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**SCREENING YOUNG WOMEN
FOR BREAST CANCER**

Outline

- **Screening:**
 - a. Current guidelines vs. USPSTF vs ACS guidelines**
 - b. Why not screen < 50?**
 - c. Data **for** screening average risk women <50**
 - d. Screening young women at increased risk**
- **New technologies to improve screening of both groups**
- **Conclusions**

Screening guidelines 2016: average risk

SBI, ACR, ACOG: Current standard

- Annual mammography beginning at 40 until life expectancy < 5 yrs.
- Yearly clinical breast exams

ACS

- Annual mammography from 45-54- but can begin at 40
- Transition to every 2 years after 55 until life expectancy <10 yrs. but can do yearly
- No breast exam by MD, no self exam

USPSTF

- 40-49 discuss w/ MD
- Biennial from 50-74
- No self exam

Why not mammography < 50?

- Missed cancers/dense breasts
- Call backs/ false positives leading to anxiety more frequent in young women
- Not as much mortality reduction
- “Over diagnosis”

Must discuss mortality AND morbidity

Data FOR screening younger women

Average risk women from 40-49

- **Screening of Young Women (SCRY): 1986-2005**
 - **Compared women invited vs. not invited to screening**
 - **16 year F/U**
 - **26-29% mortality reduction-higher for those actually screened**
 - **Higher reduction in those 45-49**
-
- **Hellquist et al Cancer 2010**

Average risk women from 40-49

- Longitudinal prospective cohort 1990-2008 compared mammo detected to MD or pt. detected cancers
- N=1977
- Mammo detected more likely to be conservable $p < 0.001$
- Mammo detected less likely to receive chemo $p < 0.001$
- 5 yr relapse free survival mammo detected 92% vs. 88% $p < 0.001$

NY experience: 2007-2010

- 43,351 mammos: 1/3 in their 40's
- 205 cancers: 20% in their 40's
- > 50% of cancers in women in their 40's were invasive

- Arleo et al AJR 2013

Average risk women from 40-49

- Retrospective 2008-2011
- N= 230 patients w/ breast cancer
149 screened/81 non -screened
- Screened vs. non-screened:
 - Earlier stage $p= 0.001$
 - Negative nodes $p=0.005$
 - Smaller tumors $p<0.001$
 - Mastectomy: 48% non-screened vs. 30% $p=0.1$
 - Chemo: 66% vs. 44% $p=0.042$

% Breast cancer mortality reduction vs. # mammograms/1000 women

The 6 “Best” Models:

USPSTF	D	E	G	M	S	W	#
Biennial 50-74:	22%	27%	21%	21%	20%	28%	11,000
STANDARD							
Annual 40-84:	38%	49%	32%	29%	35%	54%	36,500

For 25,000 more mammograms/1000 women:
6 Model Average Increased Mortality Reduction by 16.3%

[Cancer Intervention and Surveillance Modeling Network](#)

CISNET modeling

- Adding annual mammo of women 40-49 to biennial screening 50-74 increases lives saved by 27%
 - Increases life years gained by 47%
 - Saves 42% more lives & life years than biennial mammo
 - Need to screen 588 women to save 1 life w/ annual digital mammo in this age group
-
- Hendrick et al AJR 2014

**Average risk women under 50
should be screened annually**

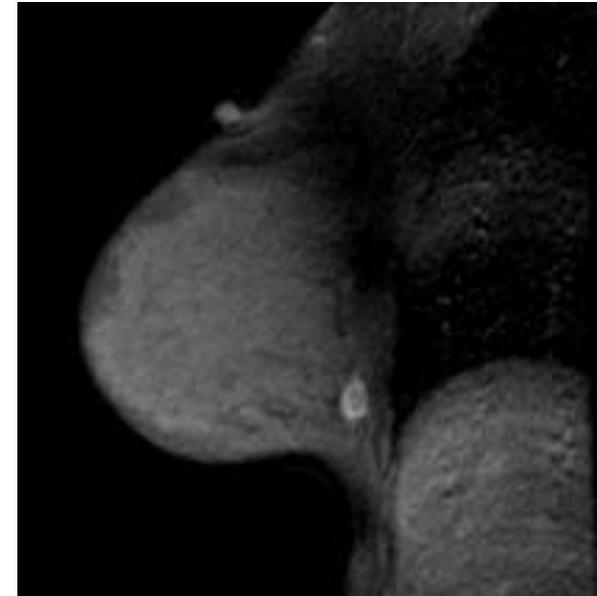
American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography

Debbie Saslow, PhD; Carla Boetes, MD, PhD; Wylie Burke, MD, PhD; Steven Harms, MD; Martin O. Leach, PhD; Constance D. Lehman, MD, PhD; Elizabeth Morris, MD; Etta Pisano, MD; Mitchell Schnall, MD, PhD; Stephen Sener, MD; Robert A. Smith, PhD; Ellen Warner, MD; Martin Yaffe, PhD; Kimberly S. Andrews; Christy A. Russell, MD (for the American Cancer Society Breast Cancer Advisory Group)

- **BRCA 1 or 2 mutation**
- **Untested first-degree relative of BRCA carrier**
- **Lifetime risk $\geq 20\%$**
 - **Defined by BRCAPRO**
 - **Other models dependent on family history**
- **Chest XRT – 10 to 30 years of age**

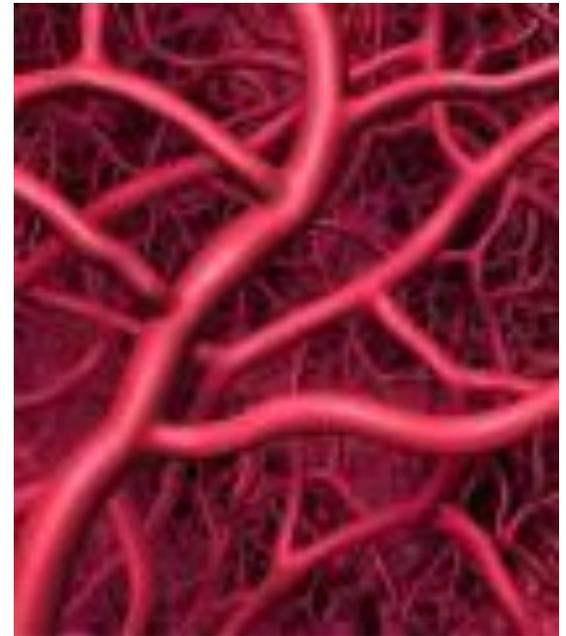
Breast MRI

- **Breast MRI: most sensitive imaging test for breast cancer detection**
- **Sensitivity due to imaging of enhancing neovascularity**
- **Limitations include cost (>\$4,000.00), claustrophobia, inability to perform in women w/ metallic implants, Gadolinium allergy & lack of specificity**
- **Not universally available**



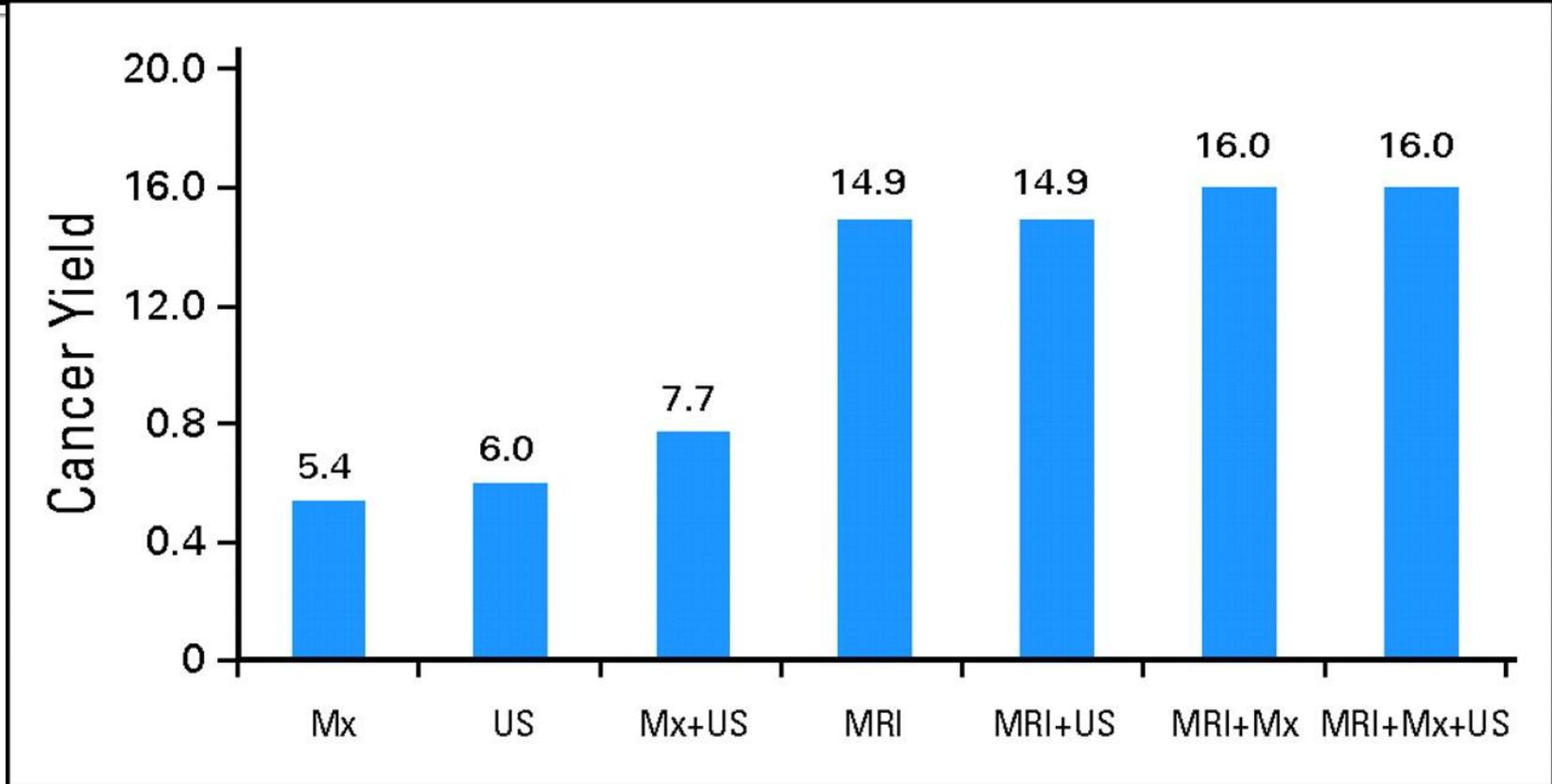
How do we identify cancers on MRI?

- Tumors create new vessels (angiogenesis)
 - VEGF
 - Vessels leak
 - A-V shunting



Courtesy of Dr. Elizabeth Morris

Cancer yield of different imaging methods, used alone or in combination.



Kuhl C et al. JCO 2010

BRCA 1 & 2 patients (n=1275)

	MRI (n=445)	No MRI (n=830)	p
Cancer	41 (9.2%)	76 (9.2%)	
DCIS/stage 1	13.8%	7.2%	0.01
Stage II-IV	1.9%	6.6%	0.02

Dutch MRISC study

N=2157, risk >15%

- BRCA 1 58% <40; 9.7%<30
- **More interval cancers in younger patients**
- 43% cancers detected only on MRI
 - 46% of ca in BRCA 1
 - 31% of ca in BRCA 2
 - 41% of ca in high risk
 - 47% in moderate risk
- 9 mm median, 62% ≤ 1 cm
- 93% overall survival vs. 74.5% in 26 historical cohorts

Do we need mammo at all?

