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Systematic Review and Meta-Analysis

Diagnostic Accuracy of Contrast-Enhanced Mammography for the Detection of Breast Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: Contrast-enhanced mammography (CEM) adds an iodine-enhanced recombined image to standard low-energy mammography and shows tumour neovascularity. It is cheaper and more widely available than breast MRI, but published estimates of its accuracy vary.

Aim: To estimate the pooled sensitivity and specificity of CEM for the diagnosis of breast cancer in women with suspicious clinical or imaging findings.

Materials and Methods: PubMed was searched from 1 January 2000 to 31 December 2023 for studies of CEM in women with suspicious breast findings that reported, or allowed reconstruction of, a 2 × 2 table against histopathology or follow-up. Risk of bias was assessed with QUADAS-2. Sensitivity and specificity were pooled with a bivariate random-effects model, and a summary receiver operating characteristic (SROC) curve was constructed. Subgroup, sensitivity and publication bias analyses were performed.

Results: Eighteen studies with 3712 lesions, breasts or patients (2043 malignant and 1669 benign) were included. Pooled sensitivity was 94.0% (95% CI 91.7 to 95.7) and pooled specificity 75.3% (95% CI 67.4 to 81.7). The positive likelihood ratio was 3.80, the negative likelihood ratio 0.08 and the diagnostic odds ratio 47.4 (33.3 to 67.5). The area under the SROC curve was 0.95. Heterogeneity was moderate for sensitivity (I^2 = 62%) and high for specificity (I^2 = 90%). Sensitivity was stable across subgroups (93.2% to 95.2%), while specificity was lower in screening recalls (64.8%). There was no evidence of publication bias (Deeks test p = 0.91).

Conclusion: CEM detects breast cancer with high sensitivity and a low negative likelihood ratio, so a negative examination makes cancer unlikely in women with suspicious findings. Specificity is moderate and varies between settings, so enhancing lesions still need tissue diagnosis.

Keywords: Breast neoplasms; Contrast media; Diagnostic accuracy; Mammography; Meta-analysis; Sensitivity and specificity.

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Introduction

Breast cancer is now the most commonly diagnosed cancer in the world. GLOBOCAN estimated 2.3 million new cases in 2020, 11.7% of all cancers, and breast cancer was the fifth leading cause of cancer death [1]. Death rates for breast cancer were higher in transitioning countries such as India than in transitioned countries, which reflects late diagnosis and limited access to imaging [1].

Full-field digital mammography and ultrasound remain the standard tools for evaluating breast symptoms and screening recalls. Mammography loses sensitivity in dense breasts. Women whose mammograms show density in 75% or more of the breast have a breast cancer risk 4.7 times that of women with density below 10%, and cancers are also harder to see in such breasts [2]. Contrast-enhanced breast MRI is the most sensitive test, but it is costly, takes time and is not available in many centres.

Contrast-enhanced mammography (CEM), also called contrast-enhanced spectral or dual-energy mammography, was first shown to be feasible in 2003, when 12 of 13 invasive cancers enhanced after iodinated contrast [3]. After injection, low-energy and high-energy images are acquired and recombined so that the iodine image shows tumour neovascularity, while the low-energy image serves as a standard mammogram [4]. A systematic review of 84 studies found that most centres used iohexol at 1.5 mL/kg, that the examination usually took less than 10 minutes and that the pooled rate of adverse reactions was 0.82%, with only one severe reaction [5].

Earlier meta-analyses gave conflicting results. A review of eight prospective studies reported a pooled sensitivity of 85% and specificity of 77% and concluded that CEM should be used only when mammography and ultrasound are inconclusive [6]. A larger review found an area under the curve of 0.94 and a diagnostic odds ratio of 55.7, with high heterogeneity between settings and reading methods [7]. As CEM is being introduced in Indian centres, an updated estimate of its accuracy is useful. This systematic review and meta-analysis aimed to estimate the pooled sensitivity and specificity of CEM for the diagnosis of breast cancer in women with suspicious findings, and to explore the sources of heterogeneity.

