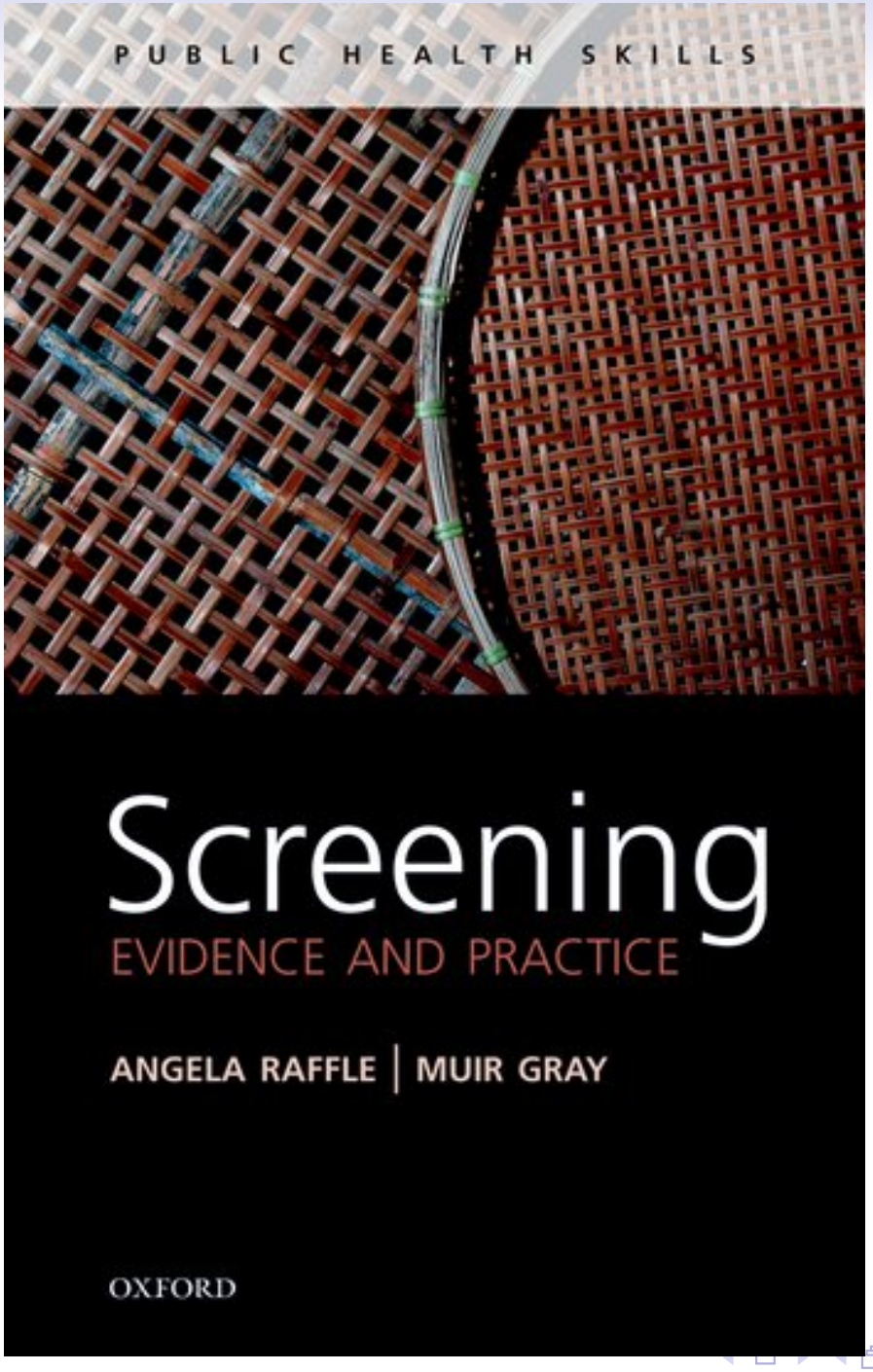
The mortality reductions produced by cancer screening:

Why do published results vary so much?

James A. Hanley

McGill University

Panel Discussion
Conference: Applied Research on Cancer Control
Montreal, Quebec
2018-05-28


PUBLIC HEALTH SKILLS
Screening
EVIDENCE AND PRACTICE
ANGELA RAFFLE | MUIR GRAY
OXFORD

Screening: Evidence and practice

Angela Raffle and Muir Gray. Oxford. 2007

Screening: Evidence and practice

Angela Raffle and Muir Gray. Oxford. 2007

All screening programmes do harm.

Screening: Evidence and practice

Angela Raffle and Muir Gray. Oxford. 2007

All screening programmes do harm.

Some do good as well and, of these, some do more good than harm at reasonable cost.

Screening: Evidence and practice

Angela Raffle and Muir Gray. Oxford. 2007

All screening programmes do harm.

Some do good as well and, of these, some do more good than harm at reasonable cost.

It is the responsibility of policy makers, public health practitioners, managers and the clinicians involved in screening to ensure that only programmes that do more good than harm at reasonable cost are implemented and, when they are implemented, that they are managed in such a way as to achieve a level of quality which will ensure that the balance of good and harm demonstrated in research is reproduced in the ordinary service setting.

The role of time

Mark Anthony in Shakespeare's Julius Caesar

The role of time

Mark Anthony in Shakespeare's Julius Caesar

"*The evil that men do lives after them;*

The good is oft interred with their bones,"

The role of time

Mark Anthony in Shakespeare's Julius Caesar

"*The evil that men do lives after them;*

The good is oft interred with their bones,"

in many **screening** contexts,

The role of time

Mark Anthony in Shakespeare's Julius Caesar

"*The evil that men do lives after them;*

The good is oft interred with their bones,"

in many **screening** contexts,

– the harm is immediate

– the good is delayed (and harder to measure)

Why the large variation in results re ’‘the good’ ?

Outline of Remarks

- First principles of screening are ignored
  - **Time** (early detection)
  - **Who** might benefit (early detection)
- Illustrations: screening for cancer of
  Prostate / Lung / Colon / Ovary / Cervix / **Breast**

Time-pattern in reduction(s) in rates

Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**

Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**
PKU screening	**Intellectual disability, ..**

Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**
PKU screening	**Intellectual disability, ..**
Vaccination	**Measles, Polio, ..**

Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**
PKU screening	**Intellectual disability, ..**
Vaccination	**Measles, Polio, ..**
TB Screening:	**TB spread**

Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**
PKU screening	**Intellectual disability, ..**
Vaccination	**Measles, Polio, ..**
TB Screening:	**TB spread**
Screen for heart defects	**Sudden death in athletes**

Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**
PKU screening	**Intellectual disability, ..**
Vaccination	**Measles, Polio, ..**
TB Screening:	**TB spread**
Screen for heart defects	**Sudden death in athletes**
Adult circumcision	**HIV**

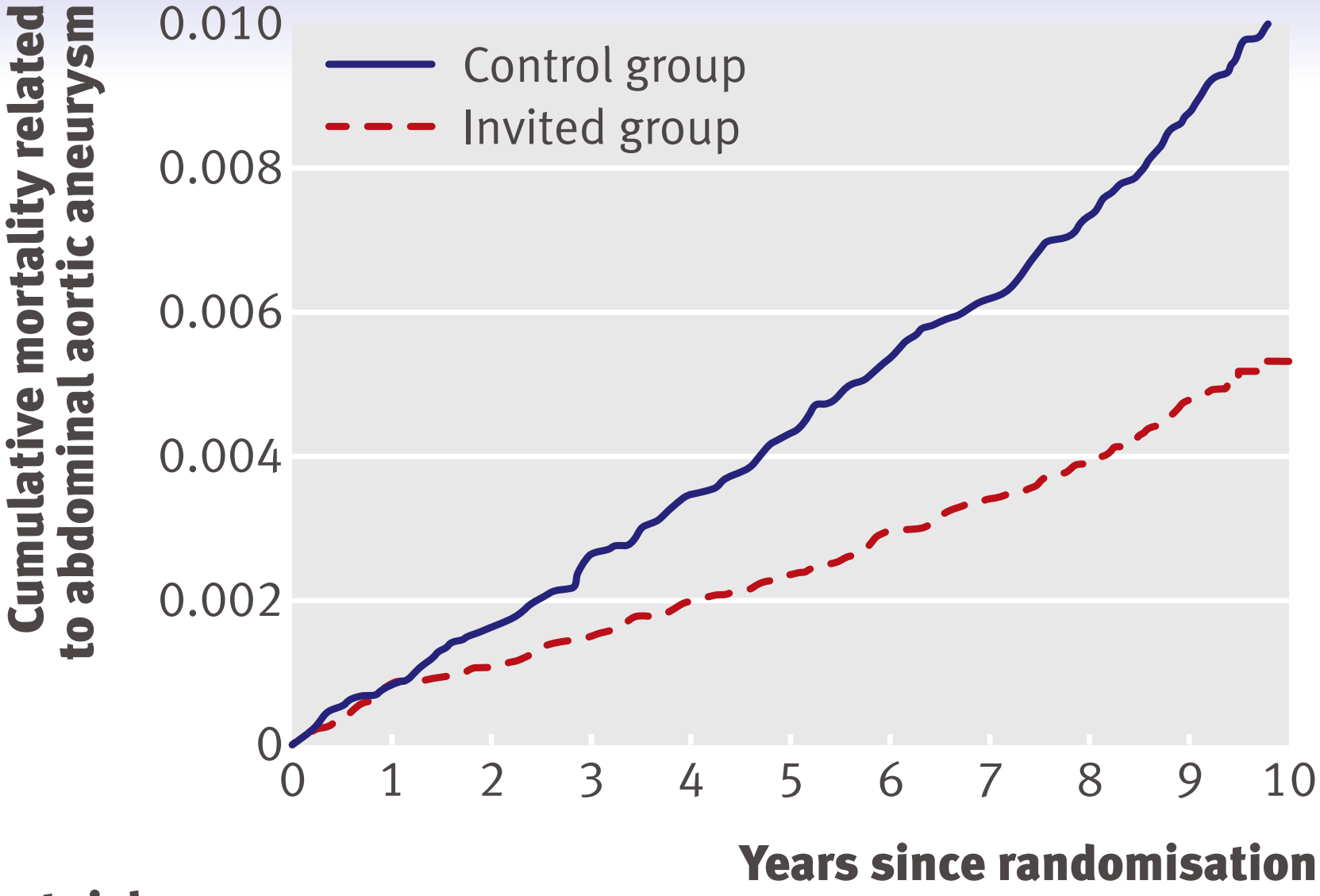
Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**
PKU screening	**Intellectual disability, ..**
Vaccination	**Measles, Polio, ..**
TB Screening:	**TB spread**
Screen for heart defects	**Sudden death in athletes**
Adult circumcision	**HIV**
Ultrasound screening	**Death from AAA rupture**

Time-pattern in reduction(s) in rates

Activity	↓ **Risk/Rate of**
PKU screening	**Intellectual disability, ..**
Vaccination	**Measles, Polio, ..**
TB Screening:	**TB spread**
Screen for heart defects	**Sudden death in athletes**
Adult circumcision	**HIV**
Ultrasound screening	**Death from AAA rupture**

↓ **virtually immediate, and sustained**



Men at risk

Control group	33 887	32 103	29 992	27 664	25 000	13 242
Invited group	33 883	32076	30 101	27 860	25 388	13 385

Time-pattern in reduction(s) in rates/levels

Time-pattern in reduction(s) in rates/levels

Agent	↓ **Risk/Rate/Level of**

Time-pattern in reduction(s) in rates/levels

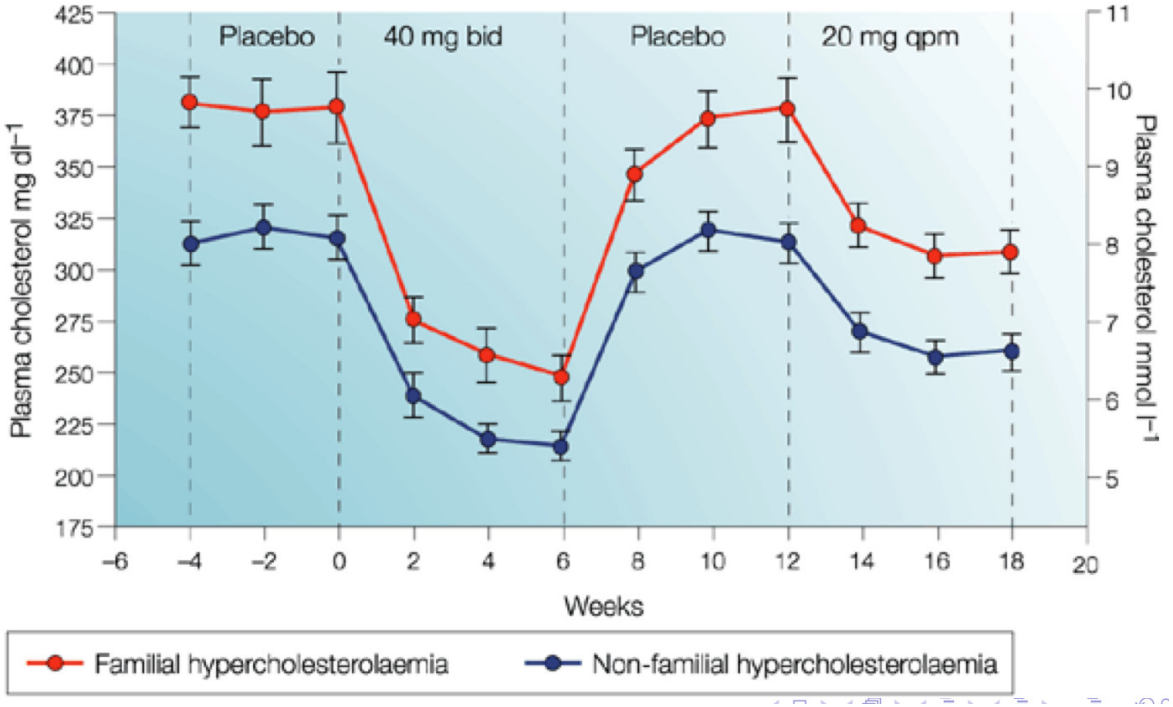
Agent	$\downarrow$ **Risk/Rate/Level of**
Blood thinners	**Stroke/MI**

