Radiology

ORIGINAL RESEARCH • BREAST IMAGING

# Comparative Performance of Contrast-enhanced Mammography, Abbreviated Breast MRI, and Standard Breast MRI for Breast Cancer Screening

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Study supported by a research grant from GE Healthcare (including effort support for S.C.P., D.S.H., I.L., D.B., M.L.B., J.M.L.) and Guerbet (in-kind equipment support). S.C.P. supported by National Institutes of Health/National Cancer Institute (R01CA207290). H.R. supported by grants from the National Institutes of Health (R01CA203883). C.I.L. supported by a grant from the National Institutes of Health/National Cancer Institute (R37CA240403). J.R.S. supported by a grant from the National Institutes of Health (R13CA275171). D.B., M.L.B., and I.L. supported by grants from the National Institutes of Health (R01CA203883, R01CA207290).

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

See also the editorial by Chang in this issue.

**Radiology 2023; 308(2):e230576 • https://doi.org/10.1148/radiol.230576 • Content codes: BR MR**

***Background:*** Contrast-enhanced mammography (CEM) and abbreviated breast MRI (ABMRI) are emerging alternatives to standard MRI for supplemental breast cancer screening.

***Purpose:*** To compare the diagnostic performance of CEM, ABMRI, and standard MRI.

***Materials and Methods:*** This single-institution, prospective, blinded reader study included female participants referred for breast MRI from January 2018 to June 2021. CEM was performed within 14 days of standard MRI; ABMRI was produced from standard MRI images. Two readers independently interpreted each CEM and ABMRI after a washout period. Examination-level performance metrics calculated were recall rate, cancer detection, and false-positive biopsy recommendation rates per 1000 examinations and sensitivity, specificity, and positive predictive value of biopsy recommendation. Bootstrap and permutation tests were used to calculate 95% CIs and compare modalities.

***Results:*** Evaluated were 492 paired CEM and ABMRI interpretations from 246 participants (median age, 51 years; IQR, 43–61 years). On 49 MRI scans with lesions recommended for biopsy, nine lesions showed malignant pathology. No differences in ABMRI and standard MRI performance were identified. Compared with standard MRI, CEM demonstrated significantly lower recall rate (14.0% vs 22.8%; difference, −8.7%; 95% CI: −14.0, −3.5), lower false-positive biopsy recommendation rate per 1000 examinations (65.0 vs 162.6; difference, −97.6; 95% CI: −146.3, −50.8), and higher specificity (87.8% vs 80.2%; difference, 7.6%; 95% CI: 2.3, 13.1). Compared with standard MRI, CEM had significantly lower cancer detection rate (22.4 vs 36.6; difference, −14.2; 95% CI: −28.5, −2.0) and sensitivity (61.1% vs 100%; difference, −38.9%; 95% CI: −66.7, −12.5). The performance differences between CEM and ABMRI were similar to those observed between CEM and standard MRI.

***Conclusion:*** ABMRI had comparable performance to standard MRI and may support more efficient MRI screening. CEM had lower recall and higher specificity compared with standard MRI or ABMRI, offset by lower cancer detection rate and sensitivity compared with standard MRI. These trade-offs warrant further consideration of patient population characteristics before widespread screening with CEM.

Clinical trial registration no. NCT03517813



*Supplemental material is available for this article.*

Contrast-enhanced breast MRI in addition to annual mammography is recommended for patients who are at a 20% or greater lifetime risk for developing breast cancer (1–3). MRI is highly sensitive in detecting malignancy but is also associated with relatively long image acquisition and interpretation times, higher cost, and lower patient tolerance compared with mammography (4,5). Together, these limitations decrease accessibility to supplemental high-risk screening and motivate the search for alternate screening techniques.

Contrast-enhanced mammography (CEM) is a vascular imaging technique that takes advantage of malignant neoangiogenesis to depict breast cancer. In CEM, standard mammographic screening views are obtained using a dual-energy technique after intravenous iodinated contrast agent administration. The dual-energy technique results in low-energy images analogous to standard full-field digital mammographic images and recombined images that show areas of contrast enhancement (6). CEM has shown promise in the diagnostic setting, depicting known imaging abnormalities recommended for biopsy at rates comparable to MRI with the advantage of higher specificity because of fewer false-positive findings (7,8). However, there are few published studies in the screening

### Abbreviations

ABMRI = abbreviated breast MRI, BI-RADS = Breast Imaging Reporting and Data System, CEM = contrast-enhanced mammography


### Summary

Breast cancer screening performance with abbreviated breast MRI was comparable to standard MRI; however, contrast-enhanced mammography demonstrated performance trade-offs that warrant further evaluation prior to widespread use.


### Key Results

- In a blinded reader study with 246 participants, contrast-enhanced mammography (CEM) demonstrated lower recall rate (difference, −8.7%; $P = .002$), lower false-positive biopsy recommendation rate (difference, −97.6 per 1000 examinations; $P < .001$), and higher specificity (difference, 7.6%; $P = .007$) than did standard MRI.
- CEM had lower sensitivity (difference, −38.9%; $P = .03$) and lower cancer detection rate (difference, −14.2; $P = .03$) compared with standard MRI.
- Abbreviated breast MRI performance metrics were comparable to standard MRI.

setting (9). If cancer detection rates of screening CEM are comparable to MRI, its shorter acquisition time, lower cost, and increased specificity may allow for increased accessibility to effective high-risk breast cancer screening and enable more timely completion of screening episodes of care through reduction in false-positive biopsy results. In particular, the relative ease of adapting current mammography units to add CEM capability presents a feasible approach to increase capacity for contrast-based breast cancer screening.

Abbreviated breast MRI (ABMRI) is a potential alternative for supplemental high-risk screening, and its use is increasing (10,11). Similar to standard MRI, ABMRI relies on differential uptake of intravenous contrast agent in identifying malignancy in lesions due to neoangiogenesis, but with fewer dynamic sequences compared with the standard protocol (12). These abbreviated examinations have demonstrated similar performance compared with standard MRI while decreasing acquisition and interpretation time (11,13,14). This efficient approach could increase MRI capacity and allow for greater access to MRI screening.

Whereas prior studies have evaluated the performance of ABMRI and CEM, to our knowledge, direct comparative performance of CEM versus ABMRI and standard MRI has not yet been evaluated. We hypothesized that CEM has higher specificity and lower recall rate compared with ABMRI and standard MRI. In this prospective study, we sought to evaluate the comparative diagnostic performance of CEM, ABMRI, and a full-protocol MRI examination based on American College of Radiology accreditation standards (hereafter, standard MRI) (15).