Materials and Methods

Protocol and Reporting: The review followed the PRISMA statement for diagnostic test accuracy studies (PRISMA-DTA) [8]. Only published data were used, so ethics committee approval was not required. The protocol was not registered.

Search Strategy: PubMed/MEDLINE was searched from 1 January 2000 to 31 December 2023 with the string: (contrast-enhanced mammography OR contrast-enhanced spectral mammography OR contrast enhanced digital mammography OR CESM OR CEDM) AND (sensitivity OR specificity OR diagnostic accuracy OR diagnostic performance) AND breast. The reference lists of included studies and earlier reviews were checked by hand. Only studies published in English before 2024 were considered.

Eligibility Criteria: Studies were included if they (a) evaluated CEM in women with suspicious clinical findings, abnormal screening mammograms or other suspicious imaging findings; (b) used histopathology, alone or with imaging follow-up, as the reference standard; and (c) reported the numbers of true-positive, false-positive, false-negative and true-negative results, or data from which these could be reconstructed. Studies were excluded if they included only malignant lesions or examined staging of known cancer, assessed asymptomatic screening populations, reported only results averaged across readers, assessed response to neoadjuvant chemotherapy, or used radiomics or artificial intelligence. Reviews, case reports, letters and technical studies were also excluded.

Data Extraction and Quality Assessment: The following were extracted on a predesigned form: first author, year, country, design, clinical setting, unit of analysis (lesion, breast or patient) and the 2 × 2 table. When a study reported more than one reader, the first or most experienced reader was used. When counts were not given, they were reconstructed from the reported number of malignant and benign lesions together with sensitivity, specificity and predictive values, and the reconstructed table was checked against every reported percentage. Risk of bias and applicability were assessed with the QUADAS-2 tool across patient selection, index test, reference standard, and flow and timing [9].

Statistical Analysis: Sensitivity and specificity were pooled with the bivariate random-effects model, which models logit sensitivity and logit specificity jointly and allows for the correlation between them [10]. The model was fitted by maximum likelihood. Positive and negative likelihood ratios and the diagnostic odds ratio (DOR) were derived from the pooled estimates, with 95% confidence intervals obtained by simulation. A summary receiver operating characteristic (SROC) curve was drawn from the bivariate parameters, and its area under the curve (AUC) was calculated. A continuity correction of 0.5 was added to all cells of studies with a zero cell. Heterogeneity was quantified with the I^2 statistic for logit sensitivity and logit specificity separately [11]. Prespecified subgroup analyses compared clinical setting (symptomatic or diagnostic work-up versus screening recall), design (prospective versus retrospective), region and publication period. Sensitivity analyses excluded the study limited to calcifications and the studies not analysed at lesion level, and a leave-one-out analysis was performed. Publication bias was assessed with the Deeks funnel plot asymmetry test, with $p < 0.10$ regarded as significant [12]. Post-test probabilities were calculated for pre-test probabilities of 10%, 30% and 50%. Analyses were carried out in Python 3 (NumPy and SciPy libraries).

Results

Study Selection: The search identified 1337 records (Figure 1). After title and abstract screening, 1297 were excluded, mostly reviews, technical and radiomics studies and studies of other outcomes. Of 40 full-text articles assessed, 22 were excluded: 10 did not allow reconstruction of a 2 × 2 table, 5 included only malignant lesions or staging of known cancer, 4 reported only reader-averaged results, 2 studied screening populations and 1 was a letter without data. Eighteen studies were included [13-30].

Characteristics of Included Studies: The 18 studies were published between 2014 and 2023 and together analysed 3712 lesions, breasts or patients, of which 2043 (55.0%) were malignant (Table 1). Ten studies were from Europe, three from China and one each from Japan, Egypt, Israel, Turkey and India.

