

# Update on Breast Imaging

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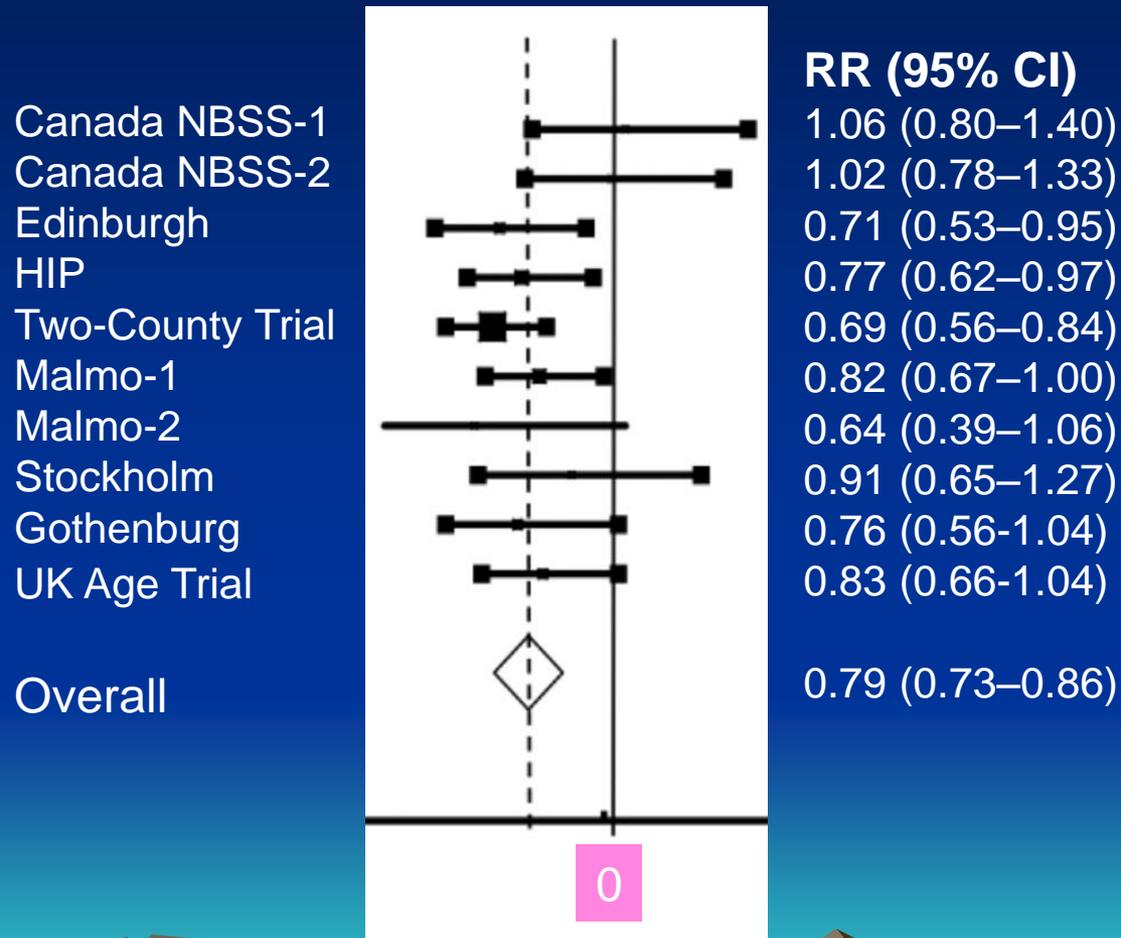
University of Calgary



**Table 1 Performance Measures for 1,960,150 Screening Mammography Examinations Performed in the US From 2002 to 2006 by Age, Based on Breast Cancer Surveillance Consortium Data as of 2009**

<b>Age</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Recall</b>	<b>PPVe</b>
40–44	73.6%	88.2%	11.8%	1.4%
45–49	80.3%	89.0%	11.2%	2.5%
50–54	82.4%	90.5%	9.7%	3.2%
55–59	84.6%	91.5%	8.8%	4.4%
60–64	84.9%	91.9%	8.5%	5.5%
65–69	84.6%	92.3%	8.0%	6.2%
70–74	84.7%	92.9%	7.5%	7.3%
75–89	86.6%	93.4%	7.1%	9.1%
<b>Total (40–89)</b>	<b>83.5%</b>	<b>90.9%</b>	<b>9.3%</b>	<b>4.1%</b>

# Relative Risks of Breast Cancer Mortality



# Swedish Two-County Trial

- 29 years
- 133065 women, age 40-74
- No CBE
- 31% decrease in death due to breast cancer among those screened with mammography



# Non RCT

- Review of 38 non-randomized studies using cohort and case control studies
  - 30-40% reduction in breast cancer mortality associated with screening
- Significant reduction in rates of positive lymph nodes, tumors >2 cm, and TNM stage II or worse
  - Gabe R, Duffy SW. Evaluation of service screening mammography in practice: the impact on breast cancer mortality. *Ann Oncol.* 2005;16(Suppl 2):ii153-62.

# Canadian National Breast Screening Study 25 Year Follow Up

89835 women 40-59 randomly assigned to mammography or control

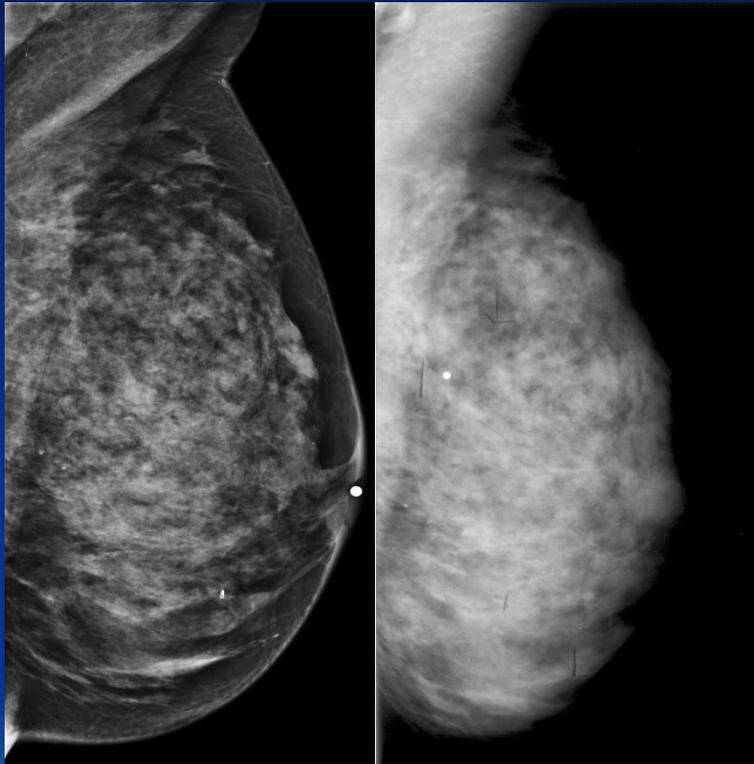
- 5 year screening period
- Found no reduction in mortality among those screened with with mammography
  - Miller et al. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ* 2014;348



# CNBSS...Flawed and Misleading

- **Reviewers confirmed**
  - **Poor equipment (even for the time period)**
  - **Poor image quality (compromised by scatter due to lack of grids)**
  - **Poor positioning**
    - **Study's physicist has stated "...in my work as reference physicist to the NBCSS, I identified many concerns regarding the quality of mammography carried out in some NBSS screening centers. That quality was far below the state of the art, even for that time"**
- **Only 32% of breast cancers were detected by screening mammography alone....typically 2/3 are**
  - **Mean tumor size 19 mm in mammography arm versus 21mm in control arm**  
**Explains the lack of mortality benefit**
- **Digital mammography, CAD, tomosynthesis**
- **National and provincial accreditations programs**

# Digital Mammography



Sub analysis of 49258 patients revealed that DM is significantly more sensitive  
In Pre or perimenopausal women, < 50 yo  
with dense breasts then CM\*

Sensitivity increases from 55-70% among  
women with dense breasts

CAD has a higher cancer detection rate  
and is 98% sensitive for calcifications

# CNBSS-Lack of True Randomization

- Same nurses that performed the clinical breast exam subsequently assigned women to screening or control group
- Results in a disproportionate number of advanced cancers in the mammography arm

Tarone RE. The Excess of Patients with Advanced Breast Cancers in Young Women Screened with Mammography in the Canadian National Breast Screening Study. *Cancer* 1995;75:997-1003.

Kopans DB, Feig SA. The Canadian National Breast Screening Study: A Critical Review. *AJR* 1993;161:755-760.



