Breast Density and Supplemental Screening

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Importance of Breast Density

Defining Breast Density

Dense breast tissue is common and normal. About 40% of women over the age of 40 years have dense breasts (1). Dense breasts are more common in younger women and the breasts tend to become more replaced by fat as the glands involute after menopause. Dense breast tissue reduces the effectiveness of mammography and increases the risk for developing breast cancer.

In clinical practice in the United States, Breast Imaging Reporting and Data System (BI-RADS) breast density categories are used in mammographic reports to indicate the degree of mammographic breast density: a) The breasts are almost entirely fatty, b) There are scattered areas of fibroglandular density, c) The breasts are heterogeneously dense, which may obscure small masses, and d) The breasts are extremely dense, which lowers the sensitivity of mammography. The last two categories are considered "dense". Of women in their early 40s, about 13% have extremely dense breasts and 44% have heterogeneously dense breasts, and by the early 70s, 2% have extremely dense and 24% heterogeneously dense breasts (1). The fifth edition of BI-RADS (2) places more emphasis on the masking effects of breast density and specifies that when there are regions of sufficient density to obscure small masses, the mammogram should be categorized as heterogeneous rather than scattered even if the overall volume of density would not typically place that study in the heterogeneous category.

Because of inherent inter- and intra-reader variability of BI-RADS density classification, computer based methods have been developed to improve consistency. Cumulus is a software program requiring manual input to outline and measure the area of breast tissue relative to overall breast area (3). More recently, automated programs have been developed that measure percent density as a function of area or volume. Percent volume of breast tissue measures will be lower than area-based methods, typically with an upper limit of 35-40% for extremely dense breasts. Several automated density programs have demonstrated high reproducibility (4) and correlation with volumetric density as measured by MRI (5).

Density and Breast Cancer Risk

At least 15 studies demonstrate at least a moderate association of mammographic density and breast cancer risk (6). Women in the extreme density group are 4- to 6-times more likely to develop breast cancer than women with fatty breasts making density at least a moderate risk factor for breast cancer that is more

important than traditional risk factors such as early menarche, late menopause, and late parity. However, when the reference category is set as scattered density, the risk of breast cancer associated with high breast density is about twice as likely. Since most women are in the middle two categories of density this is a more appropriate way to communicate risk associated with density. It should be emphasized that extreme breast density as the sole risk factor does not put women into a high lifetime or 10-year risk of breast cancer. Of note, studies evaluating breast density and risk must control for body mass index (BMI) since postmenopausal obesity is an independent risk factor for breast cancer but is inversely related to breast density.

The inclusion of density in risk models should improve performance at the individual level. The Breast Cancer Surveillance Consortium (BCSC) model includes BI-RADS density added to a modified Gail model with modest improvement (7). Work is in progress to add density to the Tyrer-Cuzick model.

Density and Masking

All radiologists interpreting mammograms understand the challenges and limitations of cancer detection for women with dense breast tissue. This results in an increased risk of interval and higher stage cancers for women with dense tissue.

Women with dense tissue are at increased risk for interval cancer, which is defined as a cancer that presents due to symptoms during the interval between recommended rounds of screening (one year in the U.S., but up to 3 years in other countries). Interval cancers can represent up to one-third of cancers diagnosed in women undergoing screening mammography (8, 9). The European Breast Cancer Screening Network reported that interval cancers represented 28% of cancers detected in the screening programs of six European countries; about two-thirds of interval cancers presented in the second year after a negative screening mammogram (10). Boyd et al found that women with >75% density (extremely dense breasts) were 17 times more likely to have an interval cancer than women with fatty breasts (11). A study by the Breast Cancer Surveillance Consortium (BCSC) found that interval cancers represented 15.7% of cancers in women with extremely dense breasts compared with 4.5% of cancers in women with fatty breasts (12). A later analysis showed that women most at risk for interval cancer were women with extremely dense breasts and Gail model 5-year breast cancer risk of $\geq$1.67% or women with heterogeneously dense breasts and 5-year risk of $\geq$2.50% (9).

