Review Article

Performance of Supplemental Imaging Modalities for Breast Cancer in Women With Dense Breasts: Findings From an Umbrella Review and Primary Studies Analysis

Franziska Lobig,[1] Amrit Caleyachetty,[2] Lucy Forrester,[2] Elizabeth Morris,[3] Gillian Newstead,[4] James Harris,[2] Michael Blankenburg[1]

Abstract

Breast cancer screening performance of supplemental imaging modalities by breast density and breast cancer risk has not been widely studied, and the optimal choice of modality for women with dense breasts remains unclear in clinical practice and guidelines. This systematic review aimed to assess breast cancer screening performance of supplemental imaging modalities for women with dense breasts, by breast cancer risk. Systematic reviews (SRs) in 2000 to 2021, and primary studies in 2019 to 2021, on outcomes of supplemental screening modalities (digital breast tomography [DBT], MRI (full/abbreviated protocol), contrast enhanced mammography (CEM), ultrasound (hand-held [HHUS]/automated [ABUS]) in women with dense breasts (BI-RADS C&D) were identified. None of the SRs analyzed outcomes by cancer risk. Meta-analysis of the primary studies was not feasible due to lack of studies (MRI, CEM, DBT) or methodological heterogeneity (ultrasound); therefore, findings were summarized narratively. For average risk, a single MRI trial reported a superior screening performance (higher cancer detection rate [CDR] and lower interval cancer rate [ICR]) compared to HHUS, ABUS and DBT. For intermediate risk, ultrasound was the only modality assessed, but accuracy estimates ranged widely. For mixed risk, a single CEM study reported the highest CDR, but included a high proportion of women with intermediate risk. This systematic review does not allow a complete comparison of supplemental screening modalities for dense breast populations by breast cancer risk. However, the data suggest that MRI and CEM might generally offer superior screening performance versus other modalities. Further studies of screening modalities are urgently required.

Clinical Breast Cancer, Vol. 23, No. 5, 478–490

Keywords: Breast cancer screening, Contrast-enhanced mammography, Digital breast tomosynthesis, Magnetic resonance imaging, Ultrasound

Introduction

Mammography is currently considered standard practice for the early detection of breast cancer by population screening. However, while screening via this imaging modality has been shown to reduce breast cancer mortality, it is not as sensitive in detecting breast cancer in mammographically dense breast tissue, compared with other breast density categories.[1]

Breast density refers to the proportion of radiodense fibroglandular tissue observed by mammogram and is categorized as dense breast by either heterogeneously or extremely dense tissue, following the American College of Radiology (ACR) BI-RADS system.[2] In the United States, 40% (27.6 million) women aged 40 to 74 years have dense breasts, with 7.4% of these women (2 million) having

Summary statement: This study evaluated the literature on screening performance of supplemental screening modalities in the dense breast population by breast cancer risk. Key results:
Studies on screening performance of supplemental screening modalities in the dense breast population by breast cancer risk are either sparse or methodologically heterogeneous.
Primary included studies suggest MRI is a promising modality for women with dense breasts and average breast cancer risk, and CEM is an encouraging alternative.[51,57]
Regardless of modality, all women with dense breasts may benefit from supplemental screening after mammography or DBT.

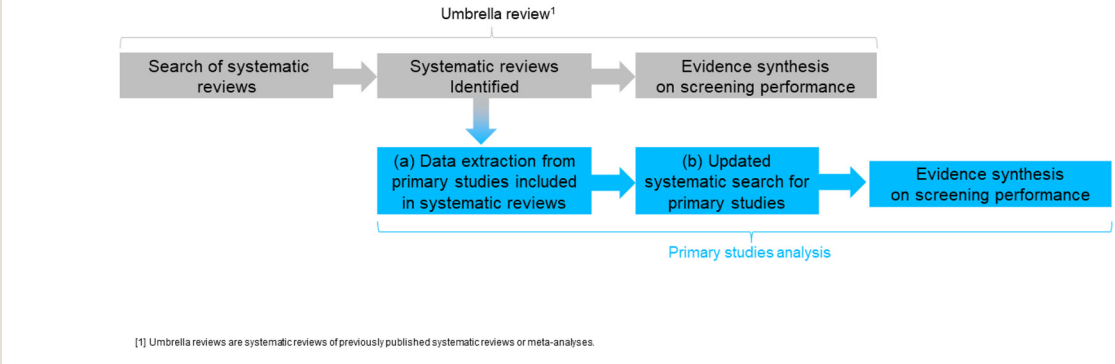
[1]Bayer AG, Berlin, Germany
[2]Wickenstones Ltd, Carlow, Ireland
[3]University of California Davis, Department of Radiology, Sacramento, CA 95817, USA
[4]The University of Chicago Medicine, Chicago, IL 60637, USA

Submitted: Nov 25, 2022; Revised: Feb 28, 2023; Accepted: Apr 14, 2023; Epub: 19 April 2023

Address for correspondence: Michael Blankenburg, Bayer AG Pharmaceuticals, Market Access - TA Pulm / WHC / Radiology, Muellerstrasse 178, 13353 Berlin, Germany
E-mail contact: michael.blankenburg@bayer.com

https://doi.org/10.1016/j.clbc.2023.04.003

Figure 1 Methodology schematic. [A] Umbrella reviews are systematic reviews of previously published systematic reviews or meta-analyses.



extremely dense breasts.[3] Having dense breasts is associated with increased false-negative findings in mammography and an associated increased risk of interval cancer (IC; cancers detected after a negative screening and before the next planned mammography).[4] ICs have a poorer prognosis compared to those detected by screening (screen-detected cancers). Furthermore, having dense breast tissue is also an independent, major risk factor for breast cancer – associated with up to 4.6-fold increased risk compared to women with nondense breasts.[4,5] Women with dense breasts therefore face increased risk from two causes.

Given the lower sensitivity of mammography with dense breast tissue compared to other breast density categories ([A] almost entirely fatty and [B] scattered areas of fibroglandular density), women may benefit from supplemental screening with alternative, more sensitive imaging modalities, such as: functional imaging techniques; magnetic resonance imaging (MRI) and contrast-enhanced mammography (CEM) and conventional imaging; ultrasound (hand-held ultrasound [HHUS], automated whole breast ultrasound [ABUS]) and digital breast tomosynthesis (DBT).

Currently, no supplemental imaging modality is considered standard of care for women with dense breasts[6] and, further, clinical society guidelines are unclear as to the optimal supplemental modality.[7] European Society of Breast Imaging (EUSOBI) recommended MRI for use in women with extremely dense breasts[8]; while the ACR and U.S. Preventive Services Task Force in 2016 found insufficient evidence to recommend for or against any particular supplemental modality.[9] Furthermore, US insurance coverage for breast cancer screening provides inconsistent access to supplemental screening for women with dense breasts.[10]

Addressing the challenges faced by women with dense breasts in accessing more sensitive supplemental modalities is hampered by limitations in the evidence base. Systematic reviews (SRs) and meta-analyses have typically included heterogeneous studies.[11] To date, evidence of screening performance has not separately been analyzed by breast density and breast cancer risk. Greater clarity on this is essential since IC rates vary according to the combination of breast density category and breast cancer risk.[12]

The objective of this review was to provide an assessment of screening performance of supplemental imaging modalities for women with dense breasts by breast cancer risk categories. To synthesize all available evidence, an umbrella review of SRs and an analysis of primary studies identified via the umbrella review, alongside an updated systematic search to include the most recent evidence, were performed.

