Current Status of Supplementary Screening With Breast Ultrasound

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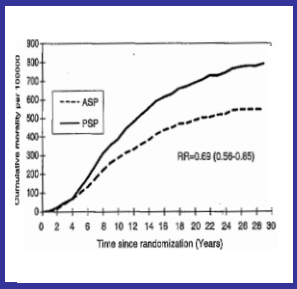
Swedish Two-County Trial: Cumulative Breast Cancer Mortality



31% Mortality Reduction
At 30 Years Follow-up

Demonstrated Benefits From Screening Mammography

- **Swedish Two-County Randomized Trial:**
  31% mortality reduction for ages 40-74
- **Swedish 7 County Service Screening Study:**
  45% mortality reduction in screenees

Tabar et al, Radiol 2011
Duffy et al, Cancer 2002

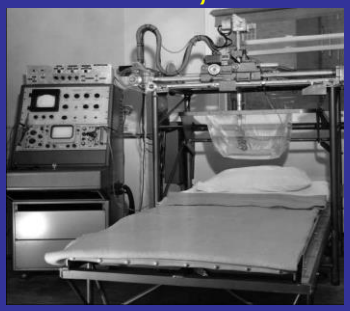
Relative Likelihood of Interval Cancers

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 < .001

Boyd et al New England J Med 2007;356:227-236

Can ultrasound find cancers missed by screening mammography?

Breast Scanner developed in Australia, 1965



Courtesy, Jack Jellins Ph.D.

Early Studies of Screening Ultrasound in 1980's

- Inadequate detection of smaller cancers
- Excessive false positive biopsies
- Performance was time consuming
- Expensive

Improvements in Breast Ultrasound in 1990's

- Better spatial resolution:
  7.5 -10 MHz transducers
- Better contrast resolution
- Stavros criteria for interpretation

Cancers Detected by Ultrasound Alone In Dense Breasts: 6 Screening Series, 1995 - 2003

- 150 cancers / 42,838 exams
- 3.5 cancers / 1,000 exams
- 90% in dense breasts
- Mean tumor size of 0.9 – 1.1 cm
- All Stage 0 or Stage I

Increased Detection: Ultrasound and Mammography vs. Mammography Alone

Study	Increased Detection
Kolb et al[1]	42%
Buchberger et al [2]	37%
Leconte et al[3]	79%

[1]Radiology 1998, 2002; [2]AJR, 1999; [3]AJR, 2003

False Positive Biopsies in Ultrasound Screening

- 2.5 x – 4.0 x higher than mammography
- Studies did not define biopsy criteria
- Higher false positive rates likely with ultrasound screening in community practice

Scientific Limitations of Screening Ultrasound Studies

- Non-blinded ultrasound interpretation
- Same radiologist read both modalities
- No documentation of technical quality or interpretive expertise

Multicenter Trial Protocol

- Independent interpretation of ultrasound and mammography
- Standardized ultrasound interpretive criteria
- High resolution ultrasound equipment
- Mammography and ultrasound technique monitored with quality control

Multicenter Trial Protocol

- Patients randomized to initial mammography or sonography
- Ultrasound performed by radiologists
- Radiologists:
  - received prior training in mammo and US interpretation
  - met interpretive performance standards prior to participation

High Risk Enrollment Requirements: At Least One of These Criteria

- BRCA-1 or 2 mutation
- Personal history of breast cancer
- Biopsy proven
  - Lobular carcinoma in situ (LCIS)
  - Atypical ductal hyperplasia (ADH)
  - Atypical lobular hyperplasia (ALH)
  - Atypical papillary lesion
- Prior radiation treatment of chest or axilla
- Gail of Claus model risk of $\geq 25\%$

Cancer Detection Rates at First Screening Round, ACRIN 6666 Trial:

Hand-held Ultrasound Screening of High Risk Women

- Mammography alone 7.6 / 1,000
- Mammography + US 11.8 / 1,000
- Supplementary yield for ultrasound 4.2 / 1,000
  or 55.3 % increase

Berg et.al. JAMA 2008

Biopsy Positive Predictive Value at First Screening Round, ACRIN 6666 Trial:

Hand-held Ultrasound Screening of High Risk Women

- Mammography with Ultrasound correlation 22.6 %
- Ultrasound alone 8.9 %
- Mammography or Ultrasound 11.2 %

Berg et.al. JAMA 2008

Results at Second and Third Screening Rounds: ACRIN 6666 Trial

- Supplementary yield of ultrasound = 3.7 cancers / 1,000 screens
- Biopsy PPV:
  Mammography alone = 38%
  Mammo + ultrasound = 16%