Even when breast cancer is detected at screening, women with dense tissue have cancers that are larger, more likely lymph node positive, and of higher stage than women without dense tissue (13, 14). Cancers in women with dense breasts are also more often multifocal or multicentric and mastectomy is more often performed (15).

At least 10 ten years of follow-up are needed to establish differences in mortality in screened or unscreened women and few studies have examined the impact of breast density on mortality with such long-term follow-up. Data from the Kopparberg Screening Program in Sweden with 25-year follow-up showed an almost double risk of death for women with dense tissue compared with non-dense tissue (RR 1.97), attributed to higher

incidence (14). Gierach et al (9) showed a relative increase in stage II and stage III disease in women with dense breasts but had insufficient follow-up to address differences in breast cancer mortality.

Masking of cancer by dense tissue has become a political issue beginning in Connecticut, which became the first state to enact legislation requiring that women receive notification about breast density with their mammography results. Advocacy efforts, generally spearheaded by women who were diagnosed with breast cancer after a negative screening mammogram (12), have now resulted in 27 state laws (16). The level of information required to be given to the patient varies from state to state with some states requiring a patient receive only a general notification *about* breast density while others require a woman be told if *her* breasts are dense. State laws share the common theme of notification to women of the possible limitations of mammography in dense breasts. With the goal of enacting a single national standard, advocacy efforts have also resulted in proposed federal legislation, the Breast Density and Mammography Reporting Act (S370), as well as consideration of a federal regulatory amendment to the Mammography Quality Standards Act (MQSA) reporting requirements (14).

Digital mammography improves performance for women with dense tissue compared with film-screen mammography (17) though the improvement is modest. Ancillary screening in addition to mammography may be indicated for women with dense tissue.

Supplemental Screening in Dense Breasts

Reduction in deaths from breast cancer has only been studied for mammography, and the majority of women who die from breast cancer never participated in screening mammography either because they were too young or because they did not comply with guidelines (18). About 19% of deaths occur from breast cancers detected on screening which had already spread at the time of diagnosis and 10% of breast cancer deaths are from interval cancers (18). Adding supplemental screening beyond mammography should allow earlier detection of cancers that would have subsequently been detected as palpable masses or at a larger size on later screening (i.e. fewer interval cancers and shift to earlier stage cancers). The mammography screening trials which produced mortality reduction from breast cancer were those with improved detection of early stage invasive cancers and reduced late stage disease (19): other methods which improve detection of node-negative invasive cancers should further reduce breast cancer mortality.

Tomosynthesis

Digital breast tomosynthesis (DBT) creates image “slices” through the breast, reducing overlap of normal dense tissue, thereby allowing improved invasive cancer detection. DBT is associated with an approximate doubling of radiation exposure when used in combination with a standard mammogram. Some facilities with DBT use software to create a “synthetic” 2D mammogram instead of a standard mammogram reducing radiation exposure to only about 1.2-times that of a standard mammogram.

Although numerous studies show an improvement in invasive cancer detection with DBT, fewer data are available to assess DBT performance in women of differing density categories. In the prospective Oslo trial, Skaane et al found improvement in cancer detection and reduced recalls for women of all density categories (20). However, the number of women in the extremely dense category was relatively small with only 6 cancers: two detected only at DBT. Ciatto et al (21), in a prospective multicenter study in Italy, showed incremental cancer detection rate (ICDR) due to DBT of 2.8 (95%CI 1.6 to 4.5) per 1000 screens among 6079 women with fatty or scattered fibroglandular tissue and 2.5 (95%CI 0.5 to 7.2) among 1215 women with dense breasts. Data were provided only in aggregate for dense and nondense breasts. In a retrospective multicenter analysis of 452,320 examinations (278,906 digital mammography alone and 173,414 digital mammography plus DBT), Rafferty et al (22) reported ICDR due to DBT of 1.0 (95%CI 0.3 to 1.6) per thousand screens in women whose breasts had scattered fibroglandular density and 1.6 (95%CI 0.9 to 2.3) in women with heterogeneously dense breasts but not different at 0.1 (95%CI -1.3 to 1.6) in women with extremely dense breasts. While inability to detect any improvement may be due to the relatively small number of women with extremely dense breasts, it is logical that in extremely dense breasts there is often a lack of soft tissue contrast within slices which still masks cancer detection even on DBT.

