Supplemental Screening for Dense Breasts

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Outline

• Anatomy and Density
• Risk of dense breasts
• Theory of Supplemental Screening
• Options for supplemental screening
  – Tomosynthesis
  – Ultrasound
  – MRI
  – Molecular Imaging
  – Contrast Enhanced Mammography
Breast Parenchyma

- Fat
- Fibrous tissue
  - Predominantly form the suspensory ligaments of Cooper
  - Divide the glandular tissue into lobes
- Glandular tissue
  - Consists of 15-20 lobes
Density

- Classified on mammography.
  - Fatty (<25% of glandular tissue)
  - Scattered (25-50% of glandular tissue)
  - Heterogeneous (50-75% of glandular tissue)
  - Extremely (75-100% of glandular tissue)
Almost entirely fat density
Scattered areas of fibroglandular density
Heterogeneously dense – “may obscure small masses”
Extremely dense – “may limit mammogram”

Not dense

Dense
What affects breast density?

- Age
- Weight
- Genetics and family history
- Menopausal hormone therapy use
- Having fewer children
Variability in Breast Density Classification

- Reported breast density can change due to multiple factors including:
  - Quality of technique
  - Patient differences
  - Radiologist variability
Reclassification

- 13-19% of women were reclassified from non-dense to dense or vice versa. Melnikow et al in Supplemental screening for breast Cancer in Women with Dense Breasts: A Systematic Review for the USPSTF
- Since breast density notification is now mandated in many states, reclassification of breast density from year to year may decrease a patient’s confidence in screening.
- Major impetus for research on automated and computer assisted breast density determination
• 28 states now have breast density legislation which requires notification of the patient of density if heterogeneously dense or extremely dense.
Pink: Enacted Law
Blue: Working on Bill
White: No action
Star: Insurance coverage Law
• 28 states now have breast density legislation which requires notification of the patient of density if heterogeneously dense or extremely dense.

• In the state of Tennessee, Breast Density Notification Law became effective January 1, 2014
Breast Density Notification

- Your mammogram shows that your breast tissue is dense. Dense breast tissue is common and is not abnormal. However, dense breast tissue can make it harder to evaluate the results of your mammogram and may also be associated with an increased risk of breast cancer. This information about the results of your mammogram is given to you to raise your awareness and to inform your conversations with your doctor. Together, you can decide which screening options are right for you. A report of your results was sent to your physician.
Why is Breast Density Important?

- Affects at least half of the population
Dense Breasts

- Approximately 40% of women have heterogeneously dense breasts.
- Approximately 10% of women have extremely dense breasts.
- Approximately 50-60% of women ages 40-44 have dense breasts while approximately 20-30% of 70-74 year olds do.
- In healthy weight women, 50-60% have dense breasts while 20-30% of obese women do.
Why is Breast Density Important?

• Affects at least half of the population
• Breast density impacts the sensitivity of detection of breast cancer on mammography.
Sensitivity

• Decreased sensitivity on mammogram
  – Carney et al found sensitivity of extremely dense breast to be 62%, compared to fatty at 88%.

• Women with dense breast tissue have cancers that are larger and more likely lymph node positive, and higher stage.

• Interval cancers are more common
Interval Cancer


- Boyd et al found women with extremely dense breasts were 17x more likely to have interval cancer than women with fatty breasts.
Why are cancers missed on mammography?

• Most commonly focal asymmetries

• Bae et al. determined the following:
  – 78% tumors were obscured by overlapping breast tissue
  – 19% interpretive errors
  – 3% not included due to difficult anatomic location or poor positioning
Why is Breast Density Important?

• Affects at least half of the population
• Breast density impacts the sensitivity of detection of breast cancer on mammography.
• Independent risk factor
Independent Risk Factor

• Previously accepted as only “masking bias” which attributed the higher risk of breast cancer solely to mass obscuration by dense breast parenchyma.

• McCormick et al. demonstrated a 4.6x increase when comparing fatty to extremely dense breasts.

• Risk difference between scattered and heterogeneously dense groups is less than 1.5x.
Risk When Standardized to Average Breast Tissue

- Women with heterogeneously dense breasts have 1.2x greater risk of developing breast cancer
- Women with extremely dense breasts have 2.0x greater risk of developing breast cancer

Sickles. Radiol Clin North Am. 2010
Risk models

- Gail
- Clause
- BRCA-Pro
- Tyrer-Cuzick

*None of these account for breast density*

- Breast Cancer Surveillance Consortium (BCSC) model includes BI-RADS density added to a modified Gail model.
Goal: Reduce Mortality

• Stage at diagnosis, especially node status remains the most important prognostic factors.