Methods

Funding and Conflicts of Interest

This work was funded by Bayer AG, and conducted by Wickenstones Ltd. Authors who are not employees of or consultants for the pharmaceutical industry (EM and GN) had control of inclusion of any data and information that might present a conflict of interest for those authors who are employees of or consultants for that industry.

Overview

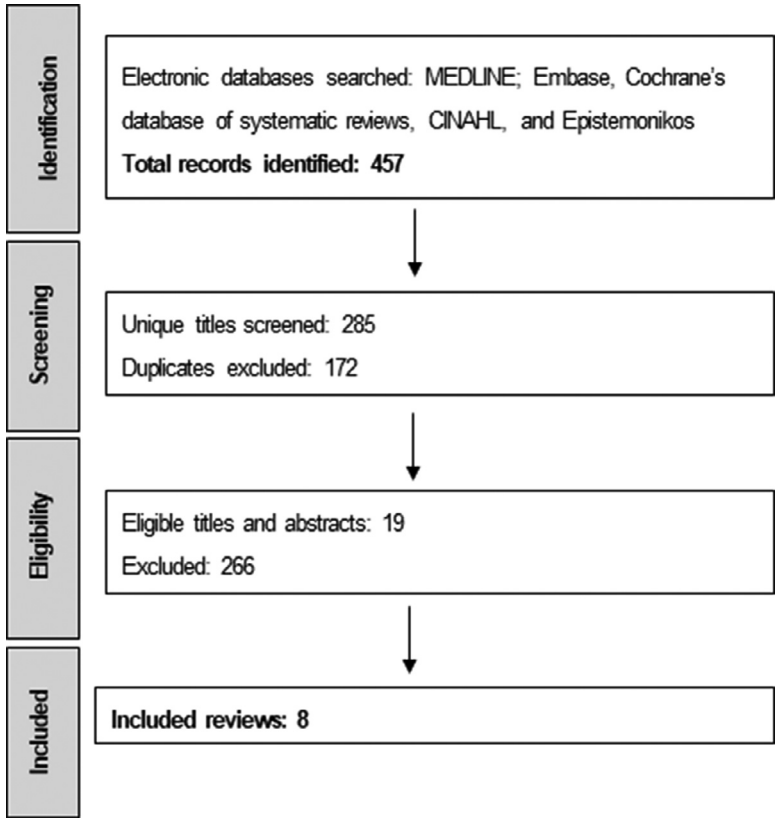
The protocol for this study was preregistered on PROSPERO: CRD42022293560. The umbrella review and updated systematic search were conducted in accordance with the Centre for Review and Dissemination (CRD) Handbook and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

As scoping searches identified that the existing literature was wide and nonhomogeneous, evidence was synthesized via two processes[1]: an umbrella review (an SR of previously published SRs or meta-analyses) and (2a) a primary studies analysis which evaluated data identified from unique primary studies contained within the SRs captured by the umbrella review; and (2b) analysis of primary studies identified by an updated systematic literature search. The methodology schematic is outlined in Figure 1.

Search Strategy and Eligibility Criteria

Umbrella Review Search Strategy. The search strategy for the umbrella review was developed iteratively. The search consisted of database specific syntax and free-text terms for "dense breasts", "mammography" and "screening test accuracy" combined with

Figure 2 PRISMA flow chart for the systematic reviews identified in the umbrella review.



terms for "systematic review" and "meta-analysis" (See S1 table for umbrella review search strategy).

The MEDLINE, Embase, Cochrane database of systematic reviews, CINAHL and Epistemonikos databases were searched electronically during October 2021 and included studies from 2000 to 2021. The search and eligibility criteria for the umbrella review were restricted to the following: SRs with or without meta-analysis, as the type of study; a population of asymptomatic women aged 40 to 75 years; and a comparison of at least one supplemental modality to mammography using screening accuracy and/or efficacy outcomes. Nineteen studies were eligible for full text review, 8 studies were then included following full text review. The 11 excluded studies did not provide specific data for the dense breast population.

The selection process of SRs for the umbrella review is summarised by the PRISMA diagram in Figure 2.

Primary Study Analysis Systematic Search Strategy. For the primary studies identified via the umbrella review, a list of studies from each included SR was compiled and duplicates removed. The remaining studies underwent full-text review according to the inclusion criteria for the updated systematic search.

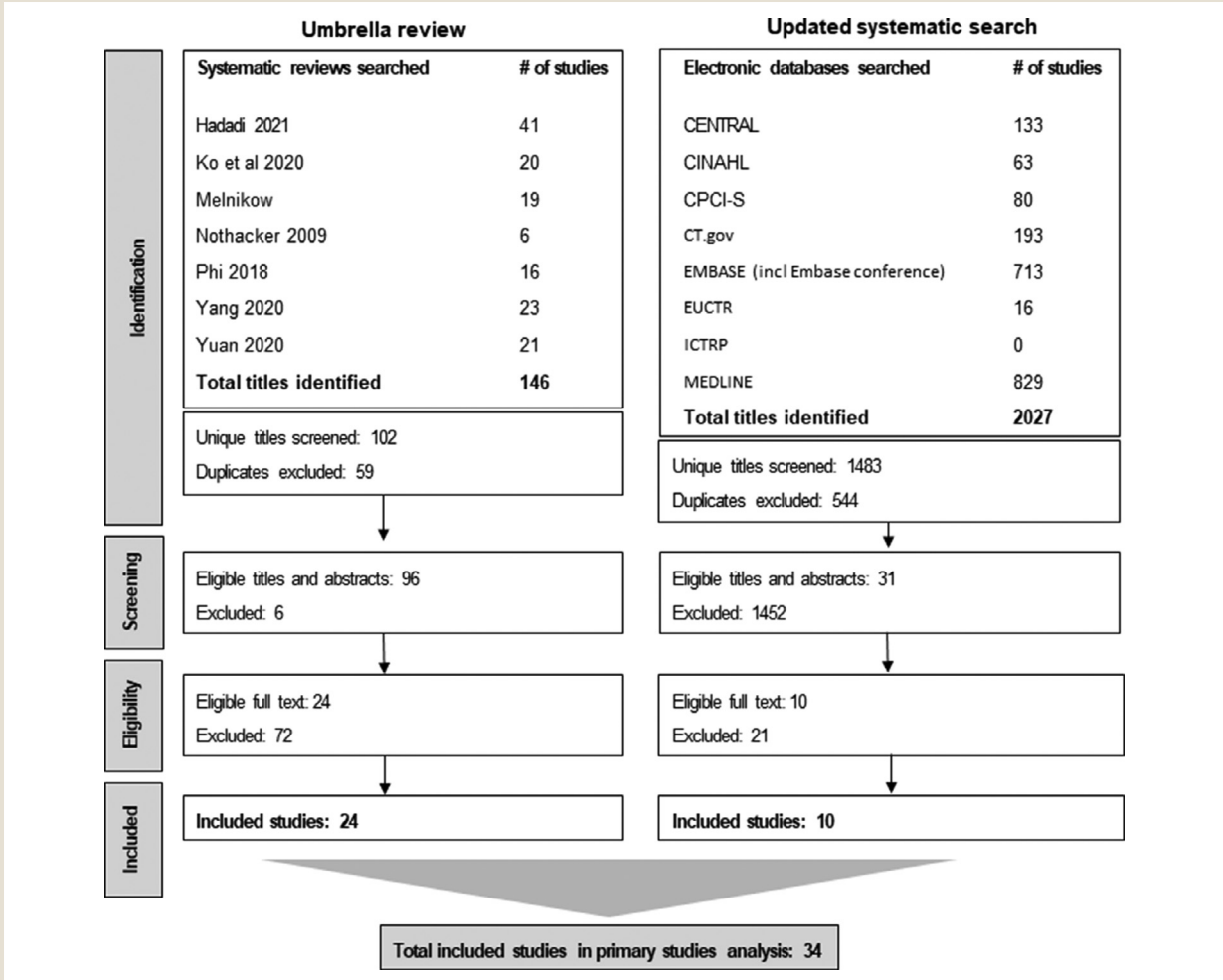
For the updated systematic search which was conducted to identify recent primary studies (2019-2021), the same search strategy and databases (MEDLINE, Embase, Cochrane database of systematic reviews, CINAHL and Epistemonikos databases) as the umbrella review were used, but only primary studies with randomized controlled trial (RCT) or observational study designs were included (See supplemental material S1 for systematic search strategy). Two researchers (BS and IM) independently screened the article titles and abstracts initially, and then subsequently by full text. Disagreements over study eligibility were resolved by consensus or recourse to a third researcher (AC).

