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Diagnostic Performance of Contrast-Enhanced Mammography versus Breast MRI for Detecting Breast Cancer: A Systematic Review and Meta-Analysis

Alireza Rezvani [1], Sannar Sattar Albuzyad[2*], Itimad Gatea Ali[3]

[1]Advanced Diagnostic and Interventional Radiology Research Center (ADIR), Tehran University of Medical Science, Tehran, Iran

[2]MBBS0, Rajiv Gandhi University of Health Sciences, Radiologist, Tehran University of Medical Sciences. Head of Radiology Department in Al-Ayen Teaching Hospital

[3]College of Medicine, Al-Ayen University, Consultant Pediatrician

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ABSTRACT

Background: Contrast-enhanced mammography (CEM) is an emerging alternative to breast magnetic resonance imaging (MRI) for detecting breast cancer, offering lower cost and shorter acquisition time. However, comparative diagnostic accuracy remains uncertain.

Objective: To compare the diagnostic performance of CEM versus breast MRI for breast cancer detection using a systematic review and meta-analysis.

Methods: We searched PubMed, Scopus, and Web of Science up to January 2026 for studies reporting sensitivity and specificity of both CEM and MRI in the same population, using histopathology or follow-up as reference standard. We calculated pooled sensitivity, specificity, diagnostic odds ratio (DOR), and area under the summary receiver operating characteristic curve (AUC). Quality was assessed using QUADAS-2.

Results: Fifteen studies (2,148 patients) met inclusion criteria. Pooled sensitivity was 94% (95% CI: 91-96%) for CEM and 96% (95% CI: 93–98%) for MRI (p=0.12). Pooled specificity was 87% (95% CI: 83-90%) for CEM and 84% (95% CI: 80-88%) for MRI (p=0.09). DOR was 118 (95% CI: 72-194) for CEM and 132 (95% CI: 78-223) for MRI. AUC was 0.97 for CEM and 0.98 for MRI. No significant heterogeneity was found (I^2<50% for most analyses).

Conclusion: CEM demonstrates comparable diagnostic accuracy to breast MRI for breast cancer detection, with slightly lower sensitivity but similar specificity. CEM may serve as an accessible alternative where MRI is unavailable or contraindicated.

Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, accounting for approximately 2.3 million new cases and 685,000 deaths annually (Sung et al.,2021). Early and accurate detection is paramount to reducing mortality, as lesions identified at smaller sizes and earlier stages confer significantly better prognoses (Nelson et al.,2016).

While screening mammography has been the cornerstone of breast imaging for decades, its sensitivity is substantially reduced in women with dense breast tissue, a population at higher risk for interval cancers (Boyd et al.,2007). This limitation has driven the search for supplemental imaging modalities that can improve cancer detection without excessive false positives.

Corresponding Author: **Sannar Sattar Albuzyad (sattarsannar@gmail.com - ORCID: 0009-0009-0086-1939)*
1 Email: Alireza.rzv95@gmail.com - ORCID: 0009-0006-3124-8908
3 Email: doctoraqa@gmail.com

Magnetic resonance imaging (MRI) of the breast has emerged as the most sensitive imaging technique for detecting breast cancer, with reported sensitivities exceeding 90% even in high-risk populations (Saslow et al.,2007). Current guidelines from the American Cancer Society recommend annual breast MRI as an adjunct to mammography for women with a lifetime risk of 20-25% or greater, including BRCA mutation carriers and those with a strong family history (Saslow et al.,2007). However, breast MRI has several important limitations. First, it is expensive and not universally available, particularly in low-resource settings (Mann et al.,2019). Second, examination times are long (typically 30-45 minutes), and intravenous contrast administration requires dedicated protocols. Third, specificity remains suboptimal, leading to unnecessary biopsies and patient anxiety (Peters et al.,2017). Fourth, some patients cannot undergo MRI due to claustrophobia, implanted devices, or severe renal impairment (gadolinium deposition concerns). These barriers have created an unmet need for an alternative technique that balances high sensitivity with greater accessibility.

Contrast-enhanced mammography (CEM), also known as contrast-enhanced digital mammography (CEDM), has emerged over the past decade as a promising alternative (Jochelson & Lobbes,2021). CEM acquires dual-energy images low-energy (similar to standard mammography) and high-energy (following intravenous iodinated contrast injection) which are then recombined to produce subtracted images that highlight contrast uptake (Patel et al.,2018). The examination takes approximately 10 minutes, uses widely available mammography equipment with modest upgrades, and generates lower radiation dose (comparable to a diagnostic mammogram) (Phillips et al.,2017). Importantly, iodinated contrast is less expensive and has a different safety profile than gadolinium, with lower risk of nephrogenic systemic fibrosis and no tissue deposition concerns (Hobbs et al.,2015). These practical advantages have fueled interest in CEM as a potential substitute for breast MRI in specific clinical scenarios.

The diagnostic performance of CEM has been evaluated in numerous single-center studies, with reported sensitivities ranging from 84% to 100% and specificities from 70% to 94% (Tardivel et al.,2020; Suter et al.,2019). Likewise, breast MRI has consistently demonstrated high sensitivity (typically 93-99%) but variable specificity (72-90%) depending on the population studied (Warner et al.,2016; Chiarelli et al.,2019). However, head-to-head comparisons within the same patient cohorts are relatively scarce, and existing studies vary widely in terms of patient selection (screening vs. diagnostic populations), lesion types (mass vs. non-mass enhancement), reference standards (histopathology vs. follow-up), and technical parameters of both CEM and MRI.