• Across 11 randomized trials, only those methods that reduced the advanced cancer rate, increasing detection of node negative invasive cancer resulted in mortality reduction.
The addition of supplemental screening should allow earlier detection of cancers that would have eventually been detected as a palpable mass or larger in size on a later screening, leading to fewer interval cancers and more earlier stage cancers with reduction in mortality.
The Unfortunate Truth

• Majority of breast cancer deaths are seen in women who did not participate in screening.
  – Too young to be screened
  – Did not comply with screening guidelines

• Approximately 19% of breast cancers detected at screening had already spread.

• 10% of breast cancer deaths are from interval screening.

Forms of Additional Screening

• Tomosynthesis
• Ultrasound
• MRI
• Molecular Breast Imaging
• Contrast Enhanced Mammography
Supplemental Screening

• Technique
• Trials
• Advantages
• Disadvantages
Digital Breast Tomosynthesis
Tomosynthesis Technique

• Acquire images through the breast at multiple angles
• Individual images reconstructed into a series of thin high-resolution slices
  – Typically 1 mm thick
  – # of slices depends on the thickness of the breast
  – Can be displayed as individual images or in a dynamic cine mode
• 2 D and 3 D images acquired or with C-view 2D images are reconstructed from 3D.
Oslo Trial

- Prospective trial comparing digital mammography alone and digital mammography plus tomosynthesis
- Across all densities:
  - 15% reduction in recall rate
  - 27% increase in cancer detection rate
  - 40% increase in detection of invasive cancer
- Low number of extremely dense with only 6 cancers total, 2 of which were DBT only.
• Prospective non-randomized trial which compared screening digital mammography to combined digital mammography and tomosynthesis

• Incremental cancer detection rate due to DBT of 2.8 per 1000 screens among 6079 women with fatty or scattered fibro glandular tissue and 2.5 among 1215 women with dense breasts.
Tomosynthesis and Digital Mammography in Dense and Nondense Breasts

• Rafferty et al used data from the previously published multicenter study (JAMA 2016).

• Increase in cancer detection rate and a reduction in recall rate for women with both dense and nondense breast tissue. These combined gains were largest for women with heterogeneously dense breasts but were not significant in women with extremely dense breasts.
Advantages of Tomosynthesis

• Easier to implement
• Positioning same for technologists as standard mammography
• The addition of tomosynthesis increases cancer detection across all breast densities.
  – Average added cancer detection yield of 1.3/1000 screens.
• Reduces false positive recalls due to overlapping normal tissue.
• There is a potential for tomosynthesis to eliminate 2D-acquisition, which significantly impacts resource utilization over ultrasound.
Disadvantages of Tomosynthesis

- Capital expenditure
- Physician read time
- Radiation dose
- PACS storage
- Calcifications
- Reimbursement
- Biopsies of tomo only findings
Screening Breast Ultrasound
Screening Breast Ultrasound

- Hand held ultrasound (HHUS)
  - Physician performed verses technologist performed
  - Standard protocol such as that used in ACRIN 6666
  - Average time to perform for ACRIN 6666 protocol was 19 minutes in the first year and 15 minutes in the third year
  - Interpretation of HHUS (performed by technologist) <1 minute
Screening Breast Ultrasound

- Automated breast ultrasound system (ABUS)
  - 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.
  - Skaane et al found it takes 15 minutes to acquire the AUS images for most breasts and one study found an average of 9 minutes to interpret them.
  - Recalls require targeted HHUS.
  - Requires capital equipment

ACRIN 6666

• Multicenter trial that evaluated the effects of adding annual screening breast ultrasound performed by expert trained physicians to annual screening mammography.

