Radiology

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Supplemental Breast Cancer Screening in Women with Dense Breasts and Negative Mammography: A Systematic Review and Meta-Analysis

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

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Background: The best supplemental breast cancer screening modality in women at average risk or intermediate risk for breast cancer with dense breast and negative mammogram remains to be determined.

Purpose: To conduct systematic review and meta-analysis comparing clinical outcomes of the most common available supplemental screening modalities in women at average risk or intermediate risk for breast cancer in patients with dense breasts and mammography with negative findings.

Materials and Methods: A comprehensive search was conducted until March 12, 2020, in Medline, Epub Ahead of Print and In-Process and Other Non-Indexed Citations; Embase Classic and Embase; Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews, for Randomized Controlled Trials and Prospective Observational Studies. Incremental cancer detection rate (CDR); positive predictive value of recall (PPV1); positive predictive value of biopsies performed (PPV3); and interval CDRs of supplemental imaging modalities, digital breast tomosynthesis, handheld US, automated breast US, and MRI in non–high-risk patients with dense breasts and mammography negative for cancer were reviewed. Data metrics and risk of bias were assessed. Random-effects meta-analysis and two-sided metaregression analyses comparing each imaging modality metrics were performed (PROSPERO; CRD42018080402).

Results: Twenty-two studies reporting 261 233 screened patients were included. Of 132 166 screened patients with dense breast and mammography negative for cancer who met inclusion criteria, a total of 541 cancers missed at mammography were detected with these supplemental modalities. Metaregression models showed that MRI was superior to other supplemental modalities in CDR (incremental CDR, 1.52 per 1000 screenings; 95% CI: 0.74, 2.33; $P < .001$), including invasive CDR (invasive CDR, 1.31 per 1000 screenings; 95% CI: 0.57, 2.06; $P < .001$), and in situ disease (rate of ductal carcinoma in situ, 1.91 per 1000 screenings; 95% CI: 0.10, 3.72; $P < .04$). No differences in PPV1 and PPV3 were identified. The limited number of studies prevented assessment of interval cancer metrics. Excluding MRI, no statistically significant difference in any metrics were identified among the remaining imaging modalities.

Conclusion: The pooled data showed that MRI was the best supplemental imaging modality in women at average risk or intermediate risk for breast cancer with dense breasts and mammography negative for cancer.

Supplemental material is available for this article.

Mammography is the main imaging modality for breast cancer detection (1–7) and is associated with reduction in breast cancer–specific mortality (1). The introduction of digital mammography was associated with 14% greater cancer detection rates (CDRs) (8). However, whereas screening mammography helps detect up to 98% of carcinomas in fatty breasts, the sensitivity declines to 30%–48% in extremely dense breasts (1,8–10).

Data from the United States suggest that 47% of the screening population has dense breasts (7,11). In addition, researchers have proven that breast density is an independent risk factor for the development of breast cancer (12–14), with an estimated four- to sixfold increase in lifetime breast cancer risk among women with extremely dense breast tissue relative to women with entirely fatty breast tissue (13). Therefore, women with dense breasts are at higher risk of developing breast cancer and at greater risk of the cancer not being detected at mammography. The latter is due to the masking effect of overlapping dense fibroglandular tissue, which is radiopaque, like most breast cancers (9,10,14). Therefore, to overcome the limitation of mammography in this subgroup of patients, supplemental imaging tests have been suggested to increase the chance of detecting a tumor before it becomes symptomatic because delayed detection is

Abbreviations

ABUS = automated whole-breast US, CDR = cancer detection rate, DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ, HHUS = handheld US, PPV = positive predictive value, PPV1 = PPV of recall, PPV3 = PPV of biopsies performed

Summary

In women at average or intermediate risk for breast cancer with dense breasts and mammography negative for cancer undergoing supplemental screening, MRI had higher detection of breast cancer compared with handheld US, automated breast US, and digital breast tomosynthesis.

Key Results

- According to polled data of 22 studies and 132 166 women at average or intermediate risk for breast cancer with dense breasts and mammography negative for cancer undergoing supplemental screening, compared with other supplemental modalities, MRI was superior in detecting breast cancer with an incremental cancer detection rate (CDR) of 1.54 cancers per 1000 screenings ($P < .001$) on metaregression analysis.
- In the absence of MRI, handheld US (incremental CDR, 0.35 per 1000 screenings; $P = .22$), automated breast US (incremental CDR, 0.26 per 1000 screenings; $P = 41$), and digital breast tomosynthesis (incremental CDR, 0.14 per 1000 screenings; $P = .22$) showed no differences in their screening performance measures.

associated with lower survival (15). The interest in applying supplemental examinations at the population level was intensified after legislative measures in the United States required women to be informed about their breast density and adjunct supplemental screening options (7,9,16,17). In this regard, the four most common supplemental modalities available are handheld breast US (HHUS), automated whole-breast US (ABUS), digital breast tomosynthesis (DBT), and breast MRI.

HHUS screening increases the detection of early invasive node-negative breast cancers in women with mammographically dense breast tissue (1,9,10,15,18–23) with an incremental CDR of 2–2.7 per 1000 screenings (24). However, it requires qualified personnel and is associated with high screening recall rates and high false-positive biopsy rates. Thereby, it can be cost prohibitive, limiting its wide implementation as a breast cancer screening modality (25–31).

ABUS showed increased sensitivity from 50% to 81% (25) with incremental CDR of 2.5 per 1000 screenings (24) and was cost-effective in asymptomatic women with dense breasts (28,29). Like HHUS, it has high recall and biopsy rates with low positive predictive values (PPVs) (30–36). Furthermore, ABUS-guided biopsy has not been developed, so HHUS is necessary for further evaluation and biopsy of findings recalled from ABUS (35).

Alternatively, DBT has shown to be a tool for addressing the mammographic masking effect in dense breasts (11,31,37–42). It can be implemented in screening either as synthetic or in so-called combination mode, also referred to as integrated three-dimensional full-field digital mammography and DBT. Both strategies have shown detection of more breast cancer than full-field digital mammography, with an incremental CDR from 2.2 to 2.5 per 1000 screenings (11,38–41,43,44).

