Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection Among Women with Dense Breasts Undergoing Screening

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Abstract

Importance: Improved screening methods for women with dense breasts are needed because of their increased risk of breast cancer and of failed early diagnosis by screening mammography.

Objective: To compare the screening performance of abbreviated breast MRI (AB-MR), and digital breast tomosynthesis (DBT) in women with dense breasts.

Design, Setting, and Participants: Cross-sectional study with longitudinal follow-up at 48 academic, community hospital, and private practice sites in the US and Germany, conducted between December 2016 and November 2017, that included average-risk women aged 40–75 years with heterogeneously dense or extremely dense breasts undergoing routine screening. Follow up ascertainment of cancer diagnoses was complete through September 12th, 2019.

Exposure: All women underwent screening by both DBT and AB-MR, performed in randomized order and read independently to avoid interpretation bias.

Main outcome measures: The primary endpoint was the invasive cancer detection rate. Secondary outcomes included sensitivity, specificity, the additional-imaging-recommendation-rate, and positive predictive value (PPV) of biopsy, using invasive cancer and DCIS to define a positive reference standard. All outcomes are reported at the participant level. Pathology of core or surgical biopsy was the reference standard for cancer detection rate and PPV; interval cancers reported until the next annual screen were included in the reference standard for sensitivity and specificity.

Results: Among 1516 enrolled women, 1444 (median age 54, range 40–75) completed both examinations and were included in the analysis. The reference standard was positive for invasive cancer with or without DCIS in 17 women, and for DCIS alone in another 6. No interval cancers were observed during follow-up. AB-MR detected all 17 women with invasive cancer, and 5/6 women with DCIS. DBT detected 7/17 women with invasive cancer, and 2/6 women with DCIS. The invasive-cancer-detection-rate was 11.8 per 1000 women [95% CI 7.4–18.8] for AB-MR versus 4.8 per 1000 women [95% CI 2.4–10.0] for DBT, a difference of 7 per 1000 women [95% CI for the difference 2.2–11.6] (exact McNemar p=0.002). For detection of invasive cancer and

DCIS, for AB-MR versus DBT, sensitivity was 95.7% [95% CI 79.0–99.2] versus 39.1% [95% CI 22.2–59.2] (p=0.001). Specificity was 86.7% [95% CI 84.8–88.4] versus 97.4% [95% CI 96.5–98.1] (p<0.001). Additional-imaging-recommendation-rate was 7.5% [95% CI 6.2–9.0] versus 10.1% [95% CI 8.7–11.8] (p=0.02). PPV was 19.6% [95% CI 13.2–28.2] versus 31.0% [95% CI 17.0–49.7] (p=0.15).

Conclusion and relevance: Among women with dense breasts undergoing screening, AB-MR, compared with DBT, was associated with a significantly higher rate of invasive breast-cancer detection. Further research is needed to better understand the relationship between screening methods and clinical outcome.

Trial registration: NCT02933489, ECOG-ACRIN (EA1141).

INTRODUCTION

Dense fibroglandular tissue represents an important reason for failed early diagnosis in women who participate in mammographic screening, and increases a woman's likelihood of being diagnosed with interval and/or advanced breast cancer.[1–3] Approximately half of the screening-relevant age group have dense breasts.[4]

Whole-breast ultrasound is often used for supplemental screening in women with dense breasts, but requires substantial human resources to perform, only moderately increases sensitivity, and is associated with high false-positive and short-term follow-up rates.[5–7]

Digital breast tomosynthesis (DBT) is a recent improvement to conventional mammography that generates quasi-3-dimensional images of the breast, improving mammographic sensitivity and specificity.[8–9] While initially only used as a supplement to digital mammography, DBT is increasingly used as a replacement.[9]

Breast magnetic resonance imaging (MRI) offers the highest cancer-detection-rate of all breast imaging modalities. Although most evidence exists for using MRI to screen the small proportion of women at very high risk of breast cancer,[9–13] there is accumulating evidence that the higher sensitivity of MRI is also seen in women at average risk.[14] However, the use of conventional, full-protocol breast-MRI to screen the large cohort of average-risk women with dense breasts will neither be practical nor cost-effective.

Abbreviated breast-MRI (AB-MR) has been introduced to reduce the complexity and cost of MRI by reducing image acquisition and interpretation time, in order to improve access to breast-MRI.[15] Multiple studies have confirmed equivalent diagnostic accuracy of AB-MR with full MRI protocols.[16] These observations have led to the consideration of utilizing AB-MR to screen women with dense breasts.

This study compared the diagnostic performance of AB-MR and DBT for screening average-risk women with dense breasts in a mixture of academic, community hospital, and private institutions. The primary objective was to compare the respective invasive cancer detection rates at the participant level.

Methods

Study design and participants

This multicenter intra-individual comparative cross-sectional study with longitudinal follow-up was conducted at 48 different institutions in the United States (47/48) and Germany (1/48), including academic institutions (24/48), and community hospitals or private practices (24/48). The National Cancer Institute Central Institutional Review Board (NCI CIRB) approved the protocol and was the IRB of record for 40 institutions; the remaining 8 institutions used their institutional IRB. Written informed consent was obtained from all participants.