The selection process of primary studies identified via the umbrella review and via the updated systematic search is summarised by the PRISMA diagram in Figure 3.

Data Extraction

Data extraction was conducted following predefined data collection forms by one researcher (LF) and independently checked by a second researcher (AC). The information collected for the primary studies included study information (author, year of publication, country, screening setting, study design, follow-up length, study size, supplemental modality examined, reference standard, per cent of women with dense breasts within the study), women's characteristics (mean age, ethnicity, personal history of cancer), screening accuracy outcomes (sensitivity and specificity), and screening

Figure 3 PRISMA flow chart for the unique primary studies identified from the umbrella review and updated systematic search (2019-2021).



efficacy outcomes (cancer detection rate [CDR], recall rate, biopsy rate, IC rate).

Data Analysis

Umbrella Review. Where pooled results were reported in the included SRs, the performance of supplemental screening modalities (accuracy [sensitivity, specificity] and efficacy [CDR (cancer detection rate), IC rate, recall rate, biopsy rate]) by breast density and cancer risk was summarised narratively.

Primary Studies Analysis. For the analysis of primary studies, the performance of screening modalities (accuracy [sensitivity, specificity] and efficacy [CDR (cancer detection rate), IC rate, recall rate, biopsy rate]) was evaluated for dense breast populations in the risk categories "average breast cancer risk" (equivalent to ACR "average-risk"), "intermediate breast cancer risk" (equivalent to ACR "increased-risk") and "mixed breast cancer risk" (included women who had either an average or intermediate breast cancer risk).[13]

Where risk categories were not clearly stated by the study, populations were assigned to the above risk categories according to the following assumptions. A study population was considered average risk if the study excluded women with either a personal history or family history (first degree relative) of breast cancer. If no information was reported on these exclusions, average risk was inferred if study recruitment was from a population-based screening program (the assumption being that any individual at higher risk would be part of a higher risk screening programme). A study population was considered intermediate risk if the study included women with either a personal history or family history (first degree relative) of breast cancer. In the absence of information on these clinical risk factors, intermediate risk was inferred if study recruitment was based on a self- or physician-referral (the assumption being that self-referring patients are probably aware of an additional risk factor they may have). A study population was considered mixed risk if there was no information on the screening population risk.

Only performance for the first round of screening (prevalent round) was analyzed since most studies only reported this screen-

Table 1 Characteristics of the 8 Systematic Reviews Included in the Umbrella Review Reporting Screening Accuracy and Efficacy Outcomes of Supplemental Modalities in Breast Cancer for Women With Dense Breasts

Author, Year	No. Databases Searched	Modalities Assessed	No. of Individual Studies	Review Period	Pooled Results for Dense Breast Populations	
Hadadi 2021[11]	6	HHUS, ABUS, DBT, CEM, MRI	41	Search completed 2019	HHUS	Sensitivity: 81%, Specificity: 84.3%
					ABUS	Sensitivity: 99.8%, Specificity: 74.6%
					DBT	Sensitivity: 91%, Specificity: 73%
					CEM	Sensitivity:83.6%, Specificity: 86.2%
					MRI	Sensitivity: 82%, Specificity: 80%
Ko 2020[15]	8	DBT	20	Search completed 2020	Sensitivity: 90%, Specificity: 90%	
Phi 2018[16]	2	DBT	16	2007-2017	CDR RR[a]: 1.33	
Melnikow 2016[19]	4	MRI, HHUS, ABUS, DBT	24	2000-2015	HHUS	Sensitivity: 80 – 83%, Specificity: 86 – 95%, CDR/1000: 4.4
					ABUS	CDR/1000: 1.9 – 15.2
					DBT	CDR/1000: 5.4 – 6.9
					MRI	Sensitivity: 75 – 100%, Specificity: 78 – 93%, CDR/1000: 3.5 – 28.6
Nothacker 2009[20]	3	ultrasound	6	2000-2008	-	
Ravert 2010[21]	6	ultrasound	15	2001-2009	Sensitivity: 13 – 100%, Specificity: 76 – 97%	
Yang 2020[17]	4	HHUS, ABUS	23	2003-2018	Sensitivity: 96%, Specificity: 93%, CDR/1000: 3.0	
Yuan 2020[18]	4	HHUS, ABUS	21	1980-2019	HHUS	Sensitivity: 99%, Specificity: 94%
					ABUS	Sensitivity: 69%, Specificity: 79%

Abbreviations: ABUS = automated whole breast ultrasound; BC = breast cancer; CDR = cancer detection rate; CEM = contrast-enhanced mammography; DBT = digital breast tomosynthesis; HHUS = handheld ultrasound; MRI = magnetic resonance imaging; RR = relative risk; - = not specified.
[a] RR of Supplemental modality vs mammography alone

ing round. Both sequential screening and simultaneous screening were considered. Sequential screening with a supplemental modality follows a negative mammogram while simultaneous screening is where the supplemental modality exam is interpreted in parallel with a mammogram.

A meta-analysis (bivariate random-effects model) to pool estimates of sensitivity and specificity by breast cancer risk was not feasible for two key reasons. Firstly, MRI, CEM, ABUS and DBT had an insufficient number of studies. Secondly, for ultrasound studies, heterogeneity was observed across study designs. This heterogeneity arose from varying follow-up times (range: 0-13 years), and in the use of the BI-RADS 3 assessment category.

Results

Umbrella Review: Heterogeneity Impairs Interpretability of Screening Performance Comparisons

Quality Assessment of Systematic Reviews Included in the Umbrella Review. Quality assessment of SRs was performed independently by two researchers (LF and AC) using the AMSTAR 2 tool.[14] According to their score, reviews were classified into three groups: low (AMSTAR score <4), moderate (AMSTAR score ≥4 and ≤7) and high quality (AMSTAR score ≥8) (See supplemental material S2 for a table of AMSTAR scoring for each review). Disagreements were resolved by consensus between the two researchers. No reviews were excluded for quality reasons.

Three SRs had AMSTAR scores that indicate high quality, while four had AMSTAR scores that indicate moderate quality (See supplementary material S2 for table of AMSTAR assessment for each study). One study had an AMSTAR score that indicates low quality.

Study Selection and Characteristics of Systematic Reviews in the Umbrella Review. Eight SRs were included from 457 records identified from the database search (Figure 2); of these, five were meta-analyses[11,15-18] and all were published between 2009 and 2021 (Table 1). Two SRs exclusively addressed the screening performance of multiple supplemental modalities,[11,19] including modalities with functional imaging capabilities such as contrast-enhanced MRI and CEM.[11] Four SRs examined supplemental ultrasound only[17,18,20,21] and the remaining two assessed supplemental DBT only.[15,16] Four presented findings following a negative mammogram (sequential screening).[17-20] Seven SRs evaluated, in pooled analyses, supplemental modality screening performance in dense breast populations. None evaluated supplemental modality screening performance by breast cancer risk.