Reduced false positive recalls have been observed with DBT across all breast densities (20-22). Haas et al found the greatest reduction in recall rate for women with extremely dense breasts with DBT (15.6% for 2D and 6.7% with DBT + 2D) (23). One single-center study found that DBT reduced the interval cancer rate across all women (24), but most studies lack sufficient follow-up to examine this.

Screening Ultrasound

Supplemental screening with ultrasound (US) after mammography has been extensively studied in women with dense breasts. Most studies have used handheld ultrasound (HHUS). Prospective multicenter trials of physician-performed HHUS have shown ICDR of 4.0 to 5.3 per 1000 (25, 26) with the first, prevalent screen, and this detection benefit persists with subsequent (incident) screening rounds (26). Slightly lower ICDR averaging 2.5 per 1000 has been observed with technologist-performed HHUS [summarized in (27). Importantly, a final assessment can be rendered for technologist-performed HHUS if standard images are obtained; only 43/16,676 (0.3%) required recall for immediate targeted US (BI-RADS 0, incomplete) across four series (27). An absolute increase in recall rate of 13-15% in year one and 7% in subsequent years has been observed when screening US is added to mammography (26, 28). About 4-5% of women screened with US may be recommended for biopsy of a benign finding (21, 26, 27), which is higher than for screening mammography where 1-2% of women screened undergo biopsy.

Standardized technique for HHUS is advocated. One widely validated protocol is that used in American College of Radiology Imaging Network (ACRIN) 6666 where survey scanning is performed in transverse and sagittal planes, with the ipsilateral arm raised, supine oblique for the outer breast and supine for the inner breast, with documentation of at least one image per quadrant and one behind the nipple for a negative examination of each breast (27). Representative simple cysts should be documented and all other lesions

should be documented in the longest (usually radial) axis and its orthogonal (usually antiradial), with and without calipers. Doppler can be helpful when internal vascularity distinguishes a potentially suspicious anechoic mass from a cyst or complicated cyst with debris. Using such standard technique, results from HHUS are as consistent as for mammography. The average examination took 19 minutes in the first year of ACRIN 6666 and nearly 15 minutes in year 3 (26); with standard documentation, interpretation of HHUS performed by a technologist takes less than one minute.

The Japanese Strategic Anti-Cancer Randomized Trial (J-START) randomized women aged 40-49 years to have the intervention of supplemental screening US after mammography (n=36,869) or mammography alone (n=36,139) (29). There was an increase in cancer detection in the intervention arm and a stage shift with a greater proportion of cancers detected at stage 0 or stage I: 144/184 (71.3%) vs. 79/107 (52.0%, p=0.019). Importantly, the interval cancer rate was cut in half in the intervention arm: 18 (0.05%) vs. 35 (0.10%, p=0.034). Similarly, Corsetti et al reported interval cancer rates comparable to women with fatty breasts when screening US was added to mammography in women with dense breasts in a prospective Italian multicenter trial (30). Interval cancers represented only 8% of all cancers (9/111) in the ACRIN 6666 study (26).

