New Evidence on the Value of Breast Cancer Screening

Robert A. Smith, PhD, Vice President, Cancer Screening

American Cancer Society

Adjunct Professor of Epidemiology

Emory University Rollins School of Public Health,
Atlanta, GA

DIALOGUE FOR ACTION® ON CANCER SCREENING AND PREVENTION
prevent cancer® FOUNDATION

2019 DIALOGUE FOR ACTION®
on Cancer Screening and Prevention
April 24-26, 2019 | Hilton Crystal City, Arlington, VA

Three Current Myths About Mammography

Recent commentaries, systematic reviews, etc. have questioned the effectiveness of mammography, arguing that:

(1) The benefit of mammography is modest

(2)Mammography only detects less aggressive cancers

(3)Advances in modern breast cancer treatments are steadily diminishing the importance of mammography

Some Background---The Evolving Evidence for Mammography Screening from the Randomized Trials

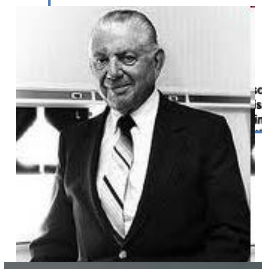
Evaluation of Periodic Breast Cancer Screening With Mammography

Methodology and Early Observations

Sam Shapiro, Philip Strax, MD, and Louis Venet, MD

screening with mammography
s being evaluated to deter-
ng breast cancer mortality

Cancer detection programs have for years emphasized the importance of early diagnosis in breast cancer. Proponents of periodic physical



Mammography service screening and mortality in breast cancer patients: 20-year follow-up before and after introduction of screening

IGINAL RESEARCH • NOUVEAUTÉS EN RECHERCHE

JAMA®

The Journal of the American Medical Association

Home | Current Issue | Past Issues | Topic Collections | CME | Multimedia | Subscribe

Periodic Breast Cancer Screening in Reducing Mortality From Breast Cancer

Sam Shapiro; Philip Strax, MD; Louis Venet, MD

From the Department of Research and Statistics, Health Insurance Plan of Greater New York (Mr. Shapiro); Mt. Sinai School of Medicine and Department of Radiology, LaGuardia Hospital (Dr. Strax); and New York Medical College and Beth Israel Medical Center (Dr. Venet), New York.

ABSTRACT

Canadian National Breast Screening Study:
1. Breast cancer detection and death rates among women aged 40 to 49 years

Anthony

s Wall, MSc

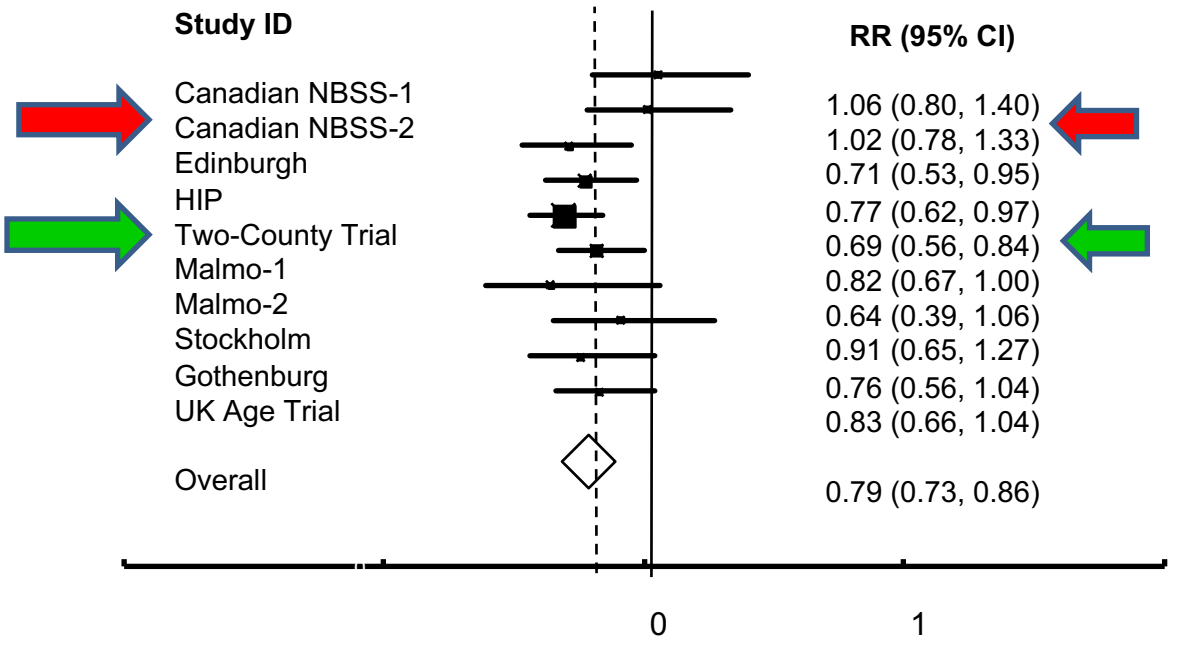
ening with
of breast
en aged 40

Randomised controlled trial of mammographic screening
women from age 40: results of screening in the first 10 years

S Moss[*,1], I Thomas[1], A Evans[2], B Thomas[3] and L Johns[1] (writing committee) for the Trial Management Group[4]

[1]Cancer Screening Evaluation Unit, Institute of Cancer Research, Brookes Lawley Building, 15 Cotswold Road, Sutton, Surrey SM2 5NG, UK; [2]National Breast Screening Training Centre, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; [3]Jarvis Breast Screening, Diagnostic and National Training Centre, Stoughton Road, Guildford, Surrey GU1 1LJ, UK

RCTs of screening mammography: Overall results show a 21% reduction in breast cancer mortality associated with an invitation to screening



Overall RR = 0.79 (95% CI: 0.73, 0.86)

Heterogeneity p = 0.3

Tabar, et al. Breast J, 2014

What explains the different outcomes in the randomized trials of breast cancer screening?