Evidence Assessment of Systematic Reviews in the Umbrella Review. Overall, the SRs highlighted that study heterogeneity is a challenge in making robust comparisons of screening performance between supplemental modalities in populations with dense breasts. For example, one SR reported supplemental ultrasound pooled summary estimates to be potentially confounded by differences in study design.[18] These differences included sample size, length of follow-up, the definition of true-positive cases, image interpretation protocols, thresholds to establish recall, and radiological reading experience. A further example of heterogeneity was an SR reporting that some of its included studies included women with initially suspicious (BI-RADS category 4) rather than negative (BI-RADs category 1 or 2) mammography exams.[4]

All supplemental modalities reported in the included SRs (MRI, CEM, ultrasound [HHUS and ABUS] and DBT) had increased sensitivity and CDRs over mammography alone for the dense breast population, despite breast cancer risk variations in the study population and design characteristics. Two SRs reported DBT had an increased specificity over mammography alone[11,15] while all other supplemental modalities reported a decrease in specificity over mammography alone. None of the SRs reported screening performance by IC rates.

Of the supplemental modalities reported in the included SRs, supplemental MRI was found to have the greatest CDR compared to CEM, ultrasound, and DBT.[11,19] CDR with supplemental MRI ranged from 3.5 to 28.6 per 1,000 screens, compared to 4.4 per 1,000 screens with supplemental HHUS[19] and 5.4 to 6.9 with supplemental DBT.[19] Regarding screening accuracy, the sensitivity of supplemental MRI ranged from 75% to 100% and specificity from 78 to 93%. These estimates were based on unpublished MRI data cited by one of the SRs.[19] One other SR provided pooled summary estimates of MRI, with 82% for sensitivity and 80% for specificity.[11] In comparison, pooled summary estimates of supplemental HHUS sensitivity and specificity were 81% and 84.3% and pooled summary estimates for CEM were 83.6% and 86.2%.[11]

Primary Studies Analysis Identified via the Umbrella Review and Updated Systematic Search: Supplemental MRI Screening Performance Versus Other Imaging Modalities

Quality Assessment of Included Studies Within the Primary Studies Analysis. To assess the quality of the included primary studies, two researchers (LF and AC) independently used the QUADAS-2 tool. Ratings were given for each of the four domains: patient selection, index test, reference standard, and flow and timing. Discrepancies were resolved by consensus. Each study was given a final designation of low or high bias based on the domain scoring (See supplemental material S3 for a table of the QUADAS-2 assessment for each study).

The QUADAS-2 assessment results of the 34 studies included in the analysis of primary studies is shown in supplemental figure S3. The assessment indicated that 26 studies were at low risk of bias, and 8 studies were at higher risk of bias. The risk of bias was mainly due to nonconsecutive sampling, and the flow and timing of the reference standard.

Study Selection and Characteristics of Primary Studies Analysis. A total of 34 unique primary studies (24 unique primary studies contained with the SRs, and 10 from the updated SR search) were included in the analysis (Table 2 and Table 3). From the umbrella review, there were 102 unique primary studies identified in the eight SRs after removing duplicates[22-37] and following full-text review, 24 primary studies (published between 2000 and 2018) were retained (Figure 3), the majority of which examined supplemental HHUS (n=19). Other modalities included ABUS (n=4) and DBT (n=2). The updated systematic search (October 2019-2021) yielded 2027 studies; 31 were primary studies considered for full-text review, following which 10 studies were retained: four studies assessing DBT, two studies assessing HHUS, two studies assessing ABUS, one study examining MRI (full protocol) and one CEM.

Overall, there were 18 primary studies included in the analysis which followed a sequential and 16 a simultaneous screening approach (Table 2).

Average Breast Cancer Risk Population: Primary Studies Analysis.

Sequential Screening. HHUS

Among the 7 sequential screening studies assessing an average risk population, 6 were observational HHUS studies[23,24,33,35,36,38] and reported a wide range of screening accuracy estimates. Sensitivity ranged from 81.3% (78/96)[23] to 100% (3/3; 9/9)[23,33,38] while specificity ranged from 64% (1064/1653)[33] to 99% (5215/5271).[35] For HHUS, the recall rate ranged from 16.5[23] to 262.1,[30] while the biopsy rate ranged from 9.3[30] to 48.3[36] per 1,000 screens. The CDR range for HHUS was 2.0[33] to 4.9,[35] per 1,000 screens. IC rates reported by two observational HHUS studies reported an IC rate of 0.0 per 1,000 and had a follow-up of 1 year or less[24,30] (Table 2 and Table 3).

MRI

A single study, an RCT, assessed MRI, which detected 95% (79/83) of breast cancers missed by mammography and identified 92% (4325/4700) of women without breast cancer.[51] The CDR for MRI was 16.5 per 1000 screens which was higher numerically compared to the CDR range for HHUS (2.0[33]-4.9,[35] per 1000 screens). MRI screening was associated with a recall rate of 94.9 per 1000 screens. The IC rate (ICR) for MRI was 2.5 per 1000 across a 2-year follow up.

Simultaneous Screening. There were 13 simultaneous screening studies assessing an average risk population. Six were DBT studies,[39-44] 4 HHUS studies,[39,45-47] and 3 ABUS studies - none assessed MRI.[48-50] Only 1 DBT study provided estimates for sensitivity (99.1%)(106/107) and specificity (94.6%).[42] As with sequential ultrasound studies, simultaneous screening studies for ultrasound varied in their screening accuracy estimates. For HHUS, sensitivity ranged from 91.7%(22/24)[46] to 93.2%(41/44),[45] with specificity ranging from 85.4% (4950/5797)[45] to 98.1(2490/2537).[46] ABUS sensitivity ranged from 97.7% (42/43)[49] to 100% (11/11)[50] with specificity ranging from 98.4 (1641/1668)[50] to 99.7% (3408/3418).[49] The highest CDR estimates (per 1,000 screens) for HHUS (7.1),[45] ABUS (12.3)[49] and DBT (13.9)[40] based on simultaneous screening

Table 2 Characteristics of the Included Studies in the Primary Studies Analysis by Breast Cancer Risk and Screening Approach

