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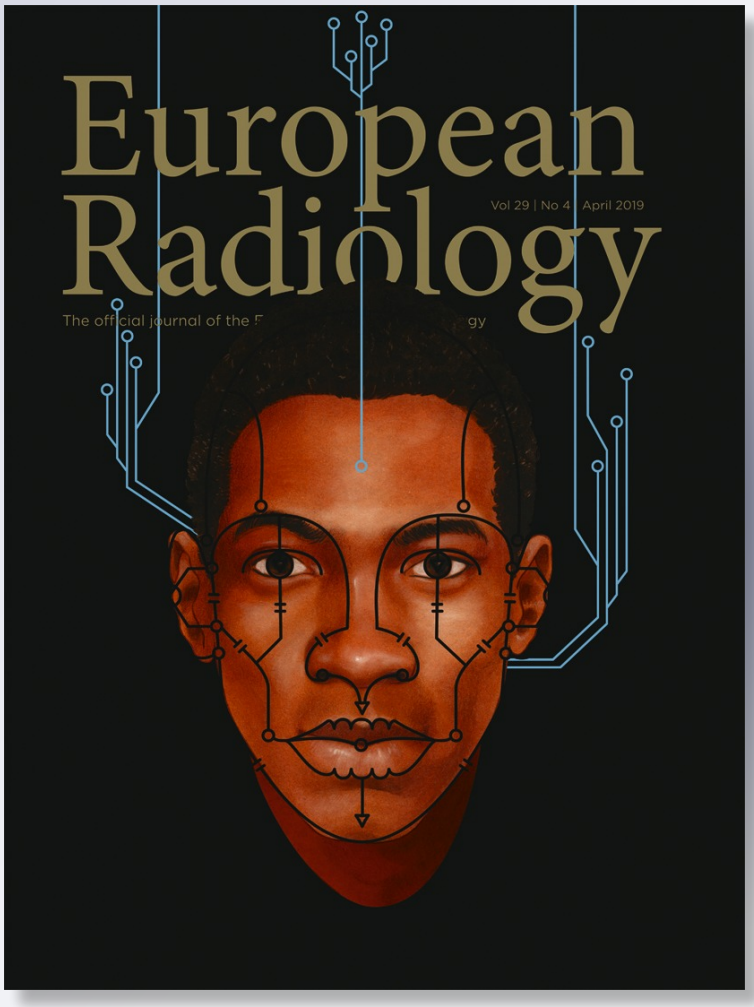

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BREAST

Breast density implications and supplemental screening

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Abstract

Digital breast tomosynthesis (DBT) has been widely implemented in place of 2D mammography, although it is less effective in women with extremely dense breasts. Breast ultrasound detects additional early-stage, invasive breast cancers when combined with mammography; however, its relevant limitations, including the shortage of trained operators, operator dependence and small field of view, have limited its widespread implementation. Automated breast sonography (ABS) is a promising technique but the time to interpret and false-positive rates need to be improved. Supplemental screening with contrast-enhanced magnetic resonance imaging (MRI) in high-risk women reduces late-stage disease; abbreviated MRI protocols may reduce cost and increase accessibility to women of average risk with dense breasts. Contrast-enhanced digital mammography (CEDM) and molecular breast imaging improve cancer detection but require further validation for screening and direct biopsy guidance should be implemented for any screening modality. This article reviews the status of screening women with dense breasts.

Key Points

- *The sensitivity of mammography is reduced in women with dense breasts. Supplemental screening with US detects early-stage, invasive breast cancers.*
- *Tomosynthesis reduces recall rate and increases cancer detection rate but is less effective in women with extremely dense breasts.*
- *Screening MRI improves early diagnosis of breast cancer more than ultrasound and is currently recommended for women at high risk. Risk assessment is needed, to include breast density, to ascertain who should start early annual MRI screening.*

Keywords Breast density · Screening ultrasound · Breast cancer · Tomosynthesis · Magnetic resonance imaging

Abbreviations

ABS	Three-Dimensional Automated Breast Sonography
ACRIN	American College of Radiology Imaging Network
ASTOUND	Adjunct Screening with Tomosynthesis or Ultrasound in women with mammography-Negative Dense breasts trial
BCSC	Breast Cancer Surveillance Consortium
BI-RADS	Breast Imaging Reporting and Data System
CESM	Contrast-enhanced spectral mammography
DBT	Digital breast tomosynthesis
DCIS	Ductal carcinoma in situ
EASY	European Asymptomatic Screening Study
ER	Estrogen receptor
EUSOBI	European Society of Breast Imaging
GC-HBOC	German Consortium for Hereditary Breast and Ovarian Cancer
HHUS	Hand-held ultrasound
ICDR	Incremental cancer detection rate
MBI	Molecular breast imaging
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PHBC	Personal history of breast cancer
PPV	Positive predictive value
STORM	Screening with Tomosynthesis or Standard Mammography trial
US	Ultrasound

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Introduction

Mammography remains the primary screening method for breast cancer as it is proven to reduce breast cancer mortality by about 20% on long-term follow-up in randomised trials [1, 2]. In observational studies, breast cancer mortality reduction is 25–31% for women invited for screening, versus 38–48% for women actually screened [3, 4]. Mammography only reduced mortality in trials where detection of node-negative invasive cancers improved as a result of screening [5].

Not all women benefit equally from mammography. Women at high risk for breast cancer because of pathogenic mutations have a high rate of 'interval cancers' detected because of lumps or other symptoms after a normal mammogram and before the next recommended screen [6–8]. Interval cancers typically have worse prognosis than screen-detected cancers. Interval cancer rates increase with increasing breast density [9] and are elevated in women with a personal history of breast cancer [10].

In women where mammography performs less well, there is interest in supplemental screening with MRI or ultrasound or other methods. Randomised trials of supplemental screening to examine mortality reduction would be prohibitively expensive and require long-term (> 10 years) follow-up, by which time the technologies will have changed so that results would be outdated. We should, instead, examine impact on intermediate endpoints, such as node-negative invasive cancer detection and interval cancer rates, which are expected to translate to reduced mortality from breast cancer [11, and references within]. In a successful screening program, interval cancers should represent fewer than 10% of all cancers. The purpose of this review is to examine such intermediate endpoints for women with dense breasts undergoing supplemental screening.

Breast density, risk and masking effect

Wolfe first related nodular dense patterns of breast tissue on mammography to risk of developing breast cancer [12], finding a 37-fold higher risk with the most nodular/dense pattern compared to the least nodular pattern. An analysis of the Dutch mammography screening program [13], which uses the Wolfe classification, showed a 41% mortality reduction in women with non-dense breasts (relative risk of death, RR, 0.59 [95% CI 0.44–0.79]) compared to a 13% reduction in women with dense breasts (RR 0.87 [95% CI 0.52–1.45]). Insofar as the confidence interval widely overlaps 1 in women with dense breasts, there may be no net benefit of mammography screening in women with dense breasts.

