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Detection of Breast Cancer With Addition of Annual Screening Ultrasound or a Single Screening MRI to Mammography in Women With Elevated Breast Cancer Risk

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Context Annual ultrasound screening may detect small, node-negative breast cancers that are not seen on mammography. Magnetic resonance imaging (MRI) may reveal additional breast cancers missed by both mammography and ultrasound screening.

Objective To determine supplemental cancer detection yield of ultrasound and MRI in women at elevated risk for breast cancer.

Design, Setting, and Participants From April 2004-February 2006, 2809 women at 21 sites with elevated cancer risk and dense breasts consented to 3 annual independent screens with mammography and ultrasound in randomized order. After 3 rounds of both screenings, 612 of 703 women who chose to undergo an MRI had complete data. The reference standard was defined as a combination of pathology (biopsy results that showed in situ or infiltrating ductal carcinoma or infiltrating lobular carcinoma in the breast or axillary lymph nodes) and 12-month follow-up.

Main Outcome Measures Cancer detection rate (yield), sensitivity, specificity, positive predictive value (PPV3) of biopsies performed and interval cancer rate.

Results A total of 2662 women underwent 7473 mammogram and ultrasound screenings, 110 of whom had 111 breast cancer events: 33 detected by mammography only, 32 by ultrasound only, 26 by both, and 9 by MRI after mammography plus ultrasound; 11 were not detected by any imaging screen. Among 4814 incidence screens in the second and third years combined, 75 women were diagnosed with cancer. Supplemental incidence-screening ultrasound identified 3.7 cancers per 1000 screens (95% CI, 2.1-5.8; $P<.001$). Sensitivity for mammography plus ultrasound was 0.76 (95% CI, 0.65-0.85); specificity, 0.84 (95% CI, 0.83-0.85); and PPV3, 0.16 (95% CI, 0.12-0.21). For mammography alone, sensitivity was 0.52 (95% CI, 0.40-0.64); specificity, 0.91 (95% CI, 0.90-0.92); and PPV3, 0.38 (95% CI, 0.28-0.49; $P<.001$ all comparisons). Of the MRI participants, 16 women (2.6%) had breast cancer diagnosed. The supplemental yield of MRI was 14.7 per 1000 (95% CI, 3.5-25.9; $P=.004$). Sensitivity for MRI and mammography plus ultrasound was 1.00 (95% CI, 0.79-1.00); specificity, 0.65 (95% CI, 0.61-0.69); and PPV3, 0.19 (95% CI, 0.11-0.29). For mammography and ultrasound, sensitivity was 0.44 (95% CI, 0.20-0.70, $P=.004$); specificity 0.84 (95% CI, 0.81-0.87; $P<.001$); and PPV3, 0.18 (95% CI, 0.08 to 0.34; $P=.98$). The number of screens needed to detect 1 cancer was 127 (95% CI, 99-167) for mammography; 234 (95% CI, 173-345) for supplemental ultrasound; and 68 (95% CI, 39-286) for MRI after negative mammography and ultrasound results.

Conclusion The addition of screening ultrasound or MRI to mammography in women at increased risk of breast cancer resulted in not only a higher cancer detection yield but also an increase in false-positive findings.

Trial Registration clinicaltrials.gov Identifier: NCT00072501

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SIX PREVIOUS SINGLE-CENTER studies[1-6] and 3 multicenter trials[7-9] have shown supplemental screening breast ultrasound significantly increases detection of node-negative invasive breast cancer in women with mammographically dense breast tissue on the first prevalence screen, consistently increasing cancer detection (yield) by 3.5 per 1000 in single-center studies and from 4.2 to 4.4 per 1000 in multicenter trials. The vast majority of cancers detected only by ultrasound have been node-negative invasive breast cancers. Until now, it was

See also p 1379.

Author Video Interview available at www.jama.com.

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unclear whether continuing ultrasound screening annually (ie, incidence screening) would result in a detection benefit.

A substantial majority of American College of Radiology Imaging Network (ACRIN) 6666 participants were at intermediate risk for breast cancer, with more than half having a personal history of breast cancer.[7] Although there was evidence from prior studies[10-13] that magnetic resonance imaging (MRI) provided considerable detection benefit beyond what combined ultrasound and mammography screens could discover in high-risk women, the combination of ultrasound and mammography might still identify the vast majority of cancers when they are node negative at a much lower cost to the health care system than the cost of an MRI, particularly when screening women with a lower prevalence of disease. A substudy of ACRIN 6666 participants was therefore undertaken to assess the rate and stage of cancers detected with a single screening MRI.

METHODS

Study Design

Study participants included women who were asymptomatic, presenting for routine annual mammography with heterogeneously dense or extremely dense breast tissue,[14] and who had at least 1 other risk factor for breast cancer (TABLE 1). Race/ethnicity was self-assigned based on fixed categories.

Each participant underwent mammographic and physician-performed ultrasonographic screening examinations in randomized order, with the interpreting radiologist for each examination masked to results of the other study, at 0 months (first screening), 12 months (second screening), and 24 months (third screening). The randomization process has been previously described,[7] and initial randomization order was maintained for subsequent screening rounds. If recommendation from either screening test was other than routine annual screening, the test was considered positive for purposes of