N=1275

MORTALITY REDUCTIONS:

- **Mammo alone vs. Mammo + MRI**

BRCA1 41.9% vs. 50.1%

BRCA2 46.8% vs. 61.6%

- **MRI alone**

BRCA1 49.0%

BRCA2 61.0%

<40: 1 invasive cancer detected by mammo only: BRCA1 pt. vs. 7 in BRCA2 carriers

Mutation carriers MSKCC

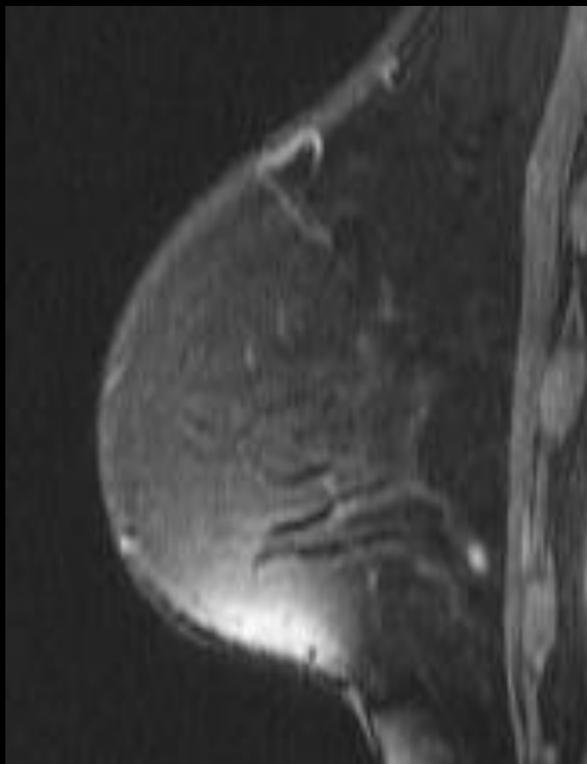
- **N= 516 w/ breast cancer**
- **159 < 40**
- **Breast MRI detected 97% of all cancers**
- **Mammo detected 79% BRCA 1 & 87% BRCA 2(p=0.03)**
- **Only 1 BRCA1 patient under 40 had cancer detected on mammo & not MRI**

Krammer...Jochelson to be presented ECR 2016

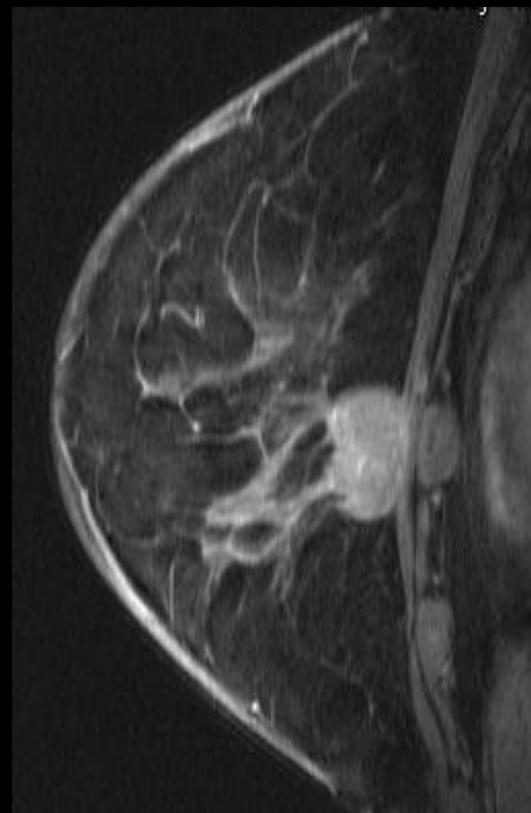
Frequency of screening for mutation carriers

- **Not completely resolved**
- **Early data seem to suggest MRI/mammo should be done separately at 6 month intervals rather than both at the same time yearly**

BRCA 1



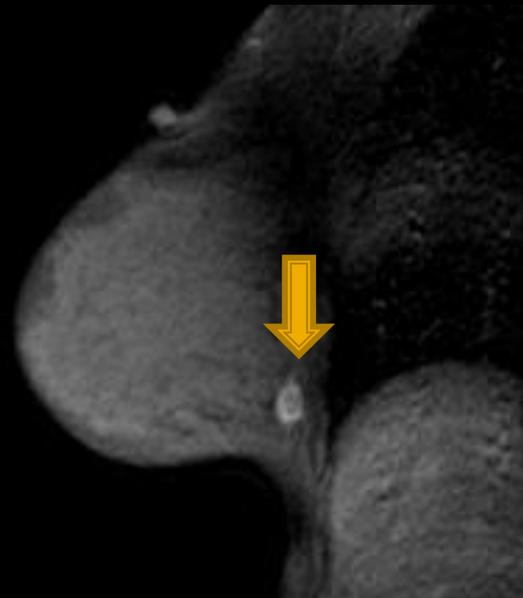
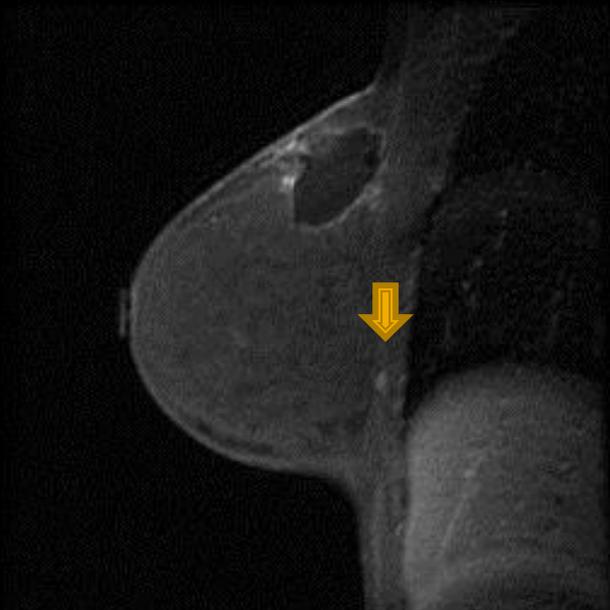
11/14/2005 BIRADS 2



7/7/2006 BIRADS 6

Mitch Schnall MD PhD

BRCA 2



5 month interval

Intermediate risk/ dense breasts

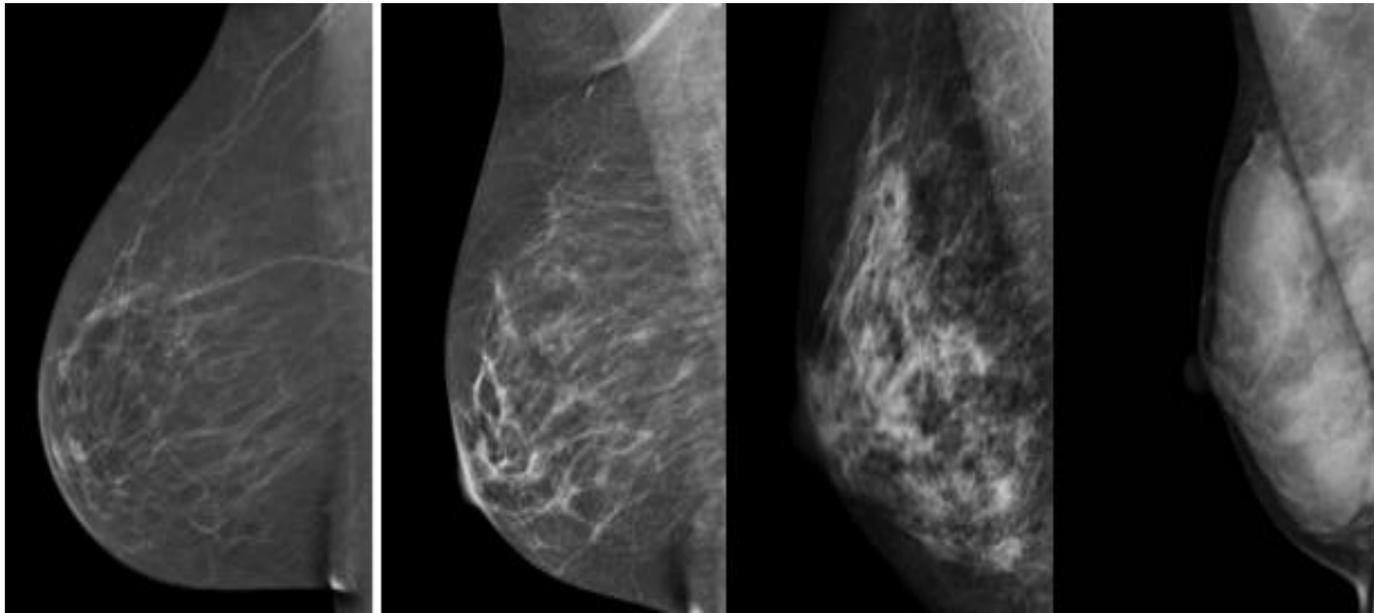
- **Personal history**
- **Family history**
- **ADH**
- **LCIS**
- **Dense breasts**

Mammo &??????

- **DATA FREE ZONE regarding BEST tests to do**

Dense breast problem

- Two- fold issue
 1. 4-6 fold increased risk of breast cancer in women w/ extremely dense breasts c/w fatty breasts
 2. Lower sensitivity of mammography in women w/ dense breasts leading to missed & interval cancers



Background National legislation is under consideration that would require women w/ mammographically dense breasts to be informed of their breast density & encouraged to discuss supplemental breast cancer screening w/ their health care providers. The number of US women potentially affected by this legislation is unknown.

Methods We determined the mammographic breast density distribution by age & body mass index (BMI) using data from 1,518,599 mammograms conducted from 2007 through 2010 at mammography facilities in the Breast Cancer Surveillance Consortium (BCSC). We applied these breast density distributions to age- & BMI-specific counts of the US female population derived from the 2010 US Census & the National Health & Nutrition Examination Survey (NHANES) to estimate the number of US women w/ dense breasts.

Results Overall, 43.3% (95% confidence interval [CI] = 43.1% to 43.4%) of women 40 to 74 years of age had heterogeneously or extremely dense breasts, & this proportion was inversely associated w/ age & BMI. Based on the age & BMI distribution of US women, we estimated that 27.6 million women (95% CI = 27.5 to 27.7 million) aged 40 to 74 years in the United States have heterogeneously or extremely dense breasts. **Women aged 40 to 49 years (N = 12.3 million) accounted for 44.3% of this group.**

Conclusion **The prevalence of dense breasts among US women of common breast cancer screening ages exceeds 25 million.** Policymakers & healthcare providers should consider this large prevalence when debating breast density notification legislation & designing strategies to ensure that women who are notified have opportunities to evaluate breast cancer risk & discuss & pursue supplemental screening options if deemed appropriate.

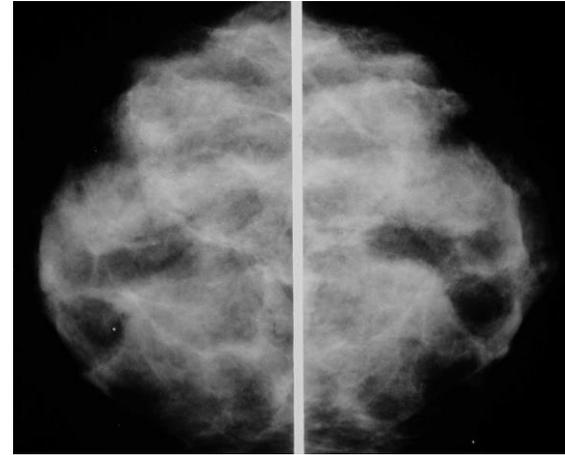
Screening ultrasound

Current default:

- Based on anatomy
- No radiation exposure
- Readily available
- “Inexpensive”

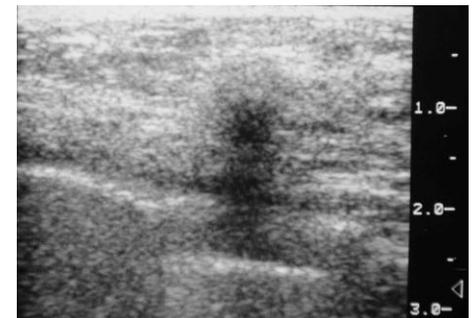
US

**4,897 WOMEN
DENSE BREASTS
31 CANCERS**



3/1000 (0.3%) CANCER DETECTION RATE

Kolb et al. 2002



ACRIN 6666 screening US

- **N=2637 women**
- **Dense breasts + 1 other risk factor**
- **~3.7 cancers per 1000**
- **Invasive cancers– not DCIS**
- **All but 1 node negative**
- **8% biopsy recommendation**
- **9% short term follow up**
- **7.4% positive biopsy rate**

J-START

- **N= 72,998 Japanese women 40-49 randomized to US or no US after mammo**
- **Average risk/ dense breasts**
- **Sensitivity: 91.1% vs 77% p=0.0004**
- **Specificity: 87.7% vs 91.4% p=0.0001**
- **# of cancers 184 vs 117**
- **Cancers in US group more frequently Stage 0/1 p=0.0194**
- **Will follow for survival advantage**

Is ultrasound really inexpensive?