Six were described as prospective and eight as retrospective, and four enrolled consecutive patients without stating the design. Fourteen studies assessed women with symptoms or suspicious findings in a diagnostic work-up, and four assessed women recalled from screening, one of them limited to suspicious calcifications [20]. Three studies were restricted to women with dense breasts [23,26,30].

Sixteen studies reported results per lesion, one per breast [18] and one per patient [14]. The reference standard was histopathology in all studies, combined with imaging follow-up for benign findings in several.

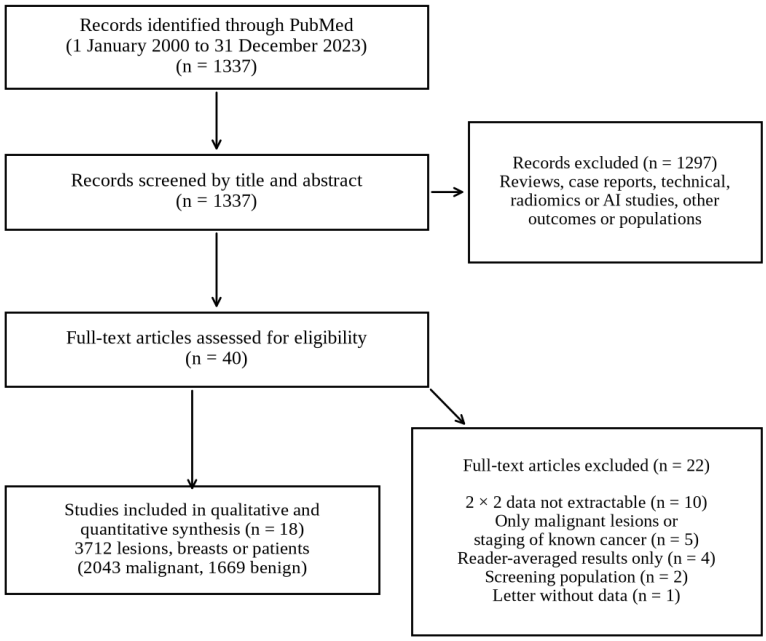


Figure 1: Flow diagram of study identification, screening and inclusion

The diagram follows the PRISMA-DTA statement.

Table 1: Characteristics of the included studies

Study	Country	Design	Setting	Unit	n (malignant/ benign)	TP/FP/FN/TN
Luczyńska 2014 [13]	Poland	Consecutive*	Symptomatic/preoperative	Lesion	173 (114/59)	114/35/0/24
Lobbes 2014 [14]	Netherlands	Prospective	Screening recall	Patient	113 (32/81)	32/10/0/71
Mohamed Kamal 2015 [15]	Egypt	Consecutive*	Symptomatic/diagnostic	Lesion	211 (109/102)	97/17/12/85
Wang 2016 [16]	China	Consecutive*	Symptomatic/diagnostic	Lesion	77 (48/29)	46/10/2/19
Tardivel 2016 [17]	France	Retrospective	Diagnostic work-up	Lesion	299 (221/78)	207/20/14/58
Mori 2017 [18]	Japan	Retrospective	Diagnostic work-up	Breast	143 (58/85)	50/5/8/80
Xing 2019 [19]	China	Retrospective	Symptomatic/diagnostic	Lesion	263 (177/86)	162/9/15/77
Houben 2019 [20]	Netherlands	Retrospective	Screening recall (calcifications)	Lesion	147 (65/82)	61/52/4/30
Travieso-Aja 2019 [21]	Spain	Retrospective	Diagnostic work-up	Lesion	644 (426/218)	397/34/29/184
Sorin 2020 [22]	Israel	Retrospective	Symptomatic (palpable)	Lesion	147 (38/109)	38/29/0/80