Gram et al [14] described five density patterns of Tabár that are used in the Swedish screening program. Only the two nodular and very dense patterns (IV and V) have been associated with increased risk of developing breast cancer of 2.4-fold, though the uniformly concave pattern I can also mask breast cancer [15, 16]. At 25 years of follow-up, women with dense breasts had a 1.9-fold higher mortality rate from breast cancer compared to women with fatty breasts, which was primarily attributed to higher incidence of disease [15].

The Breast Imaging Reporting and Data System (BI-RADS) [17] categories of breast density (developed through the American College of Radiology) are usually included in mammographic reports: (A) almost entirely fatty; (B) scattered areas of fibroglandular density; (C) heterogeneously dense, which may obscure detection of small masses, and (D) extremely dense, which lowers the sensitivity of mammography (Fig. 1). The latter two categories are considered 'dense'. In the latest edition of BI-RADS, greater emphasis is placed on the masking effect: In breasts where even a region of the breast is dense, small non-calcified masses can be hidden, and such breasts should be classified as heterogeneously dense [17].

Approximately 43% of women aged 40–74 years have dense breasts [18]. Around menopause, breast density tends to decrease in some women as the glandular tissue involutes (Fig. 2). Automated software programs have been developed for quantitative, reliable measurement of breast density [19–21]. Methods implemented for assessment of mammographic breast density include visual, semi- or fully automated approaches that include quantitative measurement of area-based or volumetric parameters. Visual, qualitative methods are based on human judgement and are therefore subjective; inter-observer variability can be significant among radiologists, whereas automated quantitative software provides results that are less subjective and more consistent [22].

Mammographic density is one of the strongest risk factors for breast cancer: Women with extremely dense breasts have a four- to sixfold higher risk of developing breast cancer compared to those with fatty breasts [16]. It is estimated that density accounts for 39% of premenopausal and 26% of postmenopausal breast cancer [23]. Breast density is now incorporated in some risk models and should be considered in risk-based screening and targeted prevention [24, 25].

Breast density decreases the sensitivity of mammography due to masking of non-calcified cancers, potentially delaying diagnosis with worse outcomes [26–28]. Studies have highlighted a decrease in the sensitivity of mammography from a level of 85.7–88.8% in women with almost entirely fatty breasts to 62.2–68.1% in women with extremely dense breasts [29, 30]; mammographic sensitivity in dense breasts is under 50% when screening ultrasound has been performed and closer to 33% in studies where MRI has been included [31]. Cancers in women

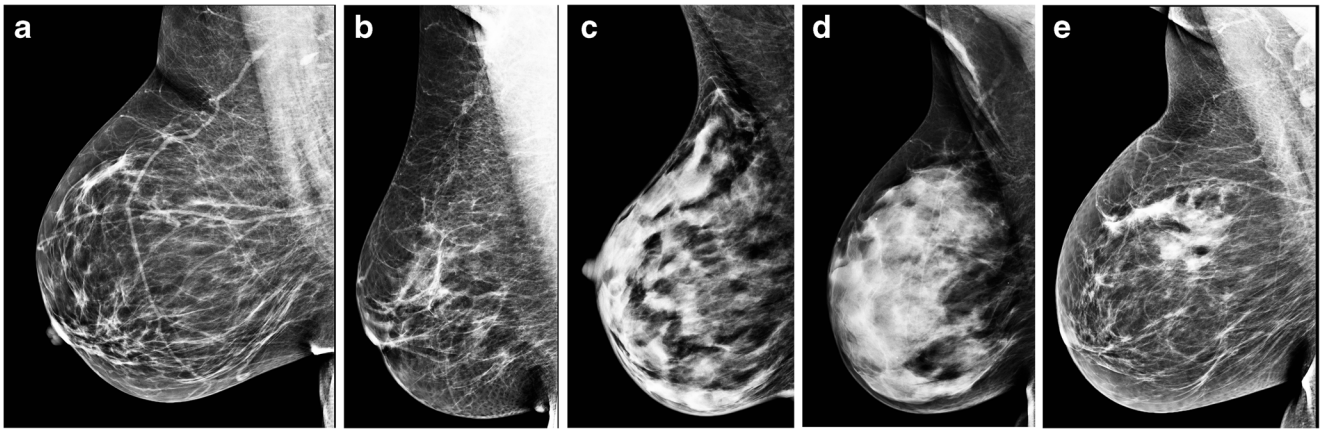

Fig. 1 Examples of each category of breast composition: (**a**) fatty; (**b**) scattered fibroglandular density; (**c**) heterogeneously dense which could obscure detection of small masses; and (**d**) extremely dense which lowers the sensitivity of mammography. A breast which is heterogeneously dense in only one quadrant as in (**e**) should be classified as heterogeneously dense.

with dense breasts tend to be larger at detection [32]; this may be due to more rapidly growing tumours, delayed detection, or both.

Full-field digital mammography has a slightly higher sensitivity compared to analogue film-screen mammography in women with dense breasts [33]. Recently the European Society of Breast Imaging (EUSOBI) and 30 national breast radiology bodies recommended the adoption of digital mammography as a first priority to improve mammographic sensitivity in women with increased breast density [34].

Beyond 2D mammography

Digital breast tomosynthesis (DBT)

Tomosynthesis, also known as 3D mammography, is a digital mammographic technique where low-dose images are acquired from multiple angles as the x-ray tube moves in an arc over the breast. Data from these projection images are typically reconstructed into 1-mm slices [35]. Automated breast density software has been developed for DBT with documented reliability of volumetric measurements [21, 36].

Three prospective population-based trials, the STORM trial from Italy [37] and the Oslo tomosynthesis trials [38, 39], showed that adding DBT to digital mammography resulted in an additional 2.7 and 2.3 cancers detected per 1,000 screens, respectively. Friedewald et al [40], using historical multicentre data, showed that adding DBT improved cancer detection by 1.2 (95% CI, 0.8–1.6) per 1,000 screens. DBT improved cancer detection and reduced recalls in the subgroups of women with scattered fibroglandular density and heterogeneously dense breasts; there was no significant drop in recalls from DBT in women with fatty breasts and no improvement in cancer detection in women with extremely dense breasts [41]. Similar results were reported by Kim et al [42]. Meta-analysis has shown an absolute reduction in recall rate of 0.8–3.6% [43] from tomosynthesis and this benefit appears sustained [44], though further validation is needed.

Screening ultrasound

Multiple studies have shown supplemental screening with ultrasound (US) after mammography in women with dense breasts increases breast cancer detection by 1.8–4.6 cancers per 1,000 women screened (Fig. 3), depending on disease prevalence [45–50]. Across 25 series, encompassing 363,886 screens, 842 cancers have been reported seen only with screening US (2.3 per 1,000) (Table 1) [26–28, 45, 47–49, 51–55, 56–63].

