images and the adjunctive AB US images; and recommended immediate management (immediate management refers to recommendation and performance of additional imaging that is necessary to determine whether a biopsy is needed), short-interval follow-up, or routine management (routine management refers to screening at the next interval advised for healthy women [eg, 1 year]). Patients were considered to be recalled for analysis purposes if their images were assigned a BI-RADS category 0 or a combined impression of immediate management.

The sensitivity and specificity of AB US screening are, to a large degree, dependent on the quality of the interpretation, and the potential exists for variation among readers and their interpretation. To minimize this potential variation, investigators who participated in this study were Mammography Quality Standards Act certified. In addition, all study radiologists participated in a standardized training program, which included Web-based training, Web-based one-on-one training, and on-site training with a radiologist experienced in AB US, prior to study initiation.

Follow-up

The final combined impression allowed for the results of the AB US review to

Figure 1

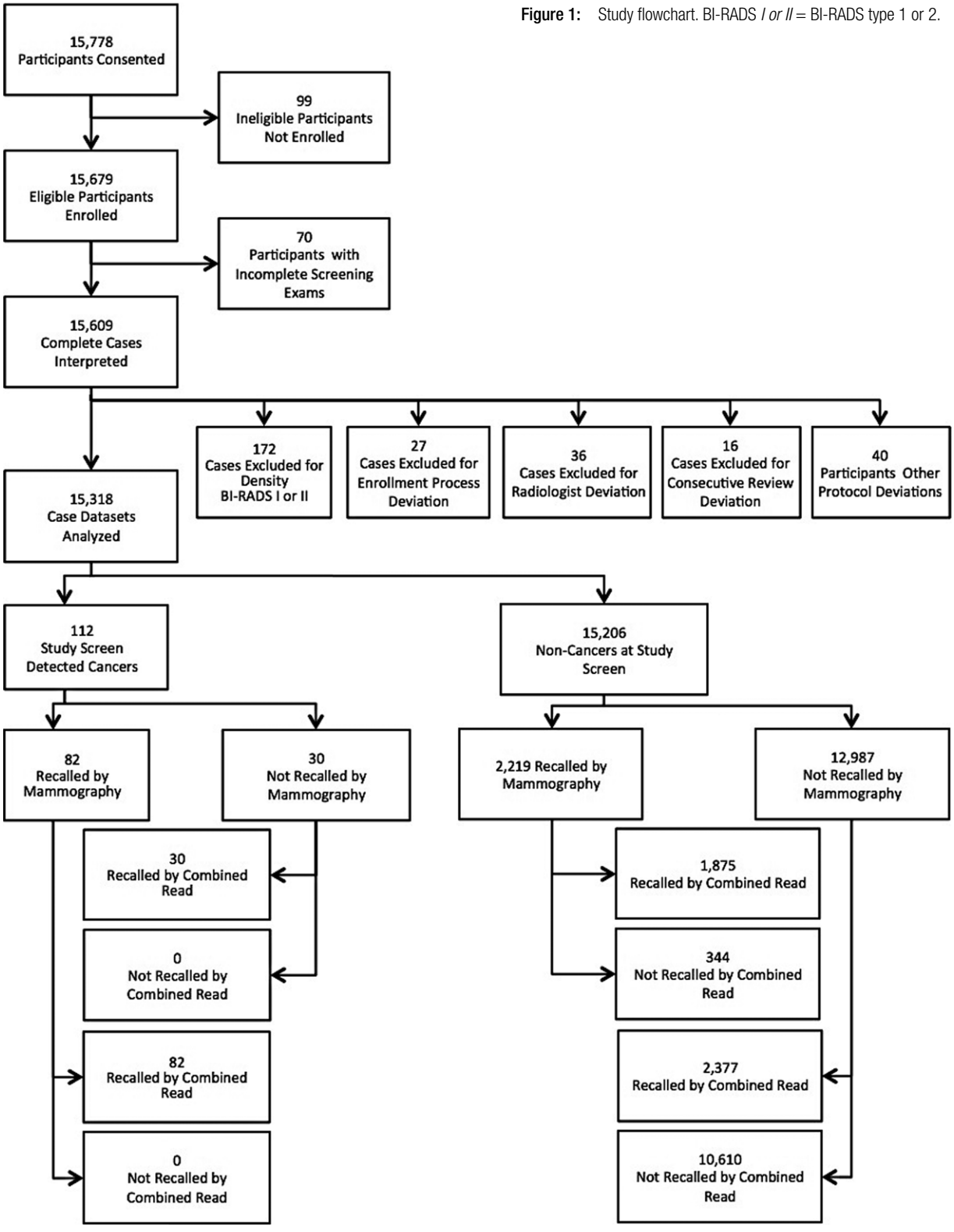

Figure 1: Study flowchart. BI-RADS *I or II* = BI-RADS type 1 or 2.

reverse a positive screening mammographic finding, theoretically obviating a mammographic callback. For example, a mass detected with mammography may have been found to be a simple cyst at AB US. Nonetheless, immediate management occurred if it was recommended on the basis of the results of either the individual mammographic assessment or the combined assessment. Women with normal, benign, or probably benign findings were followed up for 12 months, with 88% of patients completing follow-up. Women who developed breast symptoms during the follow-up period underwent the clinically indicated evaluation; the result and outcome were recorded. Only cancers detected as a result of the original screening, by using either screening mammography or AB US, were considered screening-detected cancers for the purpose of this study.

Statistical Analysis

Descriptive statistics for women with breast density classified as BI-RADS type 3 or 4 were compared. For categorical variables, the Pearson χ^2 test was used; the Fisher exact test was used for variables with low expected cell counts. For continuous variables, the two-sample *t* test was used; the Wilcoxon test was used in instances where a skewed distribution was anticipated. Findings were considered to indicate a significant difference at the $P < .05$ level.