Author, Year	Supplemental Modality	Country	Study Design	Sample Size	Mean Age (years)	Follow-up Period
Average breast cancer risk with dense breasts						
Sequential screening studies[a]						
Bakker 2019[51]	MRI	Netherlands	RCT	8061	55	2 years
Buchberger 2018[23]	HHUS	Austria	Retrospective	66680	-	1 year
Chang 2015[24]	HHUS	South Korea	Retrospective	730	-	1 year
Kim 2016[30]	HHUS	South Korea	Retrospective	3171	-	
Moon 2015[33]	HHUS	South Korea	Retrospective	2005	53	1 year
Tagliafico 2018[35]	HHUS	Italy	Prospective	3231	50	1 year
Weigert 2012[36]	HHUS	United States	Retrospective	8647	-	6 months
Simultaneous screening studies						
Harada-Shoji 2021[45]	HHUS	Japan	RCT	5797	44.5	9-13 years
Huang 2012[46]	HHUS	China	Prospective	3028	44.3	1.3 years
Korpraphong 2014[47]	HHUS	Thailand	Retrospective	12126	49.6	2 years
Starikov 2016[b39]	HHUS	United States	Retrospective	1875	-	1 year
Bernardi 2016[40]	DBT	Italy	Prospective	2592	58	Not reported
Moshina 2020[41]	DBT	Norway	RCT	14380	59	Not reported
Osteras 2018[42]	DBT	Norway	Prospective	8466	59	2 years
Pang 2021[43]	DBT	Canada	Retrospective	58281	59.3	1 year
Rose 2018[44]	DBT	United States	Retrospective	10360	-	1 year
Starikov 2016[b39]	DBT	United States	Retrospective	1397	-	1 year
Gatta 2021[48]	ABUS	Italy	Prospective	1165	49.1	2 years
Giuliano 2013[49]	ABUS	United States	Prospective	3418	54	1 year
Wilczek 2016[50]	ABUS	Sweden	Retrospective	1668	49.5	1 year
Intermediate breast cancer risk with dense breasts						
Sequential screening studies[a]						
Brancato 2007[22]	HHUS	Italy	Prospective	5227	52	2 years
Corsetti 2011[25]	HHUS	South Korea	Retrospective	260	-	1 year
De Felice 2007[27]	HHUS	Italy	Retrospective	1754	-	None
Girardi 2013[28]	HHUS	Italy	Retrospective	9960	51	1 year
Wu 2021[52]	HHUS	Canada	Retrospective	695	55	-
Simultaneous screening studies						
Lee 2019[54]	ABUS	United States	Prospective	121	53.1	1 year
Mixed breast cancer risk with dense breasts						
Sequential screening studies[a]						
Crystal 2003[26]	HHUS	United States	Retrospective	318	52	None
Hooley 2012[29]	HHUS	United States	Retrospective	648	52	> 15 months
Kolb 2002[31]	HHUS	United States	Retrospective	4897	55	Varied
Leong 2012[32]	HHUS	Singapore	Prospective	141	45	1-2 years
Parris 2013[34]	HHUS	United States	Retrospective	5519	52	None
Youk 2011[37]	HHUS	South Korea	Retrospective	1507	47	≥ 2 years

(*continued on next page*)

Table 2 (*continued*)

Author, Year	Supplemental Modality	Country	Study Design	Sample Size	Mean Age (years)	Follow-up Period
Simultaneous screening studies						
Brem 2015[55]	ABUS	United States	Prospective	15318	53.3	1 year
Kelly 2010[56]	ABUS	United States	Prospective	4419	53	1 year
Sorin 2018[57]	CEM	Israel	Retrospective	569	54	20 months

Abbreviations: ABUS, automated whole breast ultrasound; CEM, contrast-enhanced mammography; DBT, digital breast tomosynthesis; HHUS, handheld ultrasound; MRI, magnetic resonance imaging; RCT, randomized clinical trial; -, not reported.
[a] Sequential refers to studies with an initial negative mammogram
[b] Starikov 2016 contained results for both HHUS and DBT.

studies were all numerically lower than the CDR estimate from the sequential screening MRI RCT (16.5)[51] (Table 3).

Intermediate Breast Cancer Risk Population: Primary Studies Analysis. In the 7 studies with an intermediate breast cancer risk population, all assessed ultrasound only. There were 5 sequential screening studies that evaluated HHUS[22,23,27,28,52] and 1 simultaneous screening study that assessed ABUS.[54] Where screening accuracy estimates were available (n=3),[22,27,52] all HHUS studies had a 100% sensitivity with the specificity ranging from 90% (1567/1742)[27] to 98.8% (5164/5225).[22] There were no accuracy estimates for the simultaneous screening ABUS study. The CDR for HHUS studies ranged from 2.2[28] to 7.7 per 1,000 screens[53] (Table 3).

Mixed Breast Cancer Risk Population: Primary Studies Analysis. Among the eight mixed breast cancer risk population studies, all were observational studies and ultrasound was the most frequent supplemental modality examined.

HHUS

There were six sequential screening HHUS studies[29,31,32,34,37] and 2 simultaneous screening ABUS studies.[55,56] The screening accuracy estimates for HHUS were broadly similar to the intermediate breast cancer risk population; however, the CDRs varied widely. The highest CDR of 22.4 per 1,000 screens reported was based on an observational study where 62% had a personal history of cancer[37] (Table 3).

CEM

Only one simultaneous screening study assessed the screening performance of CEM,[57] 48.3% of the study population had a personal or family history of breast cancer, while 44.8% had both a personal or family history of breast cancer and dense breasts. This small observational study (n=536) reported 90.5%(19/21) and 76.1% (449/590), for sensitivity and specificity, respectively. The CDR was 31.1 per 1,000 screens.

Discussion

This study is the first to systematically assess the evidence for supplemental screening modalities in asymptomatic women with dense breasts by breast cancer risk.

Feasibility of Meta-analysis

Based on the umbrella review, previous evidence from SRs reported that MRI after a negative mammogram (sequential screening) had superior CDR and sensitivity over ultrasound, CEM and DBT. However, comparisons between these modalities were infeasible due to the evidence base identified in these SRs; there was substantial clinical heterogeneity, namely differences in underlying breast cancer prevalence across the primary studies. Nevertheless, average, intermediate and mixed breast cancer risk populations could be identified in the primary studies analysis from the umbrella review SRs and the updated systematic search. A comparison by meta-analysis of screening performance of the different screening modalities in dense breast populations by breast cancer risk was not feasible due to a lack of studies (MRI, CEM, DBT) and methodological heterogeneity (ultrasound). The findings were therefore summarised narratively.

Comparing Screening Modalities

For the average risk population, MRI had a superior screening performance (CDR) compared to the other assessed supplemental modalities HHUS, ABUS and DBT, as reported by both sequential or simultaneous screening studies. For the intermediate risk population, ultrasound (HHUS, ABUS) was the only supplemental modality assessed and its studies had a wide range of accuracy estimates. For the mixed risk population, CEM had the highest CDR (31.1 per 1000 screens) out of all 34 studies included in the primary analysis. This particular CEM study had a high proportion of women with personal and family history of breast cancer (with and without dense breasts).[57] While ICR reporting was sparse across the studies, for both MRI and CEM the ICR values had generally low estimates, which could indicate their superior effectiveness in decreasing breast cancer mortality.

While there is currently no consensus on optimal screening approach for women with dense breasts, and evidence gathered thus far does not enable full comparisons, the studies identified in the primary studies analysis suggest that supplemental MRI could be considered first choice for screening women with dense breasts and an average risk of breast cancer. The evidence for MRI as a supplemental modality is derived from a robust source – the Dense Tissue and Early Breast Neoplasm Screening (DENSE) RCT, with 2 years of follow-up.[51] The study reports higher CDRs and lower ICRs for MRI than for other modalities. In contrast, the available ultrasound

Table 3 Screening Accuracy and Performance for Supplemental Modalities of Studies in the Primary Studies Analysis by Breast Cancer Risk and Screening Approach