The proportion of invasive carcinomas detected on US that are node negative exceeded 80% in 16 of 20 studies where reported and exceeded 90% in nine of 19 studies averaging 583/688 (84.7%) overall (Table 1). Similar supplemental cancer detection was shown each year for three years in ACRIN 6666 [48]. Excellent outcomes from cancers detected at supplemental screening with US have been observed in a multicentre retrospective analysis with 7-year follow-up of 501 women reported by Kim et al [64] who found that women with US-detected cancer had 98% 5-year disease-free survival. The Japan Strategic Anti-cancer Randomised Trial (J-START) [58] showed significantly higher sensitivity in women assigned supplemental US (intervention) compared to the control group assigned only mammography. Cancers detected in the intervention arm were more frequently stage 0 and I (144/202 [71.3%] vs. 79/152 [52.0%], $p = 0.0194$).

Interval cancers are those detected because of clinical symptoms in the interval between recommended screens. Interval cancer rates are reduced by addition of screening ultrasound to mammography, and in all studies were less than 10% of all cancers [58, 65]. In the ACRIN 6666 study, the interval cancer rate was 9/111 (8%) across 3 years of study, suggesting that

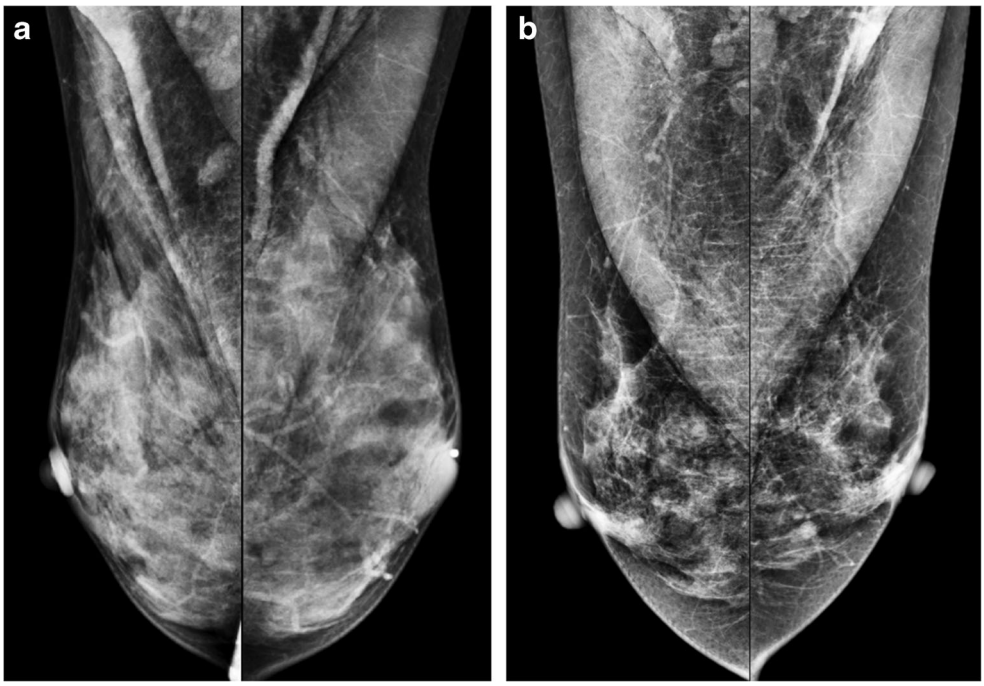

Fig. 2 Breast density tends to decrease with age, particularly around menopause. (**a**) Bilateral mediolateral oblique (MLO) mammograms in this 47-year-old woman show extremely dense parenchyma. The patient went through menopause at age 48. (**b**) Bilateral MLO mammograms 4 years later (same patient) show decrease in breast density, now heterogeneously dense, due to normal perimenopausal involutionary changes