Time-pattern in reduction(s) in rates/levels

Agent	$\downarrow$ **Risk/Rate/Level of**
Blood thinners	**Stroke/MI**
Statins	**LDL cholesterol**

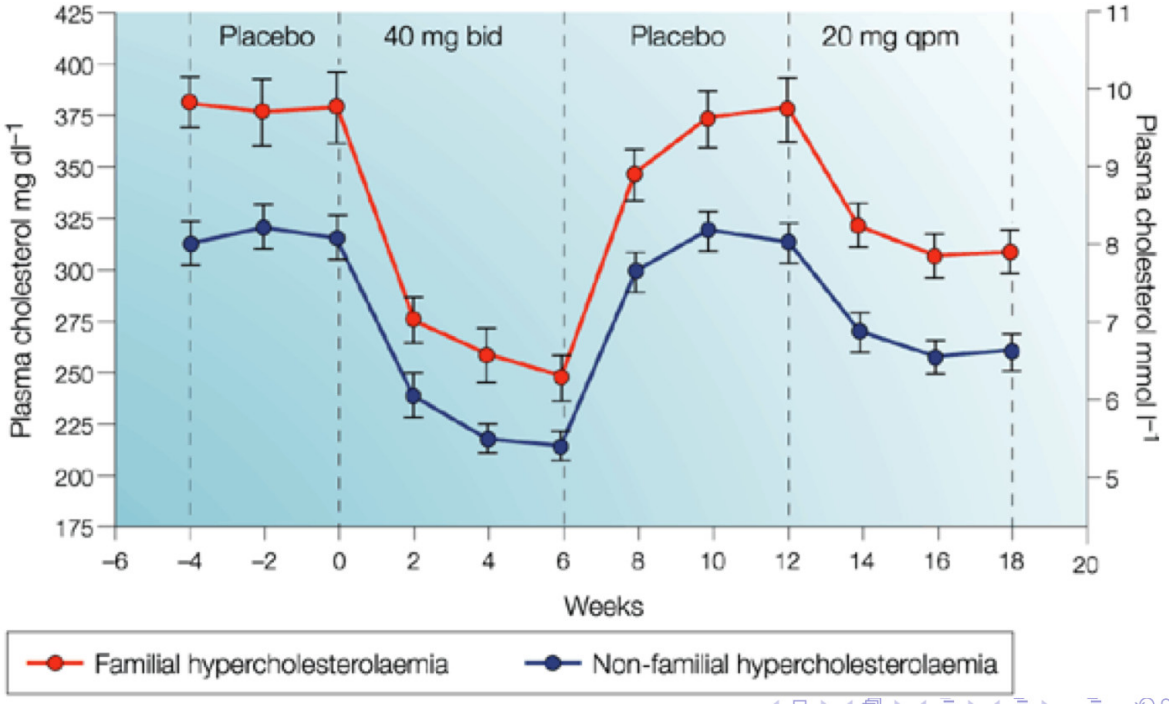
Time-pattern in reduction(s) in rates/levels

Agent	↓ **Risk/Rate/Level of**
Blood thinners	**Stroke/MI**
Statins	**LDL cholesterol**



Time-pattern in reduction(s) in rates/levels

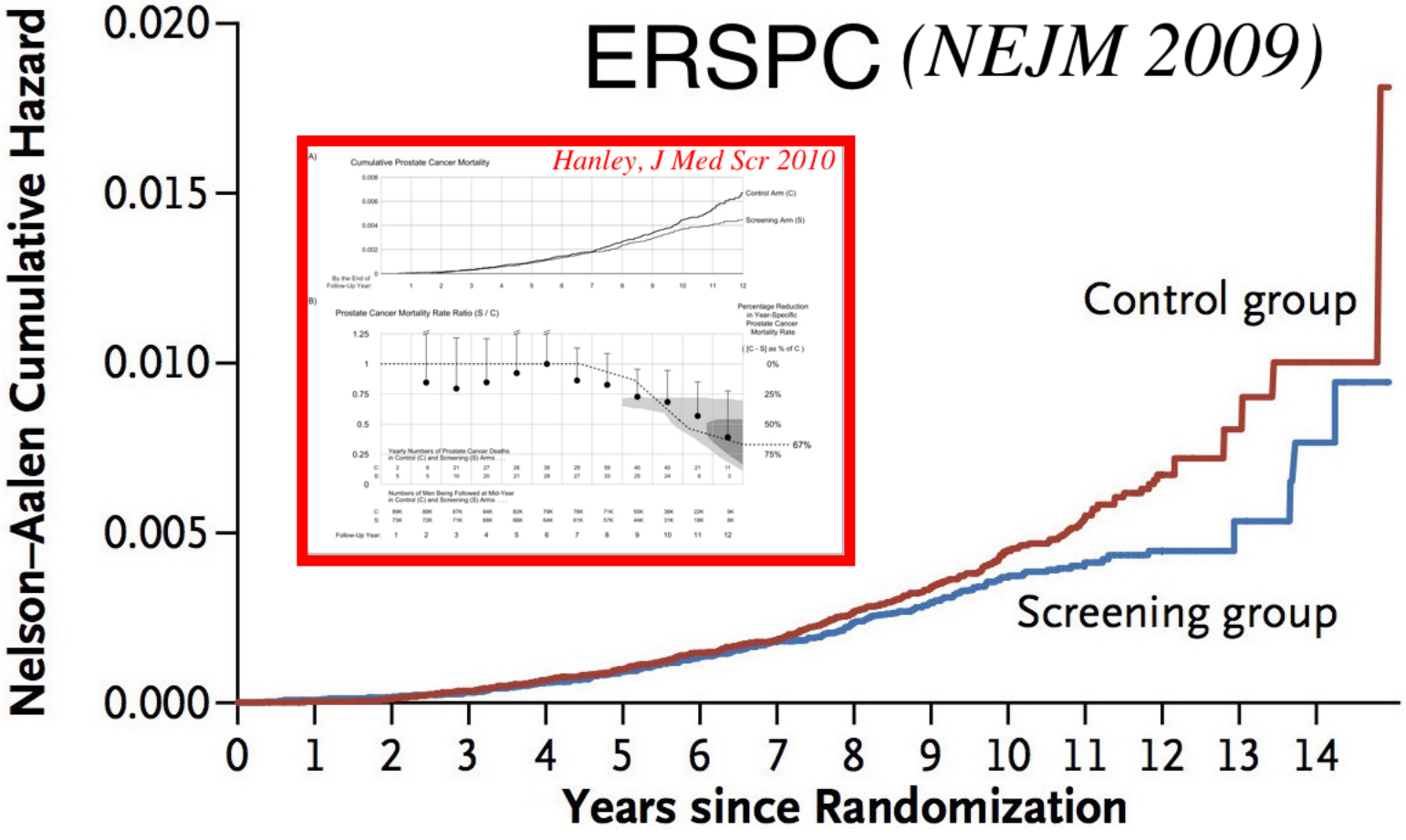
Agent	↓ **Risk/Rate/Level of**
Blood thinners	**Stroke/MI**
Statins	**LDL cholesterol**



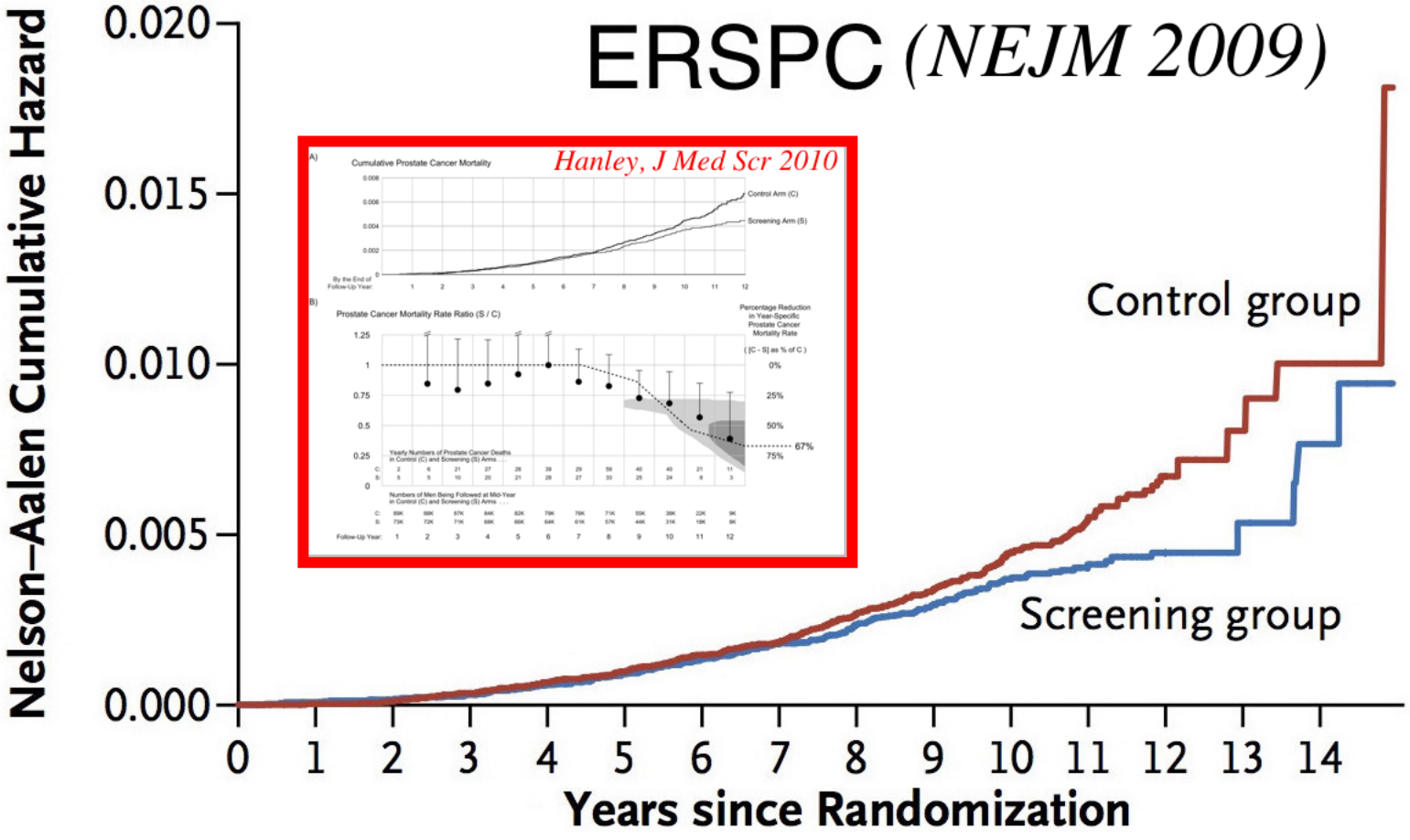
↓ **disappears when agent removed**

PROSTATE cancer screening: a ‘1-number’ reduction

PROSTATE cancer screening: a ‘1-number’ reduction



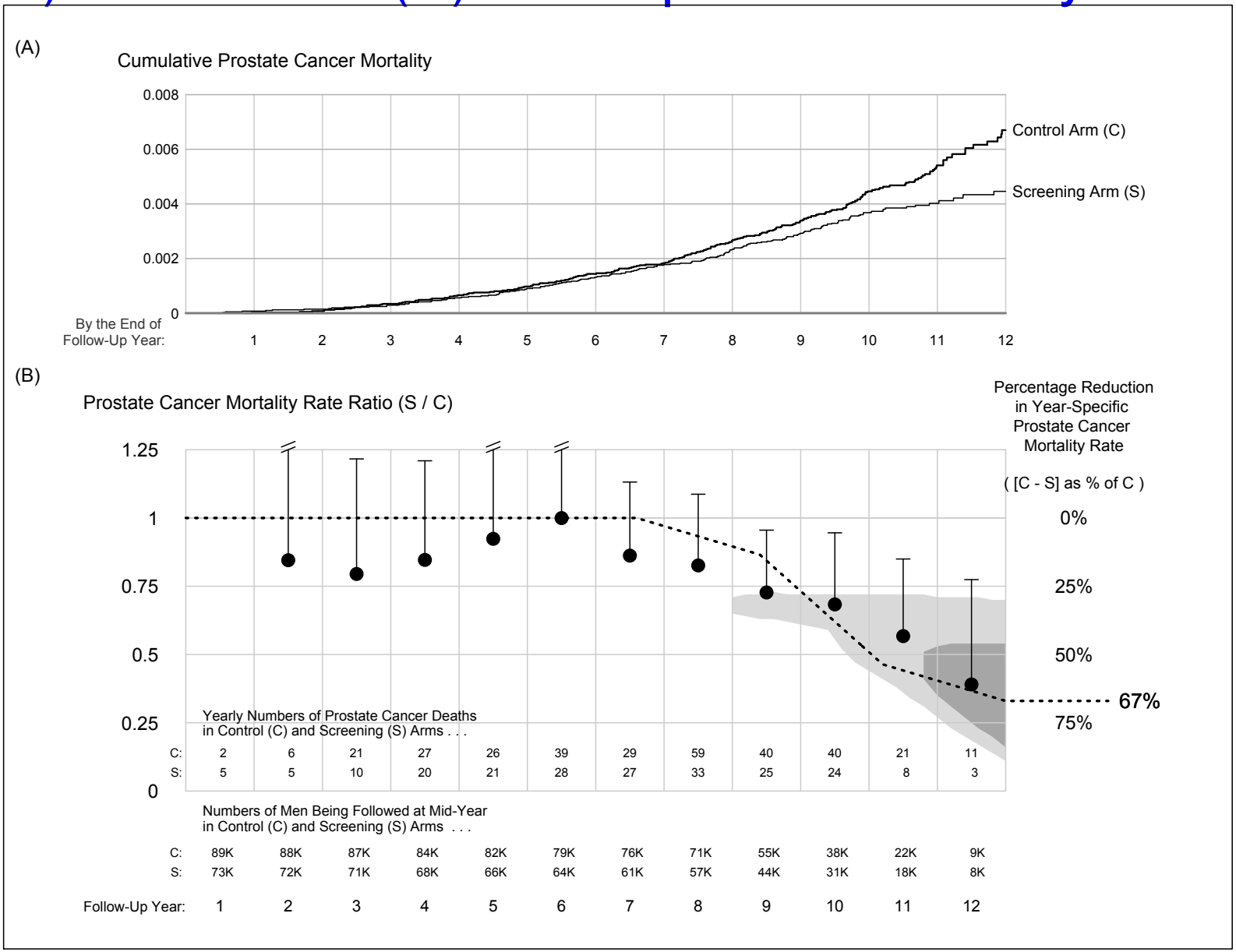
PROSTATE cancer screening: a ‘1-number’ reduction



“Average f.-up: 8.8y. **Rate ratio** for death from prostate cancer in screening group:’ **0.80** $\rightarrow$ ‘AVERAGE’ reduction of **20**%.”