## Materials and Methods

This single-institution, prospective, blinded reader study (ClinicalTrials.gov, NCT03517813) was Health Insurance Portability and Accountability Act compliant and institutional review board approved. Written informed consent was obtained from all participants. Support was provided by GE Healthcare (financial and provision of equipment) and Guerbet (provision of equipment). The authors had control of the data and information submitted for publication.

### Participants

The study population included consecutively enrolled female participants aged at least 18 years who were referred for breast MRI from January 2018 to June 2021, in one of two groups: *(a)* participants at increased risk of breast cancer referred for high-risk screening or for contralateral breast screening after newly diagnosed primary unilateral breast cancer ($n = 206$) or *(b)* participants who underwent breast MRI for any indication with an MRI finding recommended for US or MRI-guided percutaneous biopsy ($n = 40$). Participants who were pregnant, lactating, had bilateral breast implants, or had a contraindication to iodinated contrast agents were excluded.

### Examinations

All participants underwent CEM and standard MRI. CEM was performed within 14 days of standard MRI and the ABMRI was composed of a subset of sequences from the standard MRI, reflecting the ABMRI protocol in the Eastern Co-operative Oncology Group–American College of Radiology Imaging Network (known as ECOG-ACRIN) 1141 clinical trial (14). All CEM and ABMRI were deidentified, labeled according to study identifications, and stored separately from clinical examinations. Detailed imaging protocols are provided in Appendix S1.

### Reader Study

Seven readers interpreted the CEM and ABMRI examinations. All readers were board-certified radiologists with subspecialty breast imaging training (H.R., D.L.L, C.I.L., K.P.L., J.R.S., S.P., and J.M.L.; experience ranged from 2 to 15 years). Because CEM was not in routine clinical use at trial initiation, each reader was trained in CEM interpretation before the reader study with an external expert breast imaging radiologist, including didactic lectures and two case review sessions (31 cases each).

Two of the seven readers independently reviewed each CEM and ABMRI examination from the same participant in batch screening sessions separated by a washout period of at least 4 weeks. The sequence of CEM and ABMRI interpretations was randomized. Readers used a Seno Iris Review Station (GE Healthcare) and a Centricity PACS RA1000 Workstation (GE Healthcare) to review CEM and ABMRI examinations, respectively. Readers had access to a prior digital mammographic examination performed within 2 years for comparison and limited clinical information (presence of a newly diagnosed breast cancer, laterality included for interpretation, and history of mastectomy), but were blinded to the standard MRI examination results.

Readers recorded number, maximum size, and location of lesions (≤3) using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS; fifth edition; 16) mammography lexicon descriptors for low-energy CEM images and MRI lexicon descriptors for CEM low energy with

recombined images (17) and ABMRI images. For examinations performed for extent of disease evaluation in newly diagnosed unilateral breast cancer, readers evaluated only the contralateral unaffected breast. For each breast, readers recorded an initial BI-RADS assessment. Initial BI-RADS scores of low-energy CEM were limited to BI-RADS categories used at screening: BI-RADS 0, recalled from screening; or BI-RADS 1 or 2, recommendation for routine screening (16). Initial BI-RADS assessments used for interpretation of CEM and ABMRI were 0, 1, 2, 3, 4, or 5. For any initial BI-RADS 0 assessment, readers also recorded a forced final assessment limited to BI-RADS 1, 2, 3, 4, or 5 (considered to be forced because additional diagnostic evaluation was not obtained before this final assessment was recorded) (18,19). For all other initial assessment categories, the final and initial assessments were the same. No data from CEM or ABMRI were used for clinical treatment and any abnormalities observed at CEM were examined according to the institutional standard of care.

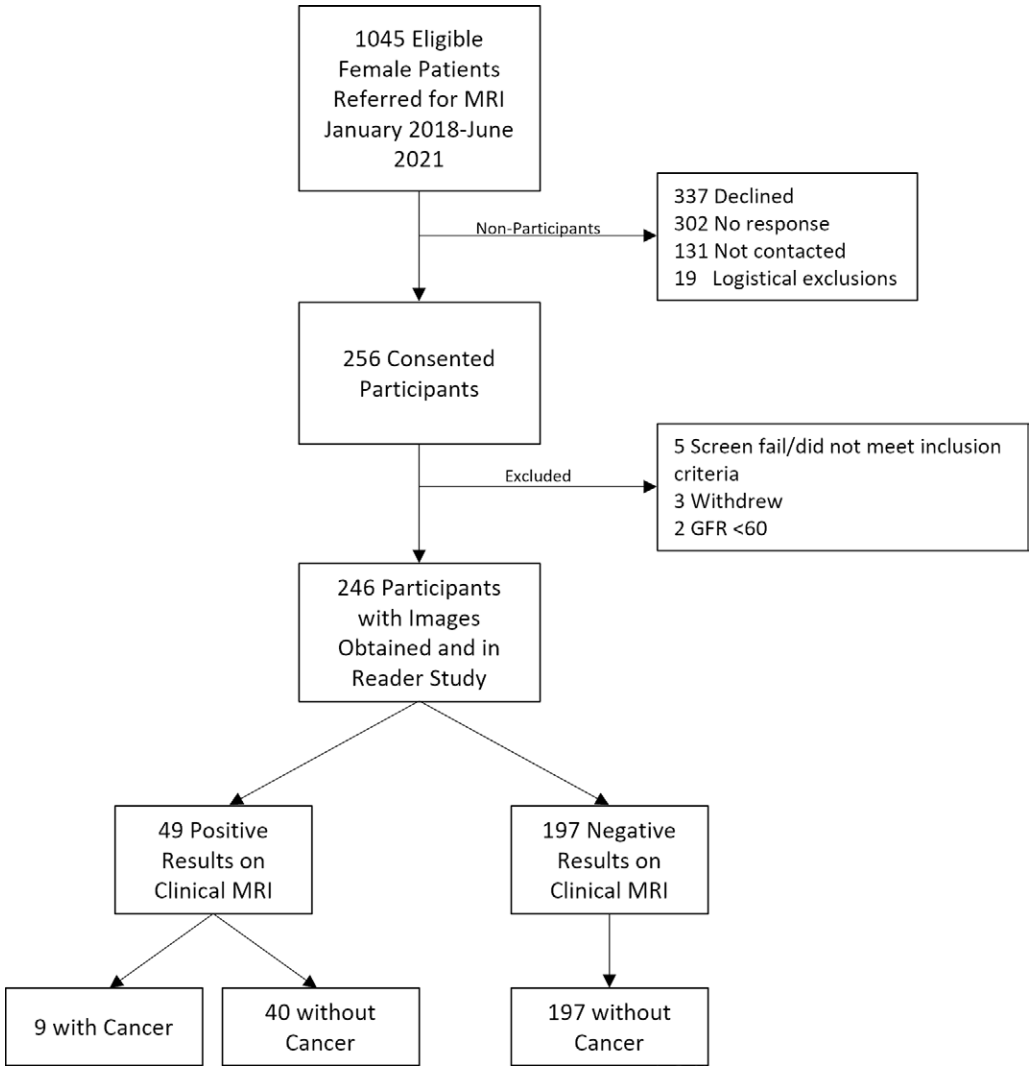


**Figure 1:** Cohort selection diagram. GFR = glomerular filtration rate.

Standard MRI examinations were interpreted at routine clinical care, where radiologists had access to all relevant clinical information and prior examinations (not including the research CEM study).