Berg et all, JA MA 2012; 307: 1394 - 1404

Limitations of Screening with Hand-held Ultrasound

- Exam time of 19 minutes (ACRIN Trial)
- Technique / Interpretation are linked and operator-dependent
- Need to document technologists' skill for screening

Significance of Screening Ultrasound Performance Time

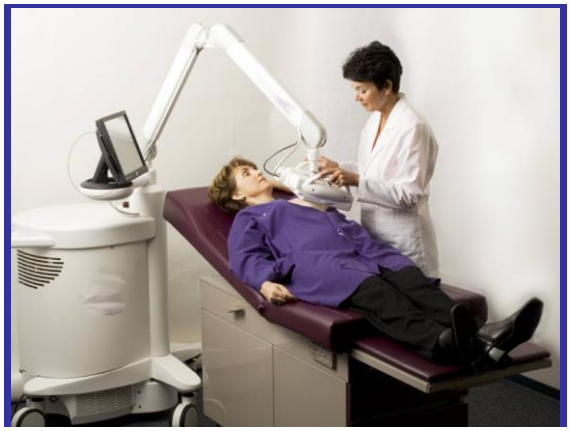
- Might lose money at screening mammography rates
- Low reimbursement might encourage excessively fast screening times
- Automated scanners might be the solution

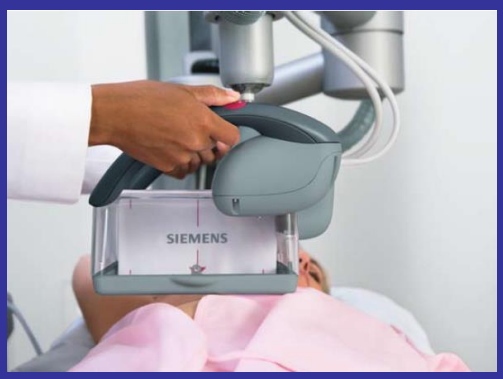
Follow-Up of Sonographic vs Mammographic Probably Benign Lesions

- Sonographic follow-up is much more time consuming and operator dependant

Methods to Facilitate Follow-Up of Probably Benign Ultrasound Lesions

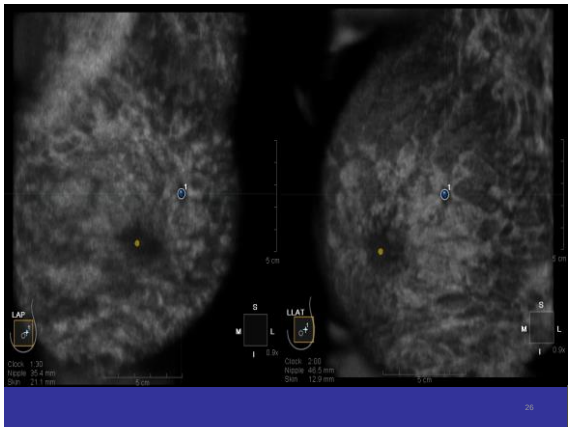
- Annual instead of 6 month follow-up
- Development of a high resolution, automated whole breast ultrasound scanner



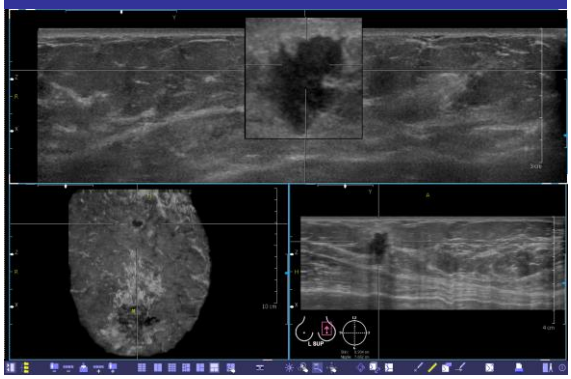


Advantages of Coronal View

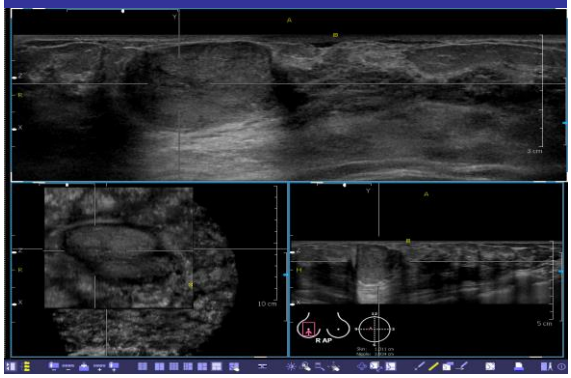
- New for breast ultrasound
- See slices of entire breast from skin to chest wall
- Tissue thickness reduced so better visualization