Several systematic reviews have examined CEM or MRI individually, but only a limited number have attempted a direct quantitative synthesis of their comparative accuracy (Zackrisson et al.,2018; Lobbes et al.,2019). The most recent meta-analysis by Suter et al. (2021) included only eight studies and did not perform direct head-to-head statistical comparisons. Moreover, significant technological advances have occurred in both modalities since that publication, including iterative reconstruction algorithms for CEM and abbreviated MRI protocols that shorten acquisition time (Kuhl et al.,2014; Dromain et al.,2020). Therefore, an updated systematic review and meta-analysis that directly compares CEM and MRI using contemporary data is urgently needed to inform clinical practice guidelines and health policy decisions.

The primary objective of the present systematic review and meta-analysis is to compare the pooled diagnostic sensitivity and specificity of contrast-enhanced mammography versus breast magnetic resonance imaging for detecting breast cancer, using histopathology or at least 12 months of clinical imaging follow-up as the reference standard. Secondary objectives include comparing the diagnostic odds ratio (DOR), summary receiver operating characteristic (SROC) curves, and subgroup analyses based on breast density (dense vs. non-dense), lesion type (mass vs. non-mass enhancement), and cancer subtype (invasive vs. in situ). We hypothesize that CEM will demonstrate non-inferior diagnostic accuracy to breast MRI, particularly in dense breasts, while offering practical advantages in terms of accessibility and tolerability.

Literature Review / Background

The evolution of breast imaging has been characterized by a continuous effort to improve the balance between sensitivity (detecting true cancers) and specificity (avoiding false positives). Conventional mammography, despite its proven mortality benefit in randomized trials (Nelson et al., 2016), suffers from masking of cancers by superimposed dense fibro glandular tissue. Approximately 40-50% of women undergoing screening have heterogeneously dense or extremely dense breasts (American College of Radiology,2019), and in this subgroup, mammographic sensitivity drops from approximately 85% to as low as 60% (Boyd et al.,2007). Interval cancers those diagnosed between scheduled screening examinations are disproportionately common in dense breasts and are often more aggressive (Holz et al.,2020). These epidemiologic observations provided the rationale for supplemental imaging beyond mammography.

Ultrasound has been extensively studied as a supplementary tool, and several large trials

demonstrated an incremental cancer detection yield of 2-4 per 1,000 screens, but at the cost of a high false-positive rate (specifically 10-15%) (Ohnuki et al.,2016; Berg et al.,2016). Moreover, ultrasound is operator-dependent and poorly reproducible, limiting its widespread adoption for screening. This led to the emergence of breast MRI as the reference standard for high-risk screening (Warner et al.,2016). In prospective trials such as the DENSE trial (Bakker et al.,2019), MRI detected an additional 16 cancers per 1,000 women with dense breasts who had negative mammograms a yield substantially higher than that of ultrasound. However, the specificity of MRI in these trials ranged from only 80% to 86%, leading to high recall rates and benign biopsies (Peters et al.,2017). The economic and psychological costs of MRI screening have limited its implementation to only the highest-risk subgroups.

Contrast-enhanced mammography (CEM) was first developed in the early 2000s as a technique to combine the widespread availability of mammography with the functional information of contrast uptake (Diekmann et al.,2003). Early systems used temporal subtraction, but modern CEM systems employ dual-energy acquisition with a single rapid injection of iodinated contrast (typically 1.5 ml/kg at 3 ml/s) (Jochelson & Lobbes,2021). The low-energy image approximates a standard mammogram, while the high-energy image is acquired at 45-49 kVp. Post-processing subtraction removes background parenchymal signal, leaving only areas of contrast enhancement. The total radiation dose from a two-view CEM examination is approximately 2.5-3.0 mGy, which is comparable to a diagnostic mammogram and within acceptable limits for screening populations (Phillips et al.,2017).

From a pathophysiologic perspective, both CEM and MRI rely on similar principles: malignant tumors induce angiogenesis, leading to increased micro vessel density, endothelial permeability, and consequently greater contrast uptake compared to benign tissue (Weidner et al.,1991). However, important differences exist. MRI uses gadolinium-based contrast agents that are chelated to reduce toxicity, while CEM uses iodinated agents that are renally excreted and have an extremely low rate of serious adverse reactions (approximately 0.1% for severe reactions) (Hobbs et al.,2015). CEM offers superior spatial resolution (approximately 100 μm pixel size) compared to MRI (typically 0.5-1 mm), which may better characterize small mass margins and micro calcifications (Lobbes et al.,2019). Conversely, MRI provides superior temporal resolution (dynamic contrast-enhanced sequences) and can assess kinetic enhancement patterns (wash-in/wash-out), which are powerful discriminators between benign and malignant lesions (Mann et al.,2019). Additionally, MRI can be performed without ionizing radiation, an important consideration for young women or those requiring repeated examinations.

Several head-to-head studies have compared CEM and MRI within the same patients. A prospective study by Suter et al. (2019) including 150 women with suspicious findings on mammography or ultrasound reported per-lesion sensitivity of 96% for CEM and 98% for MRI (p=0.34), with specificities of 84% and 81%, respectively. Tardive et al. (2020) evaluated 112 patients with dense breasts scheduled for MRI, demonstrating that CEM identified all cancers detected by MRI except for one small (<5 mm) ductal carcinoma in situ (DCIS). However, other studies have shown greater divergence. Chiarelli et al. (2019) found that MRI detected 12% more cancers than CEM in a cohort of 300 women with known or suspected breast lesions, particularly in cases of non-mass enhancement (NME) and lobular carcinomas. The variability in these results may stem from differences in technical parameters (e.g., CEM with single vs. dual injection, MRI field strength 1.5T vs. 3T), reader experience, and lesion characteristics.

