Breast Density: Significance and Risk

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Mammography Breast Density (MBD): Clinical Relevance
- Directly impacts patient care
  - Limitations of mammography
  - Associated breast cancer risk
  - Option for supplemental screening
- Assessment is the basis of most breast density research

Breast Density Notification Laws

|------|------|------|------|------|------|------|
| Required notification (effective date) | C1 | C1 | Y1 | A | B | C | D
| C2 | C1 | C1 | C1 | C1 | C1 | C1 |
| Diagnostic notification | C1 | C1 | C1 | C1 | C1 | C1 |
| Archive copy | WA, VA, WI, WY, GA | WA, VA, WI, WY, GA | WA, VA, WI, WY, GA | WA, VA, WI, WY, GA | WA, VA, WI, WY, GA | WA, VA, WI, WY, GA |
| Inactive file | C2, C5, WA, N, N | C2, C5, WA, N, N | C2, C5, WA, N, N | C2, C5, WA, N, N | C2, C5, WA, N, N | C2, C5, WA, N, N |
| NCR list of extensive breast density notification | C7, C8, C9, C10 | C7, C8, C9, C10 | C7, C8, C9, C10 | C7, C8, C9, C10 | C7, C8, C9, C10 | C7, C8, C9, C10 |
| * C5 and MBD laws remain in effect through 7/5/19 and 7/5/17, respectively unless extended by law

What is Breast Density?

Breast Density Classification
- Historic lack of standardization
  - 1970’s
    - Wolfe (N1, P1, P2, Dy, Qdy)
  - 1980
    - Boyd (A-F) 1997
    - Tabar (I-V)
  - 1993 – 2013
    - BI-RADS 1st - 5th editions

Limitations of Mammography: Masking Effect

Density ↑ sensitivity ↓
Mammographically Dense Breasts

- Common
  - 10% fatty, 40% SFG, 40% HD, 10% ED
  - USA: 40-50% of women
  - More common in younger women
    - MDB decreases with age, post menopause
      - 40’s → 46-74%
      - 50’s → 37-57%
      - 60’s → 30-44%
      - 70’s → 25-36%


BI-RADS 5th ed.

- Emphasis
  - masking effect of breast
  - correctly identifying women who may benefit from supplemental screening

- Potential for increased intra and inter-observer variability
BI-RADS 5th ed.: Variability & Shift in Assessment?

- Inter/Intra-reader Variability
  - Irshad et al.
    - Reader study: 5 radiologists, 104 2D mammograms
    - BI-RADS 4th/5th ed.
    - Intra-reader agreement: 0.84 vs. 0.77 (p<0.05): substantial
    - Inter-reader agreement: 0.65 vs. 0.57 (p<0.05): substantial
  - 10% more dense breast assessments
  - FGTHD

Breast Density Assessment

Got Dense Breasts? That Can Depend On Who Is Reading The Mammogram

July 18, 2016 · 5:01 PM ET

KATHERINE HOBSON

Breasts deemed “dense” in a mammogram tend to have less fatty tissue and more connective tissue, breast ducts and glands, doctors say. About 40 percent of women between the ages of 40 and 74 have dense breasts.

Lester Lefkowitz/Getty Images

If you’re a woman who gets screening mammograms, you may have received a letter telling you that your scan was clear, but that you have dense breasts, a risk factor for:

- Visual Challenges: Area vs. Volume
  - Automated Density Determination
    - Available for 2D and DBT
      - Automated and semi-automated
    - Quantitative
      - X-ray attenuation: measures image pixel signal
    - Objective
      - Designed to be reproducible
        - Variations may exist due to differences in positioning/amount of retrograde fat, compression
      - Does not measure location of dense breast tissue or masking

Density: Area, Volume, Subjective, Quantitative

- BI-RADS
  - Subjective visual assessment
  - Generally 2D assessment even with DBT
  - Area as well as some non-quantitative information
    - “breast complexity”
- Automated – area or volume

Automated Density Determination

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Visual Challenges: Area vs. Volume

- 2D Images of the 3D Breast
  - Volumetric measurements may vary based on compression & positioning

Area v. Volume ..... 2D is not 3D


Figure 3: Glass blocks can be used to understand why accurate measures of dense tissue cannot be derived from 2D images without other information. As shown in (b) and (c), the observer looking from the top could think there are three blocks of smoked glass when in fact three blocks of clear glass are present. The 3D breast is projected onto a 2D image, which makes visual assessment of density difficult. One must somehow factor in “how thick” or “how white” the dense tissue actually is. This is exactly the way VolparaDensity works.