## Data Collection

Participant demographic and breast cancer risk factor data (menopausal status, personal and family history of breast cancer, and genetic mutation status) were abstracted from the electronic medical record. BI-RADS findings, assessments, and recommendations were obtained from reader reporting forms for CEM and ABMRI and were abstracted from the electronic medical record for standard MRI. The reference standard of breast cancer status was ascertained through biopsy results and at least 1 year of follow-up per American College of Radiology guidance, abstracted from the electronic medical record in addition to linkage with a regional cancer registry to identify pathologic diagnoses of breast cancer both within and beyond our institution through August 30, 2022 (20,21).

## Performance Metrics

Performance metrics (examination level and breast level) were calculated separately for low-energy CEM images, CEM, ABMRI, and standard MRI, with the two readers pooled for CEM and ABMRI. Performance metrics were as follows: recall rate, cancer detection rate per 1000 examinations, false-positive biopsy recommendation rate per 1000 examinations, sensitivity, specificity, and positive predictive value of biopsy recommendation per American College of Radiology BI-RADS guidance (21) (Table S1). Recall rate, cancer detection rate, sensitivity, and specificity were calculated with positive results at screening defined as an initial BI-RADS assessment of 0 for low-energy CEM or a BI-RADS assessment of 0, 3, 4, or 5 for CEM, ABMRI, or standard MRI. False-positive biopsy recommendation rate and positive predictive value of biopsy recommendation were calculated based on an examination with positive results, defined as a BI-RADS 4 or 5 final assessment

**Table 1: Study Population Characteristics**

| Characteristic | Total No. of Participants ($n$ = 246) | High-Risk Screening ($n$ = 206)* | No. of Lesions Found at MRI Recommended for Biopsy ($n$ = 40)† |
|---|---|---|---|
| Age (y) | | | |
| 18–39 | 40 (16) | 30 (15) | 10 (25) |
| 40–49 | 78 (32) | 68 (33) | 10 (25) |
| 50–59 | 55 (22) | 49 (24) | 6 (15) |
| 60–69 | 56 (23) | 46 (22) | 10 (25) |
| ≥70 | 17 (7) | 13 (6) | 4 (10) |
| Race | | | |
| Native American/Alaskan Native | 2 (1) | 2 (1) | 0 (0) |
| Asian | 8 (3) | 5 (2) | 3 (8) |
| Black | 2 (1) | 1 (0) | 1 (2) |
| Native Hawaiian/other Pacific Islander | 2 (1) | 1 (0) | 1 (2) |
| Unknown | 38 (15) | 31 (15) | 7 (18) |
| White | 194 (79) | 166 (81) | 28 (70) |
| Ethnicity | | | |
| Hispanic/Latino | 8 (3) | 6 (3) | 2 (5) |
| Not Hispanic/Latino | 180 (73) | 151 (73) | 29 (72) |
| Unknown | 58 (24) | 49 (24) | 9 (22) |
| Menopausal status | | | |
| Premenopausal | 113 (46) | 96 (47) | 17 (42) |
| Perimenopausal | 6 (2) | 4 (2) | 2 (5) |
| Postmenopausal | 127 (52) | 106 (51) | 21 (52) |
| Family history and personal history of breast cancer‡ | | | |
| Family history of breast cancer | 128 (52) | 114 (55) | 14 (35) |
| Known genetic mutation | 45 (18) | 42 (20) | 3 (8) |
| Personal history of breast cancer§ | 136 (55) | 123 (60) | 13 (32) |
| None | 14 (6) | 2 (1) | 12 (30) |

Note.—Data are numbers of participants; data in parentheses are percentages. Percentages may not add up to 100% due to rounding. Menopausal status was determined by medical record or participant report at the time of consent. Family history of breast cancer is defined as having at least one first-degree family member or two second-degree family members diagnosed with breast cancer.

* If standard MRI performed for extent of disease evaluation, only the contralateral breast was included.

† Suspicious or highly suspicious lesion on standard breast MRI.

‡ Data sums to more than 246 because these terms are not mutually exclusive.

§ Includes 43 women with new diagnosis of breast cancer.

in the reader study or assessment reported for standard MRI. Although recall rate is not a performance benchmark typically evaluated for MRI, we included it as a clinically relevant measure reflecting participants who are not returned to routine screening and for direct comparison to CEM.

### Statistical Analysis

Absolute differences in performance metrics comparing CEM, ABMRI, and standard MRI were also calculated. The nonparametric bootstrap was used to calculate 95% CIs except when estimates were 0% or 100%, in which case the Clopper-Pearson exact method was used. Permutation tests were used to calculate *P* values based on the Mid-p approach (22). Throughout the analysis, data were treated as clustered by participant rather than fully independent. The bootstrap and permutation test resampling was performed at the participant level to account for nonindependence between multiple readers and multiple breasts per participant (23–25). With a sample size of 246, we estimated there would be 80% power (two-sided $\alpha = .05$) to detect a change in recall rate or specificity between standard MRI, CEM, or ABMRI if the true difference was 7.9% (recall rate) or 6.6% (specificity). This study was not powered to detect differences in cancer detection rate, sensitivity, and positive predictive value of biopsy recommendation due to a relatively small, expected number of cancers. All statistical calculations were performed (D.S.H.) using statistical software (R version 4.0.3; R Foundation for Statistical Computing).

## Results

### Participant Characteristics

Of 1045 eligible participants, 256 consented to participate in the study. Of these eligible participants, 246 participants enrolled in the study and contributed examinations for interpretation (median age, 51 years; IQR, 43–61 years) (Fig 1).

