



TOOLS FOR QUANTITATING BREAST DENSITY AND BREAST CANCER RISK


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DISCLOSURES

- GE Healthcare- research funding, consultant
- Hologic- Scientific advisory board
- Densitas- Advisory Board

PATIENT ADVOCACY AND BREAST DENSITY NOTIFICATION LEGISLATION

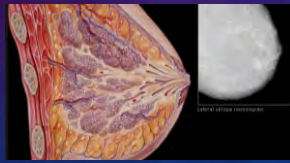
- The late Dr. Nancy Cappello
 - Diagnosed with advanced stage breast cancer in 2004
 - Founded Areyoudense.org
 - Advocacy efforts helped pass the nation's first breast density notification law in 2009 in CT
- 38 states have dense breast notification laws
- Federal legislation in process
- 8 states and DC have supplemental screening reimbursement laws
 - IL, IN, IA, CT, NJ, VT, AR, DC, CO



Advocacy and breast density inform legislation emphasize the importance of addressing implications of breast density on cancer detection


"BREAST DENSITY"

- Describes amount of fibrous, epithelial and glandular tissue in the breast relative to the amount of fatty breast tissue on mammography



BI-RADS BREAST DENSITY CLASSIFICATION

Radiologists classify breast density using a 4-level density scale:

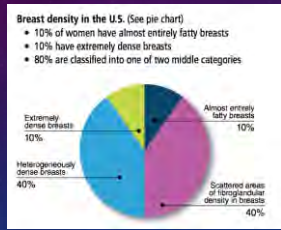


Almost entirely fatty
 Scattered areas of fibroglandular density
 Heterogeneously dense
 Extremely dense

BREAST DENSITY PREVALENCE

Breast density in the U.S. (See pie chart)

- 10% of women have almost entirely fatty breasts
- 10% have extremely dense breasts
- 80% are classified into one of two middle categories



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BREAST DENSITY – MASKING EFFECT

| | | |
|-----|-------------|-----|
| 87% | Sensitivity | 63% |
| 97% | Specificity | 89% |

Carney PA. Ann Int Med 2003

“BREAST DENSITY” POSES RISK FOR DEVELOPING BREAST CANCER

- Increases risk of developing breast cancer
- Results in higher interval cancer rates → worse prognosis
 - Higher grade, later stage at diagnosis
- Mechanisms for this are not fully understood
- Density reflects the proportion of epithelial and stromal tissue in the breast compared to non-dense fatty tissue
- Since breast cancers originate in epithelial cells, greater areas of fibroglandular tissue reflect greater number of sites of carcinogenesis

Mammographic Density and the Risk and Detection of Breast Cancer

Freeman F, Boyd, M.D., D.Sc., Helen Gao, M.Sc., Erica J. Martin, Ph.D., Lillian Kwan, M.Sc., Jennifer Shroyer, M.Sc., Evan Fletcher, M.D., M.Sc., F.R.C., Rosalind M. Young, M.D., F.R.C.P.C., Gong Chen, M.D., F.R.C.P.C., Alicia Christoff, Ph.D., Robinson Muttari, Ph.D., Sofia Martin, J. Vazir, Ph.D.

- Women with density of 75% or more had an **INCREASED** risk of breast cancer
 - Compared to women with density in <10% of mammogram
- Increased risk was **greater in younger than in older women**
- For women < median age of 56,
 - 26% of all breast cancers and 50% of interval cancers (cancers detected less than 12 months after a negative screening test) **were attributable to density** (BIRADS density ≥ 4)

CANCER IN DENSE BREASTS EFFECT ON PROGNOSIS?

- Higher rate of interval cancers → worse prognosis → worse outcome
 - Majority are **ER NEGATIVE, HIGHER TUMOR GRADE AND LARGER IN SIZE**
- Why?
 - Hypotheses: Growth factors
 - Breast stroma produces growth factors
 - More rapid tumor growth in dense tissue

Roubidoux MA. Invasive Cancers detected after breast cancer screening yielded a negative result: relationship of mammographic density to tumor prognostic factors. Radiology; 2004

INTERVAL CANCERS AND BREAST DENSITY

| Density | Odds Ratio | 95% CI |
|---------|------------|-------------|
| <10% | 1.0 | - |
| 10-24% | 2.1 | (0.9, 5.2) |
| 25-49% | 3.6 | (1.5, 8.7) |
| 50-74% | 5.6 | (2.1, 15.3) |
| >75% | 17.8 | (4.8, 65.9) |