Lu 2020 [23]	China	Prospective	Symptomatic, dense breasts	Lesion	131 (64/67)	60/8/4/59
Petrillo 2020 [24]	Italy	Consecutive*	Diagnostic work-up	Lesion	134 (81/53)	66/11/15/42
Steinhof-Radwańska 2020 [25]	Poland	Retrospective	Diagnostic work-up	Lesion	583 (327/256)	320/104/7/152
Sudhir 2021 [26]	India	Prospective	Symptomatic, dense breasts	Lesion	166 (87/79)	84/15/3/64
Yüzkan 2021 [27]	Turkey	Retrospective	Diagnostic work-up	Lesion	62 (41/21)	41/7/0/14
Cozzi 2022 [28]	Italy	Prospective	Screening recall	Lesion	124 (80/44)	75/15/5/29
Siminiak 2022 [29]	Poland	Prospective	Screening recall	Lesion	230 (44/186)	43/69/1/117
Moffa 2023 [30]	Italy	Prospective	Dense breasts, abnormal finding	Lesion	65 (31/34)	29/6/2/28

*Consecutive enrolment; design not stated. TP: true positive; FP: false positive; FN: false negative; TN: true negative. Where counts were not reported directly, they were reconstructed from the reported numbers of malignant and benign lesions and the reported sensitivity, specificity and predictive values.

Risk of Bias: Risk of bias is summarised in Figure 2. Risk was low for patient selection in 9 studies, mostly prospective series with consecutive enrolment, and unclear in 9 studies, most of them retrospective. Blinding of CEM reading to the reference standard was stated in 6 studies and unclear in the rest. The reference standard was at low risk in 8 studies that used histopathology for all lesions, and unclear in 10 that relied on follow-up for some benign findings. One study analysed only findings that were biopsied, which placed it at high risk for flow and timing [28]. No study was judged at high risk in any other domain. Concerns about applicability were low, as all studies assessed CEM as it would be used in clinical practice.

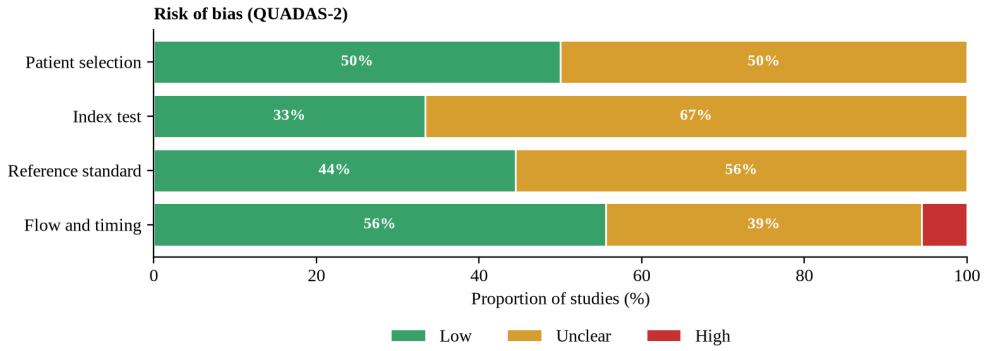


Figure 2: Risk of bias in the included studies (QUADAS-2)

Bars show the proportion of the 18 studies judged at low, unclear or high risk of bias in each QUADAS-2 domain.

Pooled Diagnostic Accuracy: Study-level sensitivity ranged from 81.5% to 100% and specificity from 36.6% to 94.1% (Figure 3). The bivariate model gave a pooled sensitivity of 94.0% (95% CI 91.7 to 95.7) and a pooled specificity of 75.3% (95% CI 67.4 to 81.7) (Table 2).

The positive likelihood ratio was 3.80 (95% CI 2.91 to 5.07) and the negative likelihood ratio 0.08 (95% CI 0.06 to 0.11). The pooled DOR was 47.4 (95% CI 33.3 to 67.5). The SROC curve lay close to the upper left corner, with an AUC of 0.95 (Figure 4). The between-study standard deviations were 0.56 for logit sensitivity and 0.77 for logit specificity, and the correlation between them was -0.77, which points to a threshold effect. Heterogeneity was moderate for sensitivity (I^2 = 62%) and high for specificity (I^2 = 90%).