Table 1. Participant Characteristics

	Screening Analysis Set, No. (%)			
	1 (n = 2659)	2 (n = 2493)[a]	3 (n = 2321)	MRI (n = 612)
Age at scan, mean (SD), y	55.2 (10.1)	56.4 (9.9)	57.7 (9.8)	56.8 (9.5)
Median (range)	55.0 (25-91)	56.0 (26-92)	57.0 (27-93)	57.0 (27-87)
Age group at scan, y				
<40	134 (5.0)	89 (3.6)	65 (2.8)	17 (2.8)
40-49	627 (23.6)	514 (20.6)	392 (16.9)	114 (18.6)
50-69	1678 (63.1)	1644 (65.9)	1597 (68.8)	429 (70.1)
>69	220 (8.3)	246 (9.9)	267 (11.5)	52 (8.5)
Race/ethnicity				
White	2467 (92.8)	2316 (92.9)	2162 (93.1)	576 (94.1)
Hispanic or Latino	265 (10.0)	233 (9.3)	209 (9.0)	83 (13.6)
Black or African American	91 (3.4)	85 (3.4)	77 (3.3)	11 (1.8)
Native Hawaiian or other Pacific Islander	4 (0.2)	3 (0.1)	4 (0.2)	1 (0.2)
Asian	90 (3.4)	82 (3.3)	71 (3.1)	22 (3.6)
American Indian or Alaskan Native	4 (0.2)	4 (0.2)	4 (0.2)	1 (0.2)
Unknown	11 (0.4)	11 (0.4)	11 (0.5)	1 (0.2)
Menopausal status				
Premenopausal[b]	609 (22.9)	554 (22.2)	502 (21.6)	155 (25.3)
Perimenopausal[c]	182 (6.8)	170 (6.8)	158 (6.8)	37 (6.0)
Postmenopausal[d]	1362 (51.2)	1294 (51.9)	1208 (52.0)	316 (51.6)
Surgical menopause	484 (18.2)	454 (18.2)	432 (18.6)	103 (16.8)
Unknown	22 (0.8)	21 (0.8)	21 (0.9)	1 (0.2)
Personal history of breast cancer (regardless of other risk factors)[e]	1426 (53.6)	1331 (53.4)	1253 (54.0)	275 (44.9)
Visually estimated breast density at scan, %				
≤25	47 (1.8)	47 (1.9)	34 (1.5)	7 (1.1)
26-40	278 (10.5)	236 (9.5)	196 (8.4)	61 (10.0)
41-60	824 (31.0)	792 (31.8)	774 (33.3)	191 (31.2)
61-80	994 (37.4)	976 (39.1)	920 (39.6)	253 (41.3)
>80	515 (19.4)	442 (17.7)	395 (17.0)	100 (16.3)
Unknown	1 (<1)	0	2 (0.1)	0
Primary risk factor[f]				
Mutation in *BRCA1* or *BRCA2*	23 (0.9)	20 (0.8)	18 (0.8)	3 (0.5)
History of prior chest, mediastinal, or axillary irradiation	8 (0.3)	6 (0.2)	6 (0.3)	2 (0.3)
Personal history of breast cancer	1413 (53.1)	1321 (53.0)	1244 (53.6)	273 (44.6)
Lifetime risk, Gail/Claus model ≥25%[g]	504 (19.0)	460 (18.5)	425 (18.3)	135 (22.1)
5-Year risk, Gail model ≥2.5%	406 (15.3)	391 (15.7)	366 (15.8)	113 (18.5)
5-Year risk, Gail model ≥1.7% and extremely dense breasts	225 (8.5)	217 (8.7)	195 (8.4)	70 (11.4)
ADH/ALH/LCIS or atypical papilloma	80 (3.0)	78 (3.1)	67 (2.9)	16 (2.6)

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging.
[a] Three participants excluded from year-1 analysis were included in year 2, for a total of 2662 unique participants.
[b] Defined as last menstrual period within prior 30 days.
[c] Defined as last menstrual period more than 30 days and less than 12 months prior.
[d] Defined as last menstrual period at least 12 months prior.
[e] Eight hundred sixty-nine of 1426 women (71.1%) with a personal history of breast cancer had lumpectomy and radiation therapy for the affected breast(s) during the study.
[f] Participants with multiple risk factors were determined to have a primary risk factor using the following hierarchy: Mutation in *BRCA1* or *BRCA2* genes; history of prior chest, mediastinal, axillary irradiation or all 3; a personal history of breast cancer; a lifetime risk, Gail model of at least 25%; 5-year risk, Gail model of 2.5% or more; 5-year risk, Gail model 1.7% or more; extremely dense breasts; and prior biopsy showing ADH, ALH, LCIS, or atypical papilloma.
[g] One participant's eligibility is based on a recalculated Gail score, for which the original score was missing.

analysis and a qualified site investigator then recorded an integrated interpretation by reviewing study mammogram and ultrasound together. Clinical management was based on integrated interpretation. If both modalities recommended routine annual follow-up, no integration was performed. *Cancers positive only on a given modality* refers to those not visible on any other modality. *Sensitivity of a modality alone* refers to the number of cancers that would have been detected if only that modality had been used and includes some cancers that were also visible on the other modality.

To be eligible for the MRI substudy, women had to have completed the third round of annual ultrasound and mammography screenings per protocol[7] and had agreed to undergo contrast-enhanced breast MRI within 8 weeks of the 24-month screening mammogram. Interpretation of each of the 3 screening approaches was blinded to results of the other examinations. A separate integrated breast-level interpretation across all 3 modalities was then performed, which determined clinical management. Women who accepted MRI had higher risk and were younger than those who declined.[15] Women enrolled at sites in the MRI substudy were less likely to have had a personal history of breast cancer; no other systematic differences were noted across sites.

Web-based data capture and quality monitoring were conducted by the ACRIN biostatistics and data management center. The study was compliant with the Health Insurance Portability and Accountability Act, received institutional review board approval from all participating sites and from ACRIN, and received approval from the National Cancer Institute Cancer Imaging Program. The study underwent data and safety monitoring committee review every 6 months.

Participants

Among the 21 sites, 2809 women were recruited between April 2004 and February 2006, 2725 of whom were eligible (FIGURE 1). Women aged at least 25 years presenting for routine mammography were eligible to participate if they met study definitions of elevated risk (Table 1) and had heterogeneously dense or extremely dense parenchyma[14] in at least 1 quadrant, either by prior mammography report or review of prior mammograms. Women were excluded if they were pregnant or lactating or if they had known metastatic disease, signs or symptoms of breast disease, breast surgery within prior 12 months, or breast implants.

For the MRI substudy, women also could not have contraindications to MRI (have a pacemaker, aneurysm clip, or other metallic implant; weigh >135 kg; or have renal impairment [have a glomerular filtration rate of <30 mL/min per 1.73 m^2 or were undergoing a dialysis regimen]). Participants provided written informed consent at their initial visit. Those participating in the MRI screening provided a second consent at MRI registration.