The primary end point was the incremental increase in cancer detection with AB US combined with screening mammography, as compared with screening mammography alone. Recommendation for recall was assessed for those ultimately diagnosed with breast cancer as a result of the trial screening episode and for those determined to be cancer free following screening. The McNemar test was used for a matched-pair comparison of recalled women who underwent screening mammography alone with those who underwent screening mammography and AB US to test for a difference in cancer detection. Specificity was measured by using the same comparison in those found not to have cancer.

Positive predictive value (PPV) was calculated by using three definitions: *(a)* the PPV (ie, the malignancy percentage) among cases that have positive results requiring immediate management at screening (PPV_1); *(b)* the PPV of all biopsy recommendations (PPV_2); and *(c)* the PPV of all biopsies performed (PPV_3). The numerator for both PPV_1 and PPV_3 is the number of biopsy-proven cancers detected at screening. Interval cancers are not included in the numerator. Patients who are lost to follow-up are included in the denominator, such that both PPV_1 and PPV_3 are conservatively reported. The 95% confidence intervals (CIs) were calculated on the basis of 1000 bootstrap samples. All analyses were conducted by using software (SAS version 9.2; SAS Institute, Cary, NC).

Results

Participant Characteristics

A total of 15 778 women consented to participate; of that number, 15 318 were eligible, provided complete screening examination results, and were classified as having BI-RADS breast density type 3 (n = 11 488, 75.0%) or type 4 (n = 3830, 25.0%) by both the technologist and radiologist (Fig 1, Table 1). Patients with BI-RADS breast density type 4 were more likely to be younger, Asian, premenopausal, and to have a lower body mass index, as compared with patients with BI-RADS breast density type 3. Patients with BI-RADS breast density type 4 were less likely to have a personal history of breast cancer but had a similar rate of a family history of breast cancer compared with patients with BI-RADS breast density type 3. *BRCA1* and *BRCA2* status was similar for patients with BI-RADS breast density type 3 and BI-RADS breast density type 4.