Because HHUS requires highly trained personnel, automated breast ultrasound (AUS) has been developed for screening. Several approaches have been explored. Prospective multicenter trials have validated AUS. Kelly et al reported an ICDR of 3.6 per 1000 (95%CI 2.3 to 5.4) with a 10% recall rate and 1.2% biopsy rate for benign disease (31) using an automated arm and standard US transducer. Another approach uses a wide (typically 15 cm) footprint transducer and requires 3 to 5 acquisitions to cover each breast, generating coronal as well as several thousand transverse images. Brem et al reported 30 cancers seen only on such AUS in 15,318 women (ICDR 2.0 per 1000) with a 13% absolute increase in recall rate (32). It takes about 15 minutes to acquire the AUS images for most breasts and one study found an average of 9 minutes to interpret them (33). As such, AUS requires much more time to interpret than HHUS and nearly all recalls from automated US require further diagnostic evaluation with targeted HHUS often on a separate day and usually on separate equipment.

As DBT use for screening increases, an important question is whether or not supplemental screening US is still beneficial after DBT. For facilities that have not yet implemented DBT, HHUS appears to produce greater improvement in cancer detection than DBT when added to standard digital mammography in women with dense (heterogeneously dense or extremely dense) breasts. In the Adjunct Screening Tomosynthesis or Ultrasound in Women with Mammography-Negative Dense Breasts (ASTOUND) trial of 3231 women at 5 centers in Italy, Tagliafico et al reported ICDR of 7.1/1000 (95%CI 4.2 to 10.0) for physician-performed HHUS compared to ICDR of 4.0/1000 (95%CI of 1.8 to 6.2, p=0.006) for DBT(34). Only one cancer was seen only on DBT. While this was mostly prevalent screening DBT and incident screening US, recall (1.6% for DBT and 2.0% for US) and false positive biopsy rates (0.7% each) were not different and quite low for both modalities. A 6200-woman prospective trial evaluating supplemental technologist-performed screening US after DBT with synthetic reconstructions in women with dense breasts is ongoing at the University of Pittsburgh School of Medicine and Weinstein Imaging Associates (35).

Magnetic Resonance Imaging

Contrast-enhanced magnetic resonance imaging (MRI) is recommended for supplemental annual screening in women of any breast density who are at high risk for breast cancer (36). If MRI is performed, screening ultrasound is of no benefit. Not all women can tolerate MRI, due to claustrophobia, most pacemakers, other metallic implants, or gadolinium allergy; one study found that about 1 in 5 women were not able to undergo a breast MRI examination (37).

MRI is more sensitive in detecting cancer than US. One study examined MRI in average-risk women of all breast densities after negative/benign mammography and physician-performed US (38). Among 1705 MRI examinations, 54 (3.2%) showed suspicious findings and 18/54 (33%) were malignant, for an ICDR of 10.6 per 1000. All cancers were lymph node negative and 11/18 (61%) were invasive with median size 10 mm. Similarly, in ACRIN 6666, even after 3 rounds of annual screening US, in a subset of 612 women, 9 cancers (8 invasive, all node negative) were found only on screening MRI (ICDR 14.7 per 1000) (26). Importantly, in studies of high-risk women (known pathogenic *BRCA* mutation carriers), MRI has been shown to shift stage at diagnosis to earlier, more curable stages and to reduce late stage disease (39).

Although cost, patient tolerance, and accessibility are major detriments to using breast MRI to screen women with the sole indication of dense breast tissue, some investigators are developing abbreviated examinations. Kuhl et al (40) developed an abbreviated examination that took only 3 minutes' scan time, relying on the precontrast and first postcontrast sequences and resulting subtraction images, and found no loss of cancer detection and no significant increase in false positives. Further validation of such an approach is needed and planned through the Eastern Cooperative Oncology Group-ACRIN trial organization.

