Screening for Breast Cancer

Examining the Paradigm

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Goal of Screening

- Detect asymptomatic breast cancers in order to reduce mortality from breast cancer
  - Prior to clinical presentation
  - Prior to palpable mass
  - Prior to metastatic spread
    - Distant metastases
    - Lymph node metastases

Overview of screening

- Results of screening trials
- Does size predict survival?
- Does reducing size improve survival?

The benefits and harms of breast cancer screening: an independent review

*Independent UK Panel on Breast Cancer Screening**

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See Editorial page 1714

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Whether breast cancer screening does more harm than good has been debated extensively. The main questions are how large the benefit of screening is in terms of reduced breast cancer mortality and how substantial the harm is in terms of overdiagnosis, which is defined as cancers detected at screening that would not have otherwise become clinically apparent in the woman's lifetime. An independent Panel was convened to reach conclusions about the benefits and harms of breast screening on the basis of a review of published work and oral and written evidence presented by experts in the subject. To provide estimates of the level of benefits and harms, the Panel relied mainly on findings from randomised trials of breast cancer screening that compared women invited to screening with controls not invited, but also reviewed evidence from observational studies. The Panel focused on the UK setting, where women aged 50–70 years are invited to screening every 3 years. In this Review, we provide a summary of the full report on the Panel's findings and conclusions. In a meta-analysis of 11 randomised trials, the relative risk of breast cancer mortality for women invited to screening compared with controls was 0·80 (95% CI 0·73–0·89), which is a relative risk reduction of 20%. The Panel considered the internal biases in the trials and whether these trials, which were done a long time ago, were still relevant; they concluded that 20% was still a reasonable estimate of the relative risk reduction. The more reliable and recent observational studies generally produced larger estimates of benefit, but these studies might be biased. The best estimates of overdiagnosis are from three trials in which women in the control group were not invited to be screened at the end of the active trial period. In a meta-analysis, estimates of the excess incidence were 11% (95% CI 9–12) when expressed as a proportion of cancers diagnosed in the invited group in the long term, and 19% (15–23) when expressed as a proportion of the cancers diagnosed during the active screening period. Results from observational studies support the occurrence of overdiagnosis, but estimates of its magnitude are unreliable. The Panel concludes that screening reduces breast cancer mortality but that some overdiagnosis occurs. Since the estimates provided are from studies with many limitations and whose relevance to present-day screening programmes can be questioned, they have substantial uncertainty and should be regarded only as an approximate guide. If these figures are used directly, for every 10 000 UK women aged 50 years invited to screening for the next 20 years, 43 deaths from breast cancer would be prevented and 129 cases of breast cancer, invasive and non-invasive, would be overdiagnosed; that is one breast cancer death prevented for about every three overdiagnosed cases identified and treated. Of the roughly 307 000 women aged 50–52 years who are invited to begin screening every year, just over 1% would have an overdiagnosed cancer in the next 20 years. Evidence from a focus group organised by Cancer Research UK and attended by some members of the Panel showed that many women feel that accepting the offer of breast screening is worthwhile, which agrees with the results of previous similar studies. Information should be made available in a transparent and objective way to women invited to screening so that they can make informed decisions.