Women with BI-RADS breast density type 4 were less likely to have had past or current hormone replacement therapy use, to have been pregnant, and to have undergone prior mammography than women with BI-RADS breast density type 3. Women with BI-RADS breast density type 4 were slightly more likely to have undergone needle aspiration and less likely to have undergone radiation in their breast intervention history compared with women with BI-RADS breast density type 3. Implants were more common in women with BI-RADS breast density type 4.

Cancer Detection

A total of 2301 women were recalled on the basis of screening mammographic results alone (Fig 2). Of these, 1957 women were also recalled on the basis of the combined read, while 344 were recalled on the basis of the results of screening mammography alone. Of the 13 107 women whose screening results were negative on the basis of screening mammography alone, 2407 had a recall recommended on the basis of the combined read. Among the women in whom a recall was recommended, 112 women with breast cancer were identified: 82 were identified by using screening mammography and cancers in an additional 30 women were identified by using AB US after no mammographic evidence of malignancy was found. Among the cancer cases where the recall recommendation differed, 30 of 30 cases were detected with the combined read and not with screening mammography alone ($P < .001$). Of the 112 cancers detected, 81 of 11 488 (0.71%) were in women with BI-RADS breast density type 3 and 31 of 3830 (0.81%) were in women with BI-RADS breast density type 4.

Cancers detected only with AB US were significantly more likely to be invasive compared with those in women who were recalled on the basis of results of screening mammography (28 of 30, 93.3%) versus 62.2% (51 of 82), with $P = .001$ (Table 2). Among the 82 cancers detected with either screening mammography alone or the combined read, 17 were detected by using screening mammography alone, 30 were detected by using AB US alone, and 65 were detected by using both screening mammography and AB US. Of the 17 cancers in women who were recalled on the basis of the results of screening mammography alone, 64.7% (11 of 17) were ductal carcinoma in