The Lancet · Saturday 13 April 1985

REDUCTION IN MORTALITY FROM BREAST CANCER AFTER MASS SCREENING WITH MAMMOGRAPHY

Randomised Trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare

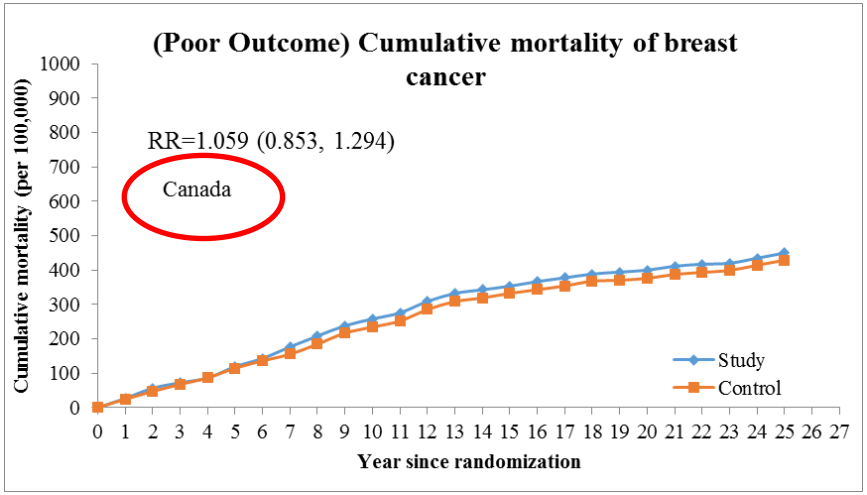
Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years

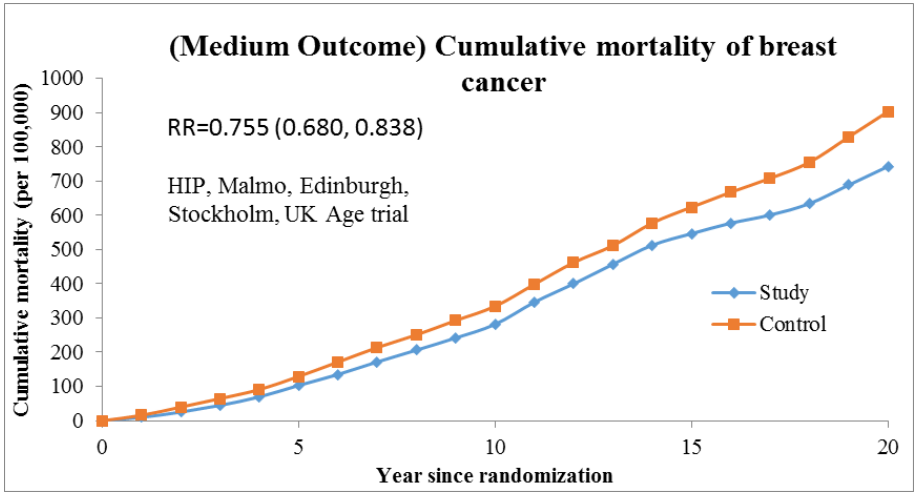
Original Article

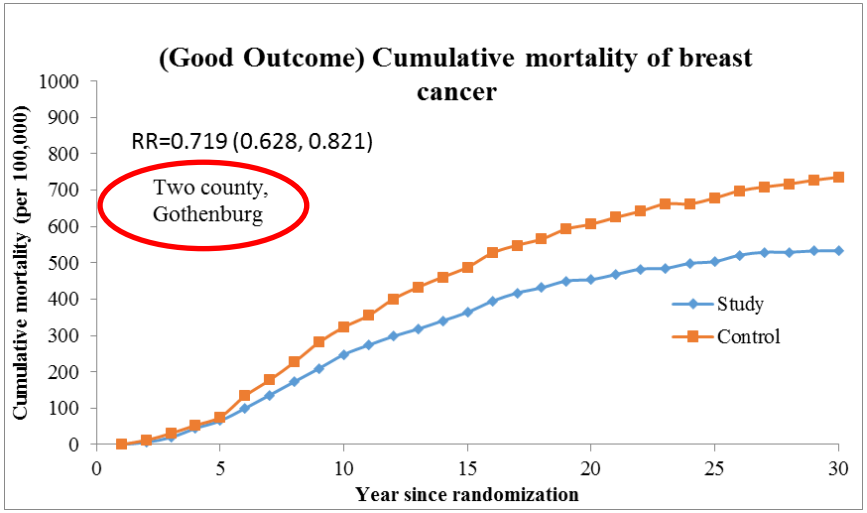
Updated Results of the Gothenburg Trial of Mammographic Screening

- The RCT mortality outcomes range from a **36% mortality reduction to 6% excess mortality**
- ***Little attention has been devoted to understanding these differences***
- It is best to ask the simple, but most important question….***How well did a trial perform in reducing the risk of being diagnosed with an advanced breast cancer?***
-

Cumulative Mortality in the Breast Cancer RCTs by the RR of Being Diagnosed with an Advanced Breast Cancer







- **Cumulative mortality outcomes reflect trial performance in reducing the risk of being diagnosed with an advanced breast cancer**