Author, Year	Supplemental Modality	Sensitivity (%)(n/N)	Specificity (%) (n/N)	Cancer Detection Rate (Per 1000 Screens)	Interval Cancer Rate (Per 1000 Screens)	Recall Rate (Per 1000 Screens)	Biopsy Rate (Per 1000 Screens)
Average breast cancer risk with dense breasts							
Sequential screening studies[a]							
Bakker 2019[51]	MRI	95.2 (79/83)	92.0 (4325/4700)	16.5	2.5	94.9	63.0
Buchberger 2018[23]	HHUS	81.3 (78/96)	99.1 (31567/31840)	3.9	-	16.5	9.3
Chang 2015[24]	HHUS	-	-	4.1	0.0	-	-
Kim 2016[30, c]	HHUS	100.0 (9/9)	74.0 (2340/3162)	2.8	0.0	262.1	46.0
Moon 2015[33, c]	HHUS	100.0 (3/3)	64.0 (1064/1653)	2.0	-	31.1	-
Tagliafico 2018[35]	HHUS	90.0 (26/29)	99.0 (5215/5271)	4.9	-	-	-
Weigert 2012[36]	HHUS	96.6 (28/29)	94.9 (7450/7851)	3.2	-	49.6	48.3
Simultaneous screening studies							
Harada-Shoji 2021[45]	HHUS	93.2 (41/44)	85.4 (4950/5797)	7.1	0.5	70	44
Huang 2012[46]	HHUS	91.7 (22/24)	98.1 (2490/2537)	-	-	-	-
Korpraphong 2014[47]	HHUS	No data	No data	7.9	-	-	7.9
Starikov 2016[b, 39]	HHUS	-	-	7.2	-	208	-
Bernardi 2016[40]	DBT	-	-	13.9	-	-	-
Moshina 2020[41]	DBT	-	-	-	-	41	-
Osteras 2018[42]	DBT	99.1(106/107)	94.6 (16787/17742)	-	-	-	-
Pang 2021[43]	DBT	-	-	6.5 (heterogenous), 4 (extremely)	-	270 (heterogenous), 266 (extremely)	-
Rose 2018[44]	DBT	-	-	3.5	-	132	20.4
Starikov 2016[b, 39]	DBT	-	-	5.3	-	104	-
Gatta 2021[48]	ABUS	No data	No data	6.8	-	26.6	14
Giuliano 2013[49]	ABUS	97.7(42/43)	99.7(3408/3418)	12.3	-	-	12.3
Wilczek 2016[50]	ABUS	100 (11/11)	98.4 (1641/1668)	6.6	3	22.8	13.8
Intermediate breast cancer risk with dense breasts							
Sequential screening studies[a]							
Brancato 2007[22]	HHUS	100.0 (2/2)	98.8 (5164/5225)	-	0.4	20.7	11.9
Corsetti 2011[25]	HHUS	-	-	7.7	0.0	-	-

(*continued on next page*)

Table 3 (*continued*)

Author, Year	Supplemental Modality	Sensitivity (%)(n/N)	Specificity (%) (n/N)	Cancer Detection Rate (Per 1000 Screens)	Interval Cancer Rate (Per 1000 Screens)	Recall Rate (Per 1000 Screens)	Biopsy Rate (Per 1000 Screens)
De Felice 2007[27, c]	HHUS	100.0 (12/12)	90.0 (1567/1742)	6.4	-	106.6	106.6
Girardi 2013[28]	HHUS	-	-	2.2	-	-	-
Wu 2021[52, c]	HHUS	100.0 (5/5)	98.3 (678/690)	7.2	1.4	24.5	-
Simultaneous screening studies							
Lee 2019[54]	ABUS	-	-	-	-	132	-
Mixed breast cancer risk with dense breasts							
Sequential screening studies[a]							
Crystal 2003[26, c]	HHUS	100.0 (7/7)	No data	4.6	0.0	-	25.0
Hooley 2012[29, c]	HHUS	100.0 (3/3)	94.9 (888/935)	4.6	-	56.7	56.7
Kolb 2002[31]	HHUS	-	-	2.5	-	-	23.9
Leong 2012[32, c]	HHUS	100.0 (2/2)	88.5 (92/104)	14.2	-	170.2	113.5
Parris 2013[34, c]	HHUS	100.0 (10/10)	96.8 (5334/5509)	1.8	-	33.5	32.8
Youk 2011[37]	HHUS	90.9 (10/10)	90.6 (394/435)	22.4	-	11.4	11.0
Simultaneous screening studies							
Brem 2015[55]	ABUS	100 (112/112)	72 (10954/15206)	7.3	-	284.9	74.3
Kelly 2010[56]	ABUS	81.0 (46/57)	No data	8.6	2.3	96	20.9
Sorin 2018[57]	CEM	90.5 (19/21)	76.1 (449/590)	31.1	3.3	-	-

Abbreviations: ABUS, automated whole breast ultrasound; CEM, contrast-enhanced mammography; DBT, digital breast tomosynthesis; HHUS, handheld ultrasound; MRI, magnetic resonance imaging; RCT, randomized clinical trial; -, not reported.
[a] Sequential refers to studies with an initial negative mammogram
[b] Starikov 2016 contained results for both HHUS and DBT.
[c] Where a paper states there has been either no follow-up (or it is assumed due to the lack of information) or no interval cancers, the number of false negatives is zero and the sensitivity is therefore 100%.

evidence reports a wide range of accuracy estimates from observational studies with typically insufficient follow-up (1 year or less), which may also explain the lower ICR of ultrasound compared to MRI.

Limitations of Ultrasound Evidence Base

In the primary studies analysis, most screening studies assessed supplemental ultrasound imaging. However, various considerations call into question the evidence base for supplemental ultrasound, especially since numerous sensitivity estimates were close to or at 100%. Firstly, the screening accuracies reported for supplemental ultrasound from observational methodology studies have low validity. The sensitivity of ultrasound is also very unlikely to be higher than MRI, since the ACRIN 6666 study showed that MRI as an add-on to supplemental ultrasound still detects a significant number of cancers.[58] Furthermore, HHUS accuracy may be overestimated as several studies had reported insufficient follow-up time periods which may result in not fully accounting for interval cancers arising from false negatives. Additionally, most of the ultrasound evidence was based on HHUS rather than ABUS. HHUS is an operator-dependent modality requiring skilled sonographers and, therefore, has a high potential for screening accuracy to vary widely.[18] Finally, the wide range of reported screening accuracy and CDR estimates for ultrasound within the average risk group can be explained by the ratio of heterogenous to extremely dense breasts, the type of screening population assessed (self-referral vs. population-based screening), different follow-up periods, and the differential use of BI-RADS criteria for intermediate findings. Several studies categorized BI-RADS 3 recommendations as negative which would overestimate ultrasound specificity.

Limitations of Functional Imaging Evidence

A typical concern in selecting MRI as the first-choice supplemental modality is the perception of high recall and false positive rates. However, the high recall rate observed in the DENSE trial may be explained by radiologists' lack of experience reading screening MRI exams for women with dense breasts during the first screening round results. The second round (incident) recall rates were much lower, 32 recalls per 1000 screens versus 94.9 per 1000 screens in the first round.[59] Furthermore, the false-positive rate of MRI may be overestimated since lesions having a false-positive diagnosis are more likely to represent proliferative and atypical histological features, which have clear clinical implications in breast cancer management.[60] The low false-negative rate of MRI should also be considered when selecting a supplemental modality. False negatives have the potential to delay the detection of breast cancer. Missed cancers are represented as interval cancers, which are typically late-stage (larger, node-positive) cancers which require more costly, aggressive treatment.[12]

CEM, where contrast-enhanced and low-energy images (which are similar to 2D mammograms) are interpreted together, is a promising alternative screening modality to MRI because of its high CDR and low ICR. While its outcomes were similar to MRI as reported in the DENSE RCT, they were based on a small observational study whose population consisted of a high proportion of women with a personal history of breast cancer.[57] Future experimental studies should enable the evaluation of the screening performance of CEM in women with average risk and dense breasts. This analysis suggests that supplemental DBT (mammography combined with DBT) is unlikely to be superior to supplemental MRI since its CDR was broadly similar to supplemental ultrasound (3.5 to 6.5 per 1000 screens). While one DBT study reported a high CDR of 13.9 per 1000 screens this could be explained by the study design using multiple sequential reads and duplicating the double-reading practice.[40]

Limitations of This Study

This umbrella review with an analysis of primary studies has some limitations. First, a summary estimate for the screening accuracy for supplemental ultrasound studies could not be produced using a bivariate random-effects meta-analysis due to an insufficient number of studies for breast cancer risk groups. Second, the primary studies analysis required assumptions to be made for studies that did not classify breast cancer risk according to ACR categories. Average risk was inferred if study recruitment was from a population-based screening program, assuming that any individual at higher risk would be part of a higher risk screening program. However, it is possible that some population-based screening programs do not exclude women with a family history of breast cancer. Any studies coming from the United States would be of women coming due to either self or physician referral, no matter their risk level. Third, the umbrella review and the updated search focused on supplemental screening in addition to mammography, not DBT. Some healthcare systems in Europe and the United States are adopting DBT as the standard screening modality. However, initial scoping searches indicated that there is no published evidence on supplemental screening modalities in addition to DBT. Further, since the evidence base for supplemental DBT suggests it does not provide a substantial improvement to mammography it is plausible to assume outcomes may be similar.