P<0.001

Higher rates of interval cancers → Worse prognosis

Boyd, NF et al. NEJM 2007; 356:227-36

HOW DO WE ASSESS BREAST DENSITY: TOOLS

TAKING A CLOSER LOOK AT MAMMOGRAPHIC DENSITY

- ACR BI-RADS Atlas provides the guidance for visual assessment of density
- Visual perception of x-ray images can be reduced to an evaluation of pixels, appearing as varying patterns and textures at varying intensities
 - Visually also assessing 3D anatomic structure projected on 2D MG imaging

3D ANATOMIC DEPICTION OF DENSITY

Extremely Dense Dense
Moderately Dense Scattered

Georgia C. Spear, MD CIBC Chicago 2019

ACR BI-RADS LEXICON – 4TH vs. 5TH EDITION

- 4th edition:
 - Based on **quantitative** percentage scale
 - Limitation: unstable cut-point categorizations
 - For example, categorizing density at 49% vs 50% dense places the same patient in density categories 2 vs 3 when in fact no substantive difference exists between the two
- 5th edition (2013): visual assessment of mammographic density in four **qualitative** categories

| 4 th Ed. ('03) | 5 th Ed. (2013) |
|---|--|
| 1 entirely fat ($<25\%$ glandular) | A The breasts are almost entirely fatty |
| 2 There are scattered fibroglandular densities (approx. 25% - 50% glandular) | B There are scattered areas of fibroglandular density |
| 3 The breast tissue is heterogeneously dense, which could obscure detection of small masses (approx. 51% - 75% glandular) | C The breasts are heterogeneously dense, which may obscure small masses |
| 4 The breast tissue is extremely dense. This may lower the sensitivity of mammography ($>75\%$ glandular) | D The breasts are extremely dense, which lowers the sensitivity of mammography <small>(Quartiles have been eliminated)</small> |

CHANGE IN BI-RADS → INTERPRETATION VARIABILITY

- Masking effect becomes stronger with BI-RADS 5th edition → may lead to an increase in c/d density categorization
- STUDY: Irshad et al describe the impact of the 5th edition of BI-RADS breast density assessment guidelines on density report patterns in AJR in 2017
- Collection of breast density data by five radiologists and for 16,907 density assignments of BI-RADS 5th edition and 19,066 density assessments using BI-RADS 4th edition
- Results (p<0.001)
 - 5% decrease in fatty assessments
 - 2.8% increase in scattered assessments
 - 2.6% increase in heterogeneously dense assessments
 - 0.4% decrease in extremely dense assessments
 - **Overall increase in dense assessments**

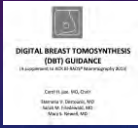
Irshad A, Laddy R, Lewis M, et al. Changes in Breast Density Reporting Patterns of Radiologists After Publication of the 5th Edition BI-RADS Guidelines. A Single Institution Experience. AJR 2017; 190(6): 943-948.

46 YO WITH BI-RADS C DENSITY WITH BI-RADS 5 CRITERIA (B WITH BI-RADS 4)

Irshad A, Laddy R, Lewis M, et al. Changes in Breast Density Reporting Patterns of Radiologists After Publication of the 5th Edition BI-RADS Guidelines. A Single Institution Experience. AJR 2017; 190(6): 943-948.

DIFFERING MAMMOGRAPHIC TECHNIQUES --> INTERPRETATION VARIABILITY

- DBT – warranted new BI-RADS
 - Breast density should be assessed on standard DM or synthesized MG, NOT on tomosynthesis slices
 - As with DM, if the two breasts differ in density, classification should be based on the more dense breast
- DBT (3D) imaging may result in a decrease in c/d categorization
 - Retrospective study of 24736 women screened with DBT versus digital mammography alone had **lower likelihood of categorization of high density breasts**
 - DBT vs digital: odds ratio, 0.69 (p<0.001); Synthetic and DBT vs digital: odds ratio, 0.43 (p<0.001)
 - **Lower likelihood to categorize high density breasts with synthetic and DBT compared to digital and DBT: odds ratio, 0.62 (p<0.001)**



Gastouros A, McCarthy AM, Pantalone L, Symchowicz M, Kontos D, Conant EF. Effect of Mammographic Screening Modality on Breast Density Assessment: Digital Mammography versus Digital Breast Tomosynthesis. *Radiology* 2019;291(2):320-327.

| | | |
|------------------|-----|-----|
| % Density | 44% | 48% |
| 4th Ed. Category | 2 | 2 |
| 5th Ed. Category | B | C |