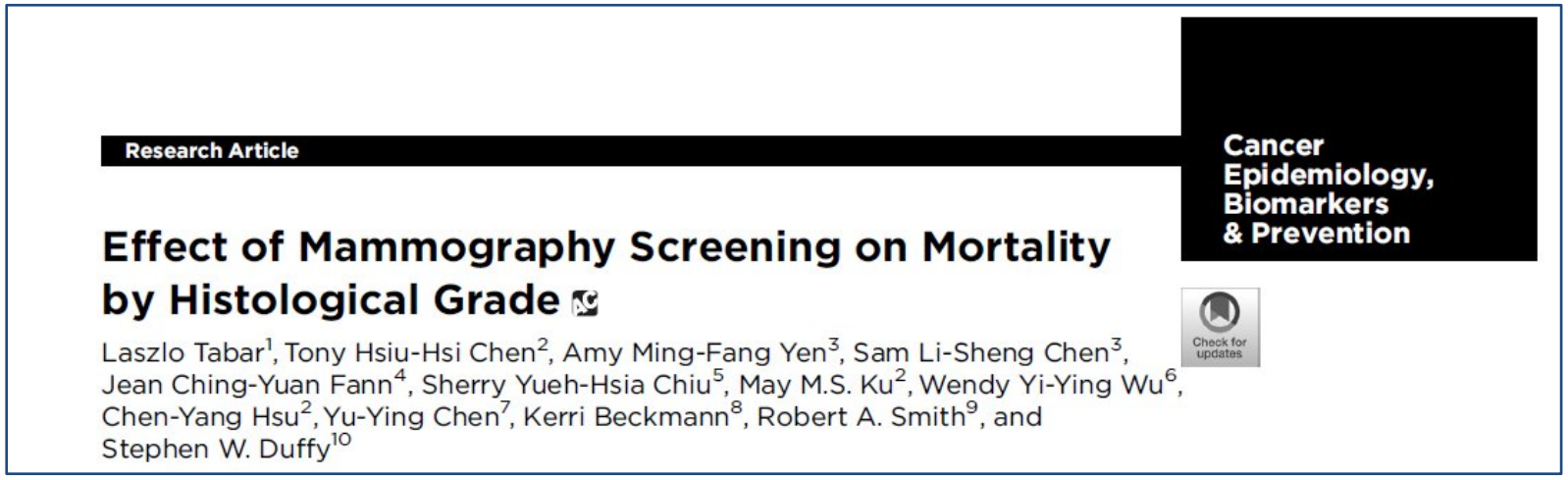
Sensitivity Analysis of Various Scenarios by Attendance Rate & Sensitivity in Randomized Controlled Trials

High Attendance/ High Sensitivity ---Shows a 33% reduction in breast cancer deaths

Low Attendance/ Low Sensitivity ---Shows only a 13% reduction in breast cancer deaths

Attendance	Sensitivity	RR for Advanced BC	Projected RR, BC Death
90%	**95%**	**0.67 (0.58, 0.76)**	**0.67 (0.58, 0.76)**
60%	95%	0.78 (0.70, 0.86)	0.74 (0.67, 0.81)
30%	95%	0.89 (0.82, 0.96)	0.81 (0.76, 0.87)
90%	75%	0.79 (0.66, 0.93)	0.75 (0.65, 0.84)
60%	75%	0.86 (0.76, 0.96)	0.79 (0.72, 0.87)
30%	75%	0.93 (0.85, 0.86)	0.84 (0.78, 0.90)
90%	55%	0.93 (0.70, 1.01)	0.84 (0.72, 0.96)
60%	55%	0.95 (0.83, 1.10)	0.85 (0.77, 0.95)
30%	**55%**	**0.96 (0.89, 1.08)**	**0.87 (0.80, 0.94)**

Chen TH, Medicine (Baltimore) 2017;96:e5684.



Research Article

Cancer Epidemiology, Biomarkers & Prevention

Effect of Mammography Screening on Mortality by Histological Grade

Laszlo Tabar[1], Tony Hsiu-Hsi Chen[2], Amy Ming-Fang Yen[3], Sam Li-Sheng Chen[3], Jean Ching-Yuan Fann[4], Sherry Yueh-Hsia Chiu[5], May M.S. Ku[2], Wendy Yi-Ying Wu[6], Chen-Yang Hsu[2], Yu-Ying Chen[7], Kerri Beckmann[8], Robert A. Smith[9], and Stephen W. Duffy[10]

Check for updates

- Background: It has been asserted that mammography screening ***preferentially benefits those with less aggressive cancers*, with lesser or no impact on more rapidly progressing and therefore more life-threatening tumors.**

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018

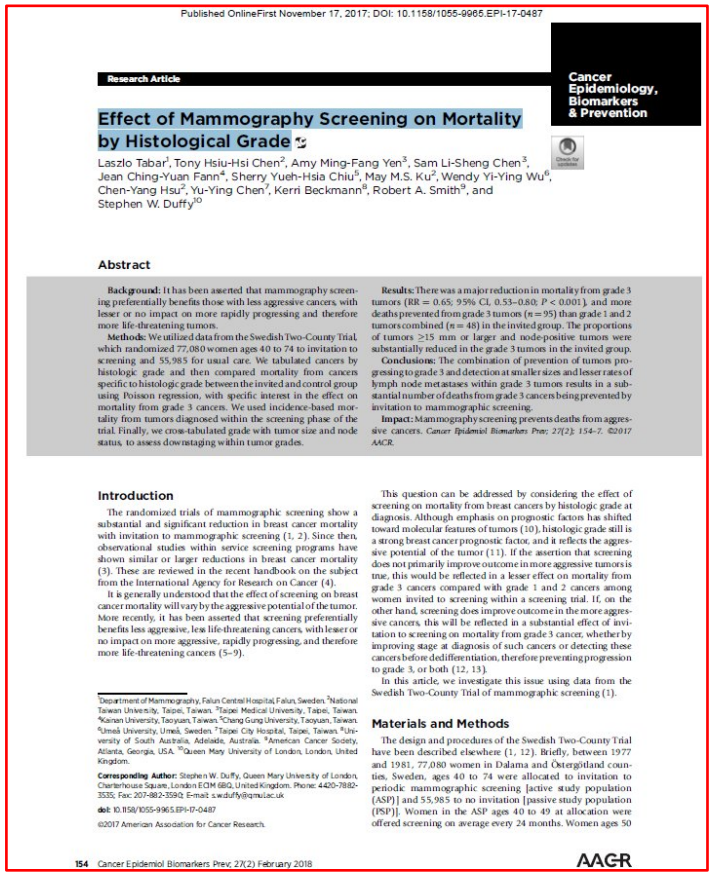
Questioning the Impact of Mammography on Reducing Deaths from Aggressive Cancers

- Welch HG. Screening mammography-a long run for a short slide? *N Engl J Med* 2010;363:1276–8.
- Esserman L, et al. Rethinking screening for breast cancer and prostate cancer. *JAMA* 2009;302:1685–92.
- Autier P, et al. Breast cancer screening: the questions answered. *Nat Rev Clin Oncol* 2012;9:599–605.
- Shieh Y, et al. Population-based screening for cancer: hope and hype. *Nat Rev Clin Oncol* 2016;13:550–65.
- Welch HG, et al. Breast-cancer tumor size, overdiagnosis, and mammography screening effectiveness. *N Engl J Med* 2016; 375:1438–47.