MRI has been widely established as a screening modality adjuvant to mammography in high-risk populations (45–47), but also showed an impact in average-risk women (incremental CDR, 15.5 per 1000 screenings) (48), especially in those with dense breasts (49). Reservations against its widespread use for screening include its high cost, limited availability, and high false-positive rate. However, in a recent trial (50), the incremental CDR of MRI was 5.8 per 1000 screenings accompanied by a strong reduction in the number of false-positive results. Abbreviated MRI demonstrated a similar sensitivity and specificity compared with a full breast MRI protocol and is being investigated (51–54) to provide a more cost-effective modality.

Despite increasing evidence of the potential benefit of these modalities in supplemental screening, there are limited clinical guidelines that explicitly recommend using any of these supplemental breast cancer screening modalities in women with dense breasts and mammography negative for cancer (55–60). Therefore, our objective was to conduct a systematic review and meta-analysis comparing the screening performance measures of the most common supplemental screening modalities available in non–high-risk patients with dense breasts and a negative mammogram.

Materials and Methods

Our protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018080402). Our meta-analysis was performed by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020, or PRISMA 2020, updated guidelines (61) and the PICO model for clinical questions (population: non–high-risk for breast cancer screening population with heterogeneously or extremely dense breasts; intervention: adjuvant modality for mammography-negative patients, HHUS, ABUS, breast MRI, and DBT; comparison: comparative group, screening mammography; and outcome measures: PPV of recall [PPV1] and of biopsies performed [PPV3], incremental CDR including invasive CDR and ductal carcinoma in situ [DCIS] detection rate per 1000 screenings, and interval cancer rates).

Literature Search

A comprehensive search was conducted in consultation with the research team by one of the study investigators, who is an information specialist (R.F., with 14 years of experience), from each database's inception until March 2020 in Medline, Epub Ahead of Print and In-Process and Other Non-Indexed Citations; Embase Classic and Embase; Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews, all from the OvidSP platform. Where available, both controlled vocabulary terms and text words were used. There was no age limit. Whereas there was no language restriction during the comprehensive literature search, 276 studies that were not written in English did not meet the eligibility criteria (Table S1, Medline search strategy).

Eligibility Criteria

All randomized clinical trials and prospective observational studies that evaluated supplemental screening modalities in patients with dense breasts, American College of Radiology densities C (heterogeneously dense) and D (extremely dense) according to

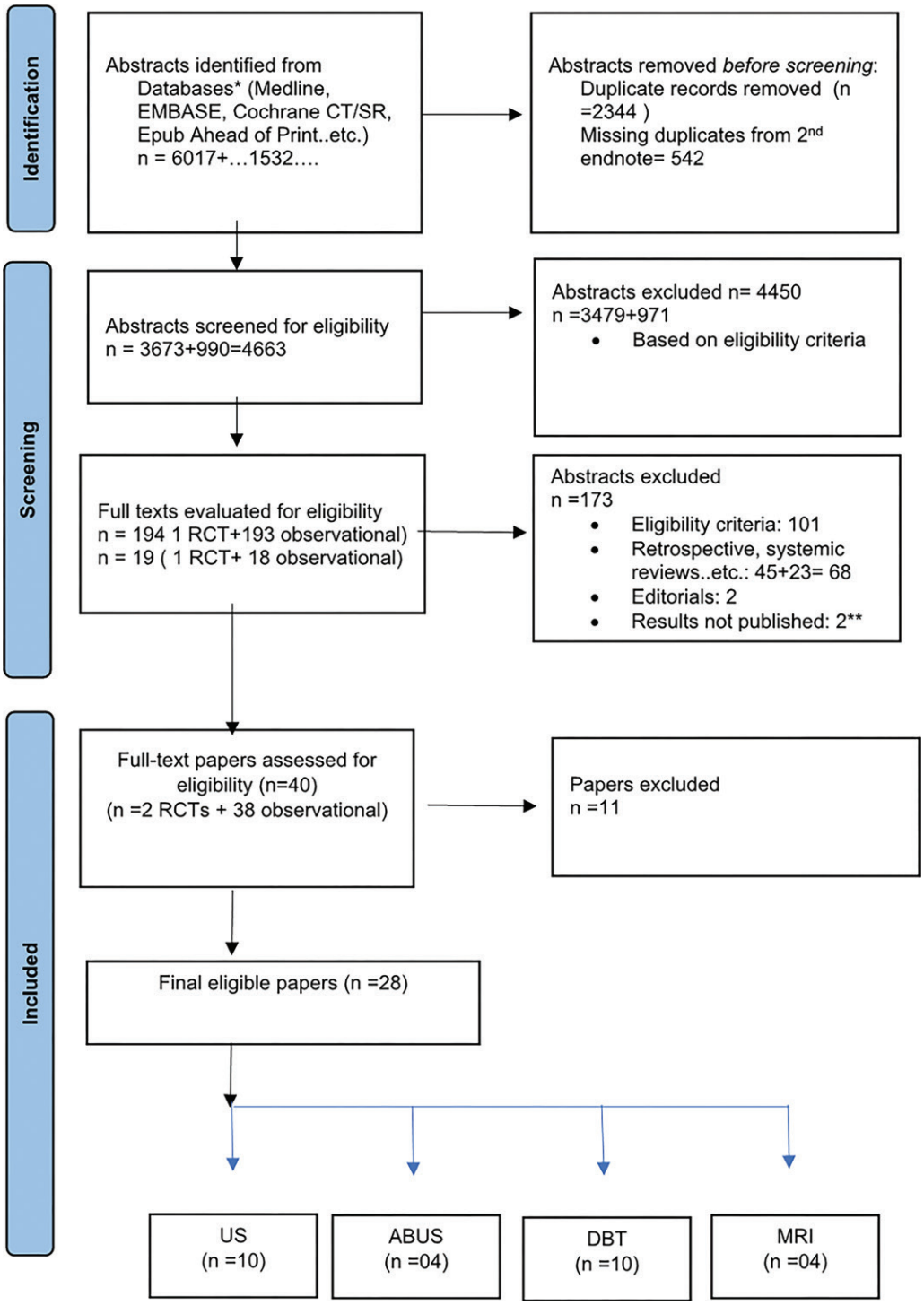

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. ABUS = automated whole-breast US, DBT = digital breast tomosynthesis, RCT = randomized controlled trial.

the lexicon from the Breast Imaging Reporting and Data System (62), and negative mammogram, in non–high-risk women despite age, were included. Categories of the assessed women at average risk or intermediate risk for breast cancer are based on prior publications (55,63). The inclusion criteria were further defined as the following: *(a)* comparative study design, where either similar population underwent at least two adjunct imaging examinations or patients were randomized to the imaging tests being compared; *(b)* the reference standard used was histopathologic analysis; *(c)* the results reported sufficient data to calculate the incremental CDR (Fig 1).