Screening methods are detailed in the eAppendix (available at http://www.jama.com). The expanded 7-point Breast Imaging-Reporting and Data System (BI-RADS)[14,16,17] assessment scale was used: a score of 1 is negative; 2, benign; 3, probably benign; 4a, low suspicion; 4b, intermediate suspicion; 4c, moderate suspicion; and 5, highly suggestive of malignancy.

Reference Standard

We defined the reference standard, which could be cancer or not, to be the most severe of biopsy results within 365 days of mammographic screening, clinical follow-up at 1 year, or both. Each mammographic screening was targeted for 365 days after the previous mammographic screening. A complete examination of all study breasts performed more than 11 full months after the previous screen was considered the next annual screen; only 88 of 7473 visits (1.2%) occurred before 11 months. The absence of a known diagnosis of cancer for a participant report at interview, review of medical records, or both at least 11 full months (330 days) after mammographic screening was considered disease negative, as were 7 cases of prophylactic mastectomies with no evidence of cancer at pathology. Biopsy results showing breast cancer (in situ or infiltrating ductal carcinoma or infiltrating lobular carcinoma) in the breast or axillary lymph nodes were considered disease positive.

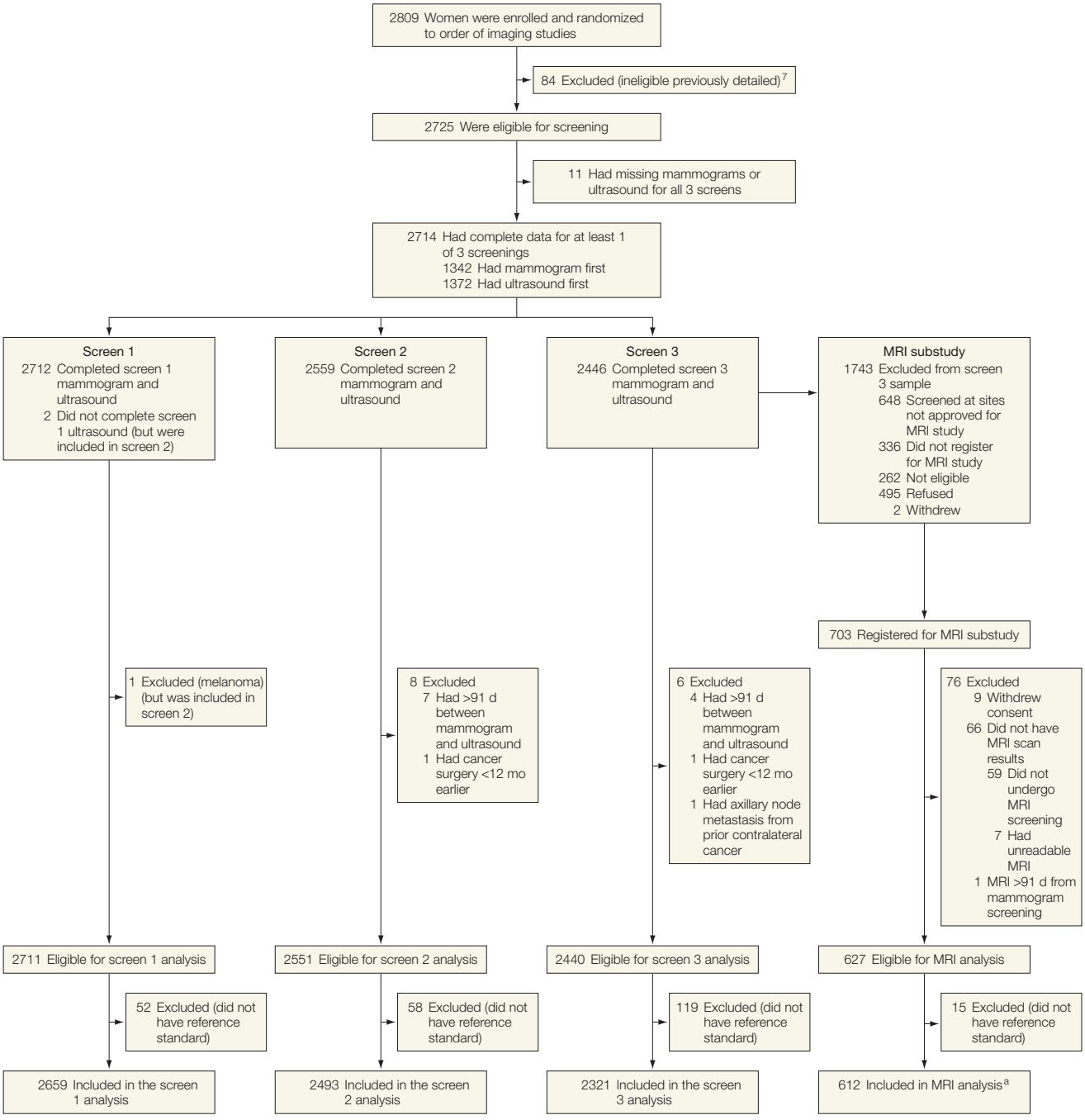
Statistical Methods

The primary unit of analysis was the participant. A participant's BI-RADS score was derived as the maximum breast level BI-RADS or the score from the breast with cancer when only 1 breast had cancer. In keeping with planned revisions to BI-RADS (Edward A. Sickles, MD, Professor of Radiology, University of California, San Francisco, written communication, November 29, 2009), a screening BI-RADS assessment score of 3, 4a, 4b, 4c, or 5 was considered test positive, provided that the recommendation was for other than routine screening. This differs from the definition of positive test results that we used in our initial publication of the first screening, wherein an assessment of 4a or higher was considered a positive test result[7]: results of the first screen have been reanalyzed and included herein. For a participant diagnosed with cancer, the breast(s) with cancer were excluded from analysis for the next annual screen.

The cancer detection rate (ie, the proportion of women with a positive screen result and a positive reference standard); sensitivity; specificity; recall rate, which is the proportion of women with a positive screen result; positive predictive value (PPV1), which is the malignancy rate among cases that test positive on screening; short-term follow-up rate; biopsy rate; and area under the empirical receiver operating characteristic (ROC) curve (AUC) using BI-RADS scores were reported. *PPV3* is defined as the rate of malignancy among cases with positive results on screening who underwent biopsy of the same lesion.[14] Interval cancers were defined as those diagnosed because of a clinical abnormality such as a lump, skin

thickening, or pathologic nipple discharge occurring in the interval between prescribed screenings (ie, less than 365 days after the last screening mammogram and before the next screen; cancers detected on an early screen performed at least 11 months after the previous screen were considered screen detected).