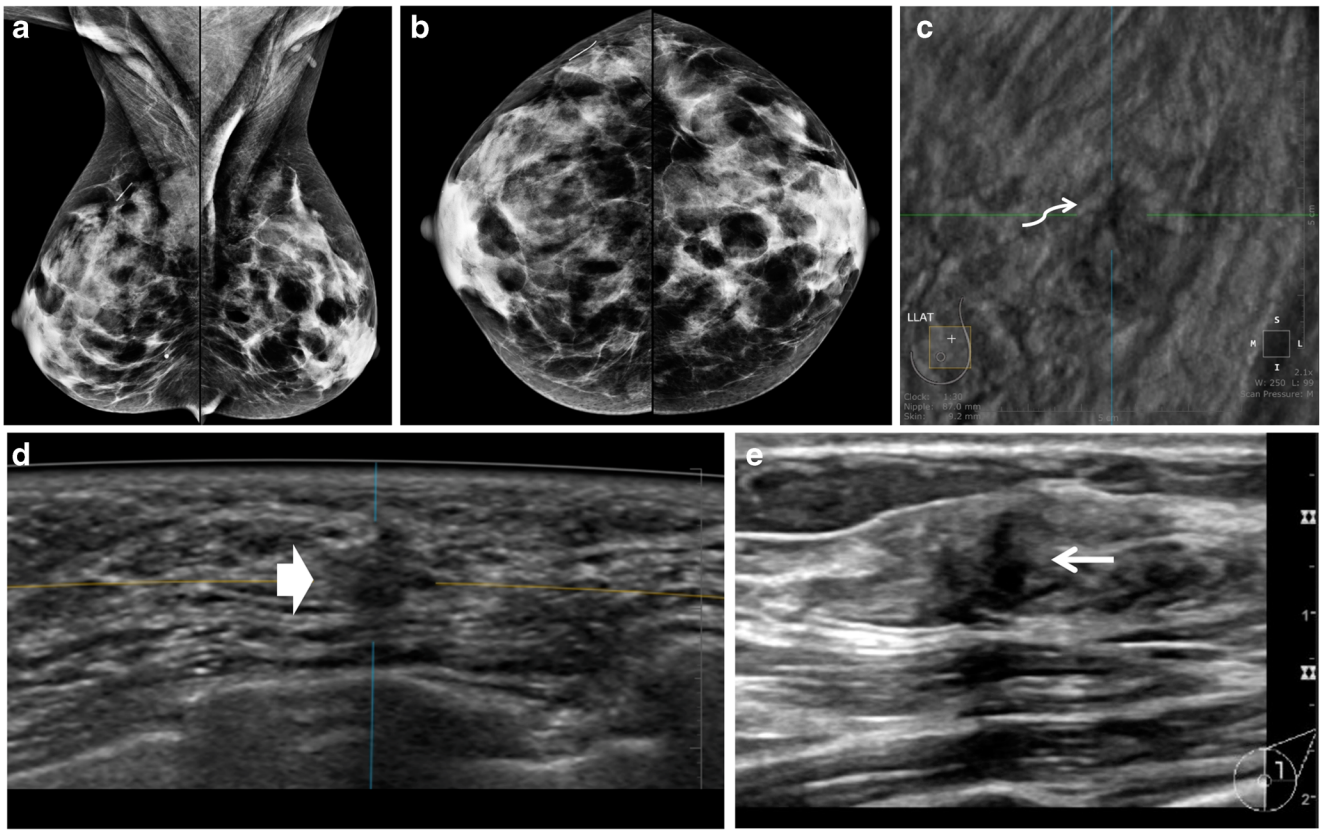

Fig. 3 This 52-year-old woman has heterogeneously dense parenchyma as seen on (**a**) MLO and (**b**) craniocaudal mammograms which are otherwise negative. Due to breast density, automated screening US (ABS) was also performed. (**c**) Coronal ABS left upper outer breast shows possible hypoechoic mass and distortion (curved arrow). (**d**) Transverse ABS confirms an irregular, hypoechoic mass (short arrow). (**e**) Targeted HHUS shows an irregular 0.9 cm mass (arrow), highly suspicious for malignancy. Biopsy showed grade 2 invasive lobular carcinoma, ER(+), PR/HER2(-), Ki-67 <1%, 0.8 cm at excision, with negative sentinel node biopsy

combined ultrasound and mammography was an effective strategy in women with a personal history of breast cancer or other intermediate risk factors and dense breasts [48]. In J-START, the interval cancer rate was halved, to 0.5 per 1000, representing 18/202 (8.9%) cancers, in the arm receiving screening US.

Analysis of results from technologist-performed handheld screening US (HHUS) using standard documentation has shown a cancer detection rate of 2.5 per 1,000 [66] that appears to be slightly lower than the 5.3 per 1,000 rate observed across physician-performed screening US studies, though in part this reflects differences in disease prevalence [45, 47, 48]. HHUS is limited by a shortage of well-trained physicians and technologists, small field of view, and the requirement that a finding must be observed during scanning (operator dependence). Importantly, however, operator dependence for screening ultrasound is not worse than variation in mammographic interpretation [67]. Berg et al found high reliability of 11 experienced breast imaging radiologists in detecting and characterising lesions larger than 9 mm with US in patients [68] and for 64 specialist radiologists for lesions 5–9 mm in size in phantoms [69].

False positives increase when ultrasound is added to mammography. A 15.1% (95% CI: 13.5–16.6) absolute increase in call-backs was observed with the first, prevalent, screen in ACRIN 6666, which dropped to 7.4% (95% CI: 6.6–8.2) for incidence screens when prior US was available [48]. For technologist-performed US, Weigert et al [59] observed a 12.0% absolute increase in recalls in the first round of screening, which dropped to an average 9.9% in subsequent years.

In order to separate detection from image acquisition, and thereby potentially improve the availability of screening US, automated breast sonography (ABS) has been developed. Typically using a field of view of 15 cm and 3–5 acquisitions per breast, ABS can provide standardised examinations and global visualisation of the breast tissue. Such an examination produces several thousand images for review; the interpretation time in published series varies between 2.9 min and 9 min [55, 57, 70, 71]. As with every imaging modality, there is a learning curve, depending on individual radiological experience and protocols [55]. ABS can be used for the measurement of breast density [72, 73], but incorporation of such techniques into clinical practice remains investigational.

ABS showed incremental cancer detection rate (ICDR) of 30 cancers among 15,318 women screened (2.0 per 1,000) in a prospective multicentre study [57]. Of the 30 cancers detected only with ABS, 28 (93.3%) were invasive with a mean size of 12.9 mm and 25/27 (92.6%) invasive cancers staged were node negative. The absolute increase in recall rate was 13.5% [57] (Table 1) and, importantly, recalls from ABS are for immediate additional evaluation usually with HHUS. By comparison, a final assessment is typically rendered from HHUS (to include biopsy or short-interval follow-up), with only 50/16,676 (0.3%) technologist-performed HHUS examinations recalled for immediate additional evaluation (BI-RADS 0) across five series [66].

A study from Sweden, the European Asymptomatic Screening STUDY (EASY), showed an ICDR of 2.4 per 1,000 women screened with ABS and almost stable recall rate of 2.3% [55]. In a reader study, ABS significantly increased detection of breast cancer with insignificant increase in false-positive rate [74]. A few studies comparing ABS and HHUS have shown similar lesion visualisation and assessments [75, 76]. Barriers to ABS implementation include the several thousand images to be reviewed with average 6-min interpretation time [55] and learning curve to dismiss artefactual posterior shadowing at the interface of fat lobules [55, 57, 71]. A few studies have shown that addition of computer-assisted detection can reduce time needed to interpret ABS without loss of diagnostic accuracy [77, 78].

Two studies have compared the performance of supplemental DBT and US in cancer detection in women with dense breasts and normal 2D mammography (Table 2). Interim analysis of first-year results among 3,231 women in the ASTOUND trial [79] reported 24 additional cancers detected (23 invasive): DBT showed 13 (ICDR, 4.0 per 1,000 screens; 95% CI, 1.8–6.2) and physician-performed HHUS significantly more at 23 (ICDR, 7.1 per 1,000 screens; 95% CI, 4.2–10.0, $p = 0.006$), while incremental false-positive recall and added biopsy rates were similarly low [79]. Destounis et al [80, 81] retrospectively analysed results from 7,146 women with dense breasts screened with DBT followed by technologist-performed HHUS. That study reported on 39 cancers (30 invasive); four of them were recognised only by DBT versus 17 (invasive) cancers solely by HHUS, with the few DBT-only detected cancers seen as calcifications [80]. Further study is ongoing.

Magnetic Resonance Imaging (MRI)

According to American College of Radiology guidelines, supplemental MRI is recommended annually beginning at age 25–30 years in women at high risk for breast cancer [82]. The National Comprehensive Cancer Network (NCCN) guidelines recommend MRI instead of mammography from ages 25–29 years in high-risk women and thereafter as a supplement to mammography [83]. Importantly the Gail and BCSC models should not be used for estimating risk pertinent to deciding on MRI screening, though the Claus model can be used [82]. NCCN recommends MRI also be considered for supplemental screening in women with prior atypical biopsy or lobular carcinoma in situ due to a lifetime risk of 20% or more [84], and the American College of Radiology recently recommended annual supplemental MRI screening for all women with a personal history of breast cancer diagnosed by age 50 years and for those diagnosed later with dense breasts [85]. The relative amount of fibroglandular tissue should be included in the MRI report, together with background parenchymal

Table 1 Results of studies examining screening ultrasound as an adjunct to mammography in women with dense breasts