Table 1

Patient Demographic and Clinical Characteristics at Enrollment

Characteristic	Total (n = 15318)	BI-RADS Breast Density		P Value*
		Type 3 (n = 11488)	Type 4 (n = 3830)	
Age (y)†	53.3 ± 10.0 (25–94)	54.0 ± 10.0 (25–94)	51.1 ± 9.6 (25–90)	<.001
Age group‡				<.001
No. < 40 y	599 (3.9)	383 (3.3)	216 (5.6)	
No. 40–49 y	5557 (36.3)	3879 (33.8)	1678 (43.8)	
No. 50–59 y	5227 (34.1)	3983 (34.7)	1244 (32.5)	
No. 60–69 y	2911 (19.0)	2398 (20.9)	513 (13.4)	
No. ≥ 70 y	1024 (6.7)	845 (7.4)	179 (4.7)	
Race or ethnicity‡				<.001
No. of whites only	11915 (77.8)	9022 (78.5)	2893 (75.5)	
No. of Hispanics, Latinas, or Spanish only	810 (5.3)	617 (5.4)	193 (5.0)	
No. of American Indians or Alaskan natives only	33 (0.2)	26 (0.2)	7 (0.2)	
No. of Asians only	657 (4.3)	425 (3.7)	232 (6.1)	
No. of blacks, African Americans, or Haitians only	1645 (10.7)	1205 (10.5)	440 (11.5)	
No. of Native Hawaiians or Pacific Islanders only	27 (0.2)	21 (0.2)	6 (0.2)	
No. of mixed race or ethnicity	108 (0.7)	81 (0.7)	27 (0.7)	
No. of unknown or other race or ethnicity	123 (0.8)	91 (0.8)	32 (0.8)	
Body mass index‡				<.001
No. with <18.5 kg/m^2	494 (3.2)	248 (2.2)	246 (6.4)	
No. with 18.5–24.9 kg/m^2	9823 (64.1)	6956 (60.6)	2867 (74.9)	
No. with 25.0–29.9 kg/m^2	3639 (23.8)	3073 (26.8)§	566 (14.8)	
No. with ≥30.0 kg/m^2	1359 (8.9)	1208 (10.5)	151 (3.9)	
Menopausal status‡				<.001
No. of premenopausal women	5839 (38.1)	4003 (34.8)	1836 (47.9)	
No. of postmenopausal women	8726 (57.0)	6925 (60.3)	1801 (47.0)	
No. with unknown status	753 (4.9)	560 (4.9)	193 (5.0)	
Risk factors‡				
No. with personal history of breast cancer	549 (3.6)	445 (3.9)	104 (2.7)	<.001
No. with family history of breast cancer	6869 (44.8)	5138 (44.7)	1731 (45.2)	.61
No. with first-degree female relative	3327 (21.7)	2487 (21.6)	840 (21.9)	.71
No. with second-degree female relative	4507 (29.4)	3387 (29.5)	1120 (29.2)	.78
No. with other female relative	618 (4.0)	455 (4.0)	163 (4.3)	.42
No. with relationship not specified	41 (0.6)	28 (0.2)	13 (0.3)	.34
No. with male relative	158 (1.0)	119 (1.0)	39 (1.0)	.93
No. with female relative with ovarian cancer	1434 (9.4)	1108 (9.6)	326 (8.5)	.037
No. with *BRCA1* or *BRCA2* mutation	154 (1.0)	120 (1.0)	34 (0.9)	.40
Hormone replacement therapy‡				<.001
No. who had not undergone therapy	10533 (68.8)	7627 (66.4)	2906 (75.9)	
No. who had undergone past or current therapy	4785 (31.2)	3861 (33.6)	924 (24.1)	
Obstetric history‡				
No. never pregnant	3252 (21.2)	2300 (20.0)	952 (24.9)	<.001
No. with at least 1 full-term pregnancy	10811 (70.6)	8303 (72.3)	2508 (65.5)	<.001
Breast screening history‡				<.001
No. who had undergone prior mammography	14421 (94.1)	10866 (94.6)	3555 (92.8)	
No. who had not undergone prior mammography	796 (5.2)	548 (4.8)	248 (6.5)	
No. who had unknown breast screening history	101 (0.7)	74 (0.6)	27 (0.7)	
Breast intervention history‡				
No. who had undergone needle aspiration	2150 (14.0)	1561 (13.6)	589 (15.4)	.006
No. who had undergone core or needle biopsy	3998 (26.1)	3028 (26.4)	970 (25.3)	.21
No. who had undergone lumpectomy	821 (5.4)	623 (5.4)	198 (5.2)	.55
No. who had undergone mastectomy	165 (1.1)	130 (1.1)	35 (0.9)	.26

Table 1 (continues)

Table 1 (continued)

Patient Demographic and Clinical Characteristics at Enrollment

Characteristic	Total (n = 15318)	BI-RADS Breast Density		P Value*
		Type 3 (n = 11488)	Type 4 (n = 3830)	
No. who had undergone radiation therapy	361 (2.4)	299 (2.6)	62 (1.6)	<.001
No. who had never undergone interventional procedures	9907 (64.7)	7453 (64.9)	2454 (64.1)	.37
Breast surgery history‡				
No. who had undergone implant placement	607 (4.0)	407 (3.5)	200 (5.2)	<.001
No. who had undergone breast reduction	180 (1.2)	136 (1.2)	44 (1.1)	.86
No. who had undergone breast lift	123 (0.8)	85 (0.7)	38 (1.0)	.13
No. who had undergone breast reconstruction	75 (0.5)	57 (0.5)	18 (0.5)	.84
No. who had never undergone breast surgery	14483 (94.5)	10908 (95.0)	3575 (93.3)	<.001

* P values are based on the χ^2 square test for categorical variables and the t test for continuous variables.

† Data are the means ± standard deviations, except where otherwise indicated. Numbers in parentheses are ranges.

§ The percentage was calculated with n = 11485, as three patients were excluded because the body mass index was missing.

‡ Numbers in parentheses are percentages. Percentages were rounded.

