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Screening Breast Ultrasound Using Handheld or Automated Technique in Women with Dense Breasts

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Abstract

In women with dense breasts (heterogeneously or extremely dense), adding screening ultrasound to mammography increases detection of node-negative invasive breast cancer. Similar incremental cancer detection rates averaging 2.1–2.7 per 1000 have been observed for physician- and technologist-performed handheld ultrasound (HHUS) and automated ultrasound (AUS). Adding screening ultrasound (US) for women with dense breasts significantly reduces interval cancer rates. Training is critical before interpreting examinations for both modalities, and a learning curve to achieve optimal performance has been observed. On average, about 3% of women will be recommended for biopsy on the prevalence round because of screening US, with a wide range of 2%–30% malignancy rates for suspicious findings seen only on US. Breast Imaging Reporting and Data System 3 lesions identified only on screening HHUS can be safely followed at 1 year rather than 6 months. Computer-aided detection and diagnosis software can augment performance of AUS and HHUS; ongoing research on machine learning and deep learning algorithms will likely improve outcomes and workflow with screening US.

Key words: breast cancer; breast density; cancer screening; screening ultrasound; automated breast ultrasound; computer-aided diagnosis; dense breasts.

Introduction

Dense breast tissue can mask breast cancer on mammography (1); further, the denser, and especially the more nodular the tissue, the greater the risk of developing breast cancer (2). Wolfe first described the increased risk of breast cancer related to parenchymal patterns in 1976 (3). The Dutch mammography screening program (4) uses the Wolfe classification, and a recent analysis showed a 41% mortality reduction in women screened regularly with mammography who had nondense breasts [relative risk (RR) of death 0.59; 95% confidence interval (CI): 0.44–0.79] compared to only a 13% reduction in women with dense breasts (RR 0.87; 95% CI: 0.52–1.45). Because the CI in the Dutch study is centered on and widely overlaps one in women with dense breasts, there may be no net benefit to mammography screening in women with dense breasts. Gram et al (5) published the Tabár classification of parenchymal patterns used in the Swedish screening program, and at 25-year-follow-up, there was a 1.9-fold higher risk of breast cancer death among women with dense breasts, compared with those with nondense breasts (6). In the United States, standardized language for reporting breast density and mammographic features was first published in 1993 by D'Orsi and Kopans (7), and then it was incorporated into the Breast Imaging Reporting and Data System (BI-RADS): A, fatty; B, scattered fibroglandular density; C, heterogeneously dense, which may obscure small masses; or D, extremely dense, which lowers the sensitivity of mammography. The latter two categories are considered "dense." Current BI-RADS classification (8) emphasizes the masking

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Key Messages

- Digital breast tomosynthesis reduces false positive rates, but cancer detection is not significantly improved in women with extremely dense breasts.
- In women with dense breasts, supplemental screening with handheld ultrasound (HHUS) or automated ultrasound (AUS) similarly increases cancer detection, and HHUS has been shown to reduce interval cancer rates.
- The diagnostic performance of AUS has been shown to be equivalent to that of HHUS, although a final assessment can typically be made from HHUS, whereas AUS typically requires targeted HHUS before rendering a final assessment for recalled findings.
- Magnetic resonance imaging provides greater sensitivity for cancer detection than US does, and it remains standard for supplemental screening of women at high risk, regardless of breast density.

effect of dense tissue and recommends categorization of the breast density as heterogeneously dense when even a portion of the breast (other than just the retroareolar region) is dense enough to obscure small masses.

The BI-RADS breast-density category (8) is currently *recommended*, but not required, to be included in the mammography report sent to the ordering provider. As of this writing, 38 states and the District of Columbia have density-inform laws requiring at least awareness of this issue be included in the mammography results letter sent to patients (9). Some states specify individual density category, and others only suggest "if you have dense breasts" without informing the woman whether she herself has dense breasts or not. Currently, results letters may detail masking and/or increased risk of developing breast cancer and recommend discussion (usually with one's healthcare provider, or, in Illinois, with the radiologist), including also other risk factors and possible supplemental screening. In a recent survey of the Society of Breast Imaging membership, 60% felt definitely and another 16% "maybe" that breast density and supplemental screening should be discussed with patients by the radiologist (10). The 15 February 2019 federal budget law included provision that the Food and Drug Administration update the national Mammography Quality Standards Act regulations to require breast density be included in the mammography report sent to the provider and also in the results letter sent to patients, and this will likely be effective in early 2021.

Breast density typically decreases with age, and particularly around menopause; about 56% of women in their 40s, 38% of women aged 55–59, and 26% of women in their 70s have dense breasts (11). Overall, 43% of women aged 40–74 have dense breasts (representing about 27.6 million American women as of 2014); only 7.4% (4.7 million American) women have extremely dense breasts (11).

Extremely dense breast tissue confers an approximately 4-fold increased risk of developing breast cancer compared to fatty tissue (2). Breast density is now incorporated into Tyrer-Cuzick (12, 13) and Breast Cancer Surveillance Consortium risk models (14). Because the majority of women have scattered fibroglandular density, some have advocated (15) use of that density category as the referent standard; heterogeneously dense tissue confers about a 1.5-fold risk, and extremely dense tissue about a 2-fold risk compared to scattered fibroglandular density. A more prominent nodular pattern (likely reflecting proliferating terminal duct lobular units) and complex, heterogeneous texture further increase risk; artificial intelligence can recognize such features and improve assessment of associated risk (16).

Because dense tissue masks some cancers on mammographic screening, breast cancers are more likely to present with symptoms in the interval between recommended screens in women with dense breasts. Such "interval cancers" are often more aggressive (especially in younger women) and in some series (17), are more likely to be larger and to have spread to axillary nodes at presentation than are cancers detected on screening. An interval cancer rate exceeding 1 per 1000 or 10% of all cancers suggests an ineffective screening strategy. The likelihood of an interval cancer diagnosis increases 18- to 31-fold with extremely dense breasts compared to fatty breasts (18, 19). Both visual BI-RADS density and quantitative breast density (using software such as LIBRA; VolparaDensity, Volpara Solutions, Wellington, New Zealand; or Quantra, Hologic, Inc., Marlborough, MA) correlate with reduced mammographic sensitivity and increased interval cancer rates (20–23). Strand et al (19) showed that interval cancers were 6.4-fold more likely in breasts with localized breast density, and large cancers (greater than 2 cm) were 11.8-fold more likely. In the Population-Based Research Optimizing Screening Through Personalized Regimens (PROSPR) Consortium, women with dense breasts were twice as likely as those with nondense breasts to be diagnosed with cancer after a negative mammogram, but only those women aged 40–49 were more likely to have poor prognosis cancers (distant metastases, node positive, estrogen- and/or progesterone-receptor–positive, or human epidermal growth factor receptor 2 (HER2)–negative invasive cancer greater than or equal to 2 cm, or triple negative or HER2-positive invasive cancer greater than or equal to 1 cm in diameter) with odds ratio (OR) 3.5 versus women aged 70–79 at diagnosis ($P = 0.048$) (17).