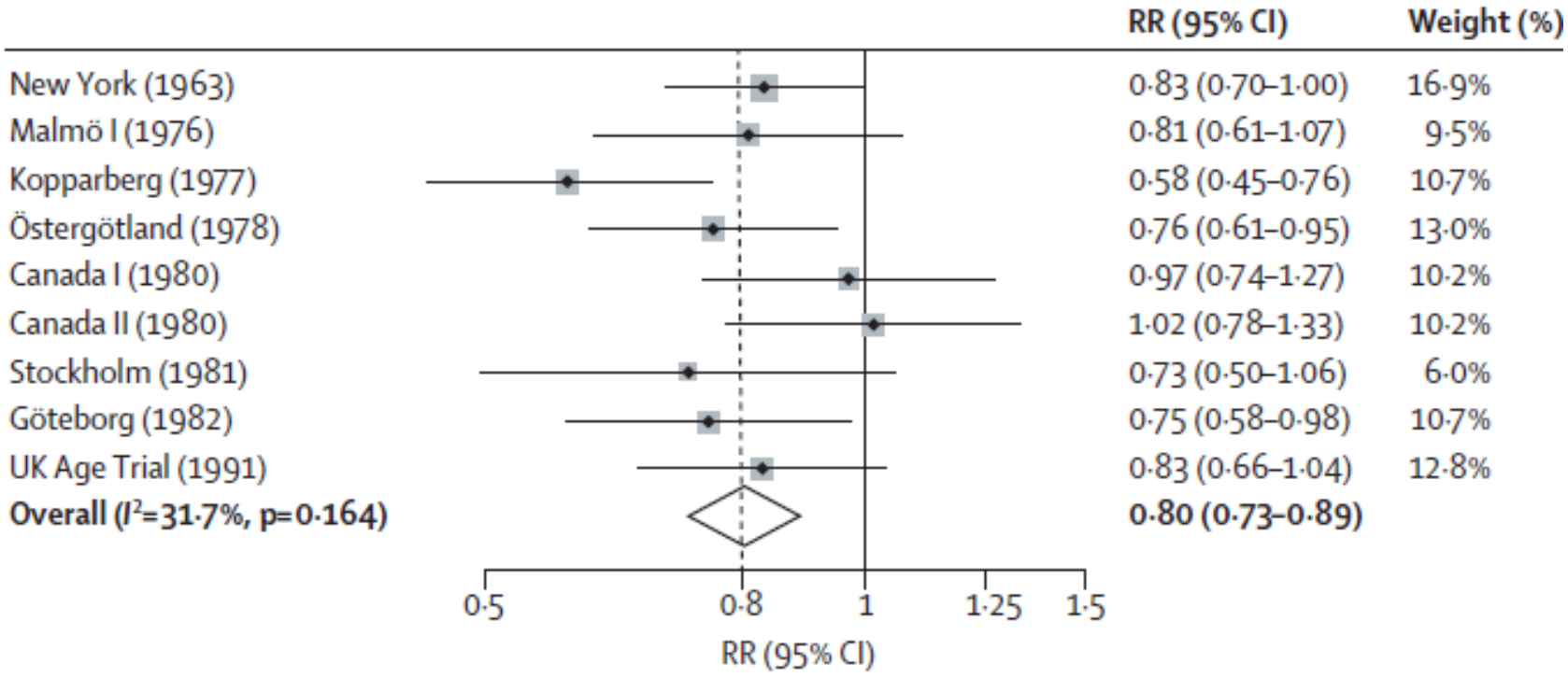
Introduction

After the recommendations made by Professor Sir Patrick Forrest in his report on breast screening in 1986,[1] women have been invited to screening through the NHS Breast Cancer Screening Programme since 1988. Since screening was established in the UK, additional follow-up data have become available from the trials on which the Forrest Report recommendations were based and from other randomised trials. Moreover, many observational studies have assessed existing population screening programmes.

This additional information has stimulated a continuing debate about the potential benefits and harms of population breast screening. The debate has focused on the reduction in mortality attributable to screening, the numbers of women overdiagnosed, and the way that the risks and benefits are communicated to women invited for screening. The arguments have become polarised between those who believe that the benefit of a decrease in mortality outweighs the harms and those who believe the opposite. These contrasting views of the evidence have arisen partly from disagreements about the validity and applicability of the available randomised controlled trials of breast screening, and partly from questions about the usefulness and interpretation of observational data for breast cancer incidence and mortality.

The debate about the benefits and harms of breast screening is not unique to the UK and its breast cancer screening programmes. In 2002, the International Agency for Research on Cancer[2] reviewed the evidence for breast screening and proposed recommendations for further research and the implementation of screening programmes. In 2009, the US Preventive Services Task Force re-examined the efficacy of various screening modalities. They recommended that women younger than 50 years do not need to be screened routinely and women aged 50–74 years should have biennial rather than annual screens.[3] The Canadian Taskforce on Preventative Health Care updated their guidelines for breast screening in 2011, and concluded that the reduction

Meta-analysis of breast cancer mortality after 13 years of follow-up in breast cancer screening trials



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RESEARCH

Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial

OPEN ACCESS

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Abstract

Objective To compare breast cancer incidence and mortality up to 25 years in women aged 40-59 who did or did not undergo mammography screening.

Design Follow-up of randomised screening trial by centre coordinators, the study's central office, and linkage to cancer registries and vital statistics databases.

Setting 15 screening centres in six Canadian provinces,1980-85 (Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia).

Participants 89 835 women, aged 40-59, randomly assigned to mammography (five annual mammography screens) or control (no mammography).

Interventions Women aged 40-49 in the mammography arm and all women aged 50-59 in both arms received annual physical breast examinations. Women aged 40-49 in the control arm received a single examination followed by usual care in the community.

Main outcome measure Deaths from breast cancer.

Results During the five year screening period, 666 invasive breast cancers were diagnosed in the mammography arm (n=44 925 participants) and 524 in the controls (n=44 910), and of these, 180 women in the mammography arm and 171 women in the control arm died of breast cancer during the 25 year follow-up period. The overall hazard ratio for death from breast cancer diagnosed during the screening period associated with mammography was 1.05 (95% confidence interval 0.85 to 1.30). The findings for women aged 40-49 and 50-59 were almost identical. During the entire study period, 3250 women in the mammography arm and 3133 in the control arm had a diagnosis of breast cancer, and 500 and 505, respectively, died of breast cancer. Thus the cumulative mortality from breast cancer was similar between women in the mammography arm and in the control arm (hazard ratio 0.99, 95% confidence interval 0.88 to 1.12). After 15 years of follow-up a residual excess of 106 cancers was observed in the mammography arm, attributable to over-diagnosis.

Conclusion Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available. Overall, 22% (106/484) of screen detected invasive breast cancers were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial.