Effect of Mammography Screening on Mortality by Histological Grade

- If screening does improve outcome in the more aggressive cancers, this will be reflected in a substantial effect of an invitation to screening on mortality from grade 3 cancer, by:
  - improving stage at diagnosis of such cancers, **or**
  - detecting these cancers before dedifferentiation, therefore preventing progression to grade 3
  - **or both**.

Swedish Two County Trial--Background and Methods



Published OnlineFirst November 17, 2017; DOI: 10.1158/1055-9965.EPI-17-0487

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Effect of Mammography Screening on Mortality by Histological Grade

Laszlo Tabar[1], Tony Hsiu-Hsi Chen[2], Amy Ming-Fang Yen[3], Sam Li-Sheng Chen[3], Jean Ching-Yuan Fann[4], Sherry Yueh-Hsia Chiu[5], May M.S. Ku[2], Wendy Yi-Ying Wu[6], Chen-Yang Hsu[2], Yu-Ying Chen[7], Kerri Beckmann[8], Robert A. Smith[9], and Stephen W. Duffy[10]

Abstract

Background: It has been asserted that mammography screening preferentially benefits those with less aggressive cancers, with lesser or no impact on more rapidly progressing and therefore more life-threatening tumors.

Methods: We utilized data from the Swedish Two-County Trial, which randomized 77,080 women ages 40 to 74 to invitation to screening and 55,985 for usual care. We tabulated cancers by histologic grade and then compared mortality from cancers specific to histologic grade between the invited and control group using Poisson regression, with specific interest in the effect on mortality from grade 3 cancers. We used incidence-based mortality from tumors diagnosed within the screening phase of the trial. Finally, we cross-tabulated grade with tumor size and node status, to assess downstaging within tumor grades.

Results: There was a major reduction in mortality from grade 3 tumors (RR = 0.65; 95% CI, 0.53–0.80; $P < 0.001$), and more deaths prevented from grade 3 tumors ($n = 95$) than grade 1 and 2 tumors combined ($n = 48$) in the invited group. The proportions of tumors ≥15 mm or larger and node-positive tumors were substantially reduced in the grade 3 tumors in the invited group.

Conclusions: The combination of prevention of tumors progressing to grade 3 and detection at smaller sizes and lesser rates of lymph node metastases within grade 3 tumors results in a substantial number of deaths from grade 3 cancers being prevented by invitation to mammographic screening.

Impact: Mammography screening prevents deaths from aggressive cancers. *Cancer Epidemiol Biomarkers Prev; 27(2); 154–7. ©2017 AACR.*

Introduction

The randomized trials of mammographic screening show a substantial and significant reduction in breast cancer mortality with invitation to mammographic screening (1, 2). Since then, observational studies within service screening programs have shown similar or larger reductions in breast cancer mortality (3). These are reviewed in the recent handbook on the subject from the International Agency for Research on Cancer (4).

It is generally understood that the effect of screening on breast cancer mortality will vary by the aggressive potential of the tumor. More recently, it has been asserted that screening preferentially benefits less aggressive, less life-threatening cancers, with lesser or no impact on more aggressive, rapidly progressing, and therefore more life-threatening cancers (5–9).

This question can be addressed by considering the effect of screening on mortality from breast cancers by histologic grade at diagnosis. Although emphasis on prognostic factors has shifted toward molecular features of tumors (10), histologic grade still is a strong breast cancer prognostic factor, and it reflects the aggressive potential of the tumor (11). If the assertion that screening does not primarily improve outcome in more aggressive tumors is true, this would be reflected in a lesser effect on mortality from grade 3 cancers compared with grade 1 and 2 cancers among women invited to screening within a screening trial. If, on the other hand, screening does improve outcome in the more aggressive cancers, this will be reflected in a substantial effect of invitation to screening on mortality from grade 3 cancer, whether by improving stage at diagnosis of such cancers or detecting these cancers before dedifferentiation, therefore preventing progression to grade 3, or both (12, 13).

In this article, we investigate this issue using data from the Swedish Two-County Trial of mammographic screening (1).

Materials and Methods

The design and procedures of the Swedish Two-County Trial have been described elsewhere (1, 12). Briefly, between 1977 and 1981, 77,080 women in Dalarna and Östergötland counties, Sweden, ages 40 to 74 were allocated to invitation to periodic mammographic screening [active study population (ASP)] and 55,985 to no invitation [passive study population (PSP)]. Women in the ASP ages 40 to 49 at allocation were offered screening on average every 24 months. Women ages 50

[1]Department of Mammography, Falun Central Hospital, Falun, Sweden. [2]National Taiwan University, Taipei, Taiwan. [3]Taipei Medical University, Taipei, Taiwan. [4]Kainan University, Taoyuan, Taiwan. [5]Chang Gung University, Taoyuan, Taiwan. [6]Umeå University, Umeå, Sweden. [7]Taipei City Hospital, Taipei, Taiwan. [8]University of South Australia, Adelaide, Australia. [9]American Cancer Society, Atlanta, Georgia, USA. [10]Queen Mary University of London, London, United Kingdom.

