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

Christopher E. Comstock, MD; Constantine Gatsonis, PhD; Gillian M. Newstead, MD; Bradley S. Snyder, MS;
Ilana F. Gareen, PhD; Jennifer T. Bergin, MD; Habib Rahbar, MD; Janice S. Sung, MD; Christina Jacobs, MD;
Jennifer A. Harvey, MD; Mary H. Nicholson, MD; Robert C. Ward, MD; Jacqueline Holt, MD; Andrew Prather, MD;
Kathy D. Miller, MD; Mitchell D. Schnall, MD, PhD; Christiane K. Kuhl, MD, PhD

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 magnetic resonance imaging (MRI) 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 United States and Germany, conducted between December 2016 and November 2017 among average-risk women aged 40 to 75 years with heterogeneously dense or extremely dense breasts undergoing routine screening. Follow-up ascertainment of cancer diagnoses was complete through September 12, 2019.

EXPOSURES All women underwent screening by both DBT and abbreviated breast MRI, performed in randomized order and read independently to avoid interpretation bias.

MAIN OUTCOMES AND MEASURES The primary end point was the invasive cancer detection rate. Secondary outcomes included sensitivity, specificity, additional imaging recommendation rate, and positive predictive value (PPV) of biopsy, using invasive cancer and ductal carcinoma in situ (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] years) 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. Abbreviated breast MRI detected all 17 women with invasive cancer and 5 of 6 women with DCIS. Digital breast tomosynthesis detected 7 of 17 women with invasive cancer and 2 of 6 women with DCIS. The invasive cancer detection rate was 11.8 (95% CI, 7.4-18.8) per 1000 women for abbreviated breast MRI vs 4.8 (95% CI, 2.4-10.0) per 1000 women for DBT, a difference of 7 (95% CI, 2.2-11.6) per 1000 women (exact McNemar *P* = .002). For detection of invasive cancer and DCIS, sensitivity was 95.7% (95% CI, 79.0%-99.2%) with abbreviated breast MRI vs 39.1% (95% CI, 22.2%-59.2%) with DBT (*P* = .001) and specificity was 86.7% (95% CI, 84.8%-88.4%) vs 97.4% (95% CI, 96.5%-98.1%), respectively (*P* < .001). The additional imaging recommendation rate was 7.5% (95% CI, 6.2%-9.0%) with abbreviated breast MRI vs 10.1% (95% CI, 8.7%-11.8%) with DBT (*P* = .02) and the PPV was 19.6% (95% CI, 13.2%-28.2%) vs 31.0% (95% CI, 17.0%-49.7%), respectively (*P* = .15).

CONCLUSIONS AND RELEVANCE Among women with dense breasts undergoing screening, abbreviated breast MRI, 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.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Christiane K. Kuhl, MD, PhD, Department of Diagnostic and Interventional Radiology, University Hospital Aachen, UKA, RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany (ckuhl@ukaachen.de).

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 as having interval and/or advanced breast cancer.[1-3] Approximately half of the screening-relevant age group has 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 digital mammography that generates quasi–3-dimensional images of the breast, improving mammographic sensitivity and specificity.[8,9] 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 the 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 useful in women at average risk.[14] However, the use of conventional, full-protocol breast MRI to screen the large number of average-risk women with dense breasts will be neither practical nor cost-effective.

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

This study compared the diagnostic performance of abbreviated breast MRI 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 2 modalities' respective invasive cancer detection rates at the participant level.

Methods

Study Design and Participants

The EA1141 study entitled Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women With Dense Breasts was conducted by the ECOG-ACRIN Cancer Research Group (https://ecog-acrin.org). This multicenter, intraindividual, comparative, cross-sectional study with longitudinal follow-up was conducted at 47 institutions in the United States and 1 institution in Germany, including academic institutions (24/48) and community hospitals or private practices (24/48). The National Cancer Institute Central Institutional Review Board (IRB) approved the protocol and was the IRB of record for 40 institutions; the remaining 8 institutions used their own individual IRBs. Written informed consent was obtained from all participants.

Key Points

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

Findings In this cross-sectional study with longitudinal follow-up including 1444 women who underwent both abbreviated breast MRI and DBT, interpreted independently, abbreviated breast MRI detected significantly more invasive cancers (17 women; 11.8 per 1000 women) than DBT (7 women; 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, abbreviated breast MRI was associated with a significantly higher rate of invasive cancer detection than DBT.

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

Per the study protocol (available in Supplement 1), clinically asymptomatic women aged 40 to 75 years 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 risk calculator (ie, no personal history of breast cancer and aged <75 years) were determined.[18]

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

Participants underwent imaging with both DBT and abbreviated breast MRI at study baseline and after 1 year; follow-up is planned for 3 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 examinations. Imaging studies were interpreted independently by 2 different board-certified breast radiologists who remained blinded to the results of the other modality. Both DBT and abbreviated breast MRI were performed within a single 24-hour period.