- Initial data from Connecticut experience
- N= 72,030 mammograms & 8,647 ultrasounds
- 28 mammographically occult cancers: 3.25/1000
- PPV: 6.7%
- BIRADS 3: 9%
- US charge \$250-reimbursed \$72
- Professional fee \$85 reimbursed \$30
- Core \$2,400

- **\$110,241.00 billed; \$60,000 paid/ breast cancer detected**

- Weigert et al The Breast Journal 2012

Is ultrasound really inexpensive?

- N= 935 w/ mixed risks & breast densities
- 3.2 cancers/1000 women screened
- Some were diagnostic patients
- PPV 6.5%
- 187 BI-RADS 3: 47 BI-RADS 4

- \$60,267/ cancer diagnosed (likely more since some patients were diagnostic)

- Hooley et al Radiol 2012

Screening MRI after combined US & mammo x 2 y: ACRIN 6666

- 16/612 (2.6%) breast cancer detected
- 12 (75%) invasive
- 14.7 additional cancers per 1000 women screened
- 9/16 (56%) seen only on MRI
 - 8/9 (89%) invasive (median 9 mm)
 - all node negative
- 2 (13%) not seen on MR, both DCIS

Tomosynthesis (DBT)

- **Technology based on anatomy**
- **Peels away overlying tissues**
- **Lesion conspicuity improves**
- **Improved margin feature analysis**
- **Detection of additional lesions**
- **May show normal tissue when mass suspected**

 **Improves sensitivity & specificity in both dense & fatty breasts**

Mammo vs. mammo + tomo: screening

- **N=12631**
- **Prospective trial**
- **Better detection rates: mammo alone 6.1/1000 vs. mammo + tomo 8.0/1000**
- **25(40%) additional INVASIVE cancers detected w/ combo**
- **No change in DCIS detection**
- **15% decrease false positives for combination**

Recall rates

	Reader Study	DM	DM+Tomo
Non-Cancer	1	55.1%	16.7%
	2	48.8%	30.1%
Cancer	1	87.2%	80.4%
	2	84.8%	85.7%

STORM trial

- **Prospective comparison study of 7292 women screened between August 2011- June 2012**
- **CA detection rate:**
 - **MG: 5.3/1000**
 - **MG+DBT: 8.1/1000**

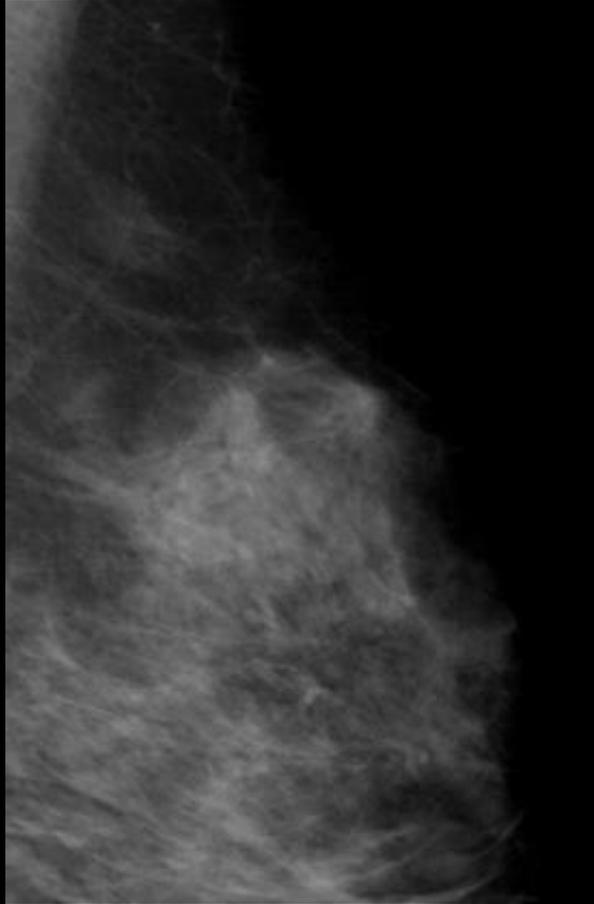
Connecticut Study

- N=13,158 at 4 sites: 7,058 MG/6100 MG+DBT
- Recall rate:
 - MG: 12.0%
 - MG+DBT: 8.4%
- Decreased recall rates for DBT among all breast densities and age groups
- Detection of cancer:
MG: 5.2/1000
MG+DBT 5.7/1000

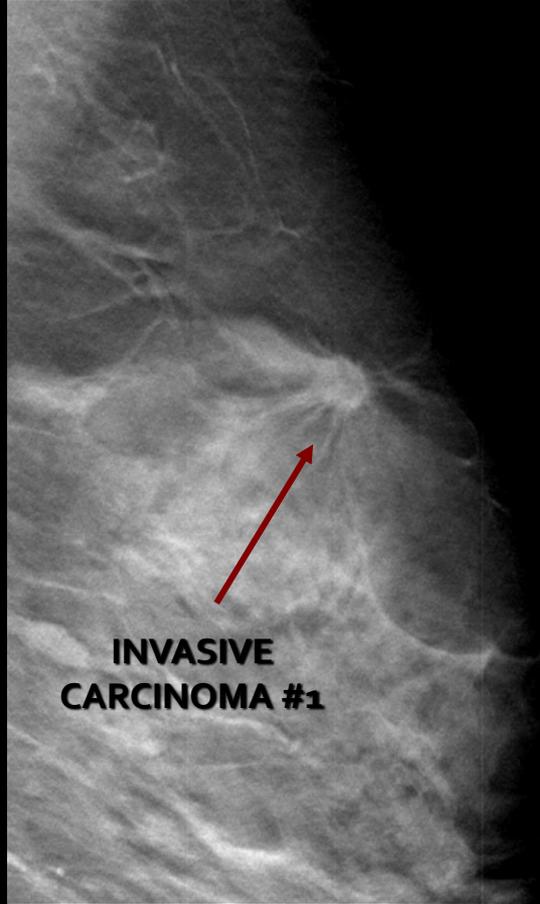
Retrospective multicenter trial

- FFDM: 281,187 vs DBT/FFDM: 173,663
 - Both academic & private practices
 - Recall rate: 10.7- 9.1%: significant
 - Detection rate: 4.2/1000-5.4/1000: significant
 - PPV for recall: 4.3% -6.4%
-
- Friedenwald et al JAMA 2014

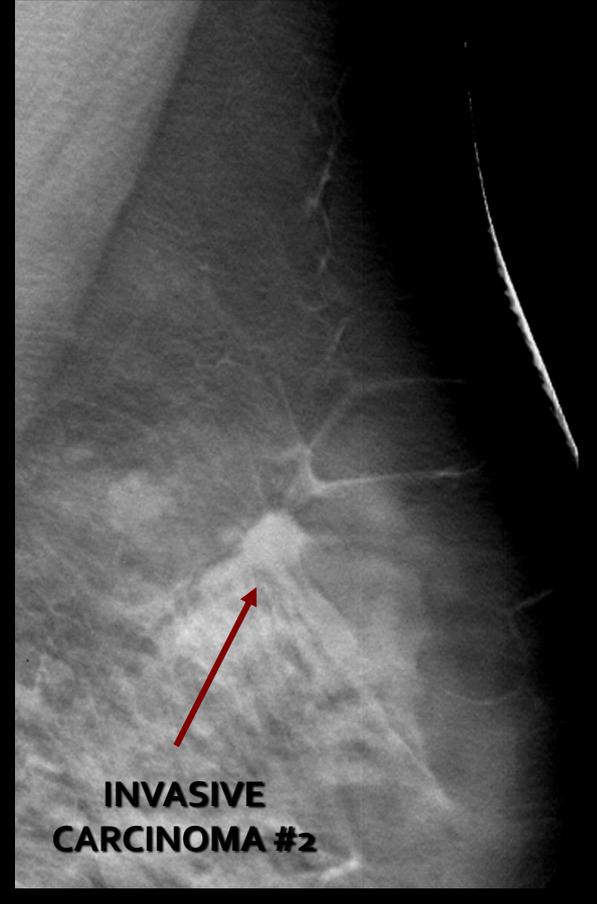
**CONVENTIONAL
MAMMOGRAM**



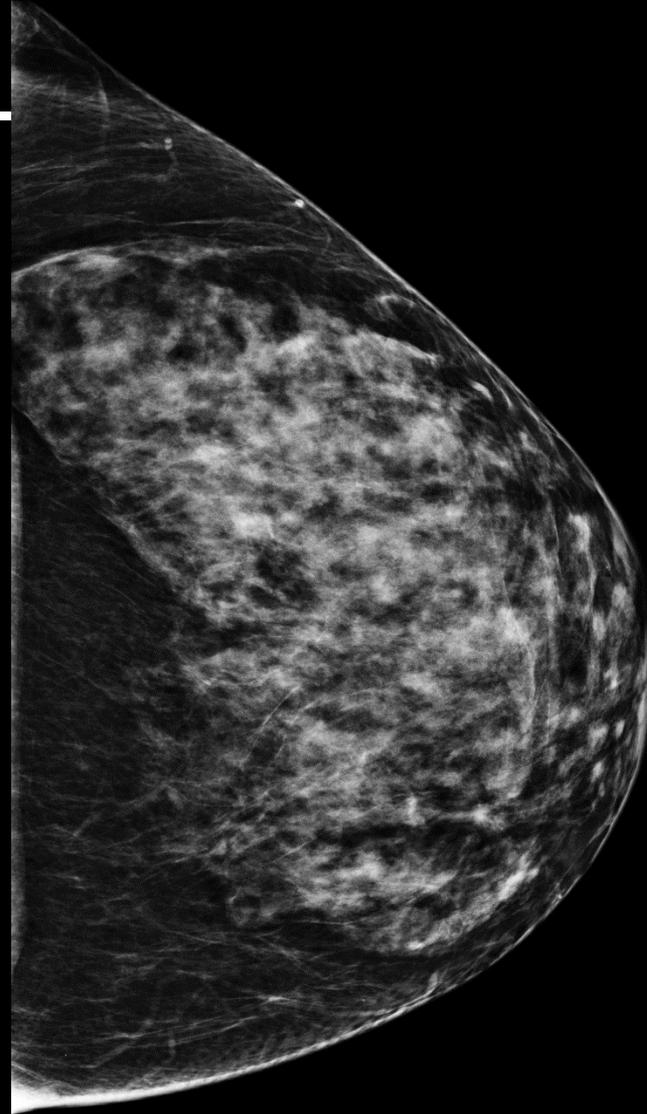
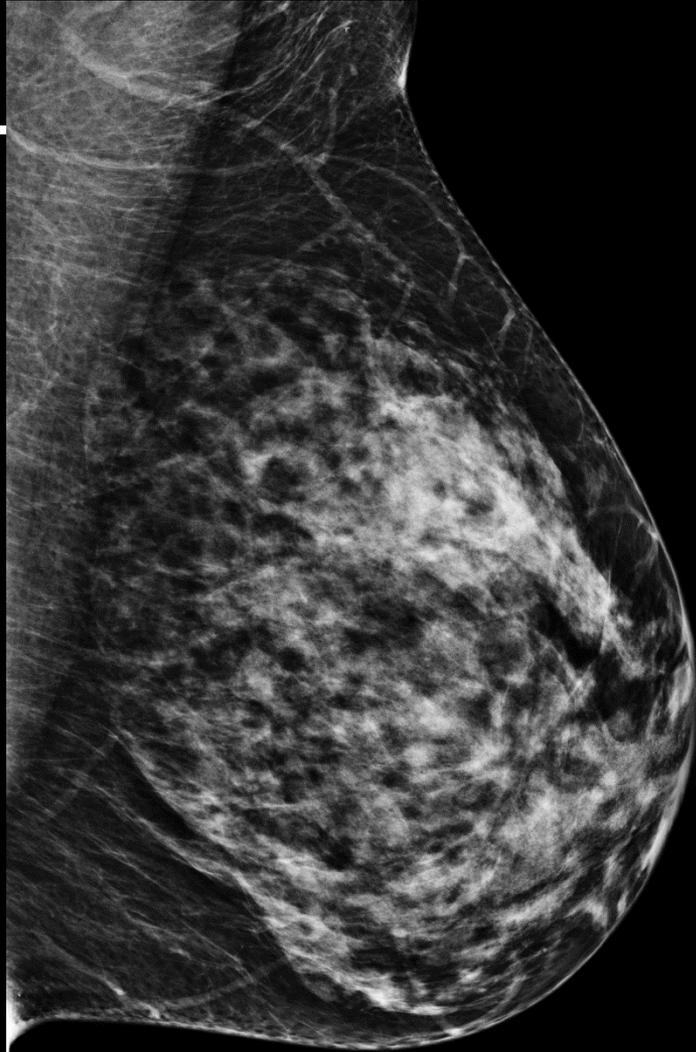
**TOMOSYNTHESIS
SLICE 1**