Digital mammography is the minimum standard in women with dense breasts, and it offers better cancer detection compared with screen-film mammography (24). Digital breast tomosynthesis (DBT) reduces false positive callbacks and improves cancer detection in most women but, because of lack of inherent tissue contrast, cancer detection is not significantly improved in extremely dense breasts (25, 26). Over 40% of breast cancers may go undiagnosed in extremely dense breasts (20).

Mammography reduces breast cancer mortality because it improves detection of invasive cancer before involvement of axillary nodes (27). Other methods that improve detection of such cancers should benefit women; both handheld ultrasound (HHUS) and automated ultrasound (AUS) have been shown to improve node-negative invasive cancer detection after mammography in women with dense breasts. Importantly, magnetic resonance imaging (MRI) is more sensitive than is the combination of mammography and ultrasound (US) (28): women who qualify for screening MRI should have MRI instead of screening US if they have access and are able to tolerate MRI (29). In the American College of Radiology Imaging Network (ACRIN) 6666 trial, 512/1215 (42.1%) eligible women declined MRI because of claustrophobia, time constraints, financial concerns, fear of contrast injection, or other issues (30). When MRI is performed, screening US has no added benefit (28). Abbreviated MRI (31) will reduce cost and improve access to MRI, but it still requires intravenous gadolinium-based contrast. Dual-energy contrast-enhanced mammography appears to depict invasive cancer as well as MRI does (32, 33), but it requires intravenous iodinated contrast,

whereas US is well-tolerated with no requirement for intravenous contrast.

Ultrasound technique and implementation

Screening HHUS can be performed by specialist radiologist physicians or by trained technologists. In the ACRIN 6666 trial, performed by radiologists, the minimum experience requirement was 500 breast US examinations. Investigators had to successfully detect small lesions by scanning a phantom (34) and successfully complete an interpretive skills task using BI-RADS US terminology and assessments on 70 proven cases (35). Documentation was standardized, requiring a minimum of one image from each quadrant and one behind the nipple for a negative examination (36). A single image without calipers is sufficient to document representative simple cysts seen on screening HHUS (the ACRIN 6666 protocol required documentation of the largest cyst in each quadrant in its largest diameter). For solid or complex masses, orthogonal views with and without calipers are standard, and this documentation does not constitute "additional evaluation" (37); electively, Doppler and elastography can be documented. Examination time for physician-performed HHUS was recorded in ACRIN 6666 with a median of 17 minutes in year 1, 15 minutes in year 2, and 13 minutes in year 3 (with a range up to 166 minutes) (38); typically a 30-minute slot is allotted.

Technologist training requirements for HHUS have been less well-standardized (36). In Japan, a 2-day training course with video, still images, and live scanning is conducted, and technologists have shown better video sensitivity than have physicians (39).

"Semiautomated" US (40) adapts a standard US unit and transducer to an automated arm to acquire a cine loop of about 3000 images in the standard axial plane to be viewed on special software (SonoCiné, Reno, NV); a vest and coupling gel are used. One system in development adapts AUS to acquire with mammographic compression (41).

For AUS, a minimum of three acquisitions with a 15 cm–footprint transducer are required to cover the entire breast; larger breasts may require up to 5 or 6 acquisitions, each producing up to 320 images. Golatta et al (42) found that 15% of breasts required 5 acquisitions. The acquisition time for each view is approximately 60 seconds, and total acquisition time including patient positioning averages 15 minutes for both breasts (43, 44) and can be reduced to 10 minutes (45); images are reconstructed in coronal and sagittal planes. Interpreting the resulting 1800–3000 images is time consuming; Skaane et al (46) reported an average 9-minute interpretation time for a normal bilateral examination that increased if cancer or benign findings were present. In most studies, interpretation times averaged 3–7 minutes (44, 45, 47); interpretation time decreases with increasing AUS experience of the radiologist (48).

Training specific to AUS is critical before interpreting examinations; Arleo et al (49) showed that there is a learning curve, with a 25% (43 of 174) recall rate in the first month of AUS that decreased to 13% (22 of 174) by the third month. Artifacts attributable to refractive edge shadowing from fat lobules, fibrous tissue, or poor contact at the edges of the sweep are easily recognized with experience (50); a "zipper" artifact is seen with palpable masses (50). Artifactual shadowing can usually be recognized because it usually is not reproduced across overlapping acquisitions. Use of coupling lotion rather than traditional gel minimizes trapping of air (50). Prior biopsy history and previous and current breast imaging should be available when interpreting either AUS (46) or HHUS.

Automated ultrasound images can be acquired by a sonographic or a mammographic technologist or by a well-trained medical assistant. Intensive training is mandatory to produce state-of-the art acquisitions, including proper positioning; appropriate compression throughout the breast (with a rectangular shape of acquisitions suggesting adequate compression, except for the anteroposterior view that appears donut shaped); the meticulous application of lotion evenly on the breast and an additional amount on the nipple; and the inclusion of the entire breast within the field of view (51). Barr et al (52) showed no difference in diagnostic agreement with HHUS when AUS was performed by a sonographic vs. a mammographic technologist.

A standardized review process for AUS encompasses evaluation of the coronal plane using the scroll/survey mode, and assessment of the transverse plane with cine mode (51, 53). Review of all planes of every acquisition is necessary. Normal anatomy is better visualized with wide acquisition fields; abnormalities can present as a black defect (Figure 1), with or without effects on adjacent breast tissue. Alterations in breast structure and dilated ducts with or without solid elements are easily depicted. Coordinates in all three planes (coronal, transverse, and sagittal), distance from the nipple, and depth from the skin are easily obtained (53, 54).

Assessment in multiple perspectives performs better compared with evaluation solely of the transverse plane. The coronal plane, in particular, nicely depicts architectural distortion associated with malignancies or radial scars, known as "retraction phenomenon sign." Cancers presenting as masses are more clearly identified in the transverse plane (51, 54).

In the USA, there is only one current procedural terminology code for a unilateral whole breast US, 77641, which does not specify a screening or diagnostic indication. For a bilateral examination, this is charged twice, once with a "right" and once with "left" modifier. For AUS, a 3D-reconstruction charge can be added. The International Classification of Diseases, Tenth Revision, Clinical Modification of R92.2, incomplete examination because of dense breasts, is used, together with V76.19 "other screening". As of this writing, seven states and the District of Columbia have laws mandating insurance coverage for screening US in women with dense breasts (not necessarily without copay or deductible): Connecticut, New York, Indiana, Vermont, Arkansas, Illinois, and New Jersey, although New Jersey mandates such coverage only if the breasts are extremely dense (55). In Colorado and Louisiana, insurance coverage will be mandated as of 1 January 2021. In all states, insurance will typically cover screening US if ordered by a medical provider, subject to deductible/copay.

Cancer detection and interval cancer rates with supplemental screening ultrasound

When performed by breast imaging radiologists, across 361,502 exams, 738 exams yielded cancer on supplemental screening HHUS [average supplemental cancer detection rate (CDR) of 2.0 of 1000] (Table 1). A total of 719 malignant lesions were detailed, of which 631 (87.8%) were invasive. Where detailed, 497 of 554 (89.7%) invasive cancers seen only on US were node negative. Invasive lobular carcinomas are overrepresented among cancers seen only on screening US, averaging 15%–20% of malignancies. Mean invasive cancer sizes of 7–13 mm were reported in nearly all series.