Accrual started in December 2016 and was completed in November 2017. Follow up ascertainment of cancer diagnoses was complete through September 12th, 2019.

Per protocol (eSupplement 1), clinically asymptomatic women aged 40–75 scheduled to undergo routine breast cancer screening with DBT were enrolled if they had dense breasts as reported on their most recent screening mammogram. Women with a history of benign breast biopsy, remote history of treated breast cancer, or family history of breast cancer were eligible. Women were excluded if they had a screening breast ultrasound within the past 12 months, or ever had a breast-MRI, a molecular breast imaging study, or a contrast-enhanced mammogram, or would qualify for full-protocol breast-MRI based on American Cancer Society guidelines.[17]

The individual risk scores of study participants who met criteria for the Breast Cancer Surveillance Consortium (BCSC) risk calculator (i.e., no personal history of breast cancer and aged < 75 years) were determined.[23]

Self-reported information on race and ethnicity using fixed categories was obtained to compare the sociodemographic composition of the trial to the US population.

Participants underwent imaging with both DBT and AB-MR at study baseline and after one year, and will be followed for two additional years. Central randomization (in a 1:1 ratio using permuted blocks of size 4 without replacement) was used to determine the order of the imaging exams. Imaging studies were interpreted independently by two different board certified breast radiologists who remained blinded to the results of the other modality. DBT and AB-MR were performed within a single 24-hour period.

After a positive AB-MR study, additional imaging is not considered useful to further support or refute the indication to biopsy. Hence, AB-MR is not associated with call-back. In women with a biopsy recommendation, no biopsy was performed until both studies were completed and interpreted. All suspicious findings on DBT or AB-MR were biopsied regardless of the final interpretation of the other modality. If both modalities were positive in the same breast, the site radiologist determined whether the same or different lesions were seen.

Characteristics of invasive cancers and DCIS were described using standard histopathologic and immuno-histochemical features, as well as size (largest diameter) and lymph node status in accordance with the criteria from the American College of Pathology.[19]

For follow-up, women were contacted by phone at 6 months (± 1 month) and at 11–13 months after the study baseline and prior to the second screening round. Women were asked whether they received any breast imaging since the study baseline screen, and whether they were diagnosed with breast cancer, and, if so, how the breast cancer was discovered. Pathology of core or surgical biopsy was the reference standard for cancer detection rate and PPV of biopsy; in addition, interval cancers reported during 11–13 months of follow-up, until the next annual screen, were included in the reference standard for sensitivity and specificity.

Imaging technique and interpretation

All AB-MR studies had to be completed with a total acquisition time of less than 10 minutes, and included a T2-weighted acquisition, and a T1-weighted acquisition before and after bolus injection of contrast [0.1 mml/kg body-weight gadobenate-dimeglumine (Multihance, Bracco Monroe/NJ)]. All studies were interpreted according to the Breast Imaging Reporting and Data System (BI-RADS);[18] further information is provided in eMethods 1 in eSupplement 2.

Endpoints

The primary endpoint was the rate of invasive cancer detection by each modality on the study baseline-screening at the participant level, defined as the fraction of participants in whom an invasive cancer was detected by the modality at the site of the imaging abnormality as verified by pathology (core biopsy or surgical excision).

Four secondary endpoints are included in this report: sensitivity, specificity, additional-imaging-recommendation-rate (i.e. call-back plus recommendation for short-term follow-up), and positive predictive value of biopsy (PPV). The presence of Invasive cancer and/or DCIS was defined as a positive reference standard for these end points. Additional secondary endpoints of the study that are not included in this report comprise participant-reported outcomes, tumor biology by genomic profiles, PPV and additional-imaging-recommendation rates of the second screening round, and the 3-year incident cancer rate. Data collection for these endpoints continues.

Additional exploratory endpoints included the overall cancer detection rate (invasive cancers and DCIS), the interval cancer rate, lesion-level estimates of PPV, stage of cancers at diagnosis according to AJCC 8.0[19], and characteristics of cancers based on histopathological and immune-histochemical features.

The following post hoc endpoints were not pre-specified according to the Statistical Analysis Plan (eSupplement 1): the proportion of women with invasive cancer who had a positive screening result; the proportion of women without invasive cancer, but possibly with DCIS, who had a negative screening result and the proportion of women with a positive screening result who were shown to have invasive cancer. These estimates should be interpreted with caution because all imaging studies had been interpreted with readers expected to classify as positive not only findings consistent with invasive cancer, but also findings consistent with DCIS. Point estimates and confidence intervals by modality are supplied for these post-hoc, unplanned endpoints.

Adverse events reporting

The study required expedited adverse event reporting using the Cancer Therapy Evaluation Program's Adverse Event Reporting System (CTEP-AERS). All adverse events were recorded, regardless of attribution, according to the Common Terminology Criteria for Adverse Events.