# Variability in Guidelines

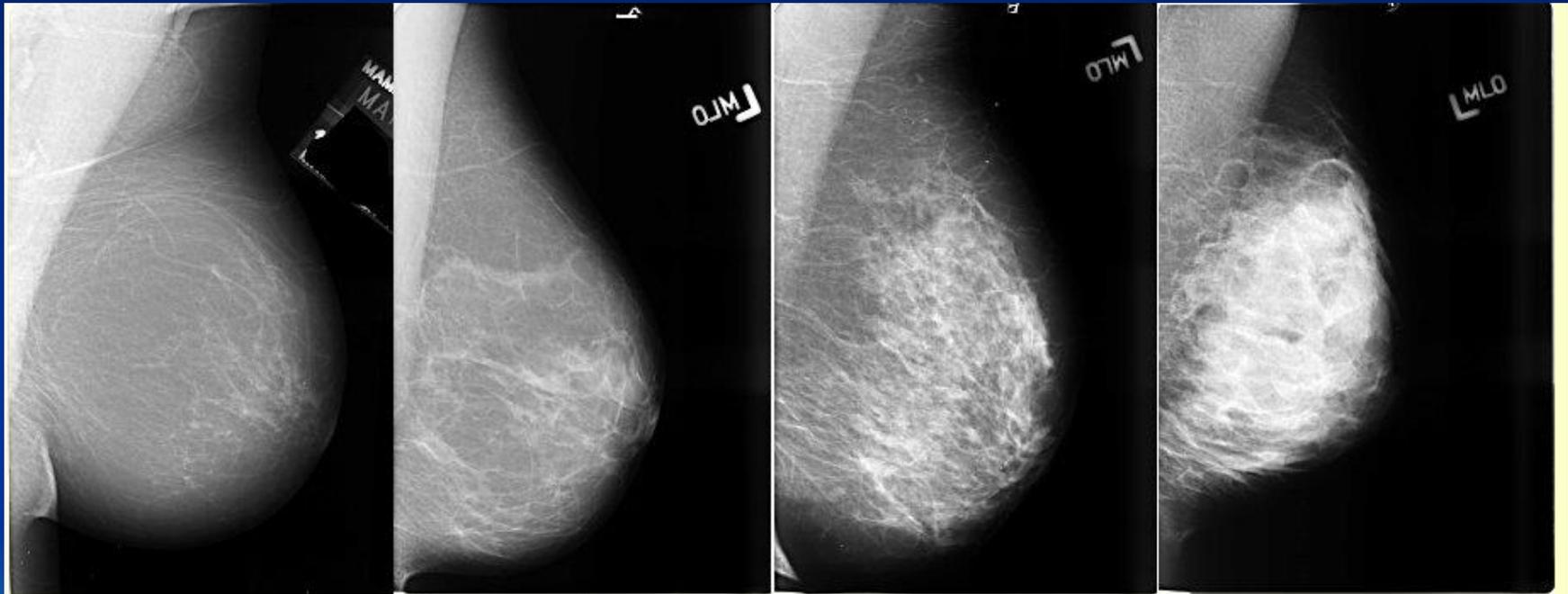
- Most guidelines do recommend routine screening mammography 50+ every 2 years
- Considerable variability in recommendations <40 years
- The following organizations recommend annual screening for women age 40-50
  - ACR/Canadian Association of Radiologists
  - ACS
  - ACOG
  - National Comprehensive Cancer Network

# Current Trends

- Customize screening protocol
  - Baseline risk
  - Baseline with dense tissue
  - Elevated risk
  - High risk



# Variability of Breast Density



Breast composition and its mammographic appearance.<sup>1</sup>

Roughly 40 percent of all women have heterogeneously dense or dense breast parenchyma

# How Should We Screen

- Sensitivity of mammography (CM) varies inversely with breast density
- While mammography has a sensitivity of 83% overall, it may be as low as ~30-50% in very dense breasts
- Specificity remains relatively high 80-93%
- >50% of all women < 50 yo have at least heterogeneously dense or dense tissue



# Density As Risk?

Boyd et al. Mammographic density and the risk and detection of breast cancer. [N Engl J Med.](#) 2007 Jan 18;356(3):227-36

**Difficult to separate the masking effect of dense tissue from the possible causal effect of density**

**If detected by screening alone will underestimate the risk of breast cancer associated with density**

**If detected within 12 months of negative mammogram the risk will be overestimated**

**This study controlled for method of detection**



# Density as Risk?

Boyd et al Reviewed 1112 matched case pairs controlled for:

-age, menarche, parity ,BMI, age at first birth, menopausal status, HRT, first degree relative, observation time

Women with >75% density had an increase risk of breast cancer compared to those with < than 10% density (odds ratio, 4.7;95% confidence interval)

Percentage of density was associated with an increased risk of breast cancer in all categories of detection

Boyd et al. Mammographic density and the risk and detection of breast cancer. [N Engl J Med.](#) 2007 Jan 18;356(3):227-36.



# Percentage Mammographic Density-PMD

Meta-analysis from 42 studies

- PMD was consistently associated with risk of breast cancer
- Women with extremely dense breasts have approximately twice the risk for breast cancer compared to women with average breast density
- Women with extremely fatty breasts have about half the risk of women with average breast density

[McCormack](#) et al. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. [Cancer Epidemiol Biomarkers Prev.](#) 2006 Jun;15(6):1159-69.

[Boyd](#) et al. Mammographic density and breast cancer risk: current understanding and future prospects.

[Breast Cancer Res.](#) 2011;13(6):223. doi: 10.1186/bcr2942. Epub 2011 Nov 1.

# Boyd et al 2011 Review

- Relative risk

Only age and BRCA status are associated with a larger relative risk than PMD

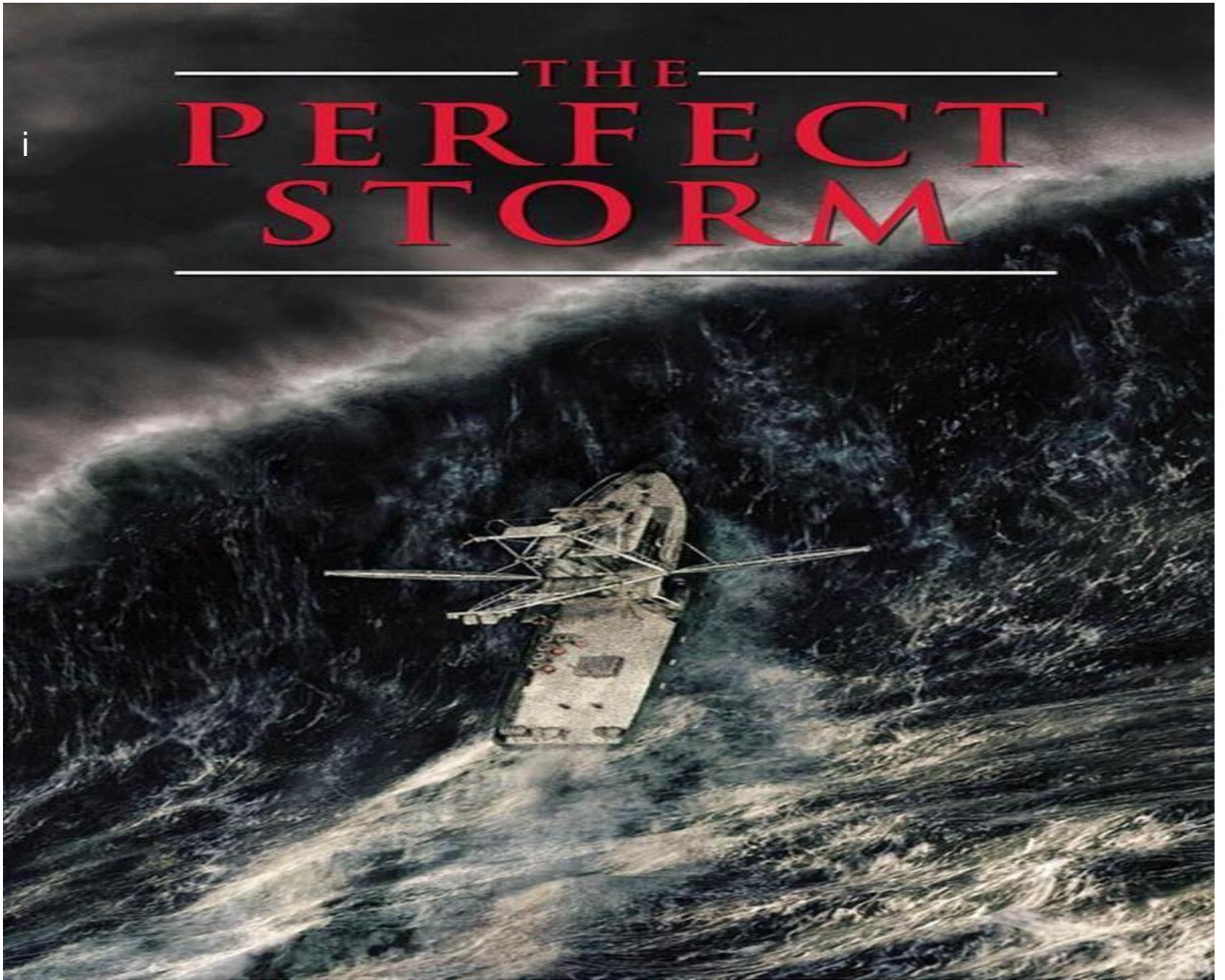
## Attributable Risk

High PMD common and if it dose impart a high relative risk...attributable risk is high...

Risk of breast cancer attributable to PMD>50% is 16%



THE  
PERFECT  
STORM



# Public Awareness of PMD

- Public awareness of masking effect and risk related to breast density has grown rapidly