Corresponding Author: Stephen W. Duffy, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom. Phone: 4420-7882-3535; Fax: 207-882-3590; E-mail: s.w.duffy@qmul.ac.uk

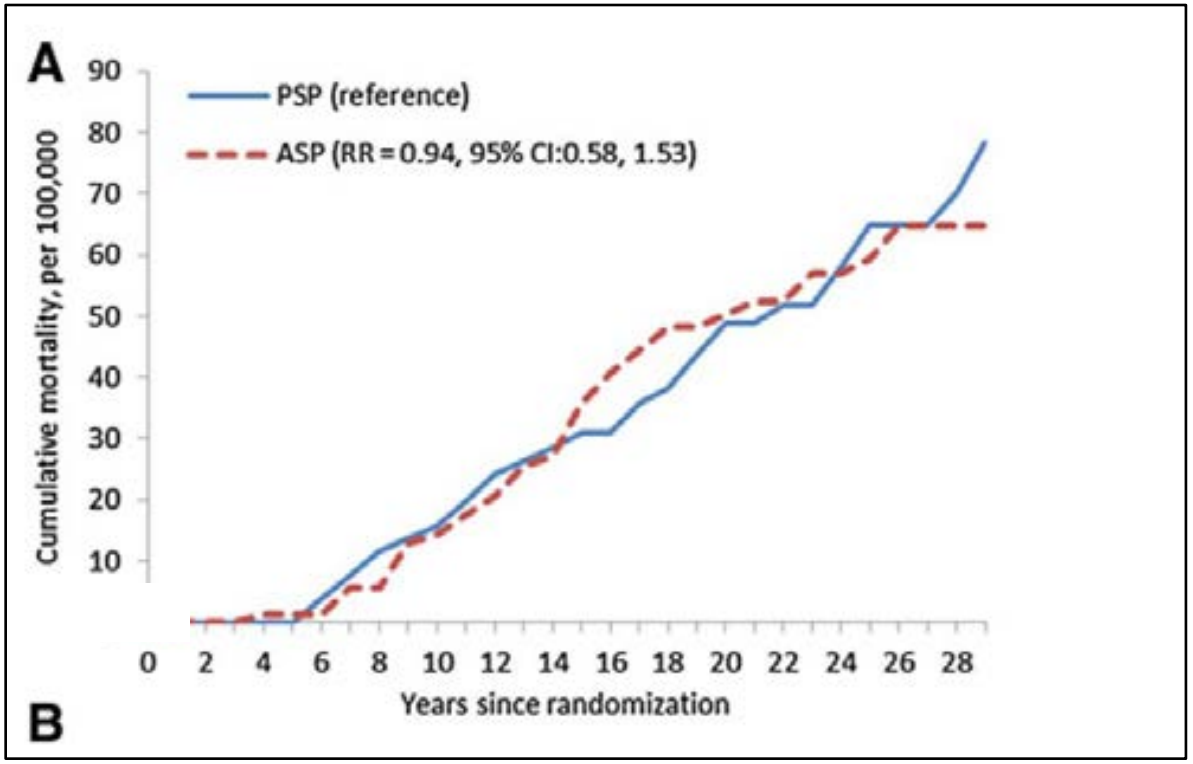
doi: 10.1158/1055-9965.EPI-17-0487

- **133,065 women ages 40-74 randomized to screening or usual care**
- **Screening phase = 7 years**
- **Screening interval**
  - **40-49 = 24 months**
  - **50-74 = 33 months**
- **Protocol**
  - **One view mammography, single reader**
  - **No physical exam**
- **1st mortality results published in 1985**
- **28 years of follow-up in this analysis**

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 2018; 27(2)

Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 1

Grade 1 tumors

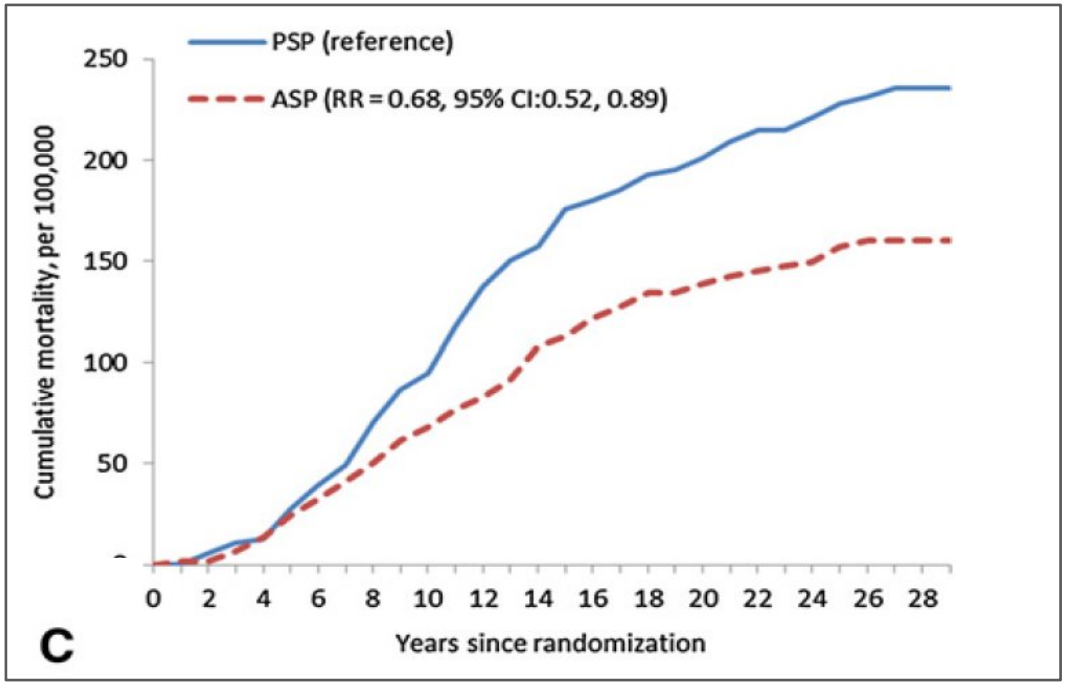


- No significant difference is seen in between the ASP and PSP in the cumulative mortality of grade 1 tumors
- RR = 0.94, **or a 6% mortality difference**