(A) Overall vs. (B) Year-specific mortality ratios

(A) Overall vs. (B) Year-specific mortality ratios



Hanley, *J Medical Screening*, 2010.

Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

*Fritz H Schröder, Jonas Hugosson, Monique J Roobol, Teuvo L J Tammela, Marco Zappa, Vera Nelen, Maciej Kwiatkowski, Marcos Lujan, Liisa Määttänen, Hans Lilja, Louis J Denis, Franz Recker, Alvaro Paez, Chris H Bangma, Sigrid Carlsson, Donella Puliti, Arnauld Villers, Xavier Rebillard, Matti Hakama, Ulf-Hakan Stenman, Paula Kujala, Kimmo Taari, Gunnar Aus, Andreas Huber, Theo H van der Kwast, Ron H N van Schaik, Harry J de Koning, Sue M Moss, Anssi Auvinen, for the ERSPC Investigators**

Summary

Background The European Randomised study of Screening for Prostate Cancer (ERSPC) has shown significant reductions in prostate cancer mortality after 9 years and 11 years of follow-up, but screening is controversial because of adverse events such as overdiagnosis. We provide updated results of mortality from prostate cancer with follow-up to 2010, with analyses truncated at 9, 11, and 13 years.

Methods ERSPC is a multicentre, randomised trial with a predefined centralised database, analysis plan, and core age group (55–69 years), which assesses prostate-specific antigen (PSA) testing in eight European countries. Eligible men aged 50–74 years were identified from population registries and randomly assigned by computer generated random numbers to screening or no intervention (control). Investigators were masked to group allocation. The primary outcome was prostate cancer mortality in the core age group. Analysis was by intention to treat. We did a secondary analysis that corrected for selection bias due to non-participation. Only incidence and no mortality data at 9 years' follow-up are reported for the French centres. This study is registered with Current Controlled Trials, number ISRCTN49127736.

Findings With data truncated at 13 years of follow-up, 7408 prostate cancer cases were diagnosed in the intervention group and 6107 cases in the control group. The rate ratio of prostate cancer incidence between the intervention and control groups was 1·91 (95% CI 1·83–1·99) after 9 years (1·64 [1·58–1·69] including France), 1·66 (1·60–1·73) after 11 years, and 1·57 (1·51–1·62) after 13 years. The rate ratio of prostate cancer mortality was 0·85 (0·70–1·03) after 9 years, 0·78 (0·66–0·91) after 11 years, and 0·79 (0·69–0·91) at 13 years. The absolute risk reduction of death from prostate cancer at 13 years was 0·11 per 1000 person-years or 1·28 per 1000 men randomised, which is equivalent to one prostate cancer death averted per 781 (95% CI 490–1929) men invited for screening or one per 27 (17–66) additional prostate cancer detected. After adjustment for non-participation, the rate ratio of prostate cancer mortality in men screened was 0·73 (95% CI 0·61–0·88).

Interpretation In this update the ERSPC confirms a substantial reduction in prostate cancer mortality attributable to testing of PSA, with a substantially increased absolute effect at 13 years compared with findings after 9 and 11 years. Despite our findings, further quantification of harms and their reduction are still considered a prerequisite for the introduction of populated-based screening.

Published Online
August 7, 2014
http://dx.doi.org/10.1016/S0140-6736(14)60525-0

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(14)61008-4

*For the full study group see appendix

Department of Urology, Erasmus University Medical Center, Rotterdam, Netherlands (Prof F H Schröder MD, M J Roobol PhD, Prof C H Bangma MD); **Department of Urology, Sahlgrenska Academy at Goteborg University, Goteborg, Sweden** (Prof J Hugosson PhD, S Carlsson MD); **Department of Urology, Tampere University Hospital, Tampere, Finland** (Prof T L J Tammela MD); **School of Medicine, University of Tampere, Tampere, Finland** (Prof T L J Tammela); **Unit of Clinical and Descriptive Epidemiology, ISPO, Florence, Italy** (M Zappa MD, D Puliti MSc); **Provinciaal Instituut voor Hygiene, Antwerp, Belgium**

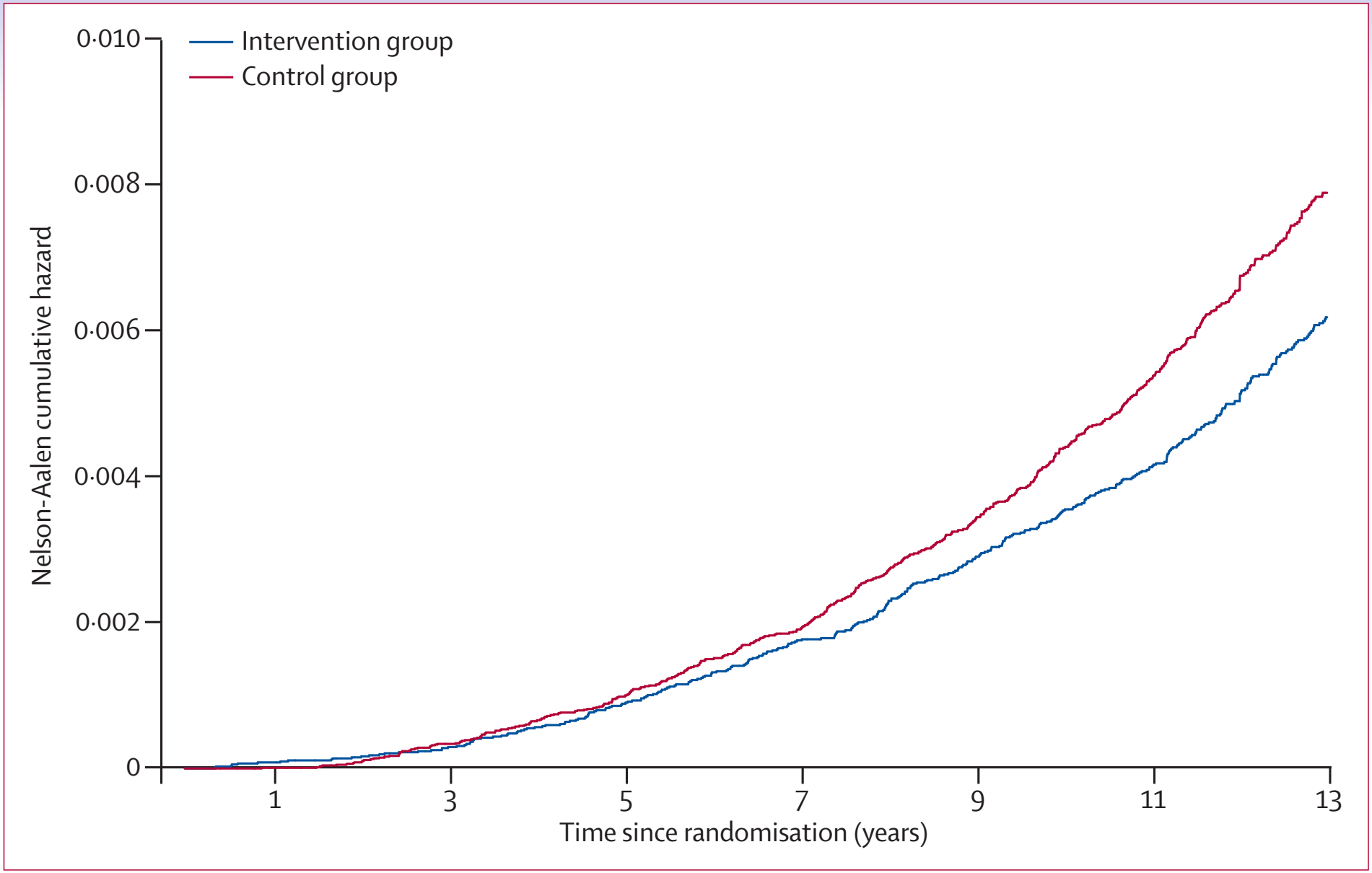


Figure 2: **Nelson–Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)**

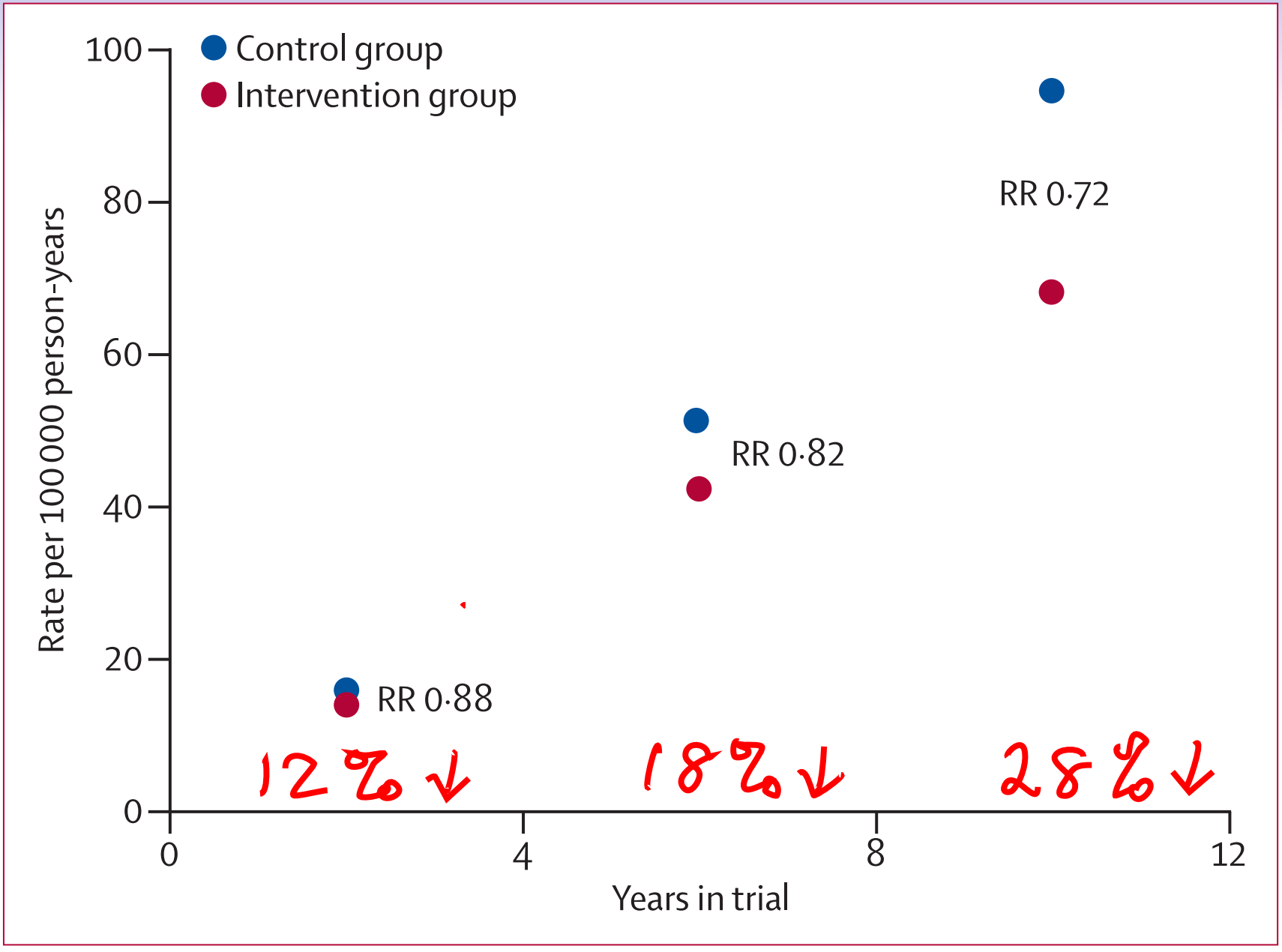
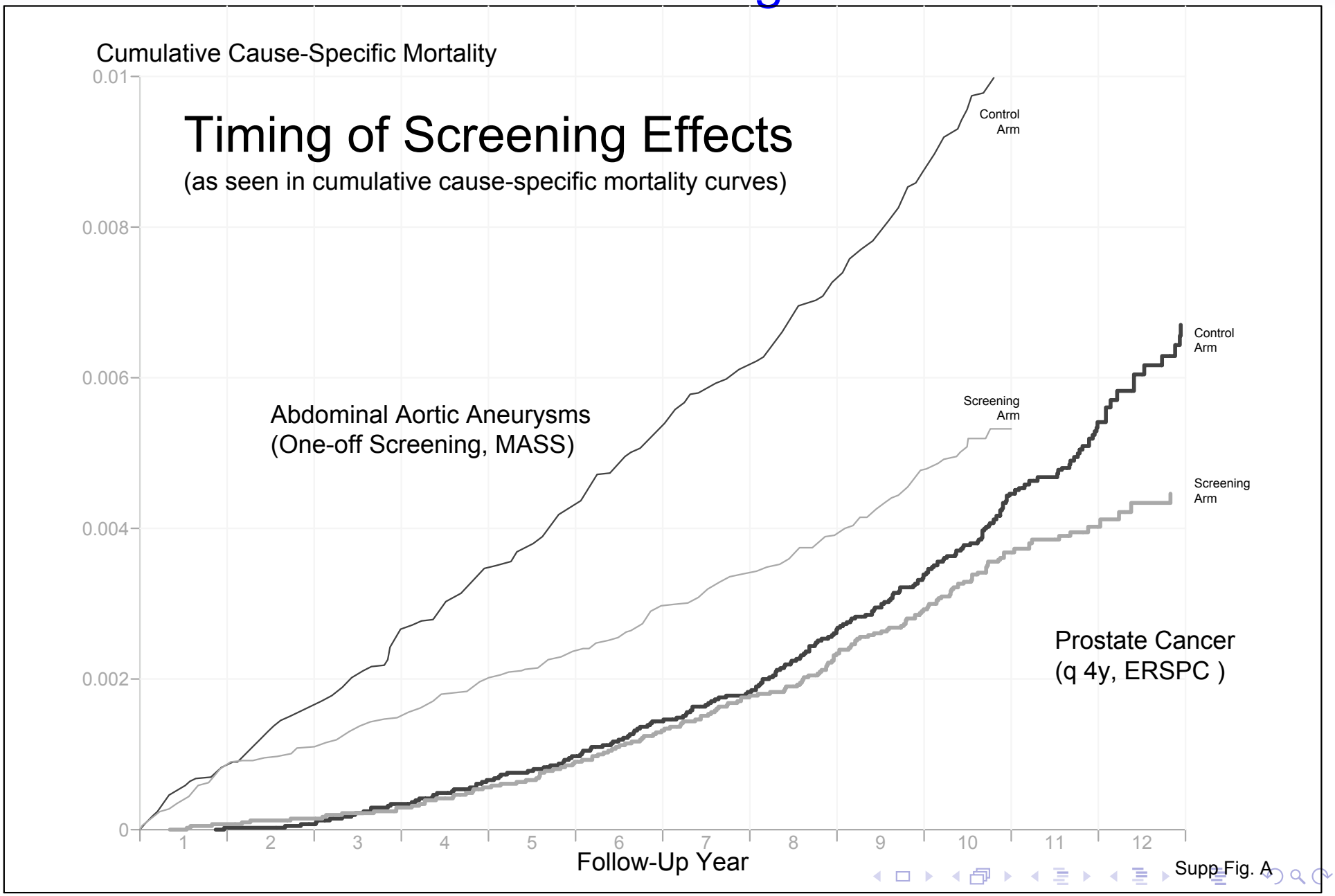