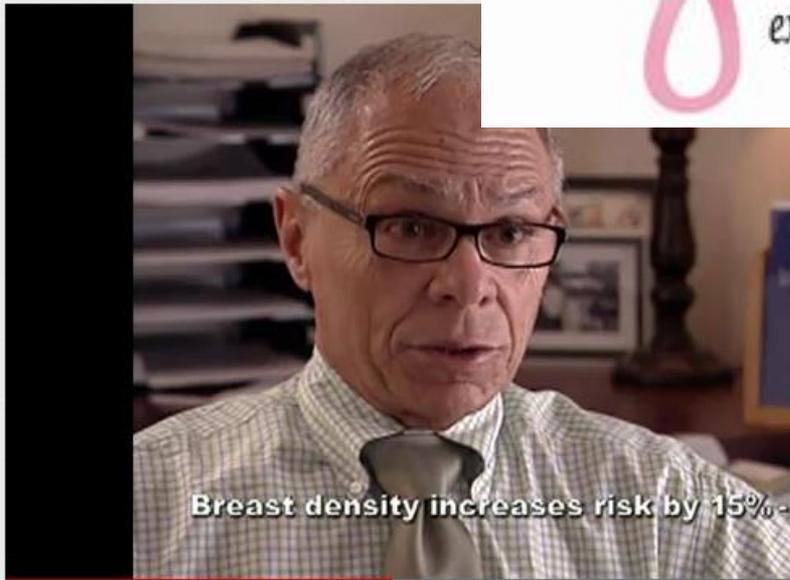


# The Cancer Risk Factor You've Probably Never Heard of



## Breast Density & Increased Risk

komensouthflorida  177 videos



0:34 / 1:32



0:25 / 2:04

# As of April 2013 California became the 5<sup>th</sup> state to legislate breast density notification

Identify the tissue is dense

That is may limit sensitivity of mammography

Is associated with an increased risk of breast cancer

Range of screening options available

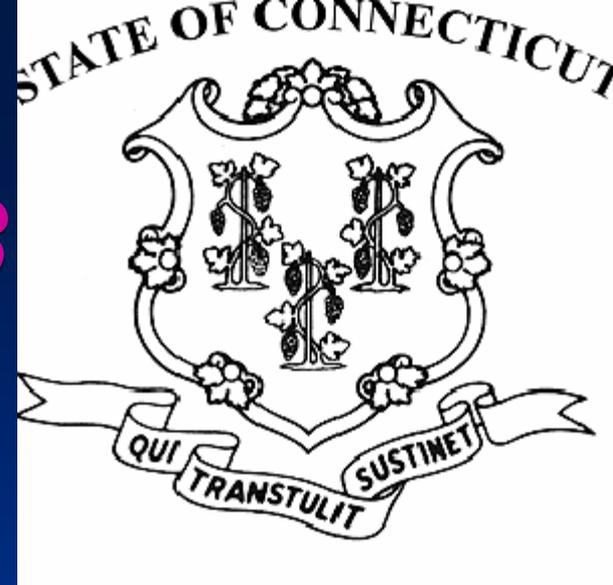
Laws in CT, NY, TX, VA, UT, IL, CA, IN, HI



# Are You Dense?

## *Substitute Senate Bill No. 458*

(2) a mammogram every year for any woman who is forty years of age or older. Such policy shall provide additional benefits for comprehensive ultrasound screening of an entire breast or breasts if a mammogram demonstrates heterogeneous or dense breast tissue based on the Breast Imaging Reporting and Data System established by the American College of Radiology or if a woman is believed to be at increased risk for breast cancer due to family history or prior personal history of breast cancer, positive genetic testing or other indications.....



## BI-RADS 5<sup>th</sup> Edition: Launched 1<sup>st</sup> Feb 2015

**Table 5. Breast Tissue**

Breast Composition Categories
a. The breasts are almost entirely fatty
b. There are scattered areas of fibroglandular density
c. The breasts are heterogeneously dense, which may obscure small masses
d. The breasts are extremely dense, which lowers the sensitivity of mammography

### 2. SUCCINCT DESCRIPTION OF THE OVERALL BREAST COMPOSITION

This is an overall assessment of the 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 breast tissue. A few co-

the volume of attenuating tissues in the breast,

# One Major Issue – How to

## Appendix: Study on Inter-reader BI-RADS Score Agreement

In this study, 309 images were scored by 15 radiologists using BI-RADS breast density. We evaluated the inter-reader variation between any pairs of two readers. There were a total of  $15 \times 14 / 2 = 105$  pairs, and about  $105 \times 309 = 32445$  individual data points. We made a 4x4 matrix to record all these data point through histogram method and the results are shown in Table 4. We found radiologists tend to agree with each other better for BI-RADS 2 and 3 cases, and the overall agreement rate between two radiologists was 61% in BI-RADS results.

**Table 4.** Inter-reader BI-RADS agreements, tested with 309 images rated by 15 radiologists

R1 \ R2	BIRADS 1	BIRADS 2	BIRADS 3	BIRADS 4	Total #	agree. (%)
BIRADS 1	698	1122	70	0	1890	37%
BIRADS 2	1122	8246	3418	115	12901	64%
BIRADS 3	70	3418	9262	1621	14371	64%
BIRADS 4	0	115	1622	1546	3283	47%
Total					32445	61%

....some radiologists never classify BI-RADS “a”, some rarely classify BI-RADS “d”..... Classification of breast density is highly

## What Physically Is Breast Density?

Breasts consist of fatty and fibroglandular (dense) tissue from x-ray perspective, so the basic volumetric parameters that define each breast are:

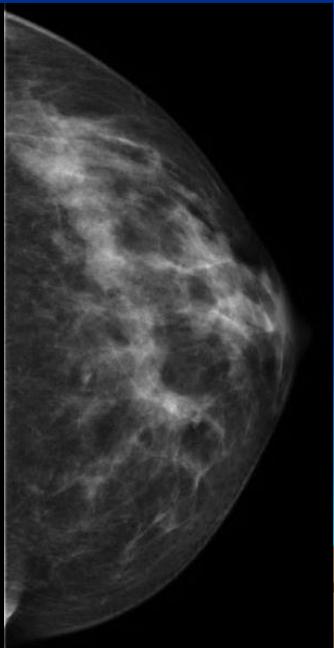
1. Volume of Fibroglandular Tissue in  $\text{cm}^3$
2. Volume of Breast in  $\text{cm}^3$
3. Volumetric Breast Density = Volume of Fibroglandular Tissue / Volume of Breast tissue

**Visually, these are difficult to estimate:**

*“Without exposure values, half-value layer information and knowledge of the compressed thickness of the breast, an accurate volume of tissue cannot be calculated”*



Prof Dan Kopans,  
Radiology, v246, #2, Feb  
2008



# Volpara

Fat is used as reference point reference point in the breast -near the chest

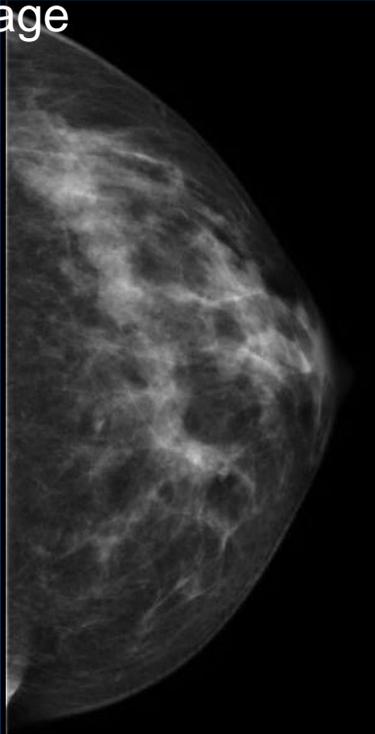
The second step is to compute the x-ray attenuation at each pixel by comparing the pixel value at the reference point to all other pixel values

Produces a density map in which the height at each pixel represents the tissue composition: higher values mean more fibroglandular or dense tissue.

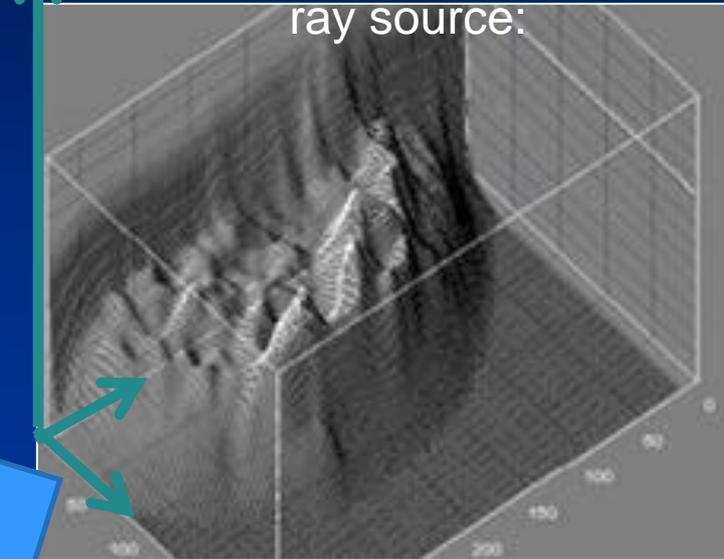


# How Does Volpara Work?

“For Processing” or Raw Image



“Density Map”, the height represents the volume of dense tissue between each pixel and the x-ray source:

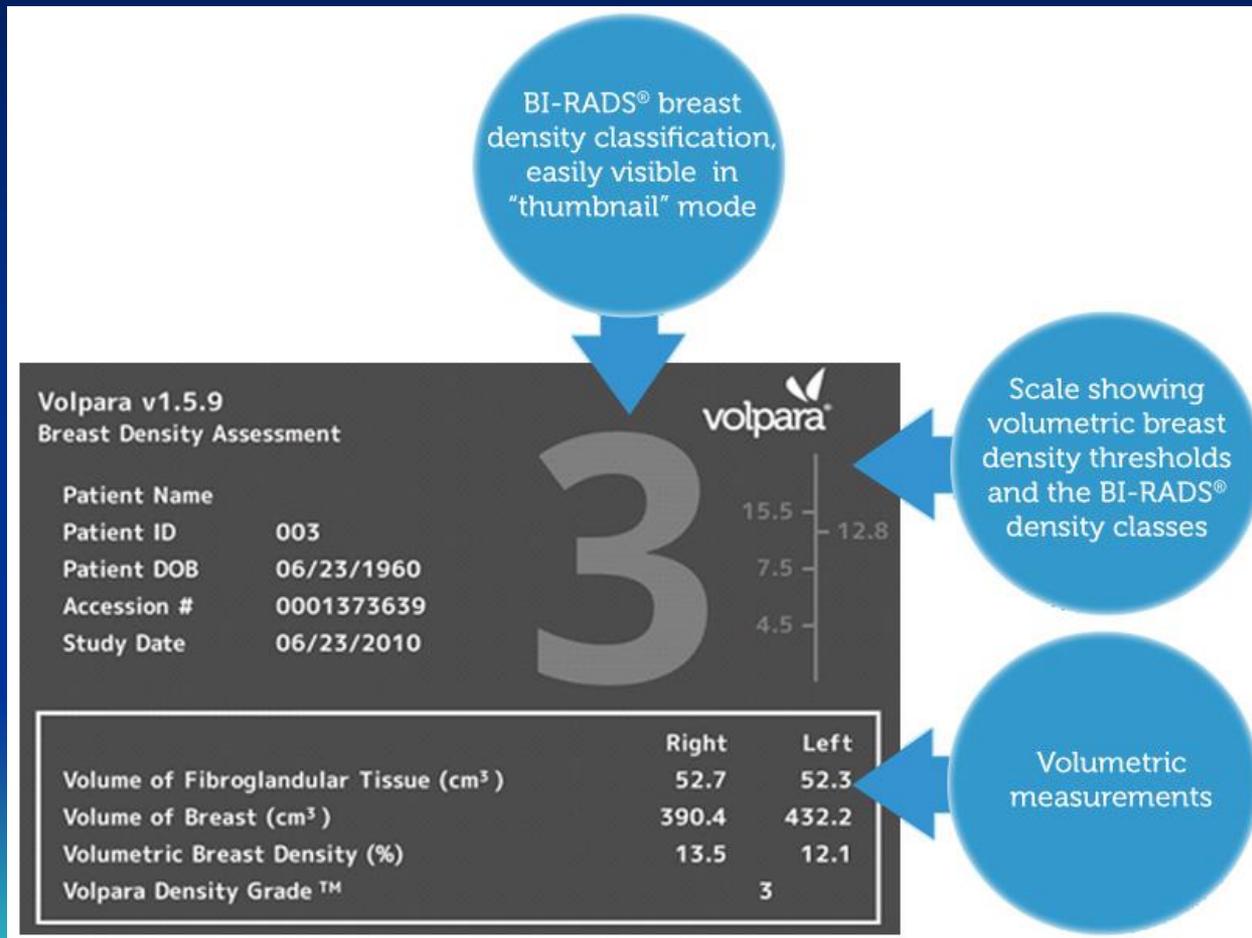


Sum the values across the image.

$$\text{Volumetric Breast Density (\%)} = 100 * \frac{\text{Volume of Fibroglandular Tissue (cm}^3\text{)}}{\text{Volume of Breast (cm}^3\text{)}}$$

Volume of Breast (cm<sup>3</sup>)

# Volpara Score Card





Volpara v1.5.9  
Breast Density Assessment

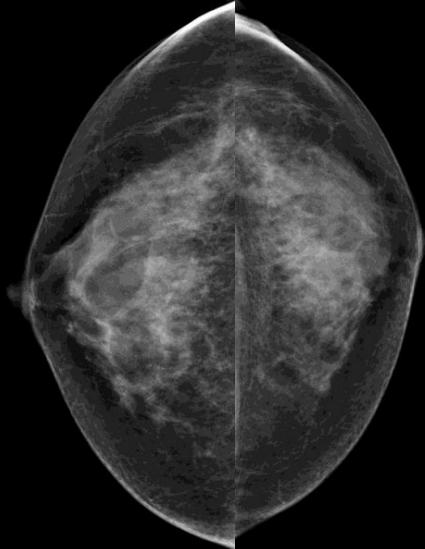


Patient Name GER\_BIRADS1  
Patient ID GER\_BIRADS1  
Patient DOB 01/01/2000  
Accession #  
Study Date 01/01/2000



	Right	Left
Volume of Fibroglandular Tissue (cm <sup>3</sup> )	29.4	37.0
Volume of Breast (cm <sup>3</sup> )	864.7	860.5
Volumetric Breast Density (%)	3.4	4.3
Volpara Density Grade™	1	

L  
Z RCC



L  
Z LCC

Volpara v1.5.9  
Breast Density Assessment

volpara®

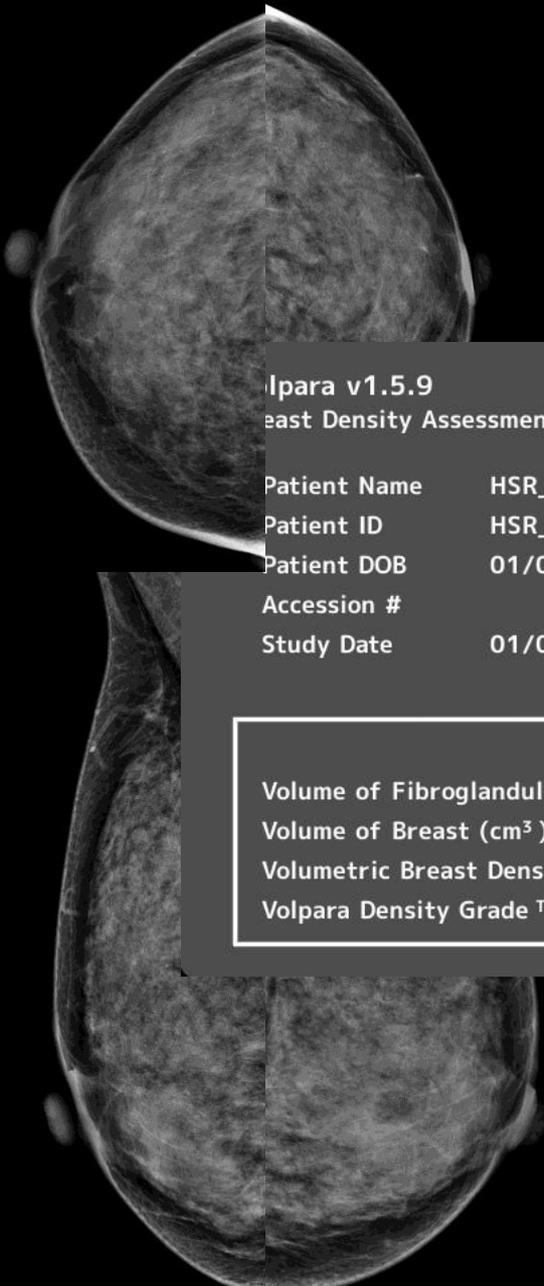
Patient Name      HSR\_BIRADS3b  
Patient ID         HSR\_BIRADS3b  
Patient DOB        01/01/2000  
Accession #         
Study Date         01/01/2000



L  
Z RMLO



	Right	Left
Volume of Fibroglandular Tissue (cm <sup>3</sup> )	34.1	37.8
Volume of Breast (cm <sup>3</sup> )	296.5	320.3
Volumetric Breast Density (%)	11.5	11.8
Volpara Density Grade™	3	



Volpara v1.5.9  
Breast Density Assessment

Patient Name HSR\_BIRADS4b  
Patient ID HSR\_BIRADS4b  
Patient DOB 01/01/2000  
Accession #  
Study Date 01/01/2000



	Right	Left
Volume of Fibroglandular Tissue (cm <sup>3</sup> )	67.1	75.5
Volume of Breast (cm <sup>3</sup> )	243.1	271.6
Volumetric Breast Density (%)	27.6	27.8
Volpara Density Grade™	4	

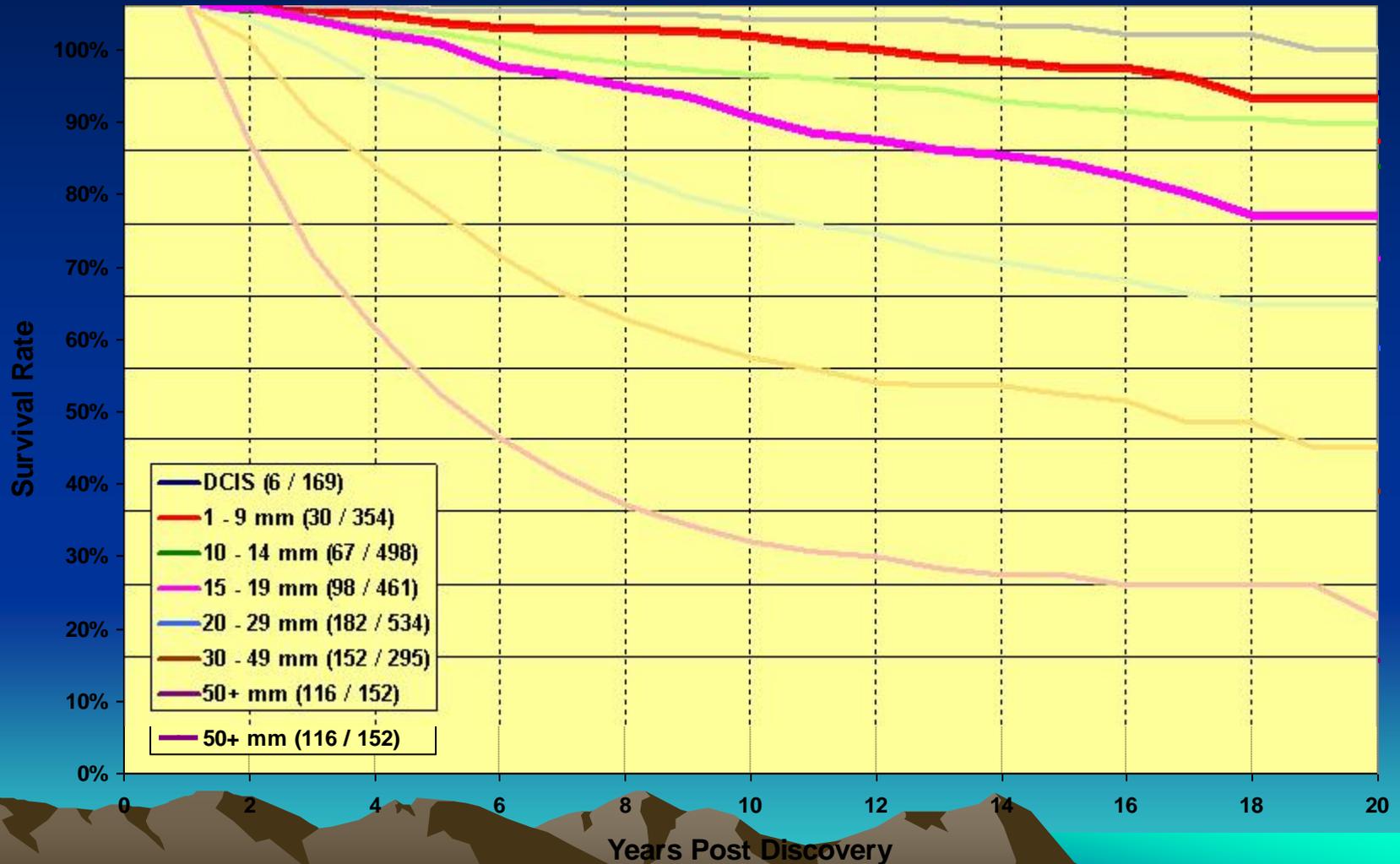


# Now What

- Objective means of assessing PMD
- Allow for rational use of supplemental Screening in appropriate cases



