Quality and Quantity: Breast Density and CADSBI 2015

Linda J. Warren, MD, FRCPC, FACR, FSBI

University of British Columbia

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Quality and Quantity: Breast Density Assessment and CAD

BREAST DENSITY

1. Background.
2. Current concepts: Density classification and risk.
3. Legislation and Public Information.
4. Pros and Cons of reporting legislation.
5. Supplementary screening.
6. BI-RADS 5th Edition concepts.

Background

- First study showing a relationship between density and breast cancer risk published in AJR in 1976.
- John Wolfe described a relationship between mammographic density and risk based on a qualitative classification.
- Incremental risk was associated with increased density.
- Boyd in NEJM in 2007 using a 5 level density classification showed a 4.7 odds ratio for screen detected cancers in densities greater than 75%; odds ratio increased to 17.8 for 12 month interval cancers.
- Computer assisted density measurements were reproducible (0.9) and there was .94 reproducibility between radiologists' subjective assessments and computer assisted method.

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Wolfe and Boyd

- Both authors suggested “masking” and rapid growth could explain the increased risk
  - concluded masking likely the principal mechanism.
  - Both suggested attention be given to supplementary modalities- US and MRI.

Possible Explanations for Association of Density and Risk:

- Evolution of premalignant histology such as ADH
- Elevated growth factors.
- Increased estrogen production due to overactive aromatase.
- Heredity.
  - Harvey: Radiology2004; 230:29-41

BI-RADS

- Developed to standardize mammography reporting terminology and assessment and recommendation categories. (1993).
- Density classification intended to inform referring physicians of decline in sensitivity with increasing density.
- Only moderate interobserver agreement k = 0.43 0.59.
- But widely used and allows study of large populations.

Legal Requirements:

- MQSA currently requires inclusion of density in report to clinician but NOT in the lay letter.
- But as of November 2014 19 states have enacted density reporting legislation.
- Most states require a statement to ask MD about supplementary screening, sometimes specifically indicating US and MRI.

Legislation Usually Requires Informing Patients:

1. That they have (heterogeneously/extremely) dense tissue.
2. That dense tissue may make it more difficult to detect a breast cancer and may also be associated with an increased risk of breast cancer.
3. That there may be a need for supplementary testing.

Relative Risks

BCSC data-2012

“d” vs “a” – 4.14.2

But “d” vs “average”1.56 1.57

Dense tissue much less associated with actual higher risk than originally thought.

Density Classification: Clinical Relevance

- Depends on distinction between:
- b - scattered areas of fibroglandular
- density and
- c - heterogeneously dense
- This relates to density notification
- ie: b = not dense; c = dense

Density Reporting Legislation

- Density notification Legislation – concerns.
- ACR Statement:
- Density not reliably reproducible.
- May cause high risk women with non dense tissue to forego screening.
- No support from randomized trials showing improved mortality with supplementary ultrasound and MRI.

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ACR.org

- Describes breast density differences on mammograms using images.
- States that breast density may increase risk of breast cancer.
- States dense tissue makes it more difficult to see cancers.
- Recommends mammograms.
- States that Ultrasound and MRI may find cancers not visible on mammograms but may cause additional testing.
- Recommends “Talk to your doctor”.
- Concludes “Get a annual mammogram from age 40”.

Breast Density Legislation “FOR”

- Can increase cancer detection.
- Can encourage personal risk/benefit assessment by enhancing awareness.
- Can help primary care physicians to educate their patients and direct them to appropriate resources .

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Breast Density Legislation "AGAINST"

- Can cause confusion about screening regimens and supplementary screening.
- Many states require notification about supplementary screening without legal provision for insurance coverage .
- Concern as to insufficient numbers of radiologists and technologists to conduct supplementary screening.
- Concern that family doctors have insufficient time and knowledge to counsel patients.

Supplementary Screening:

Tomosynthesis:

- Skaane et al, 2013 Population based – Norway
  - Cancer detection up 27%.
  - Invasive up 40%.
  - FP reduced 15%.
  - Interpretation time increase 46 seconds
- Skaane, 2014 - 2D + 3D comparison by density
  - Cancer detection increased in a + b 16%, c + d 21%.
  - But no increase in density a.

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Tomosynthesis: USA

- Friedewald et al: JAMA 2014;
- 13 Institutions:
- Cancer detection increased 29%.
- Recall rate reduction = 15%.
- Invasive cancer detection increase 41%.

Sonography: Physician Performed/ Handheld

- ACRIN 6666: Berg et al JAMA 2012.
- Radiologist performed ultrasound detected 3.7 additional cancers per thousand.
- Sensitivity for Mammograms + Ultrasound - 76%; 52% for mammogram alone.

Technologist Performed Handheld Screening Ultrasound

- Based on Connecticut Public Act 09-4.1
- Hooley et al Radiology October 2012.
- Overall cancer detection rate 3.2 per thousand, in 935 patients.
- All cancers detected were less than 1 cm and node negative.
- Insurance companies mandated to pay.