George G. Sener. ACR CIBC 2019

VARIABILITY IN VISUAL ASSESSMENT OF PERCENT DENSITY⁴

- 4 radiologists
- 300 mammograms
- % density - x-axis
- Ranges vary and distribution varies
- For ex, Rads 3 and 4, PBD 65% with wide variability in density assessment categorization

PAIRWISE COMPARISONS OF RADIOLOGISTS ON PERCENT DENSITY ASSESSMENTS

Good Correlation

| | | | |
|----|--------------|--------------|--------------|
| r1 | 0.88 0.75 | 0.91 0.64 | 0.84 0.82 |
| r2 | 0.87 0.64 | 0.86 0.68 | 0.84 0.62 |
| r3 | 0.86 0.68 | 0.84 0.62 | 0.84 0.62 |
| r4 | 0.84 0.62 | 0.84 0.62 | 0.84 0.62 |

Poor Agreement

VARIABILITY IN DENSITY CATEGORIZATION

- Density assessment evaluated in a subset of 83 breast radiologists in NCI's Population-Based Research Optimizing Screening through Personalized Regimens or PROSPR network
 - Rate of assignment of "dense" category (3/4) ranged from 6.3% of screening exams to up to 84.5%
 - Statistical adjustment for patient variables: age, body mass index, race and ethnicity had little effect on variability
 - Among women with consecutive mammograms interpreted by different radiologists through an average span of 1.2 years, there was 17.2% discordance in dense vs non-dense category assignments and women shifted in both directions

Sprague BL, Conant EF, Duggi T et al. Variation in mammographic breast density assessments among radiologists in clinical practice: a multicenter observational study. *Ann Intern Med* 2020;172(7):407-416.

TECHNOLOGIC ADVANCEMENTS: OVERCOMING VARIABILITY OF DENSITY ASSESSMENT

AUTOMATED vs SEMI-AUTOMATED ALGORITHMS

- Created to overcome subjective visual BI-RADS assessment and produce reproducible qualitative methods
- Area vs volumetric
- Reproducible, quantitative metrics and a continuous density score aid in more granular density-based risk stratification

Conant EF, Sprague BL, Kontos D. Beyond BI-RADS Density: A Call for Quantification in the Breast Imaging Clinic. *Radiology* 2018; 286(2): 401-404.

Using Volumetric Breast Density to Quantify the Potential Masking Risk of Mammographic Density

Thamalia Destounis¹
Eva Sabatini^{2*}
Rachel Highman³
Patricia Mangan⁴
Andrew Clark⁵

OBJECTIVE: The purpose of this study was to compare BI-RADS density categories with quantitative volumetric breast density (VBD) for the reporting of mammographic density (as used in locally optimized image processing algorithms) across all views of the breast to better assess masking risk.

MATERIALS AND METHODS: This retrospective study included consecutive mammograms from 10,000 breast cancer-free women identified between 2008 and 2014.

- Retrospective study of screen-detected vs interval breast cancers
- Destounis showed that quantitative volumetric measures of breast density
 - stronger association with rate of development of interval cancers compared with clinical BI-RADS assessment

Destounis T, Sabatini E, Highman R, Mangan P, Clark A. Using volumetric breast density to quantify the potential masking risk of mammographic density. *Am J Roentgenol*. 2017;208(1):222-227.

SEMI-AUTOMATED VS AUTOMATED ALGORITHMS

| | | | |
|--|---|---|--|
| Intensity histograms, thresholding, segmentation Percent density typically ranges from 0% to 100% Area-based Imaging Physics | relative physics Percent density typically ranges from 0% to 35% Volume-based Imaging Physics | HAND CRAFTED IMAGE FEATURES intensity histograms, patterns, textures Percent density typically ranges from 0% to 100% Area-based Imaging Physics | AUTOMATED IMAGE FEATURES patterns, textures Percent density typically ranges from 0% to 100% Deep Learning AI (neural networks) |
|--|---|---|--|

AREA ALGORITHMS

- Based on thresholding and segmentation that can be highly operator dependent by physicist applying filters
- Use processed or "for presentation" images
- Typically research algorithms
- Imaging physics models

VOLUMETRIC ALGORITHMS

- Require **RAW** images
- BI-RADS 4th vs 5th ed density categories defined by different cut-points on quantitative scale
- GOOD CORRELATION, POOR AGREEMENT** with visual PBD
 - Balance on raw images (not what radiologist sees)
- Derived from physics models critically dependent on:
 - identifying "lumpy" reference pixels
 - assumptions relating to breast thickness (requires equipment calibration), compression and other physics acquisition parameters