Exclusion criteria were defined as the following: retrospective studies, patients with scattered breast density (American College of Radiology density B) or entirely fatty breast (American College of Radiology density A), studies using a single-arm design assessing only one imaging modality, high-risk patients (details

Table 1: Summary of Number of Screening Patients, Number of Eligible Patients with Dense Breast and Negative Mammogram, and Patient's Characteristics in the Included Studies by Test Modality

Imaging Modality	No. of Screening Patients	No. of Patients with Dense Breast and Negative Mammogram	Patient Age Range (y)	Patient Sex
HHUS	140 613	71 921	25–96	Female
ABUS	28 899	22 540	24–94	Female
DBT	67 587	30 684	40–79	Female
MRI	43 577	7 021	30–75	Female

Note.—ABUS = automated whole-breast US, DBT = digital breast tomosynthesis, HHUS = handheld US.

regarding who met high-risk criteria are in Appendix S1) (63), symptomatic patients, pregnant and breast-feeding patients, and male patients.

Study Selection

A three-phased streamlined approach was conducted.

In phase I, results of the literature search were imported into a reference manager software (EndNote ×9.1; Clarivate Analytics) for an independent title and abstract review completed by multiple investigators (E.A., H.H., and V.F., with 6, 15, and 20 years of experience in breast imaging, respectively) to evaluate the potential relevant full-text articles and determine whether studies met the inclusion and exclusion criteria.

Phase II consisted of retrieving all full texts of potentially eligible articles and further assessment for inclusion by all investigators independently. Discrepancies were resolved by discussion and reaching consensus among investigators.

In phase III, the reviewers conducted subgroup analyses for each supplemental modality in relation to the screening performance measures of mammography. They independently assessed the risk of bias using Quality Assessment of Diagnostic Accuracy Studies–2, known as QUADAS-2, tool (64) in the included studies. Disagreements over the abstract and/or full-text review and the risk of bias were resolved through additional consensus discussions.

Data Extraction

All investigators performed data extraction independently (E.A., H.H., and V.F.). Data extraction in a batch of the first five studies was performed in conjunction to improve familiarity and consistency among the investigators. The following data were extracted into a spreadsheet program (Microsoft Excel 2016; Microsoft) using predefined forms: first author, study title, publication year, country of the corresponding author, journal of publication, study design, eligibility, number of patients (subgroups; dense/dense with a negative mammogram), screening frequency, mammographic density, patient age, screening modality (mammography, DBT, HHUS, ABUS, or MRI), adjunct modality results, incremental CDR, PPV (including PPV1 and PPV3), interval CDR, and tumor characteristics (size, invasive or in situ disease, and lymph node involvement).

Quality Assessment

Independent quality assessment of all included studies was performed using the revised tool for QUADAS-2 (64). Multiple investigators (E.A., H.H., and F.V.) assessed all articles independently for the following criteria: patient selection, index test, reference standard, flow, and timing (64,65). The following criteria were defined considered high risk of bias: random or consecutive patient selection was not used (patient selection); radiologists were not blinded to previous clinical and/or imaging data (index test 1); the method by which patients are assigned to a specific imaging test may have introduced bias, for example, if the patients were allowed to choose (index test 2); the reference standard, histopathologic analysis, was not offered equally to all patients who needed a biopsy to exclude underlying cancer (reference standard); and flow and timing for at least two index tests were performed more than 3 months apart (flow and timing). Discrepancies were resolved by consensus.

Outcomes

The primary outcome of our meta-analysis was the incremental CDR, including invasive CDR and DCIS rate of each supplemental modality. The incremental CDR (62) was defined as the number of cases of cancer detected only at the adjunct modality (not at mammography) divided by the total number of screening examinations performed, reported as a rate per 1000 screenings. In addition, secondary outcomes were included in the analysis: PPV (PPV1 and PPV3) and interval cancers. The invasive CDR and DCIS detection rates were defined as the number of detected cases of invasive cancer and in situ disease divided by the total number of screening examinations performed, reported as a rate per 1000 screenings, respectively. The PPV was defined as the total number of cases of cancer detected divided by the total number of recalled screening examinations based on abnormal findings at screening examination (PPV1) and based on biopsy results (PPV3).

Statistical Analysis

The data were handled by one of the coauthors (S. Keshavarzi) based on grouping and comparing the diagnostic performance of each supplemental screening modality. Forest plots were generated to demonstrate the data for each specific study. Results were presented separately in each subgroup and were defined by different modalities (HHUS, ABUS, DBT, and MRI). In addition, we provided the number of cancers, screens, and pooled estimates with 95% CIs for both the proportion of screen-detected cancers in all women with a recommendation other than routine screening (PPV1) and the proportion of screen-detected cancers in women with a performed biopsy (PPV3). For the incremental CDR, invasive CDR, and DCIS, rates per 1000 were used to

estimate the pool detection rates and the 95% CI. Prespecified metaregression analysis was performed by comparing the screening performance measures of different imaging modalities. To assess the heterogeneity among the studies, the I^2 value was calculated. Values greater than 50% were considered at risk for substantial variability. The results of both fixed and random effects models were provided in the forest plots. However, because the studies were from different populations, random effects model results were used to estimate the pooled rates to allow for heterogeneity between studies and within-study sampling variability. All statistical analyses were performed using software (R version 3.6.3; R Foundation for Statistical Computing) by meta and metasens packages. A P value less than .05 was considered to indicate statistical significance.