Statistical considerations

The analysis cohort consisted of all participants who received both screening examinations. The projected sample size of 1450 participants was chosen to provide 90% power to detect a difference in the invasive cancer detection rate of 9/1000 women between the modalities using a two-sided McNemar test of level 0.05 (eMethods 2b in eSupplement 2); sample size estimation was challenging because at the time of protocol development, no published studies existed on AB-MR screening of women at average risk in comparison to DBT; thus, the limited evidence on cancer detection rates for MRI screening of average risk women in comparison with digital mammography were used that reported additional invasive cancer detection between 6 and 11 per 1000.[15;20;]

The invasive cancer detection rate was estimated as the fraction of participants with invasive cancer and a positive test result (BI-RADS 3–5) at the location of the cancer indicated by core or surgical biopsy. PPV was estimated as the fraction of participants undergoing biopsy that resulted in invasive cancer or DCIS. Sensitivity was estimated as the fraction of participants with cancer (invasive or DCIS), for whom the imaging modality result was positive (BI-RADS 3–5) for a location that matched the location of the cancer indicated by the reference standard. Specificity was estimated as the fraction of participants without cancer (invasive or DCIS) by the reference standard, for whom the imaging modality result was negative (BI-RADS 1–2).

Wilson confidence intervals are reported for estimates of binomial proportions. The Wald interval with Bonett-Price Laplace adjustment is reported for the difference in invasive cancer detection rates.[21] Because of the paired design, detection rates, sensitivities, specificities and additional-imaging-recommendation-rates were compared using the exact McNemar's test. Generalized estimating equation (GEE) regression was used to compare PPV, with the p-value reported from the corresponding score test.[22] All reported p-values are two-sided. A post hoc Bonferroni adjustment was used for multiple comparisons of the primary and the four secondary endpoints (total of 5 comparisons), with p-values below 0.01 considered statistically significant.

Per protocol, endpoints were analyzed using aggregate data over all institutions. Post-hoc sensitivity analyses examining clustering by institution and using multiple imputation for missing reference standard are described in eMethods2c in eSupplement 2.

Data were analyzed using SAS version 9.4 software (SAS Institute, Cary, NC) and R version 3.4.4 software (R project; http://www.r-project.org/). The BCSC risk score was computed using publicly available software.[23]

RESULTS

Of the 1516 enrolled participants (Figure 1), 757 were randomized to undergo DBT first, and 759 to undergo AB-MR first. Six participants (0.4%) were ineligible for reasons specified in Figure 1. Of the remaining 1510 eligible women, 1444 (96%) received both exams and comprise the analysis set. Protocol adherence for the AB-MR scan time was achieved in 97% (1394/1444) of women, with a mean scan time of 8.0 (±1.3) minutes, median: 7.9; interquartile range: 7.2–9.0 minutes.

Table 1 and eTable 1 (eSupplement 2) summarize the demographic characteristics and risk distributions of the analysis cohort of 1444 women. 77% had heterogeneously dense and 15% had extremely dense breasts; 8% had dense breasts on the most recent prior mammogram used to determine study inclusion, but were non-dense at the time of the study. The BCSC risk score yielded a median 5-year risk of invasive breast cancer of 1.6% (range 0.3%–7.8%).

Primary Endpoint:

19 invasive cancers were detected in 17 women on the study baseline screening round (Table 2; Figure 2). Cancer status was known in all participants for the detection analysis. AB-MR detected the invasive cancer in all 17 women, and DBT in 7 women, yielding an invasive-cancer-detection-rate of 11.8 per 1000 women [95% CI 7.4–18.8] for AB-MR versus 4.8 per 1000 women [95% CI 2.4–10.0] for DBT, a difference of 7 per 1000 women [95% CI for the difference 2.2–11.6] (p=0.002).

Secondary Endpoints:

Sensitivity and specificity—According to the reference standard information, 23 women had cancer (invasive or DCIS) at the study baseline screen, and 1421 had remained cancer-free. Of those, 1407 had complete follow-up until the next screening date. None had breast cancer diagnosed during follow up. No cancer was reported in the remaining 14 participants, but follow-up information was incomplete; accordingly, the reference standard status was considered missing (Figure 1).

The sensitivity of AB-MR for invasive cancer or DCIS was significantly higher than that of DBT, at 95.7% (22/23) [95% CI 79.0–99.2] versus 39.1% (9/23) [95% CI 22.2–59.2] (p=0.001) (Figure 2). Specificity of AB-MR was significantly lower than that of DBT, at 86.7% (1220/1407) [95% CI 84.8–88.4] versus 97.4% (1371/1407) [95% CI 96.5–98.1] (p<0.001) (Figure 2; eFigure 2 in eSupplement 2).

Positive predictive value—PPV of biopsy for AB-MR was 19.6% (21/107) [95% CI 13.2–28.2], not statistically significantly different compared with DBT, at 31.0% (9/29) [95% CI 17.0–49.7] (p=0.15) (Figure 2).

