Automated breast ultrasound is likely to be a key player in the future of imaging for women with dense breast tissue. There has previously been a gap in the ability of technology to screen dense breast tissue. Dense tissue can not only obscure cancer when imaged with x-ray mammography, but is also a risk factor, increasing the risk of breast cancer four- to six-fold for women with fibroglandular tissue greater than 60%. Ultrasound has been proven to find cancers that are not visible with mammography. Automated breast ultrasound standardizes the use of ultrasound, producing a more comprehensive and consistent image, which physicians can review quickly and easily. There is a promising future for the use of automated ultrasound for screening women with dense breast tissue. Automated breast ultrasound is proving to be a useful adjunct to mammography, which helps to catch cancer at an earlier and more treatable stage.

**KEYWORDS:** 3D sonography  ABUS™ automated breast ultrasound  breast cancer screening  breast density  breast imaging  cancer detection  ultrasound

Mammography is still the standard in breast cancer detection, and has been shown to reduce breast cancer mortality by as much as 30% by finding small cancers at an early stage [1,2]. However, between 10 and 50% of breast cancers are not visible with mammography [3,4]. Women with dense breast tissue are more likely to have cancers not visible on a mammogram [5]. Not only is cancer less easily seen on mammograms for women with heterogeneously or extremely dense breasts, these women also have a four- to six-times increased risk for breast cancer [6]. Ultrasound (US) has been proven to be a useful adjunct to mammography and it can detect over 40% more cancers than mammography or physical examination alone [7,8]. Standard handheld US screening is limited because it is time consuming for technicians to perform and physicians to review, and it lacks consistency between operators. In response to these issues, automated whole-breast or 3D US has been under development for decades. Recent advances in automated breast US have led to devices that have been shown to be successful in preliminary studies as adjuncts to mammography. These devices provide promising US screens for women with dense tissue.

Breast cancer is the most common cancer in women, detected primarily through mammography [1,9]. Sensitivity of mammograms for the general population ranges from 77.6 to 87.0%, meaning that anywhere from 13.0 to 23.0% of cancers are not detected by mammography [3,7,10]. For women with dense breasts, mammographic sensitivity is even lower [7,8,11-13]. The enhanced clarity provided by full-field digital mammography was thought to improve the ability of radiologists to differentiate these hard-to-see cancers in dense tissue from screen-film mammography. Recent studies, however, have shown that while full-field digital mammography tends to be better at detecting cancers with certain mammographic features, such as small cancers, it has not significantly improved the screening capabilities, as over 30% of cancers are still not visible [14].

**Breast density**

Dense breast tissue is normal and very common; approximately 40% of all women have dense breasts [15]. Breast density is based on the proportion of stromal and epithelial tissue compared with the fibrofatty tissue. The stromal and epithelial tissue appears radiopaque as opposed to the radiolucent fatty tissue (Figure 1). Breast density is classified based on the Breast Imaging–Reporting and Data System (BI-RADS) of the American College of Radiologists, which classifies density into one of four categories. They are: one, almost entirely fatty (0–25% density); two, scattered fibroglandular tissue (25–50% density); three, heterogeneously dense (50–75% density); and four, extremely dense (75–100% density) [16]. A higher risk of breast cancer has been established for those women with BI-RADS 3 and 4 densities [11]. It is also more difficult to image women with dense breasts using mammography.

It has long been established that women with predominantly dense breasts are at a greater risk for breast cancer. This was first described by Wolfe...
in 1976. As mammography techniques and technology have improved through the decades, Wolfe’s conclusions have been confirmed; studies consistently show a four- to six-fold increase in breast cancer risk for women with 60% or more breast density. In comparison with predominantly fatty breasts, there is a 17.8-fold higher likelihood of an interval cancer – that is, a cancer diagnosed within 12 months of a normal mammogram, for women with extremely dense breasts.

Part of this increase in interval cancers for women with dense breasts can be attributed to the difficulty in imaging. Glandular breast tissue and cancer, as well as other breast lesions, appear white on a mammogram, making it difficult to discern a lesion from normal dense breast tissue. For this reason it is likely that, in addition to the added risk of breast cancer in women with dense breasts, their cancers are more likely to be missed at their annual mammogram screening than women who do not have dense tissue. This may result in cancers being found at a later stage once the patient notices a lump. Sensitivity of mammography decreases from 87.0% in women with fatty breasts to 62.9% in women with dense breasts, which allows for a greater number of missed cancers.