If a positive finding is made on screening mammography or DBT, women are invited to return for additional imaging workup, a process referred to as callback. This term was also used for the participants of the EA1141 study, although they underwent this workup immediately after DBT to establish a final diagnosis before abbreviated breast MRI was performed within 24 hours. After positive findings

on an abbreviated breast MRI, additional imaging is not considered useful to further support or refute the indication to biopsy. Hence, abbreviated breast MRI is not associated with callback. Women with a final BI-RADS category of 3 ("probably benign" finding) on DBT or abbreviated breast MRI underwent short-term follow-up imaging after 6 months to confirm the stability of the finding. In women with a biopsy recommendation, no biopsy was performed until both studies were completed and interpreted. All suspicious findings on DBT or abbreviated breast MRI were biopsied regardless of the final interpretation of the other modality. If both modalities had positive findings in the same breast, the site radiologist determined whether the same or different lesions were seen.

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

For follow-up, women were contacted by phone at 6 months (±1 month) and at 11 to 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 as having 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 positive predictive value (PPV) of biopsy; in addition, interval cancers reported during 11 to 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 abbreviated breast MRI 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 mL/kg of body weight of gadobenate dimeglumine [MultiHance, Bracco Diagnostics Inc]). All studies were interpreted according to the Breast Imaging Reporting and Data System (BI-RADS; categories ranging from 1 [negative] to 5 [highly suggestive of breast cancer]).[20] Further information is provided in eAppendix 1 in Supplement 2.

End Points

The primary end point 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 end points are included in this report: sensitivity, specificity, additional imaging recommendation rate (ie, callback plus recommendation for short-term follow-up), and PPV of biopsy. The presence of invasive cancer and/or DCIS was defined as a positive reference standard for these end points. Additional secondary end points 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 3-year incident cancer rate. Data collection for these end points continues.

Additional exploratory end points included the overall cancer detection rate (invasive cancers and DCIS), interval cancer rate, lesion-level estimates of PPV, stage of cancers at diagnosis according to the 8th edition of the *AJCC Cancer Staging Manual*,[19] and characteristics of cancers based on histopathological and immunohistochemical features.

The following post hoc end points were not prespecified according to the statistical analysis plan (Supplement 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 were 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 reported for these post hoc, unplanned end points.

Adverse Event Reporting

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

Statistical Analysis

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 per 1000 women between the modalities using a 2-sided McNemar test of level .05 (eAppendix 2 in Supplement 2); sample size estimation was challenging because at the time of protocol development, no published studies existed on abbreviated breast MRI screening vs DBT among women at average risk; thus, the analysis used the limited evidence on cancer detection rates by MRI screening of average-risk women in comparison with digital mammography that reported additional invasive cancer detection between 6 and 11 per 1000.[15,21]

The invasive cancer detection rate was estimated as the fraction of participants with invasive cancer and a positive test result (based on a BI-RADS category of 3 [probably benign], 4 [suspicious], or 5 [highly suggestive of malignancy]) at the location of the cancer indicated by core or surgical biopsy. The PPV was estimated as the fraction of participants undergoing biopsy who had a result of 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 categories 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 (based on a BI-RADS category of 1 [negative] or 2 [benign]).

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.[22] Because of the paired design, detection rates, sensitivities, specificities, and additional imaging recommendation rates were compared using the exact McNemar test. Generalized estimating equation regression was used to compare PPVs, with *P* values reported from corresponding score tests.[23] All reported *P* values are 2-sided. A post hoc Bonferroni adjustment was used for multiple comparisons of the primary and 4 secondary end points (total of 5 comparisons), with *P* < .01 considered statistically significant.

Per protocol, end points were analyzed using aggregate data over all institutions. Post hoc sensitivity analyses examining clustering by institution and using multiple imputation for missing reference standard data are described in eAppendix 2 in Supplement 2.

Data were analyzed using SAS version 9.4 (SAS Institute Inc) and R version 3.4.4 (R project; http://www.r-project.org/). The Breast Cancer Surveillance Consortium risk score was computed using publicly available software.[18]

Results

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

Table 1 and eTable 1 in Supplement 2 summarize the demographic characteristics and risk distributions of the analysis cohort of 1444 women. Seventy-seven percent had heterogeneously dense breasts and 15% had extremely dense breasts; 8% who had dense breasts on the most recent prior mammogram used to determine study inclusion were found to have nondense breasts at the time of the study. The Breast Cancer Surveillance Consortium risk score yielded a median 5-year risk of invasive breast cancer of 1.6% (range, 0.3%-7.8%).

Primary End Point
Nineteen invasive cancers were detected in 17 women by study baseline screening (**Table 2** and **Figure 2**). Cancer status was known in all participants for the detection analysis. Abbreviated breast MRI detected the invasive cancer in all 17 women, and DBT detected it in 7 women, yielding an invasive cancer detection rate of 11.8 (95% CI, 7.4-18.8) per 1000 women for abbreviated breast MRI vs 4.8 (95% CI, 2.4-10.0) per 1000

women for DBT, a difference of 7 (95% CI, 2.2-11.6) per 1000 women (*P* = .002).

Secondary End Points
Sensitivity and Specificity
According to the reference standard information, 23 women had cancer (invasive or DCIS) at the study baseline screen and 1421 were 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 14 participants who had incomplete follow-up information; the reference standard status for these participants was considered missing.