Additional-imaging-recommendation-rate—The call-back rate for screening DBT was 10.1% (146/1444) [95% CI: 8.7–11.8] and 0% for AB-MRI. Short-term follow-up (BI-RADS 3) was recommended for DBT in 1.2% of women (18/1444) [95% CI 0.8–2.0], all of whom also had a call-back, and for AB-MR in 7.5% of women (108/1444) [95% CI 6.2–

9.0]. Thus, additional imaging (either call-back or short-term follow-up) was required in 7.5% (108/1444) [95% CI 6.2–9.0] of women for AB-MR, and in 10.1% (146/1444) [95% CI 8.7–11.8] of women for DBT; this difference was not statistically significant after Bonferroni adjustment (p=0.02) (Figure 2).

Exploratory and post hoc endpoints

Overall cancer detection—In addition to the 19 invasive cancers observed in 17 women, 6 women were diagnosed with pure DCIS; one woman with invasive cancer also had DCIS, for a breast cancer prevalence of 23 of 1444 women, or 15.9 per 1000 women. AB-MR identified cancer in 22 of the 23 women with cancer, DBT in 9 women, for an overall cancer detection rate of 15.2 per 1000 women (22/1444) [95% CI 10.1–23.0] for AB-MR versus 6.2 per 1000 women (9/1444) [95% CI 3.3–11.8] for DBT (p=0.001) (Figure 2).

Interval cancer rate—No interval cancers were reported, leading to an estimated interval-cancer rate of 0% (0/1407) [95% CI 0%–0.27%].

Cancer characteristics by method of detection—Table 2 provides details of the invasive cancers and DCIS, including the method of detection. The median size of invasive cancer was 10.5 mm, range 4–48 mm. One of the 23 participants with cancer had positive nodes, for a node-negative rate of 96%. Figure 2 summarizes the histopathological and immuno-histochemical characteristics of cancers stratified by method of detection. Of the 7 participants with DBT-detected invasive cancers, cancer grade was low-grade in 3/7 and intermediate-grade in 4/7. These same cancers were also detected by AB-MR. Of the 10 additional participants with invasive cancer detected by AB-MR alone, cancer grade was low-grade in 3/10, intermediate-grade in 4/10, and high-grade in 3/10.

Lesion level PPV: The PPV of biopsy on the lesion level was 19.0% (24/126) [95% CI 12.6 – 27.7] for AB-MR versus 35.5% (11/31) [95% CI 19.5 – 55.5] for DBT (p=0.08).

Additional, non-pre-specified post-hoc analyses: A post-hoc analysis of the detection rate intended to adjust for clustering by site produced qualitatively similar results as in the primary analysis (eResults 1 in eSupplement 2). A post-hoc analysis of sensitivity and specificity using mixed modeling with random effects for institution and multiple imputation for missing reference standard produced qualitatively similar results as in the primary analysis (eResults 2 in eSupplement 2).

The post-hoc estimates of the analogues of sensitivity, specificity, and PPV using only invasive cancer as the reference were 100.0% [95% CI 81.6 – 100.0], 86.4% [95% CI 84.5 – 88.1], and 15.0% [95% CI 9.4 – 23.0], respectively, for AB-MR, and 41.2% [95% CI 21.6 – 64.0], 97.3% [95% CI 96.3 – 98.0], and 24.1% [95% CI 12.0 – 42.7], respectively, for DBT, and are similar to the estimates using invasive cancer or DCIS as the reference standard (eFigure 1 in eSupplement 2).

Adverse events

A total of 13 adverse events were reported in 12 women within 1 year of registration; the majority were grade 1 or less (8/13, 62%). A detailed description of reported adverse events is in eTable 2 (eSupplement 2). The most common adverse events were mild allergic reactions (3 events) and anxiety (2 events).

DISCUSSION

In this study on the performance of AB-MR for routine breast-cancer screening of average risk women with dense breasts, AB-MR was associated with a significantly higher invasive-breast-cancer detection rate compared with DBT, also referred to as 3D-mammography. The significantly higher sensitivity of AB-MR was associated with a reduced specificity, but with a PPV that was not significantly different to that of DBT. Women and referring physicians should be aware that having a screening AB-MR, especially a baseline examination, may lead to additional benign biopsies, 6 month follow up recommendations, or both. On the other hand, DBT, but not AB-MR, may require further imaging after initial screen-detected abnormalities.