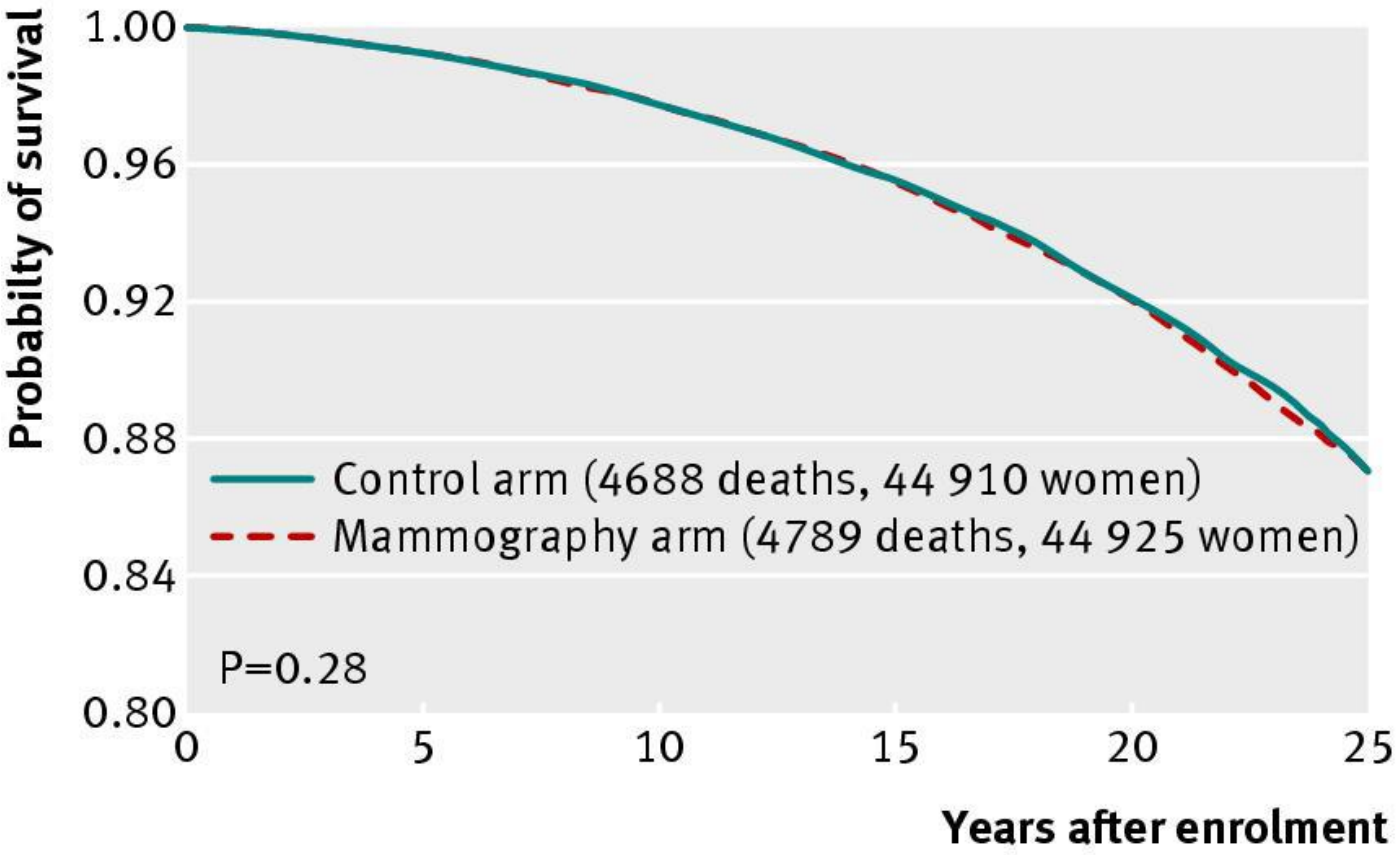
Introduction

Regular mammography screening is done to reduce mortality from breast cancer. Mammogram detected non-palpable breast cancers are smaller on average than clinically palpable breast cancers. Small breast cancers confer a better prognosis than large ones. However, survival in the context of a screening programme is not predictive of reduced mortality because of lead time bias, length bias, or over-diagnosis.[1] Thus the benefit of mammography screening must be evaluated in randomised screening trials, with breast cancer mortality as the endpoint.

Over-diagnosis refers to the possibility that a screen detected cancer might not otherwise become clinically apparent during the lifetime of the woman.[2 3] Over-diagnosis can be estimated in a randomised screening trial when a sufficiently long period has elapsed from the cessation of screening—that is, when all cancers should have become clinically apparent in both trial arms.

In 1980 a randomised controlled trial of screening mammography and physical examination of breasts in 89 835 women, aged 40 to 59, was initiated in Canada, the Canadian National Breast Screening Study.[4-7] It was designed to tackle research questions that arose from a review of mammography screening in Canada[8] and the report by the working group to review the US Breast Cancer Detection and Demonstration projects.[9] At that time the only breast screening trial that had reported results was that conducted within the Health Insurance Plan of Greater New York.[10 11] Benefit from combined

All cause mortality, by assignment to mammography or control arms (all participants)



NBSS Study

	Screened	Unscreened
Women	44,925	44,910
Cancers	666	524
Deaths	180	171

- 142 excess cancers in screening arm
- 170 women non-palpable cancer found in screening arm still alive
- How many lives were saved?