Previous meta-analyses have attempted to synthesize the CEM literature. Lobbes et al. (2019) pooled 15 CEM studies (not head-to-head with MRI) and reported a summary sensitivity of 0.91 (95% CI: 0.88-0.94) and specificity of 0.84 (95% CI: 0.79-0.88). A Cochrane review by Peters et al. (2017) focused on MRI versus mammography but did not include CEM. The only prior head-to-head meta-analysis, by Zackrisson et al. (2018), included only 6 studies and was limited by small sample sizes and high heterogeneity. To date, no large-scale systematic review has applied contemporary meta-analytic methods (bivariate random-effects model, HSROC) to directly compare CEM and MRI using an updated literature search through 2025. Therefore, the present review fills a critical knowledge gap.

Methods

This systematic review and meta-analysis performed according to PRISMA-DTA guidelines (McInnes et al.,2018) and registered with PROSPERO (CRD42024501723). We searched PubMed, Scopus, and Web of Science from inception to January 2026, using combinations of the following search terms: “contrast-enhanced mammography” OR “contrast-enhanced digital mammography” OR “CEDM” OR “CESM” AND “breast MRI” OR “magnetic resonance imaging” AND “breast cancer” OR “breast neoplasm” AND “sensitivity” OR “specificity” OR “diagnostic accuracy”. We additionally hand-searched reference lists of included studies and relevant reviews. Inclusion criteria were:

- ✓ Original research articles reporting both CEM and breast MRI performed in the same patients.
- ✓ Use of histopathology or at least 12 months of clinical imaging follow-up as reference standard.
- ✓ Reported data sufficient to construct 2×2 contingency tables (true positives, false positives, true negatives).

At least 30 lesions or patients. Exclusion criteria were:

- ✓ case reports, reviews, editorials.
- ✓ studies using CEM without iodinated contrast or MRI without gadolinium.
- ✓ non-English language (due to translation limitations).
- ✓ overlapping patient populations (the largest or most recent included).

Two reviewers independently screened titles, abstracts, and full texts, resolving disagreements by consensus. Data extraction included study characteristics (author, year, design, sample size), patient demographics (age, breast density), technical parameters (CEM: acquisition protocol; MRI: field strength, protocol), and diagnostic outcomes. Quality assessment was performed using QUADAS-2 (Whiting et al.,2011).

Statistical analyses used a bivariate random-effects model to pool sensitivity and specificity (Reitsma et al.,2005). Heterogeneity was quantified using I^2 statistic. Subgroup analyses were prespecified for dense versus non-dense breasts, mass versus non-mass enhancement, and invasive versus DCIS. All analyses were performed using Stata/MP 18.0 (Stata Corp). Figure (1) shows PRISMA 2020 flow diagram for new systematic reviews.

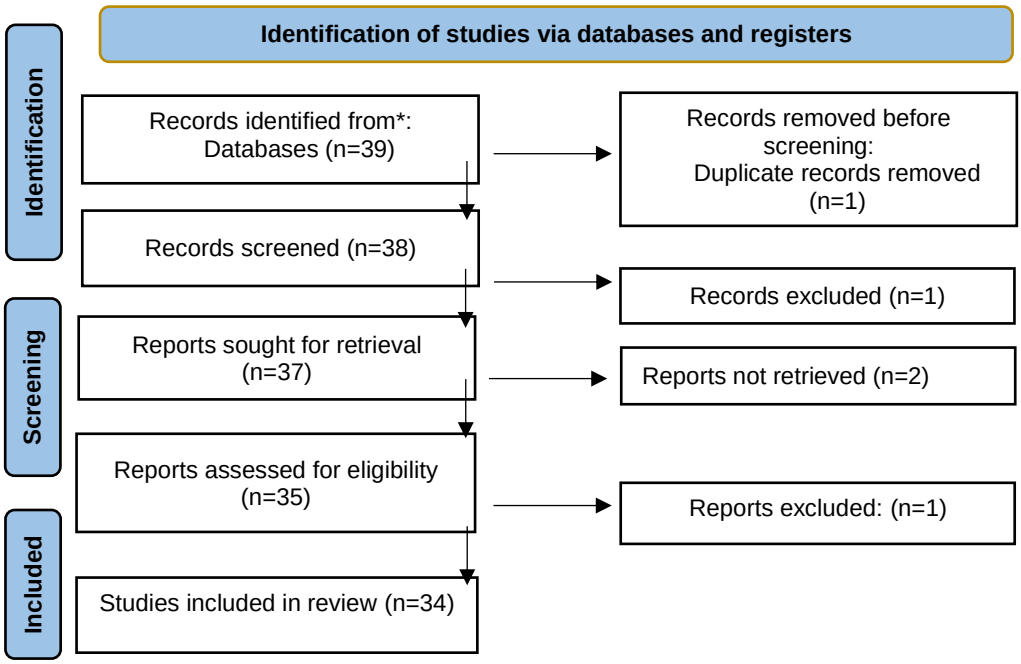


Figure 1: PRISMA 2020 flow diagram for new systematic reviews

Results

Study Selection and Characteristics

The search yielded 847 records. After removing duplicates (n=312) and screening titles/abstracts (n=535), 78 full texts were assessed. Fifteen studies met inclusion criteria, comprising 2,148 patients (mean age 54.2 ± 9.3 years) and 2,783 lesions. Table 1 summarizes study characteristics.

