

RANZCR BIG scientific meeting Queenstown, NZ, 5-8 April 2017

## Overdiagnosis in population breast screening: Implications for future screening practice

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## Acknowledgement

- I receive research support through a National Breast Cancer Foundation (NBCF Australia) **Breast Cancer Research Leadership Fellowship**

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## Breast Cancer Screening

- Increasingly **complex** scenario:
  - Vast knowledge of outcomes of breast screening: history of **polarised views** (science / political/ professional/ consumer influence) further diverge in past decade over the issue of **overdiagnosis**

### Presentation

- Briefly: benefit, harms
- Overdiagnosis in breast cancer screening
- Implications for future screening practice

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## The benefit of screening: BC mortality reduction

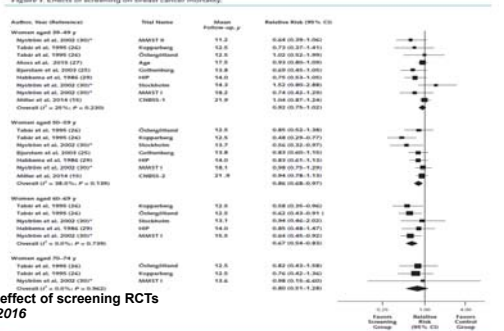
### Reducing risk of dying from breast cancer

- Highly valued effect
- Variable estimates (studies using various methods) but almost all studies show that **mammography screening associated with reduced risk of BC-specific death** (not all cause mortality)
- Benefit most established in 50-69

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Figure 3. Effects of screening on breast cancer mortality



Age-specific effect of screening RCTs  
Nelson et al 2016



## Evidence from breast screening RCTs: effect of screening on risk of advanced BC; Nelson et al 2016

Advanced BC stage III+ : meta-analysis indicated no difference with screening for women age 40-49 years RR 0.98 (CI 0.74 to 1.37) but reduced risk of advanced breast cancer with screening for age ≥50 years RR 0.62 (CI 0.46 to 0.83)



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**Evidence from observational studies & from service screening**

**Most report beneficial effect from breast screening**

- May be more relevant (than RCTs) especially if conducted in current practice in screening programs ... but prone to bias and likely to overestimate effect of screening

*Various methodologies and broad variation in estimates of benefit.*

- Incidence-based mortality studies (RR breast ca death, range **0.52-0.90**)
- Case-control studies: majority show benefit from screening and generally more favourable benefit from screening than estimated from RCTs (OR of breast ca death, range **0.42-0.92**)

Reported ranges based on: Njor et al (Euroscreen), J Med Screen 2012; Harris et al, Prev Med 2011; Schopper & De Wolf, EJC 2009; Roder et al, BCRT 2008; Gabe & Duffy, Ann Oncol 2005; and UK Independent Panel on Breast Screening report 2012.

**Breast Screening: the harms**

- Exposure to **radiation** (affects **all** screened women): small potential to induce a breast ca considered to be outweighed by potential benefit
- False-positives** (unnecessary testing & intervention): **most frequent** harm; increases with more intense screening, eg annual vs biennial → **substantial cumulative risk** over repeated screening rounds substantial (10 rounds: 20-40% depending on setting)
- Over-diagnosis** (over-detection): most **serious** harm & most debated

Population health perspective appears to over-emphasize harms: population screening is advocated to 'well' women (no symptoms), *overall more will experience one or more of the harms* than they will derive benefit (BC mortality reduction)...so public health decisions **consider the balance** (benefits vs harms) to ensure there is **net benefit**

**Major controversy: Overdiagnosis (overdetection/ OD) in Breast Screening**

**What is 'overdiagnosis' (overdetection)?** detection of cancers, which in the absence of screening, would **not** have been found and would **not** have become symptomatic, and would **not** have had any adverse consequence on the individual