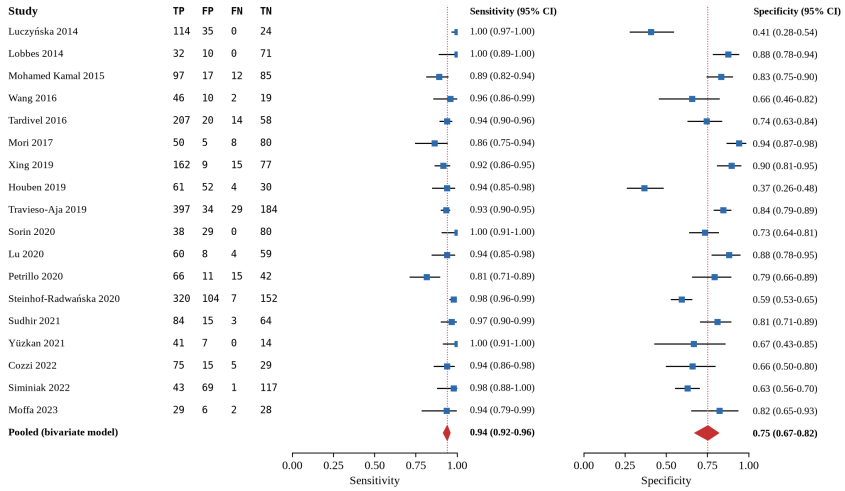


Figure 3: Forest plot of the sensitivity and specificity of contrast-enhanced mammography

Squares show study estimates with exact 95% confidence intervals; diamonds show the pooled estimates from the bivariate random-effects model. TP: true positive; FP: false positive; FN: false negative; TN: true negative.

Table 2: Pooled diagnostic accuracy of contrast-enhanced mammography (18 studies)

Measure	Estimate (95% CI)
Sensitivity (%)	94.0 (91.7 to 95.7)
Specificity (%)	75.3 (67.4 to 81.7)
Positive likelihood ratio	3.80 (2.91 to 5.07)
Negative likelihood ratio	0.08 (0.06 to 0.11)
Diagnostic odds ratio	47.4 (33.3 to 67.5)
Area under the SROC curve	0.95
I^2 for sensitivity / specificity (%)	62 / 90
Post-test probability after positive / negative CEM at 10% pre-test probability (%)	29.7 / 0.9
At 30% pre-test probability (%)	62.0 / 3.3
At 50% pre-test probability (%)	79.2 / 7.4

CEM: contrast-enhanced mammography; CI: confidence interval; SROC: summary receiver operating characteristic. Post-test probabilities were calculated from the pooled sensitivity and specificity.

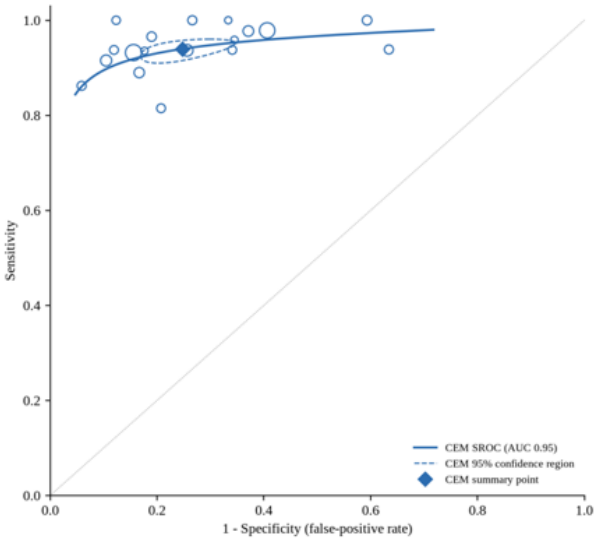


Figure 4: Summary receiver operating characteristic curve for contrast-enhanced mammography

Circles show individual studies, sized by number of lesions; the diamond shows the summary point, the dashed line its 95% confidence region and the solid line the SROC curve from the bivariate model. AUC: area under the curve; CEM: contrast-enhanced mammography; SROC: summary receiver operating characteristic.