# Finding Cancers When They're Small Saves Lives

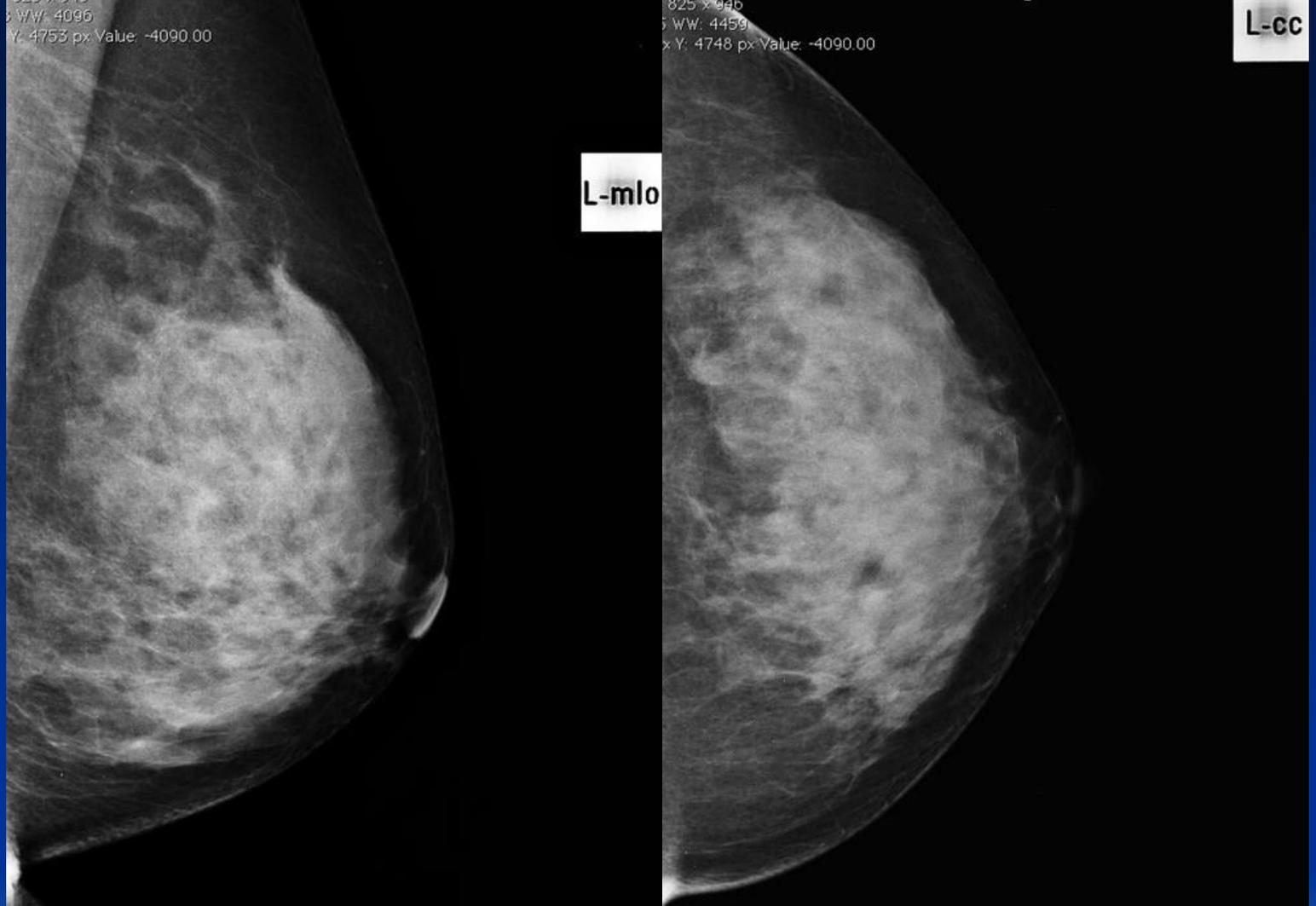


WV: 4096  
Y: 4753 px Value: -4090.00

825 x 946  
WV: 4459  
x Y: 4748 px Value: -4090.00

L-cc

L-mlo

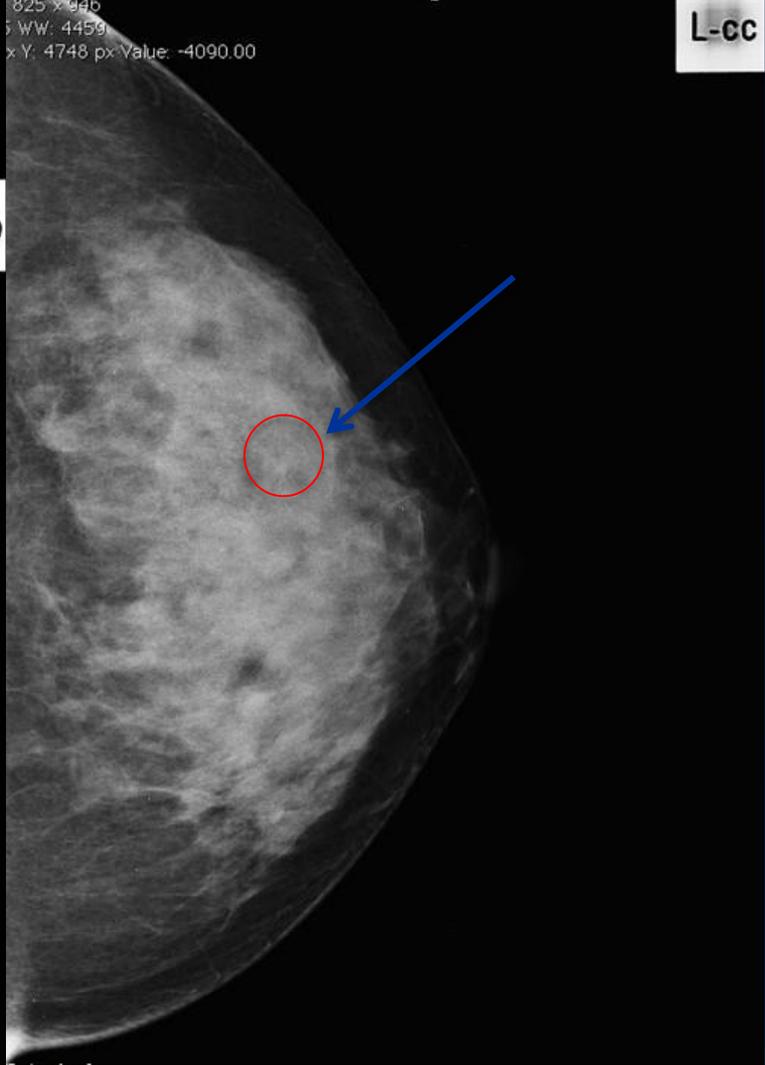


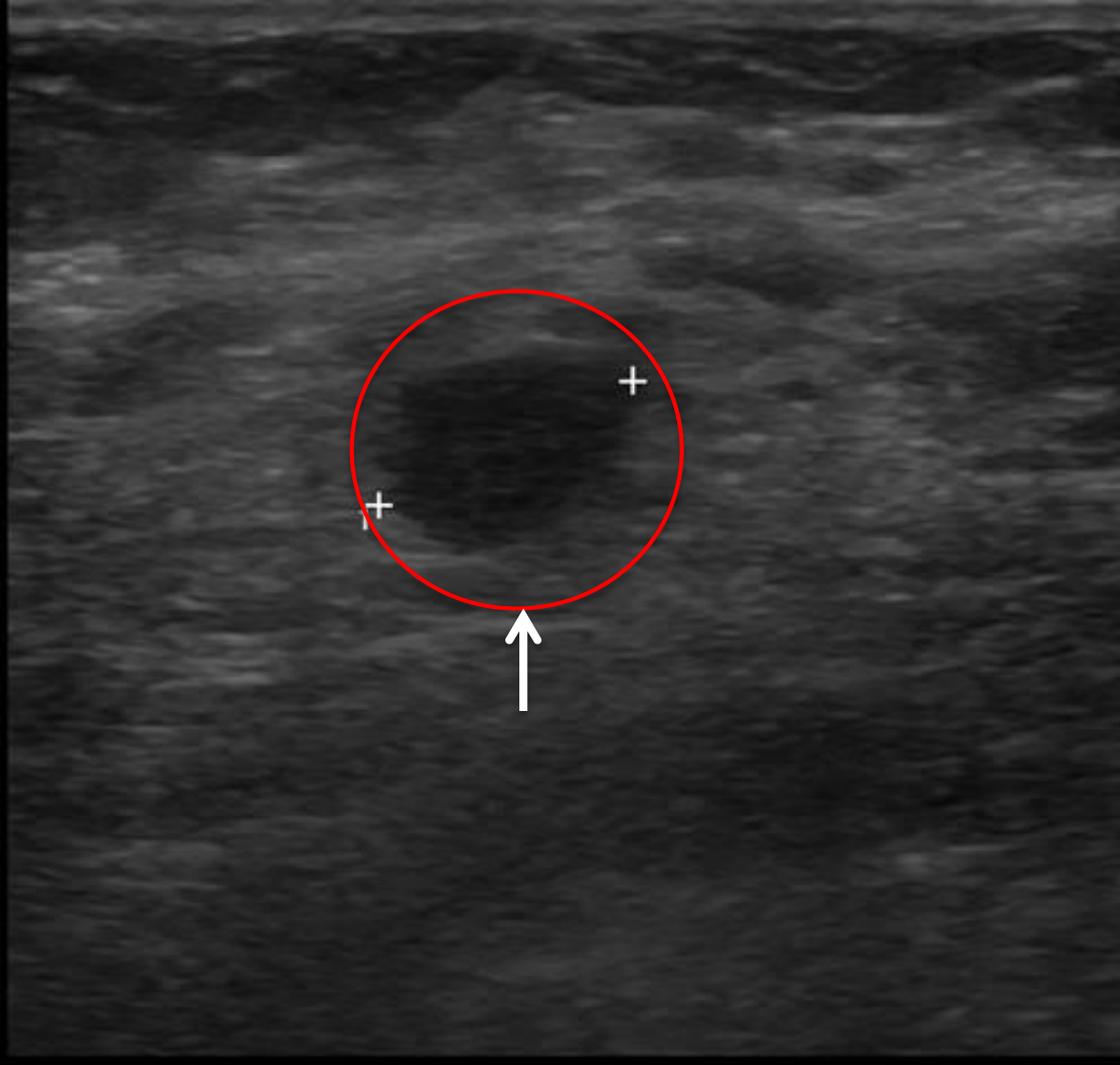
WV: 4096  
Y: 4753 px Value: -4090.00

825 x 946  
WV: 4459  
x Y: 4748 px Value: -4090.00

L-cc

L-mlo





Ultrasound  
1 cm lesion with  
Irregular margins  
*Invasive Cancer*

# Screening for Breast Cancer with Supplemental Breast Ultrasound

- ACRIN Study Investigated 2673 women at “elevated risk” from 21 different sites

Personal History of Breast Cancer 1400 (53)

Lifetime Risk  $\geq 25\%$  by Gail or Claus Model 497 (18.85)

Five Year Risk, Gail Model  $\geq 2.5\%$  403 (15.28)

Five Year Risk, Gail Model  $\geq 1.7\%$  and Extremely Dense Breasts 223 (8.46)

ADH/ALH/LCIS or Atypical Papilloma 83 (3.15)

Mutation in BRCA-1 or BRCA-2f 23 (0.87)

History of Prior Chest and/or Mediastinal and/or Axillary Irradiation 8 (0.30)

**ALL** Women Had Heterogeneously Dense Parenchyma In At Least One Quadrant

- No significant difference in age, menopausal status, use of hormones, Tamoxifen

# ACRIN RESULTS

– Diagnostic Yield was 7/1000 For Mammo Alone

This Increased to 11.8/1000 With The Addition Of  
Ultrasound

Supplemental Yield was 4.2/1000 (Range of 1.1-7.2  
Cancers/1000 Scanned)



# ACRIN

- Of the 12 Cancers Seen on Ultrasound Only 11 Were Invasive With A Median Size of 10mm and 89% Were Node Negative
- One Case of DCIS Was Identified
- However, The False Positive Rate For Mammography was 4.4%, and 8.1% For Ultrasound
- Six Month Follow-up Recommendations Were Made for 6.7% of Mammograms (1 CA)
- Six Month Follow-up Recommendations Were Made For 12.2 % Ultrasounds (5 had CA subsequently)

# Limitations

- Ultrasound Radiologist Performed
- Mean time was 19 Minutes, Range 1-90 Minutes
- Operator dependant
- Patient population was heterogeous

# Automated Whole Breast Ultrasound-AWBUS

Gathers standardized image sets-articulated arm in transverse

Ensuring overlap in visualized tissue

Standardizes breast and arm positioning to increase reproducibility

Reviewed by radiologist as a cine loop

20 min for exam/7 minutes for review by radiologist

# AWBUS

- Lower axillary lymph nodes



- Infra-Clavicular



- Far Medial



- Infra-Mammary



Kelly et al. Breast Cancer Detection Using Automated Whole Breast  