The sensitivity of abbreviated breast MRI for invasive cancer or DCIS was significantly higher than that of DBT, at 95.7% (95% CI, 79.0%-99.2%; 22 of 23 women) vs 39.1% (95% CI, 22.2%-59.2%; 9 of 23 women) (*P* = .001) (Figure 2). Specificity of abbreviated breast MRI was significantly lower than that of DBT, at 86.7% (95% CI, 84.8%-88.4%; 1220 of 1407 women) vs 97.4% (95% CI, 96.5%-98.1%; 1371 of 1407 women) (*P* < .001) (Figure 2 and eFigure 1 in Supplement 2).

Positive Predictive Value
The PPV of biopsy for abbreviated breast MRI was 19.6% (95% CI, 13.2%-28.2%; 21 of 107 women), which was not statistically significantly different compared with DBT at 31.0% (95% CI, 17.0%-49.7%; 9 of 29 women) (*P* = .15) (Figure 2).

Additional Imaging Recommendation Rate
The callback rate for screening DBT was 10.1% (95% CI, 8.7%-11.8%; 146 of 1444 women) and was 0% for abbreviated breast MRI. Short-term follow-up (BI-RADS category 3) was recommended with DBT in 1.2% of women (95% CI, 0.8%-2.0%; 18 of 1444 women), all of whom also had a callback, and with abbreviated breast MRI in 7.5% of women (95% CI, 6.2%-9.0%; 108 of 1444 women). Thus, additional imaging (either callback or short-term follow-up) was required in 7.5% (95% CI, 6.2%-9.0%; 108 of 1444 women) for abbreviated breast MRI and in 10.1% (95% CI, 8.7%-11.8%; 146 of 1444 women) for DBT; this difference was not statistically significant after Bonferroni adjustment (*P* = .02) (Figure 2).

### Exploratory and Post Hoc End Points
Overall Cancer Detection
In addition to the 19 invasive cancers observed in 17 women, 6 women were diagnosed as having DCIS alone; 1 woman with invasive cancer also had DCIS, for a breast cancer prevalence of 23 of 1444 women (15.9 per 1000 women). Abbreviated breast MRI identified cancer in 22 of the 23 women with cancer and DBT identified cancer in 9 women, for an overall cancer detection rate of 15.2 (95% CI, 10.1-23.0) per 1000 women (22 of 1444 women) for abbreviated breast MRI vs 6.2 (95% CI, 3.3-11.8) per 1000 women (9 of 1444 women) for DBT (*P* = .001) (Figure 2).

Interval Cancer Rate
No interval cancers were reported in the 1407 women with complete follow-up information, leading to an estimated interval cancer rate of 0% (95% CI, 0%-0.27%).

Figure 1. Participant Flow in a Study of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Screening
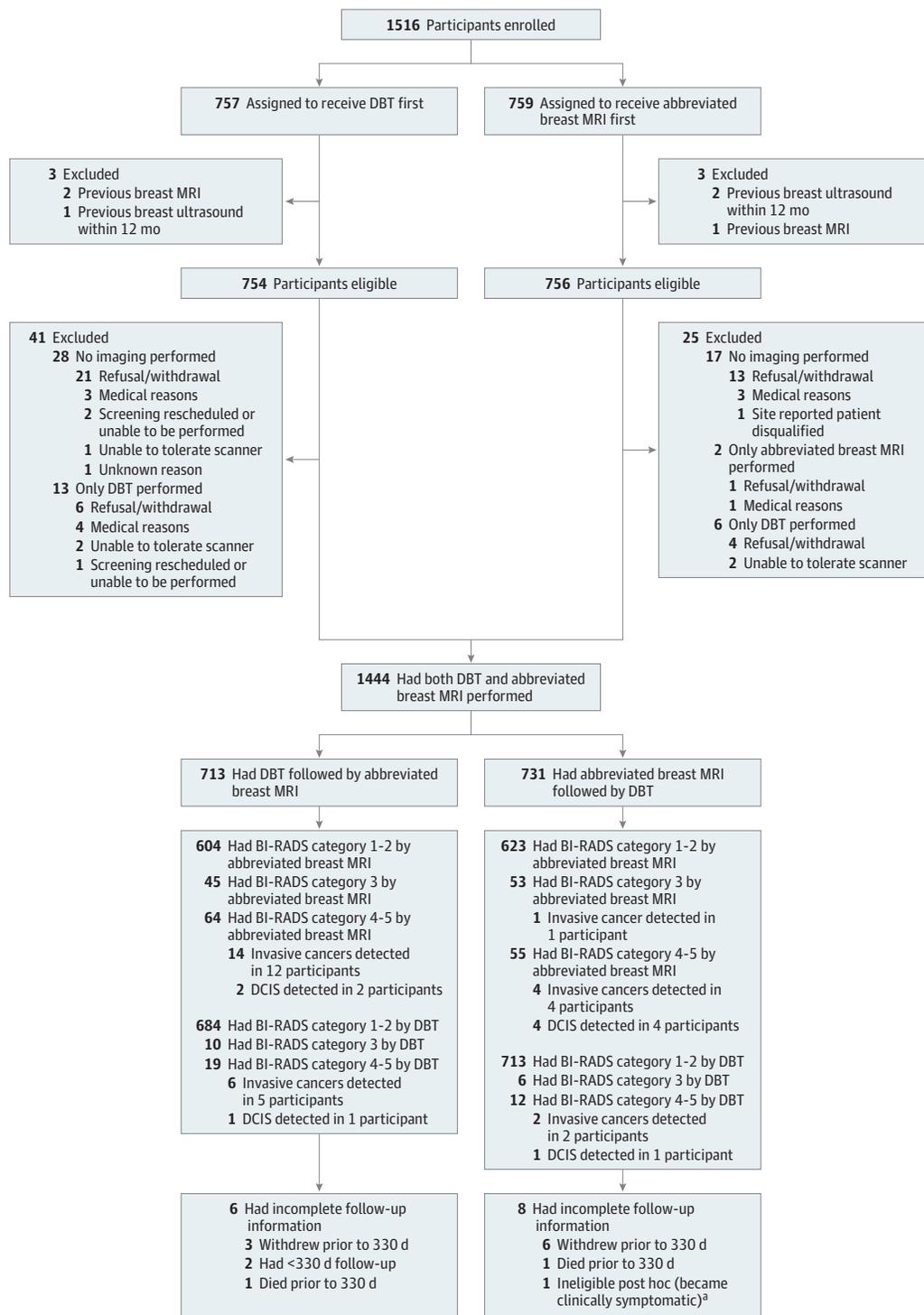
BI-RADS indicates Breast Imaging Reporting and Data System; DBT, digital breast tomosynthesis; DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging. The reference standard was positive for cancer in 23 participants at baseline (19 invasive cancers with or without DCIS in 17 women and 6 instances of DCIS alone in 6 women). Zero interval cancers were reported. No cancer was reported in the 14 participants who had incomplete follow-up information; the reference standard status for these participants was considered missing.