Figure 1. Flowchart of Protocol



Participants with negative results on both mammography and ultrasound were imputed as having negative results on integrated reading of mammography plus ultrasound: 1844 for the first screening, 1922 for the second screening, and 1912 for the third screening. The reference standard was the most severe of biopsy results within 365 days of mammographic screening, on clinical follow-up at 1 year, or both. Biopsies prompted by an early subsequent screening examination were attributed to that subsequent screen.

[a] All participants in the magnetic resonance imaging (MRI) analysis set are also in the screen 3 analysis set.

Single-year estimates of yield, sensitivity, specificity, recall rate, PPV1, short-term follow-up rate, biopsy rate, and PPV3, were determined as simple proportions with exact 95% CIs (Clopper-Pearson). The 95% CIs for differences in yield, sensitivity, specificity, recall rate, short-term follow-up rate, and biopsy rate were calculated per Fleiss et al.[18] *P* values for the above comparisons were based on the McNemar test statistic. The 95% CIs and *P* values for differences in PPV1 and PPV3 were calculated using the bootstrap-resampling method.[19] All inferences for incidence screens were based on the bootstrap-resampling method. Estimates, 95% CIs, and *P* values related to AUC were derived by using the method of Delong et al[20] for empirical ROC curves. Results for participants with a personal history of breast cancer were compared with those who had no such history by the bootstrap method. All *P* values were reported as 2-sided, with .05 set as threshold for significance. All analyses were performed by SAS 9.2 statistical software (SAS Institute Inc).

RESULTS

Participant Demographic Information

A total of 2659 eligible women with reference standard completed the first annual mammogram and ultrasound screenings; 2493, the second; and 2321, the third (Figure 1 and FIGURE 2, Table 1). Participant demographics at enrollment were previously reported.[7] Median age at enrollment was 55 years (range, 25-91 years). Approximately 29% of women were younger than 50 years at enrollment, and 23% were premenopausal (Table 1). Nearly 54% of women had a personal history of breast cancer. The median age of the 612 women in the MRI group was 57 years (range, 27-87 years); 21% were younger than 50 years at the time of the screening, 25% were premenopausal, and 45% had personal history of breast cancer. Time between screens (eTable 1) and time to perform ultrasound (eTable 2) are available at http://www.jama.com.

Cancer Detection

A total of 110 participants were diagnosed with breast cancer during the 3-year study. One woman diagnosed by mammography in the first year was diagnosed again in the third year in the contralateral breast by MRI only. Each diagnosis was counted as a separate event, for a total of 111 participant-cancer events. Of 111 diagnoses, 89 (80%) were invasive (TABLE 2). Fifty-nine cancers (53%) were detected by mammography, including 33 (30%) that were detected by mammography only; 32 (29%) by ultrasound only; and 9 (8%) by MRI only after both mammography and ultrasound screens failed to detect cancer. Eleven cancers (10%) were not detected by any imaging screen. Of 32 cancers seen only on ultrasound, 30 (94%) were invasive, with median size of 10 mm (range, 2-40 mm), and 26 of 27 (96%) of those staged were node negative.

A total of 16 of 612 women (2.6%) in the MRI substudy were diagnosed with breast cancer, 12 of 16 (75%) of whom had invasive cancer. Nine of 16 cancers (56%) were seen only on MRI after negative mammography and ultrasound results: 8 of 9 (89%) were invasive, with median size of 8.5 mm (range, 1-25 mm), and all 7 cancers that were staged were node negative (Table 2). Two invasive cancers that had been detected by ultrasound but not by mammography in the MRI substudy were also detected by MRI.

Supplemental Cancer Detection Yield

Supplemental ultrasound increased cancer detection with each annual screen beyond that of mammography, adding detection of 5.3 cancers per 1000 women in the first year (95% CI, 2.1-8.4; $P<.001$); 3.7 women per 1000 per year in each of the second and third years (95% CI, 2.1-5.8, $P<.001$; TABLE 3); and averaging 4.3 per 1000 for each of the 3 rounds of annual screening. Supplemental yield results of ultrasound after digital mammography are shown in the eAppendix. The addition of MRI screening further increased cancer detection with a supplemental cancer detection yield of 14.7 per 1000 women (95% CI, 3.5-25.9; $P=.004$ vs mammogram plus ultrasound; TABLE 4). The number of screens needed to detect 1 cancer was 127 (95% CI, 99-167) for mammography; 234 (95% CI, 173-345) for supplemental ultrasound, and 68 (95% CI, 39-286) for supplemental MRI after negative mammography plus ultrasound screening results.

Sensitivity, Specificity, and AUC

Among 4814 incidence screens in years 2 and 3 combined, 75 women were diagnosed with cancer. Sensitivity of combined mammography plus ultrasound was 57 of 75 (0.76; 95% CI, 0.65-0.85) for incidence screening, higher than mammography alone, which was 39 of 75 (0.52; 95% CI, 0.40-0.64; $P<.001$). Specificity of combined mammography and ultrasound was 3987 of 4739 (0.84; 95% CI, 0.83 to 0.85) for incidence screens, lower than the specificity of mammography alone, which was 4325 of 4739 (0.91; 95% CI, 0.90-0.92; $P<.001$; Table 3).

For 612 MRI participants, sensitivity increased from 7 of 16 (0.44; 95% CI, 0.20-0.70) with combined mammography and ultrasound to 16 of 16 (1.00; 95% CI, 0.79-1.00) with the addition of MRI ($P=.004$). Specificity was reduced to 390 of 596 (0.65; 95% CI, 0.61-0.69) after MRI vs combined mammography plus ultrasound at 503 of 596 (0.84; 95% CI, 0.81-0.87, $P<.001$; Table 4).

Overall AUC increased each year when ultrasound was added to mammography (Table 3). Adding MRI lowered apparent performance of mammography plus ultrasound because more cancers were identified by MRI (Table 4).