Although there is a close correlation between early diagnosis and breast-cancer survival, and although systematic mammographic screening has been used to improve early diagnosis for several decades, breast cancer continues to represent a leading cause of cancer death in women.[24–25] Apart from variable attendance rates, the effect of mammographic screening on breast-cancer mortality is mitigated by overdiagnosis of biologically inert, prognostically insignificant cancers,[26] but also by underdiagnosis of potentially lethal disease.[3, 27–28] Due to the masking effect of fibroglandular tissue, such underdiagnosis is especially likely in women with dense breasts, leading to persistently high rates of interval and advanced-stage cancers in these women.[1–3] Women with dense breasts are therefore underserved with regular, mammographic screening. Therefore, there is a substantial clinical need for methods that reduce underdiagnosis (interval cancers and/or diagnosis of late-stage disease) in these women.[23] The passage of state and federal breast density legislation, requiring women to be informed about their breast density and its diagnostic and prognostic implications, has contributed to this need.[29] The results of this study demonstrate that AB-MR improved breast-cancer detection in women with dense breasts; the fact that no interval cancers were observed during follow-up further supports this conclusion.

Improved early detection is an important means to reduce breast-cancer mortality in women with dense breasts. This study does not provide evidence regarding mortality, or on the degree of possible overdiagnosis. Collecting such evidence requires much larger randomized clinical trials (RCT) with long-term follow-up of at least 15–20 years. RCT on surrogate endpoints for breast-cancer mortality such as tumor-stage-at-diagnosis and/or interval cancer rates may shorten the time required to conduct definitive randomized trials.

To help gain some insight into the rate of desirable detection of relevant cancers versus undesirable detection of inconsequential disease, the characteristics of cancers detected were reported as an established proxy for their prognostic importance/likelihood of progression. Based on the distribution of nuclear grades and receptor status, the invasive cancers detected

by AB-MR did not differ from those also detected by DBT; however, the 3 high-grade invasive cancers in this study were only AB-MR detected, and missed by DBT. This is consistent with prior observations regarding the tumor characteristics of MR-only detected cancers.[30] Beyond these classifications based on standard histopathological and immuno-histochemical results, further analyses on genomic features (PAM50, Oncotype-DX) on study-detected invasive cancers and DCIS are underway. Since the prognostic importance of DCIS is controversial, the primary objective of this study was invasive cancer detection. The fact that AB-MR increased detection of pure DCIS as it increased detection of invasive cancers could be considered as possible evidence of overdiagnosis until more information is available.[31]

The study design allowed the determination of the diagnostic performance of AB-MR as an independent screening method for women with dense breasts. The results suggest that in women undergoing AB-MR, the contribution of mammography or DBT is limited; in this cohort, none of the invasive cancers, but one high-grade DCIS were only detected by DBT. This is consistent with existing evidence on the limited contribution to cancer detection of mammography in women undergoing MRI for screening. [12,14,30,32,33] Future studies are necessary to determine whether AB-MR alone could be used to screen women with dense breasts, given that mammography/DBT would add additional cost and exposure to ionizing radiation with no or limited added benefit.[34]

Uniformity across study sites was established by standardizing the AB-MR protocol and the contrast agent used (Multihance), and by providing the Society of Breast MRI interpretation algorithms. As a result, despite the fact that 47 of the 48 participating sites did not have prior practical experience with AB-MR, the cancer-detection-rate was similar to levels published by skilled MRI practices on full-protocol MRI, [10–13;30–33] and the PPV of AB-MR did not differ significantly from that of DBT. Still, at 19.6%, the PPV associated with AB-MR was on the lower end of PPV-levels published for full-protocol MRI, and the quality assurance benchmarks for full-protocol MRI screening.[35] However, these benchmarks were established for women at high risk, whereas this study included women at average risk only; the lower breast-cancer prevalence in average versus high-risk screening will per se reduce the PPV. In addition, per study inclusion criteria, all participants had to have a prior mammogram to determine breast density, but could not have had a prior breast MRI. Therefore, all of the DBT-studies, but none of the AB-MR-studies were interpreted with prior imaging for comparison – a fact that introduces a systematic bias for test specificity and PPV in favor of DBT.[36–37] In view of the well-established effect of prior imaging on reader performance, it is likely that PPV of AB-MR will further increase in subsequent screening rounds, i.e. with availability of prior AB-MR studies, and with increasing reader expertise.

AB-MR was well tolerated. Protocol adherence was high, and accrual was completed a year ahead of schedule. Participant-reported data on the acceptability of AB-MR will be reported separately.

AB-MR takes less than 10 minutes examination time; it requires the i.v. injection of a gadolinium-based contrast agent, but does not involve ionizing radiation or breast compression. It does not require new equipment beyond existing equipment for regular, full-

protocol breast MRI, and does not require specific radiologist training beyond the level required by the American College of Radiology (ACR) breast MRI accreditation. AB-MR, just as ultrasound or other imaging methods considered as supplemental or alternate screening methods for women with dense breasts, is currently not reimbursable for women at average risk. Recent studies have reported gadolinium deposition in individuals following administration of so-called linear gadolinium-based contrast agents.[38] Although to date this deposition is not known to have any clinical significance, studies are currently underway to better understand this phenomenon. With macrocyclic gadolinium-based contrast agents, gadolinium deposition is not observed; temporary retention of very small (nano-molar) amounts of the injected dose does occur, but is subsequently excreted without de-chelation. [39–40]

LIMITATIONS

This study has several limitations. First, this study does not provide evidence of the association between AB-MR and breast cancer mortality. Women with dense breasts who consider AB-MR as a screening option should be informed of this limitation. However, this lack of evidence also exists for all other existing, supplemental, or alternate screening options, including digital mammography, whole-breast ultrasound, and DBT.