**Table 2: Examination-Level Summaries**

| Variable | CEM | | ABMRI | Standard MRI† |
|---|---|---|---|---|
| | Low-Energy Only | Overall* | | |
| BI-RADS breast density and fibroglandular tissue category | | | | |
| A | 2 (0) | … | 3 (1) | 2 (1) |
| B | 138 (28) | … | 153 (31) | 72 (29) |
| C | 284 (58) | … | 252 (51) | 140 (57) |
| D | 68 (14) | … | 84 (17) | 32 (13) |
| CEM or MRI background parenchymal enhancement category | | | | |
| Minimal | … | 229 (47) | 188 (38) | 118 (48) |
| Mild | … | 167 (34) | 157 (32) | 72 (29) |
| Moderate | … | 73 (15) | 102 (21) | 38 (15) |
| Marked | … | 23 (5) | 45 (9) | 18 (7) |
| No. of lesions rated BI-RADS 0, 3, 4, or 5 | | | | |
| 0 | 404 (82) | 423 (86) | 361 (73) | 190 (77) |
| 1 | 80 (16) | 61 (12) | 108 (22) | 55 (22) |
| 2 | 8 (2) | 7 (1) | 21 (4) | 1 (0) |
| 3 | 0 (0) | 1 (0) | 1 (0) | 0 (0) |
| 4 | 0 (0) | 0 (0) | 1 (0) | 0 (0) |
| BI-RADS assessment | | | | |
| Negative (BI-RADS 1, 2) | 404 (82) | 423 (86) | 361 (73) | 190 (77) |
| Positive (BI-RADS 0, 3, 4, 5) | 88 (18) | 69 (14) | 131 (27) | 56 (23) |
| Final BI-RADS assessment‡ | | | | |
| Negative (BI-RADS 1–3) | 466 (95) | 451 (92) | 388 (79) | 197 (80) |
| Positive (BI-RADS 4, 5) | 26 (5) | 41 (8) | 104 (21) | 49 (20) |
| Final BI-RADS assessment (detailed)‡ | | | | |
| BI-RADS 1 | 191 (39) | 217 (44) | 223 (45) | 75 (30) |
| BI-RADS 2 | 258 (52) | 221 (45) | 140 (28) | 115 (47) |
| BI-RADS 3 | 17 (3) | 13 (3) | 25 (5) | 7 (3) |
| BI-RADS 4 | 25 (5) | 41 (8) | 99 (20) | 48 (20) |
| BI-RADS 5 | 1 (0) | 0 (0) | 5 (1) | 1 (0) |

Note.—Data are numbers of reads; data in parentheses are percentages. There were 492 reads of 246 examinations from each modality. Breast Imaging Reporting and Data System (BI-RADS) breast density and fibroglandular tissue categories are defined as follows: A, almost entirely fatty; B, scattered fibroglandular tissue; C, heterogeneously dense; and D, extremely dense. ABMRI = abbreviated breast MRI, CEM = contrast-enhanced mammography.

* Low energy and recombined imaging interpretation.

† Single clinical read (*n* = 246 reads of 246 examinations).

‡ Forced final BI-RADS for CEM.

Participant demographics were as follows: 78.8% (194 of 246) of participants were White, 51.6% (127 of 246) were postmenopausal, 52.0% (128 of 246) had a family history of breast cancer, and 18.3% (45 of 246) were high risk due to a known genetic mutation (Table 1).

## Examination Characteristics

Each pair of CEM and ABMRI examinations from the same patient were interpreted by two readers (492 interpretations per modality). At the examination level, BI-RADS breast density was categorized as heterogeneously dense or extremely dense for 71.5% (352 of 492) of CEM and 68.3% (336 of 492) of ABMRI examinations (Table 2). Background parenchymal enhancement was categorized as minimal or mild for 80.5% (396 of 492) of CEM and 70.1% (345 of 492) of ABMRI examinations. Breast-level summaries are in Table S2.

## Breast Cancer Characteristics

Of 49 standard MRI examinations with lesions recommended for biopsy, there were nine with malignant pathology (five with invasive ductal carcinomas, one with invasive lobular carcinoma, two with in situ disease, and one with nonbreast malignancy). Eight of the cancers were diagnosed in participants with an MRI finding recommended for US or MRI-guided percutaneous biopsy. The malignant lesions had a reported size on MRI scans of 5–115 mm, with all malignancies larger than 20 mm described as nonmass enhancement. All six invasive breast cancers were node-negative, stage IA (26).

## Examination-Level Performance Metrics

Comparative performance evaluation demonstrated that CEM had the lowest recall rate of 14.0% (69 of 492), whereas ABMRI had a recall rate of 26.6% (131 of 492) and standard MRI had