Author, year	No. of women with cancer [a]	No. of women screened	CDR per 1,000	Net added recalls due to US, n (% of screens)	Biopsy rate, n (%)[b]	PPV3 of biopsies prompted only by US (%)[c]	No. invasive, grade	Mean size (mm, range)	Node negative (%)	DCIS (% of cancers), grade	BI-RADS 3 due to US, n (%)	Comments[d]
Single-centre studies												
Gordon, 1995	30	12,706	2.4	NR	NR	44/279 (16)	44, no details about grade	11 (4–25)	NR	0	NR	Diagnostic population
Buchberger, 2000	40[e]	8,970	4.5	NR	NR	40/405 (9.9)	35, no details about grade	9.1 (4–20)	33/35 (94.3)	5 (12.5), no details about grade	NR	8,103 women in a screening population and 867 in a diagnostic population
Kaplan, 2001	5	1,862	3.2	176 (9.5)	97 (5.2)	6/96 (6.3)	5, no details about grade	9 (6–14)	5/5 (100)	1 (16.7), no details about grade	72 (3.9)	Technologist performed
Kolb, 2002	34	5,418 women, 13,547 screens	2.7	799 (5.9)	NR	37/358 (10)	36, no details about grade	9.9 (range: NR)	25/28 (89.3)[f]	1 (2.7), no details about grade	NR	1,354 exams in women with abnormal mammogram or CBE
Crystal, 2003	7	1,517	4.6	90 (5.9)	38 (2.5)	7/38 (18)	7; 1 low, 1 intermediate, 4 high grade and 1 lobular	9.6 (4–12)	6/7 (85.7)	0	NR	
Leconte, 2003	16	4,236	3.8	NR	NR	NR	14, no details about grade	7 (4–17)	NR	2 (12.5), no details about grade	NR	Included 136 women with palpable mass
Brancato, 2007	2	5,227	0.4	NR	65 (1.2)	2/65 (3.1)	2, no details about grade	NR	2/2 (100)	0	NR	Mammography-negative women
De Felice, 2007	12	1,754	6.8	NR	46 (2.6)	NR	10, no details about grade	10 (5–15)	10/10 (100)	2 (16.7), no details about grade	NR	
Youk, 2011	17	1,418	12.0	200	80 (5.6)	17/80 (21.3)	NR[g]	13 (6–20)	NR[g]	NR[g]	176 (12.4)	Mammography-negative women, retrospective database review, general screening and personal history of breast cancer subsets
Hooley, 2012	3	935	3.2	234 (25.0)	53 (5.7)	3/63 (4.8)	2, no details about grade	6.3 (5–9)	2/2 (100)	1 (33.3), no details about grade	187 (20.0)	Technologist performed
Parris, 2013	10	5519	1.8	680 (12.3)	181 (3.3)	10/181 (5.5)	10, no details about grade	9.7 (4–15)	7/9 (77.8)	0	452 (8.2)	Technologist performed
Girardi, 2013	19 22	12,171 (fatty) 9960 (dense)	1.6 2.2	NR	422 (1.9)	41/422 (9.7)	37, no details about grade	8 (5–12)	36/37 (97.3)	4 (9.8), no details about grade	NR	Mammography-negative women
Bae, 2014	329	106,829 women, 116,656 screens	3.1	NR	NR	NR	282, no details about grade	NR[h]	253/282 (89.7)	53 (15.8) no details about grade	NR	Retrospective database review
Korpraphong, 2014	19	14,483 screens	1.4	NR	NR	NR	NR	NR	NR	NR	NR	Women of all breast densities

Table 1 (continued)

Author, year	No. of women with cancer [a]	No. of women screened	CDR per 1,000	Net added recalls due to US, n (% of screens)	Biopsy rate, n (%)[b]	PPV3 of biopsies prompted only by US (%)[c]	No. invasive, grade	Mean size (mm, range)	Node negative (%)	DCIS (% of cancers), grade	BI-RADS 3 due to US, n (%)	Comments[d]
Chang, 2015	5	990	5.1	366 (37.0)	84 (8.5)	5/84 (6.0)	3 (1 low, and 2 intermediate)	6 (0–15)	3/3 (100)	2 (40)	282 (28.5)	
Moon, 2015	3	1656	1.8	592 (35.7)	86 (5.2)	2/86 (2.3)	1	9	1/1 (100)	1 (50)	504 (30.4)	1 ILC assessed as BI-RADS 3 was detected at 11 months
Wilczek, 2016	4	1,668	2.4	15 (0.9)	12 (0.7)	4/12 (33)	4 (2 low, 1 intermediate, 1 high grade)	10 (6–14)	2/4 (50)	0	NR	ABS, technologist performed
Destounis, 2017	18	4,898 women, 5,434 screens	3.3	NR	100 (2.0)	18/100 (18.0)	18 (5 low, 7 intermediate, 4 high grade and 2 not specified)	1–5 mm: 1 case; 6–10 mm: 7 cases; 11–15 mm: 4 cases; 16–20 mm: 1 case; >20 mm: 4 case; not specified: 1 case	14/18 (78.0)	0	101 (1.9)[i]	Retrospective review
Multicentre Studies												
Corsetti, 2008	37[e]	9,157	4	NR	449 (4.9)	50/449 (11.1)[j]	36, no details about grade	NR[k]	31/36 (86.1)	1 (2.7), no details about grade	NR	Self-referred women; 13/50 cancers excluded (palpable or symptoms)
Kelly, 2010	23[e]	4,419 women, 6,425 screens	3.6	557 (8.7)	75 (1.2)	23/75 (30.7)	22 (7 low, 13 intermediate, 2 high)	5 mm or less: 1 case; 6–10 mm: 13 cases; 11–20 mm: 6 cases; 21–50 mm: 1 case; >50 mm: 1 case	NR	1 (4.3), no details about grade	77 (1.2)	Automated arm, technologist acquired
Berg, 2012, prevalence	14	2,659	5.3	401 (15.1)	207 (7.8)	12/207 (5.8)	30 (11 low, 7 intermediate, 6 high, 5 lobular and 1 mixed ductal--lobular)	10 (median; range: 2–40)	29/30 (96.7)	2 (6.25) (1 intermediate- and 1 high-grade)	284 (10.7)	1st screen; at least 1 other risk factor, 20% were high-risk women; ≥ BI-RADS 3 = positive.
Berg, 2012, incidence	18	4,841 screens	3.7	356 (7.4)	242 (5.0)	18/242 (7.4)					180 (3.7)	Year 2, 3 screens; 612 women had MR screen after year 3 US screen
Weigert, 2017, prevalence	11	2,706	4.1	325 (12.0)	151 (5.6)	11/151 (7.3)	9 (1 low, 6 intermediate, 2 high)	25 (12–80)	7/9 (77.8)	2 (18.2), all intermediate grade	174 (6.4)	Technologist performed, BI-RADS 3 or higher considered recall as presented
Weigert, 2017, Incidence[l]	30	10,810 screens	2.8	1073 (9.9)	379 (3.5)	30/379 (7.9)	25 (3 low, 17 intermediate, 5 high grade)	10.9 (4–30)	20/25 (80.0)	5 (16.7) (4 intermediate, 1 high grade)	694 (6.4)	Technologist performed, BI-RADS 3 or higher considered recall as presented