Second, the cost-effectiveness of AB-MR relative to DBT was not evaluated. Since about half of women in the screening-relevant age range exhibit dense breast tissue, further risk stratification is needed, to better tailor the use of supplemental or advanced screening tests such as AB-MR. Third, although AB-MR does not require specific additional equipment beyond what is used for regular breast MRI, given the current limited availability of breast MRI in general for screening the relatively small number of women at high risk of breast cancer, the ability of centers to offer AB-MR may be limited until more MRI units are added. Fourth, since the eligibility criteria required a prior mammogram to assess breast density, the study compared an incidence DBT screen to a prevalence AB-MR screen. Fifth, the study found that AB-MR detected an additional 7 invasive cancers per 1000 women rather than 9 per 1000, an effect size the study had 90% power to detect. This estimate was based on preliminary studies of AB-MR and MRI screening for women with average risk; [15,20] all these prior studies had compared AB-MR or standard MRI with digital mammography, but not with DBT. This may account for the lower incremental cancer detection rate observed in the comparison between AB-MR and DBT. [10,12,14,15,20,32,33]

CONCLUSION:

Among women with dense breasts undergoing screening, AB-MR, compared with DBT, was associated with a significantly higher rate of invasive-breast-cancer detection. Further research is needed to better understand the relationship between screening methods and clinical outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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KEY POINTS:

Question:

What is the invasive-breast-cancer detection rate of abbreviated breast magnetic resonance imaging (AB-MR) compared to digital breast tomosynthesis (DBT) in women with dense breasts undergoing routine screening?

Findings:

This cross-sectional study with longitudinal follow up included 1444 women who underwent both AB-MR and DBT, interpreted independently, AB-MR detected significantly more invasive cancers (17 patients; 11.8 per 1000 women) than DBT (7 patients; 4.8 per 1000 women). No invasive cancer was identified by DBT alone, or as interval cancer during follow-up.

Meaning:

Among women with dense breasts undergoing screening, AB-MR was associated with a significantly higher rate of invasive-cancer-detection than DBT.
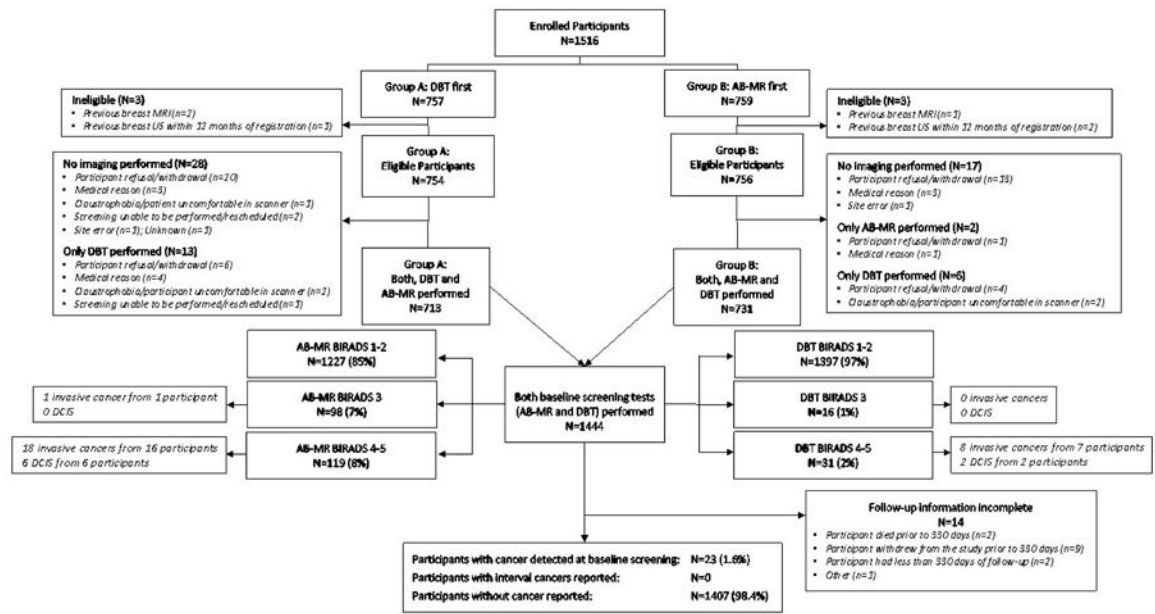
Figure 1:
Study Flow Chart

A. Diagnostic accuracy

DBT	Invasive cancer or DCIS absent	Invasive cancer or DCIS present	Total
DBT Negative	1371	14	1385
DBT Positive	36	9	45 [a]
Total	1407	23	1430