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018

Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 2

Grade 2 tumors

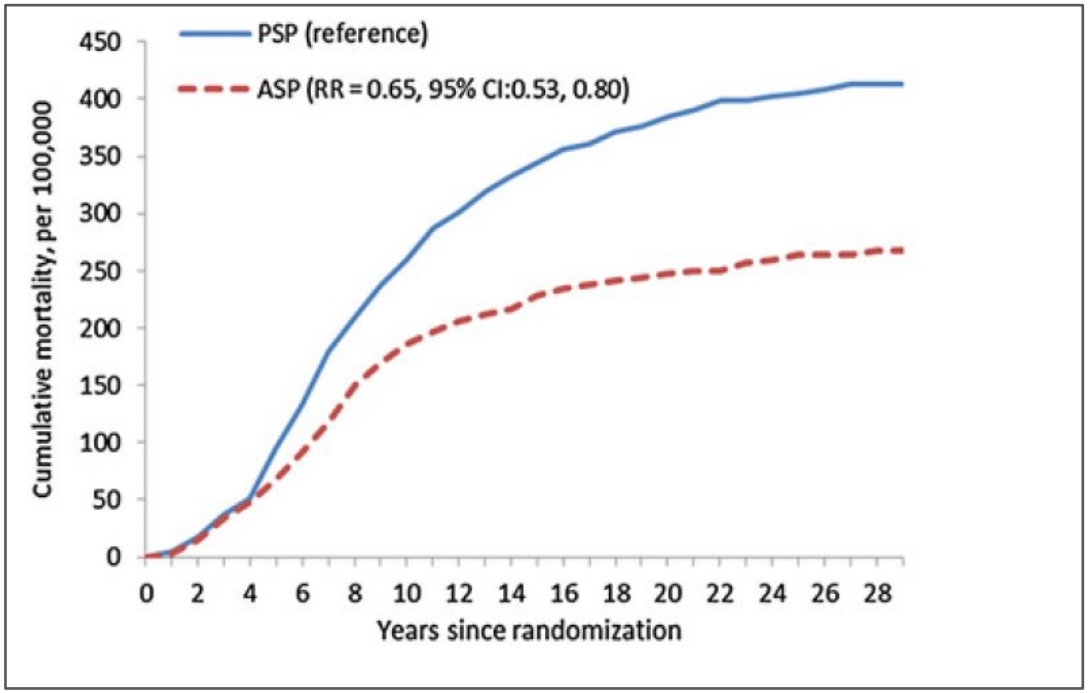


- A statistically significant difference is seen between the ASP and PSP in the cumulative mortality of grade 2 tumors
- RR = 0.68, or a 32% mortality difference

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018

Cumulative breast cancer mortality over time in the ASP and PSP for invasive breast cancers of histologic grade 3

Grade 3 tumors



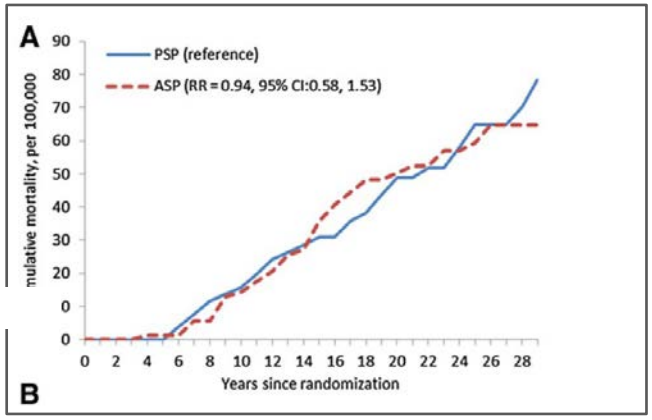
- A statistically significant difference is seen between the ASP and PSP in the cumulative mortality of grade 3 tumors
- RR = 0.65, or a 35% mortality difference

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018

Summary

- Our results shows that ***mammography screening prevents tumors from progressing to grade 3 and also detects grade 3 tumors at smaller sizes with lower rates of lymph node metastases***
- There was a 35% reduction in breast cancer mortality from grade 3 cancers in the ASP compared with the PSP, **corresponding to 95 deaths prevented**, ***almost double the number of deaths prevented for grades 1 and 2 tumors combined***
- The assertion that mammography has little effect on the natural history of aggressive breast cancers is unfounded

What do we make of the lack of difference in the cumulative mortality for grade 1 tumors?



- The RRs of mortality from grade 1, 2, and 3 cancers were 0.94, 0.68, and 0.65
- The RRs of *incidence* of grade 1, 2, and 3 tumors were 1.33, 0.89, and 0.90
- **Dividing RRs for mortality by those for incidence, we obtain 0.71, 0.76, and 0.72, *very similar figures***

This suggests that the lack of a mortality reduction in grade 1 tumors is driven by the *increased incidence* of these tumors, with a corresponding reduction in incidence of grade 2 and 3 cancers, and thus, ***the effect of screening on case fatality is similar for all grades.***

Tabar, et al. Cancer Epidemiol Biomarkers Prev; 27(2) February 2018

Do improvements in treatment make screening less important?

Screening Mammography — A Long Run for a Short Slide?