Similar results have been observed with technologist-performed screening US (Table 1). Across 64,018 technologist-performed

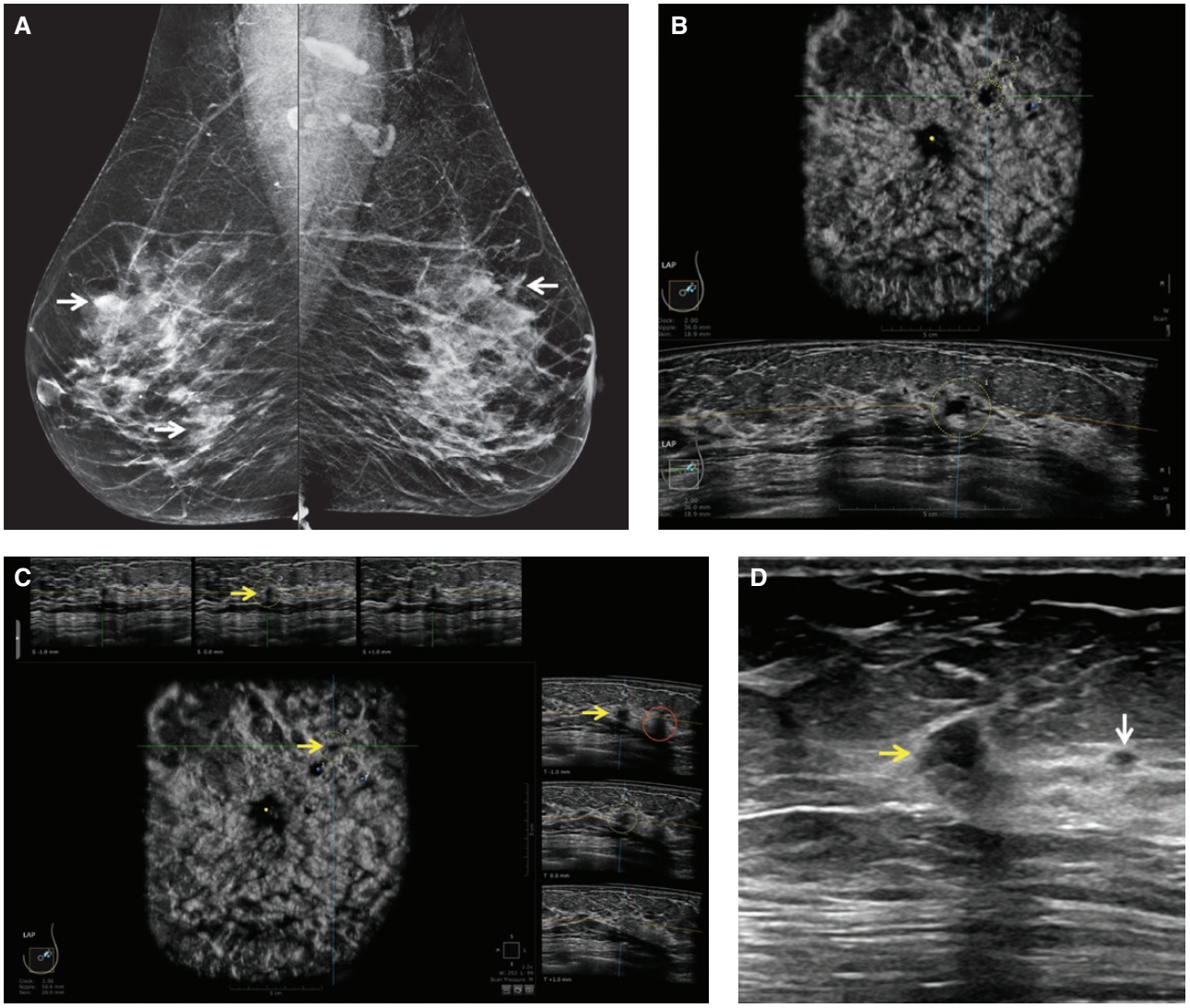

Figure 1. 63-year-old woman with cancer detected on screening automated ultrasound (AUS). **A**: Bilateral mediolateral oblique mammograms show heterogeneously dense parenchyma, which may obscure small masses. Asymmetries are noted bilaterally (white arrows), which were stable. Tomosynthesis did not show any suspicious findings. **B**: Coronal (top) anterior-posterior AUS image of the left breast shows 3 markedly hypoechoic masses in the 2 o'clock axis (yellow circles and blue dot). Transverse AUS image (bottom) shows that the largest of these masses (yellow circle, "1"), 3.6 cm from the nipple, is a simple cyst. **C**: Sagittal reconstructions (top three images) and transverse images (right three images) show the smaller irregular mass (yellow circles and arrows, "3"), for which the patient was recalled. Third small mass was also seen on AUS (marked "2" on coronal image, center), and it was a small cyst. The hypoechoic area circled in red represents artifactual shadowing. **D**: Transverse handheld ultrasound (HHUS) image of the same patient at 2 o'clock in the left breast shows an irregular mass (yellow arrow) that corresponded to the mass marked "3" on AUS. Ultrasound-guided biopsy showed invasive ductal carcinoma estrogen-and progesterone-receptor (+), human epidermal growth factor receptor-2 (-), Ki-67 less than 12%. The patient had breast-conserving surgery, confirming a 0.8 cm grade 1 invasive ductal carcinoma with 2 negative sentinel nodes. An adjacent oval hypoechoic mass (white arrow) represented a simple cyst ("2" on AUS).

HHUS, 144 cancers were detected (supplemental CDR of 2.7 of 1000). Of 144 malignancies seen only on HHUS, 124 (86.1%) were invasive, with 102 of 123 (82.9%) detailed node negative. Mean size of invasive cancers seen only on US was 9–14 mm in all series, except for the prevalence screen results of Weigert et al, where mean size was 25 mm. The recent analysis of screening US by Lee et al (84) from the Breast Cancer Surveillance Consortium has been excluded for many reasons: (1) results from mammography alone vs. mammography plus US were not in the same patients; (2) there was no systematic approach to screening US; and (3) interval cancer rates were not reported [for more complete discussion see (85)].

Across 27,163 AUS or semiautomated AUS (83) examinations, 69 cancers were found (supplemental CDR of 2.5 of 1000) (Table 1; Figure 1). Of the 69 cancers, 63 (91.9%) were invasive, with mean size 13–22 mm. Of 40 invasive cancers detailed, 36 (90.0%) were node negative.