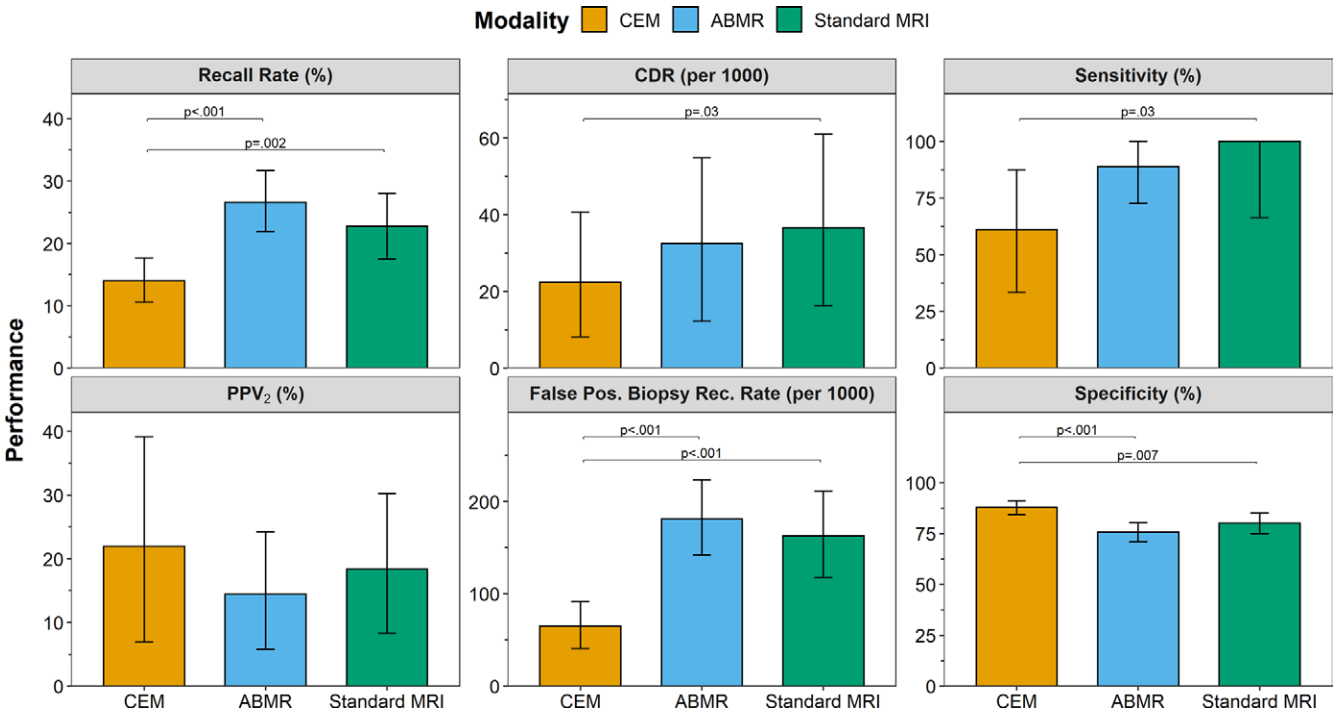


**Figure 2:** Bar charts of each performance metric summarize examination-level performance by modality, with *P* values indicating significant differences. ABMR = abbreviated breast MRI, CDR = cancer detection rate, CEM = contrast-enhanced mammography, $PPV_2$ = positive predictive value 2 (of biopsy recommendation).

a recall rate of 22.8% (56 of 246) (Fig 2, Table 3). The CEM recall rate was significantly lower than either ABMRI or standard MRI: 12.6% lower than ABMRI ($P < .001$) and 8.7% lower than standard MRI ($P = .002$) (Table 4). Although there was no statistically significant difference in recall rate between ABMRI and standard MRI detected at the examination level ($P = .11$), the ABMRI recall rate was 3% higher than standard MRI at the breast level (95% CI: 0.2, 6.0; $P = .04$) (Tables S3, S4; Fig S1).

Standard MRI had a cancer detection rate of 36.6 per 1000 examinations (nine of 246). The CEM cancer detection rate of 22.4 per 1000 examinations (11 of 492) was significantly lower than that of standard MRI (difference, −14.2; $P = .03$), whereas no statistically significant difference was identified in the cancer detection rate of ABMRI (32.5 per 1000 examinations; 16 of 492) versus that of standard MRI (difference, −4.1; 95% CI: −10.2, 0; $P = .25$). Figure 3 shows a malignancy depicted on CEM, ABMRI, and standard MRI scans. Table S5 summarizes the imaging and pathologic descriptions of each malignancy and examination-level interpretations.

For CEM, 8.3% (41 of 492) of interpretations had a final BI-RADS assessment of 4 or 5, and 21.1% (104 of 492) of ABMRI interpretations had BI-RADS 4 or 5 assessments. The false-positive biopsy recommendation rate per 1000 examinations was 65.0 (32 of 492) for CEM, 180.9 (89 of 492) for ABMRI, and 162.6 (40 of 246) for standard MRI. The CEM false-positive biopsy recommendation rate was significantly lower compared with ABMRI (difference, −115.9; $P < .001$) and standard MRI (difference, −97.6; $P < .001$). Figure 4 shows a false-positive result on CEM, ABMRI, and MRI scans.

The examination-level positive predictive value of biopsy recommendation was highest for CEM at 22% (nine of 41), followed by 18% (nine of 49) for standard MRI and 14.4% (15 of 104) for ABMRI. However, the differences between the three modalities were not statistically significant (Table 4).

Standard MRI helped detect all nine cancers, and no interval cancers were identified during the follow-up period, yielding sensitivity of 100% (nine of nine). Specifically, no cancers were identified among the 30 unique positive CEM-negative MRI cases at subsequent imaging (24 with a negative finding at subsequent MRI, four with a negative finding on mammogram >18 months after standard MRI, one with a negative finding on mammogram 6 months after MRI, and one with regional cancer registry linkage alone). ABMRI sensitivity was 88.9% (16 of 18) and was not significantly different from that of standard MRI (−11.1%; $P = .25$). CEM sensitivity was 61.1% (11 of 18), 38.9% lower than the standard MRI ($P = .03$) but was not significantly lower than ABMRI (difference, −27.8; $P = .06$). Figure 5 shows a false-negative finding at CEM examination (reported by both readers), which was a true-positive finding on ABMRI and MRI interpretations.

CEM had the highest specificity among all imaging techniques at 87.8% (416 of 492). ABMRI specificity was 75.7% (359 of 474); standard MRI specificity was 80.2% (190 of 237). CEM specificity was significantly higher than ABMRI (12.0%; $P < .001$) and standard MRI (7.6%; $P = .007$). Figure 6 shows a true-negative result at CEM, which was false-positive finding at ABMRI and MRI.

Low-energy CEM, all breast-level performance metrics, and a summary of the interreader agreement are reported in Appendix S1 and Table S6 (27).

**Table 3: Examination-Level Performance Metrics**

| Parameter | No. of CEM Reads | No. of ABMRI Reads | Standard MRI* |
|---|---|---|---|
| Recall rate | 69/492 (14.0) [10.6, 17.7] | 131/492 (26.6) [22.0, 31.7] | 56/246 (22.8) [17.5, 28.0] |
| Cancer detection rate per 1000 examinations | 11/492 (22.4) [8.1, 40.7] | 16/492 (32.5) [12.2, 54.9] | 9/246 (36.6) [16.3, 61.0] |
| FP biopsy recommendation rate per 1000 examinations | 32/492 (65.0) [40.7, 91.5] | 89/492 (180.9) [142.3, 223.6] | 40/246 (162.6) [117.9, 211.4] |
| $PPV_2$ | 9/41 (22.0) [6.9, 39.1] | 15/104 (14.4) [5.8, 24.2] | 9/49 (18.4) [8.3, 30.2] |
| Sensitivity | 11/18 (61.1) [33.3, 87.5] | 16/18 (88.9) [72.7, 100] | 9/9 (100) [66.4, 100]† |
| Specificity | 416/474 (87.8) [84.3, 91.0] | 359/474 (75.7) [70.8, 80.3] | 190/237 (80.2) [74.9, 85.0] |

Note.—Data are numerators/denominators; data in parentheses are percentages; data in brackets are 95% CIs. There were 492 reads of 246 examinations. CIs were calculated using the nonparametric bootstrap unless otherwise specified. CEM = contrast-enhanced mammography, ABMRI = abbreviated breast MRI, FP = false-positive, $PPV_2$ = positive predictive value 2.

* Single clinical read (246 reads of 246 examinations).

† Clopper-Pearson CI.