Figure 2

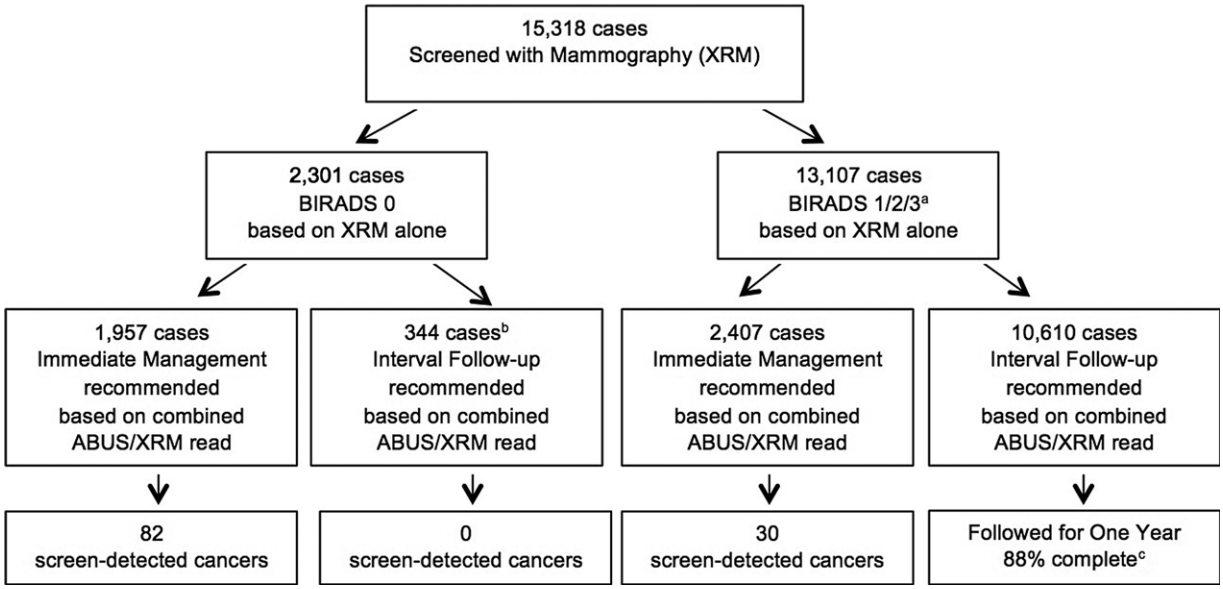

Figure 2: Outcome of screening mammography only and screening mammography with AB US *(combined ABUS/XRM read)*. *a* = Although usage of BI-RADS category 3 was discouraged, per American College of Radiology guidelines, it was not prohibited if it was part of a site's usual practice; a total of 19 patients (0.1%) received a BI-RADS category 3; none of these 19 patients had a cancer. *b* = If cases were BI-RADS category 0 based on screening mammography alone, the patients were recalled for immediate management even if the combined AB US and screening mammography recommendation was interval follow-up. *c* = Eleven percent of patients were lost to follow-up before having a 1-year follow-up, and 1% withdrew consent for additional follow-up. BI-RADS *1/2/3* = BI-RADS category 1, 2, or 3.

situ, compared with only 6.7% (two of 30) of the 30 additional cancers detected by using AB US alone. A larger percentage of invasive low-stage cancers (IA, IB) were detected with AB US alone compared with screening mammography (20 of 30, 66.7%) versus 45.1% (37 of 82).

