Controversies in Breast Imaging

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Disclosures
- I am not a radiologist
- I have no financial conflicts of interest

"laze" = Lava + Haze

The Questions
1. Is digital mammography better than conventional film mammograms?
2. What is DBT (digital breast tomosynthesis) and is it better than digital or conventional mammography?
3. Is ultrasound combined with mammography better than mammography alone?
4. What to do about dense breasts?
5. What are appropriate indications for breast MRI?

Is digital mammography better than conventional film mammograms?

Nearly a mute question: vast majority already using digital mammography
Is digital mammography better than conventional film mammograms?
- More sensitive for women < 50, extremely dense breasts, ER negative breast cancer
- Easier access, transmission and storage of images, lower average dose of radiation
- Trade-off = slightly lower specificity
- 2 RCT’s: similar to slightly improved detection rates, similar to slightly increased false positive rates, improved accuracy in younger women and women with dense breasts.

Pololu Valley Hike
- Pololu valley—end of the highway past Hawi
- 25 minutes down to black sand beach
- Can continue further to next valley

What is DBT?
(Digital Breast Tomosynthesis, 3D Mammography)
- 3-D depiction of breast using series of low-dose digital mammograms at various angles
- Better for delineating true lesions from spurious lesions caused by overlapping structures seen on routine mammography.
- For diagnostic mammo, better characterization of lesions leading to fewer biopsies

Palpable mass. Difficult to see well on mammo. Distinct edges on DBT. U/S confirmed a cyst.
Breast Tomosynthesis: patient experience

Digital Breast Tomosynthesis, 3D Mammography
- Higher radiation dose: sometimes twice as high b/c both a digital mammogram and DBT are done
- FDA approved for use with CM (not as stand-alone)
- Newer techniques have lower radiation dose but upgrading is costly
- Longer time for radiologist to read. One study twice as long

Risk of radiation induced death due to mammography ~ 2-11/100k over screening lifetime.

Breast tomosynthesis: Radiology experience

Invasive ductal carcinoma: Subtle on mammo Spiculated edges well seen on DBT

Traditional Mammo DBT

Is Breast tomosynthesis (DBT) better than mammography for routine screening?

- Multiple cross-sectional observational studies comparing DBT w CM or DM
  - Most found improved detection rates, ability to detect smaller lesions
  - Mixed results for recall rates—most showed a decrease although some showed an increase
- Largest Study in US (retrospective): 2 different populations at 2 different time points.
  - 1.2 additional cancers per 1000 screens
  - 16 fewer recalls per 1000, slightly higher biopsy rate

The USPSTF 2016: Evidence is insufficient to assess the benefits and harms of digital breast tomosynthesis (DBT) as a primary screening method for breast cancer. (*P*)

Is Breast tomosynthesis (DBT) better than mammography for routine screening?

Since USPSTF recommendation:

- Conant: prospective cohort with 1 yr f/u, 143K DM and 56K DBT
  - ↓ Recall 8.7 vs 10.4% (OR 0.68, 0.65-0.71)
  - ↑ detection 5.9/1000 vs 4.4/1000 OR 1.45 (1.1-1.9)
  - ↑ PPV: 6.4% vs 4.1% (OR 2.0, 1.5-2.7)
  - No sig diff in false negative (0.46/1000 vs 0.6/1000)

- No RCT’s yet
  - Italian RCT underway: Baseline findings showed increased detection, especially of DCIS (↑ 180%)

No sig diff in false negative (0.46/1000 vs 0.6/1000)

Increased in incidence, no concordant decrease in metastatic = Overdiagnosis

From 1978-2008:
- Decrease in mortality from 71 to 51/100k (due to screening and treatment improvements)
- Cost is an estimated 114/100k over-diagnosed (and over-treated)
Kawaihae Harbor: Lunch fish truck
- 2 mi away
- Turn right at gas station and then a quick left
- Cash only
- Shave ice across street

Is ultrasound combined with mammography better than mammography alone for screening?
- Observational studies: ultrasound detects more cancers but more false positives
- Cochrane attempted review of RCTs and large prospective studies of average risk women → no studies identified

Is ultrasound combined with mammography better than mammography alone for screening?
- Two types: handheld ultrasound and automated breast ultrasound. Appear to be comparable.
- Limitations to using: requires well-trained, skilled operators; techniques not standardized

- One newer RCT but no long term outcomes:
  - 73,000 Japanese women 40-49yo randomized to mamm or mamm+sono twice in 2 yrs
  - Increased detection in supplemental sono group (184 vs 117) and lower stages
  - 13% recalled in sono group vs 9% mamm, biopsies 4.5% vs 1.8%
- Unknown: Long term outcomes ie breast cancer mortality

Gartlehner Cochrane Reviews 2013

Ohuchi, Lancet 2016
Is MRI combined with mammography better than mammo alone for screening?