Conclusions

There remains a paucity of supplemental screening studies comparing functional imaging modalities, such as MRI and CEM, to more conventional imaging such as ultrasound. The included ultrasound studies were limited mostly by study design. The single included primary study on MRI, an RCT, demonstrated superior screening performance for MRI versus other modalities for dense breast populations with average breast cancer risk. There was no evidence for MRI in an intermediate breast cancer risk population. The single included primary study on CEM suggests that it is a promising alternative to MRI for its high CDR and low ICR; however, further studies are needed, particularly among women with average risk and dense breasts. Regardless of modality, all women with dense breasts may benefit from supplemental screening after mammography or DBT.

Clinical Practice Points

- Women with dense breasts have an increased breast cancer risk through two causes: (1) having dense breast tissue is an independent, major risk factor for breast cancer (2) having dense breasts

is associated with increased false-negative findings in mammography and thus an increased risk of interval cancer.
- To date, evidence of breast cancer screening performance has not individually been analyzed by breast density and breast cancer risk.
- The objective of this review was to provide an assessment of screening performance of currently available supplemental imaging modalities for women with dense breasts, by breast cancer risk categories. To synthesize all available evidence, an umbrella review of systematic reviews and an analysis of primary studies identified via the umbrella review, alongside an updated systematic search to include the most recent evidence, were performed.
- The recently published DENSE trial in the Netherlands produced the most robust data available for the use of supplemental MRI screening in the extremely dense breast population.[51] However, our analysis highlights that caution must be taken when making recommendations on any optimal supplemental screening modality for women with dense breasts. Additional future studies are needed which take account of breast cancer risk in this population and address methodological and analytical issues. These issues are seen with ultrasound data, where some published data doesn't align with expert clinical experience.
- The USPSTF is currently reviewing the guidelines on breast cancer screening and this original review contributes to the evidence base to support recommendations.

Funding

This work was funded by Bayer AG, and conducted by Wickenstones Ltd.

Conflicts of interest

The authors have no other conflicts of interest. Authors who are not employees of or consultants for the pharmaceutical industry (EM and GN) had control of inclusion of any data and information that might otherwise present a conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clbc.2023.04.003.

References

1. Thigpen D, Kappler A, Brem R. The role of ultrasound in screening dense breasts-a review of the literature and practical solutions for implementation. *Diagnostics (Basel)*. 2018;8(1):20.
2. Radiology ACo. *Breast Imaging Reporting & Data System (BI-RADS®) System Atlas*. 5th ed. Reston, VA: American College of Radiology; 2003.
3. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst*. 2014;106(10):dju255.
4. Eriksson L, Czene K, Rosenberg LU, Tornberg S, Humphreys K, Hall P. Mammographic density and survival in interval breast cancers. *Breast Cancer Res*. 2013;15(3):R48.
5. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2006;15(6):1159–1169.
6. von Euler-Chelpin M, Lillholm M, Vejborg I, Nielsen M, Lynge E. Sensitivity of screening mammography by density and texture: a cohort study from a population-based screening program in Denmark. *Breast Cancer Res*. 2019;21(1):111.
7. Vegunta S, Kling JM, Patel BK. Supplemental Cancer Screening for Women With Dense Breasts: Guidance for Health Care Professionals. *Mayo Clin Proc*. 2021;96(11):2891–2904.
8. Mann RM, Athanasiou A, Baltzer PAT, et al. Breast cancer screening in women with extremely dense breasts recommendations of the European Society of Breast Imaging (EUSOBI). *Eur Radiol*. 2022;32(6):4036–4045.
9. Smetana GW, Elmore JG, Lee CI. Burns RB. Should This Woman With Dense Breasts Receive Supplemental Breast Cancer Screening? *Annals of Internal Medicine*. 2018;169(7):474–484.
10. Densebreast io. Comparative Analysis of State Density Inform Efforts and Insurance Coverage. New York City; 2022.
11. Hadadi I, Rae W, Clarke J, McEntee M, Ekpo E. Diagnostic performance of adjunctive imaging modalities compared to mammography alone in women with non-dense and dense breasts: a systematic review and meta-analysis. *Clin Breast Cancer*. 2021;21(4):278–291.
12. Kerlikowske K, Zhu W, Tosteson AN, et al. Identifying women with dense breasts at high risk for interval cancer: a cohort study. *Ann Intern Med*. 2015;162(10):673–681.
13. Radiology ACo. Understanding Your Breast Cancer Risk: General Guidance. Reston, Virginia. 2020. Available from: https://www.acr.org/-/media/ACR/Files/Breast-Imaging-Resources/Care-Toolkit/Patient-Breast-Cancer-Risk-Assessment-Handout.pdf.
14. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
15. Ko MJ, Park DA, Kim SH, et al. Accuracy of digital breast tomosynthesis for detecting breast cancer in the diagnostic setting: a systematic review and meta–analysis. *Korean J Radiol*. 2021;22(8):1240–1252.
16. Phi XA, Tagliafico A, Houssami N, Greuter MJW, de Bock GH. Digital breast tomosynthesis for breast cancer screening and diagnosis in women with dense breasts - a systematic review and meta-analysis. *BMC Cancer*. 2018;18(1):380.
17. Yang L, Wang S, Zhang L, et al. Performance of ultrasonography screening for breast cancer: a systematic review and meta-analysis. *BMC Cancer*. 2020;20(1):499.
18. Yuan WH, Hsu HC, Chen YY, Wu CH. Supplemental breast cancer-screening ultrasonography in women with dense breasts: a systematic review and meta-analysis. *Br J Cancer*. 2020;123(4):673–688.
19. Melnikow J, Fenton JJ, Whitlock EP, et al. Supplemental screening for breast cancer in women with dense breasts: a systematic review for the U.S. preventive services task force. *Ann Intern Med*. 2016;164(4):268–278.
20. Nothacker M, Duda V, Hahn M, et al. Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review. *BMC Cancer*. 2009;9:335.
21. Ravert PK, Huffaker C. Breast cancer screening in women: an integrative literature review. *J Am Acad Nurse Pract*. 2010;22(12):668–673.
22. Brancato B, Bonardi R, Catarzi S, et al. Negligible advantages and excess costs of routine addition of breast ultrasonography to mammography in dense breasts. *Tumori*. 2007;93(6):562–566.
23. Buchberger W, Geiger-Gritsch S, Knapp R, Gautsch K, Oberaigner W. Combined screening with mammography and ultrasound in a population-based screening program. *Eur J Radiol*. 2018;101:24–29.
24. Chang JM, Koo HR, Moon WK. Radiologist-performed hand-held ultrasound screening at average risk of breast cancer: results from a single health screening center. *Acta Radiol*. 2015;56(6):652–658.
25. Corsetti V, Houssami N, Ghirardi M, et al. Evidence of the effect of adjunct ultrasound screening in women with mammography-negative dense breasts: interval breast cancers at 1 year follow-up. *Eur J Cancer*. 2011;47(7):1021–1026.
26. Crystal P, Strano SD, Shcharynski S, Koretz MJ. Using sonography to screen women with mammographically dense breasts. *AJR Am J Roentgenol*. 2003;181(1):177–182.
27. De Felice C, Savelli S, Angeletti M, et al. Diagnostic utility of combined ultrasonography and mammography in the evaluation of women with mammographically dense breasts. *J Ultrasound*. 2007;10(3):143–151.
28. Girardi V, Tonegutti M, Ciatto S, Bonetti F. Breast ultrasound in 22,131 asymptomatic women with negative mammography. *Breast*. 2013;22(5):806–809.
29. Hooley RJ, Greenberg KL, Stackhouse RM, Geisel JL, Butler RS, Philpotts LE. Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. *Radiology*. 2012;265(1):59–69.
30. Kim S-Y, Kim MJ, Moon HJ, Yoon JH, Kim E-K. Application of the downgrade criteria to supplemental screening ultrasound for women with negative mammography but dense breasts. *Medicine*. 2016;95(44):e5279.
31. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology*. 2002;225(1):165–175.
32. Leong LC, Gogna A, Pant R, Ng FC, Sim LS. Supplementary breast ultrasound screening in Asian women with negative but dense mammograms-a pilot study. *Ann Acad Med Singap*. 2012;41(10):432–439.
33. Moon HJ, Jung I, Park SJ, Kim MJ, Youk JH, Kim EK. Comparison of cancer yields and diagnostic performance of screening mammography vs. supplemental screening ultrasound in 4394 women with average risk for breast cancer. *Ultraschall Med*. 2015;36(3):255–263.
34. Parris T, Wakefield D, Frimmer H. Real world performance of screening breast ultrasound following enactment of Connecticut Bill 458. *Breast J*. 2013;19(1):64–70.
35. Tagliafico AS, Mariscotti G, Valdora F, et al. A prospective comparative trial of adjunct screening with tomosynthesis or ultrasound in women with mammography-negative dense breasts (ASTOUND-2). *Eur J Cancer*. 2018;104:39–46.
36. Weigert J, Steenbergen S. The connecticut experiment: the role of ultrasound in the screening of women with dense breasts. *Breast J*. 2012;18(6):517–522.