AB-MR	Invasive cancer or DCIS absent	Invasive cancer or DCIS present	Total
AB-MR Negative	1220	1	1221
AB-MR Positive	187	22	209 [a]
Total	1407	23	1430

	DBT	AB-MR
# Participants	1444	1444
# Participants with DCIS detected	2	6 [b]
# Participants with invasive cancer detected	7	17
# Participants with cancer (invasive + DCIS) detected	9	22 [b]
Sensitivity for all cancer (invasive + DCIS) [c]	39.1% (9/23) [22.2-59.2]	95.7% (22/23) [79.0-99.2]
Specificity for all cancer (invasive + DCIS) [c]	97.4% (1371/1407) [96.5-98.1]	86.7% (1220/1407) [84.8-88.4]
PPV of biopsy for all cancer (invasive + DCIS) [c]	31.0% (9/29) [17.0-49.7]	19.6% (21/107) [13.2-28.2]
Additional imaging recommendation [c]	10.1% (146/1444) [8.7-11.8]	7.5% (108/1444) [6.2-9.0]

B. Cancer detection

Participants with:	Detected by both DBT and AB-MR	Detected by DBT alone	Detected by AB-MR alone
Invasive cancer with or without DCIS	**7**	**0**	**10**
Low grade	3	–	3
Intermediate grade	4	–	4
High grade	0	–	3
ER Status positive	6	–	9
ER Status negative	1	–	1
Her2 Status positive	0	–	1
Her2 Status negative	7	–	9
DCIS alone	**1**	**1**	**4**
Low grade	0	0	0
Intermediate grade	1	0	2
High grade	0	1	2
ER Status positive	1	1	3
ER Status negative	0	0	0
ER Status unknown	0	0	1

DCIS: Ductal carcinoma in-situ; DBT: Digital breast tomosynthesis;
AB-MR: Abbreviated breast MRI; PPV: Positive predictive value
[a] More women received BIRADS 3-5 on AB-MR compared to DBT.
[b] One participant had both invasive cancer and DCIS.
[c] Estimated at the participant level.

Figure 2:
Summary of relevant study findings

Table 1 –

Baseline demographics and risk characteristics

	Eligible subjects with both scans completed (N =1444)
	N (%)
Age (years)	
Mean (SD)	54.9 (8.5)
Median (Range)	54 (40, 75)
Race	N=1361
White	1233 (91%)
Black/African American	61 (4%)
Asian	57 (4%)
Mixed race	5 (<1%)
American Indian/Alaskan Native	3 (<1%)
Native Hawaiian/Pacific Islander	2 (<1%)
Hispanic or Latino	39/1356 (3%)
Menopausal status	N=1443
Pre-menopausal	440 (30%)
Peri-menopausal	94 (7%)
Naturally post-menopausal	669 (46%)
Surgically post-menopausal	240 (17%)
Breast density from year 0 DBT	N=1444
ACR-A: Almost entirely fat	2 (<1%)
ACR-B: Scattered fibroglandular densities	115 (8%)
ACR-C: Heterogeneously dense	1108 (77%)
ACR-D: Extremely dense	219 (15%)
History of at least one 1st degree relative with breast cancer	271/1438 (19%)
History of at least one 1st degree relative with ovarian cancer	30/1438 (2%)
Prior benign biopsy with atypias	10/1423 (1%)
BCSC 5-year risk [a, b]	N=1385
Mean (SD)	1.8 (0.8)
Median (Range)	1.6 (0.3, 7.8)
BCSC 10-year risk [a]	N=1385 3.7 (1.6)
Mean (SD)	
Median (Range)	3.5 (0.9, 14.2)

DBT: Digital Breast Tomosynthesis; AB-MR: Abbreviated breast Magnetic Resonance Imaging; BCSC: Breast Cancer Surveillance Consortium

ACR-A-D: Categorization of breast density from non-dense to dense. ACR-A: Almost entirely fat (<25% fibroglandular); ACR-B: Scattered fibroglandular densities (25–50% fibroglandular); ACR-C: Heterogeneously dense breasts (51–75% fibroglandular); ACR-D: Extremely dense breasts (>75% fibroglandular). Note that women were included based on the density of the respective last screening mammogram and could have undergone involution since that last screening mammogram.

[a]BCSC risk scores could not be calculated for a total of 12 randomized subjects due to age >74 years (n=4) or previous diagnosis of breast cancer (n=8). In addition, 47 randomized subjects with either unknown or unavailable data on prior history of breast cancer were also excluded from the BCSC score summaries.

[b]The Breast Cancer Surveillance Consortium 5-year Risk Score distinguishes between low risk (< 1.0), average risk (1.0 to 1.66), increased risk (1.67 to < 6.0), and high risk (6.0).