Technologist Performed Handheld Breast Ultrasound: Connecticut

- Weigert et al RSNA 2014
- Ultrasound detection rates BI-RADS density c and d year 3 – 3.1 per 1,000 (4128); year 4 – 3 per 1,000 (3,330).
- PPV year 3 – 8.1 %; Year 4 – 16.1%.
- Percent eligible requesting ultrasound: year 3 – 32% year 4 - 30%.
- Factors effecting choice to have ultrasound – education and cost.

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Handheld and Automated Ultrasound Comparison: Mendleson et al, RSNA 2014

- BI-RADS assessments documented and compared.
- BI-RADS assessments differed in 18%.
- HH – 2; AUS -4 – 18%.
- HH – 4; AUS – 0,1,2 -30%.
- No BI-RADS mismatch led to cancer diagnosis.
- All lesions biopsied were benign.

Reasons for Mismatch

- Analysis showed many AUS 4's had hypoechoic artefacts on 1 view.
- HH BI-RADS 2 and AUS 4 – oval masses had indistinct masses.
- Clinical relevance – authors suggest AUS may be useful for detection and follow-up of multiple benign – appearing masses.

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Automated Ultrasound (Brem et al – RSNA 2015):

- Multi-institutional study – 13 facilities in US.
- on asymptomatic women and breast density c and d.
- Yield 1.9 cancers per thousand.
- Recall rate DM 15%, DM + ABUS 29%

Masking:

- BI-RADS 5th Edition committee considers masking effects of greater importance than density conferred intrinsic risks.
- Mammography remains the gold standard as the only modality proven to reduce mortality in large randomized controlled trials.
- But supplementary screening tests are now available and have been used for women with dense breasts: tied include screening breast ultrasound, tomosynthesis and MRI

Breast Composition Categories:

BI-RADS 4th edition:

“This is an overall assessment of volume of attenuating tissues in the breast, to help indicate the relative possibility that a lesion could be obscured by normal tissue and that the sensitivity of examination thereby may be compromised by dense tissue.”

BI-RADS 4th Edition Categories:

- The breast is almost entirely fat (> 25% glandular).
- There are scattered fibroglandular densities (approximately 25% - 50% glandular).
- The breast tissue is heterogeneously dense, which could obscure detection of small masses (approximately 51% - 75% glandular.
- The breast tissue is extremely dense. This may lower the sensitivity of mammography (>75% glandular).

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BI-RADS 5th Edition Categories

a. The breasts are almost entirely fatty **(fat)**.

b. There are scattered areas of fibroglandular density (**fibroglandular densities**).

c. The breasts are heterogeneously dense, **(tissue is heterogeneously dense)** which may obscure small masses.

d. The breasts **(breast tissue)** are extremely dense, which lowers the sensitivity of mammography.

Note: No percentages given in BI-RADS 5th Edition

BI-RADS 5th EditionBreast Composition: New Concepts:

1. Four categories a, b, c, d, are defined by **visually estimated** content of fibroglandular – density tissue within the breasts.
2. If the breasts are not of apparently equal density the denser breast should be used to categorize the density.

BI-RADS 5th EditionBreast Composition: New Concepts:

3. “Considerable intra and interobserver variation in visually estimating density between any two adjacent categories.”
4. “Minimal and insignificant difference in sensitivity between the densest breast in a low density category and least dense in next higher category.”

“These factors limit the clinical relevance of breast density categorization for the individual woman.”

New Categories Descriptors

a. The breasts are almost entirely fatty.

b. There are scattered areas of fibroglandular **density** (historically,

"there are scattered fibroglandular densities.")

- Avoids confusion with old descriptor "density" used to represent a discrete mammographic finding.

c. The breasts are heterogeneously dense, which may obscure small masses.

- New suggested wordings to describe **location** of dense tissue:
- "The dense tissue is located anteriorly in both breasts, and the posterior portions are mostly fatty."
- "Primarily dense tissue is located in the upper outer quadrants of both breasts; scattered areas of fibroglandular tissue are present in the remainder of the breasts."

d. The breast are extremely dense, which lowers the sensitivity of mammography.

New Concepts

- Acknowledges the reality that there may be a few coalescent areas of dense tissue in breasts with 10% dense tissue, and fatty areas in breast with 90% dense tissue.
- New Descriptors intended to reflect **masking effects** of dense fibroglandular tissue on non calcified lesions.
- Concludes that subjectively estimated density and its effect on sensitivity are more important than percentage of breast density as indicator for risk.

MRI:

- ACRIN 6666 supplementary yield 14.7 per thousand.
- Sensitivity for MRI + mammography - 0.94.
- Sensitivity for MRI + sonography – 0.95.
- Authors: Cost considerations and reduced tolerability may limit justification of MRI over ultrasound for intermediate risk work.

