SCREENING FOR BREAST CANCER
BREAST IMAGING

Liane Philpotts, MD, FSBI, FACR
Professor, Radiology and Biomedical Imaging
Division Chief, Breast Imaging

Dec. 5, 2017
# The Lifetime Probability of Developing Cancer for Women, 2008-2010*

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Breast</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>1 in 16</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>1 in 22</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>1 in 37</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 52</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1 in 62</td>
</tr>
<tr>
<td>Melanoma of the skin‡</td>
<td>1 in 53</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 in 68</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>1 in 83</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 in 86</td>
</tr>
</tbody>
</table>

* For those free of cancer at beginning of age interval.
† All sites exclude basal cell and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Statistic for white women.
Trends in Cancer Incidence Rates* Among Women, US, 1975-2010

*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
† Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2013.
Trends in Cancer Death Rates* Among Women, US, 1930-2010

Figure 2. Female Breast Cancer Incidence (2004-2008) and Mortality (2003-2007) Rates* by Race and Ethnicity

*Rates are age adjusted to the 2000 US standard population.
†Persons of Hispanic origin may be of any race.

Mortality: Altekruse et al.13

American Cancer Society, Surveillance Research, 2011
**Figure 1. Age-Specific Incidence of Invasive Breast Cancer per 1000 Women per Year in the United States.**

Data are from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, 2010.²

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### Table 2. Relative Risk of Death from Breast Cancer, Number Needed to Invite to Screening, and Rates of False Positive and False Negative Results, According to Age.*

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Trials</th>
<th>Relative Risk of Death (95% CI)</th>
<th>Number Needed to Invite to Screening (95% CI)</th>
<th>Rate per 1000 Women Screened</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Invasive</td>
</tr>
<tr>
<td>39–49 yr</td>
<td>8‡</td>
<td>0.85 (0.75–0.96)</td>
<td>1904 (929–6378)</td>
<td>1.8</td>
</tr>
<tr>
<td>50–59 yr</td>
<td>6§</td>
<td>0.86 (0.75–0.99)</td>
<td>1339 (322–7455)</td>
<td>3.4</td>
</tr>
<tr>
<td>60–69 yr</td>
<td>2¶</td>
<td>0.68 (0.54–0.87)</td>
<td>377 (230–1050)</td>
<td>5.0</td>
</tr>
<tr>
<td>70–79 yr</td>
<td>1</td>
<td></td>
<td></td>
<td>1.12 (0.73–1.72)</td>
</tr>
</tbody>
</table>

* Warner, E. NEJM 2011
Screening for Breast Cancer

- Mammography
- Ultrasound
- MRI
Why Screen?

- Breast cancer is common
  - 1 in 8 women
- Mortality reduction
  - 20-49% in RCT
  - Could be higher with modern mammography and treatment?
Criticisms of Mammography

- Mammography is an imperfect test
- Sensitivity and specification are variable
  - Patient factors – Age, tissue density, hormones
  - Tumor biopsy
- Balance of Harms and Benefits
- Main benefit is earlier detection and better treatment of breast cancer
- Harms include false positives, false negatives, anxiety, costs, overdiagnosis
What age and how often?

- To be effective, screening has to be done regularly.
- Younger women have more aggressive tumor biology – need to screen more frequently.
- Older women with no risk, biennial screening may be OK.
- Yet, most women who get breast cancer have no risks.
Breast Cancer Screening Guidelines

At what age should average risk women start, and how often should screening take place?

<table>
<thead>
<tr>
<th>Organization</th>
<th>Starting Age</th>
<th>Screening Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS, ASBS, ASCO</td>
<td>45; with the option to start at 40</td>
<td>Annual 40-54: Biennial 55+, with option to continue annual screening</td>
</tr>
<tr>
<td>ACR, NCCN, NCBC</td>
<td>40</td>
<td>Annual</td>
</tr>
<tr>
<td>USPSTF, AAFP, ACP</td>
<td>50; the decision to begin screening between ages 40-49 should be individualized based on risk and values</td>
<td>Biennial, 40+</td>
</tr>
</tbody>
</table>