The Japanese Strategic Anti-Cancer Randomized Trial (J-START) randomly assigned women aged 40–49 of all breast-density types to mammography alone or mammography plus HHUS. Initial results showed an increase in node-negative invasive cancers in the intervention arm receiving screening US and halving of the interval cancer rate to 0.5 per 1000 (86). In ACRIN 6666, there were 9 of

Table 1. Results of Supplemental Screening Ultrasound

Author, Year	Number of Screens with Cancer Outcome[a]	Number of Screens	CDR per 1000 Screens	Net Added Recalls Because of US (% of Screens)	PPV3 of Biopsies Prompted only by US (%)	N Invasive/ Total (%)	N Node Negative[b] (%)
Physician-performed HHUS							
Gordon 1995 (56)	30	12,706	2.4	NR	44/279 (16)	44/44 (100)	NR
Buchberger 2000 (57)	40	8970	4.5	NR	40/405 (9.9)	35/40 (87.5)	33/35 (94.3)
Kolb 2002 (58)	34	13,547	2.7	799 (5.9)	37/358 (10)	36/37 (97.3)	25/28 (89.3)
Crystal 2003 (59)	7	1517	4.6	90 (5.9)	7/38 (18)	7/7 (100)	6/7 (85.7)
Leconte 2003 (60)	16	4236	3.8	NR	NR	14/16 (87.5)	NR
Brancato 2007 (61)	2	5227	0.4	NR	2/65 (3.1)	2/2 (100)	2/2 (100)
DeFelice 2007 (62)	12	1754	6.8	NR	NR	10/12 (83.3)	10/10 (100)
Corsetti 2008 (63)	37	9157	4	NR	50/449 (11.1)[k]	36/37 (97.3)	31/36 (86.1)
Youk 2011 (64)	17	1418	12	200	17/80 (21.3)	NR	NR[g]
Berg 2012, prevalence (38)	14	2659	5.3	401 (15.1)	12/207 (5.8)	30/32 (93.8)	29/30 (96.7)
Berg 2012, incidence (38)	18	4841	3.7	356 (7.4)	18/242 (7.4)		
Chae 2013 (65)	24	8359	2.4	NR (1.26)	24/216 (11.1%)	23/24 (95.8)	19/20 (95.0)
Girardi 2013 (66)	19 (fatty)	12,171 (fatty)	1.6	NR	41/422 (9.7)	37/41 (90.2)	36/37 (97.3)
	22 (dense)	9960 (dense)	2.2				
Choi 2014 (67)	10	3700	2.7	132 (3.6)	NR	8/10 (80)	8/8 (100)
Bae 2014 (68)	329	116,656	3.1	NR	NR	282/329 (85.7)	253/282 (89.7)
Korpraphong 2014 (69)	19	14,483	1.4	NR	NR	NR	NR
Chang 2015 (70)	5	990	5.1	366 (37.0)	5/84 (6.0)	3/5 (60)	3/3 (100)
Moon 2015 (71)	3	1656	1.8	592 (35.7)	2/86 (2.3)	1/3 (33.3)	1/1 (100)
Cho 2016 (72)	22	48,251	0.5	NR	NR	12/22 (54.5)	NR
Klevos 2017 (73)	0	394	0	NR	NR[c]	NA[c]	NA[c]
Song 2018 (74)	22	12,230	1.8	NR	22/181 (12.2)	18/22 (81.8)	16/22 (72.7)
Buchberger 2018 (75)	36	66,680	0.5	397 (0.60)	36/201 (17.9)	33/36 (91.7)	25/33 (75.8)
Wang 2019 (76)	NR		NR	9765 (13.5)	NR	NR	NR
Overall physician-performed	**738**	**361,562**	**2.0**	**12,898/169,258 (7.62)**	**357/3313 (10.8)**	**631/719 (87.8)**	**497/554 (89.7)**
Technologist-performed HHUS							
Kaplan 2001 (77)	5	1862	3.2	176 (9.5)	6/96 (6.3)	5/5 (100)	5/5 (100)
Hooley 2012 (78)	3	935	3.2	234 (25.0)	3/63 (4.8)	2/3 (67)	2/2 (100)
Parris 2013 (79)	10	5519	1.8	680 (12.3)	10/181 (5.5)	10/10 (100)	7/9 (77.8)
Ohuchi 2016 (80)	67	36,752	1.8	1932 (5.25)	NR	55/67 (82.1)	47/55 (85.5)
Destounis 2017 (81)	18	5434	3.3	NR	18/100 (18.0)	18/18 (100)	14/18 (78.0)
Weigert 2017, prevalence (82)	11	2706	4.1	325 (12.0)	11/151 (7.3)	9/11 (81.8)	7/9 (77.8)
Weigert 2017, incidence (82)	30	10,810	2.8	1073 (9.9)	30/379 (7.9)	25/30 (83.3)	20/25 (80.0)
Overall technologist-performed HHUS	**144**	**64,018**	**2.7**	**4420/58,584 (7.54%)**	**78/864 (9.0)**	124/144 (86.1)	102/123 (82.9)
Automated Ultrasound							
Kelly 2010 (83)	23[c]	6425	3.6	557 (8.7)	23/75 (30.7)	22/23 (95.7)	NR
Choi 2014 (67)	7	1866	3.8	48 (2.6)	NR	4/7 (57.1)	4/4 (100)
Brem 2015 (43)	30	15318	2	2063 (13.5)	30/551 (5.4)	28/30 (93.3)	25/27 (92.6)
Wilczek 2016 (44)	4	1668	2.4	15 (0.9)	NR	4/4 (100)	2/4 (50)
Vourtsis 2018	5	1886	2.7	NR	NR	5/5 (100)	5/5 (100)
Overall AUS	**69**	**27,163**	**2.5**	**2683/25277 (10.6)**	**53/626 (8.5)**	63/69 (91.3)	36/40 (90.0)

Abbreviations: AUS, automated ultrasound; CDR, cancer detection rate; HHUS, handheld ultrasound; NA, not applicable; NR, not reported; PPV3, positive predictive value of biopsies performed; US, ultrasound.
[a]Number of women diagnosed with cancer.
[b]Denominators reflect those invasive cancers where nodal staging was reported. Not all women with invasive cancer had nodal staging.
[c]No cancers detected.

111 (8%) interval cancers across 7473 screening examinations (1.2 per 1000) (38). With addition of screening US to mammography, Corsetti et al (87) observed an interval cancer rate of 1.1 per 1000 for women with dense breasts, which was comparable to the 1.0 per 1000 rate for women with fatty breasts with mammography alone.

Some have advocated restricting supplemental screening US to women at higher risk of interval cancer (88) or advanced cancer (stage IIB or higher) (89). The majority of women who have dense breasts and who will develop interval breast cancer (and thereby who might benefit from supplemental screening) would be missed by most restrictive strategies. Indeed, restricting supplemental screening only to women with extremely dense breasts is estimated to allow earlier detection of only 19 of 89 (21%) interval cancers among women with dense breasts (88).

