Special Review

A Review of Supplemental Screening Ultrasound for Breast Cancer: Certain Populations of Women with Dense Breast Tissue May Benefit

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Breast density has been shown to be a strong, independent risk factor for breast cancer. Unfortunately, mammography is less accurate on dense breast tissue compared to fattier breast tissue. Multiple studies suggest a solution to this by demonstrating the ability of supplemental screening ultrasound to detect additional malignant lesions in women with dense breast tissue but negative mammography. In particular, supplemental screening ultrasound may be beneficial to women with dense breast tissue and intermediate or average risk for breast cancer, women in specific ethnic populations with greater prevalence of dense breast tissue, and women living in resource-poor healthcare environments. Although magnetic resonance imaging is currently recommended for women with high risk for breast cancer, not all women can access or tolerate a magnetic resonance imaging examination. Notably, ultrasound does not require intravenous gadolinium and may be an alternative for women with socioeconomic or medical restrictions, which limit their access to magnetic resonance imaging. Limitations of supplemental screening ultrasound include a substantial rate of false-positives, increased cost, and limited resource availability, particularly in regard to the time required for image interpretation. Additional clinical experience with this application of ultrasound, improved patient selection criteria, and new technology, such as the promising results seen with automated whole breast ultrasound, may address these limitations. In light of recent legislation in some states that has called for discussing supplemental imaging with patients who have dense breast tissue, the optimal role for supplemental screening ultrasound merits further exploration.

Key Words: Breast density; ultrasound; breast cancer; mammography; sonography.

INTRODUCTION

Worldwide, breast cancer is the second most common cancer and a leading cause of cancer death among women (1). Meta-analysis of randomized controlled trials has demonstrated decreased mortality after the implementation of mammography in women age 39–69. However, conflicting estimates of the impact of screening mammography on breast cancer-related and all-cause mortality have incited criticism that screening mammography has contributed to breast cancer overdiagnosis (2,3). As a result, further elucidation of the best imaging practices for breast cancer screening is being intensely researched. Well-established risk factors for breast cancer have been incorporated into models for clinical decision making. The Gail model is the most widely utilized validated tool, which incorporates current age, age at menarche and first parturition, race and ethnicity, family history of breast cancer in first-degree relatives, number of prior breast biopsies, and biopsy findings of atypical hyperplasia (4). Increased risk determined by the Gail model guides the prophylactic use of risk-reducing medications and the earlier use of clinical breast examinations and screening mammography. Increasingly, the use of risk factors to guide appropriate screening regimens is being explored. For example, screening with contrast-enhanced magnetic resonance imaging (MRI) is currently recommended by the American Cancer Society as a supplement to mammography in patients with greater than 20% lifetime risk of breast cancer (as assessed by either the Gail model or the BRCAPRO model), with known BRCA1/2 mutations, first-degree relatives of known BRCA1/2 mutation carriers, other cancer-associated genetic mutation carriers, and with chest radiation exposure between the ages of 10 and 30 (5).

Breast density has been shown to be a strong, independent risk factor for breast cancer. Breast density can be assessed through mammography and is described most frequently with the Breast Imaging Reporting and Data System (BI-RADS) classification. The BI-RADS lexicon includes four categories, which refer to the percentage of breast tissue that is fibroglandular: (1) almost entirely fatty, (2) scattered fibroglandular, (3) heterogeneously dense, and (4) extremely dense (6). Apart from age and specific genetic mutations, breast

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TABLE 1. ASTOUND Trial Comparison of Supplemental Screening in Addition to Mammography

Supplemental Modality	Cancer Detection Per 1000 Examinations	False-positives (%)
DBT	4	1.70
Ultrasound	7.1	2.00

DBT, digital-based tomosynthesis.

Supplemental ultrasound detects more cancers than supplemental DBT with a similar false-positive rate (17).

density is the strongest risk factor. In fact, women with extremely dense breast tissue are between four and five times more likely to develop breast cancer than women with predominantly fatty breast tissue, an association that remains strong across age groups (7–11).

