1. What is mammographic breast density?

Breast density refers to the relative amount of fibrous and glandular tissue which attenuates x-rays on a mammogram. Mammographic density does not directly correlate with amount of glandular tissue per se or tissue hardness on physical examination.

2. How is mammographic density measured?

Breast density is the ratio of the area of dense (white) tissue on a mammogram divided by the total area of the imaged breast (percent mammographic density (PMD) on a mammogram. Limitations determining breast density include the threshold set to distinguish dense and non-dense tissue, how this threshold changes with different mammographic techniques, and the actual area of breast imaged. Visual thresholding varies by reader and technique. Density assessments on digital images are often lower than film-screen images and will also vary based upon processing techniques. Because the breast is not defined by a capsule, the actual boundary is subjective. At best, PMD is an approximation. Current BI-RADS categories include both qualitative and quantitative estimates, the later will be dropped in the new BI-RADS version. Although BI-RADS uses 4 categories, density is a continuum from fatty to extremely dense. There is inter-observer variability in both qualitative and quantitative density assessments especially for category 2 and 3. Nicholson showed a 49% agreement among three readers (200 cases) with strongest agreement for category 1 and 4.

The development of automated quantitative density assessment software is an active area of research but these algorithms remain limited by the inherent limitations of breast density measurements and their accuracy has been questioned. Interestingly, these quantitative measures are often substantially lower than radiologists estimates. Nicholson showed a median computer estimate of 14.8% for radiologist determined BIRADS scattered density category, less than the expected 25-50%. Similarly, Martin showed untrained readers overestimated density by 37% compared to computer assessment. Experts have questioned the validity of 2D density measures and have proposed 3-dimensional volumetric breast density measures to more accurately reflect breast density although it is unclear if these will be significantly different than 2-D analysis.

3. Why is breast density important?

The importance of breast density is two-fold. First, mammographic density impacts the detection of breast cancer. Breast cancer sensitivity is markedly lower in women with very dense breasts than fatty breasts due to masking by dense tissue. In Carney's assessment of 329, 495 mammograms, the sensitivity of mammography in women with extremely dense breasts was 62% compared to 88% for fatty breasts. The decreased sensitivity of mammography in dense breasts is a major limitation of mammography.

Second, mammographic density is an independent risk factor for breast cancer. While there are limitations of breast density measures, multiple studies demonstrate that breast cancer risk is increased for women with dense breasts (Density 3 and 4) compared to women with non-dense breasts (Density 1 and 2). Meta-analysis by McCormick comparing (fatty(<5%) vs. extremely dense breasts), demonstrated 4.6 fold increased risk. However, 80% of women have breast densities in the middle, either scattered or heterogeneous densely and only 10% are extremely dense or fatty. Therefore, the often cited four to six fold increased risk compares two minority extremes of density and not the increased risk from an average density measure. The risk difference between scattered and heterogeneous dense groups is typically less than 1.5 X.

Breast density is not fixed but may change over time. Paradoxically, breast density tends to gradually decreases with age although overall risk increases with age. Pike has proposed it is the cumulative effect
of growth factors and hormones over life which increases risk. Boyd and Ursin have shown genetic factors account for 50-60% of variations of breast density. Mammographic assessment of density cannot differentiate fibrous tissue from glandular tissue although it is likely the percentage or amount of glandular tissue is relevant to risk. In the future, functional imaging may aid this discrimination.

4. **Is there evidence to support supplemental screening with ultrasound in women with dense mammograms?**

There are no RCT showing survival benefit of screening women with dense breasts with supplemental whole breast ultrasound screening (WB-US) in addition to mammography. Supplemental WB-US for average risk women with dense breasts is not recommended by the American Cancer Society, NCCN, or the U.S. Preventative Service Taskforce and remains controversial. Since “dense” breasts impact over half the population under 50 and 40% of women over age 50, the question of supplemental WB-US screening warrants careful scientific assessment.

The DMIST trial demonstrated that digital mammography was significantly more sensitive than film screen mammography (.59 vs .27  p < .0013) in women who were under age 50 or had dense breasts. Therefore, digital mammography should be used for women with dense breasts regardless of any decision regarding ultrasound.

Screening WB-US has been investigated in high-risk women and in women with dense breasts. WB-US in addition to screening mammography has increased cancer detection compared to mammography alone but markedly increases false positive results. The American College of Radiology Imaging Network 6666 trial evaluated physician performed WB-US in 2809 high risk women with dense breasts in at least one quadrant. At prevalent screening, the cancer detection rate increased from 7.6/1000 by mammography alone to 11.8 /1000 with mammography and WB-US. The incremental cancers were small (median size 10 mm), primarily invasive, and 89% node negative. However, false-positives were numerous with an overall 8.9% PPV (vs 23% for mammography) as well as a 12.2 % Category 3 rate. Subsequent incidence screening data shows lower recall, lower short term follow up rate with only a small decrease in detection rate. Film screen mammography was utilized in 65% of cases. Corsetti reported on 6449 women having supplemental WB-US with dense breasts. Incremental ultrasound detected 4.4/1000 cancers, similar to ACRIN 6666. Interventional procedures, primarily fna, were performed in 486 cases to detect/diagnosis 29 cancers. Berg summarized 7 WB-US screening studies involving 49,586 women. Incremental cancer detection rate was 3.6/1000. Three percent of screened women underwent biopsy and the PPV for biopsy was 15.6%. 94% of these tumors were invasive and 86% were node negative. These reports are primarily from prevalent WB-US compared to film screen mammography, an important limitation because the reported incremental detection rates may be higher than achieved with current digital mammography.

WB-US requires long scanning time, expertise, training, and incremental breast imaging radiologist time. Median scanning time for physicians in ACRIN 6666 was 19 minutes. The resources necessary to perform, read, administer, and perform downstream testing such as marked increase in biopsies may be currently lacking. Automated WB-US systems have been developed and studies are ongoing to evaluate this technology as an alternative to physician directed WB-US screening.

It is important to realize, however, that mammography and MR have consistently outperformed mammography and WB-US for very high-risk women independent of breast density (for example, BRCA-mutation carriers and those with lifetime risk of 20% or greater). Berg summarized nine series involving 4485 very high-risk women which showed a 93% sensitivity for mammography and MR but only a 52% sensitivity for mammography and WB-US. For these reasons, the American Cancer Society recommends annual mammography and MRI screening for these very high-risk women.

Selected References