Ultrasound and Mammography in Radiographically dense breasts. Eur. Radiol  
(2010) 20: 734-742

6425 studies on asymptomatic women with BIRADS density of 3 or 4  
29% (1279) had no risk factors other than dense breasts  
 $\frac{3}{4}$  of cancers occurred in this subgroup

57 Cancers were found in 56 women  
43/57 had no personal or family history

Breast cancer detection doubled from 23-46 with addition of AWBUS

Sensitivity of Mammo alone 40% increased to 81%

65% of cancers were found by AWBUS alone, cancers were smaller

Recalls were 4.2% for mammo 7.2% for AWBUS

PPV of biopsy was 39% for mammo and 38.4% for AWBUS



- Other smaller studies have found Combination of Mammography and AWBUS resulted in sensitivity of 95% which approaches that of MRI
  - Access and cost of AWBUS versus MRI
  - We are currently using Volpara density assessment in all patients
  - Those with density 3 or 4 and negative screening mammo are eligible for AWBUS at physician request
- 

# High Risk Patients and Breast Cancer Surveillance: BRCA1/2

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Foothills Medical Center  
EFW Radiology



# Role of Surveillance

- Most high risk patients will not opt for prophylactic mastectomy despite risk level: 50-85% for BRCA1/2 carriers
- 18% of 1383 BRCA 1/2 carriers chose prophylactic mastectomy
- 7% opted for chemoprevention but still require surveillance
- 49% for surveillance alone

\*Metcalf et. Al, Int J Cancer. 2008 May 1:122(9):2017-22.

# How Should We Screen

- Peak incidence of cancer in BRCA 1 is 40 yo-leading to screening beginning at 25-30 yo
- Sensitivity of conventional mammography (CM) varies inversely with breast density
- While mammography has a sensitivity of 80% overall, it May be as low as ~30-50% in very dense breasts
- >50% of all women < 50 yo have at least heterogeneously dense or dense tissue

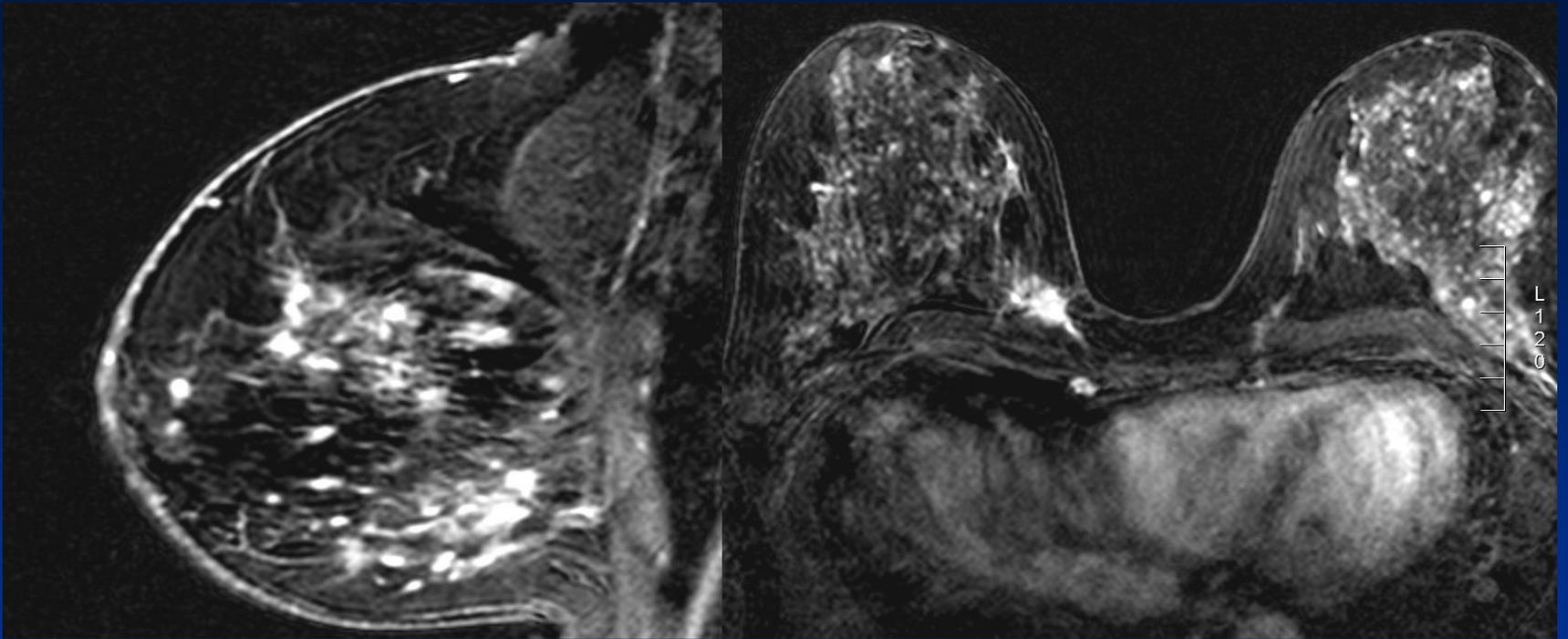


# BRCA Cancers are Different

- Interval cancer detection rate for BRCA is 35-50% with mammographic screening alone
- Doubling time may be as fast as 45 days
- Majority of cancers detected with mammo alone are invasive, larger than 1 cm and 20-56% nodes +
- BRCA 1 cancers are less likely to have calcifications
- Margins of masses may be deceptively benign in appearance
- Peak incidence of cancer in BRCA 1 is 40 yo-leading to screening beginning at 25-30 yo

