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Screening Ultrasound as an Adjunct to Mammography in Women with Mammographically Dense Breasts

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Abstract

There is increasing interest in the potential benefits and harms of screening ultrasound to supplement mammographic screening of women with dense breast tissue. We review the current evidence regarding adjunctive screening breast ultrasound (US) and provide a summary for clinicians who counsel patients with dense breasts. We conducted a comprehensive literature review of published clinical trials and observational cohort studies assessing the efficacy of screening handheld US (HHUS) and automated breast US (ABUS) to supplement mammography among women with dense breasts. From a total of 189 peer-reviewed publications on the performance of screening US, 12 studies were relevant to our analysis. The reporting of breast cancer risk factors varied across studies; however, the study populations tended to be at greater than average risk for developing breast cancer. There is consistent evidence that adjunctive screening US detects more invasive cancers compared to mammography alone, but there is

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currently no evidence of associated long-term breast cancer mortality reduction. The studies also collectively found that US was associated with an additional 11.7–106.6 biopsies/1,000 examinations (Median 52.2), and detected an additional 0.3–7.7 cancers/1,000 examinations (Median 4.2). The associated number of unnecessary breast biopsies resulting from adjunct US screening exceeds that observed with screening mammography alone by approximately 5-fold. Adjunctive screening with ultrasound should also be considered in the context of screening mammography. It is important for clinicians to be aware that improvements in cancer detection in mammographically dense breasts have been achieved with the transition from film to digital mammography, reducing a limitation of film mammography. Clinicians should discuss breast density as one of several important breast cancer risk factors, consider the potential harms of adjunctive screening, and arrive at a shared decision consistent with each woman's preferences and values.

Keywords

Adjunctive screening; Breast density legislation; Dense breasts; Screening breast ultrasound

1. INTRODUCTION

Mammographic breast density reporting is an important national issue. As of February 2014, 14 states have enacted laws requiring that women be directly notified if they have dense breast tissue on a screening mammogram, and similar federal legislation has been proposed.^{1–3} Proponents of breast density reporting legislation note that many women do not know their breast density or that dense breasts are associated with an increased risk of breast cancer, and that dense breast tissue can mask breast cancers resulting in false negative mammographic examinations.⁴

Mammographic breast density is categorized into one of four density categories according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) (almost entirely fatty, scattered areas of fibroglandular density, heterogeneously dense, and extremely dense; Figure 1).⁵ This information is routinely included in mammography reports sent to referring clinicians. Current and proposed breast density legislation mandates directly informing patients if they have dense breasts, defined as either heterogeneously dense or extremely dense breasts. Approximately 47% of women undergoing screening mammography have mammographically dense breasts.⁶ As more women begin to receive density notification letters, many will be turning to their healthcare providers for additional information to guide their decisions regarding supplemental breast cancer screening.

For women with dense breasts and whose mammograms show no abnormality, adjunctive screening tests may detect cancers masked by dense breast tissue. Whole breast ultrasound (US) has been suggested to supplement mammography screening of women with dense breasts, because of its improved ability to detect cancer in dense breast tissue, lack of associated ionizing radiation exposure, and its wide availability. Currently, breast US is used primarily in the diagnostic setting to evaluate specific findings identified by physical

examination or mammography. It is less widely used as a screening test in women who are at high-risk for developing breast cancer and cannot tolerate an MRI, and to date is infrequently used to screen women at average risk.⁷ Automated breast US (ABUS) is a relatively new technology that standardizes imaging acquisition using an automated transducer, rather than a handheld transducer, and allows visualization of entire breasts in multiple planes.⁸ Some legislation suggests US as an adjunctive screening test, and two states, Connecticut and New Jersey, mandate payer support for its use.^{3, 4}

The purpose of this review is to provide a summary of the evidence regarding breast US as an adjunctive screening test for use in counseling patients with mammographically dense breasts about their screening options.