Additional Biopsies and PPV3

The PPV3 for biopsies resulting from combined mammography plus ultrasound was 31 of 272 (0.11; 95% CI, 0.08-0.16) for the first screen and was 55 of 339 (0.16; 95% CI, 0.12 to 0.21) for incidence screens. These values were

significantly lower than those of mammography alone (19 of 65 [0.29; 95% CI, 0.19-0.42, first screening] and 37 of 97 [0.38; 95% CI, 0.28-0.49 incidence screening]; $P<.001$ for both; Table 3). The percentage of women undergoing biopsy after mammography and ultrasound decreased from 272 of 2659 (10.2%; 95% CI, 9.1%-11.4%) in year 1 to 339 of 4814 (7.0%; 95% CI, 6.3%-7.8%) for incidence screens ($P<.001$). The biopsy rates after mammography alone were 65 of 2659 (2.4%; 95% CI, 1.9%-3.1%) in year 1 and 97 of 4814 (2.0%; 95% CI, 1.6%-2.5%) for incidence screens. There were 242 of 4814 (5%) incidence screens resulting in biopsy due to addition of ultrasound, with 18 of 242 (7.4%) of these women found to have cancer.

For 612 MRI participants, the rate of biopsy after a full workup of mammography plus ultrasound was 38 of 612 (6.2%; 95% CI, 4.4%-8.4%), which increased to 81 of 612 (13.2%; 95% CI,10.7%-16.2%) with the addition of MRI ($P<.001$). The PPV3 after mammography plus ultrasound was 7 of 38 (0.18; 95% CI, 0.08-0.34) and with addition of MRI, it was 15 of 81 (0.19; 95% CI, 0.11-0.29, $P=.98$; Table 4). There were 43 of 612 (7.0%) participants biopsied only because of MRI, 8 (19%) of whom were found to have cancer.

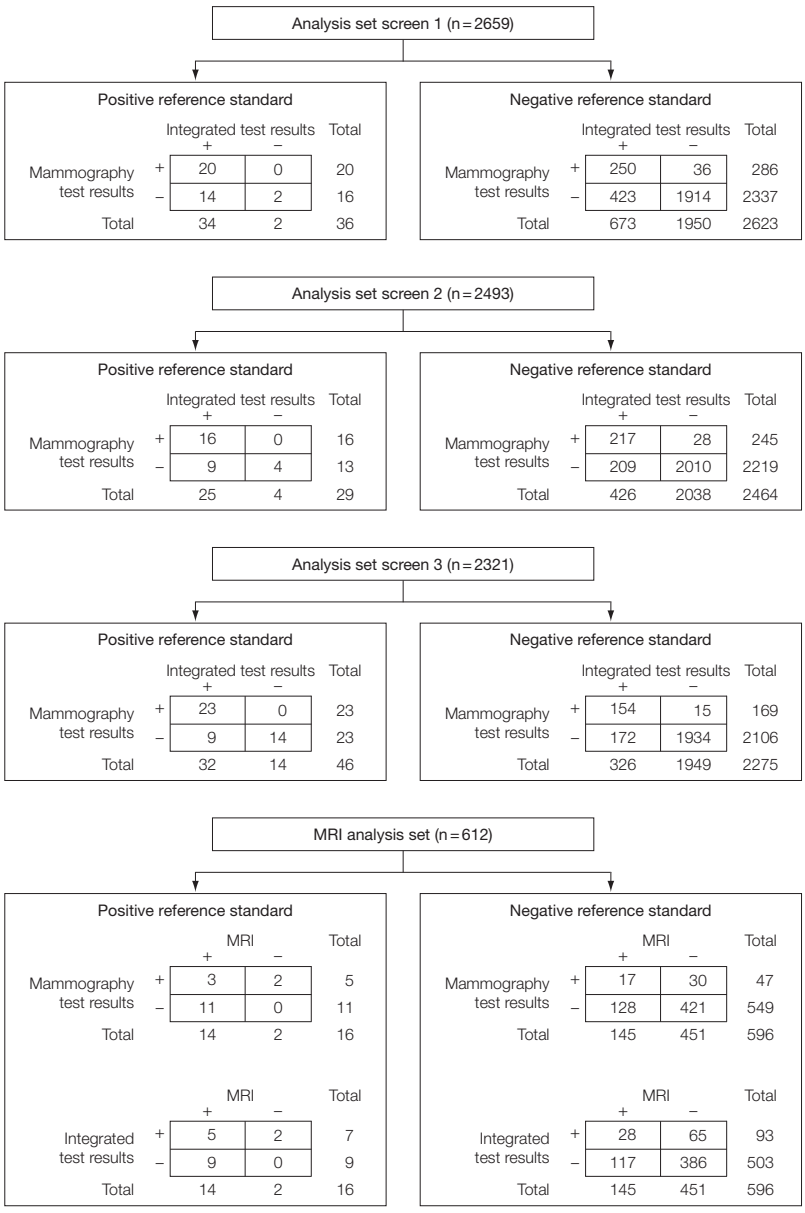
Interval Cancers

Of 20 women with cancer not seen on either mammography or ultrasound in 3 annual rounds, 9 women in the MRI cohort had their cancer detected by MRI. Another 9 cancers were identified because of clinical abnormalities found during the intervals between screens (interval cancer rate 8.1%): 2 had clinical findings in the first year; 4 in the second year; and 3 in the third year. One participant was found to have high-grade ductal carcinoma in situ because of off-study computer-assisted detection applied to mammogram (revealing calcifications) after the year-3 interpretation had been recorded. One participant with a *BRCA*1 mutation had an MRI screening off study 6 months after the third screen and was found to have a 7 mm node-negative grade III invasive ductal carcinoma.