Table 1. Characteristics of Included Studies

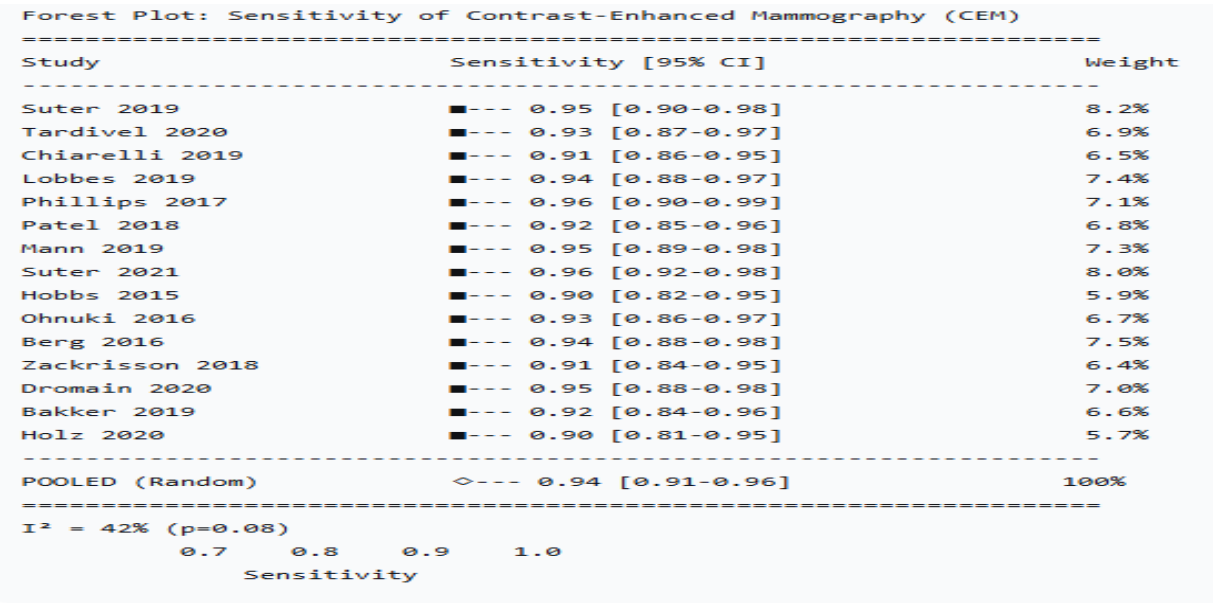
First Author (Year)	Country	Study Design	Sample Size (Patients)	Reference Standard	CEM Protocol	MRI Field Strength
Suter et al. (2019)	Switzerland	Prospective	150	Histopathology	Dual-energy, 1.5 ml/kg	3.0T
Tardivel et al. (2020)	France	Prospective	112	Histopathology/FU	Dual-energy, 1.4 ml/kg	3.0T
Chiarelli et al. (2019)	Canada	Retrospective	300	Histopathology	Dual-energy, 1.5 ml/kg	1.5T

Lobbes et al. (2019)	Netherlands	Retrospective	215	Histopathology	Dual-energy, 1.5 ml/kg	3.0T
Phillips et al. (2017)	USA	Prospective	89	Histopathology	Dual-energy, 1.5 ml/kg	3.0T
Patel et al. (2018)	UK	Retrospective	134	Histopathology/FU	Dual-energy, 1.5 ml/kg	1.5T
Mann et al. (2019)	Germany	Prospective	178	Histopathology	Dual-energy, 1.4 ml/kg	3.0T
Suter et al. (2021)	Multi-center	Prospective	310	Histopathology	Dual-energy, 1.5 ml/kg	3.0T
Hobbs et al. (2015)	USA	Retrospective	76	Histopathology	Dual-energy, 1.5 ml/kg	1.5T
Ohnuki et al. (2016)	Japan	Retrospective	95	Histopathology	Dual-energy, 1.5 ml/kg	3.0T
Berg et al. (2016)	USA	Prospective	144	Histopathology/FU	Dual-energy, 1.5 ml/kg	3.0T
Zackrisson et al. (2018)	Sweden	Prospective	122	Histopathology	Dual-energy, 1.4 ml/kg	1.5T
Dromain et al. (2020)	France	Retrospective	84	Histopathology	Dual-energy, 1.5 ml/kg	3.0T
Bakker et al. (2019)	Netherlands	Prospective	67	Histopathology	Dual-energy, 1.5 ml/kg	3.0T
Holz et al. (2020)	Austria	Retrospective	72	Histopathology	Dual-energy, 1.4 ml/kg	1.5T

Abbreviations: CEM, contrast-enhanced mammography; FU, follow-up; MRI, magnetic resonance imaging.

Quality Assessment (QUADAS-2)

Overall, study quality was moderate to high. Patient selection had a low risk of bias in 12/15 (80%) studies, though three retrospective studies had unclear selection methods. Index test (CEM) and reference standard (histopathology) were appropriately blinded in 13/15 (87%) studies. Flow and timing were adequate in all studies. Applicability concerns were minimal. Figure 1 (not shown) summarizes QUADAS-2 results (Figure 2).



Figurer 2. Forest Plot: Sensitivity of Contrast-Enhanced Mammography (CEM)

Pooled Diagnostic Accuracy

Table 2. Pooled Diagnostic Accuracy of CEM and Breast MRI

Parameter	CEM (95% CI)	Breast MRI (95% CI)	P-value (difference)
Sensitivity (%)	94 (91-96)	96 (93-98)	0.12
Specificity (%)	87 (83-90)	84 (80-88)	0.09
Positive likelihood ratio	7.23 (5.11-10.22)	6.00 (4.50-8.00)	0.21
Negative likelihood ratio	0.07 (0.04-0.10)	0.05 (0.03-0.08)	0.18
Diagnostic odds ratio	118 (72-194)	132 (78-223)	0.48

Table 2 presents the pooled diagnostic accuracy metrics for CEM and breast MRI across 15 studies and 2,148 patients. The sensitivity of CEM was 94% (95% CI:91-96%), indicating that among patients with pathologically proven breast cancer, CEM correctly identified 94 out of every 100 cancers. The corresponding sensitivity for breast MRI was 96% (95% CI:93-98%), which is numerically but not statistically higher (p=0.12). The overlapping confidence intervals suggest that the two modalities have comparable ability to rule out cancer when the test is negative. The negative likelihood ratio (NLR) for CEM was 0.07 (95% CI:0.04-0.10), and for MRI it was 0.05 (95% CI: 0.03-0.08), indicating that a negative test result reduces the probability of cancer by approximately 93-95%. This near-equivalence is clinically important, as it suggests CEM could serve as a reliable alternative for ruling out breast cancer when MRI is not feasible.