**Why does overdiagnosis occur?**

- screening mammography confers benefit (mortality reduction) by detecting cancer at early stage (including in-situ disease & early invasive)
- 'some' of early-detected malignancies revealed through screening may never have caused adverse consequences/ may not become biologically or clinically apparent
- Screening (snapshot in time) is more capable of detecting slower growing cancers .... Breast ca has heterogeneous biology**
- OD is **not** an epidemiologic myth: flip-side of coin of early-detection of cancer

**What is the magnitude of Overdiagnosis (overdetection) in breast cancer screening?**

**Divergent estimates of OD** from mammography screening: range from **0 to >50%** (Biesheuvel et al, *Lancet Oncology* 2007) reflect variable:

- Methodological approaches (can over or under-estimate OD%)
- Analytic approaches, including adjustments (over or under-estimate/ adjust)
- Definition of OD used in calculation
- Might also reflect true differences in OD frequency (different screening sensitivity & populations)

Study design	Range of estimates of breast cancer overdiagnosis
Randomised controlled trials*	10% to 22%
Cohort studies	1.0% to 19.4%
Ecological studies	1.0% to 76.0%
Modelling studies	0.3% to 31.9% ‡

**Estimates of overdiagnosis attributed to population mammography screening** (summarised from a Systematic Review by Carter, Coletti, & Harris *BMJ* 2015)

**Meta-analysis of OD estimates (same data & RCTs) from UK Independent panel: 2 different definitions; same numerator excess BCs**

**Figure 2: Meta-analysis of estimates of overdiagnosis from trials without systematic end-of-study screening of the control group.**

(A) Excess cancers as a proportion of cancers diagnosed over long-term follow-up in women invited for screening.

(B) Excess cancers as a proportion of cancers diagnosed during the screening period in women invited for screening. Weights are from random-effects analysis.

\*available at: [www.cancerresearchuk.org/sites/default/files/ibsr-fullreport.pdf](http://www.cancerresearchuk.org/sites/default/files/ibsr-fullreport.pdf)

**Press release**  
Independent breast screening review

**IBSR**  
Independent Breast Screening Review

**Tuesday 30<sup>th</sup> October 2012**

**SCREENING REDUCES BREAST CANCER DEATHS – AT THE COST OF OVERDIAGNOSIS**

**No Consensus on Overdiagnosis**

**IBSR: 1 BC death prevented: 3 BCs over-diagnosed**

**EUROSCREEN**  
2 BC deaths avoided: 1 BC over-diagnosed

The expert Panel's report, commissioned by Cancer Research UK and the Department of Health, has concluded that – having studied all the available evidence – for each breast cancer death prevented, about three overdiagnosed cases will be identified and treated. Overdiagnosis means that a cancer was detected through screening but would not have caused a problem in the woman's lifetime.

But, because it is not possible for either the woman or her doctor to know which screen-detected cancers are potentially fatal and which represent overdiagnosis, all will usually be treated, with the accompanying impact on quality of life and psychological well-being.

Estimated <b>trade-off</b> shown as a ratio between number of breast cancer deaths that are averted and cases that are overdiagnosed	
Source	Ratio of breast cancer deaths averted to cases overdiagnosed
UK's Independent Panel on Breast Cancer Screening (2012) for women invited to screening from age 50 for next 20 years	1:3

Adapted from a Review by N. Houssami, Cancer Biol Med 2017; 14: 1-8


### BC overdiagnosis: implications for future practice, population BC screening

- › Inform women (balanced, accurate information –that they can understand): shared decision-making
- › 'Benefit' from new technologies: not enough to show increased BC detection; requires evidence that this represents dx of BCs that are likely to progress
- › Change to practice/policy: careful evaluation of how it modifies balance of benefit vs harms (increased focus on well-designed service-embedded evaluations)
- › Tailored & risk-stratified screening (screen to maximise benefit)
- › Consider life expectancy when making recommendation or policy decision
- › Overtreatment: Trials of less intense treatment for low-risk screen-detected disease especially for older women ..... & stop blaming the 'treatment' guys!