Women With Personal History of Breast Cancer

A total of 1426 of 2659 participants (54%) had a personal history of breast cancer at study entry and underwent 4010 screens; 59 of 1426 (4.1%) were diagnosed with cancer (28 only ipsilateral and 29 only contralateral to the original cancer; 2 bilateral). Supplemental yield of ultrasound was the same in women with a personal history of breast cancer as in women without a personal history of breast cancer (eTable 3A available at http://www.jama.com), as was the absolute increase in

Figure 2. Outcomes of 3 Rounds of Annual Screening Mammography Plus Ultrasound



Outcomes of screening 2662 participants are detailed for mammography alone compared with integrated tests, mammography plus ultrasound, for each of the 3 screening years and also for 612 women in the MRI substudy compared with mammography alone or compared with integrated tests, mammography plus ultrasound, in year 3.

sensitivity due to added ultrasound. Supplemental ultrasound was less likely to prompt unnecessary recall or biopsy in women with a personal history of breast cancer than those without (eTable 3A). The supplemental yield of MRI screening in women with or without a personal history of breast cancer in the MRI substudy is detailed (eTable 3B). The supplemental MRI was less likely to prompt unnecessary recall or biopsy in women with a personal history of breast cancer than those without (eTable 3B).

COMMENT

In this study, annual supplemental incidence screening ultrasound detected an additional 3.7 cancers per 1000 women per year screened beyond mammography alone. The majority of cancers seen only on ultrasound were node-negative invasive cancers. Invasive lobular carcinoma and low-grade invasive ductal carcinoma were overrepresented among such cancers.

One of the major concerns about screening is the harm of extra testing and biopsies for women who do not have cancer.[21] As has been observed with mammography[22] and MRI,[11,23-25] the risk of false positives decreased significantly with annual screening ultrasound in this study compared with the first screen. However, there still remained a substantial rate of biopsies prompted only by incidence screening ultrasound, averaging 5.0% of women screened.

In a separate analysis of ACRIN 6666 participants, MRI was significantly less tolerable than mammography or ultrasound. Only 58% of ACRIN 6666 participants who were offered a screening MRI at no out-of-pocket cost accepted the invitation.[15] These barriers are in addition to high costs of MRI equipment, contrast, and examination, as well as the high rates of induced testing including biopsy, with 7% of women in this study biopsied only because of MRI findings.

Contrast-enhanced MRI has been recommended for supplemental screening of women at high risk of breast cancer, defined as those women with a lifetime risk of 20% to 25% or greater based on family history, known or suspected *BRCA* or other high-risk genetic mutations, or prior mantle radiation to the chest.[26] Across 9 series, the supplemental yield of MRI after mammography in high-risk women was 11 per 1000[27] and was 14 per 1000 among the subset who also had screening ultrasound.[11-13,25] Similar results were observed in this study of women who were mostly at intermediate risk of breast cancer.

Table 2. Summary of Cancer Detection and Characteristics for 2662 Unique Participants Screened 3 Years With Mammography and Physician-Performed Ultrasound and 612 Participants Screened With MRI in Year 3

	Detected Cancer					
	Mammography Only	Both Mammography and Ultrasound	Ultrasound Only Before MRI	Not Detected on Study Imaging	Detected by Study MRI Only	Total
No. of participants	2662	2662	2662	NA	612	NA
No. of screens	7473	7473	7473	NA	612	NA
No. of cancers	33	26	32	11	9	111
Invasive cancers	18 (55)	23 (88)	30 (94)	10 (91)	8 (89)	89 (80)
Size invasive tumor, median (range), mm	11.5 (1-55)	16.0 (3-40)	10.0 (2-40)	8.5 (2-13)	8.5 (1-25)	12.0 (1-55)
Nodal staging available[a]	15	15	27	6	7	70
Node positive, No. (%)	5 (33)	7 (47)	1 (4)	0 (0)	0 (0)	13 (19)
Cancer type and grade, No. (%)						
IDC grade	17 (52)	16 (62)	24 (75)	8 (73)	7 (78)	72 (65)
High	7 (21)	4 (15)	6 (19)	2 (18)	2 (22)[b]	21 (19)
Intermediate	6 (18)	8 (31)	7 (22)	1 (9)	1 (11)	23 (21)
Low	3 (9)	4 (15)	11 (34)	3 (27)	4 (44)	25 (23)
Cannot be assessed	1 (3)	0	0	2 (18)	0	3 (3)
ILC	1 (3)	5 (19)[c]	5 (16)	1 (9)	0	12 (11)
Mixed IDC and ILC	0	2 (8)[d]	1 (3)[d]	1 (9)	1 (11)	5 (5)
DCIS, nuclear grade	15 (45)	3 (12)	2 (6)	1 (9)	1 (11)	22 (20)
High	2 (6)	0	1 (3)	1 (9)	0	4 (4)
Intermediate	11 (33)	3 (12)	1 (3)	0	0	15 (14)
Low	2 (6)	0	0	0	1 (11)	3 (3)

Abbreviations: DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NA, not applicable. Grade was collected only for IDC and DCIS.
[a] Axillary nodal status could not be assessed for 14 participants with a personal history of breast cancer from whom nodes had previously been removed nor could they be assessed for 1 woman with a personal history of Hodgkin disease and prior nodal treatment. Node status was not determined for 1 participant older than 80 years because it would not affect her treatment planning. For 3 participants without nodal staging, the reason was unknown.
[b] Includes 1 T1mi tumor, with the grade based on the DCIS grade.
[c] Includes 1 ILC with DCIS for which grade of the ILC is missing.
[d] Includes 1 mixed IDC-ILC with associated intermediate nuclear grade DCIS.

Fewer studies have evaluated MRI in women at intermediate risk, including women with a personal history of breast cancer, prior atypical biopsy or lobular carcinoma in situ, intermediate family history of breast cancer (lifetime risk of 15%-20% per the American Cancer Society guidelines[26]), or women whose only risk factor is dense breasts. Recent studies collectively suggest that supplemental MRI screening may be reasonable for women with a personal history of breast cancer and also found false positives to be less frequent than for women with a family history of breast cancer.[28-30]

For high-risk women unable to undergo MRI,[15] and for intermediate-risk women with dense breasts, including those with a personal history of breast cancer, this study supports the use of supplemental screening with ultrasound in addition to mammography. With either MRI or ultrasound, the risks of false positives, including unnecessary biopsies, were lower for supplemental screening in women with a personal history of breast cancer than in women without. The outcomes in terms of staging, node-positive disease, and interval cancer rates achieved in this study after 3 years of programmatic screening with both ultrasound and mammography were comparable with benchmarks from studies that included MRI.[10-13,25]