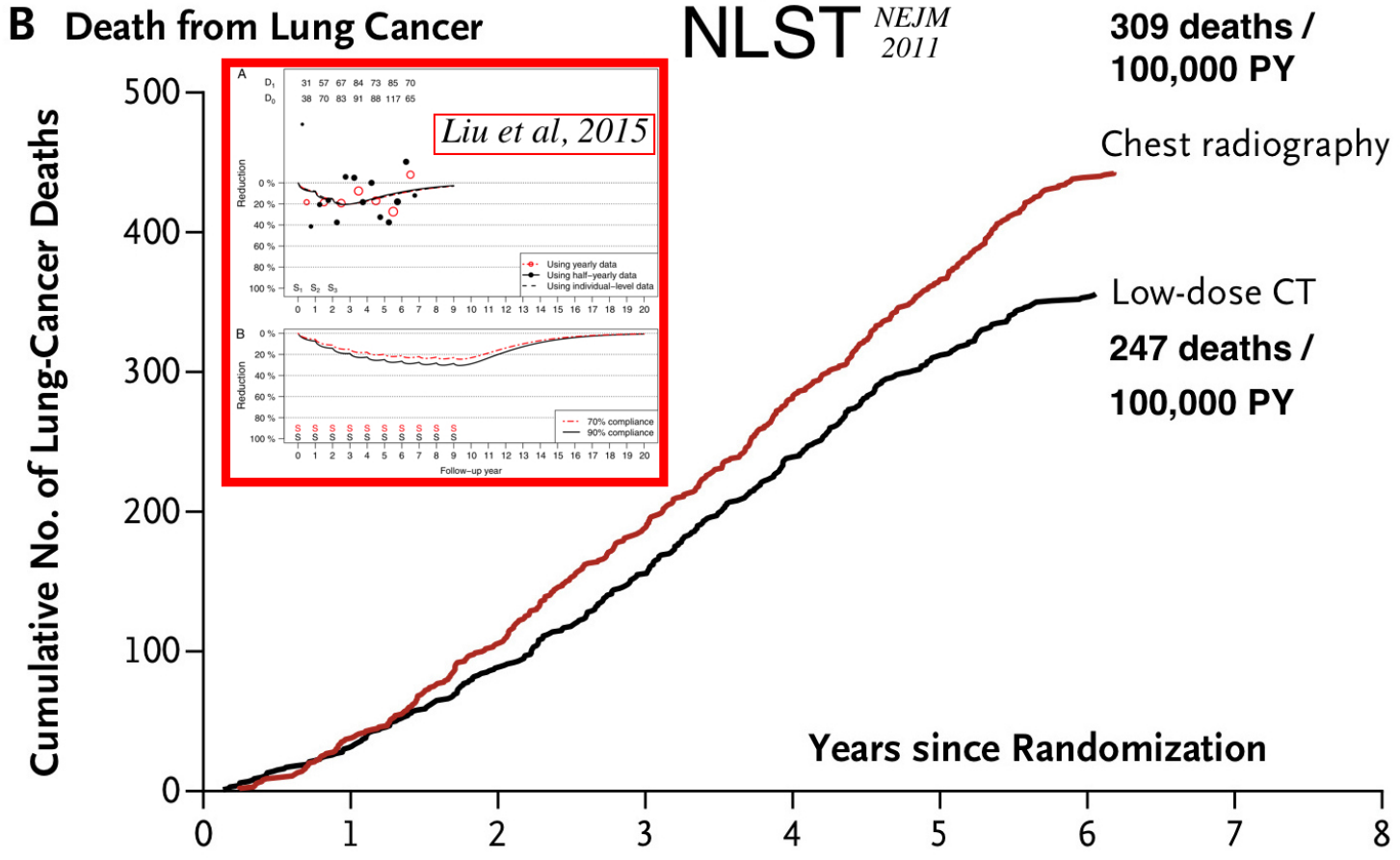
Figure 3: **Nelson-Aalen estimates of cumulative prostate cancer in both groups by 4-year periods (all centres, excluding France)**

The loneliness of the long-distance trialist



Hanley, *Epidemiologic Reviews*, 2011

LUNG cancer screening: a '1-number' reduction



With **sustained** screening, the steady-state mortality reduction would be more than **20%** observed after just the 3 trial rounds.

Mortality deficits produced by cancer screening

- Become **evident only after some delay**.
- Some time **after screening ceases**, mortality rates **revert** to those in unscreened.
  - 30 y. follow-up, Minnesota **Colon** Trial [FOBT screens for 15 years]
  - Should we expect mortality deficits in year 21 of Mayo **Lung** Trial, which screened for 6 years?

Bottom Line [1]

The unprincipled 1-number hazard-ratio (or % $\downarrow$) ignores

Bottom Line [1]

The unprincipled 1-number hazard-ratio (or % $\downarrow$) ignores

- **how many** screens

Bottom Line [1]

The unprincipled 1-number hazard-ratio (or % $\downarrow$) ignores

- **how many** screens
- **when** the **last screen** was

Bottom Line [1]

The unprincipled 1-number hazard-ratio (or % $\downarrow$) ignores

- **how many** screens
- **when** the **last screen** was
- **when follow-up ended**

Bottom Line [1]

The unprincipled 1-number hazard-ratio (or % $\downarrow$) ignores

- **how many** screens
- **when** the **last screen** was
- **when follow-up ended**
- **when mortality deficits are expected to manifest.**

First Principles of Screening

First Principles of Screening

Screening: pursuit of **earlier Dx** (& earlier Tx).

First Principles of Screening

Screening: pursuit of **earlier Dx** (& earlier Tx).

Because of the **Detectability : Curability tradeoff**, the course of many cancers, 'otherwise' fatal at $T = t$, is not altered by screen at $T = 0$.

They are too early/late to be detected/cured.

First Principles of Screening

Screening: pursuit of **earlier Dx** (& earlier Tx).

Because of the **Detectability : Curability tradeoff**, the course of many cancers, 'otherwise' fatal at $T = t$, is not altered by screen at $T = 0$.

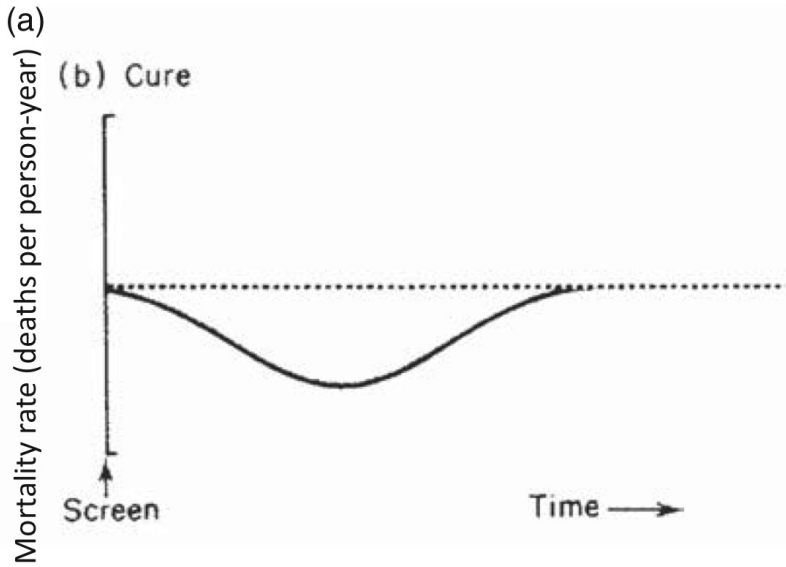
They are too early/late to be detected/cured.

Mortality deficits manifest after some delay, and disappear at some point after last screen.

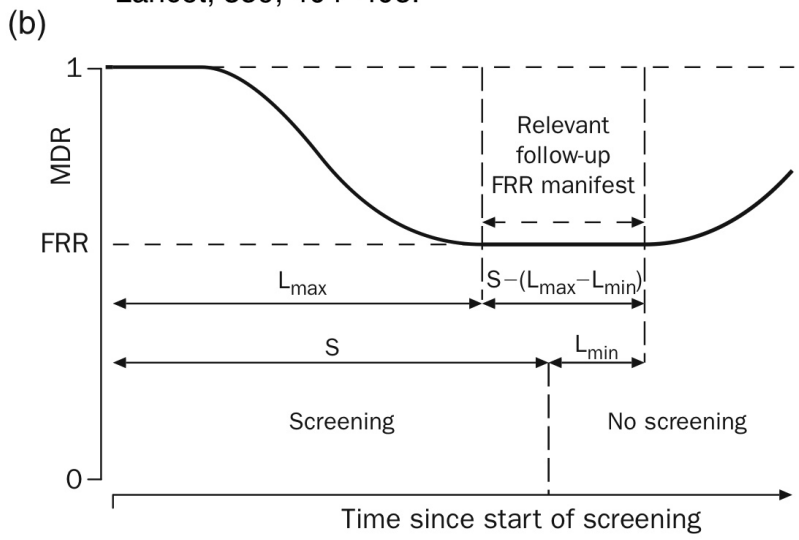
Principles → HR [or %Reduction] **function**

Principles → HR [or %Reduction] **function**

Morrison (1992). Screening in Chronic Disease. 2nd ed. New York: Oxford University Press.

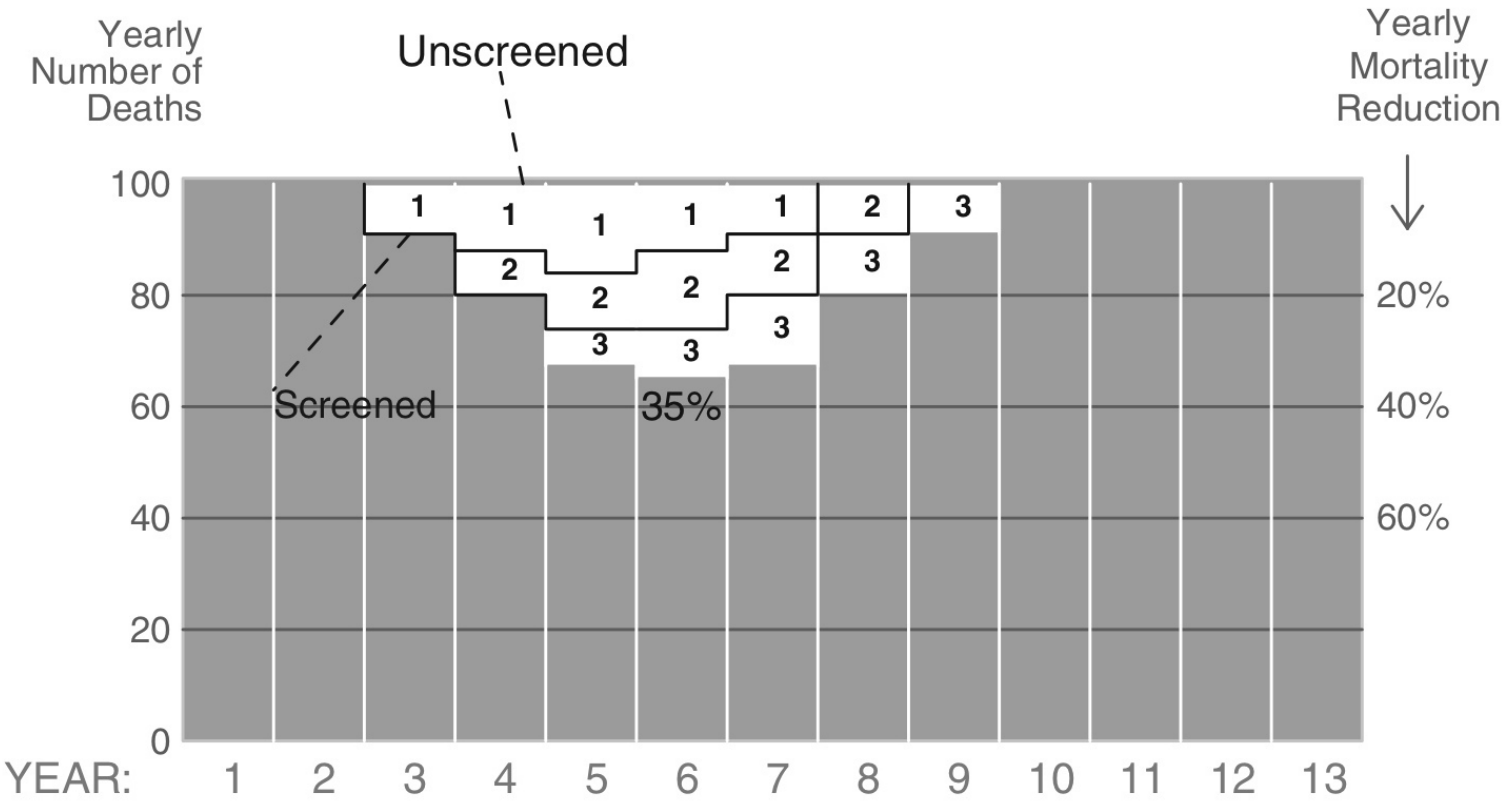


Miettinen et al. (2002). Mammographic screening: no reliable supporting evidence? Lancet, 359, 404–405.



