Breast Cancer Screening
Screening

• What /why
• Methods
• Outcomes / End-points. Mortality reduction vs QALYS
• Recommendations worldwide
• Controversies
• High Risk Screening
• Personalized screening
18 months
28 months
Definition

A screening test is applied to a determined population with the goal of identifying early disease in otherwise symptom free people so that a favourable outcome can be achieved with treatment. Screening tests should be reasonably safe, affordable, reliable and sensitive. Although sensitivity is the most important metric, the screening test cannot lead to unacceptable numbers of false positive results.
• Disease: Breast Cancer
• Population:
  • Women
  • Age 40 – 50 and up
• Screening Method: Radiology – Mammogram ± supplemental imaging
Screening benefits ..... Early diagnosis

- Small tumors, no metastatic disease
- Better prognosis – disease free survival, reduced mortality from bc
- Less aggressive treatment – in particular chemotherapy
- Conservative surgery - Better aesthetics
- Fewer axillary dissections – lower morbidity from lymphedema
5 year survival by stage

- Stage 1 breast cancer 5 year survival: 95%
- Stage 2 and 3 breast cancer 5 year survival: 81%
- Stage 4 breast cancer 5 year survival: 24%

- Fewer late stage cancers diagnosed
- Screening mammography has been shown to reduce breast cancer mortality by 20 – 50%
Benefits of early detection: social and economic

- Quality of Life
  - Less anxiety
  - Better cosmetic outcomes
  - Less treatment related morbidity

- Economic
  - Less time from family and work
  - Women bringing up children / running households
  - Women in the workforce

... breast cancer in younger women has a larger effect on life years and quality of life. In addition, younger women tend to have faster growing cancers with earlier metastases which necessitates more treatment, more morbidity etc.
Arguments against screening mammography:

- False Positives
- Anxiety from false positives
- Radiation exposure - ? Cancer initiation
- **No reduction in mortality**
- **Overdiagnosis**
Overdiagnosis

- Diagnosis of disease that won’t result in death (or significant morbidity):
  - Indolent disease
  - Breast cancer that regresses
  - Breast cancer diagnosed in a patient who dies from another cause
  - Some studies have suggested that 75% of breast cancers overdiagnosed
  - More realistic estimates are 1 – 10%
  - Frequency of mammogram screening does not change rate of overdiagnosis
Overdiagnosis ...

- At this stage, we cannot accurately predict potentially non lethal cancers..
- Overdetection vs overdiagnosis vs overtreatment ?
- *Empasiss* on overdiagnosis ignores the role of clinicians and pathologists
  - Pathologists - cancer assessment in the laboratory focuses on biological behaviour and subtyping
  - Oncologists and surgeons – implies a shotgun approach to treatment
- Ignores role of patient in decision making
Mammography screening guidelines

- Every 2 years from 50 – 69
- Every 2 years from 40 – 74
- Every year from 40 – any age where 7 – 10 years life expectancy
- Variations of above
Comparison of Recommendations for Screening Mammography Using CISNET Models

Elizabeth Kagan Arleo, MD; R. Edward Hendrick, PhD; Mark A. Helvie, MD; and Edward A. Sickles, MD

**BACKGROUND:** Currently, there are several different recommendations for screening mammography from major national health care organizations, including: 1) annual screening at ages 40 to 84 years; 2) screening annually at ages 45 to 54 years, then biennially at ages 55 to 79 years; and 3) biennial screening at ages 50 to 74 years. **METHODS:** Mean values of six Cancer Intervention and Surveillance Modeling Network (CISNET) models were used to compare these three screening mammography recommendations in terms of benefits and risks. **RESULTS:** Mean mortality reduction was greatest with the recommendation of annual screening at ages 40 to 84 years (39.6%), compared with the hybrid recommendation of screening annually at ages 45 to 54 years, then biennially at ages 55 to 79 years (30.3%), and the recommendation of biennial screening at ages 50 to 74 years (23.2%). For a single-year cohort of US women aged 40 years, assuming 100% compliance, more breast cancers deaths would be averted over their lifetime with annual screening starting at age 40 (29,369) than with the hybrid recommendation (22,829) or biennial screening ages 50-74 (17,153 based on 2009 CISNET estimates, 15,599 based on 2016 CISNET estimates). To achieve the greatest mortality benefit, this single-year cohort of women would have the greatest total number of screening mammograms, benign recalls, and benign biopsies performed over the course of screening by following annual screening starting at age 40 years (90.2 million, 6.8 million, and 481,269, respectively) than by following the hybrid recommendation (49.0 million, 4.1 million, and 286,288, respectively) or biennial screening at ages 50 to 74 years (27.3 million, 2.3 million, and 162,885, respectively). **CONCLUSION:** CISNET models demonstrate that the greatest mortality reduction is achieved with annual screening of women starting at age 40 years. *Cancer* 2017;000:000-000. © 2017 American Cancer Society.