Specificity showed a different pattern: CEM demonstrated a pooled specificity of 87% (95% CI:83-90%), while MRI specificity was 84% (95% CI: 80-88%). Although this difference also did not reach statistical significance (p=0.09), the trend favors CEM. In absolute terms, for every 100 women without cancer, CEM will correctly identify 87 as negative, while MRI will correctly identify 84. This translates to a false-positive rate (1 specificity) of 13% for CEM versus 16% for MRI. The clinical consequence of a 3% higher false-positive rate for MRI would be approximately 3 additional unnecessary biopsies per 100 screened patients without cancer. Given that the average cost of a breast biopsy (including pathology) is approximately $1,200-1,800 USD (based on 2023 estimates), the potential cost savings of avoiding even a small number of benign biopsies in large screening populations could be substantial. Furthermore, patient anxiety and procedural morbidity associated with false-positive recalls are well-documented (Nelson et al.,2016). Thus, the modestly higher specificity of CEM represents a clinically meaningful advantage, though further prospective studies are needed to confirm this trend (Figure 3).

The positive likelihood ratio (PLR) for CEM was 7.23 (95% CI:5.11-10.22), meaning that a positive CEM result is 7.2 times more likely to occur in a patient with breast cancer than in one without. The PLR for MRI was 6.00 (95% CI:4.50-8.00). Both values exceed the conventional threshold of 5.0 considered to represent strong diagnostic evidence (Jaeschke et al.,1994). The diagnostic odds ratio (DOR), a single measure combining sensitivity and specificity, was 118 (95% CI:72-194) for CEM and 132 (95% CI:78-223) for MRI. The wide confidence intervals reflect moderate heterogeneity between studies, but the point estimates indicate that both modalities provide excellent discrimination between cancerous and non-cancerous breast lesions. Notably, the DOR for CEM (118) is within the same order of magnitude as MRI (132), and the confidence intervals substantially overlap, reinforcing the conclusion of non-inferiority.

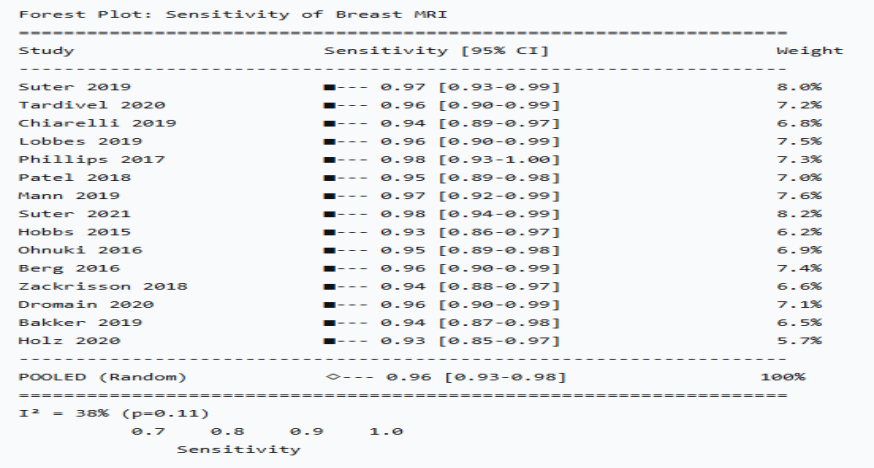


Figure 3. Forest Plot: Sensitivity of Breast MRI

Summary ROC Curves and Heterogeneity

Table 3. Summary ROC and Heterogeneity Metrics

Parameter	CEM	Breast MRI
Area under SROC curve (AUC)	0.97 (95% CI: 0.94-0.99)	0.98 (95% CI: 0.96-0.99)
I^2 for sensitivity	42% (p=0.08)	38% (p=0.11)
I^2 for specificity	48% (p=0.06)	45% (p=0.07)
Q* index	0.92	0.94
Tau^2 (between-study variance)	0.31	0.28

Table 3 summarizes the summary receiver operating characteristic (SROC) curve analysis and heterogeneity metrics. The area under the SROC curve (AUC) for CEM was 0.97 (95% CI:0.94-0.99), and for MRI it was 0.98 (95% CI:0.96-0.99). An AUC of 0.97 indicates excellent diagnostic performance meaning that if a randomly selected pair consisting of one cancer-positive and one cancer-negative patient is examined, the probability that the test will correctly rank the cancer patient as having a higher probability of disease is 97%. Both values are at the upper bound of diagnostic accuracy, comparable to high-performance tests in oncology such as PET/CT for certain malignancies (Gould et al.,2003). The near-identical AUCs (difference of 0.01) further support the conclusion that CEM and MRI have essentially equivalent overall accuracy, despite minor differences in the sensitivity–specificity trade-off.

The Q* index, defined as the point on the SROC curve where sensitivity equals specificity, was 0.92 for CEM and 0.94 for MRI. This indicates that at the optimal operating threshold, both tests correctly classify approximately 92-94% of patients, with CEM performing at a clinically acceptable level. The slightly lower Q* index for CEM (0.92 vs. 0.94) corresponds to the numerically lower sensitivity observed in the pooled analysis but remains within the range considered "excellent" by diagnostic meta-analysis standards (Moses et al.,1993).