MACHINE LEARNING ALGORITHMS

- Based on hand-crafted image features that measure patterns, textures & intensity histogram features
- May be applied to RAW or PROCESSED images
- GOOD CORRELATION, GOOD AGREEMENT** with visual PBD
- Distinct algorithms for PBD and BI-RADS 5th ed breast density scales
- Training statistical learning algorithms using large image data sets of labeled images

DEEP LEARNING ALGORITHMS

- Align with how the visual cortex processes images when radiologists visualize mammograms
- Excellent correlation & agreement with visual PBD assessments**
- Distinct algorithms for PBD & BI-RADS 5th ed breast density scales
- Training deep learning algorithms using very large image data sets of labeled images

COMMERCIALIZED ALGORITHMS

| Method | Type | Algorithm | Regulatory Clearance | STANDARD DICOM | MULTI-VENDOR |
|------------------|---|------------------|----------------------|----------------|--------------|
| Physics Models | Volumetric relative physics | Spectral Density | Y | N | N |
| | | VolparaDensity | Y | N | Y |
| | | Quantra | Y | N | Y |
| Machine Learning | Hand Crafted Image Features patterns; textures | Densitas | Y | Y | Y |
| | | DensSeeMammo | Y | Y | N |
| | | ItReveal | Y | N | Y |
| | | Quantra | Y | N | Y |
| | | Densitas | * | Y | Y |

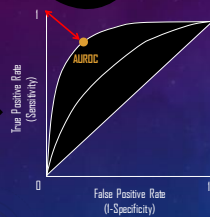
BREAST DENSITY AND BREAST CANCER RISK

BREAST DENSITY & BREAST CANCER RISK

- Visually assessed mammographic density is **strongly** associated with breast cancer risk
 - 25 years of peer reviewed literature
- The association between breast density and breast cancer risk is a **KEY validation point for any breast density algorithm**
- Mammographic breast density is **one of the strongest** breast cancer risk factors¹⁰
- Many risk models now incorporate breast density as a risk factor: Gail, Tyrer-Cuzick, BCSC (Breast Cancer Surveillance Consortium) risk calculator.

AUC CURVE

Each point on the curve represents a sensitivity/specificity pair



Optimal sensitivity and specificity
→ point in the upper left corner

↑ AUC = ↑ discrimination between individuals with and without disease

A perfect model has AUC of 1 (high spec and high sens)
A useless model has an AUC of 0.5.

∴ AUC curve can be used to demonstrate the ability of the model to predict breast cancers

BREAST CANCER RISK MODELS & MAMMOGRAPHIC DENSITY

Addition of mammographic density to both the Tyrer-Cuzick v6 and the Gail model improved the predictive performance¹¹

| AUC | Model | Density | Model + Density |
|-----|-----------------|---------|-----------------|
| | Tyrer-Cuzick v6 | 0.57 | 0.61 |
| | Gail | 0.55 | 0.59 |

• Density alone performed as well as Gail + Density

BREAST CANCER RISK MODELS

Predict 5- and 10-year risk of developing breast cancer¹²⁻¹⁶

| | Gail | Tyrer-Cuzick v8 | BCSC | BRCAPRO | Claus 1993 |
|------------------------|------|-----------------|------|---------|------------|
| Age | ✓ | ✓ | ✓ | ✓ | ✓ |
| BMI | ✗ | ✓ | ✗ | ✗ | ✗ |
| Menarche | ✓ | ✓ | ✗ | ✗ | ✗ |
| Menopause | ✗ | ✓ | ✗ | ✗ | ✗ |
| HRT | ✗ | ✓ | ✗ | ✗ | ✗ |
| Biopsy / ADH | ✓ | ✓ | ✓ | ✗ | ✗ |
| 1° FHx Breast CA | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2° FHx Breast CA | ✗ | ✓ | ✗ | ✓ | ✓ |
| 1° & 2° FHx Ovarian CA | ✗ | ✓ | ✗ | ✓ | ✓ |
| Breast Density | ✓ | ✓ | ✓ | ✗ | ✗ |

• Age and family history are common to all risk models.