HHUS versus tomosynthesis (DBT)

A few series have evaluated HHUS and DBT, and the supplemental CDR of US appears to be maintained after DBT. In the Adjunct Screening with Tomosynthesis or Ultrasound in Mammographically Negative Dense Breasts (ASTOUND)-1 trial, Tagliafico et al (90) reported results for supplemental DBT and physician-performed HHUS in 3231 women, with 11 cancers seen only on US (estimated supplemental CDR after DBT 3.4/1000); 10 of 11 (91%) were invasive with mean size 17 mm, and 8 of 10 (80%) were node negative. Destounis et al (81). reported results from 7146 paired examinations using DBT and technologist-performed HHUS and found 17 cancers only on US (supplemental CDR after DBT 2.4/1000); mean size was 13 mm. In the separate cohort reported as ASTOUND-2 (91), 14 invasive cancers with mean size 17 mm were seen only on HHUS among 5300 women who also had DBT (supplemental CDR after DBT of 2.6/1000) and 11 of 14 (79%) were node negative. Among the 24 invasive cancers seen only on HHUS after DBT in the two ASTOUND trials, 6 (25%) were invasive lobular carcinomas (Figure 2).

In a mixed screening and diagnostic population of 698 women with dense breasts and 140 cancers, Kim et al (92) found that DBT sensitivity was lower than HHUS sensitivity (91.4% vs. 96.4%, $P = 0.039$), but DBT specificity was higher than that of HHUS (83.9% vs. 73.4%, $P < 0.001$); similar results were observed for screening and diagnostic populations.

Recall rates, false positive biopsies

With HHUS, unlike AUS, lesions recommended for further testing are usually given a final assessment directly from the images obtained at screening. Across multiple series (detailed in (36)), only 0.3% of technologist-performed HHUS were given a BI-RADS 0 assessment (ie, incomplete, requiring additional imaging before giving a final recommendation). It is possible to rotate AUS images to better visualize the margins of a lesion, but this is time consuming, and there is lower resolution out of plane than there is with HHUS. Typically, targeted HHUS is needed before rendering a final assessment for lesions on a baseline AUS examination, other than for a simple cyst.

Where reported, overall 12,898 of 169,258 (7.6%) physician-performed HHUS, 4420 of 58,584 (7.5%) technologist-performed HHUS, and 2683 of 25,277 (10.6%) AUS exams prompted additional testing before the next annual screen, although rates are highly variable across series. Recall rates in Europe, in particular, are much lower than in the USA. As with any other breast imaging modality, the presence of prior comparisons reduces recall rates; the highest rates are seen with the first prevalence screen.

Across series, 2.2%–3.2% of women had a biopsy because of screening US; 3%–21% of biopsies prompted only by HHUS proved malignant (average 9%–11% in prevalent screens) an average of 8.5% of biopsies prompted by prevalent screening AUS were malignant (Table 1). The positive predictive value (PPV) of biopsies (PPV3) of semiautomated US is unusually high, at over 30%.

BI-RADS 3 lesions

Enthusiasm for implementing screening US has been dampened by the relatively high false positive rates (93). By far the most common source of false positive screening US examinations is BI-RADS 3, probably benign lesions. For mammography, these lesions have been well-validated as having a malignancy rate of less than 2%; following such lesions (usually at 6 months) has proven a safe alternative to immediate biopsy. On mammography, such lesions are typically seen on baseline imaging and require diagnostic workup before a BI-RADS 3, probably benign, assessment. By far the most common such finding is a circumscribed oval mass (or masses) in one segment of one breast that appears solid on targeted US, with focal asymmetry and grouped punctate calcifications also appropriate for BI-RADS 3 assessment (94–98).

In the ACRIN 6666 trial, the following lesions were prospectively defined as "probably benign": solitary circumscribed oval, parallel, hypoechoic or isoechoic masses with no posterior features or minimal posterior enhancement (including probable complicated cysts with debris); hyperechoic masses with central hypo- to anechoic areas suggestive of fat necrosis; and clustered microcysts. As reported by Barr et al (99), 519 of 2662 (19.5%) participants had a BI-RADS 3 lesion on at least one annual screen. Of 745 BI-RADS 3 lesions, only 6 (0.8%) proved malignant, and only 1 malignancy was identified at 6-month follow-up; the report suggested 1-year follow-up at the time of the next screening examination as a safe alternative to 6-month follow-up. Importantly, unlike in mammography, new lesions seen on annual US were still categorized as BI-RADS 3, and they had the same outcomes.

In part based on data from ACRIN 6666, complicated cysts and clustered microcysts should now be classified as BI-RADS 2, benign findings when seen on screening US (100). A total of 475 complicated cysts were seen in 376 of 2662 (14.1%) ACRIN 6666 participants, of whom 301 (80%) also had at least 1 simple cyst (100). Across 7 series (100–106), encompassing 1343 lesions, 4 (0.3%) masses considered complicated cysts proved malignant. Clustered microcysts are seen on 3.9% to 5.8% of screening US examinations, and are most common around menopause. Across 5 series (100, 101, 104, 106, 107), only 1 of 235 (0.4%) clustered microcysts proved malignant. These malignancy rates are not different from the malignancy rates of examinations assessed as BI-RADS 2, benign findings.

Solitary circumscribed solid-appearing oval masses seen only on screening US still merit surveillance, although the ideal follow-up has not been established. In younger women, the differential diagnosis is fibroadenoma, phyllodes tumor, and high-grade invasive ductal carcinoma (often triple receptor negative). Gordon et al (108), in a series of 194 masses yielding fibroadenoma on fine needle aspiration biopsy (179 of which were in women aged younger than 50 years), showed that the 95th percentile for growth in diameter in 6 months was 20% for all ages, and recommended excision above that threshold, with 2 phyllodes tumors found among 67 such enlarging masses. This experience has been translated into practice for masses that appear to