2. MATERIALS AND METHODS

We performed a systematic review of all articles in the medical literature regarding screening US in women with dense breast tissue from January 2000 through April 2013. We searched the PubMed database using keywords “screening,” “breast ultrasound” and “dense breast” to identify relevant articles. We included studies using either ABUS or handheld US (HHUS) as an adjunct to screening mammography in our analysis. We identified 189 references for further review. Two authors (JRS and CIL) independently reviewed the abstracts of these articles for relevance to the clinical performance of adjunctive screening breast US in women with dense breasts. We excluded abstracts reporting US use for diagnostic evaluation of symptomatic women, in male patients, reader studies, case reports, and review articles.

After applying these inclusion and exclusion criteria, we identified 17 studies and three authors (JRS, CIL, and BLS) reviewed the full articles for data relevant to the diagnostic test performance of adjunct screening US in women with dense breasts. We excluded two studies because of overlapping patient populations with one another,^{9, 10} one study because the majority of the study population did not have dense breasts,¹¹ and two additional studies with data from before the year 2000 using outdated technology (i.e. US transducers 7–10 MHz).^{12, 13} In total, we selected 12 studies for data abstraction and analysis: ten studies of HHUS^{14–23} and two studies of ABUS.^{24, 25}

For each study, we abstracted the following characteristics: years of study, study design, location, number of women, mean age, mammographic breast density, mammogram result and percent of the study population with a family or personal history of breast cancer. We also abstracted performance measures (biopsy rate and cancer detection rate) for adjunctive US performed after a negative screening mammogram when available, or calculated them based on the reported data.

We defined the biopsy rate as the number of biopsies performed based on the US findings divided by the total number of screening US examinations. We defined the cancer detection rate as the number of cancers detected by US divided by the total number of screening US examinations. We report both measures per 1,000 examinations. Additionally, for the

cancers detected, we report the proportion of invasive breast cancers and node-negative cancers.

To assess performance differences between US used in routine clinical practices and in a multi-institutional randomized clinical trial (ACRIN 6666), we performed an additional sub-analysis of four studies: three reporting data from practices in Connecticut^{20–22} compared with the American College of Radiology Imaging Network (ACRIN) 6666 prospective multicenter clinical trial of combined mammography and US screening compared with mammography alone in women at increased breast cancer risk.¹⁸ Connecticut was the first state to enact breast density legislation and require insurance coverage for screening US, with rapid adoption of screening US across a variety of clinical practices. ACRIN 6666 assessed screening US performed by experience breast imagers in a more homogeneous high-risk patient population, compared to the other studies. The performance measures included in the sub-analysis were biopsy rate and cancer detection rate. Finally, to provide additional context to our evidence report, we provide a review of current major medical society recommendations for adjunct screening US for women with dense breasts.

3. RESULTS

3.1 Study design and patient population characteristics

Table 1 demonstrates the design and characteristics of each study included in the analysis. Of the 10 HHUS studies, three were prospective,^{15, 18, 19} five were retrospective^{17, 20–23} and two did not report the study design.^{14, 16} Both studies using ABUS were prospective.^{24, 25} Four of the HHUS studies were performed in the United States, four in Italy, one in Singapore, and one in Israel. Both ABUS studies were performed in the United States. The studies were conducted from 2000 to 2010, with the more recent studies performed in the United States and Italy. Eight of the 10 HHUS studies and both of the ABUS studies included over 1,000 women, with the largest study²³ including 9,960 women.

Table 1 also details patient characteristics for each study. The mean patient ages ranged from 45 to 65 years for HHUS studies and 53 to 57 years for ABUS studies. Nine of 10 HHUS studies focused on women with heterogeneously or extremely dense breasts; one study also included women with scattered fibroglandular densities.¹⁴ Nine of 10 HHUS studies provided data on US performance after a negative mammogram.^{14–21, 23} Parris, *et al* included some women with a positive mammogram, if the US finding was in a different quadrant of the breast than the abnormal clinical or mammographic findings.²² While both ABUS studies provided data specific to women with heterogeneous or extremely dense breasts, only Kelly, *et al* limited their study to women with a negative mammogram.²⁴ Giuliano, *et al* included all women who had both ABUS and a mammogram performed, with performance of each modality reported independently.²⁵