MASKING EFFECT

- Sensitivity in fatty breasts can be higher than 90%
- Sensitivity in very dense breasts can be as low as 50%

| Category | BI-RADS 1 | BI-RADS 2 | BI-RADS 3 | BI-RADS 4 | BI-RADS 5 |
|------------------------|-----------|-----------|-----------|-----------|-----------|
| Interval cancer | 11.0% | 11.4% | 19.8% | 28.8% | 28.8% |
| Screen-detected cancer | 11.0% | 11.0% | 12.0% | 12.0% | 12.0% |
| Any cancer | 11.0% | 12.0% | 12.0% | 12.0% | 12.0% |
| No cancer | 1.0% | 1.0% | 1.0% | 1.0% | 1.0% |

N=7007

AUTOMATED BREAST DENSITY AND RISK

- Aclay et al. compared five different methods (visual analogue scale (VAS), Cumulus, Densitas, Quantra and Volpara) of breast density assessment and their relation to breast cancer risk.
 - various density measures were included with the Tyrer-Cuzick (4S) risk score in a logistic regression analysis to evaluate breast cancer risk.
 - VAS strongest predictor of screen-detected cancers
 - Quantra – no significant association
- Researchers concluded (Densitas and Volpara) measures had a strong association with breast cancer risk, providing a practical automated method for risk-based stratification for breast screening

A Deep Learning Mammography-based Model for Improved Breast Cancer Risk Prediction

Adama Yala, MEng • Constance Ledwith, MEd, PhD • Tal Schacter, MS • Tilly Phelan, BS • Rogina Davuluri, PhD

From the Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, 37 Vassar St., 77-100A (Cambridge, MA 02139, USA); E-mail: ayala@mit.edu and Department of Biostatistics, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

- TCR: breast density + RF**
 - Overall AUROC = 0.62
 - White: AUROC = 0.62
 - African American: AUROC = 0.45
- Hybrid: Deep Learning + RF**
 - Overall AUROC = 0.70
 - White: AUROC = 0.71
 - African American: AUROC = 0.71

Georgia Spear, CIBC, Chicago, 2019

AUTOMATED DENSITY ALGORITHMS TO PREDICT RISK

- Puliti et al. volumetric breast density and risk of advanced cancers after negative screening episode: a cohort study. *Breast Cancer research* (2018) 20: 95
 - Risk of advanced cancer is 4X increased for extremely dense compared to non extremely dense using an automated breast density measurement
- Desloutis S, Johnston L, Highnam R, Ariens A, Morgan R, Chan A. Using Volumetric Breast Density to Quantify the Potential Masking Risk of Mammographic Density. *AJR* 2017; 208: 1-6.
 - Highest breast density category associated with highest risk
 - Breast density is only risk factor associated with diagnosis of interval cancer versus screen-detected cancer
 - Highest density 3.6 fold more likely to have interval cancer diagnosis compared with other categories

IMMENSE TIMELINE

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HOW CAN WE BRING PRECISION MEDICINE INTO CLINICAL CARE?

- Deliver personalized screening on the basis of breast cancer risk
- Providing reproducible estimates of risk can lead to more effective delivery of personalized screening to improve patient outcomes
- Breast density assessment can be used to deliver personalized/precision screening based on risk**

HOW CAN WE BRING PRECISION MEDICINE INTO CLINICAL CARE?

- Breast cancer risk varies widely from woman to woman in a general screening population
 - 11.6% (average woman) to 85% (germline mutations) lifetime risk
- Cook-cutter approach to risk estimation using crude criteria based on ad-hoc categorization of risk factors leads to imprecision and either unnecessary or excessive follow-up and treatment
- Tailored screening protocols based on individual risk can:
 - Inform targeted breast cancer prevention strategies
 - Improve clinical outcomes
 - Ration resources
 - Reduce harms

CONCLUSION

- Breast density is an important risk factor for breast cancer and it is important to understand for appropriate breast cancer screening
- Reliable assessment of breast density is crucial in accurate assessment of breast cancer risk
- Reliance on clinically proven methods to address breast density and breast cancer risk is essential in providing excellent patient care
- Earlier qualitative methods are limited
- Automated methods help move us to standardizing assessment with consistency and reproducibility
- Increasing interest in this area will continue to provide information and guidance on application in a large scale breast cancer screening program

CONCLUSION

- In summary, technology's mission in today's world of breast imaging is to seek specificity without loss of sensitivity
- Safe to say that Breast Imaging is NOT a one size fits all solution
- Continued research in this arena is important to identify the best solution
- Personalized screening is THE FUTURE



THANK YOU



- Acknowledgements: M. Abdollah, Dalhousie University, Demas Inc.

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