• 2700 women with dense breast tissue and increased risk for breast cancer participated.
ACRIN 6666

- Screening ultrasound had a sensitivity of 76% and specificity of 84%.
- The addition of screening ultrasound resulted in an average of 4.3 additional cancers per thousand women screened (first round).
ACRIN 6666

- **Recall rate:**
  - 11.5% mammo alone → 26.6% mammo + u/s

- **Cancer detection rate:**
  - 7.5/100 mammo alone → 12.8 mammo + u/s

- **Biopsy rate:**
  - 2.4% mammo alone → 10.2% mammo + u/s

- **Biopsies yielding cancer:**
  - 29.2% mammo alone → 11/4% mammo +u/s

- **BIRADDS 3:**
  - 3.2% mammo alone → 13.8% mammo + u/s
Advantages to Screening Ultrasound

• Well tolerated
• Widely available
• Does not require IV contrast
• Requires no radiation
• No side effects
• No additional capital
Disadvantages to Screening Ultrasound

• Time to perform
  – Average of 19 minutes

• Manpower
  – Impractical to expect radiologists to perform

• Training
  – Training for technologists is not widely available.
  – No standardization of scanning technique
Disadvantages to Screening Ultrasound

- 76641: complete breast ultrasound, unilateral.
  - $108.85 ($361.70 for bilateral)
- False positive results
  - Biopsies yielding cancer: 29.2% mammo alone → 11/4% mammo +u/s
Screening Ultrasound

-verses-

Tomosynthesis
• Adjunct Screening with Tomosynthesis or Ultrasound in Women with Mammography-Negative Dense Breasts.

• Prospective multicenter trial in which women with dense breasts and negative 2D mammogram underwent tomosynthesis and physician performed whole breast ultrasound with independent interpretation.
ASTOUND
(Interim Results)

• Added cancer detection yield significantly higher for ultrasound (7.1/1000) than tomosynthesis (4/1000).

• Concluded: If adjunct ultrasound is performed for dense breasts, the incremental cancer detection rate from tomosynthesis is negligible.
• The majority of the ultrasound detected cancers missed on tomosynthesis were masses.

• The one cancer detected on tomosynthesis and not ultrasound was architectural distortion.

• If adjunct ultrasound is not routinely performed in mammography negative dense breasts, results support the use of adjunctive tomosynthesis.
Interval Improvement

- ASTOUND (preliminary): Demonstrated false positive recalls of 2.0% and false positive biopsies of 0.7%. These low rates likely reflect the fact that most were incidental screens (prior examinations available).
- ACRIN 6666: Incidence screens in year 2 and 3 demonstrated far fewer false positives than year 1.
- Philpotts et al (RSNA abstract): Compared year 5 to year 1; PPV of biopsies increased from 6.5% to 25%.
MRI
• MRI is recommended for supplemental screening by the American Cancer Society for the following:
  – Known BRCA-mutation carriers
  – First-degree relatives of a BRCA-mutation carrier but untested
  – Those with a lifetime risk of breast cancer equal to or greater than 20% (by BRCAPRO model or other models dependent on family history)
• If the only risk factor is dense breast tissue, lifetime risk does not meet 20%
Current MRI Protocol

• Dedicated breast coil should be used
• Pulse sequences include:
  – Axial pre-contrast T1 fat sat
  – 3 Axial post contrast T1 fat sat, every 90 seconds
  – Sagittal post contrast (4th)
  – Axial T2
  – Axial T1 non fat sat
• Subtract pre-contrast from 1st post
• MIP
• Berg et al. performed a sub-study to assess the rate and stage of cancers detected with a single screening MRI.
  – To be eligible women had to have completed the third round of annual ultrasound and mammography screenings and agree to undergo MRI within 8 weeks of the 24-month mammo.
  – Women who accepted were noted to have higher risk and were younger than those who declined. Also were less likely to have had a personal history of breast cancer.
Substudy to ACRIN 6666

• For 612 MRI participants, sensitivity increased from 7 of 16 with mammo and ultrasound, to 16 of 16 with the addition of MRI.

• Specificity reduced from 0.84 to 0.65.

• 43 of 612 participants were biopsied only because of the MRI, 8 of whom were found to have cancer.
56% absolute increase in cancer detection seen in the MRI sub-study compared to 34% absolute increase in invasive cancer detection seen by adding annual ultrasound to mammo
Sensitivity is the advantage to MRI

• Schrading et al. found in average-risk women with all breast densities, 3.2% of MRIs showed suspicious findings and 33% of those were malignant. All additional cancers were node negative.