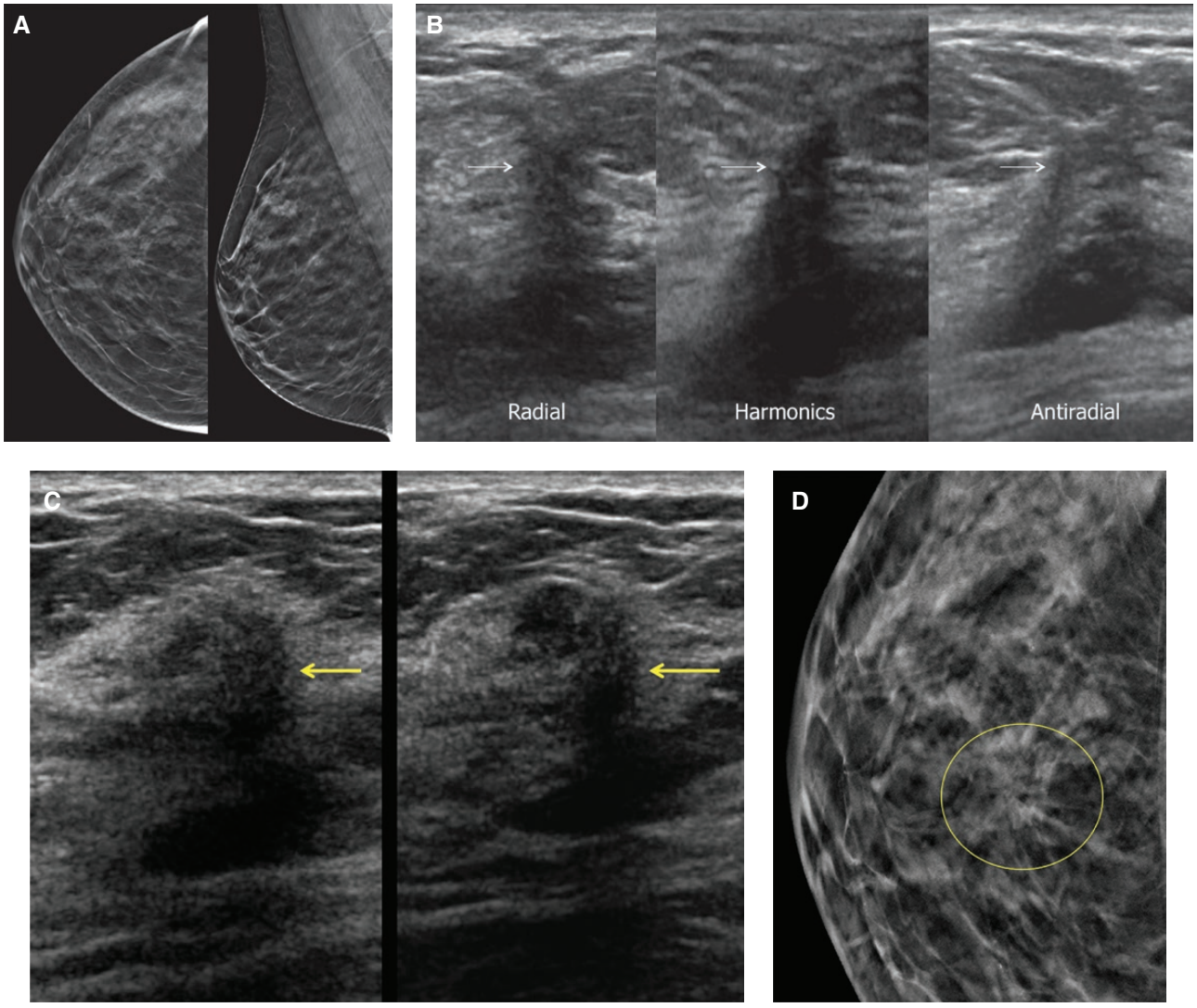

Figure 2. Invasive lobular carcinoma (ILC) seen only on screening handheld ultrasound (HHUS) in this 50-year-old woman with negative tomosynthesis. **A**: Representative craniocaudal (CC) and mediolateral oblique 1-mm tomosynthesis images show heterogeneously dense parenchyma in the upper outer quadrant. Two observers (as part of a research study) called this negative, BI-RADS 1. The patient's mother had breast cancer at age 50 years, as did her maternal great grandfather at age 60 years. **B**: Technologist-performed HHUS image (radial left and antiradial right) shows an irregular hypoechoic mass (arrows) in the right breast at 9 o'clock, 2 cm from the nipple, with posterior shadowing more evident with harmonic imaging (middle image). Because orthogonal views have been obtained, a final assessment can be rendered. One observer assessed this as BI-RADS 4B and the other as BI-RADS 4A. US-guided biopsy showed pseudoangiomatous stromal hyperplasia. False positives are mainly an issue with screening US on the first, prevalent screen, as in this patient. **C**: Screening HHUS images also showed this vague indistinctly marginated mass in the right breast at 12 o'clock, 3 cm from the nipple (yellow arrows), assessed as negative by one observer and BI-RADS 4B by a second observer. US-guided core biopsy showed ILC. **D**: Close-up of CC tomosynthesis shows very subtle distortion on one slice in retrospect (yellow circle) at the site of ILC. Lumpectomy surgery showed a 0.9 cm grade 1 ILC, estrogen- and progesterone-receptor positive, human epidermal growth factor-2 receptor negative, Ki 67 1%, and an adjacent 0.3 cm invasive ductal carcinoma; 3 sentinel nodes were negative. Invasive lobular carcinoma is overrepresented among cancers seen only on screening US.

represent fibroadenomas, assessed as BI-RADS 3 without any initial biopsy; growth of greater than 20% in diameter in 6 months generally prompts upgrade to BI-RADS 4A and biopsy. In a series of 12,514 BI-RADS 3 lesions seen on US reported by Ha et al (109), 738 (5.9%) grew more than 20% in diameter in 6 months; 8 of 420 (1.9%) were malignant when the only change was growth; and 18 of 107 (17%) were malignant when there was other suspicious change, such as margins, orientation, shape, or echo pattern. Marcon et al (110) reported on 97 women aged 34 and younger with 151 palpable probably benign masses seen on US; 25 (16%) underwent biopsy or surgery at presentation, all benign. Another 9 were upgraded to BI-RADS 4A at 6-month follow-up because of interval growth greater than 20% in diameter, yielding 5 fibroadenomas and 4 phyllodes tumors. Only 1 mass later grew, prompting biopsy at 18 months, showing fibroadenoma. Based on these results, Marcon et al (110). recommended a single 6-month follow-up of such masses in young women.

Elastography appears to be particularly helpful in evaluating solitary circumscribed oval hypoechoic masses. In the initial BE1 study of shear-wave elastography (SWE) (111), there were 181 such masses, of which 4 (2.2%) were malignant. Among 144 such masses assessed as BI-RADS 3, all 4 malignancies appeared stiff on SWE, as did another 8 (false positive) masses; another 34 (of 37 total) benign

BI-RADS 4A masses appeared soft, and biopsy could have been avoided, with a net increase in both sensitivity and specificity. Similar beneficial results were observed by Lee et al (112), applying SWE to BI-RADS 3 and 4A masses seen on screening US. On some strain elastography systems, complicated cysts show a "bull's-eye" artifact, which can also reduce unnecessary aspiration or biopsy (113).

As in screening mammography (114), multiple bilateral circumscribed solid-appearing masses seen on screening US (at least 2 in 1 breast and 1 in the other) can be assessed as BI-RADS 2, benign findings, provided each mass is carefully evaluated (Figure 3). In the ACRIN 6666 trial, 153 such findings were observed in 135 of 2172 (6.2%) evaluable participants, with no malignancies after at least 24 months of follow-up (95% CI: 0%–2.4% malignancy rate) (115). Importantly, 82 of the 135 women also had a solitary lesion separately described, and 2 of 82 (2.4%) of those masses proved malignant (115).

Several additional series have validated 12-month follow-up for BI-RADS 3 lesions seen on screening HHUS. Among 1666 screening US examinations, 689 (41.4%) were BI-RADS 3 in the series of Nam et al (116); of those, 653 had 2-year follow-up or biopsy, and only 1 malignancy (a 1.2-cm node-negative invasive ductal carcinoma) was identified, at the first 6-month follow-up, representing 0.2% of such lesions: routine annual screening was recommended. Chae et al (117) reported similar results and found that only 4 of 980 (0.4%) BI-RADS 3 lesions seen only on screening US were malignant, compared with 4 of 184 (2.2%) with a mammographic correlate (P = 0.025): 6-month follow-up was deemed appropriate when there was a correlating abnormality on mammography. In the series of Moon et al, 445 women had BI-RADS 3 lesions on screening US (118), with 3 proving malignant (0.7%), all after at least 15 months of follow-up: they concluded that 12-month follow-up was sufficient.