Table 1 (continued)

Author, year	No. of women with cancer [a]	No. of women screened	CDR per 1,000	Net added recalls due to US, n (% of screens)	Biopsy rate, n (%)[b]	PPV3 of biopsies prompted only by US (%)[c]	No. invasive, grade	Mean size (mm, range)	Node negative (%)	DCIS (% of cancers), grade	BI-RADS 3 due to US, n (%)	Comments[d]
Brem, 2015	30	15,318	2.0	2063 (13.5)	551 (3.6)	30/551 (5.4)	28, no details about grade	12.9	25/27 (92.6)	2 (6.7), no details about grade	19 (0.1)	ABS, technologist performed
Ohuchi, 2016	67	36,752	1.8	1932 (5.25)	NR	NR	55, no details about grade	14.2	47/55 (85.5)	11 (16.7), no details about grade	NR	Women aged 40-49 with any breast density
Buchberger, 2018	36	66,680	0.5	397 (0.60)	201 (0.30)	36/201 (17.9)	33, no details about grade	14 (median; 3–32)	25/33 (75.8)	3 (8.3), no details about grade	1255 (1.9)	Population-based observational study in Tyrol, Austria ages 40-69, all breast densities

ABS Automated Breast Sonography, *BI-RADS*, Breast Imaging Reporting and Data System, *CDR* cancer detection rate, *DCIS* ductal carcinoma in situ, *NR* not reported, *PPV* positive predictive value, *US* ultrasonography

[a] Number or women found to have cancer on screening ultrasound

[b] Percent of women who underwent biopsy due to screening US

[c] Percent of lesions biopsied due to screening US that were malignant

[d] Studies utilised physician (radiologist) performed handheld screening ultrasound unless otherwise specified

[e] These studies referred to numbers of cancers (and not to the number of women)

[f] Kolb et al provided this information for 28 of 36 invasive cancers

[g] Youk et al provided data about eight of ten cancers diagnosed in the general screening arm (seven of eight were DCIS or stage 1; one of eight was node positive)

[h] Bae et al did not report mean tumour size or range but 176/335 (53%) were minimal cancers and 52 (16%) were stage II

[i] Destounis et al provided this as a fraction of screens

[j] Thirteen of these women were found to have symptoms and were excluded from 'US-screen-detected' cancers

[k] Corsetti et al did not provide the mean tumour size or range but 3/36 were stage T1a, 20/36 T1b, 10/36 T1c, 2/36 T2 and 1/36 stage T3

[l] Five women with high-risk lesions are not included among women with cancer. In year 4 of Weigert et al of 3,331 US, 53 recommended biopsies, ten cancers, 358 BI-RADS 3: higher PPV3 but very high BI-RADS 3 rate

Table 2 Results of studies comparing performance of tomosynthesis (DBT) and ultrasound in women with mammography negative dense breasts

Author, year	Total no. of cancers	No. of women screened	No. of cancers detected only by DBT	No. of cancers detected only by US	CDR of DBT	CDR of US	Recall rate of DBT	Recall rate of US	PPV3 of DBT	PPV3 of US	Comments
Tagliafico, 2016	24	3,231	1	11	4.0	7.1	53 (1.7)	65 (2.0)	13/35 (37.1)	23/47 (48.0)	Mammography-negative women; interim analysis of 1st year results
Destounis, 2017	39	7,146	4	17	3.0	4.9	NR	NR	NR	NR	Retrospective review

CDR cancer detection rate per 1,000 screens, *DBT* Digital Breast Tomosynthesis, *NR* not reported, *US* ultrasonography

enhancement (BPE); BPE may correlate even more strongly with risk of developing breast cancer [86]. Breast density can be quantified on MRI but this is not routine [87].

The sensitivity of MRI in high-risk women varies across studies from 71% to 100%, but importantly is not influenced by breast density. A meta-analysis of 11 studies showed a sensitivity of 77% for the performance of MRI alone and 94% when MRI was combined with mammography [88]. However, according to recent studies, simultaneous screening mammography has minimal added value in the detection of breast cancer in women who undergo screening with MRI [89–91], particularly in women with pathogenic *BRCA1* mutations [92]. Prospective cohort studies have shown a cancer detection rate for MRI alone of 8.2–15.9 per 1,000 [88, 93–95].

In women with familial high-risk, the sensitivity of MRI is not affected by breast density; therefore, the National Institute for Health and Care Excellence [96] and the GC-HBOC [97] recommend annual MRI alone for the evaluation of women with familial high risk between the ages of 30–39 years without a personal history of the disease. Annual MRI surveillance increases the detection of small invasive cancers in pathogenic BRCA1/BRCA2 carriers. Although there are important differences in the natural history of breast cancers in *BRCA1* compared with *BRCA2* mutation carriers, an analysis by Heijnsdijk et al [92] showed that implementation of MRI improved metastasis-free survival in both carrier subgroups after an average of three rounds of screening per woman; eight interval cancers occurred in 801 *BRCA1* mutation carriers (representing 10.9% of all cancers in that subgroup, 3.6 per 1,000 screens) compared to two among 474 *BRCA2* mutation carriers (representing 3.9% of all cancers in that subgroup, 1.7 per 1,000 screens). The faster growth rate of triple-negative and basal phenotype tumours common in women with pathogenic *BRCA1* mutations should be kept in mind [98, 99]. To address this, some high-risk screening programs recommend 6-month surveillance with clinical examination and/or breast US in addition to annual screening with MRI [100], though generally screening US is not of benefit in women screened by MRI [31, 90, 91, 95]. Modelling studies suggest 6-month alternating mammography and MRI yields slightly better outcomes than concurrent annual screening, with earlier detection of node-negative invasive cancers in high-risk women [101, 102].

False-positive rates represent a point of discussion regarding MRI screening; specificity of MRI varies across studies [31, 95, 103, 104], with recall rates centred at approximately about 10% [105–107]. Positive predictive value of biopsies performed (PPV3) after MRI ranges between 22.0% and 63.2% [101–107]. As for screening mammography and ultrasound, false positives are highest for prevalent screening MRI and decrease with subsequent rounds [103].

Importantly, MRI has been shown to downstage the disease [95]. Warner et al reported reduced advanced stage (stage II–IV) disease (1.9% vs. 6.6% among matched controls not able to have MRI) and increased node-negative invasive cancers in the MRI group (85% vs. 54% in the control group) [108].