**Table 4: Comparison of Examination-Level Performance Metrics of CEM and ABMRI with Standard MRI**

| | CEM versus Standard MRI* | | ABMRI versus Standard MRI* | | CEM versus ABMRI | |
|---|---|---|---|---|---|---|
| Metric | Estimate | *P* Value | Estimate | *P* Value | Estimate | *P* Value |
| Recall rate (%) | −8.7 (−14.0, −3.5) | .002 | 3.9 (−0.8, 8.7) | .11 | −12.6 (−17.7, −7.7) | <.001 |
| Cancer detection rate (per 1000 examinations) | −14.2 (−28.5, −2.0) | .03 | −4.1 (−10.2, 0) | .25 | −10.2 (−22.4, −2.0) | .06 |
| FP biopsy recommendation rate (per 1000 examinations) | −97.6 (−146.3, −50.8) | <.001 | 18.3 (−24.4, 61.0) | .41 | −115.9 (−158.5, −75.2) | <.001 |
| $PPV_2$ (%) | 3.6 (−8.1, 16.2) | .54 | −3.9 (−10.0, 0.6) | .12 | 7.5 (−3.7, 20.2) | .13 |
| Sensitivity (%) | −38.9 (−66.7, −12.5) | .03 | −11.1 (−27.3, 0.0) | .25 | −27.8 (−50.0, −6.2) | .06 |
| Specificity (%) | 7.6 (2.3, 13.1) | .007 | −4.4 (−9.3, 0.4) | .07 | 12.0 (7.0, 17.2) | <.001 |

Note.—There were 492 reads of 246 examinations. CIs were calculated using the nonparametric bootstrap analysis. *P* values were calculated using a permutation test (Mid-p *P* value); the permutation test *P* value was used to determine statistical significance because it is more robust with small sample sizes than the bootstrap CI method. ABMRI = abbreviated breast MRI, CEM = contrast-enhanced mammography, FP = false-positive, $PPV_2$ = positive predictive value 2.

* Single clinical read (246 reads of 246 examinations).

### Adverse Events

During the study, four of 256 (1.6%) study participants who were administered intravenous iodinated contrast agent (246 participants included in analysis, three participants whose CEM examinations were excluded, and seven participants in the before-study pilot) had a documented contrast agent reaction. All reactions were mild based on American College of Radiology categorization of acute reactions (28), limited to rash and hives that did not require treatment.

## Discussion

In this prospective head-to-head comparative analysis of contrast-enhanced mammography (CEM) and abbreviated breast MRI (ABMRI) as alternatives to standard MRI for supplemental screening of patients with increased breast cancer risk, we found that CEM had significantly lower recall rate, false-positive biopsy recommendation rate, and higher specificity compared with standard MRI and ABMRI. These apparent CEM benefits were offset by significantly lower cancer detection rate and sensitivity when compared with standard MRI.

Our observed CEM sensitivity of 61.1% is below the American College of Radiology BI-RADS MRI screening benchmark of 80% (21) and also at the lower end of published reports, with the two largest studies of CEM for breast cancer screening to date reporting sensitivities of 87.5% (14 of 16 cancers) and 90.5% (19 of 21 cancers) (9,29). Our observed sensitivity is also lower compared with two recent meta-analyses of CEM and standard MRI, which reported pooled sensitivity of 91% (range across seven studies, 65%–100%) (8) and 96% (range across 15 studies, 78%–100%) (7). However, it is important to note that many studies included in these meta-analyses evaluated the performance of CEM in helping to identify lesions recommended for biopsy detected at mammography or sonography rather than lesions detected at MRI (in our study). Whereas the meta-analyses did not report lesion characteristics such as size distribution or proportion of masses versus nonmass enhancement, differences in these features (ie, potentially larger average size or greater proportion of masses for lesions depicted with conventional imaging) may be associated with the different CEM sensitivities between prior studies and our observed

results. In addition, our MRI protocol has spatial resolution that exceeds American College of Radiology accreditation standards, which likely facilitates superior depiction of lesions compared with CEM. Our institution's breast MRI examinations were performed on 3-T scanners, which maximized the signal-to-noise ratio (compared with 1.5 T), and the in-plane resolution was 0.5 mm × 0.55 mm with 1.5-mm section thickness.

Our comparative sensitivity results should also be considered in the context of the small sample size of nine malignancies among the standard MRI examinations and the corresponding 18 interpretations of breast cancer cases for CEM and ABMRI in the reader study. For example, the 27.8% lower sensitivity of CEM versus ABMRI is based on five additional positive interpretations for ABMRI (16 vs 11 for CEM). The 95% CI for the difference is relatively wide, ranging from 6.2% to 50.0%. Additional studies with larger sample sizes are needed to further evaluate the comparative performance of CEM versus alternative modalities for breast cancer screening.

We also observed favorable performance metrics for CEM, namely lower recall rate, lower false-positive biopsy recommendation rate, and higher specificity (and within American College of Radiology MRI screening benchmark range) compared with ABMRI and standard MRI. These results suggest CEM in the screening setting has the potential to improve timeliness of screening with fewer diagnostic evaluations and biopsies that ultimately reveal benign disease. Whether the trade-offs across performance metrics are acceptable in a high-risk screening population when higher cancer detection rates may be valued over fewer false-positive results is not yet established. Son et al (30) found that 70% of surveyed women were neutral or not concerned with the possibility of more false-positive results associated with contrast-enhanced screening techniques. Thus, continued evaluation of CEM performance within an appropriate screening population (ie, patients who are at intermediate risk, have a personal history of breast cancer, or have extremely dense breasts) is an additional consideration before clinical adoption in the setting of screening.