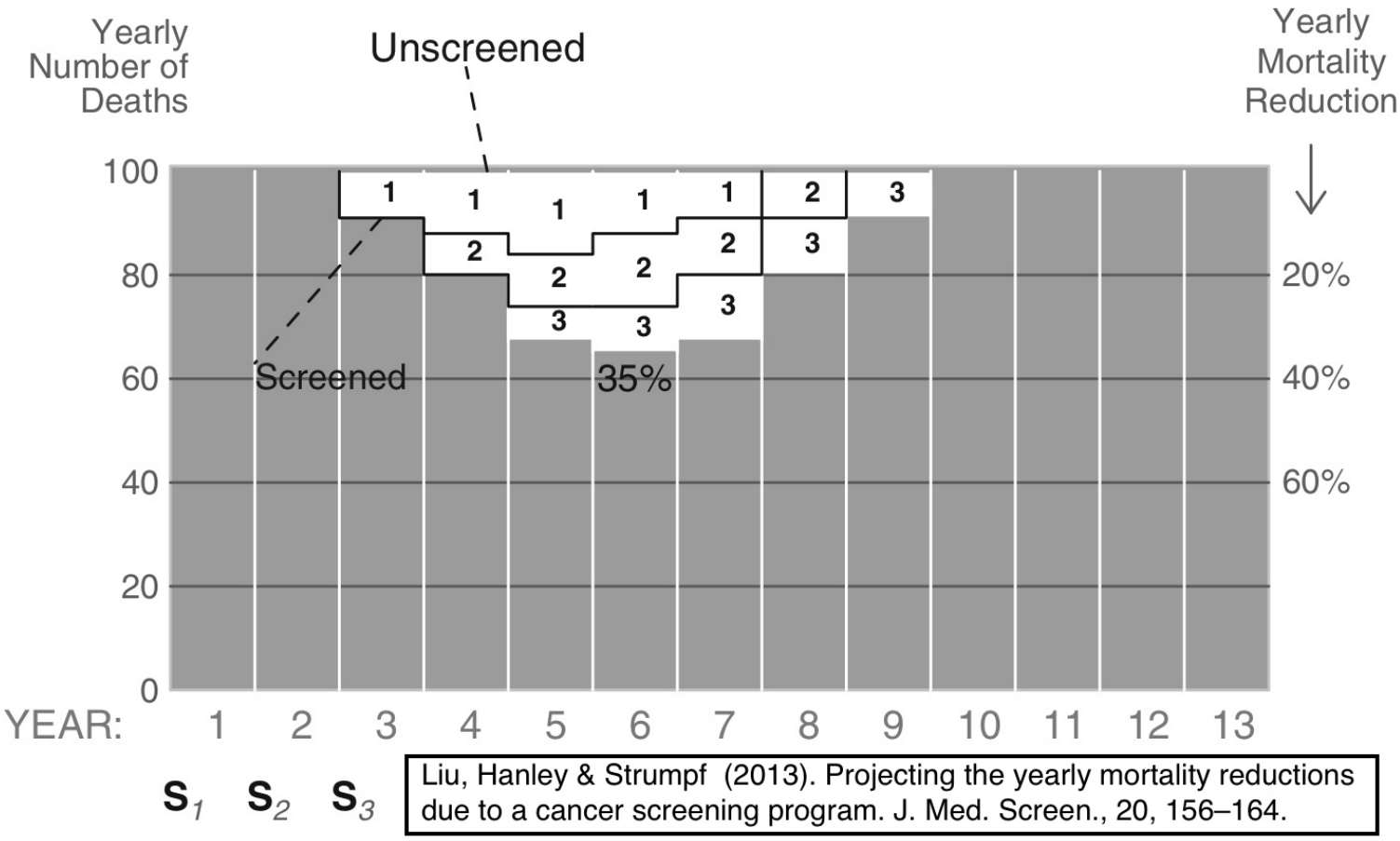
Principles → HR [or %Reduction] **function**

Principles → HR [or %Reduction] **function**



Liu, Hanley & Strumpf (2013). Projecting the yearly mortality reductions due to a cancer screening program. J. Med. Screen., 20, 156–164.

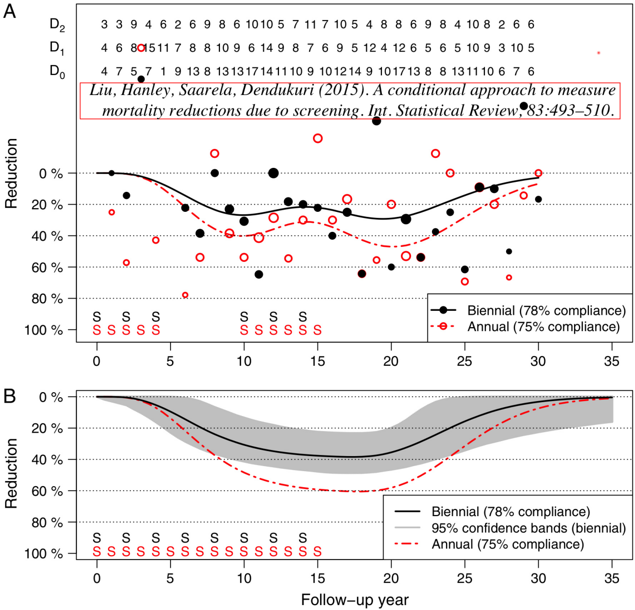
Principles → HR [or %Reduction] **function**



The **depth** & **duration** of the mortality deficits produced by **3** screenings. In women screened from **50-69**, deficits would reach their max. at ≈ age 56 & maintain this level for many age-bins.

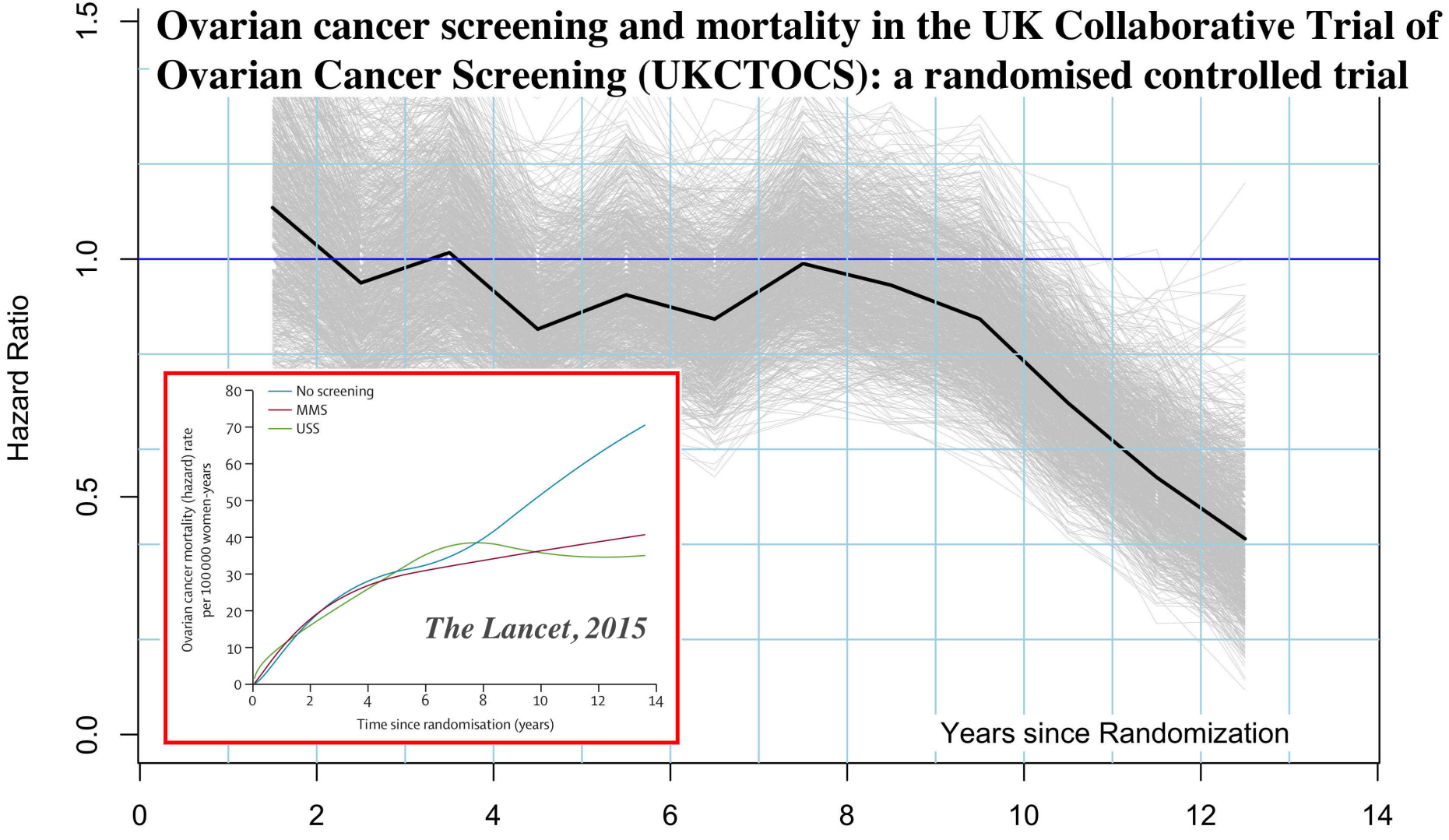
COLON Screening. HR [or %Reduction] function

COLON Screening. HR [or %Reduction] function



Ovarian Cancer. HR [or %Reduction] function

Ovarian Cancer. HR [or %Reduction] function



Bottom Line [2]

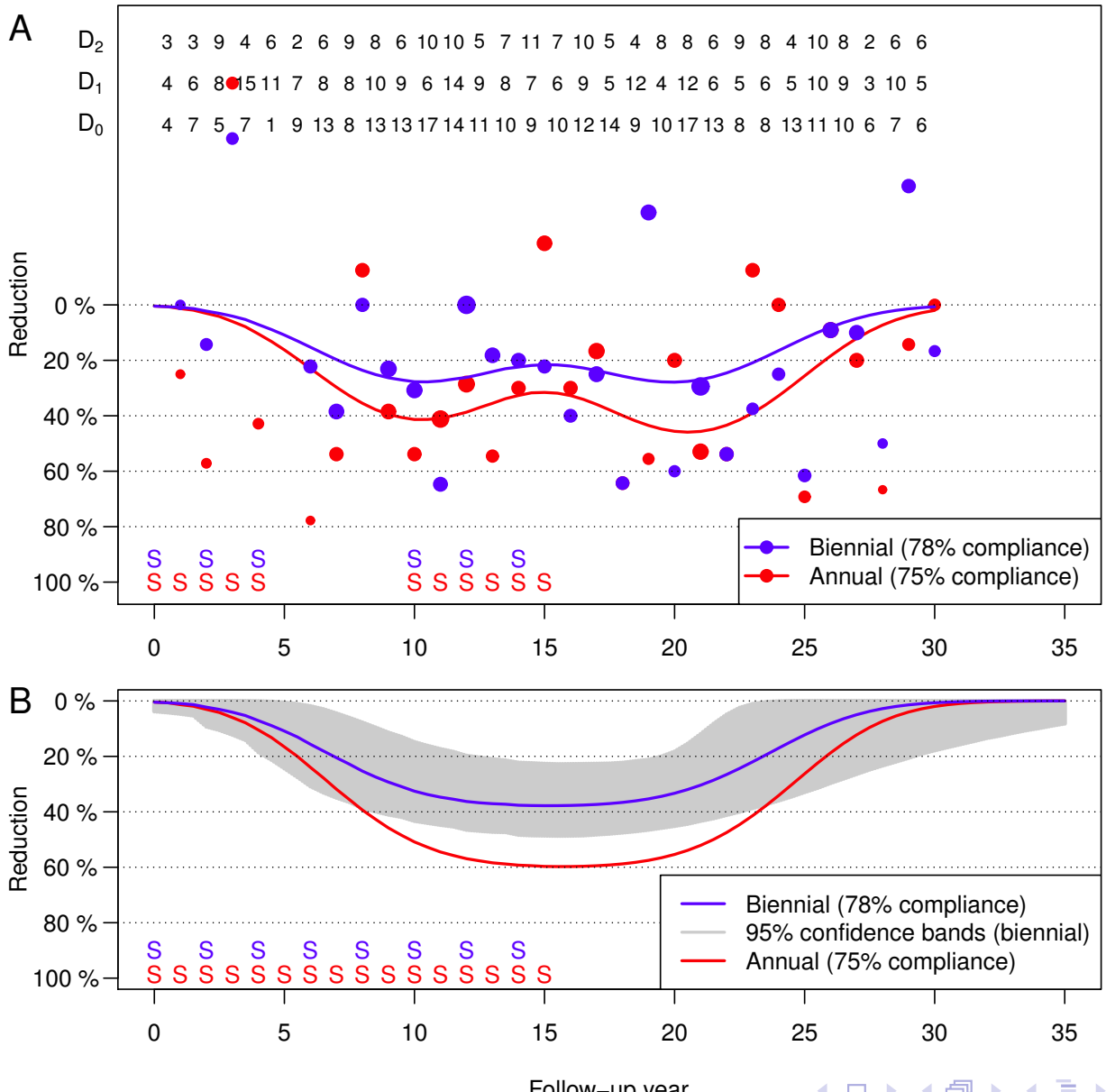
IT'S ABOUT TIME:

to not just recognize the importance of the HR function & its determinants,

but to use them in data analysis

Liu Model: A Fitted to Data; B Projected i.e., no interruption. 6 & 11 Rounds

Liu Model: A Fitted to Data; B Projected i.e., no interruption. 6 & 11 Rounds



SCREENING for BREAST CANCER

???

