Introduction

- Results of randomized trials have lead to the implementation of regional and national population based screening programs for breast cancer in at least 22 countries within the past 20 years


Breast Cancer Screening

- The primary aim of a breast screening program is to reduce mortality from breast cancer through early detection
- Unnecessary workup of lesions which show clearly benign features should be avoided in order to minimize anxiety
- Balance of benefits vs harms

Breast Screening Guidelines

- Developed to address the benefits and harms and provide best advice
- Population based screening has been proven to work
  - RCTs
  - Service Screening Results
    - UK NHS BSP,
    - Dutch Screening Program
- Does this data inform screening in the USA?
Breast Cancer Screening - Benefits

- Proven Reduction in Mortality
  - RCTs with long term follow up
  - Magnitude of benefits controversial
- Various authors have attempted to apply data for various age bands, but these RCTs were not designed to allow this type of analysis
- Benefits acknowledged for all ages
  - Benefits may vary between age bands

Breast Cancer Screening - Harms

- Can be looked at as a risk/benefit balance
- False negatives
  - Mammography the current ‘gold standard’
  - 85-96% accuracy
  - Mammographically ‘occult’ cancers
  - False reassurance that the test is negative

Breast Cancer Screening - Harms

- False positives
  - Findings that simulate malignancy
    - Eg radial scar or fat necrosis
  - Spectrum of pre-invasive disease
  - ‘Unnecessary’ biopsies
    - Benign calcifications
    - Low grade DCIS

Breast Cancer Screening - Harms

- Radiation risk
  - Task forces acknowledge that radiation risk is not a significant factor in screening (minor concern)
  - Some groups claim radiation induced cancers may occur as a result of screening younger women over a longer period
Screening Interval

- Shorter interval, pick up more of the aggressive tumors
- Still miss those that develop during ‘sojorn’ time
  - *sojorn time – growth before they become detectable
- Longer interval, miss a few more of the aggressive cancers, but more likely to have a greater proportion of better prognosis tumors
- UK trials showed 50% interval cancers occur between year 2 and 3 (therefore prefer 2 yearly)

Cancer Biology Varies with Age

- Breast Ca in general:
  - Faster growing in younger age group
  - Slower at older ages
- Proposal out of Europe based on biology
  - 40-50 yrs annual screen
  - 50-60 yrs 2 yearly screen
  - 60-70+ yrs 3 yearly screen

Screening for Breast Cancer

- Does not work for some rapidly growing tumors (which present as interval cancers)
- Also for some women who are diagnosed with a lesion which does not have the potential to kill them
  - Lead time bias
  - Low grade DCIS (progresses to low grade IDC) in 8% over 30-40 years
  - High Grade DCIS (progresses to High Grade IDC) in 85% in 5 years

^Silverstein: DCIS 2nd Edition
Over-diagnosis of DCIS

- Non-comedo DCIS is a non-obligate precursor that involves a very long clinical evolution to invasive carcinoma in approximately 50% of women.
- Evidence overwhelmingly demonstrates that DCIS is a spectrum of disease ranging from extensive, high-grade lesions, most likely requiring mastectomy for eradication, to small, low-grade lesions, which can be cured effectively by excision alone.


DCIS Spectrum and Models

- Variants in models of progression of DCIS
  - One model suggests –
    - ADH → low grade DCIS → IDC Gd 1
    - ADH → Intermediate grade DCIS → IDC Gd 2
    - High Grade DCIS → IDC Gd 3
- DCIS is a heterogeneous disease
  - Kappa stats suggest the best agreement with a combination of Van Nuys system and grading systems with 3 grades
    - EU Working Group on Breast Screening Pathology (2007)

Diagnosis

- Currently rests on needle biopsy and (less so) on surgical excision
- Needle biopsy is not a serious ‘harm’ BUT is costly
- Can we be intelligent in targeting biopsy to those women who have a lesion from which they would benefit by being treated?
- Big difference in benign biopsy rates between USA and other developed countries
  - Medico-legal exposure
  - BIRADS strict interpretations (needs refining by research)

Diagnosis – BIRADS 4

- Potential DCIS is usually lumped in the BIRADS 4 category
- Spectrum of risk of cancer between 2 and 95%
- Attempts to stratify, currently unsupported by evidence
- Patient usually end up getting biopsy
  - Mostly fibrocystic change or calcifications in benign ducts
  - Low Grade DCIS/ADH etc – patients end up getting a surgical biopsy
  - Benign to malignant ratio – USA 5:1, UK 1:1

J Pathol. 1999;187:396-402
**Studies needed to stratify**

- Large scale studies are required to determine
  - Can we reliably find imaging features (possibly combined with genetic tests or risk factors) that allow us to just watch
  - Which of these is an ‘emergency’?
- Does a small area of high grade DCIS need to be excised early?
- How long does it sojourn before turning into a killer disease?