- Visual Challenges: Area vs. Volume

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Automated Density Determination

- Moderate ➔ substantial agreement with radiologist visual assessment *
- Potential advantages
  - Better estimate breast density for cancer risk prediction
  - Monitor breast density after risk reduction interventions
  - Better stratify women with HD tissue who could benefit from supplemental screening

US & MR Breast Density Determination

- ABUS & MR can be used to determine breast density
  - Deep learning for breast segmentation in MRI
  - US & MR techniques in development

Breast Density: Clinical Practice

- Consistency is good
  - Maintains confidence in referring providers and patients
  - Variability from year to year will result in confusion
  - “On the fence/middle of the road, maybe not dense?”
    - Look at last year’s study
    - If patient is not dense and scheduled for supplemental screening, talk to patient
    - If breast density is slightly decreasing over time, consider stating this in report
      - “The breast density appears to be decreasing over time and the patient may not be classified as dense on future studies”

Breast Density & Risk

- Independent breast cancer risk factor
- Controversial
  - Degree of risk
- American Cancer Society
  - “Women who have dense breast tissue have a slightly higher risk of breast cancer compared to women with less breast tissue. It is unclear at this time why dense breast tissue is linked to breast cancer risk.”
Breast Density & Other Risk Factors for Breast Cancer

Overall, compared to other risk factors, women with extremely dense breast tissue are at intermediate risk for breast cancer.

BUT

Despite the increased risk associated with increased breast density, regardless of risk and density, all women of screening age should have routine mammography screening.

Breast Density & Cellular Factors

- Increased epithelial & stromal FGT
  - Breast cancer cells originate from epithelial cells
  - Line lobules & TDLU
  - Proliferative breast tissue increases risk
  - MBD associated w/ proliferative histology on breast bx
  - MBD may provide extracellular matrix/stroma
  - MBD supports tumor growth, angiogenesis

Breast Cancer May Prefer Dense Breast Tissue

- DCIS lesions may occur preferentially in dense areas
  - 21/22 pure DCIS lesions => within dense breast tissue
  - Mammograms at dx was compared to most recent previous mammogram
  - Independent of masking
  - Carcinogenic influence of stromal tissue?

Breast Density & Interval Cancers

- Breast cancer diagnosed within 12 mo. of a normal mammogram
  - Invasive cancer is associated with more aggressive tumor biology
  - DCIS generally less critical
    - High mammographic sensitivity, low DCIS interval cancer rates
    - HI interval cancer rate: >1/1000
Breast Density & Interval Cancers

- Destounis et al.
  - 652 screen detected cancers
  - 119 interval cancers
  - Breast density assessment (visual + automated)
  - Age, menopausal status, ethnicity, race, HRT, family history, previous biopsy
  - Breast density only RF significantly associated with interval cancers

AJR.2017;208:222-227

Breast Density & Interval Cancers

- Kerlilowske et al
  - BCSC: 800,000+ DMs in 350,000+ women
  - BI-RADS breast density
  - BCSC 5-year cancer risk
  - Interval cancer rates


Breast Density & Interval Cancers

- Kerlilowske et al
  - High interval cancer rates (>1/1000)
    - ED & 5-y risk ≥ 1.67%
    - HD & 5-y risk ≥ 2.49%
  - High interval adv. stage cancer rates (0.4/1000)
    - HD or ED & 5-y risk ≥ 2.49% → 21% women w/ dense tissue
  - Low/avg. interval cancer rates (0.6-0.9/1000)
    - HD or ED 5-y risk = 0-1.66% → 50% women w/ dense tissue

Risk Assessment

- Should we consider other risk factors in addition to density to determine the benefit and/or value of supplemental dense breast screening?
  - Benefit for the individual vs. value of health care $ in our society
    - Benefit: ED with risk of 1.66% and interval cancer rate 0.9/1000 → just below cutoff
    - Value: 50% of women would not need supplemental screening → great savings

Supplemental Screening: US or MRI

- NO study has proven a mortality reduction associated with supplemental screening
  - Decreased interval cancer rates with supplemental screening US & MRI
Performance of WBUS in Women With Dense Breasts Following DBT

- Yale study
  - Screening US supplemental CDR
  - 3.2/1000 → 1.9/1000 (40%)
  - Breast Cancer NPV 100%
  - No interval breast cancers

SWBUS: Decreased Sensitivity?