Excluding those who have bilateral mastectomy, women with a personal history of breast cancer (PHBC) have a higher risk of the disease compared to pathogenic mutation-free women with a family history [109], with lifetime risk of a second cancer exceeding 20% for those diagnosed by age 50 years or those diagnosed later with dense breasts [85]. Mammographic sensitivity is reduced and interval cancer rate is at least doubled in women with PHBC [10]. When PHBC is present, MRI has considerably increased sensitivity compared to mammography; cancer detection rate for MRI is 10–29 cancers per 1,000 screens in such women [85, 109–113]. It has been shown that the addition of MRI in the surveillance of women with PHBC before the age of 50 years improves the detection of aggressive cancers and reduces the interval cancer rate [114].

One prospective observational study was conducted by Kuhl et al [104] to investigate the utility and accuracy of MRI as a supplemental screening tool in women at average risk for breast cancer. This study showed an overall supplemental cancer detection rate of 15.5 per 1,000 screens (supplemental cancer detection rate 22.6 per 1,000 cases at initial screening and 6.9 per 1,000 cases at subsequent screening rounds) across all density categories; 85% of women with incident cancers had been screened with US also within the study. MRI-depicted cancers were small (median: 8 mm), node negative (93.4%) and 43% were high-grade; DCIS

Table 3 Performance of Abbreviated Screening Breast MRI

Author, year	No. of cancers[a]	No. of women screened	CDR per 1,000 screens	Population	Biopsy rate[b] (BR4 or 5, %)	PPV3 of bx (%)[c]	BR 3	Overall recall rate (%)
Kuhl, 2014	11	443 women 606 screens	18.2	105 women only dense 220 PHBC 118 family hx	45 (10.2)	11/45 (24.4)	53 (8.7)	98/606 (16.2)
Jain, 2016	9	591	15.2	High-risk	39 (6.6)	10/40 (25.0)	NS	39/591 (6.6)
Chen, 2017[e]	13[e]	356	36.5	Dense; 6 PHBC; 29 family hx	59 (16.6)	13/59 (22.0)[f]	NS[f]	59/356 (16.6)
Strahle, 2017	6[g]	671	8.9 all 16.3 dense	367 dense; 141 had family hx; no PHBC or known *BRCA* mutation	16 (2.4) 16 (4.4) dense	7/17 (41.2)	0	16/671 (2.4) all 16/367(4.4) dense
Panigrahi, 2017[h]	14	746 women 1052 screens	13.3	High risk	47 (6.3)	14/46 (30.4)	35 (3.3)	82/1052 (7.8)
Choi, 2018	12[i]	725 women 799 screens	15.0	PHBC	14 (1.9)	12/19[i] (63.2)	83 (10.4)[i]	97/799 (12.1)
	Magnet (T)	C+ sequences	T2/STIR		No.of invasive cancers	Mean size (mm, range)	Node negative (%)	No. of DCIS, grade
Kuhl, 2014	1.5	1 axial T1 no FS	ND		7	8.4 (4–17)	7/7 (100)	4, all gr 2-3
Jain, 2016	1.5 or 3	1 axial T1FS	ND		7	NS	NS	2[d] 1 gr2, 1 NS
Chen, 2017	3	1 axial T1FS	ND[f]		9	All ≤ 1 cm	9/9 (100)	4, 1 gr2, 3 gr3
Strahle, 2017	1.5	2 axial T1FS (@1.5 and 6 min)	T2FS		4	19 (7–40)	4/4 (100)	2[g]
Panigrahi, 2017[h]	1.5 or 3	1 axial T1FS	ND		12	10.7 (4–17)	NS	2, gr 1
Choi, 2018	1.5 or 3	1 sagittal T1FS	T2FS		7[i]	15 (5–20)	6/7 (85.7)	5[i]

For all examinations, a scout localiser and pre-contrast T1W images were obtained; subtraction of the pre-contrast MRI from the first post-contrast MRI was performed and maximum intensity projection images were created from the subtraction images.

C+ contrast-enhanced, *ND* not done, *PHBC* personal history of breast cancer, *NS* not stated, *BR* BI-RADS assessment, *IDC* invasive ductal carcinoma, *DCIS* ductal carcinoma in situ, *gr* nuclear grade

[a] Number of women found to have cancer

[b] Biopsy rate, number of women biopsied as % of women screened

[c] Number of biopsies malignant/total number of biopsies performed

[d] An additional high nuclear grade DCIS was diagnosed in a patient who also had IDC on MRI

[e] A separate publication by these authors in Academic Radiology 2017 details 16 cancers in 478 women and 41 biopsied lesions; these are likely overlapping series but extent of overlap, particularly among lesions biopsied, is unclear

[f] An additional IDC was considered probably benign on the abbreviated protocol and suspicious when diffusion-weighted imaging (DWI) was added to the abbreviated protocol; only 31 biopsies would have been performed after DWI, of which 14 were malignant

[g] Seven malignancies were identified in six women: Two lesions of DCIS were identified in one patient (overall three DCIS lesions)

[h] This series appears to entirely include what appears to be a subset published in 2016 by Harvey SC et al JACR

[i] This institution lacked MRI-biopsy capability. 83 exams were assessed as BR3 on MRI, with five upgraded to BR4 at follow-up, 4 of which proved malignant, including two DCIS, one IDC and one mucinous carcinoma: 4/83 (4.8%) BR3 exams proved malignant

represented 33% of all cancers [104]. There were no interval cancers. Those authors concluded that MRI screening improves early diagnosis of prognostically relevant breast cancer.

Berg et al [115] reported 512/1215 (42.1%) women at elevated risk declined a no-cost MRI in the final year of ACRIN 6666. Recent reports of gadolinium accumulation in parts of the brain and elsewhere have raised concerns and prompted a 'black box' warning [116], though there is no known adverse effect from this and deposition is nearly immeasurable with macrocyclic chelates of gadolinium [117]. To improve access and tolerance and reduce cost, Kuhl and colleagues [118] introduced the ultrafast, 3-min breast MRI for screening, and demonstrated that abbreviated breast MRI maintained comparable sensitivity and specificity to the full diagnostic protocol. Table 3 summarises results of abbreviated MRI to date [118–123]. The incremental cancer detection rate following abbreviated screening breast MRI ranges between 8.9 and 36.5 cancers per 1,000 screens.