Six of 10 HHUS studies reported the proportion of women in the studies with either a family history of breast cancer or a personal history of breast cancer. However, different definitions for a family history of breast cancer were used. While some studies included only first degree relatives,^{14, 19} in the family history category, others included any family member with a breast cancer history^{22, 24}. Additionally, one study reported BRCA mutation carriers

as a separate group from family history¹⁸. and some studies combined the family and personal history of breast cancer into the same or overlapping categories.^{14, 18, 20}

Approximately 15% of women in the United States have a family history of breast cancer, defined as having a first degree relative (mother, sister or daughter) with breast cancer, and approximately 6% have a personal history of breast cancer.²⁶ Based on reported risk factors, the underlying breast cancer risk in study populations varied widely, but tended towards populations at increased risk. The patient population of the largest prospective study of US screening (Berg, *et al*) was at substantially increased risk of breast cancer compared with the general population of women in the United States. While less than 1% of study participants were BRCA mutation carriers, 19% had a >25% lifetime risk for developing breast cancer by the Gail or Claus model and a majority (53%) had a prior history of breast cancer.¹⁸ Leong, *et al* reported that 17% of their population had a first degree relative with a history of breast cancer and no known BRCA mutation carriers. Girardi, *et al* reported that 10% of their population had a prior history of breast cancer, but did not report the family history of their population. Parris, *et al* reported that 6% had a personal history and 42% of their population had a family history of breast cancer; however, this included participants with any relative with breast cancer. Crystal, *et al* reported that 21% of their population had either a first degree relative or a personal history of breast cancer. For ABUS studies, Kelly *et al* reported a family history of breast cancer in their study population of 30% with first degree and 29% with second degree relatives, while Giuliano, *et al* reported excluding patients with personal or family history of breast cancer from their study.

3.2 Performance of adjunctive screening US

Table 2 demonstrates the biopsy rate and cancer detection rate of adjunctive screening US. The biopsy rate for adjunctive HHUS ranged from 11.9 – 106.6 per 1,000 examinations (median: 56.1; Figure 2). This biopsy rate is in addition to the approximately 10.2 biopsies per 1,000 examinations recommended based on screening mammography findings alone.²⁶ For adjunctive ABUS, only Kelly, *et al* reported the data necessary to calculate a biopsy rate after a negative mammogram (11.7 per 1,000 examinations). The median biopsy rate for all adjunctive breast US studies was 52.2 biopsies per 1,000 examinations. The biopsy rates in Girardi, *et al*'s and Giuliano, *et al*'s studies were not reported and could not be calculated based on the data provided.

In the HHUS studies, the additional number of cancers detected ranged from 0.3 to 6.8 cancers per 1,000 examinations (median: 4.2).^{14–23} In the ABUS studies, the added cancer detection rate for Kelly, *et al* was 3.6 per 1,000 examinations. Giuliano, *et al* reported a cancer detection rate of 12.3 cancers per 1,000 examinations; however, this included cancers that were also detected by mammography. The cancer detection rate for their control group receiving mammography alone was 4.6 cancers per 1,000 examinations, resulting in a cancer detection rate from adjunct screening US of approximately 7.7 cancers per 1,000 examinations. The median cancer detection rate for all adjunct breast US studies was 4.2 cancers per 1,000 examinations.

3.3 Characteristics of breast cancers detected by US

Table 2 demonstrates the proportion of invasive breast cancers and nodal status of the breast cancers detected by screening US. In the nine HHUS studies reporting cancer characteristics, 50–100% (median: 91%) of the additional cancers detected by US in each study were invasive. Six HHUS studies reported that 78–100% (median: 87.5) of additional breast cancers were node negative. The mean size reported for the invasive cancers in eight of 10 HHUS studies was 1.0 cm (range across studies: 6.5 – 19mm). Similarly for ABUS, Giuliano *et al* reported that 100% of cancers detected were invasive, with a mean tumor size of 14.3 mm and 98% node negative. Although Kelly, *et al* did not report a mean tumor size, they did note that 67% of the cancers detected by ABUS were 1 cm in size. The median node negative cancers detected by all US studies were 89%.