If screening ultrasound were to be adopted for women with dense breasts who are not candidates for MRI, there would be obstacles to its implementation. These include the availability of only 1 current procedural terminology (CPT) code, 76645, for breast ultrasound, with low reimbursement (2010 Medicare reimbursement averaged a global fee of $89.85 to $91.83,[31] which does not cover the costs of physicians performing and

Table 3. Screening Performance in 2662 Unique Participants Screened 3 Years With Mammography and Physician-Performed Ultrasound

	Mammography Alone		Combined Mammography Plus Ultrasound		Difference of (Mammography Plus Ultrasound) and Mammography Alone		Ultrasound Alone	
	No./Total of Women	Estimate (95% CI)	No./Total of Women	Estimate (95% CI)	Estimate (95% CI)	*P* Value	No./Total of Women	Estimate (95% CI)
Yield, per 1000								
Screen 1	20/2659	7.5 (4.6 to 11.6)	34/2659	12.8 (8.9 to 17.8)	5.3 (2.1 to 8.4)	<.001	24/2659	9.0 (5.8 to 13.4)
Screen 2,3[a]	39/4814	8.1 (5.8 to 11.1)	57/4814	11.8 (9.0 to 15.3)	3.7 (2.1 to 5.8)	<.001	34/4814	7.1 (4.9 to 9.9)
AUC								
Screen 1		0.74 (0.63 to 0.84)		0.94 (0.89 to 0.99)	0.20 (0.10 to 0.30)	<.001		0.76 (0.66 to 0.87)
Screen 2		0.75 (0.65 to 0.86)		0.89 (0.82 to 0.97)	0.14 (0.03 to 0.25)	.01		0.71 (0.58 to 0.84)
Screen 3		0.72 (0.64 to 0.81)		0.82 (0.74 to 0.89)	0.10 (0.00 to 0.18)	.04		0.62 (0.52 to 0.72)
Sensitivity, %								
Screen 1	20/36	55.6 (38.1 to 72.1)	34/36	94.4 (81.3 to 99.3)	38.9 (20.2 to 57.6)	<.001	24/36	66.7 (49.0 to 81.4)
Screen 2,3	39/75	52.0 (40.2 to 63.7)	57/75	76.0 (64.7 to 85.1)	24.0 (14.7 to 33.3)	<.001	34/75	45.3 (33.8 to 57.3)
Specificity, %								
Screen 1	2337/2623	89.1 (87.8 to 90.3)	1950/2623	74.3 (72.6 to 76.0)	−14.8 (−16.3 to −13.2)	<.001	2092/2623	79.8 (78.2 to 81.3)
Screen 2,3	4325/4739	91.3 (90.4 to 92.1)	3987/4739	84.1 (83.1 to 85.2)	−7.1 (−8.0 to −6.3)	<.001	4258/4739	89.9 (89.0 to 90.7)
Recall rate, %								
Screen 1	306/2659	11.5 (10.3 to 12.8)	707/2659	26.6 (24.9 to 28.3)	15.1 (13.5 to 16.6)	<.001	555/2659	20.9 (19.3 to 22.5)
Screen 2,3	453/4814	9.4 (8.6 to 10.3)	809/4814	16.8 (15.8 to 17.9)	7.4 (6.6 to 8.2)	<.001	515/4814	10.7 (9.8 to 11.6)
PPV1, %[b]								
Screen 1	20/306	6.5 (4.0 to 9.9)	34/707	4.8 (3.4 to 6.7)	−1.7 (−3.7 to 0.1)	.07	24/555	4.3 (2.8 to 6.4)
Screen 2,3	39/453	8.6 (6.2 to 11.6)	57/809	7.0 (5.4 to 9.0)	−1.6 (−3.1 to −0.2)	.04	34/515	6.6 (4.6 to 9.1)
Short-term follow-up rate, %								
Screen 1	84/2659	3.2 (2.5 to 3.9)	368/2659	13.8 (12.5 to 15.2)	10.7 (9.5 to 11.9)	<.001	296/2659	11.1 (10.0 to 12.4)
Screen 2,3	76/4814	1.6 (1.2 to 2.0)	256/4814	5.3 (4.7 to 6.0)	3.7 (3.2 to 4.3)	<.001	190/4814	3.9 (3.4 to 4.5)
Biopsy rate, %								
Screen 1	65/2659	2.4 (1.9 to 3.1)	272/2659	10.2 (9.1 to 11.4)	7.8 (6.7 to 8.8)	<.001	233/2659	8.8 (7.7 to 9.9)
Screen 2,3	97/4814	2.0 (1.6 to 2.5)	339/4814	7.0 (6.3 to 7.8)	5.0 (4.4 to 5.7)	<.001	266/4814	5.5 (4.9 to 6.2)
PPV3, %[c]								
Screen 1	19/65	29.2 (18.6 to 41.8)	31/272	11.4 (7.9 to 15.8)	−17.8 (−26.7 to −9.3)	<.001	21/233	9.0 (5.7 to 13.4)
Screen 2,3	37/97	38.1 (28.5 to 48.6)	55/339	16.2 (12.5 to 20.6)	−21.9 (−28.7 to −14.7)	<.001	31/266	11.7 (8.1 to 16.1)

Abbreviations: AUC, area under the curve; PPV, positive predictive value.
[a] Screen 2,3 refers to incidence screens in years 2 and 3 (ie, at 12 and 24 mo after study entry respectively).
[b] Defined as the malignancy rate among women with a positive screening test (ie, assessment of BI-RADS 3 or higher and recalled from screening for further testing or short-interval follow-up).
[c] Defined as the malignancy rate among women with a positive screening test who underwent biopsy of the same lesion.

interpreting a thorough screening examination). While supplemental cancer detection rates with technologist-performed screening ultrasound were similar to physician-performed ultrasound in one series,[4] there remains a shortage of qualified breast ultrasound technologists.

There are a few limitations to this study. Additional node-negative invasive cancers were found by adding screening ultrasound to mammography in each incidence screen, and increasing detection of such cancers correlates with mortality reduction.[32] However, we did not have a control group with no ultrasound performed with which we could compare clinical outcomes, and mortality was not assessed. In Japan, the ongoing Japan Strategic Anti-Cancer Randomized Trial (J-START) of biennial mammography, with or without technologist-performed screening ultrasound does have such a control group.[33] We only performed a single screening MRI, and false positives would be expected to decrease in subsequent years.[11,23] Not all sites in the original ACRIN 6666 protocol were able to offer MRI.