[a] Patient became clinically symptomatic between date of study consent and date of screening; patient was then excluded from study.

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, leading to a node-negative rate of 96%. Figure 2 summarizes the histopathological and immunohistochemical characteristics of cancers stratified by method of detection. Among the 7 participants with invasive cancers that were detected by DBT, cancer grade was low in 3 and intermediate in 4. These same cancers were also detected by abbreviated breast MRI. Among the 10 participants with invasive cancer that was detected by abbreviated breast MRI but not by DBT, cancer grade was low in 3, intermediate in 4, and high in 3.

Lesion-Level PPV

The PPV of biopsy at the lesion level was 19.0% (95% CI, 12.6%-27.7%) (24 of 126 lesions) for abbreviated breast MRI vs 35.5% (95% CI, 19.5%-55.5%) (11 of 31 lesions) for DBT (*P* = .08).

Additional Nonprespecified Post Hoc Analyses

A post hoc analysis of the detection rate intended to adjust for clustering by site produced qualitatively similar results as the primary analysis (eAppendix 3 in Supplement 2). A post hoc analysis of sensitivity and specificity using mixed modeling with random effects for institution and multiple imputation for missing reference standard also produced qualitatively similar results as the primary analysis (eAppendix 4 in Supplement 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 abbreviated breast MRI 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 2 in Supplement 2).

Adverse Events

A total of 13 adverse events were reported among 12 women within 1 year of registration; 8 (62%) were grade 1 or lower. A detailed description of reported adverse events is available in eTable 2 in Supplement 2. The most common adverse events were mild allergic reactions (3 events) and anxiety (2 events).

Discussion

In this study of the performance of abbreviated breast MRI for routine breast cancer screening of average-risk women with dense breasts, abbreviated breast MRI was associated with a significantly higher invasive breast cancer detection rate compared with DBT, also referred to as 3-dimensional mammography (ie, the most advanced breast imaging method of digital radiography). The significantly higher sensitivity of abbreviated breast MRI was associated with a reduced specificity, but with a PPV that was not significantly

different from that of DBT. Women and referring physicians should be aware that having a screening abbreviated breast MRI, especially a baseline examination, may lead to additional benign biopsy findings, 6-month follow-up recommendations, or both. On the other hand, DBT, but not abbreviated

Table 1. Baseline Demographics and Risk Characteristics of Participants Completing Both DBT and Abbreviated Breast MRI (N = 1444)

Characteristics	Value
Age, y	
Mean (SD)	54.9 (8.5)
Median (range)	54 (40-75)
Race, No. (%)	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, No./total (%)	39/1356 (3)
Menopausal status, No. (%)	n = 1443
Premenopausal	440 (30)
Perimenopausal	94 (7)
Naturally postmenopausal	669 (46)
Surgically postmenopausal	240 (17)
ACR category of breast density from year 0 DBT, No. (%)[a]	
A: Almost entirely fat	2 (<1)
B: Scattered fibroglandular densities	115 (8)
C: Heterogeneously dense	1108 (77)
D: Extremely dense	219 (15)
History of ≥1 first-degree relative, No. (%)	n = 1438
With breast cancer	271 (19)
With ovarian cancer	30 (2)
Prior benign biopsy with atypias, No./total (%)	10/1423 (1)
Breast Cancer Surveillance Consortium risk score, %[b]	n = 1385
5-y risk	
Mean (SD)	1.8 (0.8)
Median (range)	1.6 (0.3-7.8)
10-y risk	
Mean (SD)	3.7 (1.6)
Median (range)	3.5 (0.9-14.2)

Abbreviations: DBT, digital breast tomosynthesis; MRI, magnetic resonance imaging.