Results

Study Demographics and Risk of Bias

The meta-analysis PRISMA diagram is shown in Figure 1. An initial 7549 studies underwent title and abstract screening. Phase I screening resulted in 213 potentially eligible articles retrieved for full-text review. Further exclusion of retrospective studies and editorial articles resulted in 40 eligible articles. Finally, we included 22 articles (4,10,19,20,25,28,29,32,34,36,38,39, 44,48,49,52,66–71) encompassing 261 233 screened patients, 120 081 of whom had dense breasts and a negative mammogram. However, Chen et al (52) assessed abbreviated MRI protocol and full-diagnostic MRI protocol in the same article, and Lång et al (38,39) assessed different performance metrics of the same population in two distinct articles. Kim et al (10) and Tagliafico et al (32,70) assessed HHUS and DBT in the same population, and Bernardi et al (44) assessed digital mammography with DBT (combination mode) and synthetic mammography in the same article. Therefore, considering the sum of screened patients with different imaging modalities, 132 166 women with dense breasts and mammography negative for cancer met the inclusion criteria. Ten articles (4,10,19,20,25,32,67–70) reported on HHUS (71 921 patients with dense breasts; age range, 25–96 years), four articles (28,29,34,36) reported on ABUS (22 540 patients with dense breasts; age range, 24–94 years), three articles (48,49,52) reported on MRI (7021 patients with dense breasts; age range, 30–75 years), eight articles (9,32,38,39,44,66,70,71) reported on DBT (30 684 patients with dense breasts; age range, 40–79 years). Table 1 summarizes the number of screening patients, number of eligible patients with dense breasts and mammography negative for cancer, and patient characteristics in the included studies by test modality. Table S2 provides a summary of the included studies.

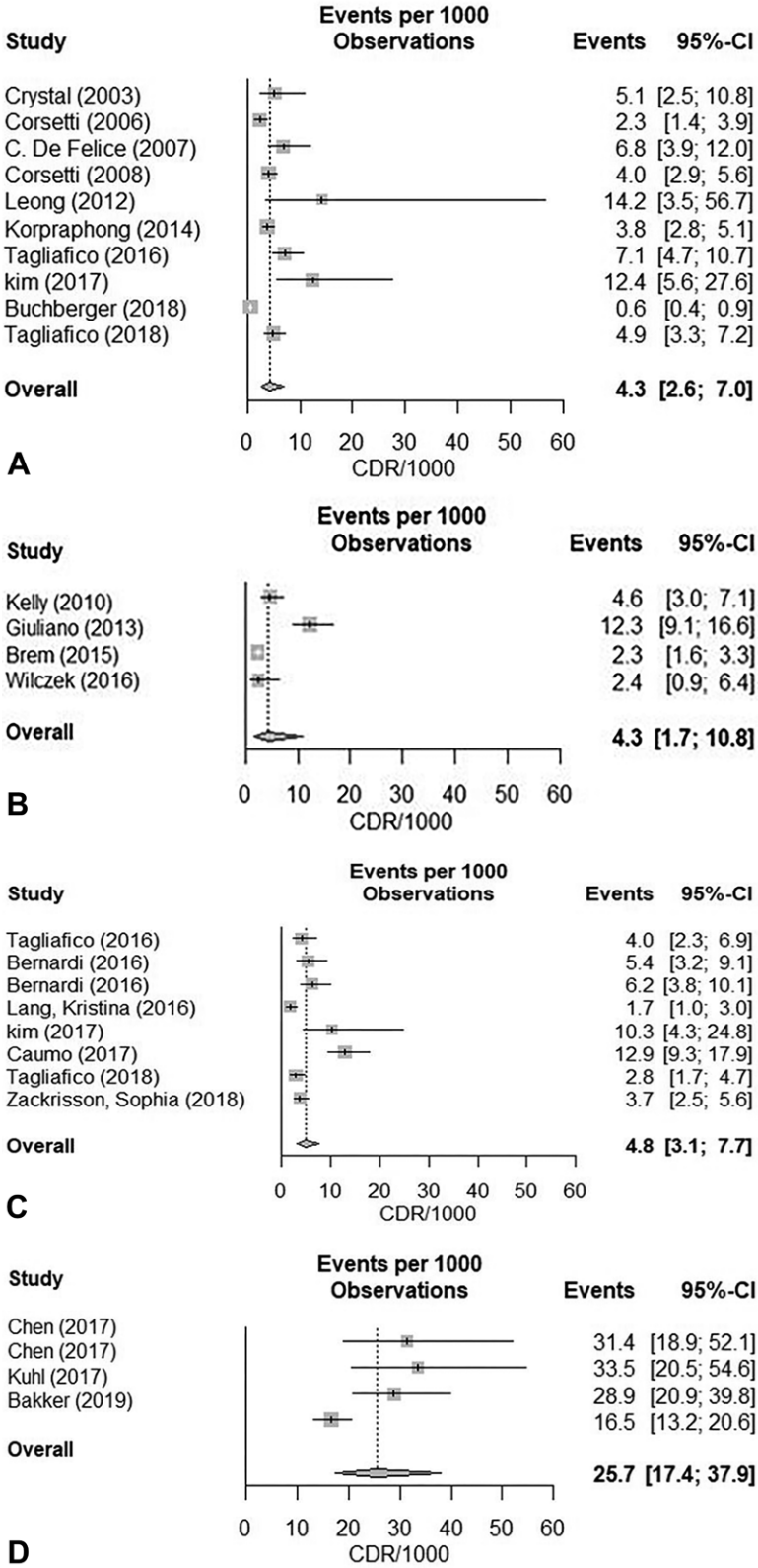

Figure 2: Forest plots show the incremental cancer detection rate (CDR) per 1000 screenings per modality. **(A)** Studies with handheld US. **(B)** Studies with automated whole-breast US. **(C)** Studies with digital breast tomosynthesis. **(D)** Studies with MRI.