Subgroup and Sensitivity Analyses: Sensitivity was consistent across subgroups (Table 3).

Specificity was 77.8% in symptomatic or diagnostic work-up and 64.8% in screening recalls, with wide and overlapping confidence intervals.

Specificity was also higher in studies from Asia, the Middle East and Africa (81.9%) than in European studies (69.1%).
Prospective and retrospective studies, and older and newer studies, gave similar results. In the three studies of women with dense breasts, sensitivity ranged from 94% to 97% and specificity from 81% to 88% [23,26,30].

Excluding the study limited to calcifications [20] raised the pooled specificity to 77.0%, and restricting the analysis to lesion-level data changed the estimates little. In the leave-one-out analysis, pooled sensitivity ranged from 93.2% to 94.4% and specificity from 73.6% to 77.0%, so no single study drove the results.

Table 3: Subgroup and sensitivity analyses

Analysis	Studies	Units	Sensitivity, % (95% CI)	Specificity, % (95% CI)	DOR	AUC
All studies	18	3712	94.0 (91.7 to 95.7)	75.3 (67.4 to 81.7)	47.4	0.95
Symptomatic or diagnostic work-up	14	3098	94.2 (91.2 to 96.3)	77.8 (70.4 to 83.8)	57.3	0.94
Screening recall	4	614	95.2 (91.1 to 97.5)	64.8 (44.1 to 81.1)	36.9	0.94
Prospective	6	829	95.0 (91.9 to 96.9)	78.5 (69.2 to 85.5)	69.4	0.95
Retrospective	8	2288	94.4 (91.9 to 96.1)	75.7 (61.3 to 85.9)	52	0.95
Europe	10	2512	94.5 (91.1 to 96.6)	69.1 (57.6 to 78.6)	38.3	0.95
Asia, Middle East and Africa	8	1200	93.5 (90.0 to 95.8)	81.9 (74.3 to 87.6)	65	0.95
Published before 2019	6	1016	93.2 (87.9 to 96.2)	77.4 (61.2 to 88.1)	46.7	0.94
Published 2019 or later	12	2696	94.3 (91.4 to 96.2)	74.0 (65.0 to 81.3)	46.7	0.95
Excluding calcification-only study	17	3565	94.3 (91.7 to 96.1)	77.0 (70.4 to 82.6)	55.3	0.94
Lesion-level data only	16	3456	94.3 (92.1 to 96.0)	72.5 (64.5 to 79.3)	44.1	0.95

All estimates are from the bivariate random-effects model. AUC: area under the summary receiver operating characteristic curve; CI: confidence interval; DOR: diagnostic odds ratio.

Publication Bias: The Deeks funnel plot showed no asymmetry (p = 0.91), so there was no evidence of small-study effects (Figure 5).

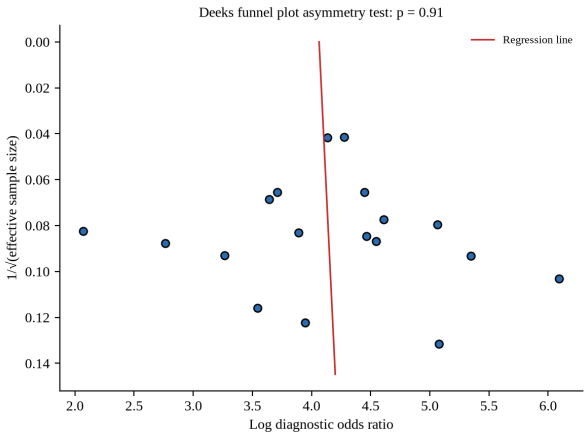


Figure 5: Deeks funnel plot for publication bias

Each point is a study. The regression line of the log diagnostic odds ratio against the inverse square root of the effective sample size is shown; a non-significant slope indicates no asymmetry.