Invasive Ductal Carcinoma



Benign Fibroadenoma



Advantages of Automated Whole Breast Scanners

- Rapid acquisition time of 10 minutes
- Does not require physician performance
- Allows batch reading
- Can be integrated efficiently into breast center workflow

Interpretive Aspects of Automated Breast Ultrasound (ABUS)

- Suspicious findings may need hand-held confirmation and evaluation
- Hand-held transducer required for ultrasound-guided biopsy
- Some ABUS units have attached hand-held transducers

Automated Scanner with Handheld Capability

Increased Cancer Detection by Adding ABUS to DM For Screening Dense Breasts

All Cancers	31%	19 / 62
DCIS	6%	2 / 31
Invasive Cancers	55%	28 / 51
Stage 1A or 1B	54%	20 / 37

Brem RF, Tabar L, Duffy SW, et al. Radiology 2014 online

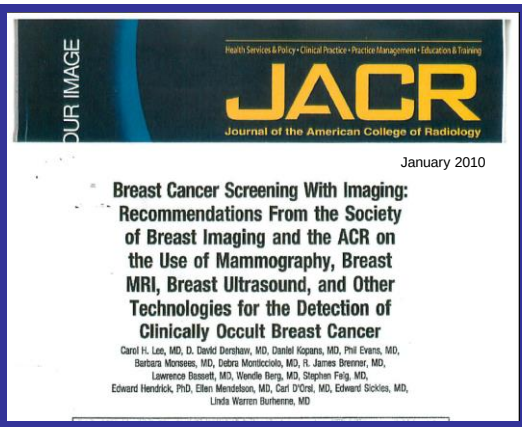
Effect of Adding ABUS to DM for Screening Dense Breasts

	DM	DM + ABUS
Cancers/1000	5.4	7.3
Recall Rate	15.0%	28.5%
PPV – 3 (False + Biopsy Rate)	14.0%	9.8%

Brem RF, Tabar L, Duffy SW. Radiology 2014 online

False Positive Biopsies in Ultrasound Screening

- Greater than with mammography
- Yet, US-guided core biopsy is:
  - Faster than stereotactic
  - Less invasive than excisional



Relative Advantages of Supplementary Screening Modalities

- Ultrasound vs MRI
  - Less expensive equipment
  - More easily available
  - Faster examination
  - No intravenous contrast
- MRI vs Ultrasound
  - More sensitive test

High Risk Triple Screening Studies with Mammography, Ultrasound, and MRI

	Cancer Detection
Combined Mammo and Ultrasound	55%
Combined Mammo and MRI	93%

Warner et al, JAMA 2004; Kuhl et al, J Clin Oncol 2005; Sardanelli, et al, Radiol 2007; Lehman et al, Radiol 2007

Current Screening Recommendations

- Mammography
  - Annually from age 40 for average risk women
  - May begin earlier for high risk women
- MRI
  - Annually if lifetime risk >20%
  - No recommendation for 15 – 20 % lifetime risk
  - No MRI if risk < 15%
- Ultrasound
  - Possibly for dense breasts

2010 ACR/SBI Guidelines for Screening Women with Dense Breasts as Only Risk Factor

- Addition of ultrasound to mammography may be useful
- Considerations include:
  - lack of reimbursement,
  - exam performance time,
  - high false positive biopsy rate,
  - insufficient personnel to perform and interpret studies

Preliminary Comparison of Automated Breast Ultrasound and Digital Breast Tomosynthesis for Supplementary Screening of Dense Breasts

	ABUS	DBT
Early Detection Rate	Increased	Increased
Ionizing Radiation	No	Yes
Recall Rule	Increased	Decreased
False Positive Biopsy Rate	Increased	Decreased
Reimbursement	Dx Only	$60 Extra

Research Agenda for Screening Dense Breasts

- How to reduce false positive bx's for masses detected by us alone
- Compare screening with ABUS vs. hand-held transducers: detection rates, cancer size, recall rates

Research Agenda for Screening Dense Breasts

- Which breast densities and age groups benefit most from tomosynthesis vs. 2D digital ?
- Compare ABUS and tomosynthesis vs. tomosynthesis alone .