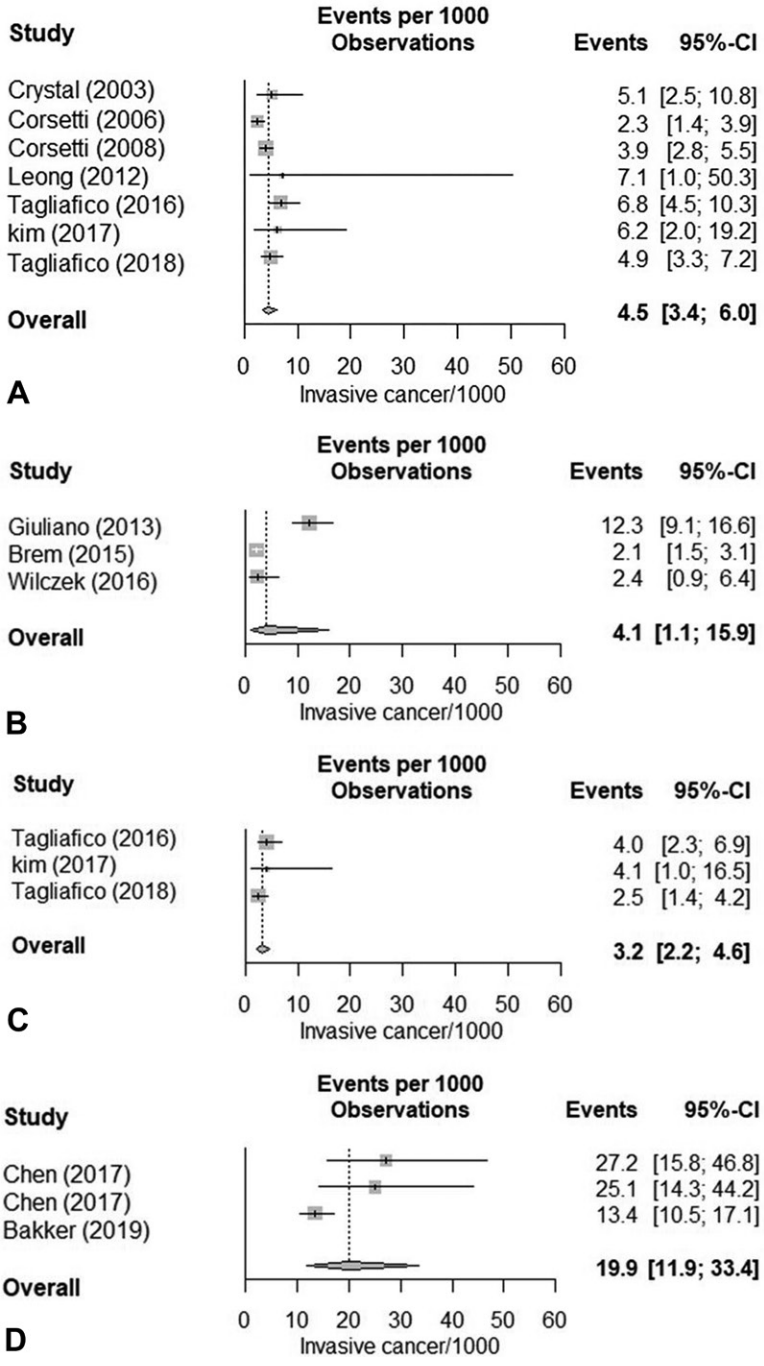

Figure 3: Forest plots show invasive cancer detection rate per 1000 screenings per modality. **(A)** Studies with handheld US. **(B)** Studies with automated whole-breast US. **(C)** Studies with digital breast tomosynthesis. **(D)** Studies with MRI.

performed more than 3 months apart). Table S3 summarizes the risk of bias.

Data Synthesis and Pooling

Of 132 166 screened patients with dense breasts and mammography negative for cancer who met the inclusion criteria, 541 cancers missed at mammography were detected by using supplemental modalities. Forest plots and pooled estimates of the mean incremental CDR, invasive CDR, PPV1, and PPV3 are shown in Figures 2–5. Forest plots and pooled estimates of interval cancer and DCIS are in Figures S1 and S2. The forest plots showed a higher MRI incremental CDR compared with other supplemental modalities. The incremental CDR of MRI is 25.7 (95% CI: 17.4, 37.9); for HHUS, 4.3 (95% CI: 2.6, 7.0); ABUS, 4.3 (95% CI: 1.7, 10.8); and DBT, 4.8 (95% CI: 3.1, 7.7). The completed results are summarized in Table 2.

Not all studies documented the tumor stage of the additional invasive cancers detected at each modality. The smallest tumor size with negative node involvement was depicted at MRI (mean size, 9.5 mm) in the study by Bakker et al (49), followed by HHUS (mean size, 11.83 mm) (4,10,19,32,67,70), DBT (mean size, 13.0 mm) (10,32,70), and ABUS (mean size, 16.3 mm) (28,29,36).

I^2, P value, and t^2 are presented, and I^2 values greater than 50% were considered at risk for substantial variability (65). Only MRI was associated with a low risk of heterogeneity for incremental CDR (I^2 = 31%), DCIS (I^2 = 14%), and PPV3 (I^2 = 34%). DBT, HHUS, and MRI were associated with a low risk for substantial heterogeneity for invasive CDR (I^2 = 15%, I^2 = 29%, and I^2 = 36%, respectively). Otherwise, all modalities and all parameters were associated with statistically significant heterogeneity. The heterogeneity index using the I^2 statistic is quantitatively shown in Table S4.

Table 3 shows the metaregression models and P values corresponding to the two-sided metaregression analyses comparing each imaging modality statistically for incremental CDR, invasive CDR, DCIS, PPV1, and PPV3, using mammography as a reference. Metaregression models showed that MRI was statistically superior to other supplemental modalities with MRI incremental CDR per 1000 screenings (1.54; 95% CI: 0.74, 2.33; P < .001) versus HHUS (−0.35; 95% CI: −0.77, 0.08; P = .11), ABUS (−0.26; 95% CI: −1.07, 0.56; P = .53), and DBT (−0.14; 95% CI: −0.58, 0.29; P = .51). We found no evidence of differences in PPV1 and PPV3. A limited number of studies prevented assessing interval cancer metrics. Moreover, in an attempt to provide another supplemental modality as an alternative to MRI, when excluding MRI, no evidence of a difference in screening performance measures was identified among the remaining imaging

Of 8061 participants invited for MRI, Bakker et al (49) considered 103 patients (1%) ineligible for MRI without further clarification, which was not considered a potential risk of bias because of the small number of participants excluded. Nevertheless, a potential risk of bias was found in all other studies. The main sources contributing to a high or unclear risk of bias were related to patient selection (from nonrandomization) or the index test (radiologists unblinded to previous imaging or clinical data), and/or flow and timing (eg, at least two index tests were

modalities (HHUS, −0.35 [95% CI: −0.78, 0.09; P = .12]; ABUS, −0.26 [95% CI: −1.09, 0.57; P = .54]; DBT, −0.14 [95% CI: −0.58, 0.29; P = .52]; Table 4). The negative CI corroborates the nonstatistical significance of HHUS, ABUS, and DBT compared with MRI and when MRI is excluded.