[a] American College of Radiology (ACR) categorization of breast density from nondense to dense as follows: A, almost entirely fat, <25% fibroglandular; B, scattered fibroglandular densities, 25%-50% fibroglandular; C, heterogeneously dense, 51%-75% fibroglandular; and D, extremely dense, >75% fibroglandular. Women were enrolled in the study based on density at the last screening mammogram and could have undergone involution since then.

[b] The Breast Cancer Surveillance Consortium risk score distinguishes among low risk (<1.0%), average risk (1.0% to ≤1.66%), increased risk (1.67% to <6.0%), and high risk (≥6.0%). Risk scores could not be calculated for 12 participants because they were aged >74 years (n = 4) or had a previous diagnosis of breast cancer (n = 8). In addition, 47 participants with either unknown or unavailable data on history of breast cancer were excluded.

Table 2. Characteristics of Screen-Detected Cancers

Observed Cancer[a]	Case[a]	Lesion Detected by Abbreviated Breast MRI	Lesion Detected by DBT	ACR Breast Density[b]	Age, y	Type of Cancer[c]	Largest Diameter, mm[c]	Maximum Reported Grade[c]	Estrogen Receptor Status[c]	Progesterone Receptor Status[c]	ERBB2 Status[c]	Breast Cancer Surveillance Consortium Risk Score, % 5-Year Risk	10-Year Risk
1	1	Yes	Yes	C	62	DCIS	15	2	Positive	Positive	Not performed	2.79	5.62
2	2	Yes		C	69	DCIS	20	2	Positive	Positive	Not performed	3.24	6.17
3	3	Yes		C	68	DCIS	10	2	Positive	Negative	Not performed	4.64	8.82
4	4	Yes		C	71	DCIS	10	3	Positive	Negative	Not performed	2.10	3.95
5	5	Yes		C	68	DCIS	5	3	Not performed	Not performed	Not performed	2.08	4.02
6	6a	Yes		D	63	DCIS	30	2	Positive	Not performed	Not performed	3.40	6.77
7	7		Yes[d]	D	40	DCIS	70	3	Positive	Positive	Not performed	1.25	3.13
8	8	Yes		B	62	IDC	4	1	Positive	Positive	Negative	2.04	4.13
9	9	Yes		B	65	ILC	16	2	Positive	Negative	Negative	1.50	2.97
10	10a	Yes	Yes	C	62	IDC	11	1	Positive	Positive	Negative	1.92	3.88
11	10b	Yes	Yes	C	62	IDC	9	2	Positive	Positive	Negative	1.92	3.88
12	11	Yes		C	72	IDC	8	2	Positive	Positive	Negative	NA[e]	NA[e]
13	12	Yes		C	67	ILC	14	2	Positive	Positive	Negative	3.14	6.08
14	13a	Yes	Yes	C	56	ILC	25	2	Positive	Positive	Negative	2.41	5.07
15	13b	Yes		C	56	ILC	25	2	NA	NA	NA	2.41	5.07
16	14	Yes	Yes	C	64	IDC	18	2	Negative	Negative	Negative	2.89	5.73
17	15	Yes	Yes	C	48	IDC	10	1	Positive	Positive	Negative	1.07	2.43
18	16	Yes		C	47	IDC	10	1	Positive	Positive	Negative	0.99	2.21
19	17	Yes	Yes	C	44	IDC	NA[f]	2	Positive	Positive	Negative	1.39	3.28
20	18	Yes		C	52	IDC	24	3	Negative	Negative	Positive	1.92	4.19
21	19	Yes	Yes	C	46	Mixed IDC/ILC	48	1	Positive	Positive	Negative	0.93	2.16
22	20	Yes		C	51	IDC	10	3	Positive	Negative	Negative	2.01	4.41
23	21	Yes		C	70	IDC	10	2	Positive	Negative	Negative	4.80	8.96
24	22	Yes	Yes	C	41	IDC	10	1	Positive	Positive	Negative	0.61	1.50
25	23	Yes		D	53	IDC	10	1	Positive	Positive	Negative	4.83	10.21
26	6b	Yes		D	63	IDC	14	3	Positive	Positive	Negative	3.40	6.77

Abbreviations: DBT, digital breast tomosynthesis; DCIS, ductal carcinoma in situ; ERBB2, Erb-B2 receptor tyrosine kinase 2; IDC, invasive ductal cancer; ILC, invasive lobular cancer; MRI, magnetic resonance imaging; NA, not available.

[a] Observed numbers signify sequentially numbered individual cancers, and cases signify unique participants. Participants with more than 1 cancer have separate cancers distinguished by "a" and "b."

[b] See Table 1, footnote a, for description of American College of Radiology (ACR) categorization of breast density.

[c] Grade is the highest reported grade across core and surgical biopsies. For estrogen receptor, progesterone receptor, and ERBB2 status, if either the core biopsy or surgical biopsy had positive findings, value is reported as positive. Largest diameter, ductal carcinoma pattern, and invasive pattern are taken from surgical pathology.