# Screening Breast MRI

- No RCT of Screening Breast MRI with mortality as outcome
  - All trials have demonstrated MRI to be more sensitive than mammography for IDCA
  - Detected cancers are smaller, more likely to be node negative
  - Screening MRI is associated with a lower interval cancer detection



# American Cancer Society Guidelines for Screening MRI

**Recommend annual MRI screening (on the basis of evidence from non-randomised screening trials and observational studies)**

- *Proven BRCA mutation*
- • Untested first-degree relative of *BRCA* carrier
- • Lifetime breast cancer risk between 20% and 25% or
- • Radiation to chest between age 10 and 30 years
- • Li-Fraumeni syndrome and first-degree relatives
- • Cowden syndrome and first-degree relatives

**Insufficient evidence to recommend for or against MRI screening**

- • Lifetime risk between 15% and 20%
- • Heterogeneously or extremely dense breast on mammography
- • Women with a personal history of breast cancer, including ductal carcinoma in situ, LCIS and ADH

**Recommend against MRI screening Women at 15% or lower LTR**



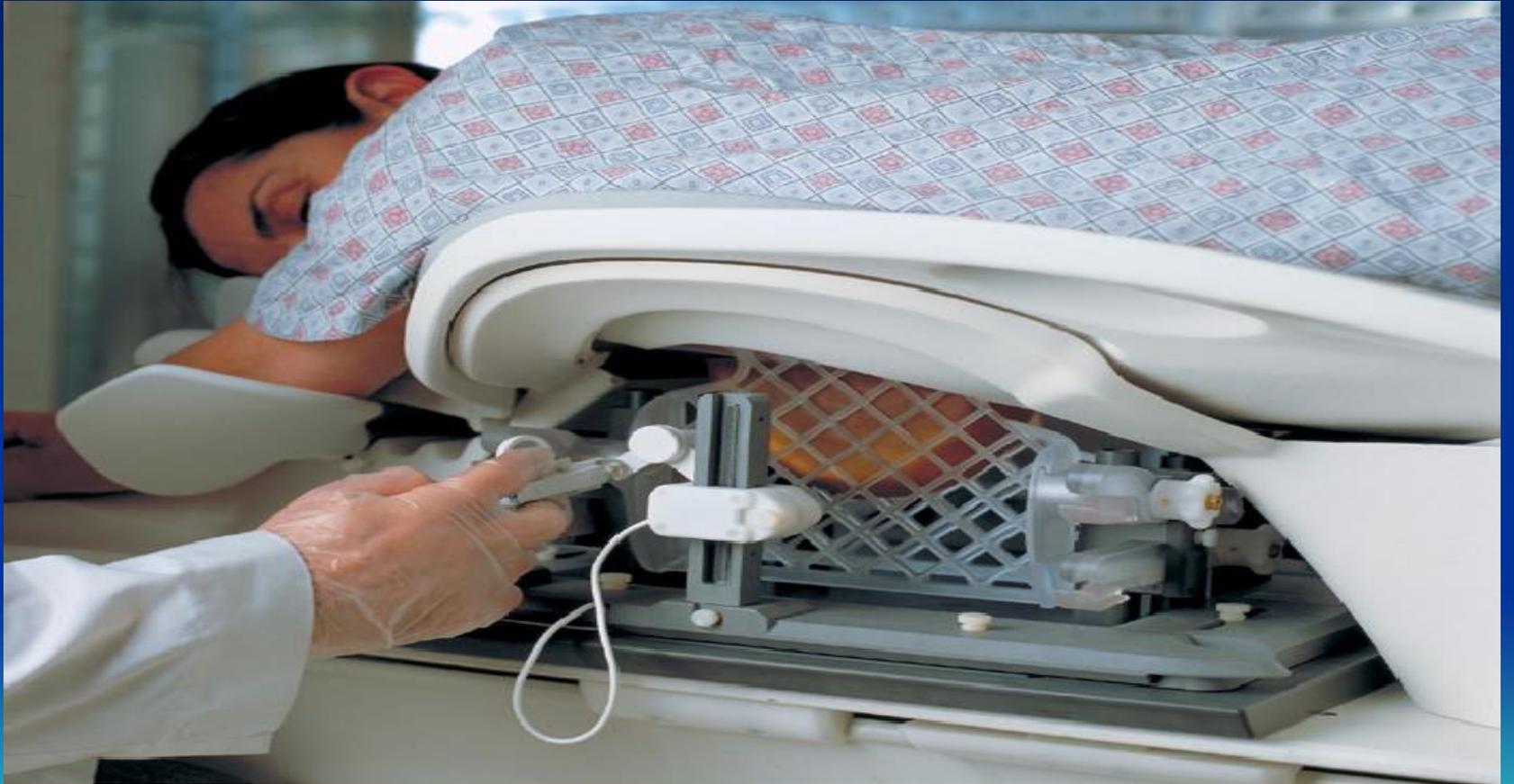
# Cost Analysis

- Computer generated models suggest that addition of annual screening MRI in BRCA1/2 carriers would result in a decrease in mortality by 23%
- Cost: 1<sup>st</sup> scan has resulted in:
  - up to 24% 6 month follow-up
  - up to 17% biopsy recommendation

Patient education is key

Research suggests that this is not a deterrent for those who choose surveillance only





## *Pre-Operative Ipsilateral Extent of Disease*

- Meta-analysis MRI demonstrates additional foci of disease in 16% patients
- Given that the IBTR in women with BCT at 10 years without preoperative MRI is < 10% preoperative MRI value is questionable
- On balance available data do not support that MRI improves pt selection for BCT or that it reduces negative margins at initial surgical excision or IBTR
- Invasive Lobular Carcinoma may be an exception...
  - One study on 267 patients demonstrated MRI lower re-excision rates by 9%
  - *Morrow et al. MRI in Breast Cancer Screening, Diagnosis and Treatment. Lancet 2011; 378: 1804–11*

# Contralateral Breast Cancer

- Studies have demonstrated contralateral synchronous cancer at MRI in 3-30% of patients
- This is higher than clinically observed nearly 50% on average have been DCIS
- Suggests they may not be clinically significant or that they would be treated with adjuvant systemic therapy
- Use of Tamoxifen associated with 62% reduction in contralateral cancer
- Currently in-sufficient evidence to suggest that the detection of contralateral cancers would change pt outcome



## Selection of Surgery after Neoadjuvant Chemotherapy

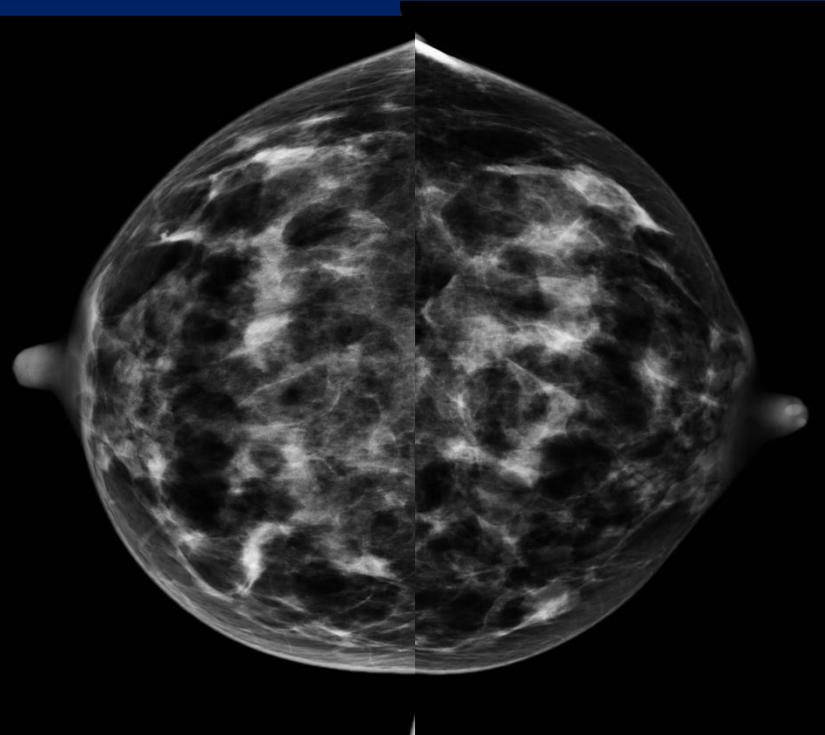
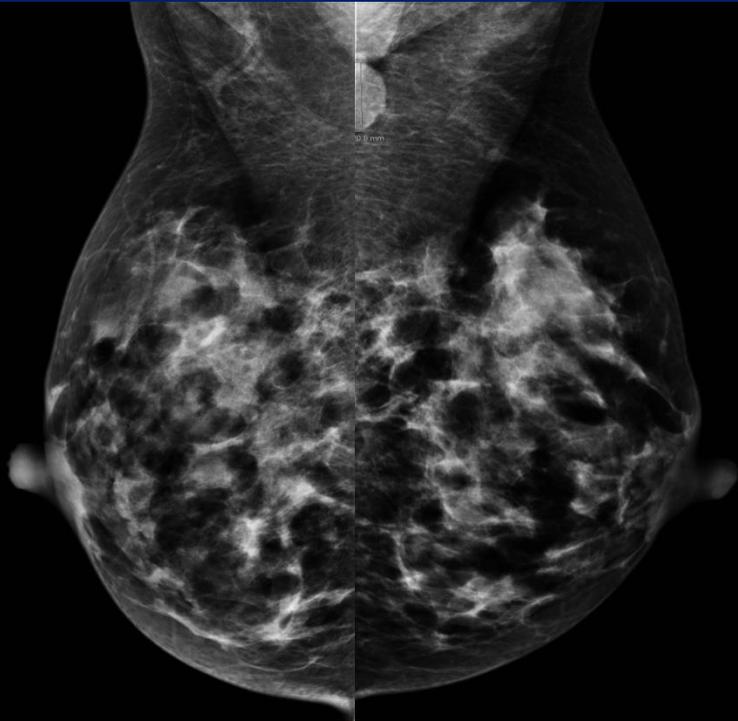
- MRI is more reliable than exam, mammo or ultrasound in predicting pathological complete response and size of residual tumor and LN
- However, there is insufficient evidence that this translates into improved ability to select patients for BCT over mastectomy