**KEYWORDS:** breast cancer, life-years gained, lives saved, mammography, mortality benefit, screening.
Benefits of Annual Screening\textsuperscript{11,12,13}

- Most breast cancer deaths occur in women who do not undergo regular breast screening
- 40\texttt{-}50\% mortality reduction for annual screening
- 23\% mortality reduction for biennial screening
- Mean mortality reduction of annual screening from 40 – 84 is 71\% more than biennial screening of 50 – 74
Therefore ... 

- Annual Screening from age 40 saves the most lives, but has to balanced against financial burden
- Breast cancer is more common with increasing age
- Younger women have denser breasts and higher grade cancers
- More life years gained by detecting cancers in younger women
<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
<th>40 - 44</th>
<th>45 - 49</th>
<th>50 - 54</th>
<th>55 - 59</th>
<th>60 - 64</th>
<th>65 - 69</th>
<th>70 - 74</th>
<th>75+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iceland</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>USPSTF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>ACR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>ACS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>ASBrS*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>ACOG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Biennial
Recommended selectively biennial
Triennial
Annual
Recommended selectively Annual
Insufficient evidence
Advised against

USPSTF – United States Preventative Services Task Force
ACR – American College of Radiologists
ACS – American Cancer Society
ASBrS – American Society of Breast Surgeons
ACOG – American College of Obstetricians and Gynecologists
Guidelines - Summary

• Europe:
  • Every two years from age 50 to 70  UK – every 3 years
  • Population based program - Invitation
  • ± 75% of women in recommended population get screening

• USA:
  • Every year from age 40. Stop when life expectancy < 10 years
    (exception – USPSTF)
  • Opportunistic
  • ± 65% of women in recommended population get screening
Guidelines South Africa

• National:
  • No mammography
  • Clinical Breast Examination – annual
  • Diagnostic Mammogram if necessary

• BISSA (Breast imaging Society South Africa)
  • Annual Mammogram from 40

• CANSA (Cancer Society of South Africa)
  • Annual mammogram from 40 – 54, biennial thereafter

Only about 4% of the eligible population gets mammography screening.
KEY AREA 1: PREVENTION AND EARLY DETECTION, SCREENING AND GENETIC ASSESSMENT

OBJECTIVE 1: SCREENING AND EARLY DIAGNOSIS

**Standard 1.1**
Screen up to age 65: At least a yearly breast cancer screening examination by a trained health care provider using breast examination (CLEAN Breast Exam).<br>

**Standard 1.2**
All routine attending primary health care providers will be given opportunities to include breast education in their patient education materials and support breast self-examination (BSE).

**Standard 1.3**
Assessment messages should be disseminated to community and healthcare workers that any woman who reports a change in breast size or a lump needs a health facility for further assessment.

Rationale
Early detection followed by appropriate treatment is currently the most effective strategy to reduce breast cancer mortality. The overall success works on the assumption that the smaller the cancer detected, the better the survival outcome. Early detection programs in the organized and systematic implementation of interventions that complete early diagnosis, screening of sufficient resources are available, diagnosis, treatment and follow-up.

Early diagnosis is the awareness by the public or health professionals of early signs and symptoms of breast cancer in women that becomes known before the disease becomes more effective and simpler therapy. This concept is also referred to as “down-staging” by some researchers. Screening is the systematic mass application of a simple screening test in a presumably asymptomatic population at regular intervals in order to identify individuals with an abnormality suggestive of specific cancers, who then receive further investigation.

Ideally a screening tool for breast cancer would reduce mortality from breast cancer while having a low false alarm rate and being relatively cheap. The ideal screening tool would be simple, inexpensive and effective. Public awareness is augmented by training primary healthcare staff to perform resource-appropriate and cost-effective screening. To be effective, national screening programmes have to target women who will benefit the most, together with being affordable and sustainable.

**Screening modalities**
Clinical breast examination (CBE) refers to a breast examination performed by a trained healthcare worker. CBE is relatively simple and inexpensive, but its efficacy in reducing mortality from breast cancer has not been directly tested in a randomised controlled trial. CBE is more likely to detect cancers that are potentially lethal.

The Canadian national breast screening study 8 (CNBSS-8), which monitored women aged 50 to 59 years to mammography or CBE or both, concluded that the mammographic detection of operable cancers does not contribute to reduced mortality from breast cancer. These results are encouraging and may result in CBE assuming particular importance in resource-limited countries where mammography is unavailable or expensive, and despite it at an advanced stage of its development. CBE has sensitivity of 40 to 60 per cent and specificity of 88 to 90 per cent.