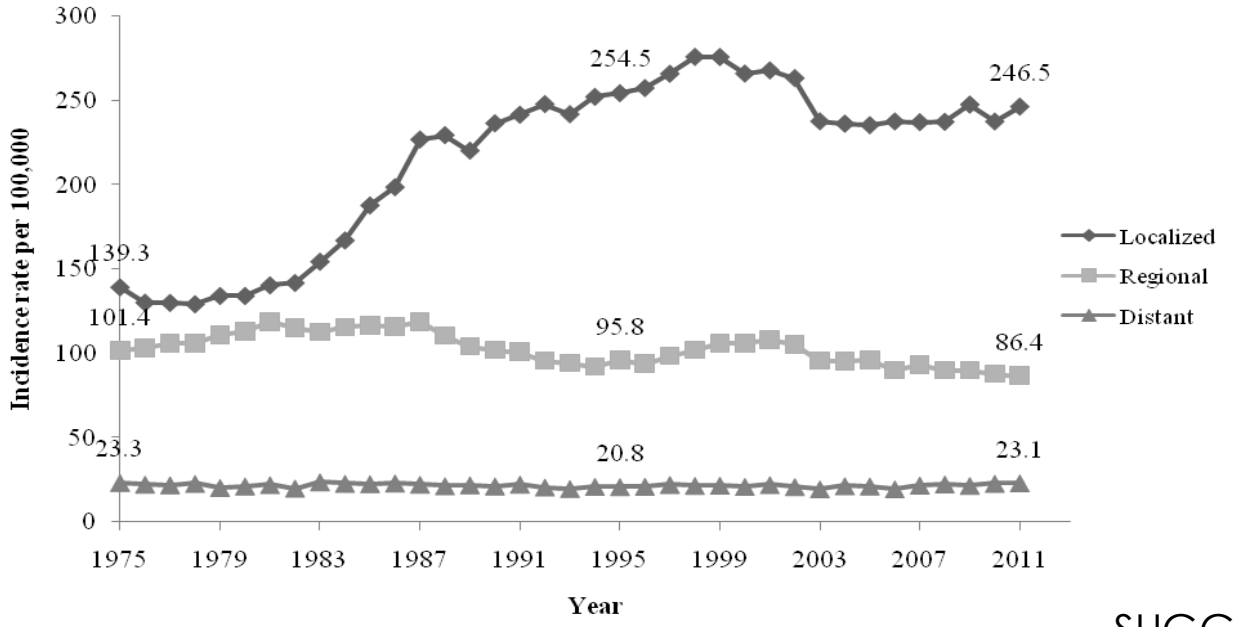
50 ? 20 ? 0 ?

- Why is no reduction in mortality observed?
  - Study design
  - Overdiagnosis
  - Palpability
  - Biology

Why are mortality rates declining?

- Prevention
- Screening
- Improved survival

Age-standardized incidence rates of localized, regional and distant breast cancers in US White: SEER 9, 1975-2011, age ≥ 50 years



SUGGESTS OVERDIAGNOSIS

SUGGESTS SCREENING INEFFECTIVE

- Increase of 107 for localized cancers
- Decrease of 13 for regional/distant cancers

Why are mortality rates declining?

- Prevention 
- Screening 
- Improved survival 

Premise: Size predicts survival

- Basis for breast cancer screening
  - Screen for size of cancers
  - Not for nodal status, grade
- Reducing size at diagnosis will improve survival

Questions

- Does size predict survival
  - for all ages?
  - for node positive breast cancer?
  - for triple negative cancers?
  - for BRCA1 associated cancers?
  - for non-palpable cancers?
  - for palpable cancers?

- Is tumour palpability an adverse prognostic factor independent of size?

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EPIDEMIOLOGY

Age of diagnosis, tumor size, and survival after breast cancer: implications for mammographic screening

Steven A. Narod

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Abstract If mammographic screening is to be recommended to women aged <50, it is necessary that mammographic screening leads to the detection of small cancers and that the survival rate of young women with small cancers is superior to that of women with larger cancers. We reviewed the survival experience of 2,173 patients with invasive breast cancer. There were 392 cancer-specific deaths in the cohort after a mean of 8.9 years of follow-up. We estimated the effects of young age (age <50) of tumor size (in cm) and of mammogram detected (vs. palpable) on breast cancer survival in the cohort. Young age, tumor size >2 cm and tumor palpability were strong and independent predictors of breast cancer mortality in the cohort. The 10-year survival rate for young women with small mammogram-detected breast cancers (<1 cm) was 94%, compared to 86% for women with palpable cancers in the same size group ($P < 0.01$). Women with a small non-palpable breast cancer that is diagnosed through a mammogram experience very good survival, compared to women with a palpable breast cancer of similar size. Our findings suggest that mammography preferentially detects cancers with good prognosis and calls into question the assumption that detecting breast cancers when they are small by mammography will impact upon mortality from breast cancer.

Keywords Breast cancer · Prognostic factors · Mammography · Survivorship

This investigation involved human subjects. However, informed consent was not required by the ERB because no subject was contacted.