Supplemental Cancer Detection Yield

The combined imaging approach of screening mammography and AB US generated a total yield of 7.3 cancers per 1000 women screened (95% CI: 4.2, 6.6; $P < .001$) compared with 5.4 cancers per 1000 women screened (95% CI: 5.9, 8.7; $P < .001$) for screening mammography alone (Table 3). The

Table 2

Cancer Detection Method and Characteristics for 112 Cancers in Women Who Were Recalled

Clinical Data	Cancers Detected Using SM Only	Cancers Detected Using SM and AB US	Total Cancers Detected Using SM	Cancers Detected Using AB US Only	Combined Study Screening-Detected Cancers	*P* Value*
No. of cancers	17	65	82	30	112	
Parenchymal density†						.20
No. with BI-RADS type 3	12 (70.6)	50 (76.9)	62 (75.6)	19 (63.3)	81 (72.3)	
No. with BI-RADS type 4	5 (29.4)	15 (23.1)	20 (24.4)	11 (36.7)	31 (27.7)	
Cancer type						
No. of DCIS cancers†	11 (64.7)	20 (30.8)	31 (37.8)	2 (6.7)	33 (29.5)	.001
No. of invasive cancers†	6 (35.3)	45 (69.2)	51 (62.2)	28 (93.3)	79 (70.5)	
No. of IDC cancers†	5 (29.4)	33 (50.8)	38 (46.3)	21 (70.0)	59 (52.7)	
No. of ILC cancers†	1 (5.9)	10 (15.4)	11 (13.4)	4 (13.3)	15 (13.4)	
No. of other invasive-type cancers†	0	2 (3.1)	2 (2.4)	3 (10.0)	5 (4.5)	
Size of cancers (mm)‡	5.2 ± 3.4	14.1 ± 7.7	13.0 ± 7.8	12.9 ± 8.0	13.0 ± 7.9	.77
No. with nodal staging available§	6 (100)	42 (93.3)	48 (94.1)	27 (96.4)	75 (94.9)	>.99
No. node positive‖	0	2/42 (4.8)	2/48 (4.2)	2/27 (7.4)	4/75 (5.3)	.62
Anatomic stage#						.84**
No. of stage IA or IB cancers	6 (35.3)	31 (47.7)	37 (45.1)	20 (66.7)	57 (50.9)	
No. of stage IIA or IIB cancers	0	9 (13.8)	9 (11.0)	5 (16.7)	14 (12.5)	
No. of stage IIIA, IIIB, or IIIC cancers	0	2 (3.1)	2 (2.4)	2 (6.7)	4 (3.6)	
No. of stage IV cancers	0	0	0	0	0	
No. of unknown cancers	0	3 (4.6)	3 (3.7)	1 (3.3)	4 (3.6)	

Note.— AB US = 3D automated breast US, DCIS = ductal carcinoma in situ, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, SM = screening mammography. Cancers Detected Using SM Only column head = cancers in women recalled by using screening mammography only, Cancers Detected Using SM and AB US column head = cancers in women recalled by using both screening mammography and AB US, Total Cancers Detected Using SM column head = cancers in women recalled by using screening mammography (total), and Cancers Detected Using AB US Only column head = cancers in women recalled by using AB US only.

* For comparison of total cancers detected using screening mammography with cancers detected using AB US only.

† Numbers in parentheses are percentages, and percentages were rounded.

‡ For invasive cancers only. Data are means ± standard deviations, except *P* values.

§ These data include 15 micrometastases (12 from Cancers Detected Using SM and AB US column and three from Cancers Detected Using AB US Only column), none of which were node positive. Numbers in parentheses are percentages, and percentages were rounded.

‖ Data are numbers used to calculate the percentages. Numbers in parentheses are percentages, and percentages were rounded.

For invasive cancers only. Numbers in parentheses are percentages, and percentages were rounded.

** This *P* value excludes unknowns and noninvasive cancers.

difference in yield was an additional 1.9 detected cancers per 1000 women screened (95% CI: 1.2, 2.7; $P < .001$). The corresponding increase in the recall rate per 1000 women screened was 150.2 (95% CI: 144.1, 155.7; $P < .001$) for screening mammography alone and 284.9 (95% CI: 278.0, 292.2; $P < .001$) for the combined imaging approach. The increase in sensitivity at screening for the combined imaging approach versus mammography alone was 26.7% (95% CI: 18.3%, 35.1%; $P < .001$); the difference in specificity was −13.4% (95% CI: −14.0%, −12.8%; $P < .001$). The increase in the biopsy rate was 36.0 per 1000 women screened (95% CI: 32.9, 39.2). The PPVs decreased with the combined imaging approach compared with screening mammography alone, with 3.6% (82 of 2301) versus 2.6% (112 of 4364) for PPV_1 and 14.0% (82 of 586) versus 9.8% (112 of 1138) for PPV_3.