- **Advantages**: higher sensitivity (but lower specificity) than mammography, unaffected by breast density, no radiation
- **Practical limitations**: expensive, limited availability, need special equipment and expertise to biopsy MRI-detected lesions
- **No studies** in low/average risk women and not recommended by any organization
Q1: 43 yo woman with normal mammo 2 yrs ago but with "extremely dense" breasts. No other breast cancer risk factors. She would like your recommendation re: screening.

A. Wait until age 50 and then get mammo
B. Regular (film) mammo
C. Digital mammo
D. Breast Tomosynthesis (DBT)
E. Mammo plus ultrasound
F. Mammo plus MRI

Breast Density

- Radiologic finding only: Does not correlate with physical exam findings
- Varies with age, parity, estrogen use, BMI, menstrual cycle
- Changes quickly ie from one year to the next

Grading breast density

- BI-RADS scale:
  a. Breasts fatty
  b. Scattered fibroglandular density
  c. Heterogeneously dense → may obscure small masses
  d. Extremely dense → decreases mammo sensitivity
- No gold standard exists. Breast volume ≠ Birads
- Reproducibility: Inter- and intraobserver agreement:
  a. Good for 4-grade scale (kappa 0.71),
  b. Excellent for distinguishing a & b vs c & d (kappa=0.81).
  c. Poor for the intermediate categories (b, c, Kappa 0.25, 0.28)
Dense breasts are common
- Very common → ~50% of US screening population are c or d.
  - Cohort of 7000: BI-RADS a=8%, b=37%, c=46%, d=9%
- Inversely related to age.

![Graph showing breast density by age group](image)

Dense breasts & breast cancer risk
- Dense breasts affect breast cancer risk in 2 ways: by decreasing sensitivity of mammogram and possibly as an independent RF for cancer
- Independent RF for invasive breast cancer? Compared with general population (not comparing high to low density):
  - RR 1.2 for heterogeneously dense breasts (BI-RADS c)
  - RR 2.1 for extremely dense breasts (BI-RADS d)
- Absolute risk of breast cancer in 45 yo, avg breast density, no FH, no prior breast biopsy vs same woman with extremely dense breasts: 7/1000 vs 13/1000
- But... No increased mortality in women with dense breasts

Hard to tease out effect of breast density
- The increased risk due to breast density depends on other RF's present (interaction) and is not clearly an independent RF
  - Not a RF in woman at very high risk of breast cancer
  - Black women have lower breast density but higher risk of aggressive breast cancer
  - Asian women have higher breast density but lower breast cancer rates
  - Age and BMI increase risk for breast cancer but are associated with decrease in breast density

Breast density notification laws
- 32 states have laws requiring notification after mammogram if high breast density. A federal bill also introduced 2015 (not enacted).
- 4 states mandate insurance coverage for additional w/u
- What is the benefit to women's health?
  - Treatment for breast density?
  - Does it help identify women to get special services?
  - Can we screen more intensely to achieve better health?

From FL: “This information will lead to informed conversations between patients and healthcare providers about a woman's cancer risk and screening options.”
Letters patients receive can lead to more misunderstanding than understanding....

“Your mammogram may show that you have dense breast tissue as determined by the Breast Imaging Reporting and Data System established by the American College of Radiology. Dense breast tissue is very common and is not abnormal. However, in some cases, dense breast tissue can make it harder to find cancer on a mammogram and may also be associated with a risk factor for breast cancer. Discuss this and other risks for breast cancer that pertain to your personal medical history with your health care provider.”

New Jersey’s Letter

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Non-Dense</th>
<th>Extremely Dense</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film</td>
<td>85%</td>
<td>68%</td>
</tr>
<tr>
<td>Digital</td>
<td>Similar to film</td>
<td>82%</td>
</tr>
</tbody>
</table>

Sensitivity of mammography in dense breasts

- Increasing density is associated with decreasing sensitivity
- Digital mammmo is more sensitive than traditional film when breasts are dense

DBT vs digital mammom in dense breasts

- Limited evidence thus far...
- Study of 3200 women self-referred with dense breasts and normal mammom → DBT detected additional 4 breast cancers per 1000 screens
- 13K women for screening mammom, lower recall rate for DBT with greatest reduction for women with dense breasts

The USPSTF 2016: evidence is insufficient to assess the benefits and harms of digital breast tomosynthesis (DBT) as a primary screening method for breast cancer. (* *)

Talafuse, J Clin Dec 2016
Hass, Radiology, 2013
DBT vs digital mammo in dense breasts

Meta-analysis of observational studies:
- Increased detection
- Mixed recall rates

Supplemental screening with u/s or MRI in women with dense breasts
- Up to 20% of cancers are mammographically occult
- ~50% of women have dense breasts
- Implementing supplemental screening has large potential for harm due to increased false-positives and unclear benefit
- Options include ultrasound (hand-held or automatic) and MRI

Great Road Trip: Akaka Falls and/or Hawaii Tropical Botanical Gardens

Supplemental screening with u/s or MRI in women with dense breasts
- Limited data from clinical trials and observational studies suggest increased cancer detection rates at expense of increased biopsies
  - Detection: 7.6 per 1000 → 11.8 per 1000
  - PPV 22.6% → 11.2%
- Systematic review of 12 studies, varying cancer RF’s
  - Additional 12-107 biopsies per 1000 exams (median 52)
  - Detection of 0.3-7.7 cancers (median 4.2)
- More than 5x increase in number of unnecessary biopsies
- More than 90% of positives were false positive
Cost effectiveness of u/s for women with mammographically dense breasts?