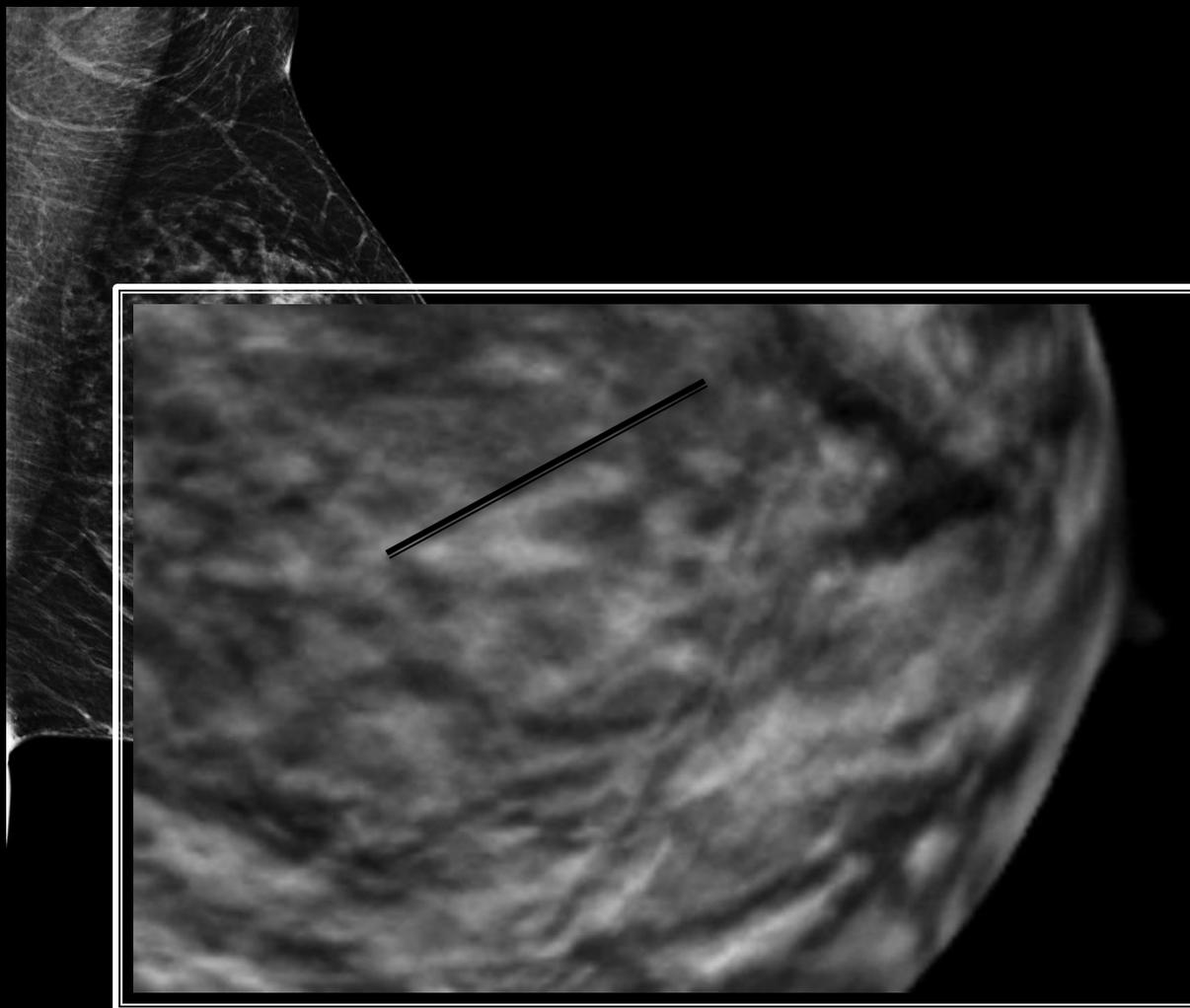
**TOMOSYNTHESIS
SLICE 2**

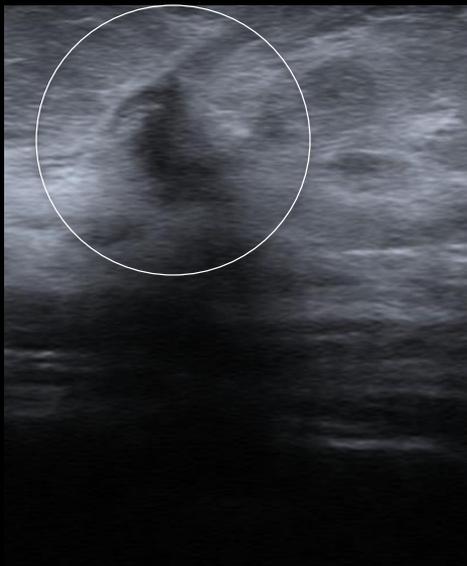


MLO and CC Views

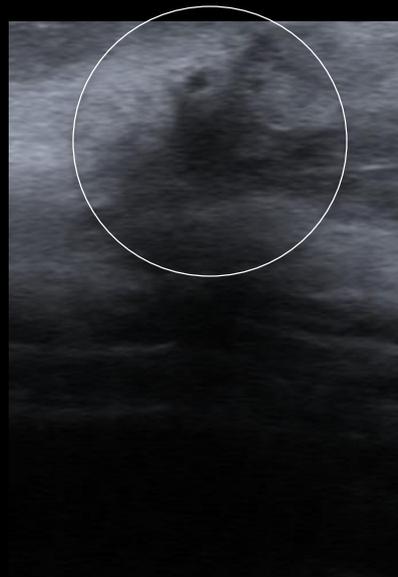


Tomosynthesis

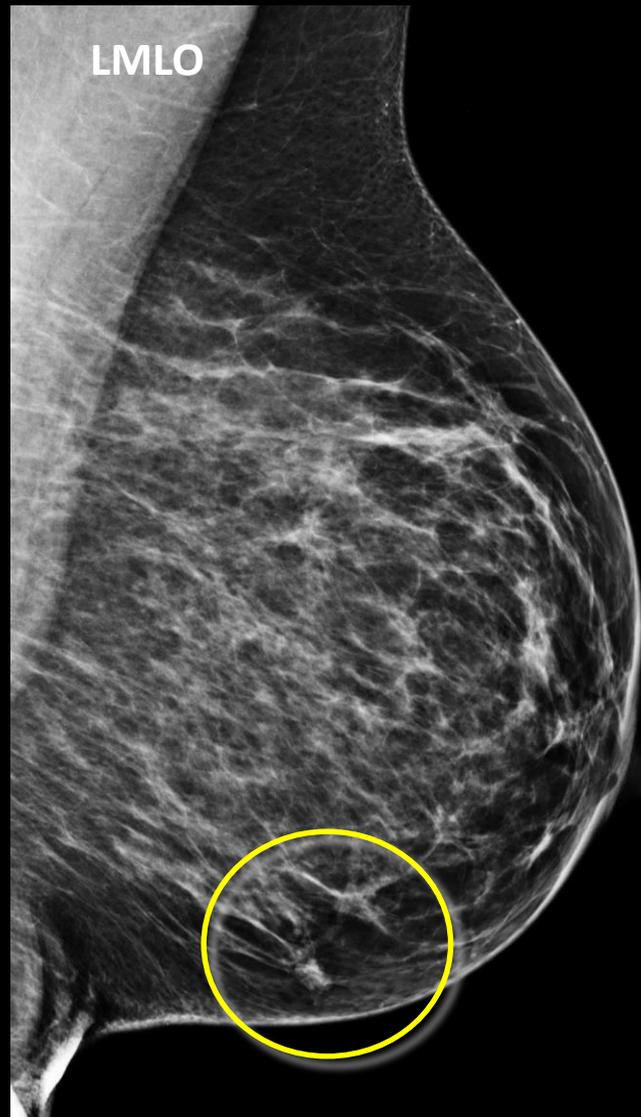




9:00 2 CM FN ANTI-RADIAL



9:00 2 CM FN RADIAL |

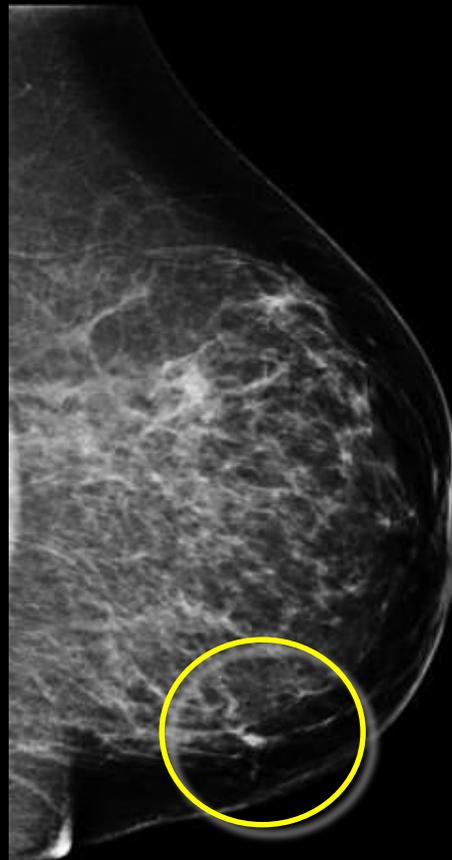


LMLO

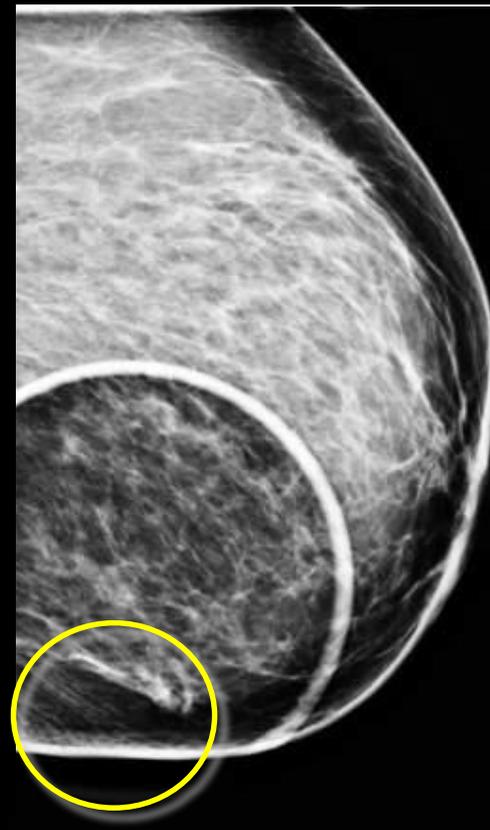
Courtesy of Janice Sung
MD



LMLO

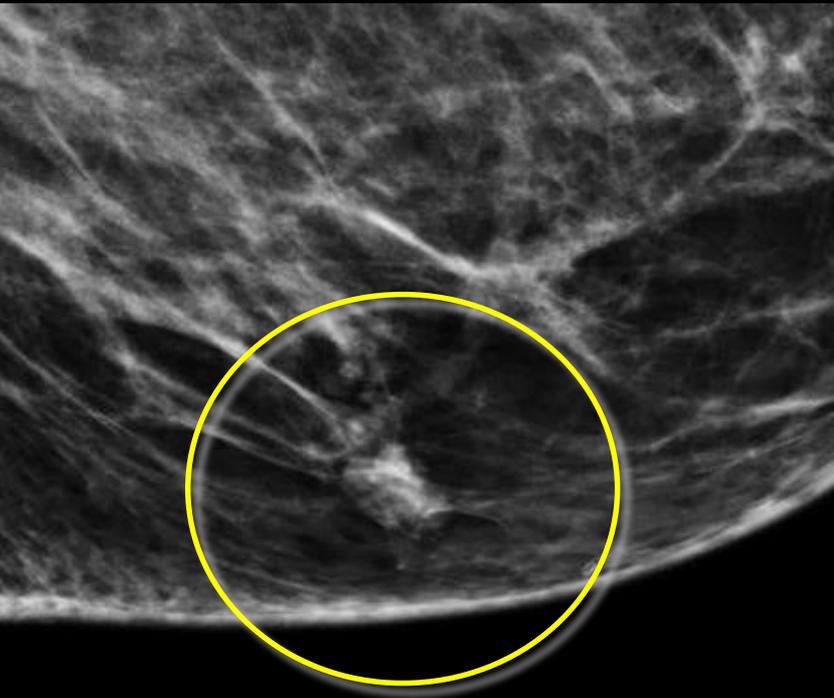


LLM

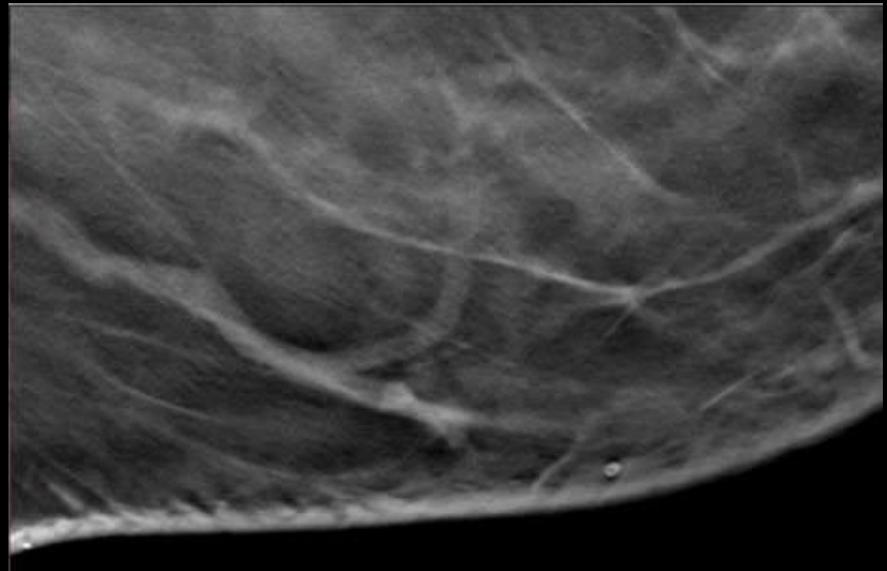


LSMLO

Digital Mammo (2D)



Tomo Slices (3D)



Tomosynthesis

- Detects ~additional 1 to 2 cancers/1000
- Fewer call backs
- PPV improved
- Twice the radiation exposure/ still w/i guidelines
- Takes longer to read
- More expensive
- May replace full field digital mammography for routine screening

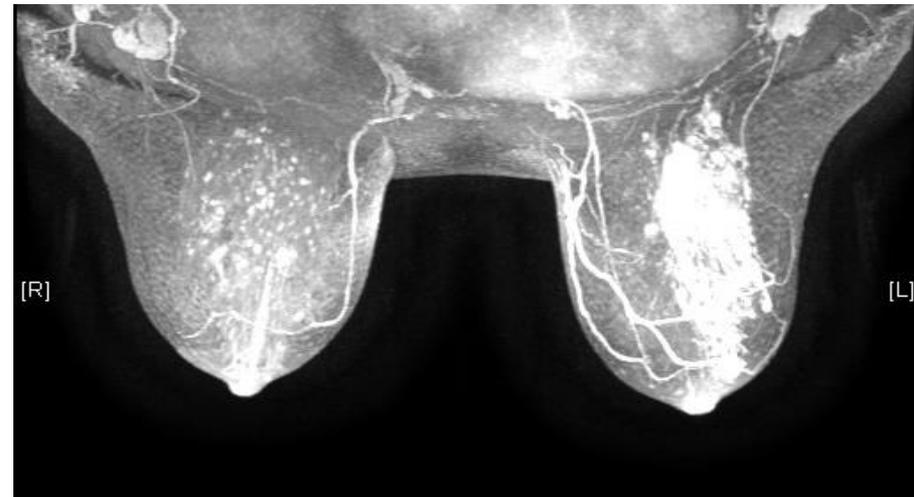
Abridged breast MRI

- Abridged MRI screening protocol could:
 - Decrease magnet & technologist time
 - Decrease reading time
 - Decrease cost, possibly making MRI more accessible

Abridged MRI

- Prospectively read 606 screening MRIs in 443 women
- Protocol 3 minutes vs. 17 for full exam
- Full abbreviated protocol 28 seconds to read
 - Sensitivity 100%, Specificity 94.3%
- MIP: 2.8 seconds to read
 - Sensitivity 90.9%

- Kuhl et al J Clin Oncol 2014