• ACRIN 6666 found that even after 3 rounds of annual screening ultrasound, 8 additional cancers (all node negative) were found on MRI.
Disadvantages to MRI

• High false positives
• Average acquisition time between 30-60 minutes
• High direct and indirect costs
• Reduced tolerability
• Nephrogenic systemic fibrosis in patients with acute or chronic renal disease
• Limited availability in small communities
• May not be reimbursed for lifetime risk <20%
Abbreviated Protocol

- Kuhl et al. Journal of Clinical Oncology 2014
  - Abbreviated protocol included the first post-contrast subtracted images and a MIP
  - Acquisition time of 3 minutes
  - Expert radiologist reading time of the MIP of 3 seconds sufficient to establish the absence of breast cancer with a NPV of 99.8%.
  - Reading time for the entire abbreviated protocol was <30 seconds with a diagnostic accuracy equivalent to the full diagnostic protocol
  - Additional cancer yield of 18.2 per 1000 in women prescreened by screening ultrasound and mammo
Abbreviated Protocol

- Harvey et al produced similar results in 2016 in JACR
  - 568 cases reviewed with no difference in cancers detected
  - Scan times decreased by 18.8 minutes per case
  - Interpretation time was 1.55 minutes for the abbreviated protocol
  - Review of the full protocol led to a significant change in final BIRADS in 12 of 568 (2.1%) of cases
EA1141

• ECOG-ACRIN study
• Comparison of abbreviated breast MRI and digital breast tomosynthesis in breast cancer screening in women with dense breasts.
Molecular Breast Imaging
Molecular Breast Imaging

- Tc-99m Sestamibi
- Strong affinity to cancer cells
- Prescribed dose 8 mCi corresponding to an effective radiation dose of 2.4 mSv.
- Image immediately with the breast in light compression in both MLO and CC projections.
- Exposures between 7-10 minutes per view
Digital Mammography vs. Molecular Breast Imaging

Negative
17 mm Cancer

https://mcnewsblog.wordpress.com/2008/09/03/breast-cancer-molecular-breast-imaging-mammography/
• Purpose was to assess the diagnostic performance of supplemental screening MBI in women with dense breasts.
• 1585 participants: 21 were diagnosed with cancer.
  – 2 detected by mammo only
  – 14 by MBI only
  – 3 by both
• When added to screening mammography, MBI yielded a supplemental cancer detection rate of 8.8/1000 women with dense breasts.
• Recall rate increased from 11.0% in mammo alone to 17.6% for the combination.
• The biopsy rate increased from 1.3% to 4.2%.
Shermis et al.

• Study performed on women ages 25-90 with BIRADS 1 or 2 on screening mammogram within 100 days.
• 94% had breast density heterogeneously dense or extremely dense (6% had a lower density with complex pattern)
• Lifetime risk ranged from 6.1%-17.2%
Shermis et al.

- MBI had a positive finding in 8.4% which led to additional diagnostic evaluation.
- Of 143 women, 13 malignancies were detected (11 invasive, 2 DCIS)
- 7 malignancies in heterogeneously dense breasts and 6 in extremely dense breasts
- Recall rate 8.4%
- Incremental cancer detection rate 7.7%
- PPV1 9.1%
Advantages to MBI

• Less expensive compared to MRI (5x)
• Utilizes functional imaging to overcome the limitations of anatomic imaging
• 3x more sensitive than mammography
Disadvantages of MBI

- Radiation exposure is to the whole body, not just the breast.
- The effective dose of radiation to the body is 5x the dose from digital mammo (although still less than background radiation per year).
- The typical dose of 740 MBq has been considered excessive for screening.
  - Studies using 300 MBq
- Increase in recall rate and biopsy rate.
Contrast-Enhanced Mammography
Technique

• A mammography unit adapted to obtain both high energy and low energy images within seconds of each other is used.

• Images are processed to provide an “iodine image”
  – Similar in appearance to subtraction images in angiography.

• Requires injection of iodinated contrast similar to CT.
Advantages

• Patient tolerance may be better than for MRI.
• Sensitivity may be comparable to MRI and specificity higher than MRI.
  – Mori et al. found contrast enhanced mammography to be superior to standard mammography in dense breasts.
Disadvantages

• Requires injection of iodinated contrast.
• No direct method for biopsy at this time.
End the Confusion

PURPOSE

To end the confusion surrounding when and how often a woman should get a mammogram. Too many people/organizations are saying too many confusing, dangerous and contradictory things about breast cancer screening.

1. There is danger in the confusion around screening mammography. The danger is the risk to a woman’s life.
2. Women need clear and accurate information with which to discuss mammography screening with their providers (shared decision-making).
3. Concerns include delaying or foregoing screening mammography which can lead to increased mortality.

END THE CONFUSION
END THE CONFUSION

The Society of Breast Imaging developed this whiteboard animation to end the confusion around when and how often women should get mammography screening. Take a few minutes to watch it and then share it.

https://www.sbi-online.org/endtheconfusion/Home.aspx