- Early studies: PPV3 = 6 – 10%
- Later studies: Specificity Improving
  - J-Start (Ohuchi et al. Lancet 2016)
    - Specificity Mammo + SWBUS = 88%
    - Mammo (alone) = 91%
  - ASTOUND SWBUS (Tagliafico, et al IJ 2016)
    - PPV3 = 48%
- Yale SWBUS data
  - Year 1 PPV3 = 6% (Hooley et al Radiology 2012)
  - Year 5 PPV3 = 29% (Philpotts et al RSNA 2015)

FAST MR Screening

- Proposed for average risk women with dense breasts
- Kuhl et al. JCO 2014
  - 606 exams/427 women with dense breasts
  - Mild-moderate risk/no mammo
  - Acquisition time of 3 min
  - pre/post T1WI + subtraction/IV contrast
  - Expert read of MIP = 3 sec
  - Supplemental CDR = 11/606 (18.2/1000)
- 2 y validation: No interval cancers
  - NPV MR 99%
  - SP/PPV: 94.3/24.4 (similar to full MR protocol)

MR Background Parenchymal Enhancement (BPE)

- Associated with breast cancer risk
  - Independent of breast density
  - Potential to improve risk assessment
- Visual BI-RADS assessment*
  - Single first post contrast sequence
- Quantitative measures**
  - Wash in slope
  - Signal enhancement ratio volumes

What else are we learning about high mammographic density (HMD)?

- Dontchos, et al Radiology 2015
  - 23 high risk women/matched case controlled study
  - 9x risk of breast cancer
  - Mild, moderate or marked BPE
- BPE pattern, MRI amount FGT, MBD
  - Not significantly different
  - BPE may be a biomarker for breast cancer risk
  - High MBD in very high risk women may not be the only associated risk factor

* King et al. Radiology 2011,260:1
** Wu et al. Breast Ca Research 2016, 18:76
Loco-regional Recurrence

- HMD increases risk of LRR
  - Mastectomy*
    - HMD best predictor of locoregional recurrence
      - HR 3.6 p=0.25
  - BCT**
    - HR 6.6, p=0.071 (extremely dense)
    - Not associated with increased risk of metastases or death

* Huang et al, Br Ca Res (2016) 18:120
** Park et al, Int J Rad Onc (2009) 73:1

How are tamoxifen, MBD, and Risk Related?

- Do women who do not metabolize tamoxifen well experience less of a breast density decline?
- Tamoxifen directly effects breast density and results in decreased breast cancer risk?

Isn’t Fat Associated with Breast Cancer?

- Park et al: HMD, obesity, & LLR s/p BCS
  - HMD & obesity negative confounders
    - HMD not found in obese women
  - Obesity & HMD independently associated with LRR
    - Multivariate analysis
      - HMD => HR 6.6
      - Obesity => HR 19.3
    - HMD + Extracellular matrix
      - Contribute to resistance of residual tumor cells to radiation

Breast Density: Future

- Breast Complexity
- Better MBD assessment
  - DBT, US, MR
  - Advance overall risk assessment
  - Marker for treatment response
- More research
  - Define association of breast density & cancer risk
  - Improve imaging techniques focused on MBD
  - Biologic behavior of breast cancer + MBD

Isn’t Fat Associated with Breast Cancer?

- BMI is a breast cancer risk factor
- Low breast density, BMI>30kg/m² & breast cancer have a increased risk of death
  - BMI, large adipocyte size, breast microenvironments
    - provide a stimulus for tumor growth
Should we be informing women of their breast density?

- YES
- Breast density is important
- Breast density awareness is positive
  - Patients and medical research
- Shared patient decision making
  - Radiologists are on forefront of clinical management

**Thank you**

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