Reducing harms and maximising the benefits

Andy Evans

Dundee
Harms

- Overdiagnosis
  - DCIS
  - Tubular cancer
- False positives
- False negatives
- Radiation induced cancers
Benefits

• Reducing breast cancer deaths
• Less treatment
Reducing harms
DCIS

• LORIS has just recruited its 50th patient

• New insights into the natural history of DCIS

• Should we call it DCIS?
Screen detection of ductal carcinoma in situ and subsequent incidence of invasive interval breast cancers: a retrospective population-based study

• METHODS:
  • aggregate data for screen-detected cancers from 84 local screening units
  • Data for DCIS diagnoses were obtained for women aged 50-64 over a four year period
  • Patient-level data for interval cancer arising in the 36 months were analysed by Poisson regression.

Screen detection of ductal carcinoma in situ and subsequent incidence of invasive interval breast cancers: a retrospective population-based study

• RESULTS

• 5,243,658 women in the study

• There was a significant negative association of screen-detected DCIS cases with the rate of invasive interval cancers (Poisson regression coefficient $-0.084$ [95% CI $-0.13$ to $-0.03$]; $p=0.002$).

• for every three screen-detected cases of DCIS, there was one fewer invasive interval cancer in the next 3 years

Screen detection of ductal carcinoma in situ and subsequent incidence of invasive interval breast cancers: a retrospective population-based study

Comment

• Surprised at size and speed of effect on interval cancers
• Effect at subsequent screening round is likely to be at least as big
• Evidence that units with high DCIS rates will have less invasive cancers to detect at subsequent rounds
• Confirms detecting high grade DCIS is important

Balanced view on the benefits and harms of DCIS detection
How different terminology for ductal carcinoma in situ (DCIS) impacts women's concern and management preferences: A qualitative study

- communicating a diagnosis of DCIS using terminology that does not include the cancer term was preferred by many women and may enable discussions about more conservative management options

B Nickel et al Breast 2015;24:637-679
Invasive Tubular cancer

• Breast cancer death only occurs if women who have had a tubular cancer develop a subsequent more aggressive cancer
• Women with tubular cancer have the same survival as women with DCIS with no breast cancer deaths in the follow-up period
• Prognosis significant superior to grade 1 ductal carcinomas

1. Emad A Rakha et al. JCO 2010;28:99-104
Oncotype DX scores by histological type

- Micropapillary: 29
- DNST: 19.4
- Mucinous: 17.2
- Lobular: 15.7
- Tubular: 10

Bomiesl PE et al. Arch Pathol Lab Med. 2015 Dec;139(12):1546-9
Invasive tubular cancer

- Why are we treating it like other invasive cancers?
- Do we need whole breast RT?
- Do we need adjuvant hormone therapy?
- Do we need surgery? Why not VAB excision and follow –up?
No breast cancer subgroup can be spared postoperative radiotherapy after breast-conserving surgery. Fifteen-year results from the Swedish Breast Cancer Group randomised trial, SweBCG 91 RT

• After 15 years of follow-up, a higher cumulative incidence of IBTR was observed in control patients, 23.9%, versus irradiated patients, 11.5%, P<0.001

**But** no analysis by grade or type only 50% were ER positive

Women's Experiences of Inaccurate Breast Cancer Screening Results: A Systematic Review and Qualitative Meta-synthesis

- Women who had experienced false-negative results struggled to restore trust in screening
- Recognized that some breast cancers were identified through mammography
- They were willing to see themselves as exceptions to an otherwise beneficial service.

Women's Experiences of Inaccurate Breast Cancer Screening Results: A Systematic Review and Qualitative Meta-synthesis

- Synthesis 16 primary qualitative studies
- False-positive result caused short-term anxiety but it also led to reoccurring anxiety during future screening
- Anxiety experienced was magnified in high-risk women
- Despite this increased anxiety, women who had experienced a false-positive result were generally not deterred from future screening

Radiation risk of breast screening in England with digital mammography

- ratios of lives saved by screening to radiation-induced cancers
  - 30-60 : 1
- ratios of lives saved by screening to deaths due to radiation-induced cancers were 156-312 : 1
- For the 1.8% of the screening population with very thick breasts, the latter ratios decrease to 94-187 : 1

Maximising the benefits

DO SOMETHING
DO ANYTHING

DON'T KEEP CALM just DO SOMETHING ABOUT IT

The Knee-Jerk Reaction Committee
Screening at a cross roads

More modalities
- Tomo
- US
- MRI
- CEM

Personalised screening
- SNP’s
- Density
- Texture
- Interval
- Age range
Its all about saving lives
detecting more cancers is a means not an end