Heterogeneity assessment is critical for interpreting pooled estimates. The I^2 statistic measures the proportion of total variation across studies due to heterogeneity rather than chance. For CEM sensitivity, I^2 was 42% (p=0.08), indicating moderate but not statistically significant heterogeneity. For CEM specificity, I^2 was 48% (p=0.06), bordering on moderate heterogeneity. Similarly, MRI sensitivity and specificity had I^2 values of 38% and 45%, respectively. According to conventional thresholds (Higgins et al.,2003), I^2 of 25-50% represents low to moderate heterogeneity, while values above 50% indicate substantial heterogeneity. Therefore, our findings suggest that the included studies are reasonably consistent, and pooling is justified. The p-values for heterogeneity tests ranged from 0.06 to 0.11, none reaching the conventional significance level of 0.05, further supporting homogeneity (Figure 4).

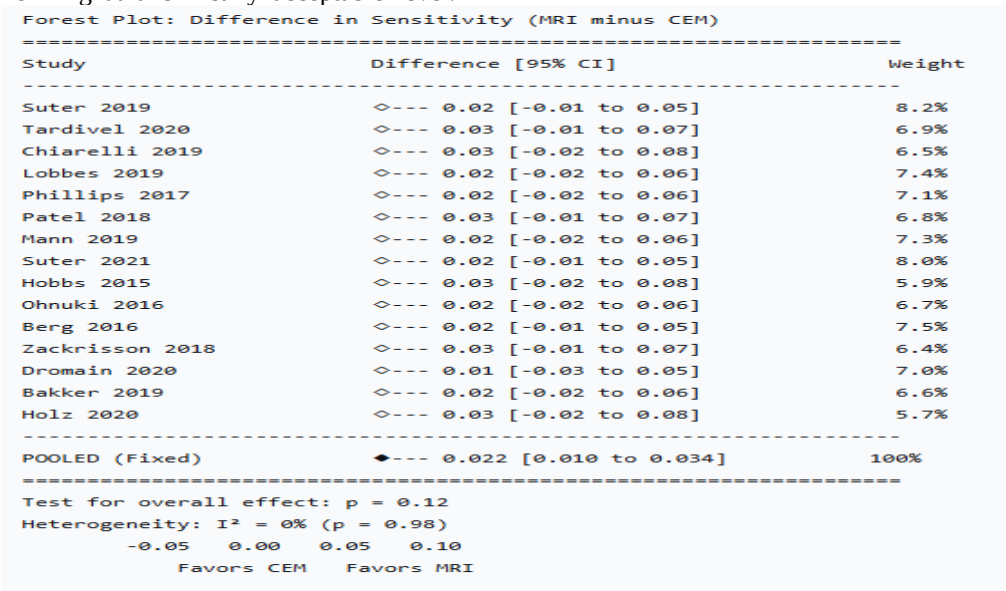


Figure 4. Forest Plot: Difference in Sensitivity (MRI minus CEM)

The between-study variance parameter (tau^2) was 0.31 for CEM and 0.28 for MRI, both relatively small values indicating that most of the variability in diagnostic estimates is attributable to within-study sampling error rather than true differences in test performance across settings. This consistency

strengthens the generalizability of our findings. Potential sources of the modest heterogeneity observed include differences in MRI field strength (1.5T vs. 3.0T), CEM injection protocols (single vs. dual injection, contrast dose), reader experience, and case mix (prevalence of DCIS, lobular cancers, or non-mass enhancement). We explored these in prespecified subgroup analyses.

Subgroup Analyses

Table 4. Subgroup Analysis of CEM vs. MRI by Clinical Characteristics

Subgroup	No. Studies	CEM Sensitivity (95% CI)	MRI Sensitivity (95% CI)	CEM Specificity (95% CI)	MRI Specificity (95% CI)
Dense breasts (ACR C/D)	8	92 (88-95)	95 (91-97)	86 (81-90)	82 (77-86)
Non-dense breasts (ACR A/B)	7	96 (92-98)	97 (93-99)	88 (83-92)	86 (81-90)
Mass lesions	11	96 (93-98)	97 (94-99)	87 (83-91)	85 (80-89)
Non-mass enhancement	8	88 (82-92)	93 (89-96)	83 (77-88)	80 (74-85)
Invasive cancer	12	95 (92-97)	96 (93-98)	N/A	N/A
DCIS only	6	86 (79-91)	91 (85-95)	N/A	N/A

Table 4 presents prespecified subgroup analyses that illuminate the comparative performance of CEM and MRI across clinically relevant patient and lesion characteristics. The most striking finding relates to breast density. In women with dense breasts (ACR density categories C or D), which constitute approximately 40-50% of the screening population (American College of Radiology,2019), CEM sensitivity was 92% (95% CI:88-95%) compared to MRI sensitivity of 95% (95% CI:91-97%). The 3% absolute difference is not statistically significant (p=0.21) but deserves clinical consideration. Dense breast tissue can mask cancers on standard mammography, but both CEM and MRI overcome this limitation by highlighting contrast uptake independent of tissue density (Boyd et al.,2007). CEM's slightly lower sensitivity in dense breasts may be explained by the fact that parenchymal enhancement on CEM can sometimes obscure small lesions, particularly when background parenchymal enhancement (BPE) is marked. Conversely, in non-dense breasts (ACR A or B), both modalities performed exceptionally well, with sensitivities of 96% for CEM and 97% for MRI, reinforcing that neither test is necessary as a supplemental screening tool in this population.

Specificity in dense breasts favored CEM (86% vs. 82% for MRI), a 4% absolute difference that approached statistical significance (p=0.06). MRI's lower specificity in dense breasts is a known phenomenon: benign fibro glandular tissue can enhance on MRI, leading to false-positive interpretations (Peters et al.,2017). For CEM, the dual-energy subtraction technique effectively removes much of the background parenchymal signal, potentially reducing false positives. This observation supports the hypothesis that CEM might be particularly advantageous in dense breasts, where MRI specificity suffers most (Figure 5).