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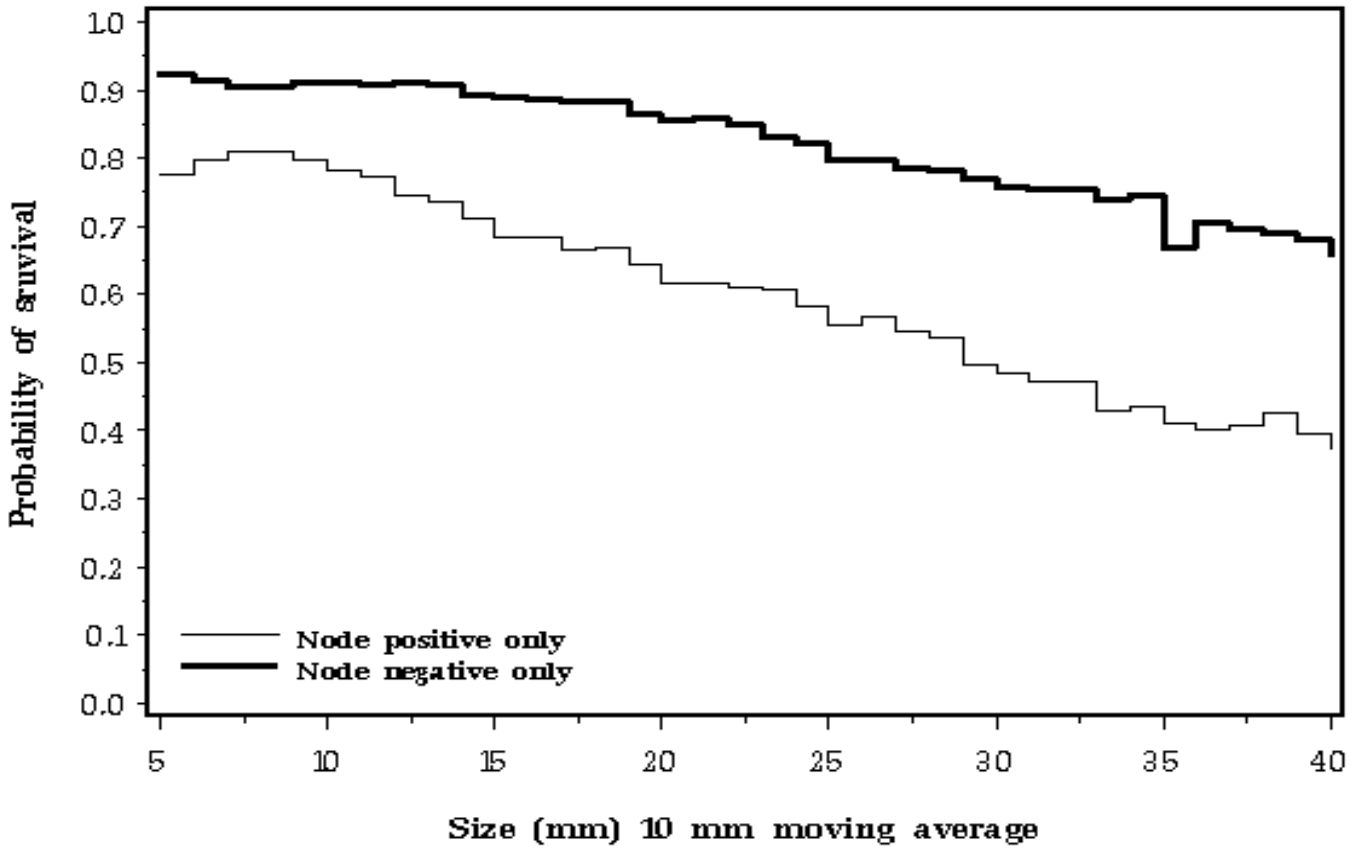
Introduction

The question of whether or not to recommend mammography to women between the ages of 40 and 50 persists many years after the relevant trial data have been published [1–4]. Several factors motivate the discussion, including test sensitivity, disease prevalence, the cost of screening, and the consequences of a false-positive result. However, the fundamental question underlying the debate is "what is the mortality experience of women in a mammography screening program compared to that of unscreened women?" To justify the recommendation for routine mammography, it is necessary that the survival of women under age 50 with small newly detected cancers be superior to that of women with larger cancers. However, a survival difference alone is not sufficient evidence to recommend mammography. For various reasons, such as lead-time bias and length–time bias, survival may be superior for women with screen-detected cancers than for women with clinically detected cancer, without necessarily improving mortality. It is also possible that small non-palpable cancers that are detected by mammography have little metastatic potential; if so, then identifying them in a screening program might not necessarily impact on mortality.