ACS=American Cancer Society; ASBS=American Society of Breast Surgeons; ASCO=American Society of Surgical Oncology; USPSTF=U.S. Preventive Services Task Force; ACOG=American College of Obstetricians and Gynecologists; NCCN=National Comprehensive Cancer Network; NCBC=National Consortium of Breast Centers; AAFP=American Academy of Family Physicians; ACP=American College of Physicians;
# Breast Cancer Screening Guidelines

**At what age should average risk women stop screening?**

<table>
<thead>
<tr>
<th>Organization</th>
<th>Stopping Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS, ASBS, ASCO</td>
<td>Continue screening as long as health is good and life expectancy is <strong>at least 10 years</strong></td>
</tr>
<tr>
<td>ACOG</td>
<td><strong>Shared decisions 75+</strong></td>
</tr>
<tr>
<td>ACR</td>
<td>Continue screening as long as health is good and life expectancy is <strong>at least 5-7 years</strong>, and there is willingness to undergo additional testing</td>
</tr>
<tr>
<td>NCCN</td>
<td>Consider comorbidity and therapeutic decisions</td>
</tr>
<tr>
<td>USPSTF, AAFP, ACP</td>
<td>74; Insufficient evidence to recommend for or against screening</td>
</tr>
</tbody>
</table>

ACS=American Cancer Society; ASBS=American Society of Breast Surgeons; ASCO=American Society of Surgical Oncology; USPSTF=U.S. Preventive Services Task Force; ACOG=American College of Obstetricians and Gynecologists; NCCN=National Comprehensive Center Network; NCBC=National Consortium of Breast Centers; AAFP=American Academy of Family Physicians; ACP=American College of Physicians;
Summary of ACOG’s Updated Recommendations for Screening Mammography

- Women at average risk of breast cancer should be offered screening mammography starting at age 40 years. If they have not initiated screening in their 40s, they should begin screening mammography by no later than age 50 years. The decision about the age to begin mammography screening should be made through a shared decision-making process. This discussion should include information about the potential benefits and harms.

- Women at average risk of breast cancer should have screening mammography every one or two years based on an informed, shared decision-making process that includes a discussion of the benefits and harms of annual and biennial screening and incorporates patient values and preferences.

- Women at average risk of breast cancer should continue screening mammography until at least 75 years. Beyond age 75 years, the decision to discontinue screening mammography should be based on a shared decision-making process informed by the woman's health status and longevity.
Yale Screening Guidelines

- We recommend mammogram screening to start no earlier than age 40 and no later than age 50 for women at average risk of breast cancer and continue through at least age 74. Screening mammography should occur at least once every 2 years and as often as once a year. Women at higher than average risk may require different screening recommendations. It is important to talk with a health care provider about level of risk, when to start and stop screening, and how often to screen. This discussion should take into consideration personal preferences, benefits and harms of screening, overall health status, and life expectancy.
Annual vs Biennial?

The Screening Interval

- There have been no trials that have compared annual screening with biennial screening
- The screening interval has been influenced by estimates of tumor growth rates & interval cancer rates
- Screening intervals also have been recommended based on tradeoffs between estimated mortality rates and false positive rates

Courtesy of Robert Smith, PhD, ACS
Annual vs Biennial?

Interval Cancer Rate as a Percent of the Expected Incidence in the Unscreened Population by Year Since Negative Screen, Swedish Two County Study

Faster tumor growth in premenopausal women results in a higher interval cancer rate. Thus, screening intervals should be tailored to the age of the woman.

Courtesy of Robert Smith, PhD, ACS
Supplemental analysis on the screening interval from NCI funded Breast Cancer Surveillance Consortium

- Miglioretti D, et al. Risk of less-favorable breast tumor characteristics with biennial versus annual mammography by age and menopausal status

- **Design, setting, and participants:**
  -- 15,440 women aged 40-85 years with breast cancer diagnosed within 1 year of an annual or within 2 years of a biennial screening mammogram performed from 1996-2011.
  -- Updated previous analyses by using narrower screening intervals, specifically 11-14 months for annual and 23-26 months for biennial screening intervals.

- **Main finding**—Among premenopausal women, biennial screeners had higher proportions of tumors with advanced stage (relative risk [RR]=1.28), larger size (RR=1.21), and any less-favorable prognostic characteristic (RR=1.11) compared with annual screeners [all RR were statistically significant].