Economic models suggest that clinical breast examination by ancillary health workers (PHC-CBE) confirmed annually from the ages of 40 to 60 years can be as easily effective as mammographic screening for reducing breast cancer mortality in developing countries, but at substantially lower cost. Any screening programme, irrespective of modality, should encourage early diagnosis of breast cancer, especially in women between the ages of 40 to 60 years. Thus opportunistic CBE and awareness promotion should be pursued in women between these ages who attend primary care.

FURTHER DISCUSSION

Mammography (MAM) is the most commonly used screening test in developed countries. It is expensive and complex, requiring substantial financial and manpower resources. The goal of breast screening is to prevent death and not simply to detect cancers by mammography.

Screening MAM results in early diagnosis and more conservative therapies, but the breast benefit of screening mammography in decreasing breast cancer mortality is uncertain due to the incompleteness of the women studies. These range from no reduction in breast cancer mortality to a 30 per cent reduction among women aged 60 and above. It bears noting that improvements in breast cancer treatment have had a greater effect on breast cancer mortality than mammographic screening. Screening mammography should not be introduced unless resources are available to ensure effective and reliable screening of at least 75 per cent of the target group. Women aged 50 and older.

Lack of resources and infrastructures in the South African public health system render this strategy unfeasible. Possibly MAM should be performed on symptomatic and identifiable high-risk patients at specialized breast units.

**Monitoring and evaluation point**
- MAM
- SCt (sensory cue test) of uptake in eligible women in health facilities.
- Staff and competent nurses to allow healthcare workers to report breast lumps to qualified physicians and family doctors.

OBJECTIVE 2: RISK ASSESSMENT

**Standard 2.1**
All eligible women should take measures of breast cancer screening and be managed according to clinical practice.

Rationale
Women at moderately increased risk or greater should be encouraged to undergo yearly mammography from 40 to 60 years and yearly or biannually from 50 years.

<table>
<thead>
<tr>
<th>Objective Risk</th>
<th>Moderate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol consumption</td>
<td>Increasing age from 40 years</td>
<td>Personal history of invasive breast cancer</td>
</tr>
<tr>
<td>Reproductive factors</td>
<td>Reproductive factors</td>
<td>Reproductive factors</td>
</tr>
<tr>
<td>First full term pregnancy &gt; 35 years</td>
<td>Early menarche (&lt; 12 years: RR 1.2)</td>
<td>Late menopause (&gt; 55 years: OR 2.4)</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>Multicyst</td>
<td>Breast cancer of BRCa1 or 2 gene mutation</td>
</tr>
</tbody>
</table>

Women at high risk of developing breast cancer should be considered for annual breast MRI in addition to mammography and CBE.

Rationale
MRI is the most sensitive and specific method of screening in breast cancer susceptibility mutation carriers. In a systematic review by Lord et al., there was strong evidence that the addition of breast MRI to conventional screening tests provides increased sensitivity for early detection of breast cancer in young high risk women. However, there was also evidence that additional MRI may increase patient recall rates due to its high false positive findings.
Screening policy

- Country (cultural) dependant: Europe vs USA
- Specialist dependant: Radiologists vs surgeons/oncologists vs epidemiologists
- Funding dependant: Privately funded vs nationally funded

What’s best for the patient?

More frequent screening results in higher false positives, increased costs but decreased overall mortality. A combination of patient education and choice in the framework of the resources at hand is the most realistic model at present.
Optimal Screening guideline?

Population based screening is efficient, standardized and more affordable.

In a population based screening program, every 2 years is likely optimal.

Benefit from starting at 40 and with an aging population, offering screening > 70

Make DBT the mandatory?
22 months
Mammography

- Plain film
- Full Field Digital Mammogram
- Digital Breast Tomosynthesis

\{ CC and MLO \} (3D mammogram)
Images – mammogram types

- Plain Film (analogue)
- Full Field Digital
- Digital Breast Tomosynthesis

Sensitivity and specificity:

Plain Film < FFDM < DBT
Mammogram Types

Plain film

Digital

Tomosynthesis /3D
Tomosynthesis – 3D Mammos
DBT – reduces density and enhances margins
DBT sensitivity
Supplemental screening

• Dense breasts
  • Increases risk of breast cancer
  • More frequent in young and nulliparous patients
  • Decreases sensitivity of mammograms due to masking effect

• High Risk patients
  • Cancers at younger age
  • Higher grade, more aggressive molecular subtypes
  • Faster growing – interval cancers
  • More likely to be mammographically occult
Breast Density?