Mammograms are effective breast cancer screenings because they find cancer at an earlier, more treatable stage than if they are found by palpation. Mammograms have been shown to reduce mortality from breast cancer by 30%, and only 18% of mammography screen-detected cancers are late-stage cancers, as opposed to 47% of those detected clinically. Therefore, cancers that are missed at the time of mammogram screening are eventually found at a later stage with a worse prognosis. Considering the higher likelihood of an interval cancer occurring in women with dense breasts, and the fact that interval cancers are likely to be larger and found at a later stage, it is important that these women have additional screening options to ensure that cancers are caught at an early and treatable stage.

Alternative screening methods

There has been some success in alternative screening methods. Many women with a very high risk for breast cancer (greater than 20% lifetime risk) due to family or personal history of breast cancer, or a genetic predisposition, opt to undergo MRI or breast-specific γ-imaging as an additional screening for cancer. These examinations, however, are more expensive and more time consuming. Breast-specific γ-imaging exposes patients to radiation and requires an injection. MRI also requires an injection and, in addition, can be inaccessible to patients due to obesity or pre-existing conditions, such as renal insufficiency or an implanted device, and is generally not well tolerated by patients.

The most reasonable and promising imaging modality to be used for screening women with dense breasts is US. US has long been proven to be a helpful diagnostic tool in breast imaging. On US, breast tissue appears white, but many lesions appear dark gray or black, making it possible for radiologists to distinguish lesions in dense breast tissue. US is most frequently used for the additional visualization of palpable areas and abnormalities seen on a mammogram. It is useful in the differentiation between solid and cystic masses.

A number of studies have examined the use of US as a screening adjunct to mammography, particularly for women with dense breasts. In 2002, Kolb et al. found that US was able to
Recent advances: automated breast US

In response to this, new technologies have been developed in order to create a reproducible, comprehensive and efficient US scan of the breast. Most of these technologies are new to the market, but it is an exciting, rapidly developing area that is sure to be beneficial for women with dense breasts. Four devices, the SonoVu Automated Breast US System (ABUS™) by USystems, the Acuson S2000™ Automated Breast Volume Scanner (ABVS) by Siemens, the Automated Whole Breast US (AWBU) by SonoCine, and the 3D Multimodal Ultrasonic Tomography (MUT) show great promise in the emerging field of automated 3D US.

ABUS, developed by USystems and recently acquired by General Electric (CT, USA), has been under study since 2009 in a comprehensive, multicenter clinical trial to compare the sensitivity of mammography and the combination of mammography and ABUS together. So far, of 15,143 women ≥25 years of age with ≥50% density and no symptoms who had the ABUS screening examination in addition to their screening mammogram, 26.8% of all cancers found were seen by ABUS alone and of those, 92.0% were invasive (Figure 2) [28]. Recently, at The Breast Cancer Research Institute, Nova Southeastern University College of Medicine (FL, USA), ABUS, in combination with mammography, detected 12.3 breast cancers per 1000 screening examinations of asymptomatic women with dense tissue, as opposed to 4.6 cancers per 1000 screens detected by mammography alone [29]. The false-positive rate for ABUS is not yet known. ABUS is the only device cleared by the US FDA for screening women with dense breast tissue. The cost for the procedure varies among institutions, although it is typically affordable.

ABUS uses a 14–16 MHz high-frequency ultra-broadband transducer housed in a paddle that is held by the technologist and used to lightly compress the breast against the chest wall. Images are obtained in the transverse view, per standard US, over a 15 × 18 × 5.0 cm area and then stored in a 3D block. A minimum of three views are captured of each breast: anterior–posterior, medial and lateral. A separate view station allows for viewing the images in reconstructed 2-mm coronal or the original transverse views. The size of the coronal sections is large enough to avoid unnecessary slices and a too large file size, but remains small enough to match the size of an individual terminal ductal lobular unit so as not to miss small abnormalities. The axilla of the breast can also be thoroughly imaged with additional views.