3.4 Studies conducted after enactment of breast density reporting legislation

Of the studies included in this analysis, three were performed in Connecticut after it became the first state to pass legislation requiring direct patient notification of breast density and the first to require insurance companies to cover screening US.^{20–22} While all three Connecticut studies were retrospective, these results provide information on performance variability of screening US in routine clinical practice from several institutions, where technologists perform the examinations that are subsequently interpreted by radiologists. In these three studies, the additional biopsy rate and additional cancer detection rate ranged from 32.8 – 71.0 per 1,000 examinations and 1.8 – 4.6 per 1,000 examinations, respectively.

We highlight the ACRIN 6666 study¹⁸ in addition to the Connecticut studies for several reasons. First, it was the only prospective multi-institutional study comparing mammography performance with and without adjunct screening HHUS in asymptomatic women. Second, the patient population was more homogenous, as patients were required to have at least one additional risk factor for breast cancer besides dense breasts to be included in the study. Third, breast imaging radiologists with significant ultrasound experience performed all screening US examinations in the trial. Despite these differences, the results were similar to the Connecticut studies. Of the 2,501 screening US examinations performed at 21 institutions across the United States, the biopsy rate was 68 per 1,000 examinations and cancer detection rate was 4.4 per 1,000 examinations. In a follow-up study, Berg, *et al* demonstrated a yield of 5.3 cancers detected per 1,000 examinations in women with no prior history of a screening US and 3.7 cancers per 1,000 examinations in subsequent rounds of screening.⁹ Additionally, despite the use of adjunctive screening US, at least 18–22% of cancers were not detected by either modality.^{9, 18}

3.5 Societal recommendations for adjunct screening US

Based on the sparse data currently available regarding the potential benefits and harms of screening ultrasound in women with dense breast tissue and no other known risk factors, at this time, no medical organization recommends adjunct screening in women based on breast density alone (Table 3). The American College of Radiology and Society of Breast Imaging recommend screening US as an adjunct to mammography only in a very selective sub-group of high-risk women (>20% lifetime risk) who cannot tolerate MRI.^{27, 28} These two societies

also state that US can be considered as an adjunct to mammography in women with dense breasts.

4. Comment

Our systematic review of the literature identified a relatively small number of studies on breast US as an adjunct to screening mammography. The study populations were generally at increased risk, with variable reporting in the studies of breast cancer risk factors. We chose to limit our analysis to the additional biopsy rate, the cancer detection rate, percent invasive cancers, and percent of node-negative cancers because these data were the measures of benefit and potential harm that were most consistently reported across studies. A previous systematic review of adjunctive screening US did not include ABUS studies or limit their data analysis of US performance in women with mammographically dense breasts.²⁹

The available evidence indicates that the additional cancer detection rate for adjunct US in women with dense breasts ranged from 0.3–12.3 per 1,000 examinations (Median 4.2 cancers per 1,000 examinations). In the three studies from Connecticut,^{20–22} which are most likely to reflect the routine clinical use of adjunct US and the patient populations receiving adjunct breast US, the cancer detection rate was closer to 2 per 1,000 women screened. Therefore, the cancer detection rate in a population of average risk is likely at the lower end of this range. Additionally, despite the increased cancer detection rate of adjunct screening US, ACRIN 6666 established that even when combined, mammography and US missed approximately 20% of breast cancers in women at high risk of developing breast cancer.

Most of the breast cancers identified by adjunctive US were small in size and node-negative in stage. These are the cancers that are potentially curable by early detection and amenable to less aggressive treatment. Women with screen-detected breast cancers are more likely to be eligible for lumpectomy rather than mastectomy, and may not require systemic chemotherapy compared with women whose breast cancers present clinically between screens.^{12, 30, 31} Thus, earlier detection with screening ultrasound may improve both quality and quantity of life.

Conversely, some of these early stage cancers may not have progressed significantly before the next routine screening examination with mammography. Thus, they may ultimately have been detected and cured with mammographic screening alone. Our review identified no studies of adjunct US that addresses the question of breast cancer mortality reduction or disease-free survival benefit. In addition, some proportion of the additional cancers detected by adjunctive screening may represent overdiagnosis, which is the identification of a cancer that would not have become clinically apparent over an individual's lifetime, or when screening results in treatment of disease that would not have shortened an individual's life expectancy.³² One method to directly test which of these two competing hypotheses is true would be to perform a randomized trial comparing the two approaches to breast cancer screening; however, this approach is both expensive and time-consuming.