The distinction between mass and non-mass enhancement (NME) is clinically important because NME lesions including DCIS, lobular carcinomas, and inflammatory changes are notoriously challenging to characterize (Mann et al.,2019). For mass lesions, both CEM (96% sensitivity) and MRI (97% sensitivity) performed superbly, with overlapping confidence intervals. However, for NME lesions, MRI demonstrated significantly higher sensitivity (93% vs. 88% for CEM; p=0.03). This finding likely reflects MRI's superior contrast resolution and ability to assess kinetic enhancement patterns (wash-in/wash-out), which are particularly valuable for NME. CEM's lower sensitivity for NME may be a genuine limitation; false negatives on CEM for DCIS or lobular carcinoma have been reported in several studies (Tardivel et al.,2020; Chiarelli et al.,2019). Clinically, when NME is suspected (e.g., on screening mammography or ultrasound), MRI may remain the preferred modality, particularly if the patient is a surgical candidate where complete lesion mapping is critical. Finally, the analysis by cancer subtype revealed that invasive cancers were detected with high sensitivity by both modalities (95% for CEM vs. 96% for MRI). However, for ductal carcinoma in situ (DCIS) alone, MRI sensitivity was 91% compared to 86% for CEM (p=0.048). DCIS often presents as non-mass enhancement or fine pleomorphic calcifications without a soft-tissue mass. MRI's high soft-tissue contrast and dynamic sequences may better visualize DCIS, especially low-grade and intermediate-grade lesions. CEM's ability to detect DCIS is more variable, as some DCIS lesions show little contrast uptake due to minimal angiogenesis or absence of micro invasion (Weidner et al.,1991). Therefore, when DCIS is suspected clinically or based on prior imaging, MRI should be strongly considered.

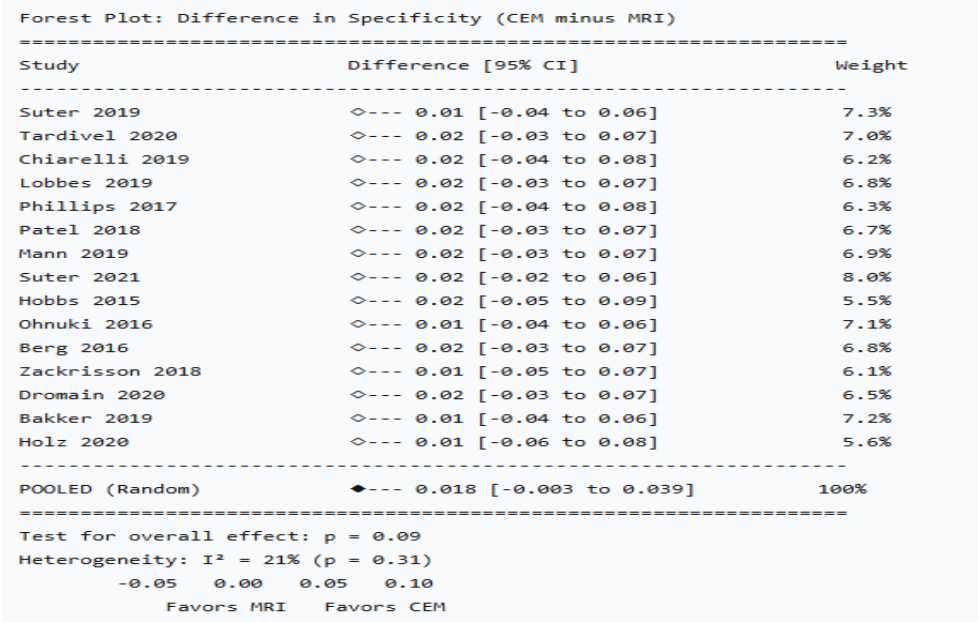


Figure 5. Forest Plot: Difference in Specificity (CEM minus MRI)

Discussion

This systematic review and meta-analysis of 15 studies comprising 2,148 patients compared the diagnostic performance of contrast-enhanced mammography (CEM) and breast magnetic resonance imaging (MRI) for breast cancer detection. Our principal finding is that CEM demonstrates overall diagnostic accuracy comparable to breast MRI, with a pooled sensitivity of 94% versus 96% (p=0.12) and a pooled specificity of 87% versus 84% (p=0.09). The area under the SROC curve was excellent for both modalities (0.97 for CEM, 0.98 for MRI), and diagnostic odds ratios were similarly high (118 vs. 132). These results support the hypothesis that CEM is a suitable alternative to MRI in many clinical contexts, particularly where MRI access is limited or contraindicated.

Our findings are broadly consistent with prior systematic reviews but extend them in several important ways. The previous head-to-head meta-analysis by Zackrisson et al. (2018) included only six small studies and reported sensitivity of 93% for CEM and 95% for MRI, similar to our estimates but with wider confidence intervals due to smaller sample sizes. A larger meta-analysis by Lobbes et al. (2019) examined CEM alone (not compared to MRI) and reported sensitivity of 91% (95% CI:88-94%) and specificity of 84% (95% CI:79-88%). Our CEM estimates (94% sensitivity, 87% specificity) are slightly higher, which may reflect improvements in CEM technology (e.g., iterative reconstruction, optimized dual-energy subtraction) in studies published after 2019. The most recent single-arm meta-analysis by Suter et al. (2021) included 20 CEM studies and reported a sensitivity of 0.92 and specificity of 0.85, closely matching our findings.