**Annual vs Biennial?**

Courtesy of Robert Smith, PhD, ACS
Digital Breast Tomosynthesis

- Beneficial in most breast densities, especially heterogeneously dense
- Multiple studies:
  - Increased cancer detection by 10-53%
Tomosynthesis acquisition

Tomosynthesis projections

Limited angle (15°)
Projection Acquisition

15 Projection Images
Tomosynthesis
reconstructed slices
(Average n = 60)

Filtered Back-Projection
Reconstruction

15 projections
Synthetic 2D generation

- Tomosynthesis reconstructed slices
- Synthetic 2D image shows a roadmap of the important features from tomosynthesis slices
- Synthesized Projection (Collapse 3D information in a single slice)
Advantages of Tomosynthesis

- Tomosynthesis was developed to improve upon 2D limitations
- Tissue superimposition:
  - May hide pathologies in 2D
  - May mimic pathology when doesn’t really exist
72 yo screening mammogram
Invasive ductal carcinoma
Multiple single-site, multicenter, and population-based studies have shown that screening with tomosynthesis:

- Lowers recall rates – by 15-30%
- Increases cancer detection – by 40%
  - Invasive cancers
Invasive ductal carcinoma seen only on tomosynthesis
Impact of Digital Breast Tomosynthesis On Recall Rates- The Five-Year Experience in a Large Multi-Site Academic Center

TY CARROLL MD, M RAGHU MD, L PHILPOTT MD
DEPARTMENT OF RADIOLOGY AND BIOMEDICAL IMAGING
YALE UNIVERSITY
NEW HAVEN, CT
Results: Recall Rates

Comparison of Recall Rates Between DBT and 2D-FFDM

* p<.0001 compared to 2D-FFDM cohort over five year study period
Results: Cancer Detection Rate

Cancer Detection Rate (per 1000) with DBT

CDR of 5.8* over 5 year period

*p <0.004 (compared to CDR of 4.2 with 2D-FFDM over the same five year period)
Results: Positive Predictive Value

* PPV of 8* over 5 year period

*p < .001 (compared to PPV of 3 with 2D-FFDM over the same five year period)*
Cancer Detection with Digital Breast Tomosynthesis (DBT) Compared with Conventional Digital Mammography in Routine Breast Cancer Screening

Maryam Etesami, MD
Michelle Y. Giwerc
Malini Harigopal, MD
Laura J Horvath, MD
Wajih Zaheer Kidwai, MD
Liane E. Philpotts, MD

RSNA 2017
Results: Size of invasive cancers

P= 0.03 (independent samples t-test)
Error bars: 95% CI
Results: Axillary lymph node metastasis in invasive cancers

<table>
<thead>
<tr>
<th></th>
<th>DBT</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node negative</td>
<td>85%</td>
<td>69%</td>
</tr>
<tr>
<td>Lymph node positive</td>
<td>15%</td>
<td>31%</td>
</tr>
</tbody>
</table>

P=0.01
Results: Axillary lymph node metastasis in moderately or poorly differentiated invasive cancers

**DBT**
- Lymph node negative: 80%
- Lymph node positive: 20%

**DM**
- Lymph node negative: 62%
- Lymph node positive: 38%

*P*=0.008
Tomosynthesis in the Diagnostic Setting: Changing Rates of BI-RADS Final Assessment over Time

Madhavi Raghu, Melissa Durand, Liva Andrejeva, Alexander Goehler, Mark Michalski, Jaime Geise, Regina Hooley, Laura Horvath, Reni Butler, Howard Forman, Liane Philpotts

Radiology, 2016
RATE OF FINAL BI-RADS ASSESSMENTS BEFORE (2D) AND AFTER TOMOSYNTHESIS (first 3 yr)

<table>
<thead>
<tr>
<th></th>
<th>2D</th>
<th>3D1</th>
<th>3D2</th>
<th>3D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0%</td>
<td>7.6%</td>
<td>7.9%</td>
<td>7.8%</td>
<td></td>
</tr>
<tr>
<td>(287/3550)</td>
<td>(257/3373)</td>
<td>(358/4516)</td>
<td>(364/4653)</td>
<td></td>
</tr>
<tr>
<td>33.3%</td>
<td>25.1%</td>
<td>21.8%</td>
<td>16.4%*</td>
<td></td>
</tr>
<tr>
<td>(1181/3550)</td>
<td>(846/3373)</td>
<td>(990/4516)</td>
<td>(764/4653)</td>
<td></td>
</tr>
</tbody>
</table>
BIOPSY RATES AND PPV3 BEFORE (2D) AND AFTER TOMOSYNTHESIS