Discussion

This large, real-world, observational study of women with dense breasts who presented consecutively for routine screening mammography demonstrated improved detection of mammographically occult breast cancer by using AB US over screening mammography alone. Breast cancer was diagnosed at screening in 112 women: in 82 women, by using screening mammography, and in an additional 30 women, by using AB US. By using combined screening mammography and AB US, 1.9 additional cancers per 1000 women screened were detected compared with the rate by using screening mammography alone. More important, nearly all of the cancers detected with the additional AB US screening were invasive cancers (51 of 82, 62.2%) for screening mammography with AB US and 93.3% (28 of 30) for AB US alone. In addition, cancers detected with AB US were probably a lower stage (20 of 30, 66.7%) (stage IA or IB) at diagnosis. The

Table 3

Results in 15 318 Patients Screened Sequentially with Mammography Alone versus 3D AB US with Screening Mammography

Statistical Data	Screening Mammography Alone	Combined Screening Mammography and AB US Read	Difference*
No. of women recalled	2301	4364	2063
No. of cancers found	82	112	30
Yield per 1000 women screened	5.4 (4.2, 6.6)	7.3 (5.9, 8.7)	1.9 (1.2, 2.7)
Sensitivity at study entry (%)	73.2 (64.9, 81.7)	100	26.7 (18.3, 35.1)
PPV_1 (%)†	3.6 (82/2301)	2.6 (112/4364)	−1.0
95% CI	32.8, 4.4	2.1, 3.1	−1.4, −0.6
No. of women not recalled	13 017	10 954	2063
No. of noncancers in women not recalled (n = 15 206)‡	12 987	10 954	2033
Specificity (%)	85.4 (84.9, 86.0)	72.0 (71.3, 72.7)	−13.4 (−14.0, −12.8)
No. of women recalled per 1000 women screened	150.2 (144.1, 155.7)	284.9 (278.0, 292.2)	134.6 (128.4, 141.0)
No. with biopsy recommended	610	1179	569
Per 1000 women screened	39.8 (36.7, 43.2)	77.0 (72.9, 81.0)	37.1 (34.0, 40.3)
PPV_2 (%)†	13.4 (82/610)	9.5 (112/1179)	−3.9
95% CI	10.7, 16.2	7.8, 11.3	−5.5, −2.3
No. with biopsy performed	586	1138	552
Per 1000 women screened	38.3 (35.3, 41.5)	74.3 (70.4, 78.2)	36.0 (32.9, 39.2)
PPV_3 (%)†	14.0 (82/586)	9.8 (112/1138)	−4.1
95% CI	11.2, 16.8	8.1, 11.7	−5.7, −2.5

Note.— Unless otherwise indicated, numbers in parentheses are the 95% CIs.

* Data are the differences between the combined read versus screening mammography alone.

† Numbers in parentheses were used to calculate the percentage estimates.

‡ The number 15 206 was calculated as 112 subtracted from 15 318.

corresponding increase in the recall rate per 1000 women screened was 284.9 (95% CI: 278.0, 292.2; $P < .001$) for the combined imaging approach, with a decrease in PPV values. An additional 552 biopsies were performed to identify the 30 additional cancers.

The effect of these findings, which indicates that clinically important cancers (ie, invasive cancers) were detected with the addition of AB US compared with screening mammography alone, suggests positive implications for potential detection, treatment, and prognosis in patients with dense breasts. Specifically, with the addition of AB US, we identified cancers that were challenging to detect by using mammography. Notably, however, the PPVs and specificity decreased with the increase in cancers detected with AB US. The high false-positive rate in this study is not unprecedented with evaluation of new screening modalities and is consistent with the relatively high rate of cancers detected. It is by no means inevitable that it would translate directly into routine practice. In a preliminary analysis of 1676 women screened in Sweden, using double-reading with consultation in the case of disagreement, a recall rate of only 2.3% was observed, while a substantial increase in sensitivity was observed (18). Similarly, in a preliminary multireader, multicase study, the investigators showed an increase in sensitivity of 24% without any significant decrease in specificity (19).