Discussion

This meta-analysis of 18 studies and 3712 lesions, breasts or patients found that CEM has a pooled sensitivity of 94.0% and a pooled specificity of 75.3% for breast cancer in women with suspicious findings. The negative likelihood ratio of 0.08 means that a negative CEM lowers the probability of cancer substantially. At a pre-test probability of 30%, a negative examination leaves a residual probability of about 3%. The positive likelihood ratio of 3.8 is more modest, so an enhancing lesion still needs biopsy.

These results agree with the most comprehensive earlier review, which found an AUC of 0.94 and a

DOR of 55.7 across 60 studies, compared with our AUC of 0.95 and DOR of 47.4 [7]. Our pooled sensitivity was higher than the 85% reported by Suter and colleagues, whose review was limited to eight prospective studies, some of them early series [6]. Specificities in the two reviews were similar. Our sensitivity in women with dense breasts, 94% to 97%, matches the 95% pooled sensitivity found in nine studies of dense breasts in the earlier review [7], and it is relevant because mammography performs poorly in such women [2].

The main limitation of CEM is its specificity. Benign lesions such as fibroadenomas, papillomas and inflammatory changes can enhance, and background parenchymal enhancement can produce false-positive findings [4]. Specificity was lowest in the study limited to calcifications, at 36.6%, where enhancement did not reliably separate benign from malignant calcifications [20], and in the preoperative series of Luczyńska and colleagues, at 41% [13].

It was also lower in screening recalls. In this setting, most findings are small and many are benign, and the reading threshold tends to be low. Even so, CEM can reduce unnecessary biopsies. In a two-centre study of screening recalls, a CEM-based work-up would have avoided biopsy for 16.4% of suspicious findings, and all five cancers it missed were ductal carcinoma in situ visible as calcifications on the low-energy images [28]. Reading the low-energy and recombined images together is therefore essential. Higher specificity in Asian, Middle Eastern and African studies may reflect differences in case mix, as these series included more symptomatic women with larger palpable lesions, and differences in reading thresholds. The negative correlation between logit sensitivity and logit specificity indicates a threshold effect: studies that called more lesions positive gained sensitivity at the cost of specificity. Standardised reporting with the BI-RADS lexicon for CEM, and use of enhancement descriptors such as intensity and pattern, may improve consistency between centres [4,15].

CEM has practical advantages for Indian practice. It uses equipment that many centres already have, takes less than 10 minutes and costs much less than MRI [4,5]. In the only Indian study included, CEM had a sensitivity of 96.5% in women with dense breasts, higher than that of synthetic mammography, tomosynthesis or tomosynthesis with ultrasound [26].

The extra radiation dose is small, and adverse reactions to iodinated contrast are rare and mostly mild [5]. CEM may therefore be a useful problem-solving tool when mammography and ultrasound are inconclusive and MRI is not available or is contraindicated.

Strengths and Limitations: This review used the bivariate model recommended for diagnostic accuracy studies, assessed risk of bias with QUADAS-2 and explored heterogeneity with subgroup, sensitivity and leave-one-out analyses. It has limitations. Only PubMed was searched, and only studies published in English before 2024 were included, so some eligible studies may have been missed. Many 2 × 2 tables had to be reconstructed from reported percentages, which may introduce small rounding errors.

Most studies were small, single-centre series, half were retrospective, and blinding of readers was often not reported. The units of analysis differed between studies, and heterogeneity in specificity remained high after subgroup analysis. Only one study came from India, so the results may not fully apply to Indian women.

Conclusion

Contrast-enhanced mammography has high sensitivity and a low negative likelihood ratio for breast cancer in women with suspicious findings, with consistent performance across settings, designs and regions.

Its specificity is moderate and varies between settings, so enhancing lesions still need tissue diagnosis. CEM is a reasonable alternative when breast MRI is unavailable or contraindicated. Large prospective multicentre studies from India, with standardised reading criteria, are needed.

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