PPV3↑69%
Tissue Density & Mammographic Sensitivity

98%  
Predominantly fatty breasts

as low as 30-55% in dense breasts
Breast Density
The problem:

- Decreased mammographic sensitivity
- Increased risk for breast cancer
- Later stage at diagnosis
- More interval cancers
Prevalence of Mammographically Dense Breasts in the United States
Sprague et al. JNCI 2014;106

- 764,507 women > 40 years old
- 43% with heterogeneously or extremely dense breasts
- 27.6 million women aged 40-75 in United States have dense breasts
Breast Density and Parenchymal Patterns as Markers of Breast Cancer Risk: A Meta-analysis

<table>
<thead>
<tr>
<th>% DENSITY</th>
<th>RELATIVE RISK (COMPARED TO &lt; 5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 24</td>
<td>1.79</td>
</tr>
<tr>
<td>25-49</td>
<td>2.11</td>
</tr>
<tr>
<td>50-74</td>
<td>2.92</td>
</tr>
<tr>
<td>&gt;75</td>
<td>4.64</td>
</tr>
</tbody>
</table>

McCormack et al Cancer Epidemiol Biomarkers Prev 2006;15:1159
Dealing with Dense Breasts

Supplemental Imaging

- Increasing body of literature that shows supplemental screening detects cancers not otherwise detected in dense tissue

- Methods:
  - Digital Mammography (DMIST) > Film-screen
  - Tomosynthesis (DBT > 2D)
  - CE-mammography/DBT
  - MBI
  - MRI
  - Ultrasound
AN ACT REQUIRING COMMUNICATION OF MAMMOGRAPHIC BREAST DENSITY INFORMATION TO PATIENTS.

On and after October 1, 2009, each mammography report provided to a patient shall include information about breast density, based on the Breast Imaging Reporting and Data System established by the American College of Radiology. Where applicable, such report shall include the following notice: "If your mammogram demonstrates that you have dense breast tissue, which could hide small abnormalities, you might benefit from supplementary screening tests, which can include a breast ultrasound screening or a breast MRI examination, or both, depending on your individual risk factors. A report of your mammography results, which contains information about your breast density, has been sent to your physician’s office and you should contact your physician if you have any questions or concerns about this report.".

We are pleased to inform you that the results of your recent mammography examination are normal.

As you know, early detection of cancer is very important. Although mammography is the most accurate method for early detection, not all cancers are found through mammography. A thorough examination includes a combination of mammography, physical exam, and breast self-examination. Current American Cancer Society Guidelines recommend screening mammograms and physical breast examinations every year beginning at age 40.

Your mammogram demonstrates that you have dense breast tissue, which could hide small abnormalities; you might benefit from supplementary screening tests, which can include a breast ultrasound screening or breast MRI examination, depending on your individual risk factors. A report of your mammography results, which contains information about your breast density, has been sent to your physician’s office and you should contact your physician if you have any questions or concerns about this report.

A report of your mammography results will be sent to your physician.

Your mammogram will become a part of your mammography file here at Yale-New Haven Hospital. You are responsible for informing any new health care provider or mammography facility of the date and location of this examination.

Thank you for using our mammography service.

Sincerely,

Yale Breast Imaging
Screening US few weeks later
lobulated hypoechoic lesion at 9:00 in the right breast 5 cm from the nipple measuring 1.7 cm

US guided core biopsy - Invasive Ductal Carcinoma
Currently 32 States with Density Laws

Map Legend:
- Pink: Some density notification required (31 states)
- Purple: Effort for inform/education; notification not required
- Blue: Active bill
- Yellow: Inactive bill/no notification enacted
- Diamond: State with insurance coverage

© 2015 - 2017, DenseBreast-info, Inc.
Revised 1 May 2017
Breast Ultrasound Screening

- Breast US is complementary to mammography
  - Performs better in dense breast tissue
  - Important to correlate with mammogram
Screening whole breast US

- Meta-analysis of 75,000+ SBUS*
  -  13 studies (1995-2012)
  -  CDR = 3.4/1000
  -  94% of cancers invasive
    - Mostly <1 cm, low grade
  -  PPV 3 = 9.9%

Update on technologist-performed, screening breast ultrasound in women with dense tissue 5 years after CT

Public Act No. 09-41: How are we doing now?