Magnitude of reductions being achieved with contemporary mammography

???

Magnitude of reductions being achieved with contemporary mammography

Estimates from (non-experimental) population-based studies

Population-based studies **using WHO mortality data**

Population-based studies **using WHO mortality data**

BMJ

BMJ 2011;343:d4411 doi: 10.1136/bmj.d4411

RESEARCH

Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database

Philippe Autier *research director*[1], Mathieu Boniol *senior statistician*[1], Anna Gavin *director*[2], Lars J Vatten *professor*[3]

[1]International Prevention Research Institute, 95 Cours Lafayette, 69006 Lyon, France; [2]Northern Ireland Cancer Registry, Belfast, Northern Ireland, UK; [3]Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway

Abstract

Objective To compare trends in breast cancer mortality within three pairs of neighbouring European countries in relation to implementation of screening.

Design Retrospective trend analysis.

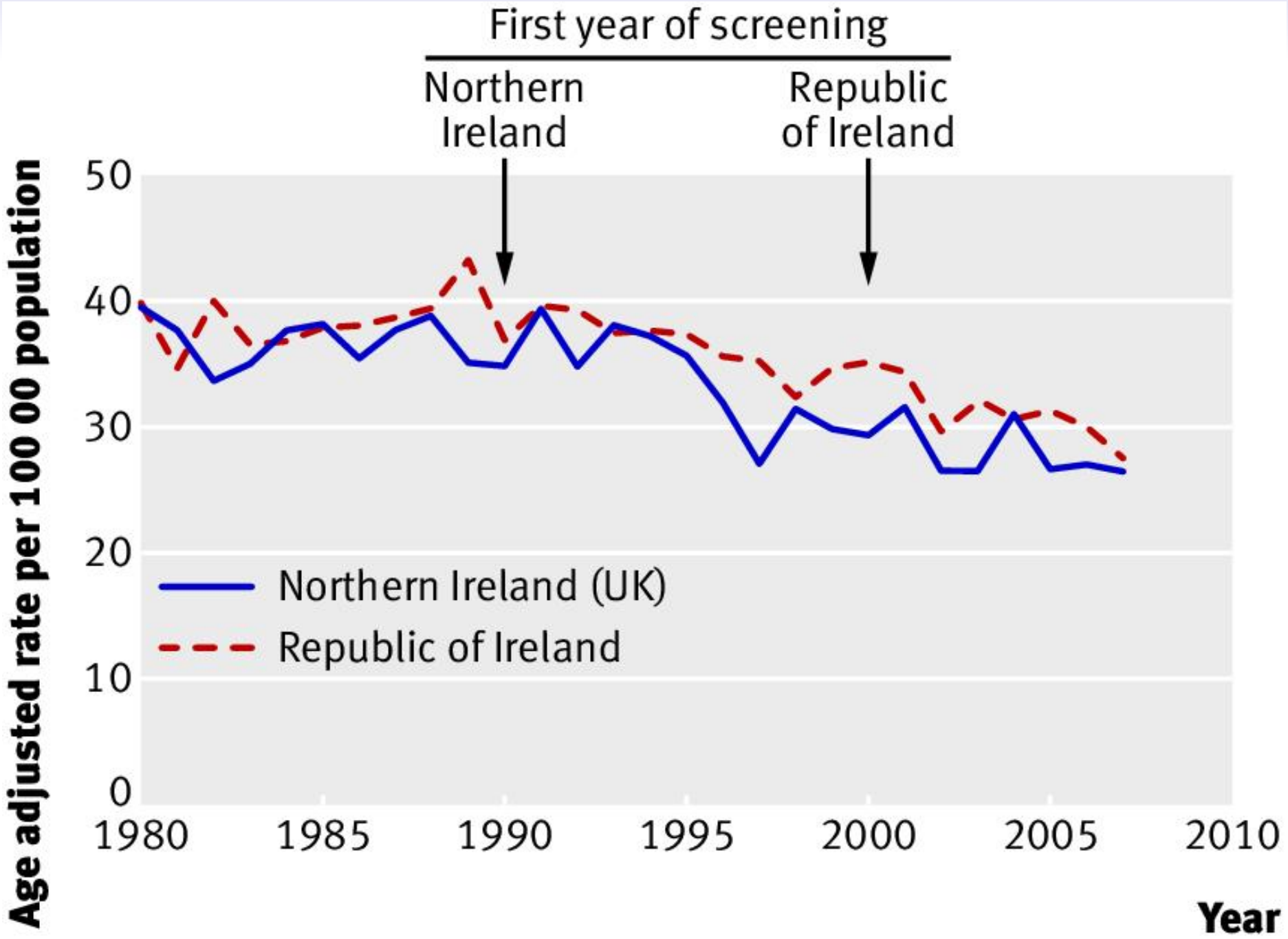
Setting Three country pairs (Northern Ireland (United Kingdom) *v* Republic of Ireland, the Netherlands *v* Belgium and Flanders (Belgian region south of the Netherlands), and Sweden *v* Norway).

Data sources WHO mortality database on cause of death and data sources on mammography screening, cancer treatment, and risk factors for breast cancer mortality.

Main outcome measures Changes in breast cancer mortality calculated from linear regressions of log transformed, age adjusted death rates. Joinpoint analysis was used to identify the year when trends in mortality for all ages began to change.

Results From 1989 to 2006, deaths from breast cancer decreased by 29% in Northern Ireland and by 26% in the Republic of Ireland; by 25% in the Netherlands and by 20% in Belgium and 25% in Flanders; and by 16% in Sweden and by 24% in Norway. The time trend and year of downward inflexion were similar between Northern Ireland and the Republic of Ireland and between the Netherlands and Flanders. In Sweden, mortality rates have steadily decreased since 1972, with no downward inflexion until 2006. Countries of each pair had similar healthcare services and prevalence of risk factors for breast cancer mortality but differing implementation of mammography screening, with a gap of about 10-15 years.

Conclusions The contrast between the time differences in implementation of mammography screening and the similarity in reductions in mortality between the country pairs suggest that screening did not play a direct part in the reductions in breast cancer mortality.


First year of screening
Northern Ireland
Republic of Ireland
Age adjusted rate per 100 00 population
50
40
30
20
10
0
1980
1985
1990
1995
2000
2005
2010
Year
Northern Ireland (UK)
Republic of Ireland

Why this big-data approach DILUTES the impact

Why this big-data approach DILUTES the impact

Most of the breast cancer deaths in Northern Ireland in the early 1990s involved cancers that had been DIAGNOSED BEFORE the screening was introduced.

Why this big-data approach DILUTES the impact

Most of the breast cancer deaths in Northern Ireland in the early 1990s involved cancers that had been DIAGNOSED BEFORE the screening was introduced.

These women could not have been helped by the program.

Why this big-data approach DILUTES the impact

Most of the breast cancer deaths in Northern Ireland in the early 1990s involved cancers that had been DIAGNOSED BEFORE the screening was introduced.

These women could not have been helped by the program.

Screening pursues not-yet-diagnosed cancers (so as to treat them earlier)

Another study that uses **WHO mortality data**

Effectiveness of and overdiagnosis from mammography screening in the Netherlands: population based study

Philippe Autier,[1,2] Magali Boniol,[2] Alice Koechlin,[1,2] Cécile Pizot,[2] Mathieu Boniol[1,2]

[1]University of Strathclyde Institute of Global Public Health at iPRI, Allée Claude Debussy, 69130 Ecully, Lyon, France

[2]International Prevention Research Institute, Lyon, France

Correspondence to: P Autier philippe.autier@i-pri.org

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2017;359:j5224
http://dx.doi.org/10.1136/bmj.j5224

Accepted: 5 September 2017

ABSTRACT

OBJECTIVE

To analyse stage specific incidence of breast cancer in the Netherlands where women have been invited to biennial mammography screening since 1989 (ages 50-69) and 1997 (ages 70-75), and to assess changes in breast cancer mortality and quantified overdiagnosis.

DESIGN

Population based study.

SETTING

Mammography screening programme, the Netherlands.

PARTICIPANTS

Dutch women of all ages, 1989 to 2012.

MAIN OUTCOME MEASURES

Stage specific age adjusted incidence of breast cancer from 1989 to 2012. The extra numbers of in situ and stage 1 breast tumours associated with screening were estimated by comparing rates in women aged 50-74 with those in age groups not invited to screening. Overdiagnosis was estimated after subtraction of the lead time cancers. Breast cancer mortality reductions during 2010-12 and overdiagnosis during 2009-11 were computed without (scenario 1) and with (scenario 2) a cohort effect on mortality secular trends.

RESULTS

Overdiagnosis has steadily increased over time with the extension of screening to women aged 70-75 and with the introduction of digital mammography. After deduction of clinical lead time cancers, 32% of cancers found in women invited to screening in 2010-12 and 52% of screen detected cancers would be overdiagnosed.

CONCLUSIONS

The Dutch mammography screening programme seems to have little impact on the burden of advanced breast cancers, which suggests a marginal effect on breast cancer mortality. About half of screen detected breast cancers would represent overdiagnosis.

Introduction

The primary goal of cancer screening is to decrease cancer mortality. Cancer screening affects cancer mortality by reducing the number of advanced cancers with poor prognosis. In populations where screening is widespread, decreases in the incidence of advanced cancer should be the first sign that screening effectively reduces cancer mortality.[1-4] This indicator has the advantage of being independent of treatment. It was recommended for the monitoring of the effectiveness of breast screening by the International Agency for Research on Cancer handbook on breast screening published in 2002 and by proponents of mammography screening.[5-8]

Ages when Screened for BC ≠ Ages at Death from BC

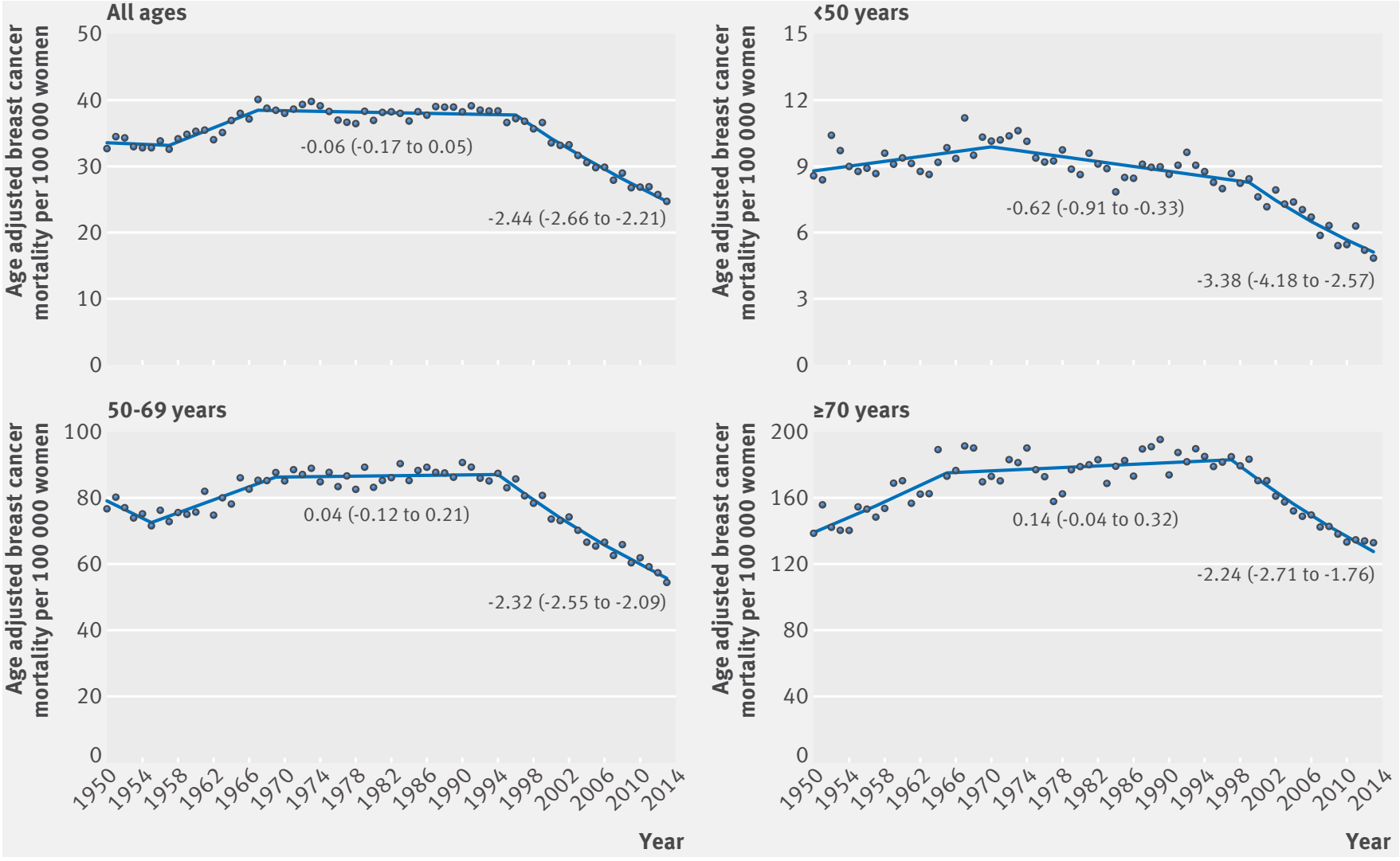


Fig 2 | Trends in age adjusted breast cancer mortality by age group in women in the Netherlands, 1950 to 2013. Figures are the annual percentage changes (95% confidence intervals) for the two last periods with stable trend according to joinpoint analysis