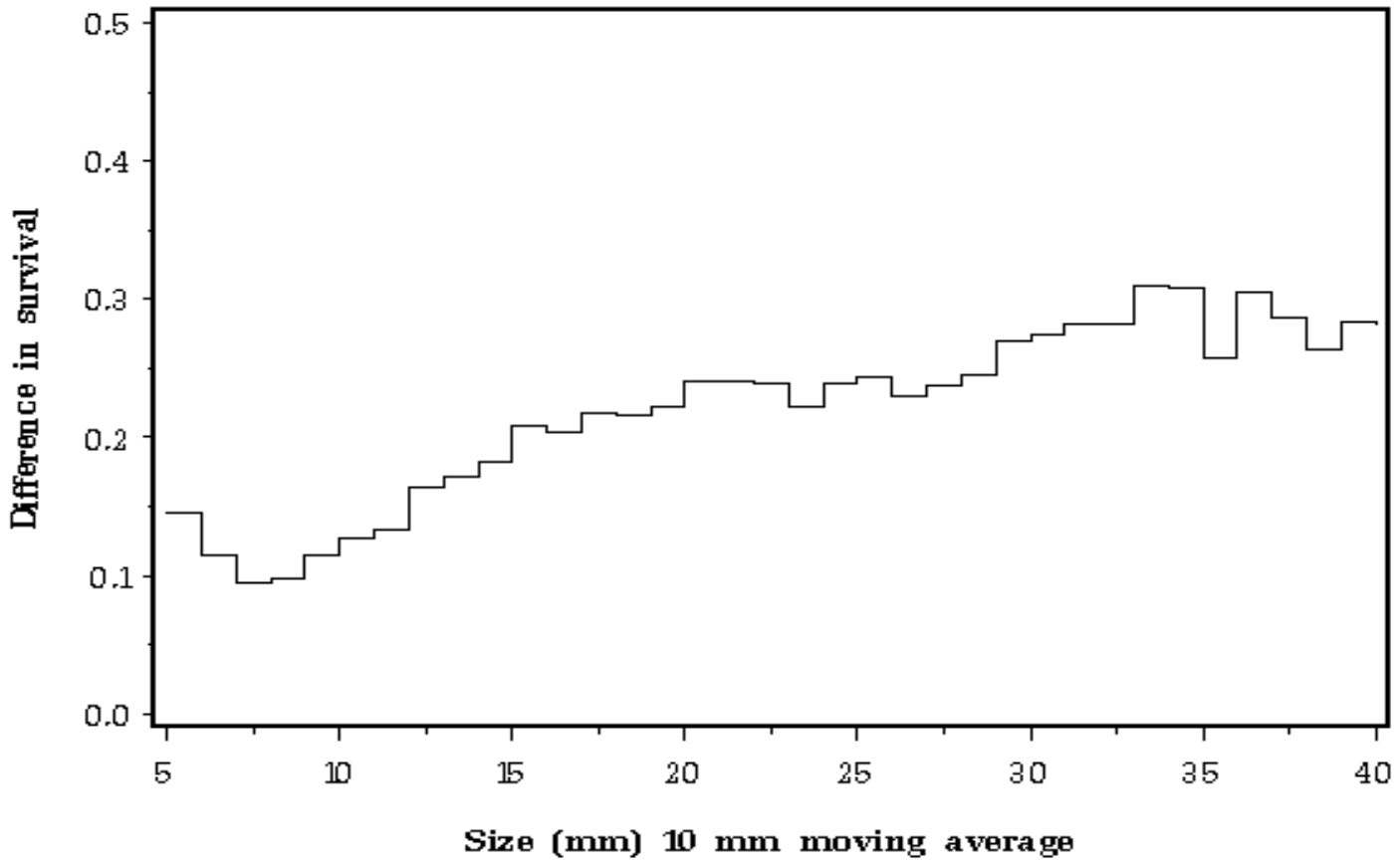
We and others have raised the point that tumor size is not an invariant predictor of survival in breast cancers of all histologic subtypes [5]. Recent studies report that size is, in fact, a relatively poor predictor of survival in women with

Fifteen year survival after breast cancer diagnosis, by mean tumour size



The decrease in mortality associated with decrease in size is greater for node negative than node positive cancers

Difference in 15 year survival associated with node positivity, by mean tumour size



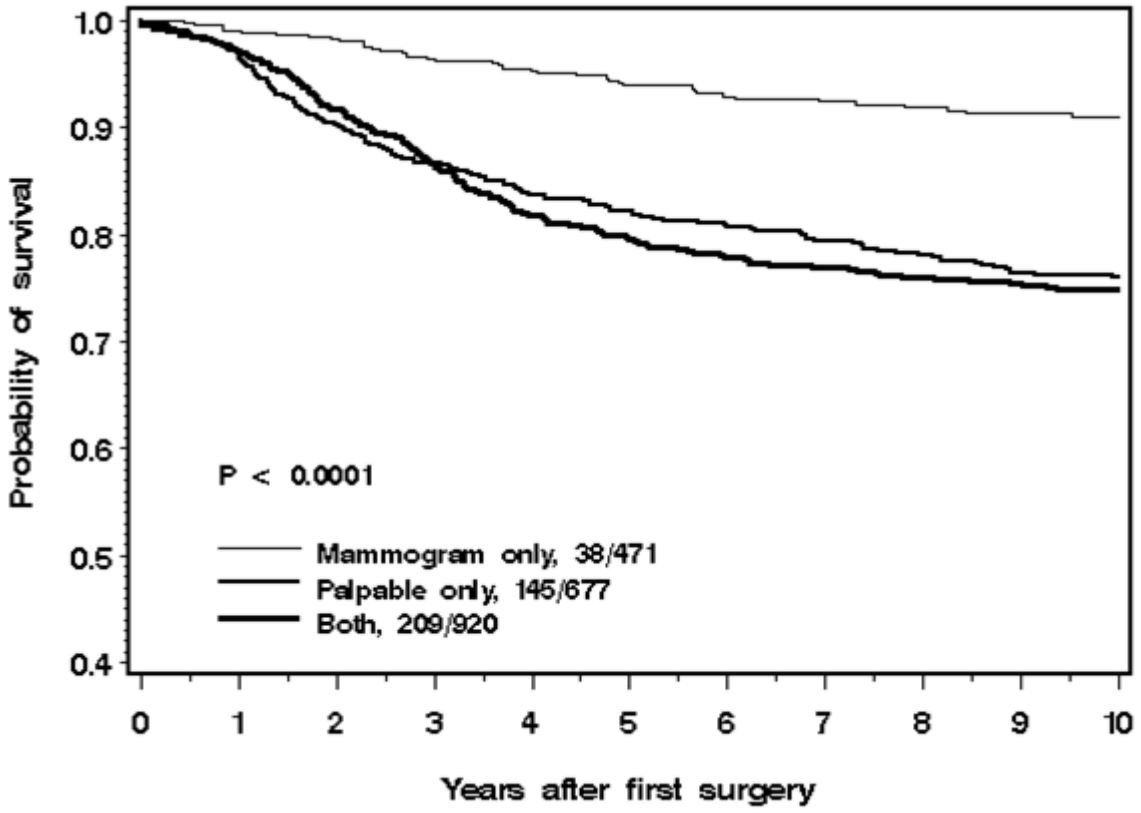
- The goal of screening is to identify cancers when they are small and node-negative

- The benefit of screening is largely from identifying women when the cancers are relatively large and node-positive

Is tumour palpability a prognostic factor independent of size?