Molecular Breast Imaging

Single-center studies have been performed using molecular breast imaging (MBI) for supplemental screening of women with dense breasts, the vast majority of whom had no other known risk factors for breast cancer. MBI requires injection of radioactive material, ^{99m}Tc-sestamibi, a radiotracer originally developed for cardiac imaging. The breast is positioned similar to a mammogram and stabilized with gentle compression (much less than a mammogram) between two detectors (41) or between one plastic paddle and a detector (42), and imaged for 10 minutes per view. A typical examination takes a minimum of 40 minutes for both breasts. The typical dose of about 740 MBq (20 mCi) has been considered excessive for use as a screening test (43). In two recent studies using a lower dose of 300 MBq (8.1 mCi) and encompassing over 3000 women, ICDR of MBI after digital mammography in women with dense breasts was 8.8 per 1000 (95%CI 5.4 to 11.2) (44) and 7.7 per 1000 (95%CI 4.5 to 13.1) (45) respectively. In the first series (44), 11/14 (79%) cancers seen only on MBI were invasive with median size 0.9 cm and 9/11 (82%) were node negative; in the second series (45),

11/13 (85%) of cancers were invasive, with median size 1.0 cm, and 10/11 (91%) with staging were node negative. False-positive recall was prompted by MBI in 100/1545 (6.5%) and 130/1683 (7.7%) of women without cancer in the two respective series, and PPV of MBI-prompted biopsy was 17/51 (33%) and 12/62 (19%). Direct MBI-guided biopsy exists at present only for single-head systems but has been submitted to the Food and Drug Administration for one of the dual head systems.

Importantly, radiation exposure is to the whole body and not just the breast with molecular breast imaging; effective dose (which considers radiation sensitivity of all exposed organs) is estimated at 2.5 mSv with a 300 MBq (8.1 mCi) injection, which is about five-fold that from digital mammography, and twice that from combination digital mammography and DBT, but less than background radiation at 3 mSv per year (46). Another analysis examined expected lives saved from early breast cancer detection versus mortality from radiation-induced cancers and found the benefit-to-radiation-risk ratio of annual MBI to be about 5 at ages 40-49 years compared to 13 for mammography and, that by age 70-79 (due to lower risk from radiation), such ratios are about 9 for MBI versus 93 for mammography (47). No data on interval cancer rates have been published using MBI, but the Mayo Clinic is now offering MBI to women with dense breasts every other year.

Contrast-enhanced Mammography

Contrast-enhanced digital mammography (CEDM) utilizes a mammography machine adapted to perform both high and low energy images within seconds of each other. This is also referred to as contrast-enhanced spectral mammography (CESM). Post processing provides an “iodine image” similar to that of subtraction images in angiography. This technique requires intravenous injection of iodinated contrast at doses similar to that of computed tomography. This technology is being explored for screening. Based on diagnostic work in women with known cancer (48, 49), sensitivity is likely comparable to MRI and specificity may be higher. In the diagnostic setting, CEDM has been demonstrated to be superior to standard mammography in women with dense breasts (50, 51). There is no direct method to biopsy suspicious findings seen only on CEDM: MRI must be performed at times.

Patient tolerance may be better for CEDM than for MRI (52)though both require intravenous injection. The risk of a fatal contrast reaction is estimated to be less than 1 in 150,000 examinations. Mild to moderate contrast reactions may occur in a small number of patients and it is incumbent on breast imagers to be comfortable managing these reactions.

Summary

In summary, about 40% of women having regular screening mammography have dense breasts. Dense breast tissue increases the risk of breast cancer and impairs detection of noncalcified cancers on mammography, which can result in later stage at diagnosis. Digital mammography is better than film mammography in women with dense breasts. DBT improves cancer detection compared to standard digital mammography in women with heterogeneously dense breasts but may be less effective in women with extremely dense breasts due to lower internal contrast. MRI is recommended for supplemental screening in

women at high risk of breast cancer regardless of breast density, but cost and availability limit its use for general screening. Ultrasound improves detection of early stage invasive breast cancer and is the most frequently used supplemental screening modality. It appears that screening US is of benefit even after DBT provided the woman is willing to accept an increased risk of false positives. Fast MRI, molecular breast imaging, and contrast-enhanced mammography all show promise in improved cancer detection after mammography in women with dense breasts but require broader validation. Surrogate endpoints of stage shift, reduced node-positive disease, and reduced interval cancer rates should be accepted as proof of benefit of supplemental screening (53).

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