Population-based studies that emulate RCTs

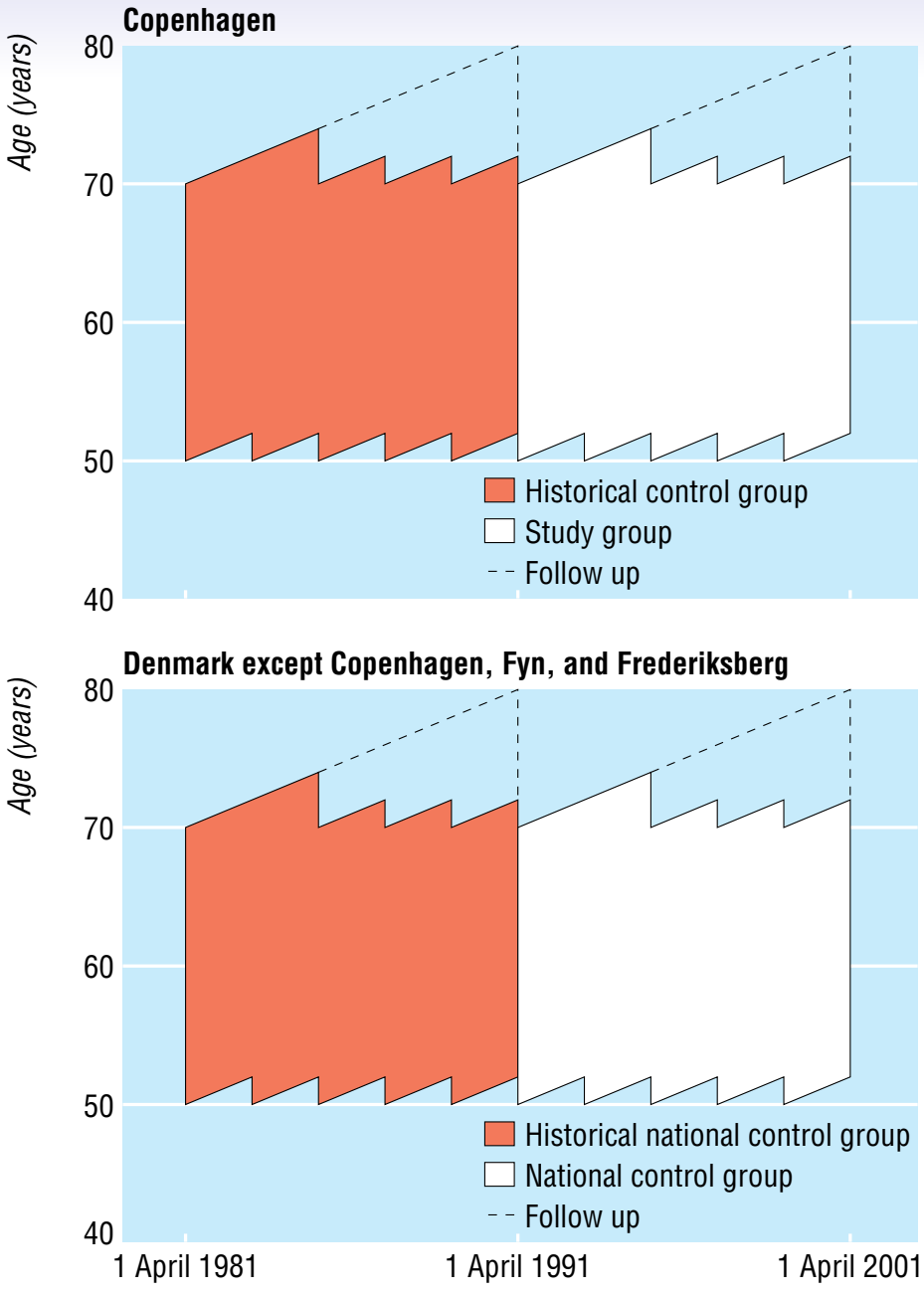
Population-based studies that emulate RCTs

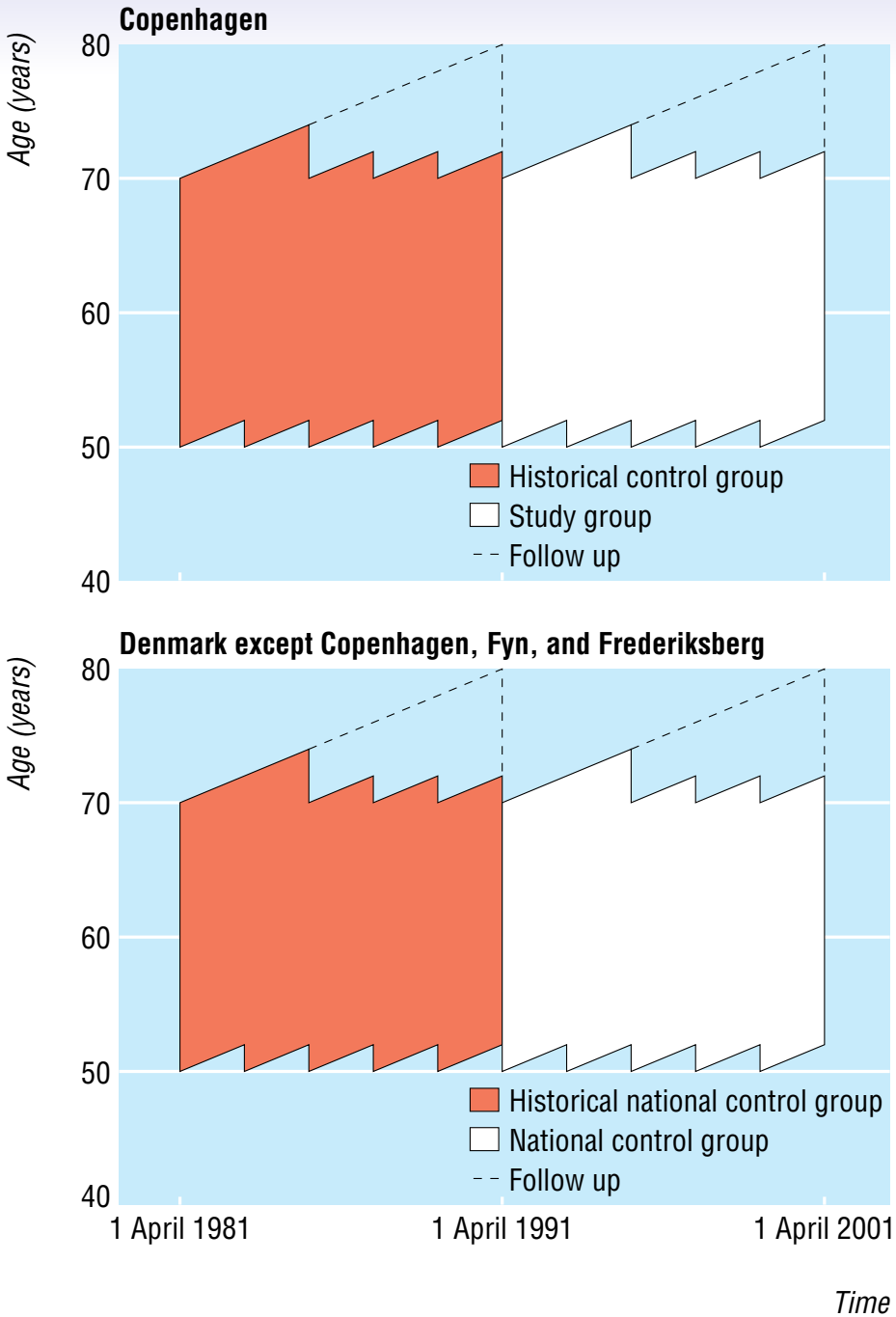
Cite this article as: BMJ, doi:10.1136/bmj.38313.639236.82 (published 13 January 2005)

Papers

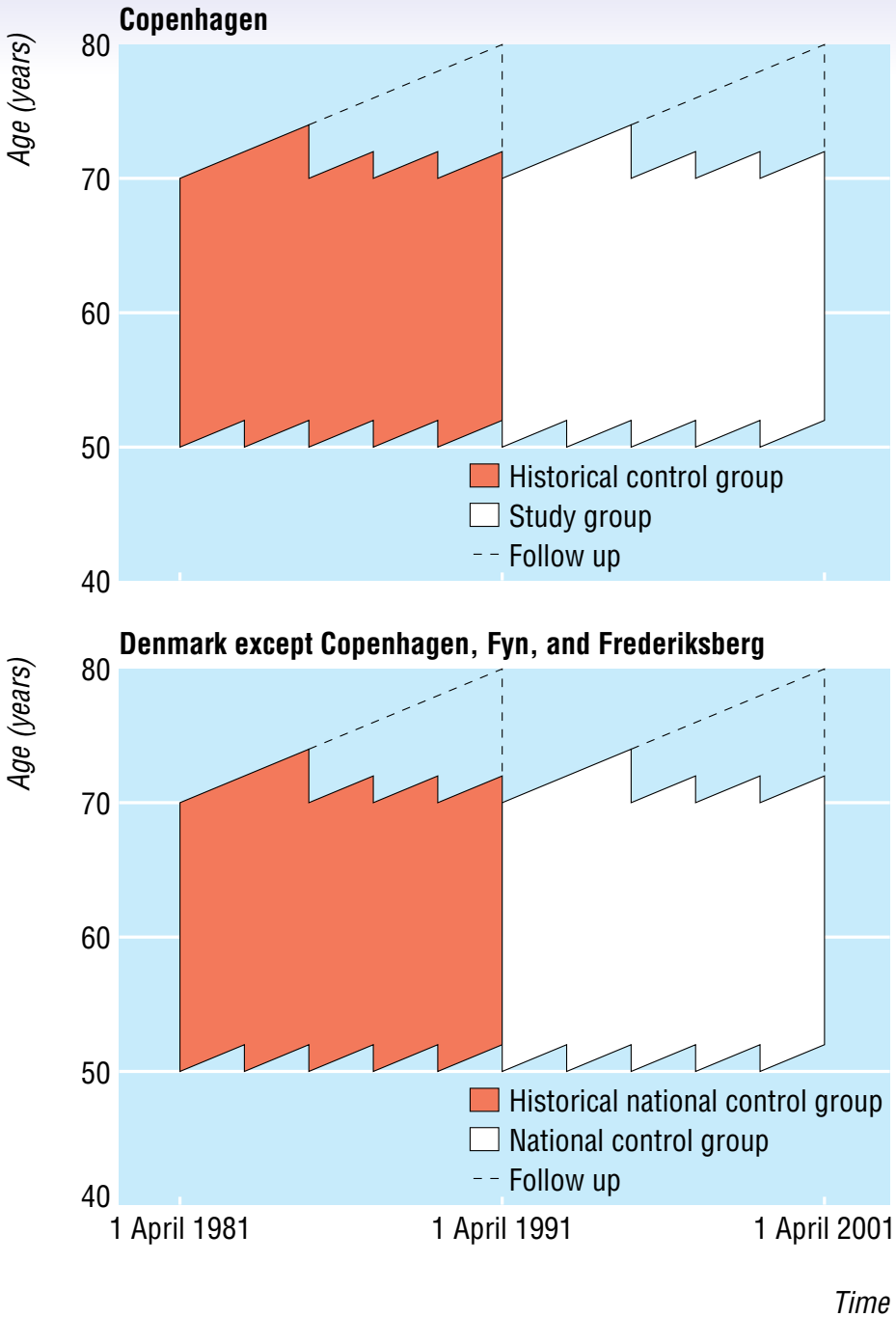
Breast cancer mortality in Copenhagen after introduction of mammography screening: cohort study

Anne Helene Olsen, Sisse H Njor, Ilse Vejborg, Walter Schwartz, Peter Dalgaard, Maj-Britt Jensen, Ulla Brix Tange, Mogens Blichert-Toft, Fritz Rank, Henning Mouridsen, Elsebeth Lynge


Copenhagen
Age (years)
80
70
60
50
40
Historical control group
Study group
Follow up
Denmark except Copenhagen, Fyn, and Frederiksberg
Age (years)
80
70
60
50
40
Historical national control group
National control group
Follow up
1 April 1981
1 April 1991
1 April 2001
Time



Authors excluded women with prevalent breast cancer on their invitation date or pseudo-invitation date.



Authors excluded women with prevalent breast cancer on their invitation date or pseudo-invitation date.

i.e., they focused on women who were eligible for the program, or would have been, had it been available in that region or at that time.