Good outcome may not be related to tumour size but to tumour palpability

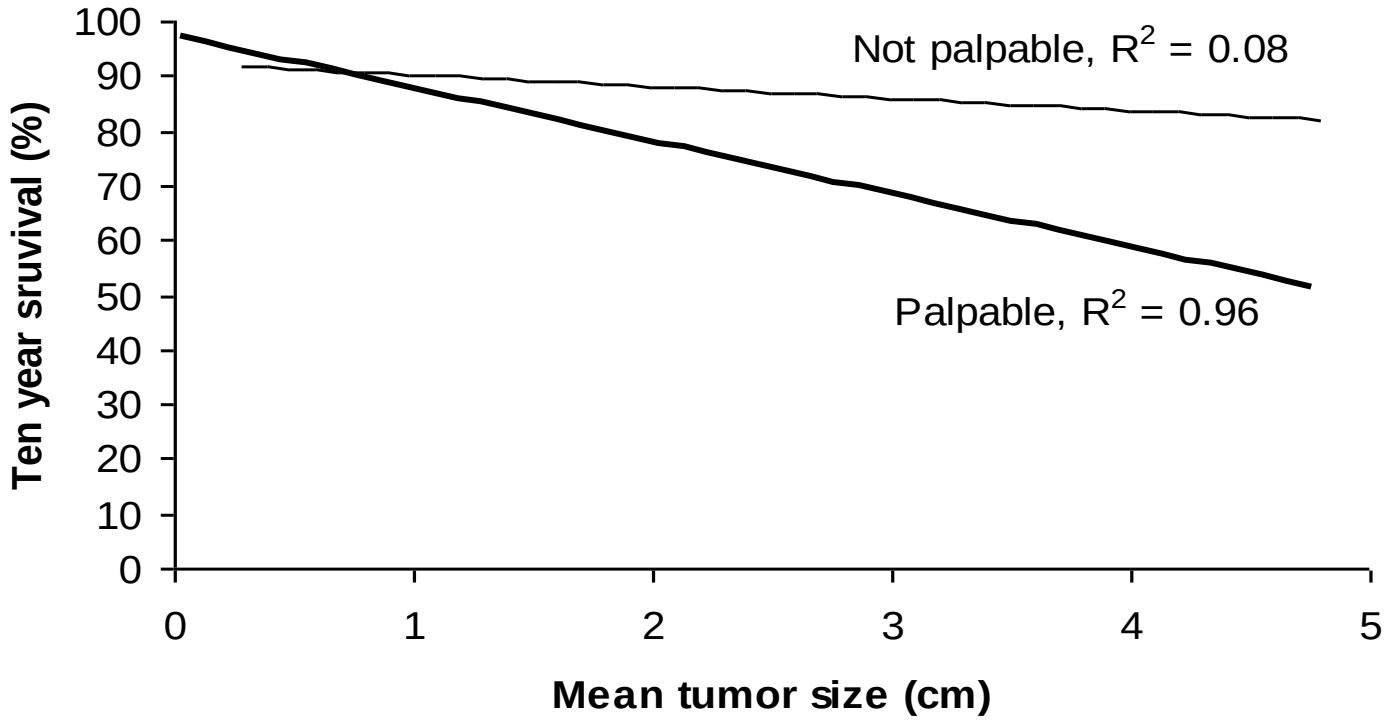
Survival after breast cancer by mammographic-detected versus palpable



Relative Risk (RR) of death of breast cancer in 10 years after first surgery. Women aged >=50 at diagnosis.

Variables	Univariate RR(95%CI)P	Multivariate RR(95%CI)P
Size (cm)		
0 - 1	1	1
1- 2	1.92 (1.21-3.05) 0.005	1.61 (1.00-2.60) 0.05
2 - 5	4.57 (2.96-7.05)<0.0001	3.57 (2.24-5.69)<0.0001
Detected by Mammogram alone		
No	1	1
Yes	0.37 (0.25-0.55) <0.0001	0.58 (0.38-0.88) 0.01

Tumour size and survival, by palpability



Predictions

- Screening trials that show a benefit have done so by reducing the size of palpable cancers
- Not reported in Swedish trials
- Screening will work best when the average cancer in controls is large and node-positive
- Evidence in favor of population screening is inadequate

Why do women like screening?

- Consider three women
  - Negative mammogram
    - "I am grateful I don't have cancer!"
  - Positive Mamogram, negative biopsy
    - "I am relieved I don't have cancer"
  - Positive Mamogram, positive biopsy
    - "Thank God I caught it early!"

The NEW ENGLAND JOURNAL of MEDICINE

MEDICINE AND SOCIETY

Invisible Risks, Emotional Choices — Mammography and Medical Decision Making

Lisa Rosenbaum, M.D.

That may be why overdiagnosis does not resonate emotionally. We do not see women walking around with "an overdiagnosis". Instead we see breast-cancer survivors.