The impact of breast density on breast cancer mortality is twofold: it remains an inherent risk for developing breast cancer after adjusting for other associated risk factors and also complicates cancer detection through screening mammography (10,12). Full field digital mammography has inherent limitations in imaging dense breast tissue because greater superimposition of tissue can make lesions more difficult to visualize. Technological advances in mammography have improved the ability of this modality to detect cancer in women with dense breast tissue. Specifically, digital breast tomosynthesis (DBT) has been utilized to overcome the limitations of standard full field digital mammography in dense breast tissue. Studies of DBT have demonstrated improved cancer detection and significantly reduced recall rates with the addition of DBT to mammography for women with dense breasts (13–16). Still, both ultrasound and MRI have a higher sensitivity than DBT for dense breast tissue (DBT: 87.4%; ultrasound: 91.6%; MRI: 98.3%). Also, the ASTOUND trial (Table 1), the largest prospective study to date for women with dense breast tissue and negative mammography, recently demonstrated increased cancer detection with supplemental ultrasound compared to DBT (ultrasound: 7.1 per 1000 women; DBT: 4.0 per 1000; $P = 0.006$), with a similar false-positive recall rate (ultrasound: 2.0%; DBT: 1.7%) (17). The combined use of DBT with ultrasound is being explored as a means to improve the recall rates observed with ultrasound screening for women with dense breasts (18), as DBT has been demonstrated to improve specificity. However, a recent retrospective study found that the improvement in recall rate observed with DBT is negated by the addition of ultrasound regardless of breast density classification (19). In a complementary role, DBT is currently being investigated as a method for assessing breast density and may allow for more accurate density assessments than standard full field digital mammography, allowing centers that utilize DBT to more effectively identify women with increased breast density for supplemental screening protocols (13–15,18).

In light of the challenges of imaging dense breast tissue with mammography, consideration of breast density in screening recommendations likely has potential to improve the sensitivity and specificity for detecting malignant lesions. Observational studies suggest that patients who will benefit from screening breast MRI in addition to screening mammography can be identified by considering the patient's breast density category relative to her Gail model percentage (20,21). At present, no large randomized clinical trial has completed investigating the effects of supplemental MRI screening in women with dense breasts, but the ongoing DENSE trial is expected to address this question in the coming years (22). The American Cancer Society (ACS) currently recommends the use of supplemental screening MRI in women with high risk for breast cancer, including women with dense breast tissue. However, the ACS does not consider increased breast density alone as a sufficient indicator for supplemental screening MRI (5). The optimal supplemental imaging modality for women with dense breast tissue and average to intermediate risk for breast cancer remains a topic of much study and debate.

ADVANTAGES OF SUPPLEMENTAL SCREENING ULTRASOUND IN PATIENTS WITH DENSE BREAST TISSUE

Although screening MRI in high-risk populations may reduce breast cancer mortality, there could still be an important role for ultrasound screening. Breast ultrasound does not offer additional benefit in patients who already undergo MRI screening (23,24). Even in high-risk patients with dense breast tissue, however, the use of MRI is limited by high cost, availability of equipment and trained personnel, contrast administration, and ability of patients to tolerate the examination. Limited-protocol MRI has been demonstrated to detect breast cancer and can reduce examination time substantially compared to a standard protocol (10–15 minutes vs 30–40 minutes) (25). Although abbreviating the MRI protocol may improve the tolerability of this examination for some patients, recent studies have demonstrated that intravenous gadolinium exposure is associated with deposition in the brain (26,27). In contrast to MRI, ultrasound is widely available, well tolerated, and does not require intravenous contrast administration. For patients with elevated risk and increased breast density who could benefit from MRI but cannot tolerate or access screening examinations, ultrasound may be the ideal supplemental screening option.

Multiple observational studies support the ability of supplemental ultrasound to detect additional malignant lesions in women with dense breast tissue but negative mammography. Supplemental sonography detected between 3 and 4.6 additional cancers per 1000 supplemental screening ultrasound examinations (28–31). To date, the ACRIN 6666 trial is the largest randomized multicenter study of supplemental screening ultrasound. The ACRIN 6666 study included women with BI-RADS density of heterogeneously dense or extremely dense, as well as at least one additional risk factor: elevated risk (as assessed by either the Gail or Claus model), personal history of breast cancer, prior atypical breast biopsy, and/or