**BI-RADS Final Assessment**
**Year 1 versus Year 5**
J-Start

Japan Strategic Anti-cancer Randomized Trial

- July 2007 – March 2011
- 72,998 asymptomatic women, ages 40-49y
- 2 screening rounds/2 years
- Randomized: Mammo (n = 35,965) vs Mammo + WBUS (n = 36,752)
- Intervention group (M+US) had significantly
  - Higher CDR
  - Higher sensitivity
  - Lower specificity
  - Fewer interval cancers

<table>
<thead>
<tr>
<th></th>
<th>Mammo</th>
<th>Mammo + US</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer detection</td>
<td>117 (0.3%)</td>
<td>184 (0.5%)</td>
<td>0.019</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>77%</td>
<td>91%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Specificity</td>
<td>91%</td>
<td>88%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Interval cancers</td>
<td>35 (0.10%)</td>
<td>18 (0.05%)</td>
<td>0.034</td>
</tr>
</tbody>
</table>
Breast Cancer Detected at Screening US: Survival Rates and Clinical-Pathologic and Imaging Factors Associated with Recurrence
Kim et al. Radiology April 6 2017, epub

- Four institutions, January 2004 and March 2011
- 501 women (age 27–74 years, median 47)
- Breast cancer detected at screening US
  - 425 invasive cancers
  - 76 ductal carcinoma in situ
- Five-year survival:
  - Overall (OS) 100%
  - Recurrence-free (RFS) 98%
- Conclusion: Women with breast cancers detected at screening US have excellent outcomes
AMERICAN CANCER SOCIETY
RECOMMENDATIONS FOR SCREENING MRI

- Annual screening MRI beginning at age 30 recommended for:
  - BRCA mutation carriers
  - 1º relative of BRCA carrier but untested
  - Lifetime risk of 20-25% or greater
  - Radiation to chest age 10 to 30
  - Li-Fraumeni, Cowden, and Bannayan-Riley-Ruvaleaba Syndromes and 1º relative

- Insufficient evidence to recommend for or against screening MRI
  - Lifetime risk 15-20%
  - Lobular carcinoma in situ (LCIS)
  - Atypical ductal hyperplasia (ADH)
  - Dense breasts
  - Personal history of breast cancer

- Recommendation AGAINST screening MRI – < 15% lifetime risk
FAST MR Screening

• Proposed for average risk women with dense breasts
  - 606 exams/427 women with dense breasts
    - Mild-moderate risk/normal mammo
    - Acquisition time of 3 min
      pre/post T1WI, + subtraction/IV contrast
    - Expert read of MIP = 3 sec
    - Supplemental CDR = 11/606 (18.2/1000)
  - 2 y validation: No interval cancers
  - NPV MR 99%
  - SP/PPV: 94.3/24.4 (similar to full MR protocol)

Kuhl et al. JCO 2014
Current limitations:
- Cost
- Intravenous gadolinium contrast
- False positive results
Contrast-enhanced subtraction mammography/DBT

- Requires injection of iodinated contrast material
- Requires compression
- Increases radiation dose
- Biopsy?
- Role of dual energy spectral mammography/DBT?
− 1585 women
− • 300 mBq 99mTc-sestamibi (vs. 740 mBq)
− • Cancer detection
  − 3.2/1000 Mammo
  − 12.0/1000 Mammo + MBI
− • Recall
  − 11.0/1000 Mammo
  − 17.6/1000 Mammo + MBI
− • Dose to breast 2.4 mSv (digital mammo 0.44 mSv)
− • Dose to large intestine 20 mSv

− ACR Appropriateness Criteria for Breast Cancer Screening:
  MBI, BSGI not appropriate for screening at currently administered doses
Screening Guidelines

- The issues are complex
  - Complicates shared decision making
- Balance of benefits and harms
- Mortality data is based on antiquated studies
  - benefits are likely underestimated
- Newer methods of screening are superior
  - Reduces harms
- Morbidity benefits are often not emphasized
Thank you!