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Fast MRI:
Kuhl et al JCO; August 2014

- Abbreviated Protocol.
- First postcontrast MIP.
- 1 pre: 1 post contrast acquisition.
- MRI acquisition time 3 minutes.
- Radiologist reading time 3 seconds for MIP.
- Yield 18.2 per thousand.
- NPV 99.8%; 10 of 11 cancers.

Quantitative Density Evaluations

- Early methods calculated areas using algorithms from digital imaging data.
- Later developments led to software for volumetric measurements.
- Objective measurement expressed as per breast volume and percent density.
- One system – uses texture and density algorithms which are not volume based.
- Good correlation among volume based systems.

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Readers Density Assessment Compared With Quantitative Methods

- Low correlation between observer's scores and automated analysis – Morrish et al: RSNA 2015.
- Possibly related to observer's application of a semi volumetric approach to assessment rather than are based (when compared with area based measurements).
- Technical reason – Software analyzes raw data: observer's estimate of density based on processed images with option to use image manipulation.
- Automated results vary between systems and this needs to be considered in informing patients.

What's Current In CADe 2015

Objectives:

- Illustrate why CAD developed.
- Show how it works in a busy clinical practice.
- Address current challenges.
  - False marks.
  - Dismissed marks.
- Potential and Future.

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Screening Mammography is Challenging

- Low prior probability – 3 – 10/1000
- False negative interpretations due to:
  - Radiologist fatigue
  - Complex breast structure
  - Subtle findings

Missed Cancers

- These are biopsy-proven cancers documented on subsequent screening mammograms or presenting with clinical findings before the next scheduled mammogram.
- These are usually analyzed in clinical settings as retrospective reviews, but with more effort reviews can be conducted blindly.
- The “hindsight bias” in retrospective analyses to determine “missed cancers” has been demonstrated to result in doubling of the number of positive interpretations.

Harvey et.al. AJR 1993; 161: 1167-1172, Warren Burhenne et. al. Radiology 2002; 215: 554-562, and Gordon et.al. Radiology 2007; 245: 411-415).

Radiologists and False Positive Marks

- 100 SFM screening mammograms BI-RADS 1 or 2 reviewed retrospectively.
- 2 different CAD versions used –SecondLook v5.0, CADx and SecondLook v7.2 were compared.
- CAD marks and radiologists' ease of dismissing false positive marks were recorded together with breast density.
- Results showed marks identified in one or the other version but not both, 88.6% - v5 and 90.1% from v7.2 were deemed very easy, or easy to dismiss.
- Current SFM studies report 2 -3 false positives per case.
- Recent studies for FFDM cite similar results – 2-3 FP

Mahoney et.al. (Journal of Digital Imaging, October 2011)

CAD and Digital Mammographic Imaging Screening Trial (DMIST)

- Cole et al, AJR October 2014.
- Based on original report in NEJM 2005 – 49,528 participants.
- Reader study conducted with 2 sets of 300 cases; 150 cancers each.
- 14 Radiologists interpreted iCAD set; 15 – R2 Image Checker
- AUC without /with – 0.71 vs. 0.72 for each system respectively.
- Sensitivity differences not significance – 0.49 vs. 0.51
- Variability in reader performance in both systems ranged from 20 -80%.

Factors To Explain Lack Of Change In Performance: Dismissal of Positive Marks Cole et al, AJR 2014

- High numbers of CAD marks - 0.78 per image.
- Compare reader sensitivities of 0.49 and 0.51 with stand alone CAD sensitivities of 0.75 and 0.73.
- This implies that readers IGNORED TRUE POSITIVE MARKS.
- No effect of prior training; but some had only 4 months CAD experience.

Important limitations: Authors:

- No priors available.
- No requirement to localize cancer beyond laterality.

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Clinically Missed Cancers: How Effectively Can Radiologists Use CADe

Nishikawa et al, AJR 2012:

- 300 cases ; 66 cancers; 8 readers
- Cancer cases were 1 year intervals
- Sensitivity increased with CAD 9.9%
- But 71% of correct prompts ignored
- NO correlation with number of prompts
- But correlation with annual volume (2,000 – 6,000)

Nishikawa Recommendations:

- Review of prior CAD positive cases to learn types of cancers overlooked and from CAD – marked “threshold” cancers.
- CADx systems to emphasize detected lesions
- ie, reference cases can be made available for retrieval.
- Retrieved regions of interest known to be either cancer cases or false detections.
- Method has potential for improving radiologists use of CADe.

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CAD Potential - 2015

- False positive reduction.
- Scholarly and meticulous study of reasons for dismissal of true positive remarks.
- Training to improve CAD interpretation ie which marks to ignore.

CAD and the Busy Radiologist

- Reduces fatigue, time investment reasonable.
- Increase confidence – not false reassurance – this can only happen in the absence of satisfaction of search method.
- The radiologist remains the final decision maker.
- Current prospectively obtained data show that most of us are assisted by CAD - more cancers are detected with a reasonable increase in recall.