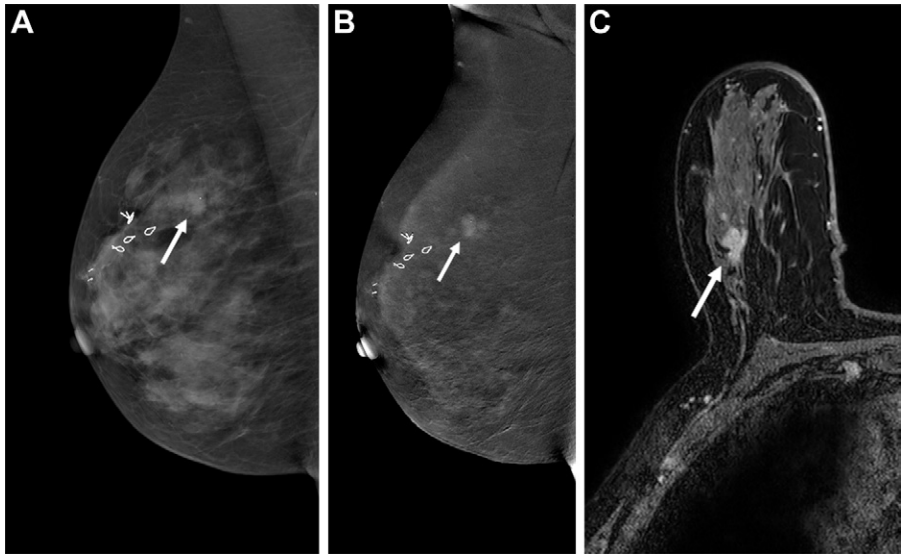


**Figure 3:** Contrast-enhanced mammograms (CEMs; **A, B**) and MRI scan **(C)** with true-positive findings in a 73-year-old participant with personal history of right breast ductal carcinoma in situ treated with lumpectomy and newly diagnosed left breast invasive lobular carcinoma (not shown), who presented for contralateral right breast screening. **(A)** Mediolateral oblique low-energy and **(B)** mediolateral oblique recombined CEMs of the right breast show an irregular contrast-enhanced mass with irregular margins in the upper outer quadrant (arrows). **(C)** Axial contrast-enhanced breast MRI sequence shows an irregular contrast-enhanced mass with irregular margins that is suspicious for cancer in the upper outer quadrant of the right breast (arrow). Pathology revealed recurrent invasive ductal carcinoma and ductal carcinoma in situ, Nottingham grade I, that was estrogen receptor positive, progesterone receptor positive, and human epidermal growth factor receptor 2 receptor negative.

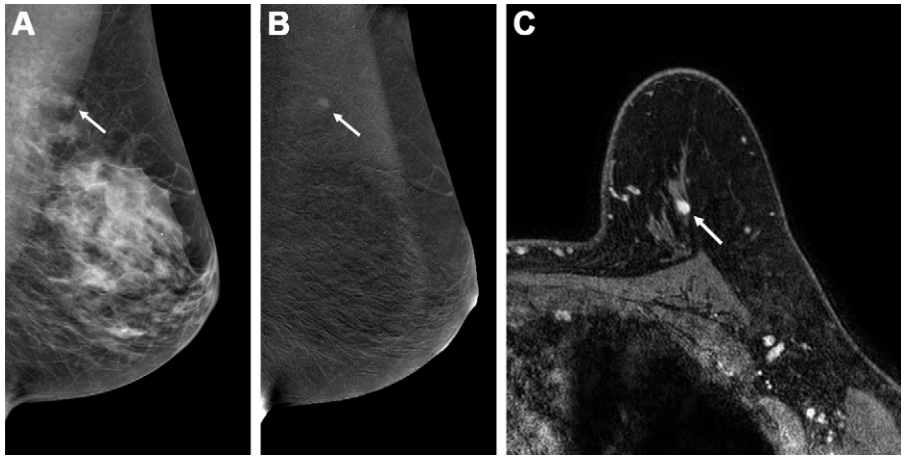


**Figure 4:** Contrast-enhanced mammograms (CEMs; **A, B**) and MRI scan **(C)** show a false-positive finding in a 63-year-old participant with newly diagnosed screen-detected right breast ductal carcinoma in situ; the patient presented for contralateral left breast screening. **(A)** Mediolateral oblique low-energy and **(B)** mediolateral oblique recombined contrast-enhanced images of the left breast show an oval enhancing mass with irregular margins in the upper outer quadrant (arrows). **(C)** Axial contrast-enhanced breast MRI scan shows a 6-mm oval mass with irregular margins in the upper outer quadrant of the left breast (arrow). Pathology from MRI-guided biopsy showed florid sclerosing adenosis.

We did not detect statistically significant differences in performance metrics between ABMRI and standard MRI. Although our study may have been underpowered to detect small differences in performance metrics, our results are consistent with meta-analyses evaluating the performance of ABMRI versus standard MRI. Baxter et al (31) and Geach et al (13) found no significant differences in ABMRI performance compared with standard MRI across heterogeneous study designs. For

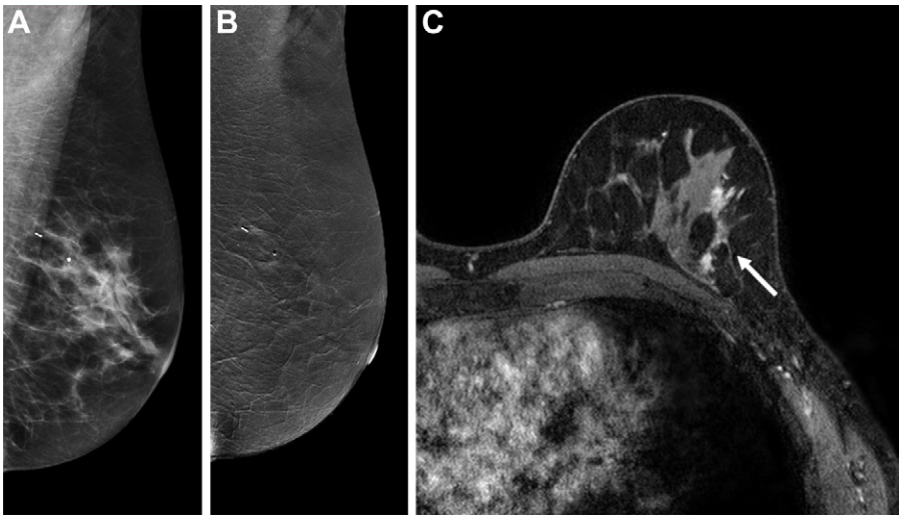


**Figure 5:** Contrast-enhanced mammograms (CEMs; **A, B**) and MRI scan **(C)**. CEM shows a false-negative finding and MRI/abbreviated breast MRI scan shows a true-positive finding in a 61-year-old participant with partner and localizer of breast cancer gene 2, or *PALB-2*, mutation and remote history of benign needle biopsy in the left breast presenting for high-risk screening. **(A)** Mediolateral oblique low-energy and **(B)** mediolateral oblique recombined images of the left breast from the CEM reported as Breast Imaging Reporting and Data System (BI-RADS) category 2 (benign). **(C)** Axial contrast-enhanced breast MRI scan shows 31-mm nonmass enhancement in the inferior left breast reported as BI-RADS category 4 (arrow). Pathology from MRI-guided biopsy revealed ductal carcinoma in situ and final surgical pathology revealed invasive ductal carcinoma with ductal carcinoma in situ, Nottingham grade III, estrogen receptor positive, progesterone receptor negative and HER-2 receptor positive.