Discussion

The best supplemental breast cancer screening modality in non–high-risk patients with dense breasts and mammography negative for cancer remains to be determined. Our results showed that MRI was statistically superior to other supplemental modalities with incremental cancer detection rate per 1000 screenings (1.54; 95% CI: 0.74, 2.33; P < .001) versus handheld US (−0.35; 95% CI: −0.7, 0.08; P = .11), automated whole-breast US (−0.26; 95% CI: −1.07, 0.56; P = .53), and digital breast tomosynthesis (−0.14; 95% CI: −0.58, 0.29; P = .51). No differences in positive predictive value (PPV) of recall or PPV of biopsies performed were identified. The limited number of studies prevented assessing interval cancer metrics. Excluding MRI, no difference in any metrics was identified among the remaining imaging modalities.

Our results confirm the expected higher CDR of breast MRI as an adjunct breast screening modality in women with dense breasts and mammography negative for cancer, which has been widely documented in the high-risk population (72–82). The results of our study also comply with previously published studies that demonstrated the benefit of MRI in detecting breast cancer in a population at intermediate risk, including those with a personal history of breast cancer (83). It is essential to emphasize the demonstrated superiority of MRI in depicting the smallest invasive disease (invasive CDR, 1.31; 95% CI: 0.57, 2.06; P ≤ .001) and in detecting DCIS (1.91; 95% CI: 0.10, 3.72; P = .04), which according to previous studies (84,85) may impact long-term survival.

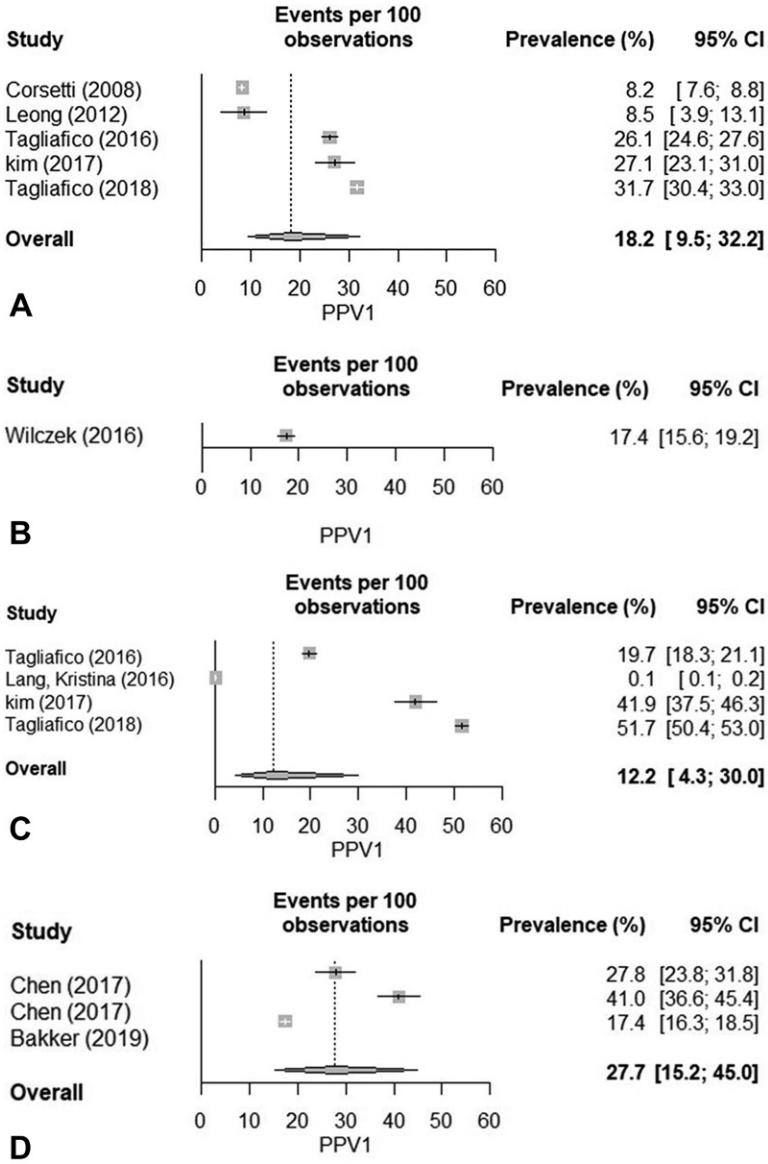

Figure 4: Forest plots show positive predictive value of recall (PPV1) per modality. **(A)** Studies with handheld US. **(B)** Studies with automated whole-breast US. **(C)** Studies with digital breast tomosynthesis. **(D)** Studies with MRI.

As shown on the incremental CDR forest plot (Fig 2), the number of studies of HHUS that met the inclusion criteria exceeded those of MRI and ABUS, which is understandable because HHUS is widely available due to its low cost and lack of radiation (86). However, even in a few studies, the effect of MRI in incremental CDR was large enough for a statistically significant difference, with an MRI incremental CDR of 25.7 (95% CI: 17.4, 37.9). For ABUS, the point estimates were smaller, indicating that the statistically nonsignificant results were caused by smaller effect sizes and not by lack of statistical power, with ABUS incremental CDR of 4.3 (95% CI: 1.7, 10.8).

Although metaregression analysis shows that there is no statistically significant difference in the MRI PPV1 or PPV3, which can be attributed to fewer MRI studies included in the analysis, MRI showed generally higher PPVs compared with HHUS and ABUS (PPV1 of MRI vs HHUS vs ABUS, 27.7 [95% CI: 15.2, 45.0] vs 18.2 [95% CI: 9.5, 32.2] vs 17.4 [95% CI: 15.6, 19.2], respectively; and PPV3 of MRI vs HHUS vs ABUS, 34.3 [95% CI: 24.8, 45.1] vs 9.1 [95% CI: 3.3, 22.5] vs 22.8 [95% CI: 1.6, 84.7], respectively). This may represent another important benefit of MRI in this setting because higher false-positive rates increase patient anxiety and the cost burden on the health care system from additional imaging workup, short-interval follow-up, or biopsy (87).