37. Youk JH, Kim EK, Kim MJ, Kwak JY, Son EJ. Performance of hand-held whole-breast ultrasound based on BI-RADS in women with mammographically negative dense breast. *Eur Radiol*. 2011;21(4):667–675.
38. Kim WH, Chang JM, Koo HR, et al. Impact of prior mammograms on combined reading of digital mammography and digital breast tomosynthesis. *Acta Radiol*. 2017;58(2):148–155.
39. Starikov A, Drotman M, Hentel K, Katzen J, Min RJ, Arleo EK. 2D mammography, digital breast tomosynthesis, and ultrasound: which should be used for the different breast densities in breast cancer screening? *Clin Imaging*. 2016;40(1):68–71.
40. Bernardi D, Macaskill P, Pellegrini M, et al. Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. *Lancet Oncol*. 2016;17(8):1105–1113.
41. Moshina N, Aase HS, Danielsen AS, et al. Comparing screening outcomes for digital breast tomosynthesis and digital mammography by automated breast density in a randomized controlled trial: results from the to-be trial. *Radiology*. 2020;297(3):522–531.
42. Østerås BH, Martinsen ACT, Gullien R, Skaane P. Digital mammography versus breast tomosynthesis: impact of breast density on diagnostic performance in population-based screening. *Radiology*. 2019;293(1):60–68.
43. Pang JX, Newsome J, Sun M, et al. Impact of switching from digital mammography to tomosynthesis plus digital mammography on breast cancer screening in Alberta, Canada. *J Med Screen*. 2021;29:38–43.
44. Rose SL, Shisler JL. Tomosynthesis impact on breast cancer screening in patients younger than 50 years old. *AJR Am J Roentgenol*. 2018;210(6):1401–1404.
45. Harada-Shoji N, Suzuki A, Ishida T, et al. Evaluation of adjunctive ultrasonography for breast cancer detection among women aged 40-49 years with varying breast density undergoing screening mammography: a secondary analysis of a randomized clinical trial. *JAMA Netw Open*. 2021;4(8).
46. Huang Y, Kang M, Li H, et al. Combined performance of physical examination, mammography, and ultrasonography for breast cancer screening among Chinese women: a follow-up study. *Curr Oncol*. 2012;19(Suppl 2):eS22–eS30.
47. Korpraphong P, Limsuwarn P, Tangcharoensathien W, Ansusingha T, Thephamongkhol K, Chuthapisith S. Improving breast cancer detection using ultrasonography in asymptomatic women with non-fatty breast density. *Acta Radiol*. 2014;55(8):903–908.
48. Gatta G, Cappabianca S, La Forgia D, et al. Second-generation 3D automated breast ultrasonography (Prone ABUS) for dense breast cancer screening integrated to mammography: effectiveness, performance and detection rates. *J Pers Med*. 2021;11(9):875.
49. Giuliano V, Giuliano C. Improved breast cancer detection in asymptomatic women using 3D-automated breast ultrasound in mammographically dense breasts. *Clin Imaging*. 2013;37(3):480–486.
50. Wilczek B, Wilczek HE, Rasouliyan L, Leifland K. Adding 3D automated breast ultrasound to mammography screening in women with heterogeneously and extremely dense breasts: report from a hospital-based, high-volume, single-center breast cancer screening program. *Eur J Radiol*. 2016;85(9):1554–1563.
51. Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI screening for women with extremely dense breast tissue. *N Engl J Med*. 2019;381(22):2091–2102.
52. Wu T, Warren LJ. The added value of supplemental breast ultrasound screening for women with dense breasts: a single center Canadian experience. *Can Assoc Radiol J*. 2022;73(1):101–106.
53. Corsetti V, Houssami N, Ferrari A, et al. Breast screening with ultrasound in women with mammography-negative dense breasts: evidence on incremental cancer detection and false positives, and associated cost. *Eur J Cancer*. 2008;44(4):539–544.
54. Lee JM, Partridge SC, Liao GJ, et al. Double reading of automated breast ultrasound with digital mammography or digital breast tomosynthesis for breast cancer screening. *Clin Imaging*. 2019;55:119–125.
55. Brem RF, Tabar L, Duffy SW, et al. Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. *Radiology*. 2015;274(3):663–673.
56. Kelly KM, Dean J, Comulada WS, Lee SJ. Breast cancer detection using automated whole breast ultrasound and mammography in radiographically dense breasts. *Eur Radiol*. 2010;20(3):734–742.
57. Sorin V, Yagil Y, Yosepovich A, et al. Contrast-enhanced spectral mammography in women with intermediate breast cancer risk and dense breasts. *AJR Am J Roentgenol*. 2018;211(5):W267–WW74.
58. Berg WA, Zhang Z, Lehrer D, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA*. 2012;307(13):1394–1404.
59. Veenhuizen SGA, de Lange SV, Bakker MF, et al. Supplemental breast MRI for women with extremely dense breasts: results of the second screening round of the DENSE Trial. *Radiology*. 2021;299(2):278–286.
60. Kuhl CK, Keulers A, Strobel K, Schneider H, Gaisa N, Schrading S. Not all false positive diagnoses are equal: o the prognostic implications of false-positive diagnoses made in breast MRI versus in mammography /digital tomosynthesis screening. *Breast Cancer Res: BCR*. 2018;20(1):13.