Comparison of cancer detection with HHUS and AUS in diagnostic series

How does AUS compare with HHUS in cancer depiction? Table 2 summarizes series where both HHUS and AUS were performed in a variety of patient populations, and a recent meta-analysis of Wang and Qi (119) included some of these series. Comparable sensitivity was observed for both approaches [averaging 90.6 and 90.8% for HHUS and AUS respectively in (119)], with ductal carcinoma in

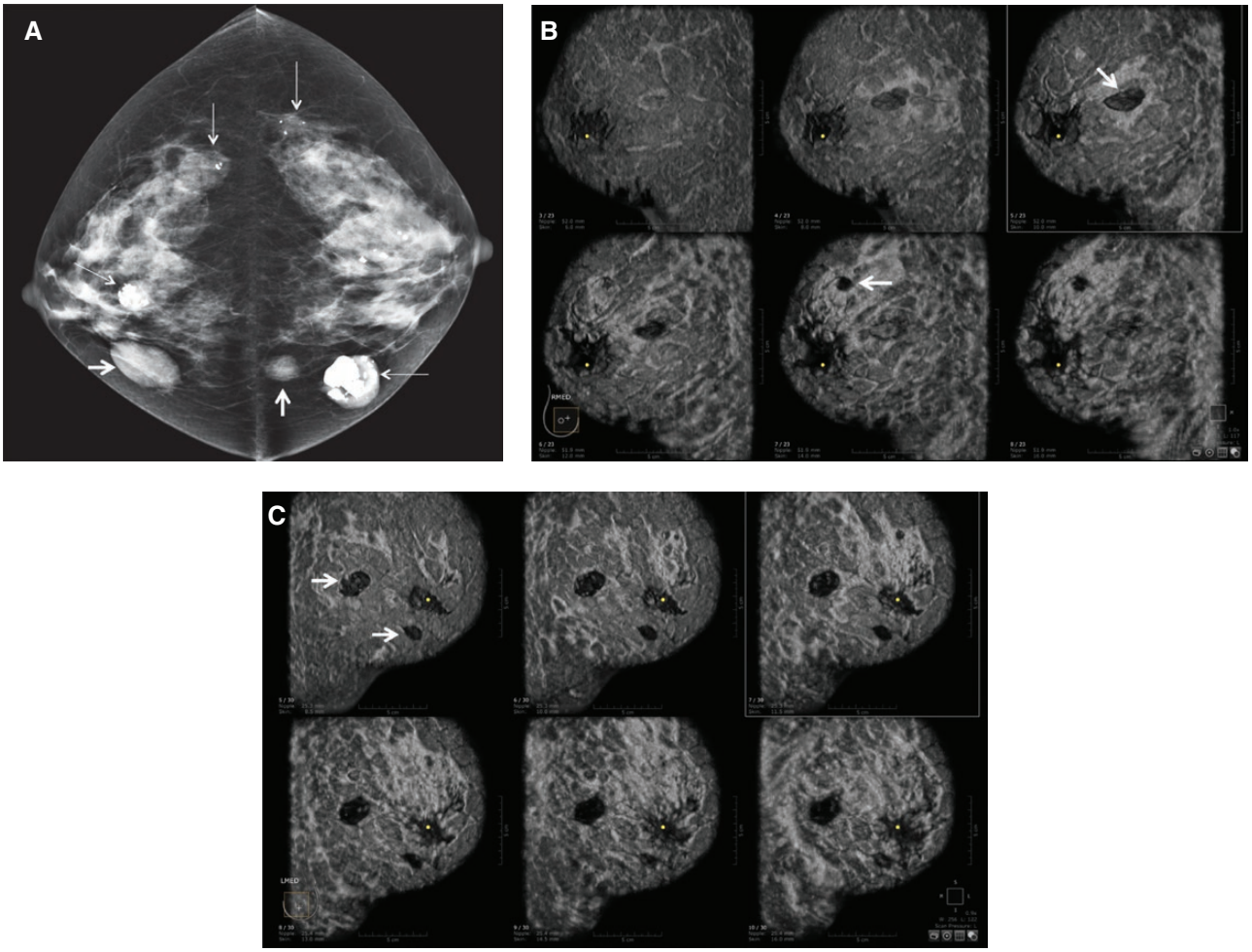

Figure 3. Multiple bilateral fibroadenomas in a 59-year-old woman. **A**: Craniocaudal mammograms show multiple bilateral oval and round masses (short arrows), some of which are calcifying (long arrows), consistent with fibroadenomas that have been stable for over 11 years. **B**: Multiple coronal images from medial automated ultrasound (AUS) acquisition of the right breast show multiple circumscribed masses (arrows). Yellow dots indicate the nipple (marked by the technologist on initiating scanning). **C**: Multiple coronal images from medial AUS acquisition of the left breast also show multiple circumscribed masses (arrows). Automated ultrasound readily depicts multiple bilateral circumscribed masses: BI-RADS 2, benign findings.

Table 2. Comparison of Malignant and Overall Lesion Detection on Handheld Ultrasound versus Automated Ultrasound