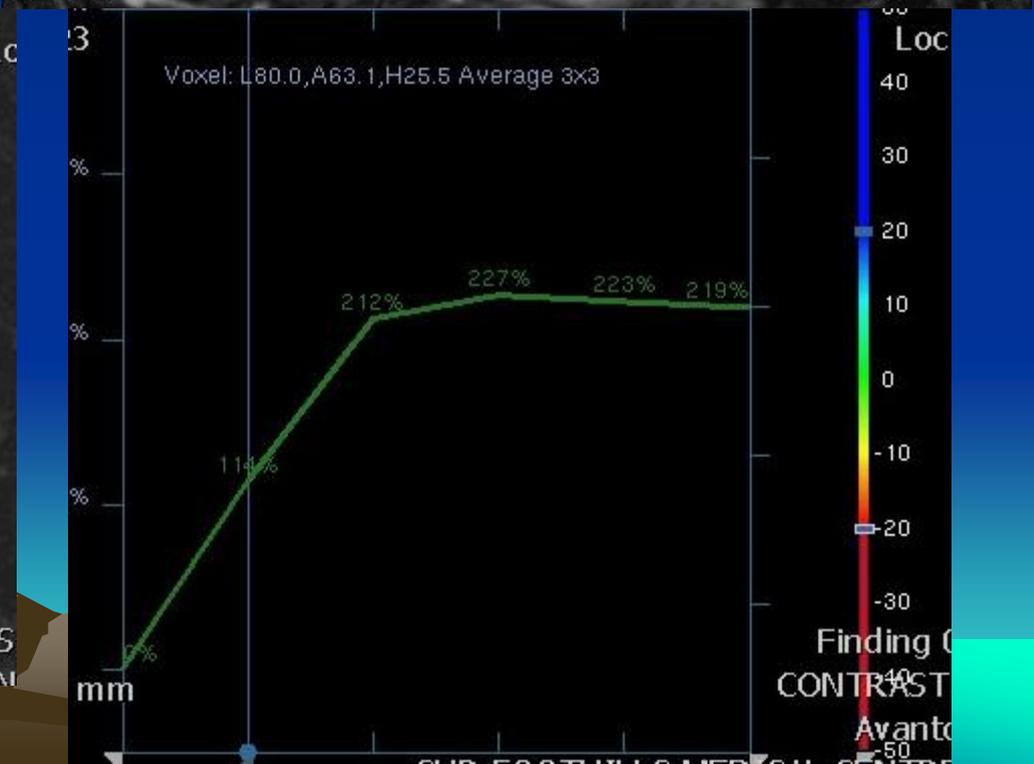
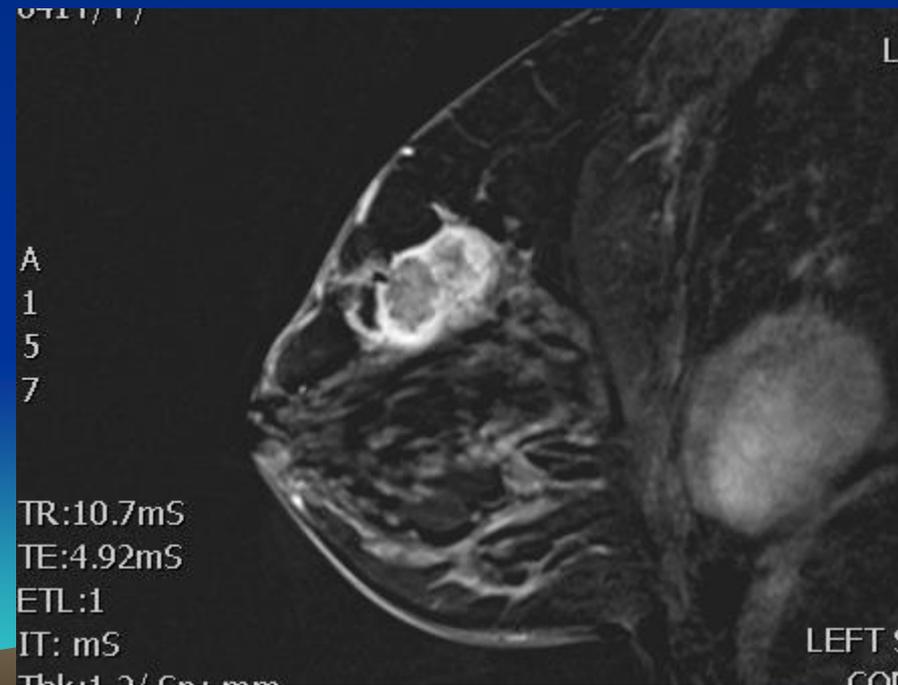
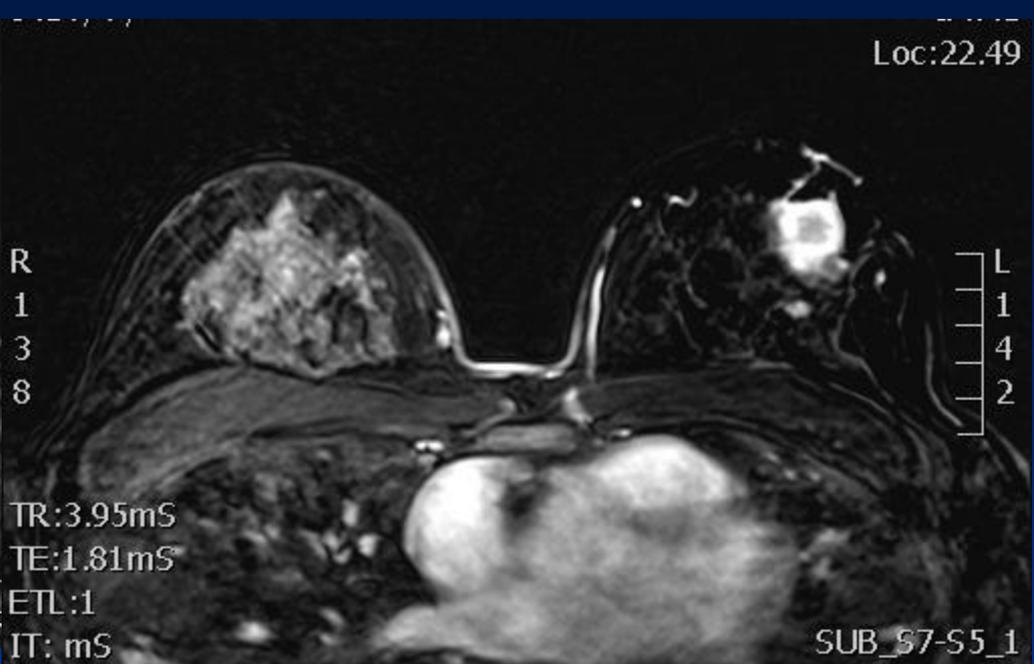
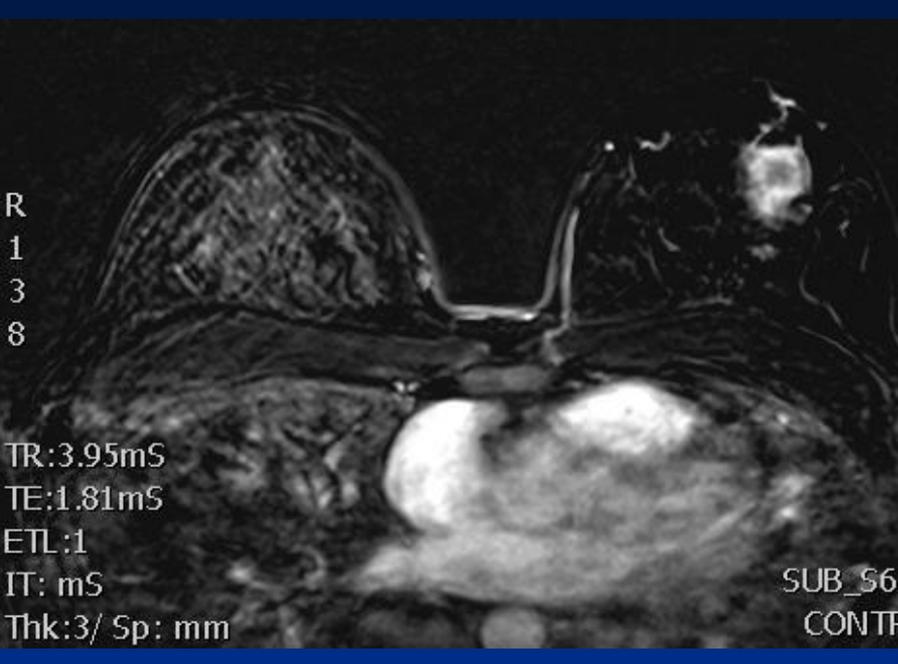


# Detection of Occult Primary

- Positive axillary node occurs from occult malignancy accounts for <1% of BC
- Pooled sensitivity of several small studies shows MRI to be 90% sensitive in detection of occult cancer
- Allows for lumpectomy and boost radiation







# Summary

- Mammography remains the mainstay of screening and the only screening modality to demonstrate a decrease in mortality
- Trend to tailor screening based on risk and density...despite lack of endpoint data
- Scattered and fatty breast for average risk women-mammography remains gold standard
- Breast Density as both a risk factor and its masking effect on mammograms has made it to “Prime Time”
- There is a need for objective density assessment and rational approach to supplemental screening tools such as AWBUS
- AWBUS may fill the gap as a supplemental screening tool for those with dense breasts and an intermediate risk level



# ....Everything Changes