- Patient data from BCSC used 3 simulation models to evaluate sono as a supplement to mammo.
- In women with heterogeneously or extremely dense breasts, prevention of 3.6 death/10,000 50-74 yo.
- Cost = 354 biopsies/1000 w biennial screening for 25 yrs.
- Cost = $325,000 per qaly gained.

Supplemental MRI for women with dense breasts?

- Similar to supplemental U/s, MRI increases sensitivity but at the expense of increased false positives and biopsies.
- Systematic review of 3 studies of MRI after negative mammogram.
- Recall rates 24%.
- Detection of 3.5 to 29 additional cancers per 1000 exams.
- Most women had other RF for breast cancer in addition to breast density (intermediate to high risk).
- Compared with U/s, MRI much more expensive and less available.

So.... what do we do with dense breasts?

- There are no major guidelines that advise breast density as the sole factor in determining need for supplemental screening.
- Use digital (as opposed to traditional film) mammography.
- Extremely dense breasts (birads d) are more clearly a risk factor for breast cancer than heterogeneously dense (birads c).
- Consider DBT—although not studied in RCT vs digital mammograms, many are doing both at same time.
- Improved sensitivity, unclear affect on recall rates.

So.... what do we do with dense breasts?

- Another option is to use risk calculator and discuss additional imaging if intermediate risk (15-20%).
- But current models don’t incorporate breast density.
- Ultrasound preferable due to lower cost.
- Make sure insurance covers or she can afford to pay for it.
- This is an evidence-free zone.
- Bottom Line: for women at average risk of breast cancer but with dense breasts, most recommend against routine supplemental screening.
Back to breast density notification laws

What is the benefit to women’s health?
- Treatment? No treatment exists to decrease breast density and even if it did, we would have to study to ensure that it would decrease breast cancer.
- Special services? Density doesn’t help us identify women for special services because it does not predict risk alone—must use in conjunction with other risk factors and risk prediction is difficult given interaction with breast density with age, BMI and race.
- Different Screening? Screening more intensely increases detection and also cost but with increased biopsies and work-ups and no evidence it improves health. It may in fact cause more harm than good.

Q1: 43 yo woman with normal mammogram 2 yrs ago but with “extremely dense” breasts. No other breast cancer risk factors. She would like your recommendation re: screening.

A. Wait until age 50 and then get mammogram
B. Regular (film) mammogram
C. Digital mammogram
D. Breast tomosynthesis (DBT)
E. Mammo plus ultrasound (evid insuff, esp in women with dense breasts as only risk)
F. Mammo plus MRI (only for women with >20% risk of breast cancer)

Definitely
Maybe, limited evidence

What are appropriate indications for breast MRI?

Screening high risk women (>20% lifetime risk)
- NCCN and ACS recommend Mammo + MRI annually starting at age 25
- Increased detection, diagnosis at earlier stage, cost effective but significantly less specific (0.95 vs 0.86)
- However, no evidence of reduced mortality or disease-free survival
Other indications for breast MRI?
- Evaluation of breast implant complications (better than u/s but u/s more readily available)
- Detection of occult primary breast cancer in women with mets to axillary lymph nodes
- Differentiating post-op scarring/radiation change from recurrence of breast cancer

MRI not recommended for....
- Work-up of breast pain
- Inconclusive imaging (negative MRI doesn’t eliminate need for biopsy so unclear utility of MRI for this indication) → get a biopsy instead
- Routine pre-op evaluation of women with breast cancer
- Measurement of response to adjuvant chemotherapy

Other Technologies
- Thermography?
- Ultrasound Elastography?
- Electrical Impedence Scanning?
- And... contrast-enhanced dual energy digital mammography, high-field strength MRI, magnetic resonance spectroscopy, diffusion weighted imaging, breast specific gamma imaging, and positron emission mammography

Conclusions
- Dense breasts are a real problem—not because they are so risky but because our legislators are pushing us to do additional testing despite lack of evidence of any effectiveness.
- We need RCT evidence of mortality benefit (and not just better detection) to evaluate screening modalities
Specific Conclusions

- There is insufficient evidence to recommend breast tomosynthesis for routine screening (though promising)
- There is insufficient evidence for supplemental u/s or MRI in average risk or in women with dense breasts
- Of the options discussed, if a woman is medium risk or desires something further for dense breasts, DBT is probably best option to recommend
- Although MRI is recommended to screen high risk women, no mortality benefit has been shown