Worldwide availability of MRI remains limited not only from lack of sufficient scanners but also because of its high cost, which prevents accessibility to available scanners and causes a lack of fellowship-trained expertise. Although the shorter image acquisition and interpretation times of abbreviated MRI potentially represent a more cost-effective alternative in this

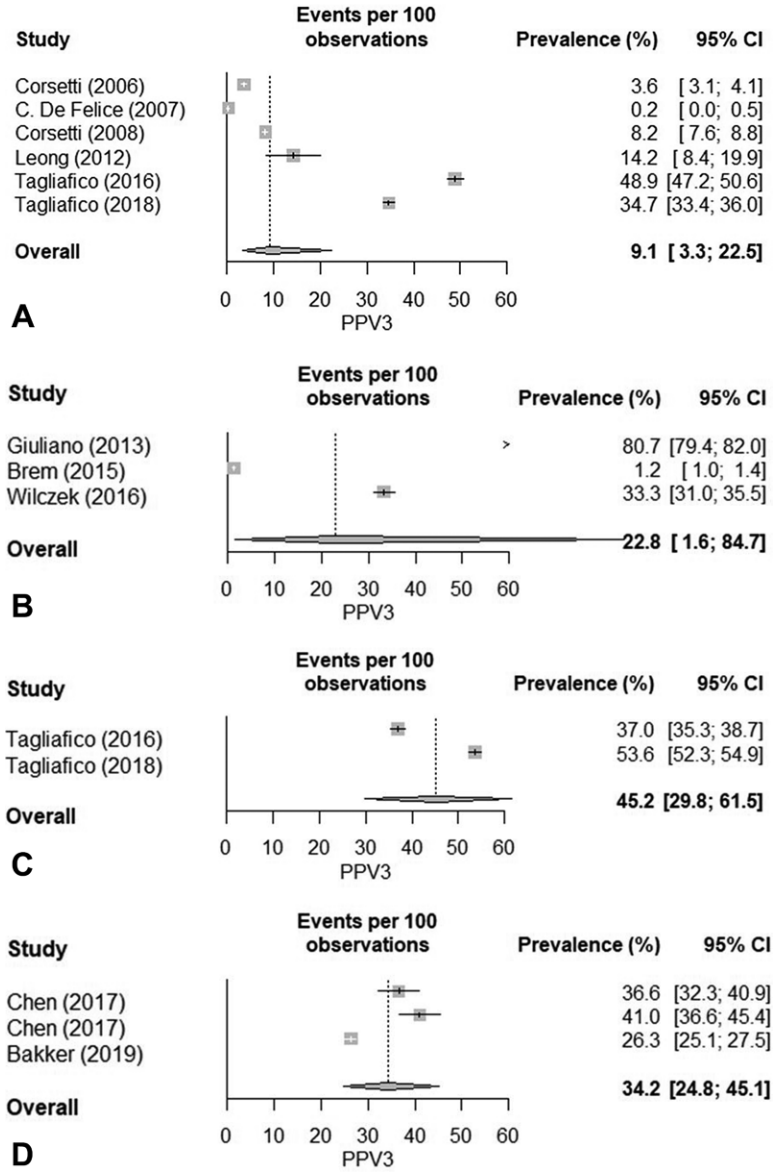

Figure 5: Forest plots show positive predictive value of biopsies performed (PPV3) per modality. **(A)** Studies with handheld US. **(B)** Studies with automated whole-breast US. **(C)** Studies with digital breast tomosynthesis. **(D)** Studies with MRI.

scenario (54), the need for contrast agent injection and the known gadolinium accumulation in the brain with both the standard and abbreviated MRI protocols have uncertain clinical significance (88). None of the other potential supplemental modalities showed similar performance to MRI in the incremental rate of cancer detection and, therefore, understanding the pros and cons, MRI is considered the best supplemental imaging modality.

Point estimate I^2 showed higher variability among the studies, which may be attributed to the variable selection of patients between studies (eg, differences in inclusion criteria, such as differences in patient age), as shown in Table S3. This could be attributed to different design methods (we included a combination of randomized controlled trials and observational longitudinal prospective studies) and publication bias, potentially impacting the estimated effect across the studies (89). We used the random effects model to enable summarization of the results and to draw conclusions despite the heterogeneity. The random effects model assumes that the estimated effect varies around some overall average estimated effect, whereas the fixed effects model assumes that each study used the same fixed common estimated effect (90). In addition, based on the incremental detection rate point estimates and CIs (Table 3), bias in the individual studies had a minimal impact on the results. Despite the variability within modalities, the large observed effects across all MRI studies allowed us to conclude that MRI has superior performance to the other modalities. However, the high heterogeneity makes it difficult to draw conclusions about the relative effectiveness of HHUS, ABUS, and DBT.

Our study had limitations. First, retrospective studies were excluded from the analysis to reduce the potential confounders associated with selection bias. This exclusion limited the number of studies and, therefore, statistical power. Second, most of the included studies assessed breast density by subjective visual assessment. Therefore, some patients may have been inaccurately assessed as having dense breasts. Third, there is evidence that DBT performance is limited in those with extremely dense breasts (density D) (9,36,65). As such, the combination of heterogeneously dense breasts (density C) and extremely dense breasts (density D) could have influenced the result. Also, some patients may have been misinterpreted as an average or intermediate risk because of a lack of perception of combined factors that could lead to high-risk profile. We expect that artificial intelligence may surpass these current limitations by allowing automatic assessment of breast density and risk stratification. Finally, our meta-analysis only included studies that were published until March 2020. Therefore, an update of these results is expected as more evidence emerges on the usefulness of the current modalities discussed or even other modalities, such as vascular imaging modalities (eg, contrast mammography, molecular imaging studies), which can merge morphologic and functional imaging, providing information about anatomic changes and metabolic activity of breast tissue, regardless of breast density (91–94).