H. Gilbert Welch, M.D., M.P.H.

Thus, the increased awareness about the importance of promptly seeking care for overt breast abnormalities (there is no debate about diagnostic mammography) and the widespread use of adjuvant therapy have probably combined to make screening now less important.[4,5]

Original Article

The Incidence of Fatal Breast Cancer Measures the Increased Effectiveness of Therapy in Women Participating in Mammography Screening

László Tabár, MD[1]; Peter B. Dean, MD[2]; Tony Hsiu-Hsi Chen, PhD[3]; Amy Ming-Fang Yen, PhD[4]; Sam Li-Sheng Chen, PhD[4]; Jean Ching-Yuan Fann, PhD[5]; Sherry Yueh-Hsia Chiu, PhD[6]; May Mei-Sheng Ku, MSc[3]; Wendy Yi-Ying Wu, PhD[7]; Chen-Yang Hsu, PhD[3]; Yu-Ching Chen, MD[8]; Kerri Beckmann, PhD[9]; Robert A. Smith, PhD[10]; and Stephen W. Duffy, MSc[11]

- Women and their health care providers need a reliable answer to this important question: If a woman chooses to participate in regular mammography screening, ***then how much will this choice improve her chances of avoiding a death from breast cancer compared with women who choose not to participate?***

Cancer 2018, DOI: 10.1002/cncr.31840

The Incidence of Fatal Breast Cancer

- Using the incidence rates of fatal cancers within 10 & 20 years from diagnosis directly compares cancers diagnosed during the study period in women participating and not participating in mammography screening.
- *Over a 58 year period, if treatment has reduced the importance of early detection, then it will be evident in differences in breast cancer death rates in exposed and unexposed women*

- This method considerably **reduces the risk of lead time bias** given the long duration of follow-up, and **length bias**, given that the denominator is the population at risk

Methods

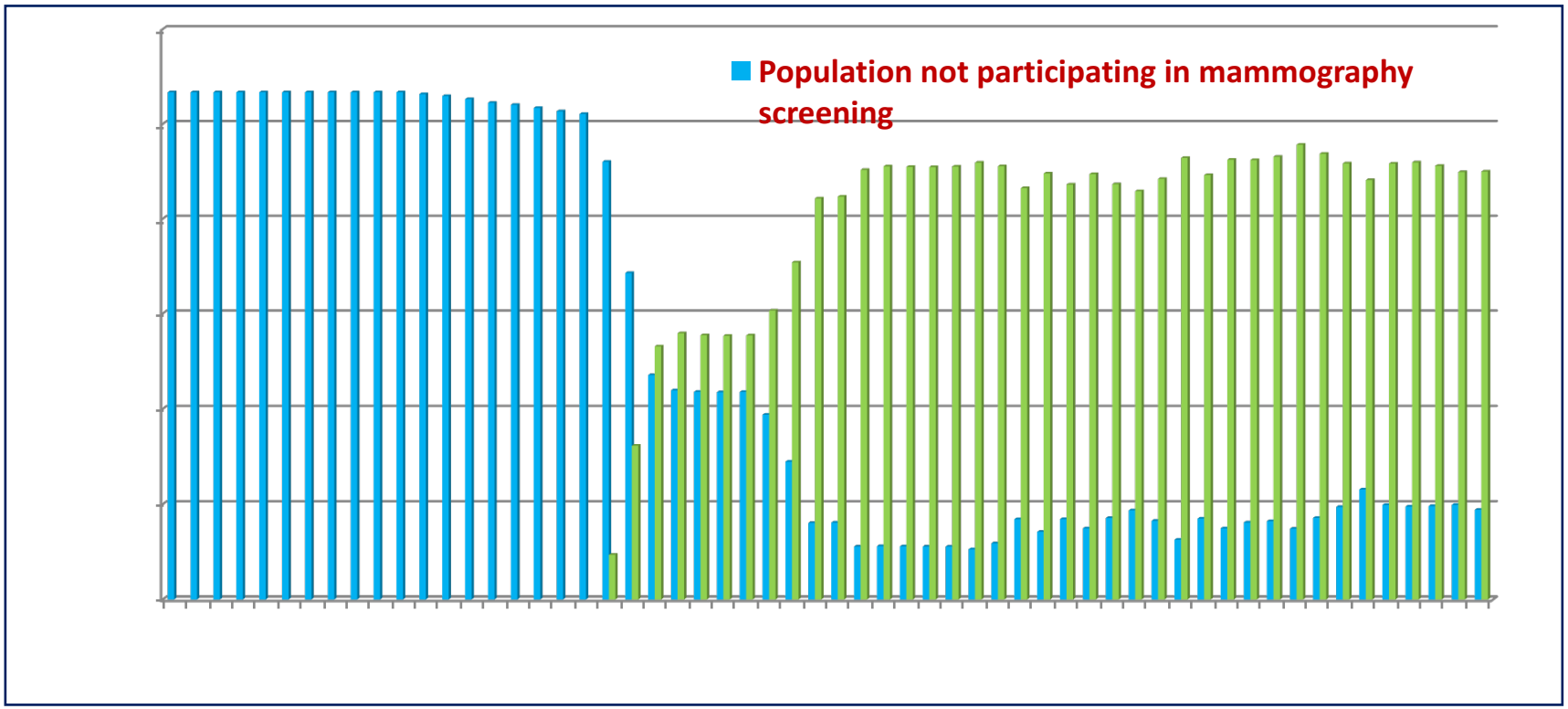
- We used registries for the study population, screening history, breast cancer incidence, and disease-specific death data in a defined population in Dalarna County, Sweden.
- We calculated **(1) the annual incidence of breast cancer,** and (2) **the annual incidence of breast cancers that were fatal within 10 and within 11-20 years of diagnosis** in women aged 40-69 who either participated or did not participate in mammography screening during a 39-year period (1977-2015).
- **All patients were treated with stage-specific therapy according to the latest national guidelines, irrespective of the mode of detection.**

Annual population of women not participating and women participating in mammography screening. Women aged 40-69. Statistics of Dalarna, Sweden, 1958-2015