Study	N Women	N Cancers	N Cancers Detected HHUS (%)	N Cancers Detected AUS (%)	N Total Lesions	N Total Detected HHUS (%)	N Total Detected AUS (%)	Patient Population
Wenkel et al 2008 (122)	35	13	13 (100)	13 (100)	30	30 (100)	28 (93.3) 29 (96.7) 29 (96.7) 29 (96.7) 29 (96.7)	Breast abnormality elsewhere on palpation or imaging; 5 observers
Kotsianos-Hermle et al 2008 (123)	97	39 x 2	76 (97.5)	75 (96.2)	107	NS	NS	Pain, lump, or US-suspicious lesion; physician-performed US; 2 observers
Wojcinski et al 2011 (124)	50	14	14 (100)	10 (73.2) 14 (100)	27	NS	NS	Case set derived from HHUS; 2 observers; 23 normal (9 recalled on AUS); 13 benign (8 recalled)
Lin et al. (2012) (125)	81	15	15 (100)	15 (100)	95	95 (100)	95 (100)	Clinical findings; r = 0.478 HHUS vs. path; 0.616 for AUS
Wang et al. (2012) (126)	155	103	101 (98.0)	102 (99.0)	165	158 (95.8)	161 (97.6)	Lesions scheduled for biopsy after screening mammography or US
Wang et al. (2012) (127)	213	85	77 (90.6)	81 (95.3)	239	236 (98.7)	238 (99.6)	Lesions scheduled for biopsy after screening mammography or US
Zhang et al. (2012) (128)	81	9	NS	NS	99	60 (60.6) 85 (85.9)	89 (89.9) 99 (100)	Women referred for US, mix of symptomatic and mammographic abnormalities; 2 examiners
Kim et al. (2013) (129)	38	50	49 (98)	45 (90) 44 (88) 48 (96)	66	62 (93.9)	57 (86.3) 56 (84.8) 55 (84.8)	50 malignant lesions; women with known cancers; 3 AUS readers
Chae et al 2013 (130)	58	13	12 (92.3)	13 (100)	80	65 (81.3)	205/240** (87.5)	80 suspicious lesions seen on MRI in 58 women with newly diagnosed cancer; US before MRI; **3 readers (240 potential detections)
Chen et al 2013 (131)	175	67	59 (88.1)	62 (92.5)	219	NS	NS	Consecutive Chinese women with BI-RADS 3–5 masses; technologist-performed HHUS
Xiao et al. (2015) (132)	200	76	71 (93.4)	72 (94.7)	273	194 (71.1)	273 (100)	From screening; lesions going to biopsy; retrospective; for malignancies, results shown are when BI-RADS ≥ 3 is considered a positive test
Gollata et al (2014) (42)	983	119	NS	88 (73.9)	242	NS	NS	Malignancies; mixed screening and diagnostic; another 12 visible in retrospect on AUS; excluded 53 microcalcification lesions
Kuzmiak et al 2015 (133)	25	7 × 5	34 (97.1)	34 (97.1)	30	NS	NS	BI-RADS 4/5 lesion on diagnostic workup; 5 observers; physician-performed HHUS
Kim et al 2016 (134)	40	32	28 (87.5)	31 (96.9)	76	66 (86.8)	72 (94.7)	Women with breast cancer undergoing pretreatment MRI
Jeh et al 2016 (135)	173	46	45 (97.8)	45 (97.8)	206	194 (94.2)	171 (83.0)	Consecutive women scheduled for US-guided or stereotactic biopsy
Choi et al 2016 (136)	42	25	24 (96.0)	24 (96.0)	43	31 (72.1)	32 (74.4)	Suspicious microcalcifications on mammography
Schmachtenberg 2017 (137)	28	15	15 (100)	14 (93.3)	75	54 (72)	59 (78.7)	Breasts with at least 1 lesion visible on MRI
Hellgren 2017 (138)	113	26	23 (88.5)	23 (88.5)	NS	NS	NS	Suspicious mammographic lesion on screening
Girometti et al 2017 (139)	131	31	27 (87.1)	26 (83.9)	186	133 (71.5)	129 (69.3)	Women with BI-RADS 2–5 findings on MRI then had AUS and HHUS; one 6 mm IDC missed only on AUS
Choi et al 2018 (140)	786	184	148 (80.4) 151 (82.1) 152 (82.6)	144 (78.3) 151 (82.1) 147 (80.0)	831	831 (100)	831 (100)	Consecutive women with symptoms or abnormal screening with lesions seen on both AUS and HHUS; 3 observers; BI-RADS 3 considered negative
Zhang et al 2018 (141)	1973	394	392 (99.5)	387 (98.2)	839	NS	NS	Symptoms; MRI or biopsy for truth; physician-performed HHUS; BI-RADS ≥ 3 positive
Niu et al 2019 (142)	398	103	84 (81.6)	95 (92.2)	599	NS	NS	Mix of symptoms and screening; technologist-performed HHUS; 3 DCIS benign on HHUS but suspicious on AUS

Abbreviations: AUS, automated ultrasound; DCIS, ductal carcinoma in situ; HHUS, handheld ultrasound; IDC, invasive ductal carcinoma; MRI, magnetic resonance imaging; NS, not stated.

situ (DCIS) manifesting as calcifications and lesions less than 5 mm in size overrepresented among lesions missed on both HHUS and AUS. Similarly, only 164 of 374 (43.9%) potential lesion detections were made for lesions 3.1–5 mm in size versus 38 of 44 (86%) of those 9.1–11 mm and 64 of 66 (97%) of those greater than 11 mm by a subset of ACRIN 6666 investigators in a series of 10 women with multiple lesions (120). Operator dependence of HHUS is not worse than the variability in mammographic interpretation (121). Automated ultrasound has been shown to outperform HHUS in depiction of architectural distortion in the coronal plane in a cohort of 1886 women with dense breasts (45).

Of 22 DCIS events in the ACRIN 6666 trial, 18 (82%) were seen on mammography, and 5 (23%) on US (P = 0.002); 15 were seen only on mammography; 2 only on US; 3 on both; and 2 on neither (143). A greater number of invasive cancers was seen on screening US than on mammography, and those seen on US were more likely node negative; 34 of 53 (64%) on US were node negative compared with 18 of 41 (44%) on mammography (P = 0.003) (143).

Artificial intelligence and computer-assisted detection and diagnosis

Computer-assisted diagnosis (CADx) in HHUS has been shown to improve specificity for both experienced (from 76.6% to 80.3%) and inexperienced (from 71.8% to 77.1%) radiologists (144). Moreover, 3D-electromagnetic tracking technology may help ensure complete coverage of the breast tissue in HHUS (145).

Deep learning–based CADx can improve diagnostic performance by improving specificity (72.8%–92.5% without versus 82.1%–93.1% with CADx), accuracy, and PPV in distinguishing malignant from benign masses on HHUS (146). Computer-assisted diagnosis may be especially beneficial for inexperienced breast radiologists in diagnostic evaluation and characterization of breast masses on HHUS (147).

Cloud-based artificial intelligence decision-support software (BreastDS, Koios Medical, Chicago, IL) is available for HHUS, using a supervised machine learning approach based on tens of thousands of radiology images and corresponding pathologic truth. The radiologist can click on a lesion, and the software provides feedback (benign, probably benign, suspicious, or malignant) (148).

Computer-aided detection and diagnosis software has also been developed and is Food and Drug Administration–approved for AUS, with the aim to reduce interpretation time (QVCAD, QView Medical, Los Altos, CA, developed on over one million AUS images). The QVCAD system automatically extracts features from suspicious areas (greater than 5 mm) and creates a "suspiciousness score." It can also act as a navigation roadmap providing colored circle marks for possibly malignant findings. Jiang et al (149) evaluated impact on diagnostic accuracy and reading time among 18 radiologists: average interpretation time was 3 minutes 33 seconds per case without QVCAD, and 2 minutes 24 seconds with QVCAD without loss of accuracy. Similar results were observed by van Zelst et al (150). Ongoing research is aimed at developing advanced algorithms and improving workflow of AUS.

Summary

With proper training and experience, screening US consistently improves detection of node-negative invasive cancer in women with dense breasts on mammography. Similar results have been observed after DBT. Addition of screening US to mammography results in low interval cancer rates in women with dense breasts. Ultrasound should be performed as a supplement and not a replacement for mammography. BI-RADS 3 lesions seen only on screening HHUS can be safely evaluated at 1 year follow-up, particularly for lesions that are soft on elastography, and this approach greatly reduces false positives. Automated ultrasound produces similar improvements in cancer detection and may perform better in detection of architectural distortion, but callbacks require HHUS before final assessment. Computer-assisted diagnosis shows promise in improving specificity for inexperienced observers, and can reduce interpretation time for AUS. MRI has far greater sensitivity for cancer detection, and it remains standard for women at high risk, regardless of breast density.

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Conflict of interest statement

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