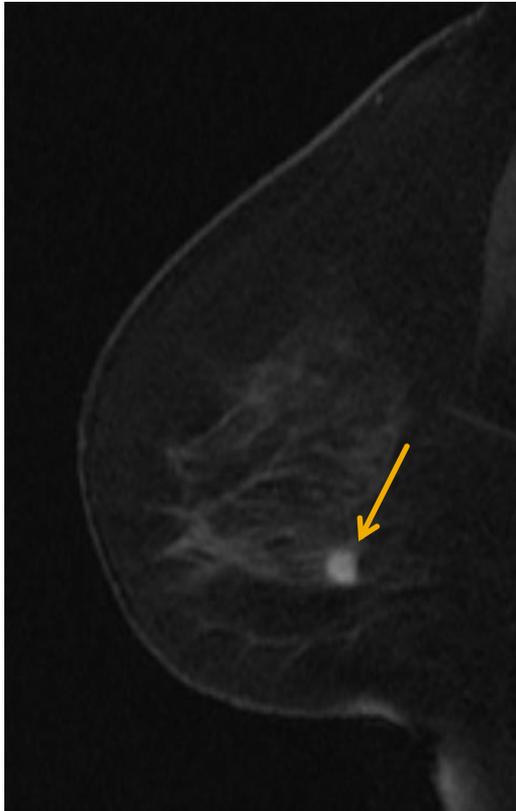
Abridged Breast MRI

- **N= 100 patients w/ known cancers**
- **3 sequences evaluated (15 min to perform) (mean 59 seconds to read)**
- **>95% of cancers visualized on a single MRI sequence**
- **Sensitivity increased to 100% w/ history & prior exams**

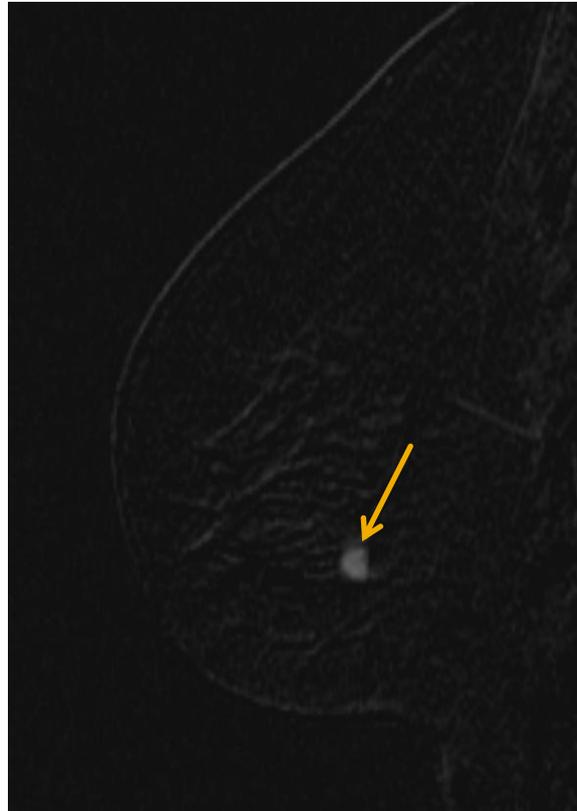
- **Mango et al Eur J Radiol 2014**

Abridged MRI: screen detected cancer

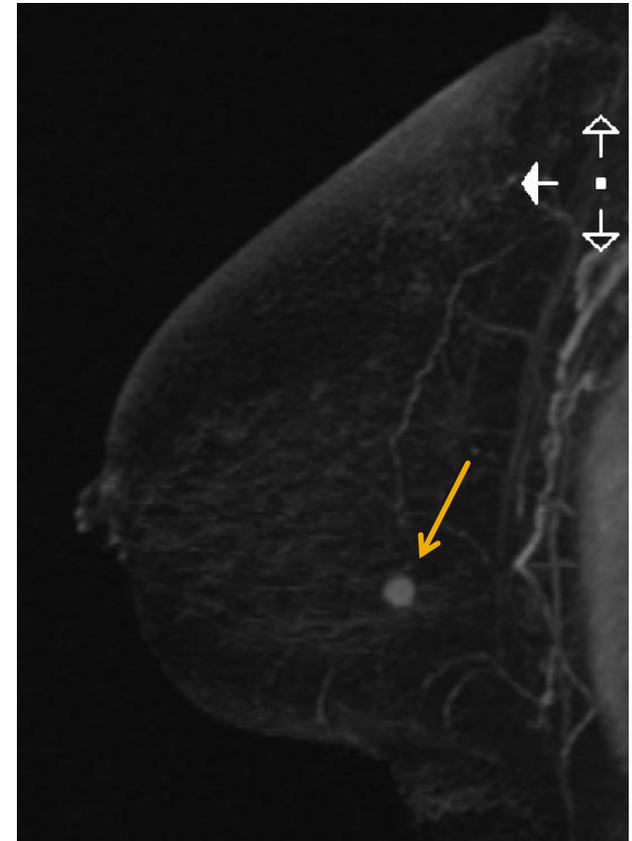
First post-contrast



First post-contrast sub



Subtraction MIP



59 y/o female w/ contralateral breast carcinoma. New 1 cm irregularly enhancing mass in LLOQ: IDC

Mango et al

BUT

- **MRI not universally available**
- **Certain patients cannot have MRI due to metallic implants, claustrophobia or allergy to gadolinium**
- **Very expensive**
- **Too many false positives**

**Based on MRI's ability to detect blood flow for
better cancer detection**

Contrast Enhanced Mammography

Intravenous contrast

- **Omnipaque 350; 1.5 ml/kg (CT contrast)**
- **Injected via power injector: 3ml/sec.**
- **First imaging ~ 3 minutes post-injection**
- **4 views with high and low energy images obtained w/i 5 minutes of completed injection**
- **Images processed by subtracting out background tissue**

What are the risks ?