In 1 participant (case 9), the histologic description of a lobular invasive cancer corresponded to intermediate grade, although no specific grading information was provided.

[d] Digital breast tomosynthesis reported 2 lesions that were the same pathological lesion (a single 70-mm DCIS).

[e] Breast Cancer Surveillance Consortium risk scores were not computed because of a previous diagnosis of breast cancer.

[f] This participant had invasive disease by vacuum-assisted core biopsy, but there was no residual cancer in the surgical biopsy specimen which showed only benign changes with atypia. Thus, tumor size data from surgical pathology are not available; however, the lesion size was 11 mm by abbreviated breast MRI and 9 mm by DBT.

Figure 2. Summary of Relevant Study Findings

Diagnostic accuracy of detection of invasive cancer or DCIS						
Imaging modality	**DBT**			**AB-MRI**		
Invasive cancer or DCIS	**Absent**	**Present**	**Total**	**Absent**	**Present**	**Total**
Negative test result	1371	14	1385	1220	1	1221
Positive test result	36	9	45[a]	187	22	209[a]
Total	1407	23	1430	1407	23	1430

Rate of detection of invasive cancer and DCIS		
Imaging modality	**DBT**	**AB-MRI**
Total participants	1444	1444
Invasive cancer detected	7	17
DCIS detected	2	6[b]
Invasive cancer or DCIS detected	9	22[b]
Sensitivity (95% CI)[c]	39.1% (22.2%-59.2%) [9/23]	95.7% (79.0%-99.2%) [22/23]
Specificity (95% CI)[c]	97.4% (96.5%-98.1%) [1371/1407]	86.7% (84.8%-88.4%) [1220/1407]
PPV of biopsy (95% CI)[c]	31.0% (17.0%-49.7%) [9/29]	19.6% (13.2%-28.2%) [21/107]
Additional imaging recommendation (95% CI)[c]	10.1% (8.7%-11.8%) [146/1444]	7.5% (6.2%-9.0%) [108/1444]

Primary end points: Invasive cancer detected, DCIS detected, Invasive cancer or DCIS detected.
Secondary end points: Sensitivity, Specificity, PPV of biopsy, Additional imaging recommendation.

Characteristics of detected invasive cancer and DCIS			
Imaging modality	**Detected by DBT alone**	**Detected by AB-MRI alone**	**Detected by both DBT and AB-MRI**
Participants with invasive cancer (with or without DCIS)	0	10	7
Low grade	-	3	3
Intermediate grade	-	4	4
High grade	-	3	0
ER positive	-	9	6
ER negative	-	1	1
ERBB2 positive	-	1	0
ERBB2 negative	-	9	7
Participants with DCIS only	1	4	1
Low grade	0	0	0
Intermediate grade	0	2	1
High grade	1	2	0
ER positive	1	3	1
ER negative	0	0	0
ER status unknown	0	1	0

DBT indicates digital breast tomosynthesis; DCIS, ductal carcinoma in situ; ER, estrogen receptor; ERBB2, Erb-B2 receptor tyrosine kinase 2; AB-MRI, abbreviated breast magnetic resonance imaging.

[a] More women had a Breast Imaging Reporting and Data System (BI-RADS) category of 3 to 5 by abbreviated breast MRI than by DBT.

[b] One participant had both invasive cancer and DCIS.

[c] Estimated at the participant level and including callback and recommendation for short-term follow-up.

breast MRI, 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 for several decades to improve early diagnosis, 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.[18] The passage of state and federal 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 abbreviated breast MRI 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 degree of possible overdiagnosis. Collecting such evidence requires much larger randomized clinical trials with long-term follow-up of at least 15 to 20 years. Randomized clinical trials on surrogate end points 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 vs undesirable detection of inconsequential disease, the characteristics of cancers detected were reported as an established proxy for their prognostic importance or likelihood of progression. Based on the distribution of nuclear grades and receptor status, the invasive cancers detected by abbreviated breast MRI did not differ from those also detected by DBT; however, the 3 high-grade invasive cancers occurring in this study were detected only by abbreviated breast MRI and were missed by DBT. This is consistent with prior observations regarding the tumor characteristics of cancers detected only by MRI.[30] Beyond these classifications based on standard histopathological and immunohistochemical results, further analyses of the genomic features (eg, PAM50 assay, Oncotype DX Breast Recurrence Score) of study-detected invasive cancers and DCIS are under way. Because the prognostic importance of DCIS is controversial, the primary objective of this study was invasive cancer detection. The fact that abbreviated breast MRI increased detection of pure DCIS as it increased detection of invasive cancers could be considered possible evidence of overdiagnosis until more information is available.[31]

The study design allowed the determination of the diagnostic performance of abbreviated breast MRI as an independent screening method for women with dense breasts. The results suggest that in women undergoing abbreviated breast MRI, the contribution of mammography or DBT is limited; in this cohort, none of the invasive cancers and only 1 high-grade DCIS were detected by DBT alone. 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 abbreviated breast MRI 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 abbreviated breast MRI protocol and the contrast agent used (gadobenate dimeglumine) and by providing the Society of Breast MRI interpretation algorithms. As a result, despite that 47 of the 48 participating sites did not have prior practical experience with abbreviated breast MRI, the cancer detection rate was similar to levels reported by skilled MRI practices on full-protocol MRI,[10-13,30-33] and the PPV of abbreviated breast MRI did not differ significantly from that of DBT. Still, at 19.6%, the PPV associated with abbreviated breast MRI 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-risk vs 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 abbreviated breast MRI 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 the PPV of abbreviated breast MRI will further increase in subsequent screening rounds, ie, with availability of prior abbreviated breast MRI studies and with increasing reader expertise.