### Do we inform Women about OD from breast screening? YES, we should

No simple answer on how to do so but we have ethical responsibility to provide honest & accurate information to women

- › Develop & test information (involve all stakeholders; different perspectives)
- › Qualitative studies: eliciting information on how/whether women can understand information on OD, focus group methods
- › Quantitative studies: formally measuring impact of providing OD information on comprehension, intention to screen or screening participation



### RCT of a Decision Aid to inform women on OD (adapted from Hersch et al, Lancet 2015)

Results (women aged 48-50 years, n=838 interviewed post-intervention)

**Compared with the control DA, the intervention DA resulted in:**

- › Improved knowledge about breast screening (29% vs. 17% 'adequate')
- › Less positive attitudes to having breast screening (69% vs. 83% 'positive')
- › **Reduced intention to have breast screening in next 2-3 yrs (74% vs. 87%)**
- › **More women making an informed choice (24% vs. 15%)**
- › Less worry about developing breast cancer

**Use of a decision aid including information on overdiagnosis to support informed choice about breast cancer screening: a randomised controlled trial**

Published Online: February 19, 2015  
http://dx.doi.org/10.1016/S0140-6736(15)00000-4  
New England Journal of Medicine

### RCT of a Decision Aid to inform women on OD (Follow-up of RCT participants)

**Results at follow-up of participants (>80%)**

**Compared with the control DA, the intervention DA had no effect on self-reported participation in screening:**

- › At 12 months: 29% vs 29% (no difference)
- › At 24 months: 50% vs 51% (no difference)
- › Significantly more DA women retained adequate conceptual knowledge (34% vs. 20%, p<0.01) – from Hersch et al (abstract 2017)

### Evidence on new screening technologies: more BC detection not equivalent to screening benefit

Assess incremental mortality reduction to determine additional screening benefit however this is *not feasible*: unlikely that decisions can wait 10+ years: indirect (surrogate) measures of benefit

New technology with enhanced BC detection→ is it adding more into the pool of OD or more into benefit (a bit of both)?

Increased BC detection: critical to show that finding 'extra' cancers translates into less interval BC and/or less advanced BCs

These surrogate measures hard to assess statistically (needs large datasets), and less ability to show effect in annual screening, therefore increasing need for 'collaborative' studies that are planned prospectively.




International /multicentre collaborations to provide key evidence on effect of new screening technologies

Effectiveness of digital breast tomosynthesis (3D-mammography) in population breast cancer screening: *A protocol for a collaborative individual participant data (IPD) meta-analysis*

> primary end-point: interval BC rates

Investigators: Nehmat Houssami, Sophia Zackrisson, Kristina Lång, Solveig Hofvind, Daniela Bernardi, Kylie Hunter, Lisa Askie, Per Skaane (+ others: new collaborative teams 2017-18)

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**Breast Screening: A framework for future practice**  
Adapted from a review by N. Houssami, Cancer Biology & Medicine 2017

**Improve benefit:**  
Improve detection of biologically-relevant BC→ early-detection strategies leading to reduction in advanced disease or interval cancer rates  
Risk-tailored screening (target those at most risk of BC)  
Factor likely life-expectancy and overall health when making individual screening recommendations

**Reduce harm:**  
Biennial rather than annual population BC screening  
Policy or practice or technology changes → evidence that false-recalls are not increased (or are decreased); evidence that change will *not preferentially increase overdiagnosis*  
Risk-tailored screening (less screening, or less intensive screening, of those at lowest risk of BC)  
Factor likely life-expectancy and overall health when making individual screening recommendations

**Optimise balance between benefit and harms of breast cancer screening**

**Embed evaluations into screening practice:**  
Evaluate changes to screening (including new technologies) using rigorous methods; underpin by economic evaluations  
Consider collaborative and/or randomised trials to assess impact of practice changes on benefit/harm balance  
Build large-scale datasets (screening measures, tumour biology, treatment) for monitoring and for research

**Foster society and individual values:**  
Factor societal and ethical perspectives into all components of screening framework  
Provide complete and balanced information on screening outcomes to support women in making informed decisions about screening participation

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