- **Iodinated contrast administration**
 - a. Follow criteria for CT contrast administration**
 - b. Patients have reactions to Gadolinium too**
- **Radiation dose ~20% > routine screening mammogram or the equivalent of one extra image**

CESM

- **>100,000 performed world wide**
- **44 U.S CESM installations: some w/ > 1 unit**
- **BAIC/MSKCC volume:**

2013: 110

2014: 207

2015: 652

Early CESM data

- **N=120**
- **UNILATERAL CESM + mammo c/w mammo or mammo + US:**
- **Pts recalled from screening or problem solving**
- **Sensitivity: CESM 93% vs mammo 78%**
- **26% benign lesions enhanced**
- **CESM + mammo > mammo alone (p=0.045) & mammo + US (trend)**
- **CESM + mammo significantly more accurate than mammo + US due to better specificity**

Dromain et al Eur Radiol 2011

(Confirmed in multireader study: Breast Cancer Research 2012)

BILATERAL CESM IN KNOWN CANCER

■ MAMMOGRAPHY:	■ 42/52 (81%)
■ CESM:	50/52 (96%)
■ MRI:	50/52 (96%)

Contrast mammography: dense breasts

- Multireader study of mammo vs. contrast mammo
- N=70 pts w/ at least 1 suspicious lesion
- Sensitivity improved from 35% to 59%

- Diekmann et al Eur J Radiol 2011

CESM in dense breasts

- 89 Patients w/ dense breasts
- 100 lesions
- Low energy images were read blinded to post contrast images
- With CESM, sensitivity improved from **71.5% to 92.7%**
- Specificity improved from **51.8% to 67.9%**

Cheung et al Eur Radiol 2014

CESM in Normal Risk Screening Patients: 113 pts w/ Abnormal Screening Mammos

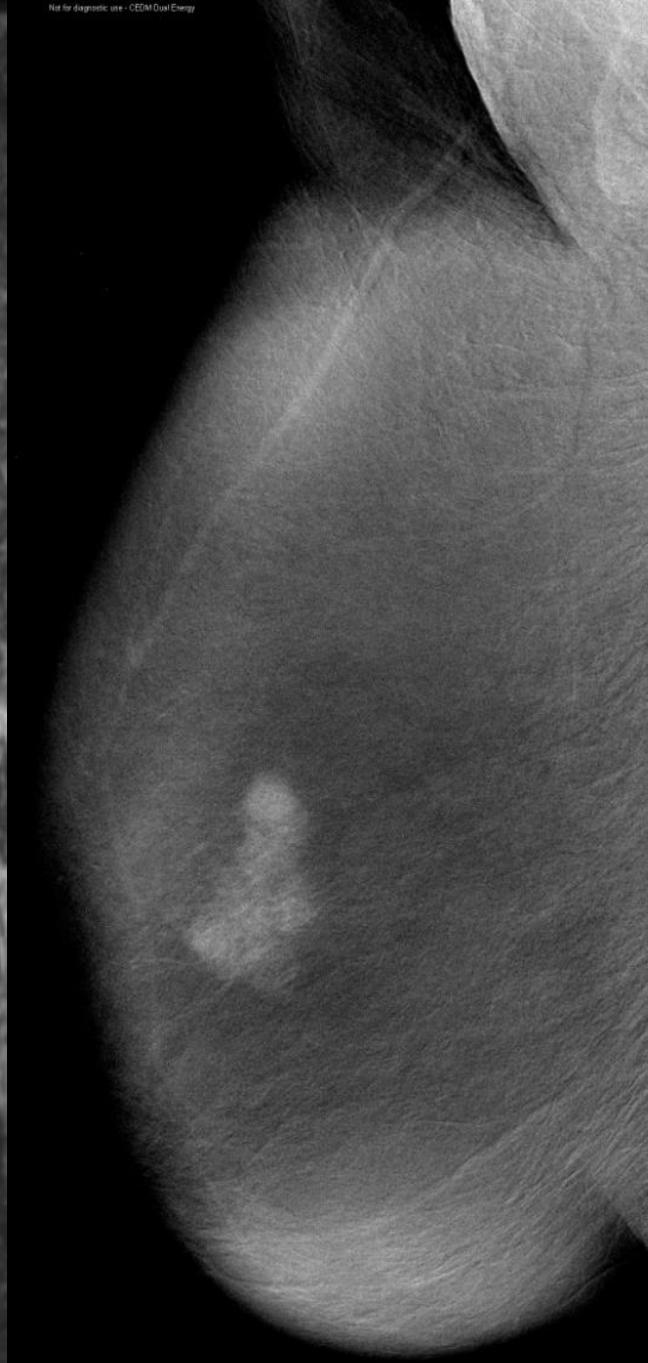
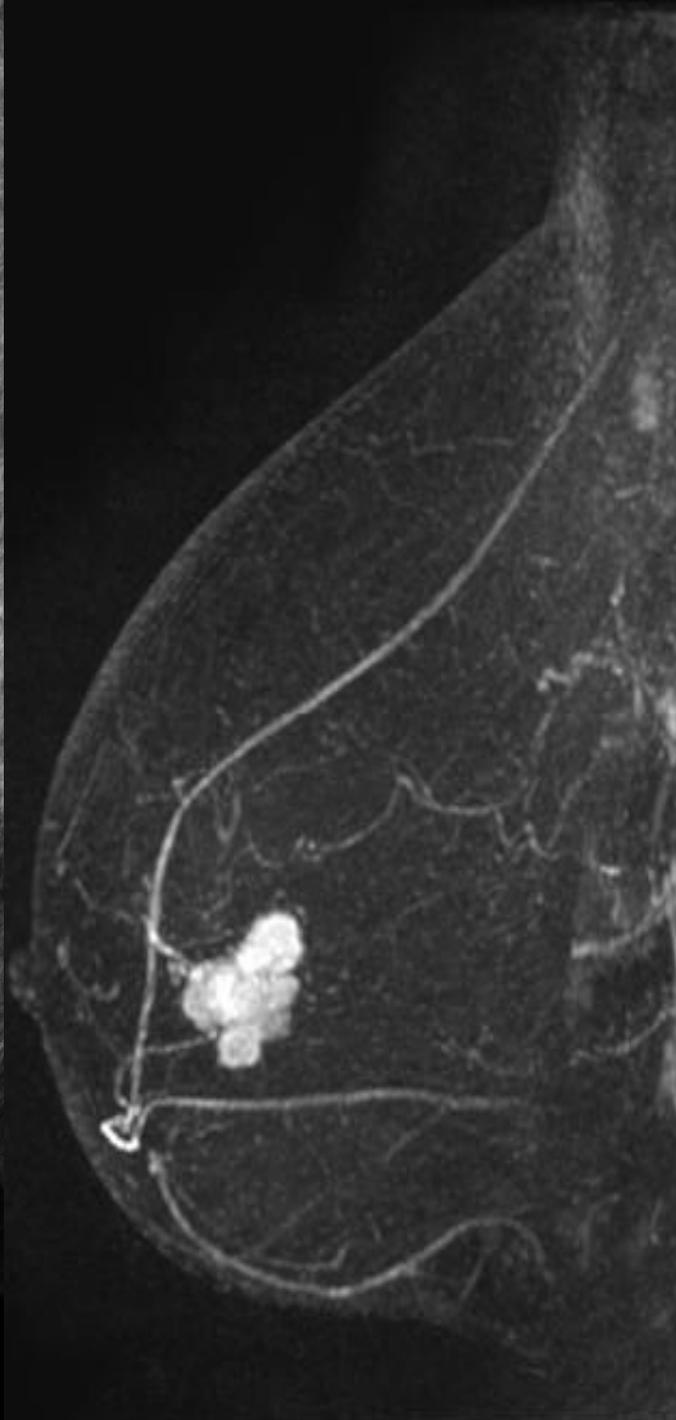
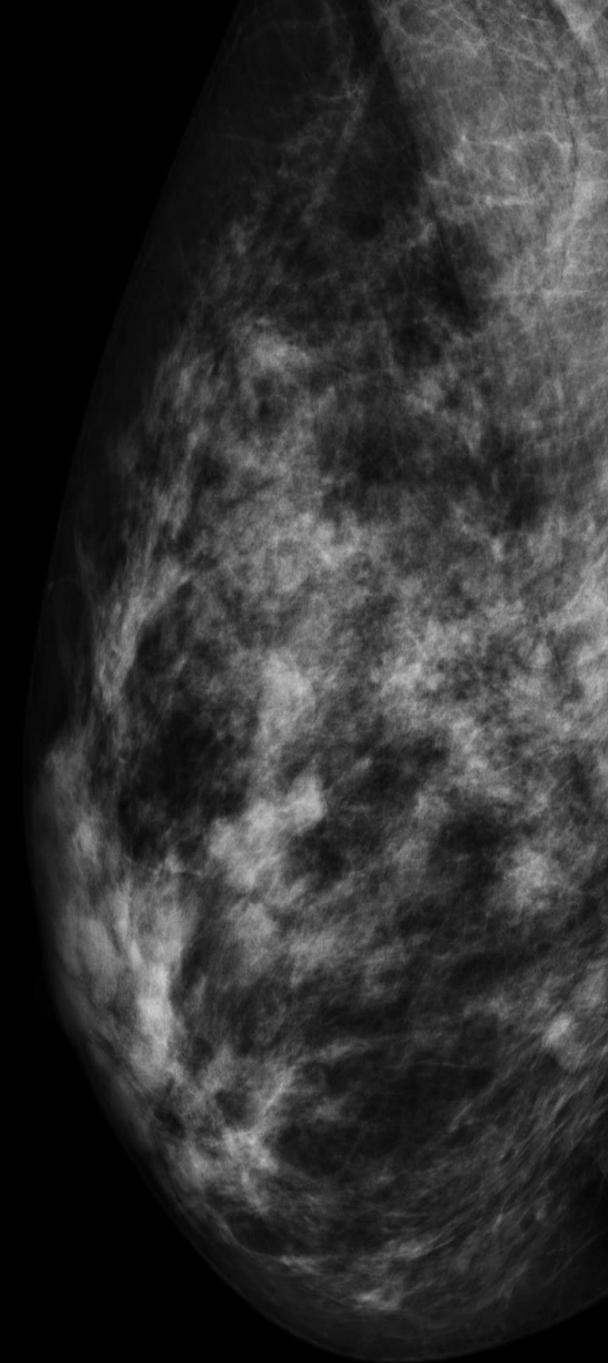
MAMMO