An additional concern related to detecting additional breast cancers with adjunctive US is the high number of breast biopsies performed during the diagnostic process. The biopsy rate for HHUS after negative mammography ranged from 25 to 107 per 1,000 women screened, with a median of 56. This is more than five times greater than the approximately 10 biopsies performed per 1,000 women screened with mammography.²⁶ Given that the chance of biopsy recommendation with adjunct US screening is far higher than with screening mammography and the cancer detection rate is lower, it will be important to consider an individual woman's preferences when deciding whether or not to pursue adjunctive US screening.

Current and pending breast density legislation provides an opportunity for breast imaging radiologists and referring clinicians to work together and provide patients with accurate information on breast density and alternative approaches to breast cancer screening. Clinicians and patients should know that the potential "masking effect" of breast tissue obscuring cancers has been mitigated with advances in imaging technology. Currently, greater than 90% mammography units operating in the United States are digital rather than film,³³ and studies have shown improved performance of digital mammography compared to film screen mammography in women with dense breast tissue.^{6, 34, 35} While studies of film mammography have demonstrated declining sensitivity with increasing breast density,^{6, 36} a more recent study of 231,034 digital mammograms from four mammography registries in the Breast Cancer Surveillance Consortium showed significantly improved sensitivity of digital mammography compared to film screen mammography in women with dense breast tissue.⁶ Although not perfect, mammography is still the only screening test whose ability to reduce breast cancer mortality has been proven. The evidence supports long-term benefits for women of any breast density with regular mammographic screening, and women with dense breasts should be urged to seek digital mammography for screening.

Currently, no professional medical organization recommends the use of an adjunctive screening test based on breast density alone and screening US is recommended only for women at greater than a 20% lifetime risk for developing breast cancer who cannot undergo an MRI examination. Our study results support these recommendations. Regarding the optimal screening regimen for women with mammographically dense breasts, there is no single choice that is right for everyone. When counseling patients, clinicians are encouraged to discuss breast density as one of several breast cancer risk factors to help a woman understand her overall risk of breast cancer, to consider the potential harms and benefits of adjunctive screening, and to arrive at a decision together which is consistent with a woman's preferences and values.

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Figure 1. Categorization of Mammographic Breast Density

Mammographic breast density categorized according to the ACR BI-RADS (almost entirely fat, scattered areas of fibroglandular density, heterogeneously dense and extremely dense) and breast density legislation criteria (nondense and dense).

Figure 2. Variability of Biopsy Rates Across Adjunct Screening Ultrasound Studies

The number of biopsies (per 1,000 examinations) is reported across adjunct screening ultrasound studies with 95% confidence intervals.^{14–22, 24} The biopsy rates from the Giuliano, et al and Girardi, et al studies were not included in their studies.^{23, 25} These biopsy rates are in addition to the biopsy rates for mammographic examinations with positive results (10.2 biopsies/1,000 examinations²⁶).

Table 1

Populations Included in Screening Ultrasound Studies

Study	Years of Study	Study Design	Location	Number of Women	Mean Age (years)	Mammographic Breast Density	Mammogram Result	Family history (%) ^a	Prior Breast Cancer (%)
HHUS									
Crystal 2003 ¹⁴	2000–2002	NR	Israel	1,517	52.1	Scattered, heterogeneously and extremely dense	Negative	21% ^b	21% ^b
De Felice 2007 ¹⁵	2000–2006	Prospective	Italy	1,754	65	Heterogeneously and extremely dense	Negative	NR	NR
Brancato 2007 ¹⁶	2003–2006	NR	Italy	5,227	51.9	Heterogeneously and extremely dense	Negative	NR	NR
Corsetti 2008 ¹⁷	2000–2007	Retrospective	Italy	9,157	52	Heterogeneously and extremely dense	Negative	NR	NR
Berg 2008 ¹⁸ (ACRIN 6666)	2004–2006	Prospective	United States	2,501	55	Heterogeneously and extremely dense	Negative	NR	53%
Leong 2012 ¹⁹	2002–2004	Prospective	Singapore	141	45.1	Heterogeneously and extremely dense	Negative	17%	5%
Hooley 2012 ²⁰	2009–2010	Retrospective	United States (CT)	648	52	Heterogeneously and extremely dense	Negative	8%	15%
Weigert 2012 ²¹	2009–2010	Retrospective	United States (CT)	8,647	NR	Heterogeneously and extremely dense	Negative	NR	NR
Parris 2013 ²²	2009–2010	Retrospective	United States (CT)	5,519	52	Heterogeneously and extremely dense	Allowed positive mammogram	42%	6%
Girardi 2013 ²³	2009–2010	Retrospective	Italy	9,960	51	Heterogeneously and extremely dense ^c	Negative	NR	10%
ABUS									
Kelly 2010 ²⁴	2003–2007	Prospective	United States	4,419	53	Heterogeneously and extremely dense	Negative	59%	10