In conclusion, in patients with dense breasts and mammography negative for cancer undergoing supplemental breast cancer screening, MRI showed superior detection of breast cancer compared with handheld US, automated whole-breast US, and digital breast tomosynthesis. It is too early to advocate worldwide for the implementation of

Table 2: Pooled Estimates of the Mean Screening Performance Measures for Each Supplemental Imaging Modality

Parameter	HHUS	ABUS	DBT	MRI
Incremental CDR per 1000 screenings	4.3 (2.6, 7.0)	4.3 (1.7, 10.8)	4.8 (3.1, 7.7)	25.7 (17.4, 37.9)
Invasive CDR per 1000 screenings	4.5 (3.4, 6.0)	4.1 (1.1, 15.9)	3.2 (2.2, 4.6)	19.9 (11.9, 33.4)
Interval cancer per 1000 screenings	0.6 (0.4, 0.9)	3.0 (1.2, 7.2)	NA*	0.8 (0.3, 2.2)
Incremental DCIS per 1000 screenings	0.5 (0.1, 4.5)	0.1 (0, 0.6)	1.0 (0.1, 12.6)	4.4 (2.3, 8.4)
PPV1	18.2 (9.5, 32.2)	17.4 (15.6, 19.2)	12.2 (4.3, 30.0)	27.7 (15.2, 45.0)
PPV3	9.1 (3.3, 22.5)	22.8 (1.6, 84.7)	45.2 (29.8, 61.5)	34.2 (24.8, 45.1)

Note.—Data are in 32 166 screened patients with dense breasts and a negative mammogram. A total of 541 cancers missed at mammography were detected. Data in parentheses are 95% CIs. ABUS = automated whole breast US, CDR = cancer detection rate, DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ, HHUS = handheld US, NA = not applicable, PPV1 = positive predictive value of recall, PPV3 = positive predictive value of biopsies performed.

* Due to limited number of studies (either one or no studies for that specific variable).

Table 3: Metaregression Comparing the Screening Performance Measures of Different Imaging Modalities

Performance Measure*	β Value	Standard Error	*P* Value†
PPV1			
HU	0.19 (−0.89, 1.27)	0.55	.73
ABUS	−0.22 (−3.44, 2.99)	1.64	.89
DBT	−0.42 (−1.54, 0.70)	0.57	.46
MRI	0.38 (−1.53, 2.30)	0.98	.70
PPV3			
HU	−0.63 (−1.49, 0.24)	0.44	.16
ABUS	1.23 (−0.71, 3.17)	0.99	.21
DBT	0.60 (−0.46, 1.65)	0.54	.27
MRI	0.21 (−1.39, 1.82)	0.82	.79
Incremental CDR per 1000 patients			
HU	−0.35 (−0.77, 0.08)	0.22	.11
ABUS	−0.26 (−1.07, 0.56)	0.41	.53
DBT	−0.14 (−0.58, 0.29)	0.22	.51
MRI	1.54 (0.74, 2.33)	0.40	<.001
Incremental DCIS per 1000 patients			
HU	−0.54 (−1.59, 0.52)	0.54	.32
ABUS	−1.27 (−3.78, 1.24)	1.28	.33
DBT	−0.29 (−1.52, 0.94)	0.63	.64
MRI	1.91 (0.10, 3.72)	0.92	.04
Invasive CDR per 1000 patients			
HU	−0.30 (−0.70, 0.09)	0.20	.14
ABUS	−0.24 (−1.01, 0.53)	0.39	.54
DBT	−0.22 (−0.69, 0.25)	0.24	.36
MRI	1.31 (0.57, 2.06)	0.38	<.001

Note.—For interval cancer, because the number of studies were so limited the model could not be fitted. Standard error is a measure of the uncertainty in the regression parameter due to the observed variability across studies and the sample size. ABUS = automated whole breast US, CDR = cancer detection rate, DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ, HHUS = handheld US, NA = not applicable, PPV1 = positive predictive value of recall, PPV3 = positive predictive value of biopsies performed.

* Mammography was treated as the reference group for comparison in the metaregression models.

† The *P* values correspond to the two-sided metaregression analyses comparing each imaging modality. A *P* value less than .05 was considered to indicate statistical significance.

supplemental MRI because more studies are needed to make conclusions about the relative effectiveness of the other modalities and because the effectiveness of MRI, in terms of mortality reduction and cost-effectiveness analysis, has not yet been examined; this is the next logical step to consolidate these preliminary findings.

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Table 4: Metaregression Comparing the Screening Performance Measures of Different Imaging Modalities Excluding MRI

Performance Measure*	β Value	Standard Error	*P* Value†
PPV1			
HHUS	0.19 (−0.9, 1.29)	0.56	.73
ABUS	−0.22 (−3.5, 3.05)	1.66	.89
DBT	−0.42 (−1.56, 0.72)	0.58	.47
PPV3			
HHUS	−0.63 (−1.5, 0.26)	0.45	.16
ABUS	1.23 (−0.75, 3.2)	1.01	.22
DBT	0.59 (−0.48, 1.68)	0.55	.28
Incremental CDR per 1000 screenings			
HHUS	−0.35 (−0.78, 0.09)	0.22	.12
ABUS	−0.26 (−1.09, 0.57)	0.42	.54
DBT	−0.14 (−0.58, 0.29)	0.22	.52
Incremental DCIS per 1000 screenings			
HHUS	−0.53 (−1.61, 0.54)	0.55	.33
ABUS	−1.26 (−3.82, 1.29)	1.30	.33
DBT	−0.29 (−1.54, 0.97)	0.64	.65
Invasive CDR per 1000 screenings			
HHUS	−0.30 (−0.7, 0.1)	0.20	.14
ABUS	−0.24 (−1.02, 0.54)	0.39	.55
DBT	−0.22 (−0.69, 0.26)	0.24	.37

Note.—For interval cancer, because the number of studies were so limited the model could not be fitted. Standard error is a measure of the uncertainty in the regression parameter due to the observed variability across studies and the sample size. Data in parentheses are 95% CIs. ABUS = automated whole breast US, CDR = cancer detection rate, DBT = digital breast tomosynthesis, DCIS = ductal carcinoma in situ, HHUS = handheld US, NA = not applicable, PPV1 = positive predictive value of recall, PPV3 = positive predictive value of biopsies performed.

* Mammography was treated as the reference group for comparison in the metaregression models.

† The *P* values correspond to the two-sided metaregression analyses comparing each imaging modality. A *P* value less than .05 was considered to indicate statistically significant difference.

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