Abbreviated breast MRI was well tolerated. Protocol adherence was high and accrual was completed a year ahead of schedule. Data on participant acceptability of abbreviated breast MRI will be reported separately.

Abbreviated breast MRI takes less than 10 minutes of examination time; it requires intravenous 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 or specific radiologist training beyond the level required by the American College of Radiology's breast MRI accreditation. Currently, abbreviated breast MRI is not reimbursable for women at average risk, similar to ultrasound or other imaging methods considered to be supplemental or alternative screening methods for women with dense breasts. 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 under way to better understand this phenomenon. With macrocyclic gadolinium-based contrast agents, gadolinium deposition is not observed; temporary retention of very small (nanomolar) amounts of the injected dose does occur but is subsequently excreted without dechelation.[39,40]

Limitations

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

Second, the cost-effectiveness of abbreviated breast MRI relative to DBT was not evaluated. Because 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 abbreviated breast MRI. Third, although abbreviated breast MRI 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 abbreviated breast MRI may be limited until more MRI units are added. Fourth, because the eligibility criteria required a prior mammogram to assess breast density, the study compared an incidence DBT screen to a prevalence abbreviated breast MRI screen. Fifth, the study found that abbreviated breast MRI 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 abbreviated breast MRI and standard MRI screening for women with average risk[15,21]; all of these prior studies compared abbreviated breast MRI 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 abbreviated breast MRI and DBT.[10,12,14,15,21,32,33]

Conclusions

Among women with dense breasts undergoing screening, abbreviated breast MRI, 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.

REFERENCES

1. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356(3):227-236. doi:10.1056/NEJMoa062790

2. Kerlikowske K, Cook AJ, Buist DS, et al. Breast cancer risk by breast density, menopause, and postmenopausal hormone therapy use. *J Clin Oncol*. 2010;28(24):3830-3837. doi:10.1200/JCO.2009.26.4770

3. Holm J, Humphreys K, Li J, et al. Risk factors and tumor characteristics of interval cancers by mammographic density. *J Clin Oncol*. 2015;33(9):1030-1037. doi:10.1200/JCO.2014.58.9986

4. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst*. 2014;106(10):dju255. doi:10.1093/jnci/dju255

5. Ohuchi N, Suzuki A, Sobue T, et al; J-START Investigator Groups. Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. *Lancet*. 2016;387(10016):341-348. doi:10.1016/S0140-6736(15)00774-6

6. Berg WA, Blume JD, Cormack JB, et al; ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer.

JAMA. 2008;299(18):2151-2163. doi:10.1001/jama. 299.18.2151

7. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med*. 2015; 162(3):157-166. doi:10.7326/M14-0692

8. Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. *JAMA*. 2014;311(24):2499-2507. doi:10.1001/jama.2014. 6095

9. Zackrisson S, Lång K, Rosso A, et al. One-view breast tomosynthesis versus two-view mammography in the Malmö Breast Tomosynthesis Screening Trial (MBTST): a prospective, population-based, diagnostic accuracy study. *Lancet Oncol*. 2018;19(11):1493-1503. doi:10.1016/ S1470-2045(18)30521-7

10. Warner E, Plewes DB, Hill KA, et al. Surveillance of *BRCA1* and *BRCA2* mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA*. 2004;292(11):1317-1325. doi:10.1001/jama.292. 11.1317

11. Kriege M, Brekelmans CT, Boetes C, et al; Magnetic Resonance Imaging Screening Study Group. Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N Engl J Med*. 2004;351(5): 427-437. doi:10.1056/NEJMoa031759

12. Kuhl C, Weigel S, Schrading S, et al. Prospective multicenter cohort study to refine management recommendations for women at elevated familial risk of breast cancer: the EVA trial. *J Clin Oncol*. 2010;28(9):1450-1457. doi:10.1200/JCO.2009.23. 0839

13. Berg WA, Zhang Z, Lehrer D, et al; ACRIN 6666 Investigators. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA*. 2012;307(13): 1394-1404. doi:10.1001/jama.2012.388

14. Kuhl CK, Strobel K, Bieling H, Leutner C, Schild HH, Schrading S. Supplemental breast MR imaging screening of women with average risk of breast cancer. *Radiology*. 2017;283(2):361-370. doi:10. 1148/radiol.2016161444

15. Kuhl CK, Schrading S, Strobel K, Schild HH, Hilgers RD, Bieling HB. Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection-a novel approach to breast cancer screening with MRI. *J Clin Oncol*. 2014;32(22):2304-2310. doi:10.1200/JCO.2013.52. 5386

16. Kuhl CK. Abbreviated magnetic resonance imaging (MRI) for breast cancer screening: rationale, concept, and transfer to clinical practice.