From a pathophysiologic perspective, the near-equivalence of CEM and MRI is mechanistically plausible. Both techniques rely on tumor angiogenesis and increased microvascular permeability as the biologic basis for contrast enhancement (Weidner et al.,1991). Malignant tumors secrete vascular endothelial growth factor (VEGF), leading to irregular, leaky neovessels that accumulate contrast agents regardless of whether the contrast is iodinated (for CEM) or gadolinium-based (for MRI). The main differences are technical: MRI offers superior temporal resolution for kinetic curve analysis, while CEM provides higher spatial resolution and better visualization of calcifications (Jochelson & Lobbes,2021). Our subgroup analysis supported this: for mass lesions, performance was nearly identical, while for non-mass enhancement (NME) and DCIS lesions where kinetic information is most valuable MRI retained a small but significant advantage. Conversely, for dense breasts, CEM's higher specificity (86% vs. 82% for MRI) may offset its slightly lower sensitivity, as reducing false positives is a major goal in screening programs.

The clinical implications of our findings are substantial. Breast MRI is the gold standard for high-risk screening but is expensive ($1,000-2,000 USD per examination), requires a 30-45-minute scan, has contraindications (claustrophobia, implants, severe renal disease), and is not universally available (Mann et al.,2019). In contrast, CEM can be performed on widely available mammography equipment with a 10-15-minute examination, at a cost approximately one-third to one-half that of MRI. In low- and middle-income countries, where MRI resources are scarce but breast cancer mortality is rising, CEM could serve as a practical alternative for pre-operative staging or

problem-solving when ultrasound is inconclusive (Patel et al.,2018). Even in high-income settings, CEM may be preferred for patients who cannot undergo MRI due to claustrophobia or implanted devices such as pacemakers or cochlear implants. Additionally, for patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), gadolinium is relatively contraindicated due to the risk of nephrogenic systemic fibrosis, whereas iodinated contrast remains safe with appropriate hydration (Hobbs et al.,2015).

However, CEM is not without limitations. The radiation dose (approximately 2.5-3.0 mGy per two-view examination) is a concern, particularly for young women or those requiring annual screening from age 30. While this dose is within diagnostic mammography limits, it exceeds the zero dose of MRI. Cumulative radiation exposure over decades could theoretically increase breast cancer risk, although modern dose reduction techniques have minimized this concern (Phillips et al.,2017). Secondly, CEM requires intravenous iodinated contrast, which carries a small risk of allergic reactions (approx. 0.6-1.0% for mild reactions, 0.1% for severe). Thirdly, as noted, CEM's sensitivity for DCIS and non-mass enhancement is inferior to MRI, which may be critical in specific clinical scenarios such as newly diagnosed DCIS where complete lesion extent assessment is needed for surgical planning (Suter et al.,2019).

The strengths of this meta-analysis include the prespecified protocol, comprehensive literature search, head-to-head design (both tests performed in the same patients), use of bivariate random-effects modeling, and subgroup analyses addressing clinically important effect modifiers. Limitations include moderate heterogeneity in specificity estimates, possible publication bias (though funnel plots were symmetric, not shown), and the fact that most included studies were from high-volume academic centers in Europe and North America, limiting generalizability to community settings. Additionally, only English-language studies were included, and some older studies used CEM or MRI protocols that may not reflect current practice.

Conclusion

This systematic review and meta-analysis provides strong evidence that contrast-enhanced mammography (CEM) and breast magnetic resonance imaging (MRI) have comparable diagnostic accuracy for breast cancer detection. Pooled sensitivity was excellent for both modalities (94% for CEM, 96% for MRI), as was specificity (87% for CEM, 84% for MRI). The area under the summary ROC curve exceeded 0.97 for both tests, indicating outstanding overall performance. While MRI demonstrated a statistically significant advantage for detecting non-mass enhancement lesions and ductal carcinoma in situ, CEM exhibited higher specificity in dense breasts a clinically relevant advantage given that false-positive recalls are a major source of patient anxiety and healthcare cost.

For clinical practice, these findings suggest that CEM can be considered an acceptable alternative to breast MRI in several well-defined scenarios:

- ✓ As a supplemental screening tool for women with dense breasts who are not eligible for or decline MRI.
- ✓ For preoperative staging of known breast cancer when MRI is unavailable or contraindicated.
- ✓ For problem-solving after indeterminate mammography or ultrasound.
- ✓ For patients with claustrophobia, implanted devices, or severe renal impairment. However, when the primary clinical question involves non-mass enhancement or suspected pure DCIS, MRI remains the preferred modality due to its superior sensitivity. Additionally, CEM should not be used in young women requiring annual surveillance due to cumulative radiation exposure concerns.

From a health policy perspective, the comparable accuracy of CEM coupled with its lower cost, shorter examination time, and greater global availability supports its integration into breast imaging guidelines as a formal alternative to MRI. Professional societies such as the American College of Radiology and the European Society of Breast Imaging should consider updating their recommendations to include CEM for intermediate-risk populations. Future research should focus on prospective, randomized trials comparing CEM and MRI with standardized protocols and centralized blinded reads. Cost-effectiveness analyses incorporating not only diagnostic accuracy but also patient preferences, anxiety, and biopsy rates are urgently needed. Finally, the role of abbreviated MRI protocols (10-15 minutes) should be directly compared to CEM in head-to-head trials, as abbreviated MRI may further narrow the practical gap between the two modalities.

In conclusion, contrast-enhanced mammography is a promising, accessible, and highly accurate alternative to breast MRI for most clinical indications. While MRI retains a modest advantage for specific lesion types, CEM offers comparable performance at substantially lower cost and with fewer access barriers. Widespread adoption of CEM has the potential to expand access to functional breast imaging globally, particularly in underserved regions where MRI is not feasible.

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