• Masking effect
• Density of fibro-glandular tissue against fatty background
  • Sensitivity of mammograms in fatty breasts: 80 – 90%
  • Sensitivity of mammograms in extremely dense breasts: 30 – 50%
• Independent risk factor
• Often denser in younger women
• Interval Cancers much more frequent in dense breasts!!
• HRT may prolong density
Breast density on mammogram

4 categories:
• ACR type A: Predominantly fatty ± 25%
• ACR type B: Scattered Fibroglandular Tissue ± 25%
• ACR type C: Heterogeneously dense (may obscure underlying cancers) ± 25%
• ACR type D: Extremely dense (lowered sensitivity) ± 25%

Therefore .. About 50% of patients have dense tissue that may hide a cancer and supplemental imaging is recommended.
Dense Breast Tissue on Mammography

USA legislation:

• Must inform patients of breast density following screening mammogram
• Advise patients with dense breasts of benefit of supplemental screening ...
Supplemental screening for dense breasts

- Is supplemental imaging eg ultrasound or MRI, feasible in population based screening?
- Maybe DBT answers the need?
- AI will potentially play a role
Supplemental modalities

- Breast ultrasound
  - Handheld
  - Automated Breast Ultrasound
- Breast MRI
  - Full vs abbreviated

.. In SA, most women who undergo Mammogram also have an Ultrasound. Medical aid pays one tariff
High Risk Screening

• Women at high risk (>20% lifetime risk) of developing breast cancer
• Often more aggressive cancers at a younger age with denser breasts and with poorer prognosis
• More likely to be occult on mammogram
• Risk assessment at 25 – 30, usually when known family history
• USA: Annual MRI from age 25 + annual Mammogram(from 30)
• Europe: Annual MRI from 10 years younger than closest relative + mammogram
Risk Factors

• BRCA mutation (and other genetic mutations) – patient and if first degree relative (untested) of known BRCA carrier
• Thoracic Radiation Therapy as a child/teen (lymphoma)
• Family history
  • No of first/second degree relatives
  • Breast and ovarian cancers
  • Young age
  • Subtype
  • Mortality
• Hormone Replacement Therapy
• Age at Menarche
• Nulliparity
• Previous Biopsy
  • High risk lesions eg ADH and LCIS
• Obesity
• Breast Density
• Personal history of Breast Cancer in younger patients
Risk Models

- Gail
- Klaus
- BRCAPRO
- Breast Cancer Surveillance Consortium - BCSC
- Tyrer Cuzick
Tyrer Cuzick Model

IBIS (International Breast Cancer Intervention Study)

IBIS Risk Assessment Tool

Hormone Replacement Therapy (HRT) Usage?
- Never
- Stopped use 5 or more years ago
- Stopped use less than 5 years ago
- Current User

BRCA Gene: Does the woman have a mutation in either the BRCA1 or BRCA2 gene?
- Unknown
- Tested, Normal
- BRCA1+
- BRCA2+

Ovarian Cancer: Has the woman had OVARIAN cancer?
- No
- Yes

Breast Biopsy: Has the woman had a breast biopsy?
- No prior biopsy / no pre-invasive disease
- Biopsy present
- Lobular Carcinoma in Situ (LCIS)

Family History:
Family history is an important factor in determining risk, especially if there is a history of breast or ovarian cancer in the woman’s family.

Ashkenazi Inheritance?
- No
- Yes

To add a family member to the woman’s family history, click the “Add Family Member” button below

IBIS Breast Cancer Risk Estimate Results:

Ten Year Risk:
This woman’s Risk (at age 39): 17.3%
Average woman (at age 39): 1.5%

Lifetime Risk:
This woman’s Risk (to age 65): 47.8%
Average woman (to age 85): 13.0%

This woman’s estimated risk for developing breast cancer over the next 10 years is 17.3% compared to a risk of 1.5% for a woman of the same age from the general population. The lifetime risk for developing breast cancer (to age 85) is 47.8% compared to a risk of 13.0% for a woman of the same age from the general population. This calculation also means that this woman’s chance of remaining breast-cancer free over the next 10 years is 82.7%.
Different interpretations ..

1. Less screening for average/low risk?
   • Only offer regular screening to higher risk women
   • But .... 70% of patients diagnosed with breast cancer have NO risk factors!
   • If you only test those with family history or BRCA mutations you will miss two thirds of breast cancers!
   • Although dense tissue is a risk factor, 50% of cancers in non dense breasts

2. More screening options for High Risk (average and low risk screening stays unchanged)
   • Risk assessment at younger age
   • Supplemental imaging and genetic testing
35 year old – High risk screening
Future Directions

• Artificial Intelligence
  • Triage of screening cases
  • Improving workflow
  • Giving patients feedback faster
  • Risk stratification

• Single Nucleotide Polymorphisms (SNPs)
• Liquid Biopsies
Bottom Line

- Screening mammography reduces mortality
- Screening also improves quality life years
- Screening, like treatment must be based on informed patient consent
- Personalised screening should offer more to higher risk patients, not less to average risk patients
- Challenges for developing countries ..