Pre-Screening Era

Trial Period

Screening & New Therapies Era

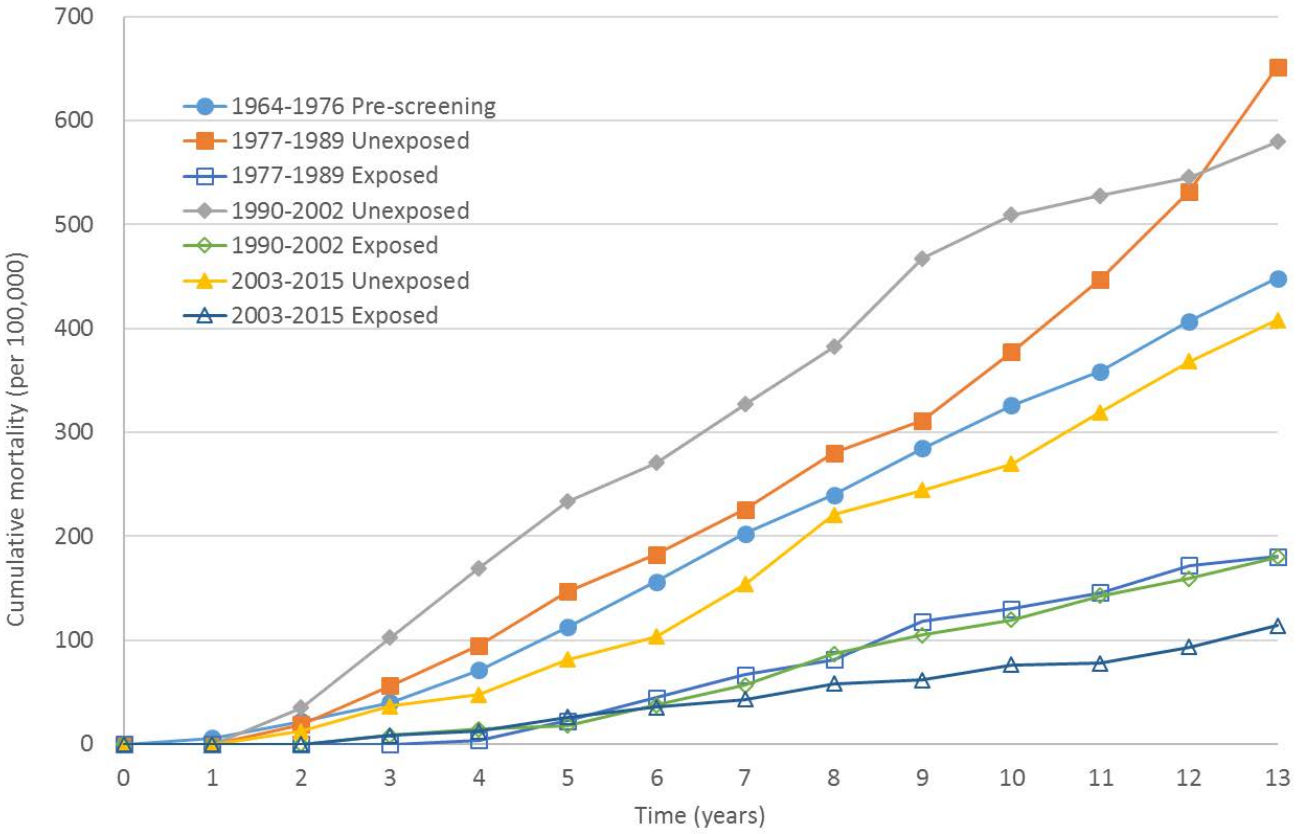


Results

- Women who chose to participate in an organized breast cancer screening program had a ***60% lower risk of dying from breast cancer within 10 years after diagnosis*** (RR=0.40, 95% CI 0.34 - 0.48) compared with corresponding risk of breast cancer death in non-participants

- There was a ***47% lower risk of dying from breast cancer within 20 years after diagnosis*** (RR=0.53, 95% CI 0.44 - 0.63) compared to the corresponding risks for the non-participants.

Cumulative incidence-based breast cancer mortality in the pre-screening period, and in the three screening periods by screening exposure



2003-2015, Unexposed

2003-2015, Exposed

Conclusion

- **All breast cancer patients benefit from advances in breast cancer therapy**
- ***Women who have participated in mammography screening obtain a significantly greater benefit from the therapy available at the time of diagnosis than do women who have not participated.***

Early detection doesn't matter???

Consider the consequences of early vs. advanced stage at diagnosis

- Increased probability of requiring mastectomy
- Near and long-term adverse effects of radiation therapy, adjuvant therapy, and chemotherapy
- Upper-body impairments
- Increased risk of lymphedema
- Increased risk of breast cancer death

Conclusion: Prevailing myths about mammography screening have been shown to unfounded

- **Regular attendance in mammography screening:**
  - –Results in a significant decreases in death from breast cancer among the most aggressive cancers, and in fact, in all histologic grades
  - –Insures a substantially greater benefit from the stage-specific therapy at the time of diagnosis compared with women who did not attend screening

Acknowledgements

The Swedish Two County Research Group

- Laszlo Tabar, MD, Department of Mammography, Falun Central Hospital, Falun, Sweden
- Peter Dean, MD, University of Turku, Turku, Finland
- Tony Hsiu-Hsi Chen, PhD, National Taiwan University, Taipei, Taiwan
- Amy Ming-Fang Yen, PhD, Taipei Medical University, Taiwan
- Sam Li-Sheng Chen, PhD, Taipei Medical University, Taiwan
- Jean Ching-Yuan Fann, PhD, Kainan University, Taiwan
- Sherry Yueh-Hsia Chiu, PhD, Chang Gung University, Taiwan
- May Mei-Sheng Ku, PhD student, National Taiwan University, Taipei, Taiwan
- Wendy Yi-Ying Wu, PhD, Umeå University, Sweden
- Chen-Yang Hsu, MD, National Taiwan University, Taipei, Taiwan
- Yu-Ching Chen, MD, Taipei City Hospital
- Kerri R. Beckmann, PhD, University of South Australia, Adelaide, Australia
- Robert A. Smith, PhD, American Cancer Society, Atlanta GA, USA
- Stephen W. Duffy, MSc, Queen Mary University of London, UK

Thank you