Of the 17 cancers detected by using screening mammography alone, 64.7% (11 of 17) were ductal carcinoma in situ, compared with 6.7% (two of 30) of the cancers detected by using AB US alone. Despite the favorable diagnosis and high cure rate (96%–98%) of ductal carcinoma in situ (20), these cancers are prone to overdiagnosis and overtreatment (14,21). In addition, there is some evidence that most of the mortality benefit from screening derives from the detection of early-stage invasive cancers (22,23).

The rates of additional cancers identified by using handheld US range between 1.9 and 5.3 additional cancers per 1000 women screened compared with mammography alone (15,24–29). The American College of Radiology Imaging Network, or ACRIN, 6666 trial (29), the largest trial to date of physician-performed screening breast US, reported detection of 5.3 additional cancers per 1000 women screened in the 1st year of screening and 3.7 per 1000 women screened in subsequent years. However, the population studied was at high risk for breast cancer, and in that population, MR imaging is recommended for surveillance (15). The researchers in a study (30) of imaging in the preoperative assessment of breast cancer found that, unlike mammography, the sensitivity of MR imaging and that of US was unaffected by breast density. In addition, many single-institution studies have shown similar results, with an average of 0.35% additional breast cancer yield with

whole-breast, handheld screening US (14). Investigators in studies (31,32) with the use of two-dimensional AB US in high-risk women found an increase of 3.6 cancers per 1000 women screened, with a corresponding increase in recalled women from 4.2% to 9.6%.

Most of the studies (14,15,29,33) in which researchers evaluated MR imaging or US in women with dense breasts included high-risk women with additional risk factors for breast cancer, such as a personal or family history of breast cancer or the presence of the *BRCA1* or *BRCA2* mutation. In our study, the criterion for inclusion was that the woman was asymptomatic and had dense breast tissue, and we did not require women to be at increased risk for breast cancer. It is, therefore, not surprising that, in our study, we found fewer additional cancers per 1000 women screened, as the prevalence of disease was lower.

MR imaging is limited by high cost, relative lack of availability, variable patient tolerance, and the requirement for contrast material injection (14). US is inexpensive, well tolerated by patients, and does not require the use of ionizing radiation. AB US aims to remedy the issues of handheld US of operator dependence, image variability, and physician time for acquisition, as all images are acquired by using standardized views and by nonphysician personnel. The automated imaging process of AB US is faster to acquire and requires less training than handheld US. The standardized review process allows quick navigation through the breast and rapid review of many images. Using US with an efficient work flow in the screening environment, as well as the advantage of US to detect cancer, may well be the solution for a currently unanswered need of detection of mammographically occult breast cancer in women with dense breasts.

There were limitations to this study. Initial screening for our study was performed by technologists and research coordinators, who may have excluded women with dense breasts. This may also have biased radiologists toward a dense breast reporting category; however, this bias existed insofar as a radiologist may have been hesitant to contradict the original assessment of breast density. Although measures were implemented to minimize variation among readers and their interpretation, the quality of the interpretation may have affected sensitivity and specificity. Mortality was not assessed in our cohort, and, thus, it was not possible to quantify whether the detection of additional cancers actually decreased the mortality rate. Because of the sequential design of interpretations, the stand-alone performance of AB US was not tested. Finally, as an observational study, there was no control group in which to compare clinical outcomes.

In summary, in our study, we found that there is an increase in cancer detection by using AB US to supplement mammography among women with dense breasts, producing detection of an additional 1.9 cancers per 1000 women screened, and most of these cancers were clinically important.

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