CONCLUSION

The cancer detection benefit from supplemental screening ultrasound seen on the first screening persisted with each annual screening. Rates of biopsy for findings seen only on ultrasound remained substantial on incidence screens, representing 5% of women, with only 7.4% of those women found to have cancer. Risks of false-positives were lower in women with a personal history of breast cancer than in women without.

As has been seen in other studies,[10,11,25,34] MRI significantly increased detection of early breast cancer beyond that seen with mammography or mammography combined with ultrasound. The 56% absolute increase in cancer detection seen in the MRI substudy (16 of

Table 4. Screening Performance in 612 Participants Screened by Magnetic Resonance Imaging After 3 Annual Mammography and Ultrasound Screenings

	Combined Mammography Plus Ultrasound	Combined Mammography Plus Ultrasound Plus MRI	Difference of (Mammography Plus Ultrasound Plus MRI) and (Mammography Plus Ultrasound)		Mammograhy Alone	Combined Mammography Plus MRI	Difference of (Mammography Plus MRI) and Mammography Alone		MRI Alone
			Estimate (95% CI)	*P* Value[a]			Estimate (95% CI)	*P* Value[b]	
Yield (95% CI), per 1000[c]	11.4 (4.6 to 23.4)	26.1 (15.0 to 42.1)	14.7 (3.5 to 25.9)	.004	8.2 (2.7 to 19.0)	26.1 (15.0 to 42.1)	18.0 (5.8 to 30.1)	<.001	22.9 (12.6 to 38.1)
No./total	7/612	16/612			5/612	16/612			14/612
AUC (95% CI)	0.69 (0.55 to 0.83)	0.95 (0.91 to 0.99)	0.26 (0.11 to 0.42)	<.001	0.63 (0.47 to 0.78)	0.94 (0.90 to 0.98)	0.31 (0.16 to 0.46)	<.001	0.87 (0.75 to 0.98)
Sensitivity (95% CI), %	43.8 (19.8 to 70.1)	100.0 (79.4 to 100.0)	56.3 (25.7 to 86.8)	.004	31.3 (11.0 to 58.7)	100.0 (79.4 to 100.0)	68.8 (39.8 to 97.7)	<.001	87.5 (61.7 to 98.4)
No./total	7/16	16/16			5/16	16/16			14/16
Specificity (95% CI), %	84.4 (81.2 to 87.2)	65.4 (61.5 to 69.3)	−19.0 (−22.3 to −15.6)	<.001	92.1 (89.7 to 94.1)	70.6 (66.8 to 74.3)	−21.5 (−24.9 to −18.0)	<.001	75.7 (72.0 to 79.1)
No./total	503/596	390/596			549/596	421/596			451/596
Recall rate (95% CI) , %	16.3 (13.5 to 19.5)	36.3 (32.5 to 40.2)	19.9 (16.6 to 23.3)	<.001	8.5 (6.4 to 11.0)	31.2 (27.6 to 35.0)	22.7 (19.2 to 26.2)	<.001	26.0 (22.5 to 29.6)
No./total	100/612	222/612			52/612	191/612			159/612
PPV1 (95% CI), %[d]	7.0 (2.9 to 13.9)	7.2 (4.2 to 11.4)	0.2 (−3.8 to 4.0)	.92	9.6 (3.2 to 21.0)	8.4 (4.9 to 13.2)	−1.2 (−8.0 to 4.6)	.70	8.8 (4.9 to 14.3)
No./total	7/100	16/222			5/52	16/191			14/159
Short-term follow-up rate (95% CI), %	4.6 (3.1 to 6.5)	19.6 (16.5 to 23.0)	15.0 (12.0 to 18.0)	<.001	0.5 (0.1 to 1.4)	16.3 (13.5 to 19.5)	15.8 (12.8 to 18.9)	<.001	15.8 (13.0 to 19.0)
No./total	28/612	120/612			3/612	100/612			97/612
Biopsy rate (95% CI), %	6.2 (4.4 to 8.4)	13.2 (10.7 to 16.2)	7.0 (4.8 to 9.2)	<.001	1.6 (0.8 to 3.0)	9.6 (7.4 to 12.3)	8.0 (5.7 to 10.3)	<.001	8.5 (6.4 to 11.0)
No./total	38/612	81/612			10/612	59/612			52/612
PPV3 (95% CI), %[e]	18.4 (7.7 to 34.3)	18.5 (10.8 to 28.7)	0.1 (−8.8 to 8.8)	.98	50.0 (18.7 to 81.3)	25.4 (15.0 to 38.4)	−24.6 (−51.2 to 3.7)	.08	23.1 (12.5 to 36.8)
No./total	7/38	15/81			5/10	15/59			12/52

Abbreviation: MRI, magnetic resonance imaging; PPV, positive predictive value.
[a] *P* value that observed difference of combined mammography plus ultrasound, and MRI vs mammography plus ultrasound occurred by chance.
[b] *P* value that observed difference of combined mammography and MRI vs mammography alone occurred by chance.
[c] Yield is the cancer detection rate.
[d] Defined as the malignancy rate among women with a positive screening test (ie, assessment of BI-RADS 3 or higher and recalled from screening for further testing or short-interval follow-up).
[e] Defined as the malignancy rate among women with a positive screening test who underwent biopsy of the same lesion.

16 vs 7 of 16) was greater than the 34% absolute increase in invasive cancer detection (71 of 89 vs 41 of 89) seen by adding annual ultrasound to mammography in the main ACRIN 6666 study. However, given the low clinically detected interval cancer rate of 8% in the main ACRIN 6666 protocol and given the fact that all interval cancers remained node-negative at diagnosis, it is unclear that the added cost and reduced tolerability of screening MRI are justified in women at intermediate risk for breast cancer in lieu of supplemental screening with ultrasound. Despite its higher sensitivity, the addition of screening MRI rather than ultrasound to mammography in broader populations of women at intermediate risk with dense breasts may not be appropriate, particularly when the current high false-positive rates, cost, and reduced tolerability of MRI are considered.

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