ABUS separates image acquisition and interpretation. Unlike handheld US, the entire data set is acquired, and following acquisition is reviewed by the physician, thereby obviating the need to rely on the interpretation of the technologist to determine whether a lesion is present without requiring a physician to perform
the US study himself/herself. If a physician were to perform a handheld US examination, he or she may spend 20–30 min scanning a patient; ABUS can be operated by a technologist and the images can be read by a physician in 173.4 s on average [30]. The stereotyped method of image acquisition makes for an easily reproducible examination, and the automation allows for standardization across device operators. Many of the drawbacks of handheld US are resolved by ABUS.

ABUS was designed as a screening tool. In the authors’ practice, ABUS is used solely for screening patients. Additional use of the equipment for US biopsy guidance would hinder patient flow, as fewer patients could be screened. Furthermore, handheld US is better suited and designed for biopsy guidance.

The Acuson S2000 ABVS produced by Siemens is similar in design and operation to the SomoVu ABUS. While less comprehensive research has been carried out on this device, it was successful in detecting 81% of lesions that had previously been seen on mammography, demonstrating that it is reliable for lesions greater than 1.2 cm, of which it detected 92% [31]. This lesion size is larger than cancers reported with ABUS, but additional research is needed to further define the characteristics of cancers detected with ABVS [27].

The AWBU produced by SonoCine takes a slightly different approach to whole-breast US. This device uses a handheld transducer controlled by an automated mechanical arm that moves the transducer in a specific pattern of overlapping longitudinal rows [32]. The AWBU software then creates a cine loop for interpretation, creating the appearance of real-time imaging [32]. In a study of this device used to evaluate 4419 high-risk women at the time of their routine mammograms, AWBU achieved
a positive predictive value of 38%, a marked improvement over the 11% positive predictive value of handheld US in the ACRIN 6666 trial [32–34].

A prototype has been under study at the University of Athens (Greece): 3D MUT uses ultrasonic tomography of the pendulant breast in a water bath to create a 3D representation [35]. The device has shown some promise in its ability to correctly classify benign and malignant lesions in a study of 25 patients with lesions ≥0.10 cm [35].

3D automated US is certain to be a significant contributor to the future of breast imaging and early cancer detection. Currently, the primary concern for the use of US to screen women with dense breasts in addition to mammography is a high false-positive rate compared with that of mammography, and the possibility of unnecessary procedures. The ACRIN 6666 trial demonstrated an increase in biopsies as a result of added US screening, although the risk of false positives decreased significantly with additional annual screenings [14]. With further study of lesions and their appearance with 3D automated US, and integration of the examination into annual screenings, the specificity will likely increase and biopsies of benign lesions will decrease.

Concurrent development of other technologies may also aid in the accurate identification and diagnosis of breast disease. Computer-aided detection (CAD) has been developed for 3D US volumetric images. One system from the University of Michigan (MI, USA) has found that CAD improves radiologists’ ability to distinguish benign from malignant masses [36]. CAD has also recently been applied to ABUS, and been found to be successful in feature extraction and classification of breast tumors in images generated by ABUS [37]. Elastography may be helpful as a future application of 3D US. It is a measure of the stiffness of tissue computed from US imaging that may help to rule out benign lesions, reducing unnecessary biopsies [38]. The integration of elastography in clinical practice is just beginning and requires significant additional research. As whole-breast US is an emerging technology, additional tools such as Doppler and contrast-enhanced US are being evaluated and integrated.

Overall, the 3D view available through ABUS and similar US screening methods helps radiologists to gain a better understanding of a patient’s breast compared with the 2D mammographic view, especially if that patient has dense breasts that limit the imaging capabilities of mammography. 3D mammography, or tomosynthesis, is another new technology being implemented in many practices across the USA. It has been shown to reduce recall rates for women undergoing screening mammography and increase diagnostic accuracy, but it is unclear as to whether or not it aids radiologists in the detection of cancer in dense breast tissue [39]. Further studies to define the incremental increase in cancer detection in women with dense breasts are still needed.