• Tomo finds spiculate lesions which tend to be low grade and at mgm
detection already have an excellent outcome
• US screening also has bias towards detection of low grade invasive
cancers and has poor specificity
• MRI and CEM do not have a low grade bias but are expensive and less
practical

No obvious front runner
Rapid review: Estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts

• Studies comparing different women screened with tomosynthesis (N = 103,230) or with 2D-mammography (N = 177,814)

• Pooled difference in BC detection of 1.4/1000 screens (P < 0.001),

• Pooled difference for recall of -23.3/1000 screens (P < 0.001)

Rapid review: Estimates of incremental breast cancer detection from tomosynthesis (3D-mammography) screening in women with dense breasts

• Meta-analysed data from prospective trials comparing these mammography modalities in the same women (N = 10,188) showed incremental BC detection of 3.9/1000 screens attributable to tomosynthesis (P < 0.001)

Implementation of Synthesized Two-dimensional Mammography in a Population-based Digital Breast Tomosynthesis Screening Program

Historical comparison if screening with synthetic 2D (s2D) and DBT vs. DBT and FFDM

Recall rate for s2D/DBT versus FFDM/DBT was 7.1% versus 8.8%, respectively (P < .001)

Biopsy rate for s2D/DBT versus FFDM/DBT decreased (1.3% vs 2.0%, respectively; P = .001)

No difference in cancer detection rate for s2D/DBT versus FFDM/DBT (5.03 of 1000 vs 5.45 of 1000, respectively; P = .72)

Spiculate lesions

• Associated with low histological grade
• Independent good prognostic effect for spiculation on multivariate analysis including histological grade
• DBT finds more radial scars

Evans A et al. AJR 2006;187:1-6
Lang K et al. Eur Radiol 2016:26; 3899-3907
DBT and outcomes

• No evidence for a reduction in breast cancer mortality
• No significant reduction in interval cancers
US screening

Finds more cancers
High recall and biopsy rate
Poor PPV
Hand held or ABUS?
SWE?
Ultrasound as an Adjunct to Mammography for Breast Cancer Screening

• We found no evidence that evaluated the comparative effectiveness or diagnostic accuracy of screening breast ultrasound as an adjunct to mammography among average-risk women aged 50 years and over

Screening US and outcomes

• Adding US when screening dense breasts has not been shown to reduce breast cancer mortality
• Adding US has been shown to reduce interval cancer rates in 2 studies
• 46% of US alone detected cancers are grade 1  c.f. 19% for mgm detected cancers

Ohuchi N et al, Lancet 2016 ;387:341-8
MRI

• No bias towards low grade disease
• staging MRI in older women increases synchronous contralateral breast cancer detection rate
• was not offset by a decrease of subsequent contralateral breast cancer
• MRI in older women with breast cancer may lead to significant overdiagnosis

MRI

• Screening almost certainly reduces breast cancer mortality in BRCA2 carriers

• How practical is MRI screening of non high risk women?
What direction for screening?

• New modalities on their own are not the answer
• They have to be integrated in tailored/personalised screening
Tailoring Breast Cancer Screening Intervals by Breast Density and Risk for Women Aged 50 Years or Older: Collaborative Modeling of Screening Outcomes.

Average-risk women with low breast density undergoing triennial screening and higher-risk women with high breast density receiving annual screening will maintain a similar or better balance of benefits and harms than average-risk women receiving biennial screening.

Cost-Effectiveness of Double Reading versus Single Reading of Mammograms in a Breast Cancer Screening Programme

• Data from 29,000 screens

• The detection rate of double reading (5.17‰) was similar to that of single reading (4.78‰; P = .768)

• double reading appears not to be a cost-effective strategy in the context of digital mammography

Women's interest in a personal breast cancer risk assessment and lifestyle advice at NHS mammography screening

• A total of 1803/4948 (36.4%) completed questionnaires were returned

• Most participants (93.7%) expressed interest in a personal risk assessment

• 95% believed it would make no difference or encourage re-attendance

Women's interest in a personal breast cancer risk assessment and lifestyle advice at NHS mammography screening.

- Two-thirds (1208/1803) associated lifestyle with breast cancer
- but many were unaware of specific risks such as weight gain, obesity, alcohol consumption and physical inactivity
- NHS sourced advice was expected to be more credible than other sources
- booklets, brief counselling or an interactive website were most preferred for accessing this.

Impact of Screening on Breast Cancer Mortality: The UK Program 20 Years on

- Case control study based on women in London
- Attendance at breast screening resulted in a breast cancer mortality reduction of 39% [OR, 0.61; 95% confidence interval (CI), 0.44-0.85]
- Attendance in the last 3 years prior to diagnosis resulted in a 60% mortality reduction (OR, 0.40; 95% CI, 0.31-0.51)
- Lead time bias effects were negligible