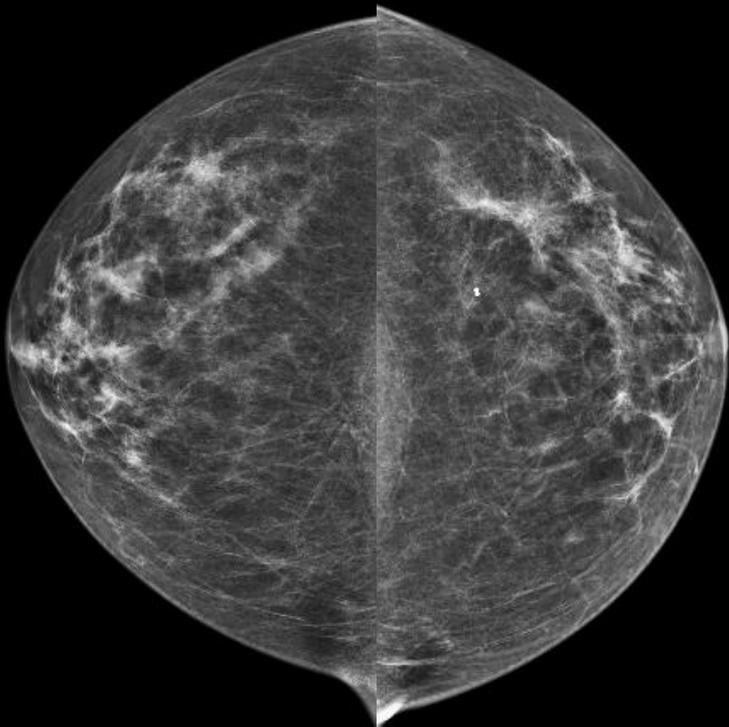
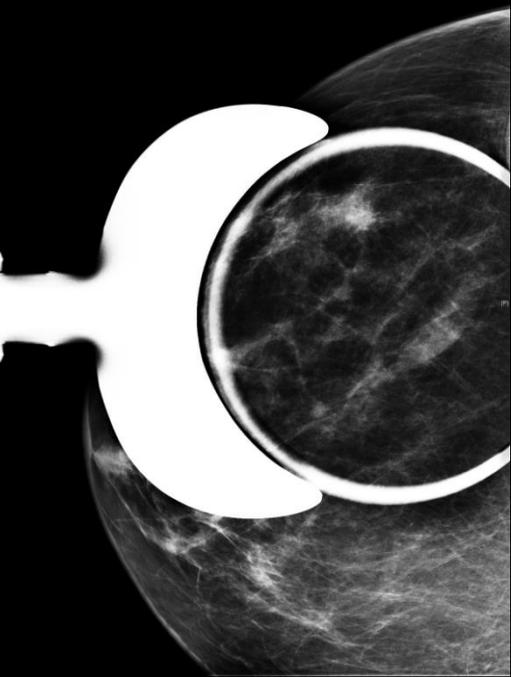
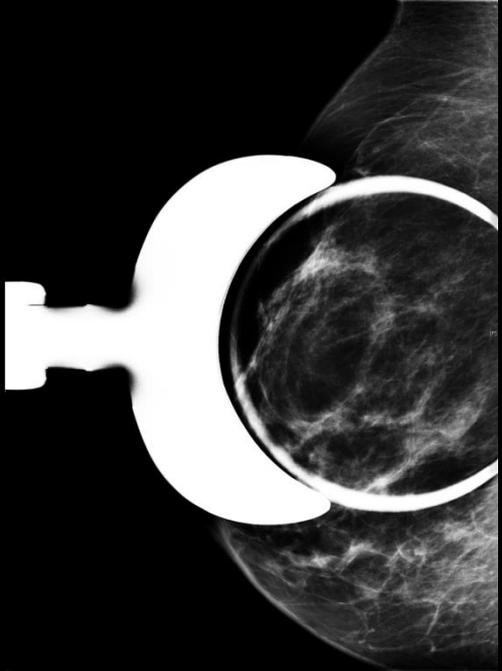
- **Sensitivity: 96.9%**
- **Specificity: 42.0%**
- **PPV: 39.7%**
- **NPV: 97.1%**

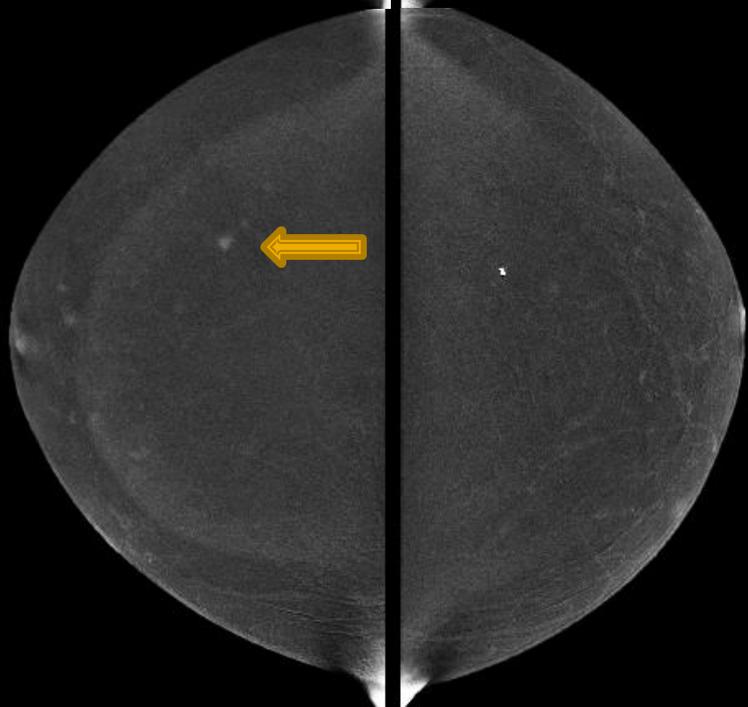
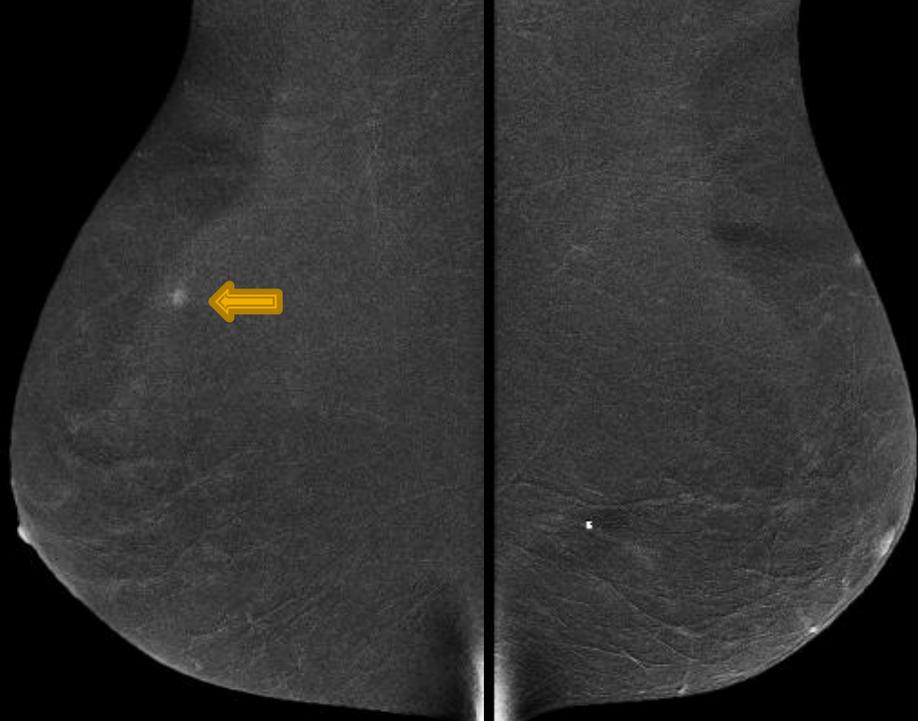
CESM

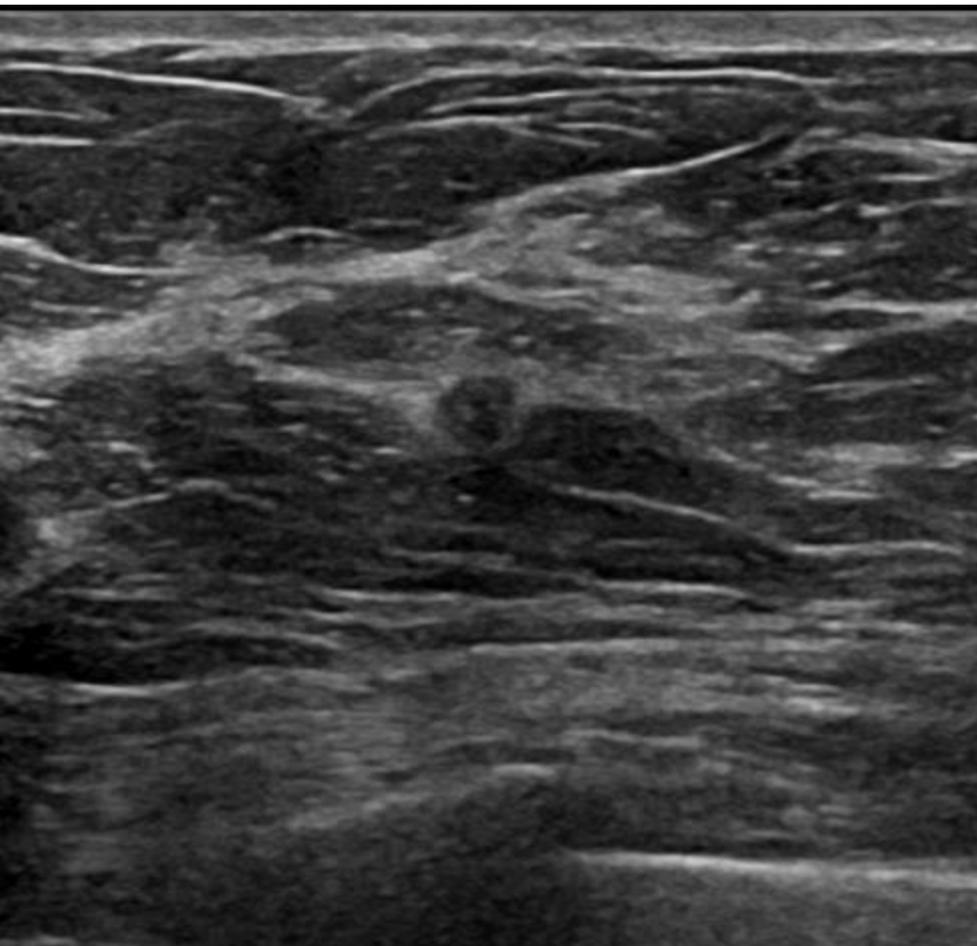
- **Sensitivity: 100%**
- **Specificity: 87.7%**
- **PPV: 76.2%**
- **NPV: 100%**