Annu Rev Med. 2019;70:501-519. doi:10.1146/ annurev-med-121417-100403

17. Saslow D, Boetes C, Burke W, et al; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57(2):75-89. doi:10.3322/ canjclin.57.2.75

18. Vachon CM, Pankratz VS, Scott CG, et al. The contributions of breast density and common genetic variation to breast cancer risk. *J Natl Cancer Inst*. 2015;107(5):dju397. doi:10.1093/jnci/dju397

19. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017. doi:10.1007/978-3-319-40618-3

20. D'Orsi CJ, Sickles EA, Mendelson EB, et al. *ACR BI-RADS Atlas, Breast Imaging Reporting and Data System*. Reston, VA: American College of Radiology; 2013.

21. Schrading S, Kuhl CK. MRI screening of women at average risk of breast cancer. *J Clin Oncol*. 2013;31 (suppl 26). doi:10.1200/jco.2013.31.26_suppl.21

22. Fagerland MW, Lydersen S, Laake P. Recommended tests and confidence intervals for paired binomial proportions. *Stat Med*. 2014;33(16): 2850-2875. doi:10.1002/sim.6148

23. Leisenring W, Alonzo T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. *Biometrics*. 2000;56(2): 345-351. doi:10.1111/j.0006-341X.2000.00345.x

24. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2018: a review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2018;68(4):297-316. doi:10.3322/caac.21446

25. Njor SH, Schwartz W, Blichert-Toft M, Lynge E. Decline in breast cancer mortality: how much is attributable to screening? *J Med Screen*. 2015;22(1): 20-27. doi:10.1177/0969141314563632

26. Puliti D, Duffy SW, Miccinesi G, et al; EUROSCREEN Working Group. Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. *J Med Screen*. 2012;19 (suppl 1):42-56. doi:10.1258/jms.2012.012082

27. Kirsh VA, Chiarelli AM, Edwards SA, et al. Tumor characteristics associated with mammographic detection of breast cancer in the Ontario breast screening program. *J Natl Cancer Inst*. 2011;103(12): 942-950. doi:10.1093/jnci/djr138

28. Porter PL, El-Bastawissi AY, Mandelson MT, et al. Breast tumor characteristics as predictors of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst*. 1999;91(23):2020-2028. doi:10.1093/jnci/91.23.2020

29. Keating NL, Pace LE. New federal requirements to inform patients about breast density: will they help patients? *JAMA*. 2019;321(23):2275-2276. doi: 10.1001/jama.2019.5919

30. Sung JS, Stamler S, Brooks J, et al. Breast cancers detected at screening MR imaging and mammography in patients at high risk: method of detection reflects tumor histopathologic results. *Radiology*. 2016;280(3):716-722. doi:10.1148/radiol. 2016151419

31. Kuhl CK. Why do purely intraductal cancers enhance on breast MR images? *Radiology*. 2009; 253(2):281-283. doi:10.1148/radiol.2532091401

32. Lo G, Scaranelo AM, Aboras H, et al. Evaluation of the utility of screening mammography for high-risk women undergoing screening breast MR imaging. *Radiology*. 2017;285(1):36-43. doi:10.1148/ radiol.2017161103

33. van Zelst JCM, Mus RDM, Woldringh G, et al. Surveillance of women with the *BRCA1* or *BRCA2* mutation by using biannual automated breast US, MR imaging, and mammography. *Radiology*. 2017; 285(2):376-388. doi:10.1148/radiol.2017161218

34. M Ali RMK, England A, McEntee MF, Mercer CE, Tootell A, Hogg P. Effective lifetime radiation risk for a number of national mammography screening programmes. *Radiography (Lond)*. 2018;24(3):240-246. doi:10.1016/j.radi.2018.02.001

35. Lee JM, Ichikawa L, Valencia E, et al. Performance benchmarks for screening breast MR imaging in community practice. *Radiology*. 2017; 285(1):44-52. doi:10.1148/radiol.2017162033

36. Frankel SD, Sickles EA, Curpen BN, Sollitto RA, Ominsky SH, Galvin HB. Initial versus subsequent screening mammography: comparison of findings and their prognostic significance. *AJR Am J Roentgenol*. 1995;164(5):1107-1109. doi:10.2214/ajr. 164.5.7717214

37. Vreemann S, Gubern-Mérida A, Schlooz-Vries MS, et al. Influence of risk category and screening round on the performance of an MR imaging and mammography screening program in carriers of the *BRCA* mutation and other women at increased risk. *Radiology*. 2018;286(2):443-451. doi:10.1148/radiol. 2017170458

38. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*. 2014;270(3):834-841. doi:10.1148/radiol.13131669

39. Jost G, Frenzel T, Boyken J, Lohrke J, Nischwitz V, Pietsch H. Long-term excretion of gadolinium-based contrast agents: linear versus macrocyclic agents in an experimental rat model. *Radiology*. 2019;290(2):340-348. doi:10.1148/radiol. 2018180135

40. Tibussek D, Rademacher C, Caspers J, et al. Gadolinium brain deposition after macrocyclic gadolinium administration: a pediatric case-control study. *Radiology*. 2017;285(1):223-230. doi:10.1148/ radiol.2017161151