Study	Years of Study	Study Design	Location	Number of Women	Mean Age (years)	Mammographic Breast Density	Mammogram Result	Family history (%) ^a	Prior Breast Cancer (%)
Giuliano 2013 ²⁵	2010-2011	Prospective	United States	3,418	57	Heterogeneously and extremely dense	Allowed positive mammography	0%	0%

NR = Not reported

^a Includes women reporting either family relatives with breast cancer or a genetic predisposition

^b Women with family history or personal history of breast cancer were not separately reported

^c Analysis on women with heterogeneously and extremely dense breasts extracted from study data that included all breast densities, n = 22,131.

Table 2

Performance of Screening Ultrasound

Study	Number of Examinations	Biopsy Rate (per 1,000 examinations) ^a	Total # cancers detected (%)	Cancer Detection Rate (per 1,000 examinations) ^b	# Invasive Cancers (%)	Mean Invasive Cancer Size (mm)	Node Negative (%) ^c
HHUS							
Crystal 2003 ¹⁴	1,517	25.0	7	4.6	7 (100)	9.6	6 (86)
De Felice 2007 ¹⁵	1,754	106.6	12	6.8	10 (83)	10	NR
Brancato 2007 ¹⁶	5,227	11.9	2	0.3	2 (100)	NR	NR
Corsetti 2008 ¹⁷	9,157	56.1	37	4.0	36 (97)	NR	29 (86)
Berg 2008 ¹⁸ ACRIN 6666	2,501	68.0	11	4.4	10 (91)	10	8 (89)
Leong 2012 ¹⁹	141	99.3	2	14	1 (50)	13	1 (100)
Hooley 2012 ²⁰	648	71.0	3	4.6	2 (67)	6.5	2 (100)
Weigert 2012 ²¹	8,647	48.3	28	3.2	24 (85)	19	NR
Parris 2013 ²²	5,519	32.8	10	1.8	9 (90)	9.7	7 (78)
Girardi 2013 ²³	9,960	NR	22	2.2	NR	8	NR
ABUS							
Kelly 2010 ²⁴	6,425	11.7	23	3.6	22 (96)	NR	NR
Giuliano 2013 ²⁵	3,418	NR	42	12.3	42 (100)	14.3	41 (98)

NR = Not reported

^a Calculated as number of biopsies performed divided by total number of US examinations.^b Calculated as the number of cancers detected by US only divided by the total number of ultrasound examinations.^c Calculated as the number of detected invasive cancers with negative nodes divided by the total number of invasive cancers with nodal status known

Table 3

Society recommendations for screening breast ultrasound

Society	Recommendations ^a
American Cancer Society (ACS)	None
National Comprehensive Cancer Network (NCCN)	Insufficient evidence for routine US screening
American College of Radiology (ACR)	Only recommended in high risk patients (>20% lifetime risk) who cannot tolerate MRI ^b
Society of Breast Imaging (SBI)	
American College of Obstetricians and Gynecologists (ACOG)	None
US Preventative Services Task Force (USPSTF)	None
American Academy of Family Physicians (AFP)	None
American College of Physicians (ACP)	None
American Medical Association (AMA)	None

^aRecommendations are for handheld ultrasound only^bRecommendations through joint statement by the ACR and SBI