**Guidelines**

- Many groups have produced guidelines
  - American Cancer Society
  - US PSTF
  - AMA and NCCN
  - UK NHS BSP
  - European Guidelines

**Guidelines**

- With some groups, guidelines keep changing
  - Recent US PSTF recommendations
    - After supporting screening women under 50 yrs in their last edition (2002), they turned tail in 2009
    - Used incomplete early data, especially from the UK National Age Trial
    - Recognized that there was benefit, but decided not enough to recommend screening for this group
    - Did not understand the issues that underestimated the benefits
US Preventive Services Task Force

- Latest Guidelines November 2009
- Recommendations:
  - NO routine screening mammography in women aged 40 to 49 years
  - Biennial screening mammography for women aged 50 to 74 years
  - No BSE
  - No CBE after 40 years

Ann Int Med 151;10:727-737

US PSTF Recommendations

- There is convincing evidence that screening with film mammography reduces breast cancer mortality, with a greater absolute reduction for women aged 50 to 74 years than for women aged 40 to 49 years

US PSTF Guidelines

- Used the CISNET Breast Cancer Modeling Group to provide data from comparative decision models on optimal starting and stopping ages and intervals for screening mammography
- The data they fed in were ‘incorrect’ or ‘worst-case scenario’, which has led to an underestimation of benefits from screening

US PSTF Guidelines

- The Task Force counts DCIS as an insignificant disease, and therefore a false positive/harm
- They ignored the pathological and outcome data presented earlier
- Most (69%) DCIS found at screening* is high grade
- Screen detected ductal carcinoma in situ (DCIS): over-diagnosis or an obligate precursor of invasive disease?

Guidelines

- Based on long term follow up data of Swedish 2 Counties Trial (the best RCT) and the early results from the UK Age Trial
  - Data supports screening under 50’s
  - Mortality reduction 35-40% (some disagree with this finding)
  - Years of ‘productive life’ saved
- Is the cup “half full” or “half empty”
- Cost effectiveness issues

Guidelines

- BSE and CBE
  - Not really controversial, but for women under 50 years, if you take away screening mammography, you also take away the only tests that could potentially pick up a cancer early

Guidelines

- If the USPSTF had introduced the idea of ‘de-authorizing’ examination then they would have not met with too much controversy
- If the USPSTF had introduced the idea of biennial mammography screening there would likely have been a splutter of response
- By including a controversial must discuss with physician rule on under 50’s – engendered much bad feeling

Guidelines

- American Cancer Society and the American College of Radiology continue to strongly support screening women from 40 years
Questions arising -

- Who benefits from screening?
  - Can we identify women who will benefit from mammographic screening?
  - Can we identify women at risk of ‘aggressive’ disease and target them with preventative therapy?
    - Move them into the group that would also benefit from screening, without presenting as interval cancers

Dangers of implementing guidelines

- How many family physicians can have a sensible discussion about whether a woman should have a mammogram between 40 and 50?
- It is hard enough for those of us exposed to all the arguments
- No such thing as a ‘low risk’ under 50 woman yet
  - 93 - 95% of breast cancer in under 50’s is not related to family history
  - Changes in insurance coverage as a result

Who **DOES NOT** benefits from screening?

- Can we determine which women will, or are, developing an ‘indolent’ type of cancer?
- Can we prevent unnecessary biopsy in this group?
- Is breast density a good measure for who will benefit from mammography, and who will not?
  - The jury is out
What hope for future screening?

- Targeted to ‘HIGH RISK’ groups
  - BRCA 1, BRCA 2 etc
- Relationship of breast cancer risk and breast density
- ACS recommendations
  - Risk >20%-25%
  - Annual MRI
  - Annual Mammography

Screening for High Risk Women

- Screening MRI is recommended for women with an approximately 20–25% or greater lifetime risk of breast cancer
- This also includes patients treated for Hodgkin’s Lymphoma by mantle irradiation

Breast MRI

- MRI is highly sensitive to small abnormalities but not as specific as some other modalities when it comes to diagnosing cancerous lesions in breast tissue
- Specificity is relatively low
  - Blind-spots
  - DCIS
  - Mammography is complimentary

Breast MRI

- Lots of false positives
- Foci of enhancement or enhancing breast tissue, analogous to breast density in obscuring a potential cancer
High Risk Screening with US

- **ACRIN 6666 trial**
  - Performed by enthusiasts
  - Sensitivity similar to MRI

EARLY RESULTS
- Significant False Positives
- Substantial increase in the number of benign biopsies

GUIDELINES

CLOSE THOUGHTS

Comparisons with Europe

- USPSTF decided to suggest screening intervals similar to Europe with 2 yearly screens
- Objections to this include
  - Ave screening interval now 18 months
  - Dartmouth data show a wide variation in uptake of screening within a 2 year period (10% in some areas to nearly 70%)
  - USA does not do ‘population screening’
    - More an opportunistic type of screening
- USPSTF missed the opportunity to call for a national screening program
Breast Cancer Screening Guidelines

- **Summary**
  - Mammography Screening works
  - Various guidelines exist
  - Most contentious guideline – screening under 50
  - Other types of cancer screening being tested
    - BUT with significant HARMS!
- **CHALLENGES**
  - Can we be more intelligent in how we do the whole screening process?
  - Lack of comprehensive data collection in the USA