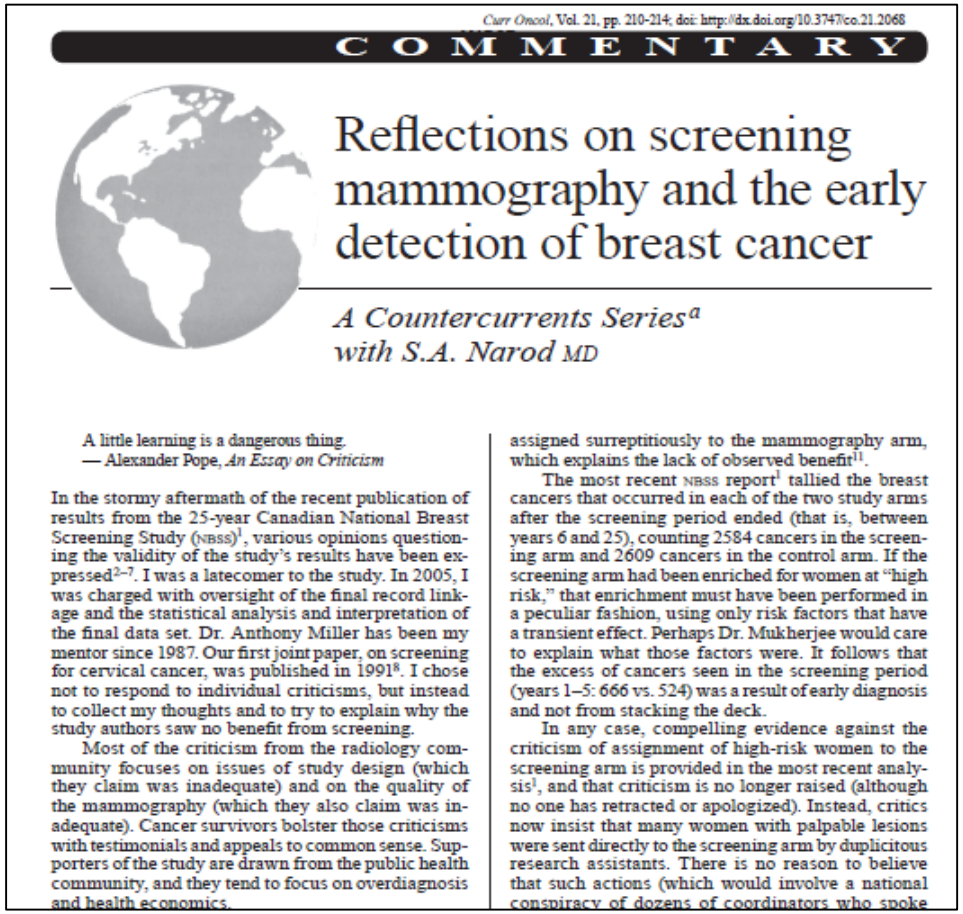
"Thank goodness I had a mammogram and caught it early".

NEJM, current issue

Conclusions

- Reduction in cancer size does not lead to a reduction in mortality
- Metastatic potential declines as size of tumour increases
- Improvement in survival for a fixed reduction in size greater for node positive tumours than node-negative tumours
- Tumour palpability is an adverse prognostic factor, *independent of size*
- Overdiagnosis accounts for much of the impression of benefit
- Screening does not reduce mortality from breast cancer
- Women like it anyways

Further Reading



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COMMENTARY

Reflections on screening mammography and the early detection of breast cancer

A Countercurrents Series[a]
with S.A. Narod MD

A little learning is a dangerous thing.
— Alexander Pope, *An Essay on Criticism*

In the stormy aftermath of the recent publication of results from the 25-year Canadian National Breast Screening Study (NBSS)[1], various opinions questioning the validity of the study's results have been expressed[2–7]. I was a latecomer to the study. In 2005, I was charged with oversight of the final record linkage and the statistical analysis and interpretation of the final data set. Dr. Anthony Miller has been my mentor since 1987. Our first joint paper, on screening for cervical cancer, was published in 1991[8]. I chose not to respond to individual criticisms, but instead to collect my thoughts and to try to explain why the study authors saw no benefit from screening.

Most of the criticism from the radiology community focuses on issues of study design (which they claim was inadequate) and on the quality of the mammography (which they also claim was inadequate). Cancer survivors bolster those criticisms with testimonials and appeals to common sense. Supporters of the study are drawn from the public health community, and they tend to focus on overdiagnosis and health economics.

assigned surreptitiously to the mammography arm, which explains the lack of observed benefit[1].

The most recent NBSS report[1] tallied the breast cancers that occurred in each of the two study arms after the screening period ended (that is, between years 6 and 25), counting 2584 cancers in the screening arm and 2609 cancers in the control arm. If the screening arm had been enriched for women at "high risk," that enrichment must have been performed in a peculiar fashion, using only risk factors that have a transient effect. Perhaps Dr. Mukherjee would care to explain what those factors were. It follows that the excess of cancers seen in the screening period (years 1–5: 666 vs. 524) was a result of early diagnosis and not from stacking the deck.

In any case, compelling evidence against the criticism of assignment of high-risk women to the screening arm is provided in the most recent analysis[1], and that criticism is no longer raised (although no one has retracted or apologized). Instead, critics now insist that many women with palpable lesions were sent directly to the screening arm by duplicitous research assistants. There is no reason to believe that such actions (which would involve a national conspiracy of dozens of coordinators who spoke

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