Mean difference between CESM & pathology 1.4mm

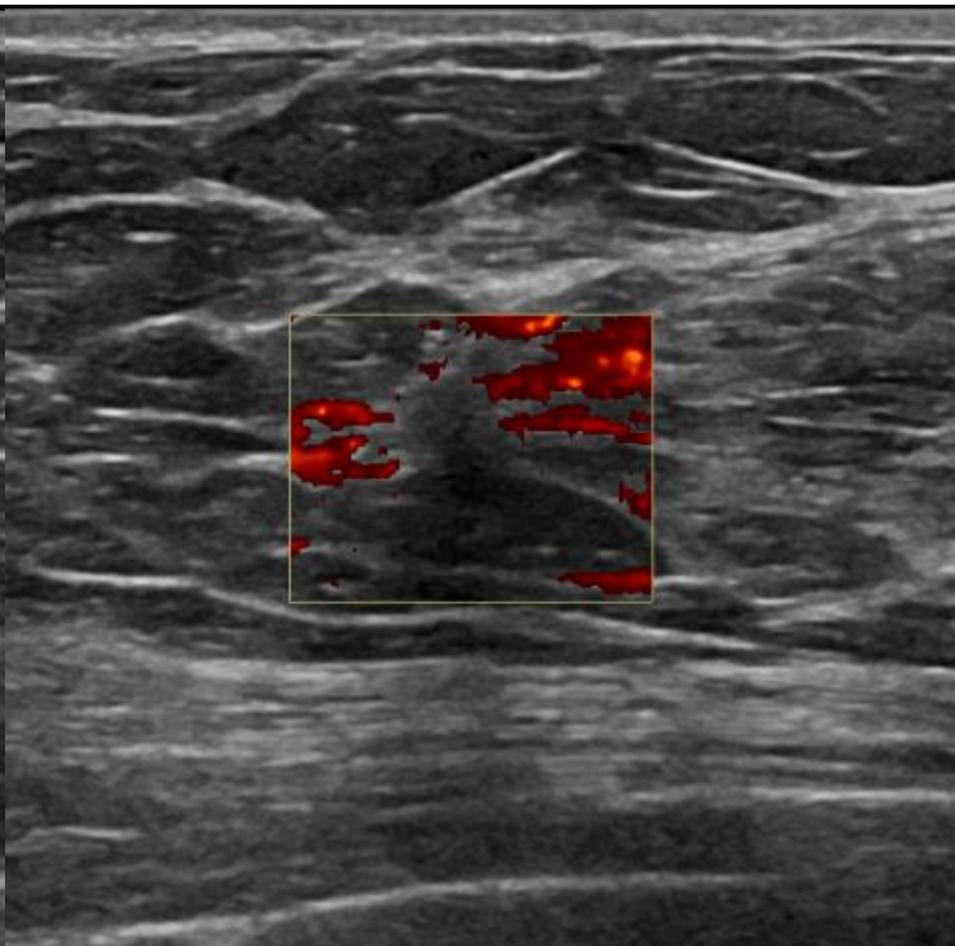




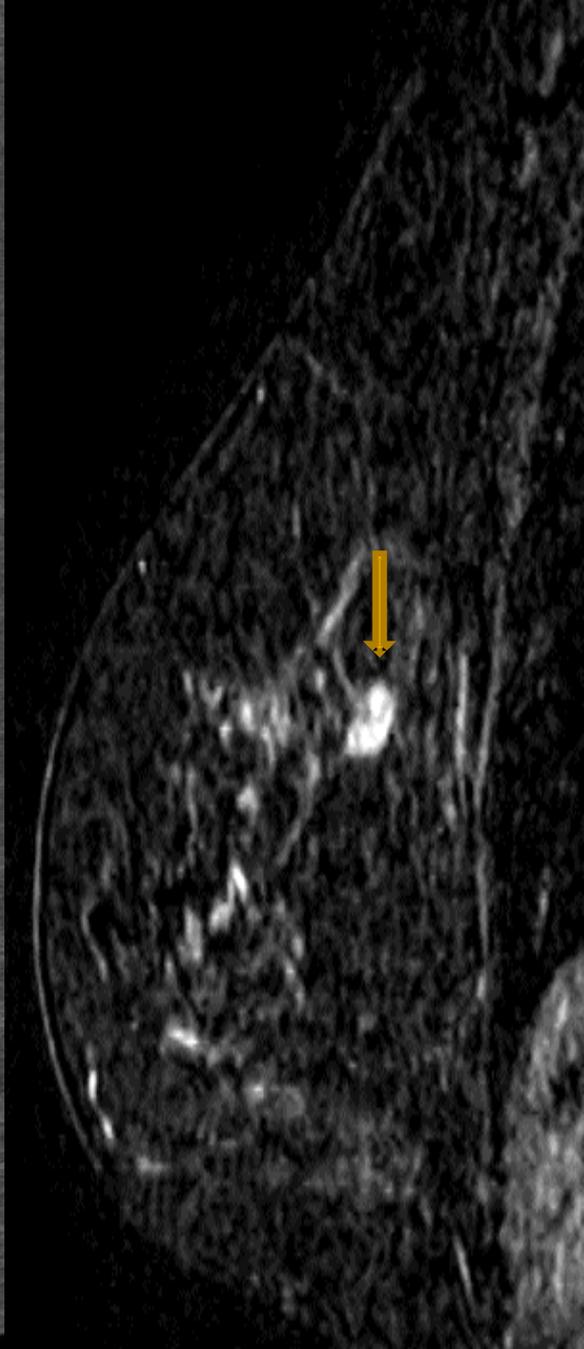
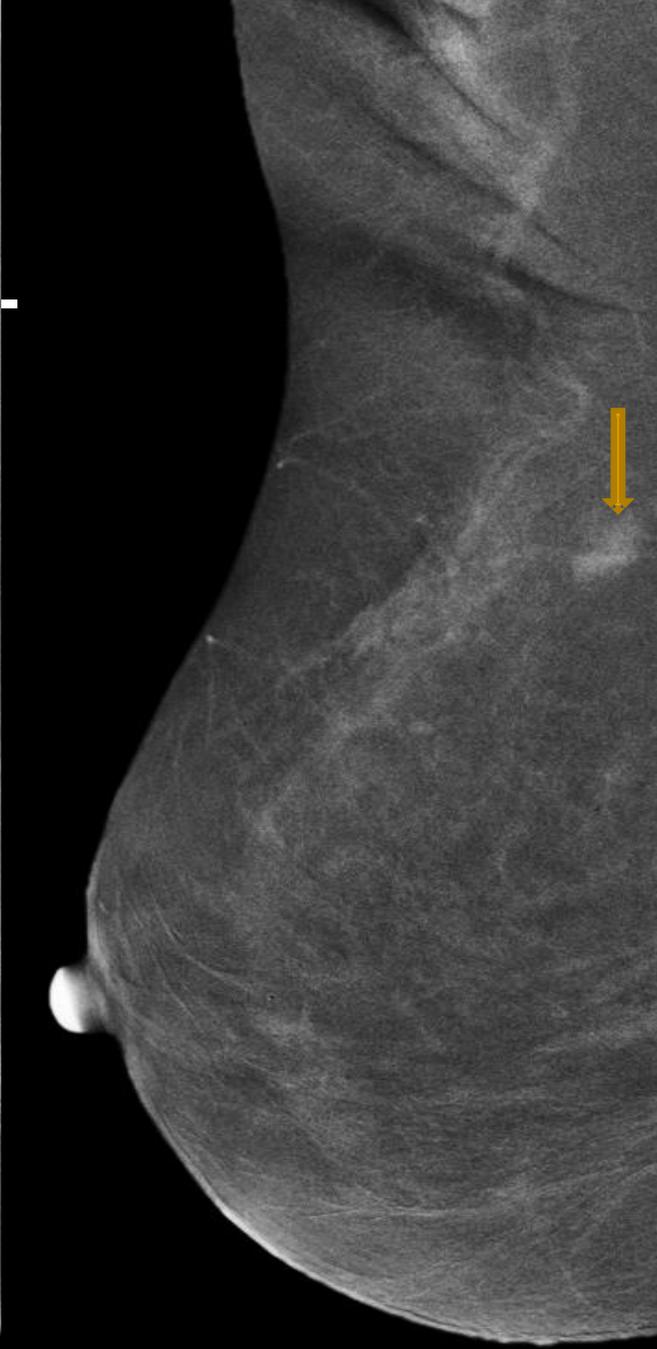
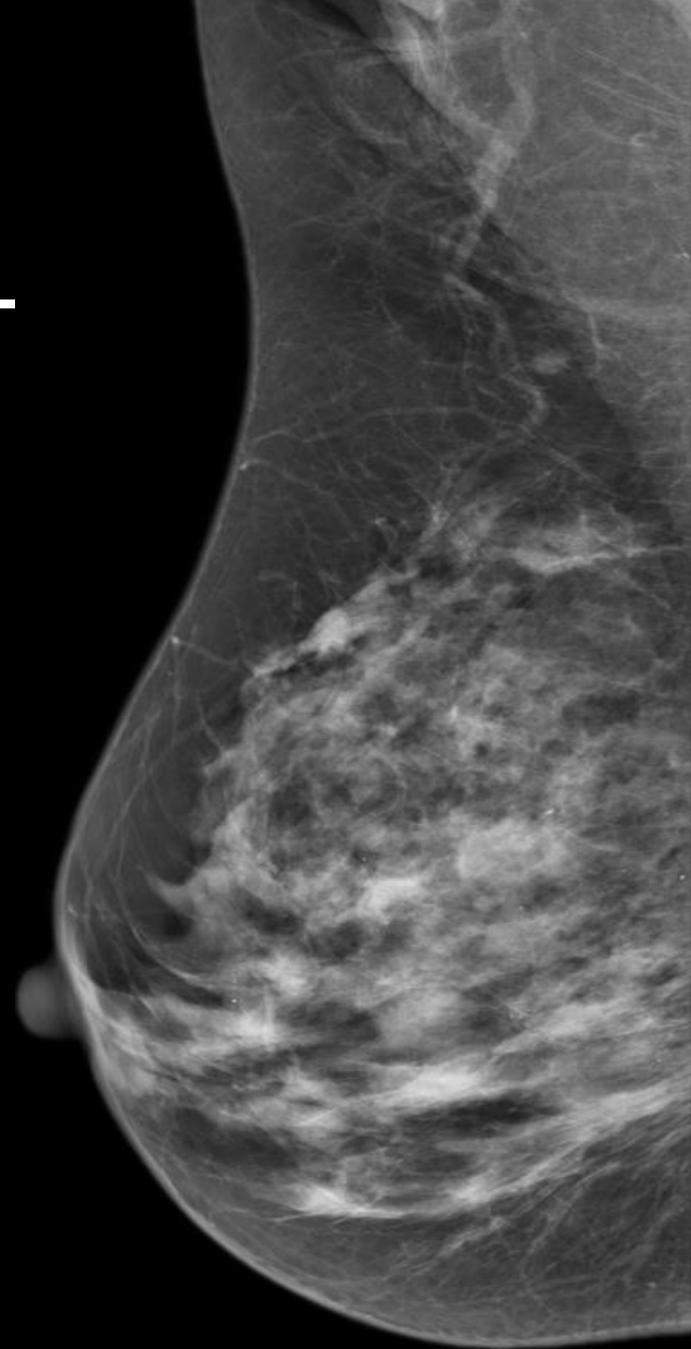




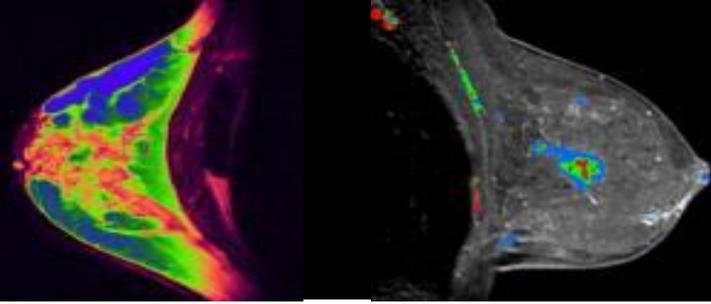
RT BREAST 11:00 6CM ANTIRADIAL



RT BREAST 11:00 6CM RADIAL



Conclusions



- Yearly mammography in average risk women from 40-49 significantly reduces **mortality**
- Yearly mammography in average risk women from 40-49 significantly reduces **morbidity**
- Average & intermediate risk women age 40-49 **SHOULD** undergo annual screening
- Intermediate risk/women w/ dense breasts may benefit from additional imaging
- High risk women 40-49 benefit from screening w/ mammography & MRI every 6 months

Conclusions

- **“Given the weight of the evidence that mammography screening is associated w/ a significant reduction in the risk of dying from breast cancer after age 40 years, a more productive discussion would be focused on how to improve the performance of mammography screening”***

* **Oeffinger et al JAMA 2015**

Conclusions

- **Ultrasound, tomosynthesis, MRI & contrast mammo will all detect more cancers than mammo alone**
- **MRI detects ~97% of cancers**
- **Tomosynthesis reduces call backs**
- **CESM improves sensitivity & specificity**
- **Prospective trials comparing the efficacy of these techniques are underway. Physiology will likely trump anatomy**
- **Proof of clinical advantage will take longer**



**Don't stop screening women 40-49:
Do it better!!!**