Future perspectives

There has been exploratory effort to evaluate contrast-enhanced spectral mammography (CESM) in the screening of women with dense breasts. In preliminary studies, CESM shows cancer detection comparable to MRI, with improved specificity [124], though few data from screening are yet published. Jochelson et al [125] reported results from 307 women at increased risk who had screening CESM and MRI; two invasive cancers were seen on both modalities and one DCIS was seen only on MRI. PPV3 was 2/13 (15% for CESM) and 3/21 (14%) for MRI. There were more BI-RADS 3 assessments on MRI, with reduced specificity of MRI, but biopsy capability has only recently become available for CESM [125]. Unenhanced MRI technique using diffusion weighted imaging (DWI) is another promising modality

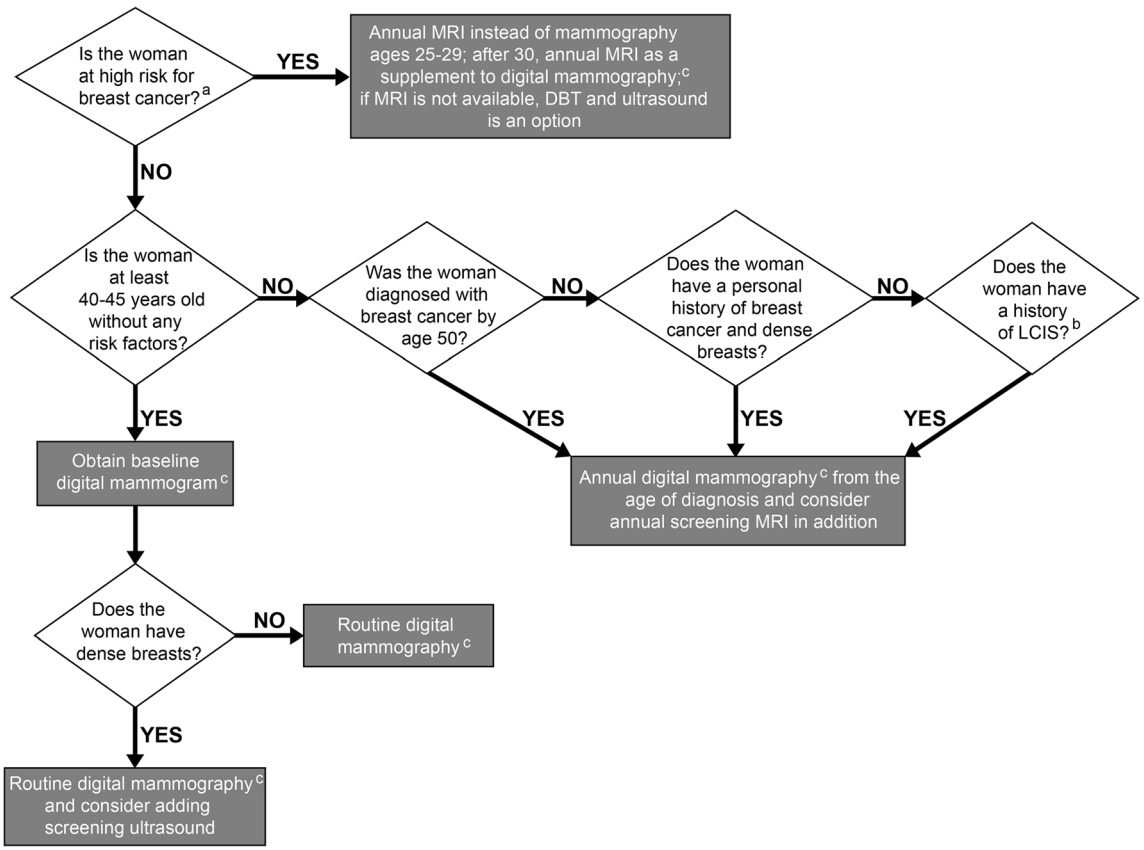

Fig. 4 Flow chart illustrating a screening decision support tool according to risk stratification. [a]High risk is defined as: women with a known or suspected pathogenic mutation in BRCA, TP53, CHEK2, PTEN, ATM, CDH1, STK11 and PALB2; women having a lifetime risk greater than 20% according to acceptable models that determine risk of pathogenic mutations, with Tyrer-Cuzick model the most accurate at the population level (and which includes breast density as a risk factor); women treated with chest or mantle radiation therapy by age 30 years and at least 8 years prior. [b]A personal history of lobular carcinoma in situ confers almost as high a risk as personal history of breast cancer and such women should consider supplemental screening with MRI, especially if the breasts are dense. Atypical lobular hyperplasia (ALH) and atypical ductal hyperplasia (ADH) confer 20–25% lifetime risk as well but there are no studies showing improved cancer detection in women with ALH or ADH who undergo MRI screening in addition to mammography. [c]Digital breast tomosynthesis (DBT) with synthetic reconstructions can be used instead of digital mammography

for the detection of challenging, mammographically occult breast cancers in women with dense breasts; the advantage of DWI is the ability to distinguish between normal microscopic tissue and malignancy without the use of intravenous gadolinium [126], though generalisability of DWI remains problematic [127].

Molecular breast imaging (MBI) is functional rather than anatomic imaging; standard views are obtained similar to mammography, i.e. craniocaudal and mediolateral oblique projections, for 10 min each, while mild compression is applied after intravenous injection of 99mTc-sestamibi [128]. Recent studies evaluating MBI as a supplemental screening technique for women with dense breasts have shown an ICDR ranging between 7.5 and 8.8 per 1,000; the median size of cancer detected only by MBI is approximately 1.0 cm. The additional recall rate is 5.9–8.4%, while PPV3 varies between 19% and 33% [129–131].

Breast density inform and current practice

The potential impact of supplemental screening is gaining global attention from patients and policymakers. In the USA, 35 states have enacted legislation requiring some notification about breast density following a mammogram [132] supplemental screening can be performed if ordered by a referring physician. In the UK Canada, and Australia, advocacy groups are making great efforts encouraging the density discussion; the website DenseBreast-info.org was developed to educate both patients and providers in the USA and will soon add content specific to healthcare providers in Europe. In France and Germany, for women with extremely dense breasts, a supplemental physician-performed US has been provided for many years and women are informed of this option in Greece. In Austria, since 2013, the Austrian Breast Cancer Early Detection Program provides supplemental US in women reported to have dense breasts on mammography. Currently, no clear guidelines have been established for widespread supplemental screening; a proposal for risk-adapted screening is illustrated in Fig. 4.

Conclusions

The sensitivity of mammography is lower in women with dense breasts. Digital mammography has improved sensitivity compared to film-screen mammography and should be widely adopted in women with dense breasts. Breast density has been established as an independent risk factor for breast cancer, and cancers tend to be more advanced at diagnosis compared to women with fatty breasts. US detects significantly more early-stage, invasive breast cancers than screening with mammography alone, leading to acceptably low interval cancer rates; however, a shortage of trained operators has precluded widespread implementation of HHUS. ABS is a promising technique but remains limited by the time to interpret and false positives. Tomosynthesis has been widely implemented in place of 2D mammography and has been shown to reduce significantly the recall rate and to increase the cancer detection rate, although it is less effective in women with extremely dense breasts, and cancers may remain obscured in women with heterogeneously dense breasts. Supplemental screening with MRI in high-risk women has been shown to reduce late-stage disease and improve metastasis-free survival; the high cost has restricted MRI use to date. Widespread assessment of risk to include breast density and ascertain those women who should start early annual screening to include MRI is needed. Abbreviated MRI protocols may reduce cost and increase accessibility to women of average risk with dense breasts. Other methods such as CESM and MBI improve cancer detection but require further validation for screening.

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Compliance with ethical standards

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Methodology
• Review article

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