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Table 2 –

Screen-detected cancers

Obs [a]	Case	Lesion detected at AB-MR [b]	Lesion detected at DBT [b]	Breast density	Age	Type of cancer	Largest diameter [c] (mm)	Maximum reported grade [c]	ER [c]	PR [c]	HER2 [c]	BCSC 5-year risk score	BCSC 10-year risk score
1	1	+	+	ACR-C	62	DCIS	15	2	Positive	Positive	Not performed	2.79	5.62
2	2	+		ACR-C	69	DCIS	20	2	Positive	Positive	Not performed	3.24	6.17
3	3	+		ACR-C	68	DCIS	10	2	Positive	Negative	Not performed	4.64	8.82
4	4	+		ACR-C	71	DCIS	10	3	Positive	Negative	Not performed	2.10	3.95
5	5	+		ACR-C	68	DCIS	5	3	Not performed	Not performed	Not performed	2.08	4.02
6	6a	+		ACR-D	63	DCIS	30	2	Positive	Not performed	Not performed	3.40	6.77
7	7 [d]		+ [d]	ACR-D	40	DCIS	70	3	Positive	Positive	Not performed	1.25	3.13
8	8	+		ACR-B	62	IDC	4	1	Positive	Positive	Negative	2.04	4.13
9	9	+		ACR-B	65	ILC	16	2	Positive	Negative	Negative	1.50	2.97
10	10a	+	+	ACR-C	62	IDC	11	1	Positive	Positive	Negative	1.92	3.88
11	10b	+	+	ACR-C	62	IDC	9	2	Positive	Positive	Negative	1.92	3.88
12	11	+		ACR-C	72	IDC	8	2	Positive	Positive	Negative	N/A [e]	N/A [e]
13	12	+		ACR-C	67	ILC	14	2	Positive	Positive	Negative	3.14	6.08
14	13a	+	+	ACR-C	56	ILC	25	2	Positive	Positive	Negative	2.41	5.07
15	13b	+		ACR-C	56	ILC	25	2	Not available	Not available	Not available	2.41	5.07
16	14	+	+	ACR-C	64	IDC	18	2	Negative	Negative	Negative	2.89	5.73
17	15	+	+	ACR-C	48	IDC	10	1	Positive	Positive	Negative	1.07	2.43
18	16	+		ACR-C	47	IDC	10	1	Positive	Positive	Negative	0.99	2.21
19	17 [f]	+	+	ACR-C	44	IDC	N/A [f]	2	Positive	Positive	Negative	1.39	3.28
20	18	+		ACR-C	52	IDC	24	3	Negative	Negative	Positive	1.92	4.19

Obs [a]	Case	Lesion detected at AB-MR [b]	Lesion detected at DBT [b]	Breast density	Age	Type of cancer	Largest diameter [c] (mm)	Maximum reported grade [c]	ER [c]	PR [c]	HER2 [c]	BCSC 5-year risk score	BCSC 10-year risk score
21	19	+	+	ACR-C	46	Mixed IDC/ILC	48	1	Positive	Positive	Negative	0.93	2.16
22	20	+		ACR-C	51	IDC	10	3	Positive	Negative	Negative	2.01	4.41
23	21	+		ACR-C	70	IDC	10	2	Positive	Negative	Negative	4.80	8.96
24	22	+	+	ACR-C	41	IDC	10	1	Positive	Positive	Negative	0.61	1.50
25	23	+		ACR-D	53	IDC	10	1	Positive	Positive	Negative	4.83	10.21
26	6b	+		ACR-D	63	IDC	14	3	Positive	Positive	Negative	3.40	6.77

AB-MR: Abbreviated breast Magnetic Resonance Imaging; DBT: Digital Breast Tomosynthesis; ER: Estrogen receptor status; PR: Progesterone receptor status; HER2: Human epidermal growth factor receptor 2; DCIS: Ductal carcinoma in situ; IDC: Invasive ductal cancer; ILC: Invasive lobular cancer; ACR-C: Heterogeneously dense breasts; ACR-D: Extremely dense breasts;

[a] 'Obs' signifies a count of each individual cancer, and 'Case' signifies each unique participant, where participants with more than one cancer have separate cancers distinguished by 'a' and 'b' (e.g. 6a, 6b).

[b] A '+' denotes that the cancer was detected by the modality; a blank cell denotes that the cancer was not detected by the modality.

[c] Grade shown is the highest reported grade across the core and surgical biopsy. For ER, PR, HER2, if either the core or surgical biopsy reported positivity, the value is reported as positive. Largest diameter, ductal carcinoma pattern and invasive pattern are from the surgical pathology. In one case (no. 9), the histologic description of a lobular-invasive cancer corresponded to intermediate grade, although no specific grading information was provided

[d] DBT reported 2 lesions which were both of the same pathological lesion (a single 70 mm DCIS).

[e] BCSC risk scores could not be computed for this participant due to a previous diagnosis of breast cancer.

[f] N/A, not available. This case had invasive disease (IDC) by vacuum assisted core biopsy, but there was no residual cancer in the surgical biopsy specimen which contained only benign changes with atypia. Thus, tumor size data from surgical pathology are not available; however, the lesion size was 11 mm by AB-MR and 9 mm by DBT.