**Conclusion**

3D automated breast US is the most promising new technology for the detection of breast cancer in women with dense breasts. There had previously been a lack of options for one of the largest groups at elevated risk for breast cancer, with no reasonable method of screening beyond mammography. 3D screening US will probably fill the void to improve the sensitivity of yearly breast cancer examination for women with dense breasts. There is still more to be explored in these new technologies, including the possible use of CAD and elastography. However, devices such as ABUS are capable of detecting cancers occluded by dense tissue on mammography and give radiologists a more comprehensive image of the breast.

Mammography is effective and sufficient for the majority of the population with predominantly fatty tissue at average risk for breast cancer; it will detect nearly 90% of breast cancers [4]. Women at high risk for breast cancer due to a genetic predisposition or family or personal history of breast cancer typically undergo MRI or breast-specific γ-imaging as an additional screening. These screenings are effective and reasonable for this population; they are not, however, reasonable for the 40% of women with dense breast tissue [16]. ABUS is an effective and efficient screening examination for women with dense breast tissue at intermediate risk for breast cancer. With the successful implementation of ABUS, the hope is that the prevalence of interval cancers will decrease and breast cancer will be caught in women with dense breast tissue at an earlier, more treatable stage.

**Future perspective**

The use of ABUS and similar devices is likely to increase rapidly as more data becomes available, supporting its ability to detect cancers missed by mammography. In 5–10 years, ABUS, as an adjunct to mammography, may well become the standard of care for women with dense...
breast tissue. Further study on the appearance of benign and malignant lesions on ABUS will lead to more accurate diagnoses of cancer, fewer false positives, less additional imaging and fewer unnecessary biopsies. Eventually, other technologies may be used in combination with whole-breast US, such as CAD and elastography, to enhance the ability to identify and diagnose lesions.

**Executive summary**

**Background**
- Mammography remains the gold standard in breast imaging and cancer detection.
- Despite recent advances, mammography fails to detect 10–50% of cancers.

**Dense breast tissue**
- Density is based on the proportion of stromal and epithelial tissue to fibrofatty tissue.
- Dense tissue is common; it occurs in 40% of women.
- Women with dense tissue have a four- to six-fold higher risk of breast cancer.
- Dense tissue can obscure cancers on x-ray mammography.

**Alternative screening methods**
- MRI and breast-specific γ-imaging are useful for women at high risk for breast cancer due to family or personal history, or genetic predisposition.
- MRI and breast-specific γ-imaging are expensive, time consuming and inaccessible or uncomfortable to some patients, limiting their use to high-risk patients.
- These examinations are not feasible for all women with dense breast tissue at intermediate risk for breast cancer.
- Ultrasound has been proven to be useful in the detection of mammographically occult cancers, although it is time consuming, operator-dependent and not easily reproducible.

**New technologies: automated breast ultrasound**
- New technologies aim to standardize the use of ultrasound to make it more convenient and less time consuming.
- Automated breast ultrasound is the only device thus far that has been US FDA cleared for screening, it has been found to detect a significant number of cancers not visible on mammography.
- Other technologies are being developed that may similarly aid in cancer detection.

**Future perspective**
- Automated ultrasound screenings should become a routine part of breast imaging examinations for early cancer detection in women with dense tissue.
- The understanding of lesion characteristics can be refined to reduce the false-positive rate and prevent unnecessary procedures for women with benign lesions.
- Other technologies may be combined with breast ultrasound to improve lesion detection and diagnosis.

**Conclusion**
- Mammography alone can miss half of the cancers that occur in women with dense tissue at intermediate risk for breast cancer.
- Automated breast ultrasound is an efficient and reliable screening solution for finding earlier stage, mammographically occult cancers in women with dense breast tissue.

**References**

Papers of special note have been highlighted as:
* of interest
** of considerable interest


Automated breast ultrasound: a novel approach to screening women with dense breasts

28 Connecticut (USA) legally mandates that doctors inform women of their breast density and that ultrasound screening be covered by insurance companies for women with dense breast tissue. These laws led to the common practice of ultrasound as a screening tool. This study reports the use of ultrasound as a screening method for women with dense breasts in clinical practice.
31 Preliminary results of automated breast ultrasound in screening women with dense breast tissue show that automated breast ultrasound improves cancer detection rate and is a valuable tool for clinical practice.
35 First experiences with automated whole-breast ultrasound show improved cancer detection rate and a promising future for this device in clinical screening.