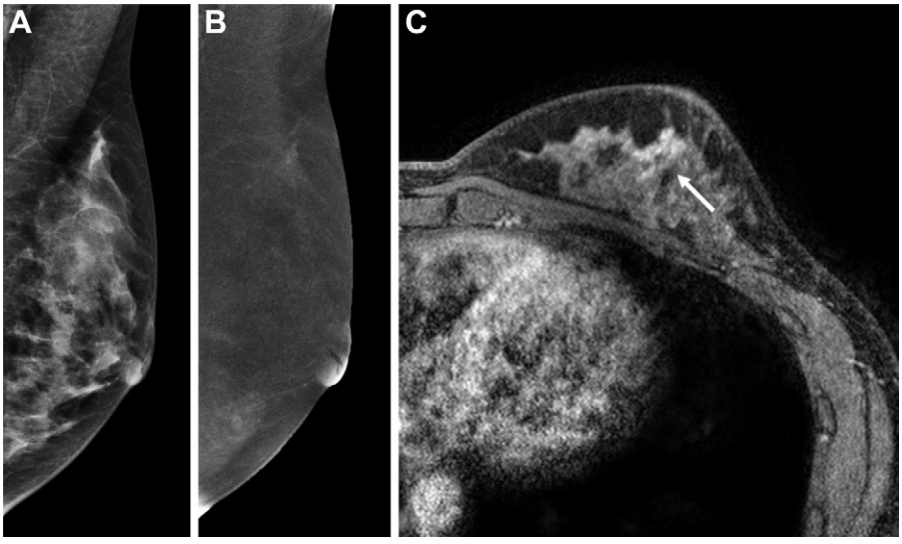


**Figure 6:** Contrast-enhanced mammograms (CEMs; **A, B**) and MRI scan **(C)**. CEM true-negative finding and abbreviated breast MRI/standard MRI with false-positive findings in a 25-year-old participant with left breast nipple discharge. **(A)** Mediolateral oblique low-energy and **(B)** mediolateral oblique recombined images of the left breast from the CEM reported as Breast Imaging Reporting and Data System (BI-RADS) category 1 (negative). **(C)** Axial contrast-enhanced breast MRI scan shows 9-mm focal nonmass enhancement in the inferior left breast reported as BI-RADS category 4 (arrow). Pathology from MRI-guided biopsy revealed breast parenchyma with dense fibrous stroma and focal fragment of cyst wall.

example, Baxter et al (31) found that in screening studies the pooled sensitivity and specificity of ABMRI were 90% (95% CI: 79, 96) and 92% (95% CI: 86, 95), respectively, compared with standard MRI sensitivity of 92% (95% CI: 77, 97) and specificity of 95% (95% CI: 91, 97). Our findings and those of previous studies suggest that ABMRI could be an appropriate alternative to standard MRI.

Our study had limitations. The limitations included the small number of cancers found on standard MRI scans and the sample size of the study overall. Including participants with lesions recommended for biopsy increased the number of malignancies and having independent interpretations by two readers for each CEM and ABMRI examination increased the power of this study; however, future studies with larger sample sizes are still needed. All pathologic diagnoses of cancer were identified based on the results at standard MRI, findings exclusively observed on CEM or ABMRI images were not biopsied, and no interval cancers were detected after linkage with a regional cancer registry resulting in an observed MRI sensitivity of 100%, reflecting a bias in favor of standard MRI. The increased prevalence of positive cases (a characteristic of enriched cohort study designs) may have biased the cancer detection thresholds of readers (32–34). Finally, readers had differential experience with CEM versus ABMRI and standard MRI, which may have contributed to the observed differences in comparative performance. Breast MRI scans are interpreted in our routine clinical practice and because ABMRI sequences are a subset of full protocol MRI, we expected to observe comparable performance of ABMRI and standard MRI. However, CEM was used only as a research examination. We addressed the relative inexperience with CEM with training that exceeded the 1-hour training previously shown to result in consistent interpretation with a 21-CEM case set (35).

In conclusion, our study results found no statistically significant difference between abbreviated breast MRI (ABMRI) and standard MRI protocols, suggesting that ABMRI may be a comparable alternative for high-risk screening, with the benefit of increased efficiency and potentially lower cost compared with standard MRI. Although contrast-enhanced mammography (CEM) had fewer recalls, fewer false-positive biopsy recommendations, and higher specificity, this was offset by lower cancer detection rate and sensitivity compared with standard MRI. Further evaluation of comparative performance and patient acceptance of trade-offs

across performance metrics is necessary before widespread adoption of CEM in breast cancer screening is warranted.

**Acknowledgment:** The authors acknowledge Jordana Phillips, MD, for providing contrast-enhanced mammography training for study readers.

**Author contributions:** Guarantors of integrity of entire study, **S.P., J.M.L.**; 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; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **M.B.L., H.R., J.R.S., D.B., J.M.L.**; clinical studies, **S.C.P., H.R., D.L.L., C.I.L., K.P.L., J.R.S., I.L., D.B., M.L.B., J.M.L.**; experimental studies, **S.C.P., D.B.**; statistical analysis, **D.S.H., I.L.**; and manuscript editing, all authors

**Data sharing:** All data generated or analyzed during the study are included in the published paper.

**Disclosures of conflicts of interest: M.B.L.** No relevant relationships. **S.C.P.** Consulting fees from Guerbet; honoraria from Stanford University Global Breast Cancer Conference, U.S. Department of Defense (DOD) Congressionally Directed Medical Research Programs (CDMRP) Programmatic Review Panel, National Institutes of Health (NIH) Study Section Friends for An Earlier Breast Cancer Test, Department of Defense, and CDMRP Breast Cancer Research Program; support for meetings from Eastern Cooperative Oncology Group–American College of Radiology Imaging Network, NIH/NCI, DOD DCMRP, Society of Breast Imaging Global Breast Cancer Conference; patents submitted; scientific advisory board member, Seoul National University Hospital; co-chair, NCI Quantitative Imaging Network Executive Committee; in-kind support to institution from Philips Healthcare, Microsoft. **D.S.H.** Institutional grants from Philips Healthcare, Canon Medical Systems USA. **H.R.** Consulting fees from Guerbet; travel support from EUSOBI for Annual Meeting 2022 attendance. **D.L.L.** No relevant relationships. **C.I.L.** Royalties from Oxford University Press, McGraw Hill, UpToDate; participation on a data safety board from GRAIL; personal fees for journal editorial board work from the American College of Radiology. **K.P.L.** No relevant relationships. **J.R.S.** Grants from RAD-AID, Novartis, GE Healthcare outside this study;; payment for patient navigation panel from Novartis; director of the Breast Health Global Initiative and RAD-AID USA and Peru. **S.P.** No relevant relationships. **I.L.** No relevant relationships. **D.B.** No relevant relationships. **M.L.B.** No relevant relationships. **J.M.L.** No relevant relationships.

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