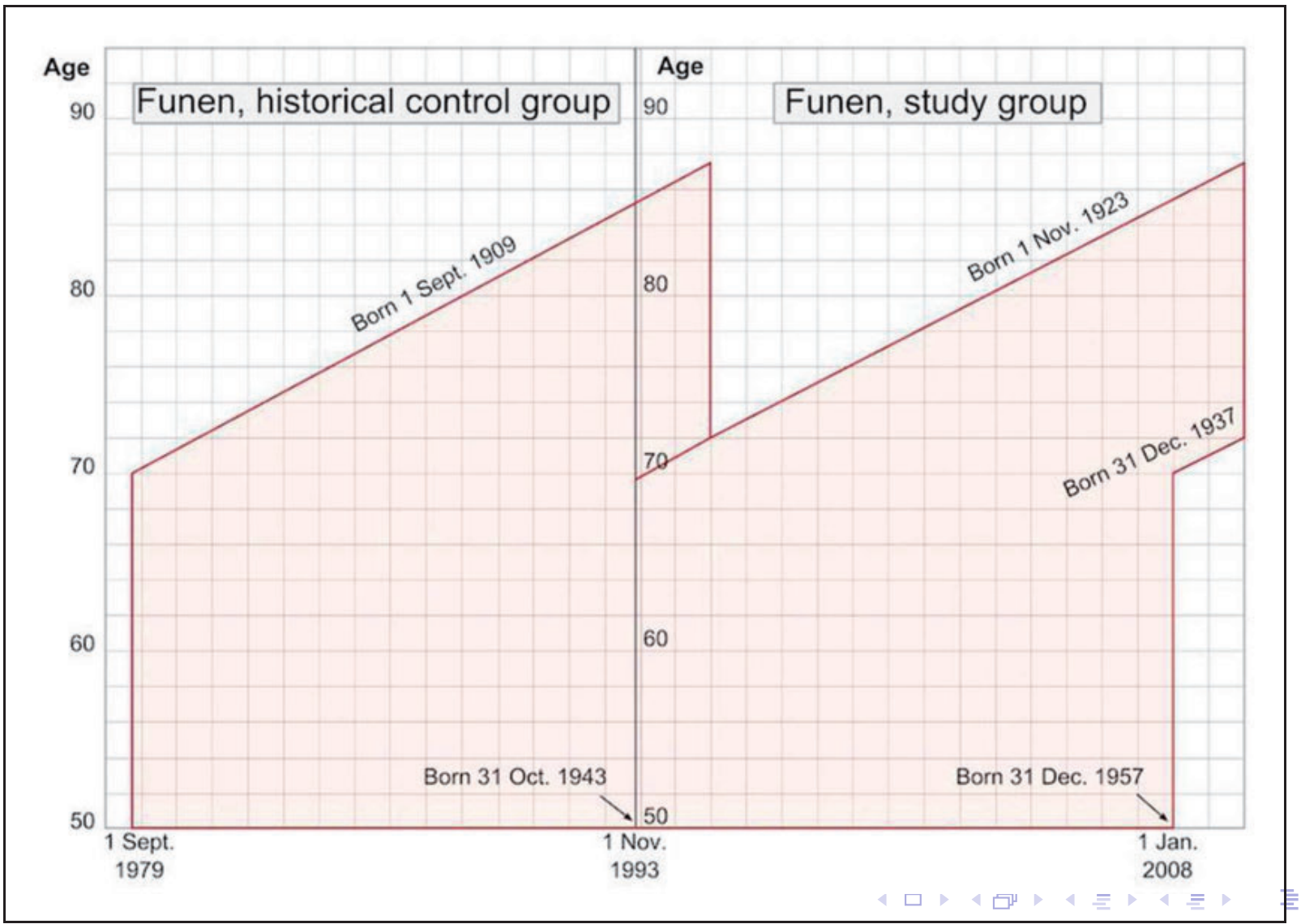
in FUNEN

Decline in breast cancer mortality: How much is attributable to screening?

J Med Screen
2015, Vol. 22(1) 20–27

DOI: 10.1177/0969141314563632
msc.sagepub.com
SAGE

Sisse Helle Njor[1], Walter Schwartz[2], Mogens Blichert-Toft[3] and Elsebeth Lynge[1]



Breast cancer mortality in mammographic screening in Europe: a review of incidence-based mortality studies

Sisse Njor, Lennarth Nyström, Sue Moss, Eugenio Paci, Mireille Broeders, Nereo Segnan, Elsebeth Lynge and The Euroscreen Working Group (members listed at the end of the paper)

J Med Screen 2012;**19 Suppl 1**:33–41
DOI: 10.1258/jms.2012.012080

Objectives To estimate the impact of service mammography screening on breast cancer mortality using European incidence-based mortality (IBM) studies (or refined mortality studies). IBM studies include only breast cancer deaths occurring in women with breast cancer diagnosed after their first invitation to screening.

Methods We conducted a literature review and identified 20 publications based on IBM studies. They were classified according to the method used for estimating the expected breast cancer mortality in the absence of screening: (1) women not yet invited; (2) historical data from the same region as well as from historical and current data from a region without screening; and (3) historical comparison group combined with data for non-participants.

Results The estimated effect of mammography screening on breast cancer mortality varied across studies. The relative risks were 0.76–0.81 in group 1; 0.75–0.90 in group 2; and 0.52–0.89 in group 3. Study databases overlapped in both Swedish and Finnish studies, adjustment for lead time was not optimal in all studies, and some studies had other methodological limitations. There was less variability in the relative risks after allowing for the methodological shortcomings.

Conclusions Based on evidence from the most methodologically sound IBM studies, the most likely impact of European service mammography screening programmes was a breast cancer mortality reduction of 26% (95% confidence interval 13–36%) among women invited for screening and followed up for 6–11 years.

See end of article for authors' affiliations

Correspondence to: Sisse Njor, Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, DK 1353 Copenhagen K, Denmark; sissenj@sund.ku.dk

Accepted for publication 20 June 2012

Republic of Ireland

2 phases, 8 years apart

RESEARCH ARTICLE

Mortality reductions due to mammography screening: Contemporary population-based data

James A. Hanley[1☯]*, Ailish Hannigan[2☯], Katie M. O'Brien[3☯]

1 Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montréal, Québec, Canada, **2** Graduate Entry Medical School, University of Limerick, Limerick, Ireland, **3** National Cancer Registry Ireland, Cork, Ireland

☯ These authors contributed equally to this work.
* james.hanley@McGill.CA

OPEN ACCESS

Citation: Hanley JA, Hannigan A, O'Brien KM (2017) Mortality reductions due to mammography screening: Contemporary population-based data. PLoS ONE 12(12): e0188947. https://doi.org/10.1371/journal.pone.0188947

Editor: Sabine Rohrmann, University of Zurich, SWITZERLAND

Received: August 9, 2017

Accepted: November 15, 2017

Published: December 20, 2017

Abstract

Our objective was to compare breast cancer mortality in two regions of the Republic of Ireland that introduced a screening programme eight years apart, and to estimate the steady-state mortality deficits the programme will produce. We carried out age- and year-matched between-region comparison of breast cancer mortality rates, and of incidence rates of stage 2–4 breast cancer, in the eligible cohorts. The regions comprised counties that, beginning in early 2000 (region 1) and late 2007 (region 2), invited women aged 50–64 to biennial mammography screening. The data were supplied by the National Cancer Registry, Central Statistics Office. As impact measures, we used age-and-year-matched mortality (from breast cancers diagnosed from 2000 onwards), rate ratios and incidence rate ratios in the compared regions from 2000 to 2013. Ratios were adjusted for between-region differences in background rates. In cohorts too old to be invited, death rates in regions 1 and 2 were 702 per 0.91 and 727 per 0.90 million women-years respectively (Ratio 0.96). In the eligible cohorts, they were 1027 per 2.9 and 1095 per 2.67 (Ratio 0.88). Thus, rates in cohorts that could have benefitted were 9% lower in region 1 than region 2: (95%CI: -20%, +4%). The

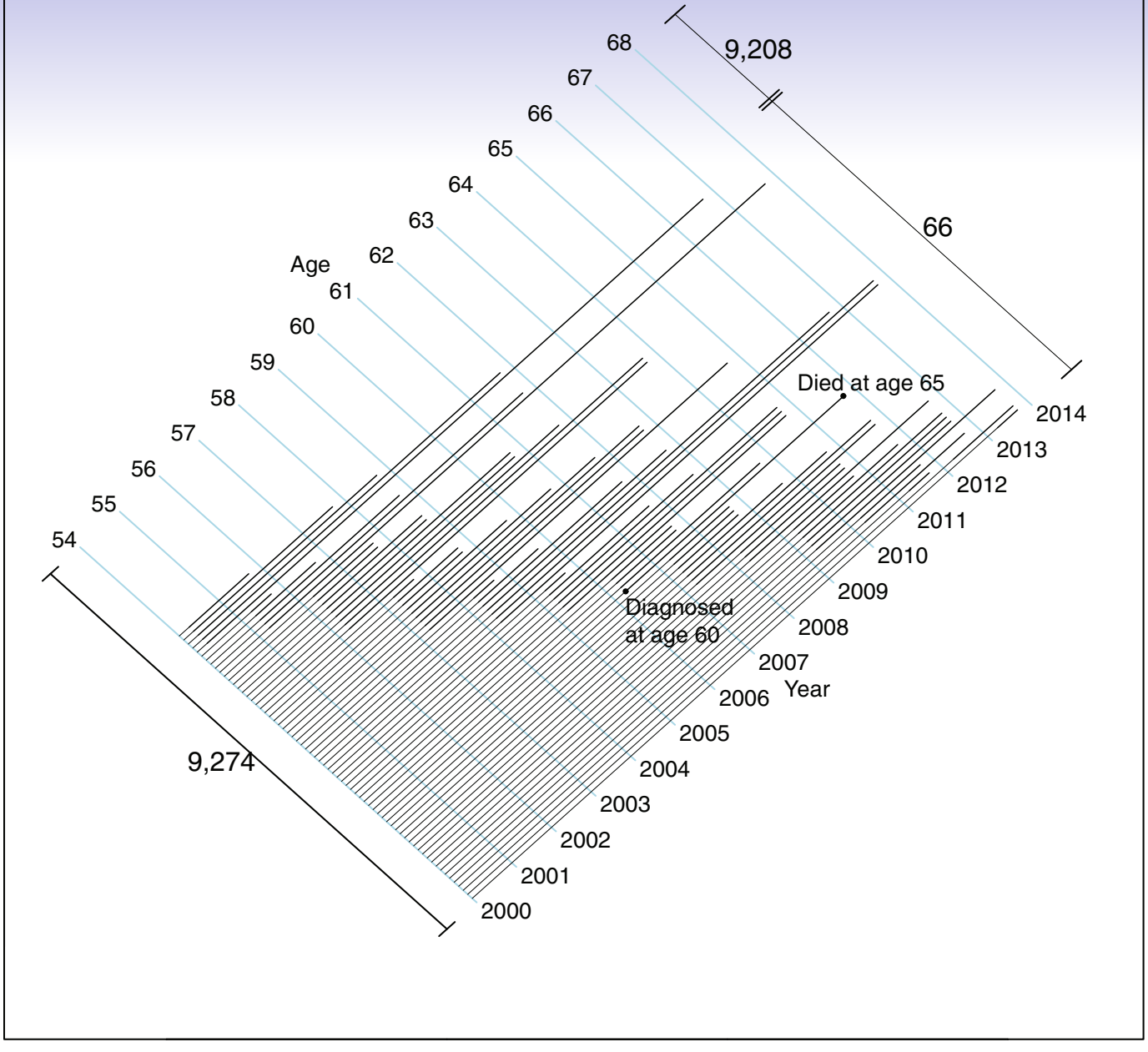


Fig 1. The ages when they were diagnosed with, and died of, breast cancer: 66 women in one selected cohort in region 2. Some 9,274 women, aged 54 in the year 2000, followed to the end of 2013. This cohort received just two screening invitations, at ages 62 and 64, too late to alter the course of these 66 fatal cancers. The lengths of the lighter portions of the lines are the maximal amounts by which screening might have advanced their diagnosis and treatment. Lines are drawn diagonally to orient readers to the full Lexis diagrams used in Figs 2 and 3.

Year and Age: Usefulness of (2-D) Lexis Diagram

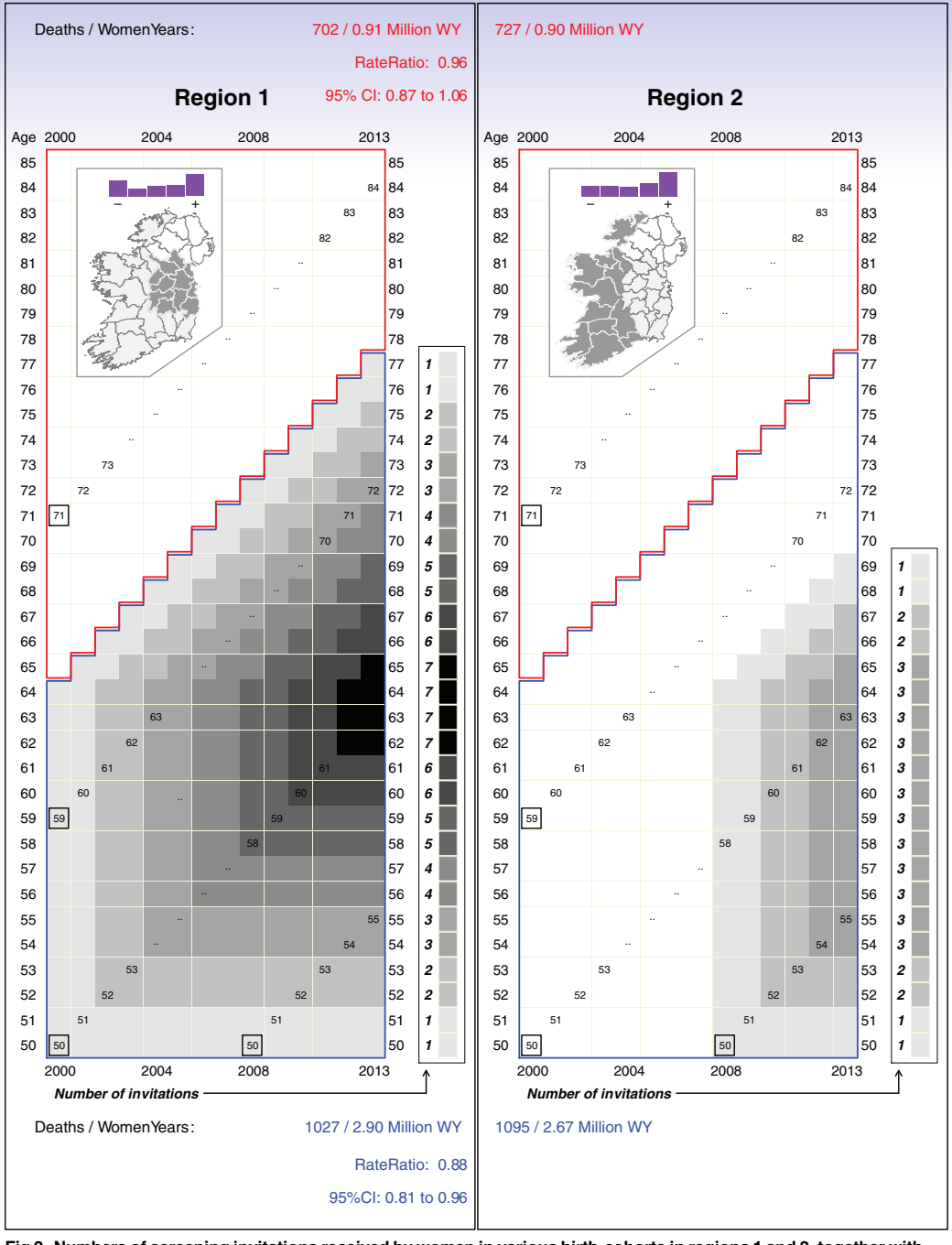


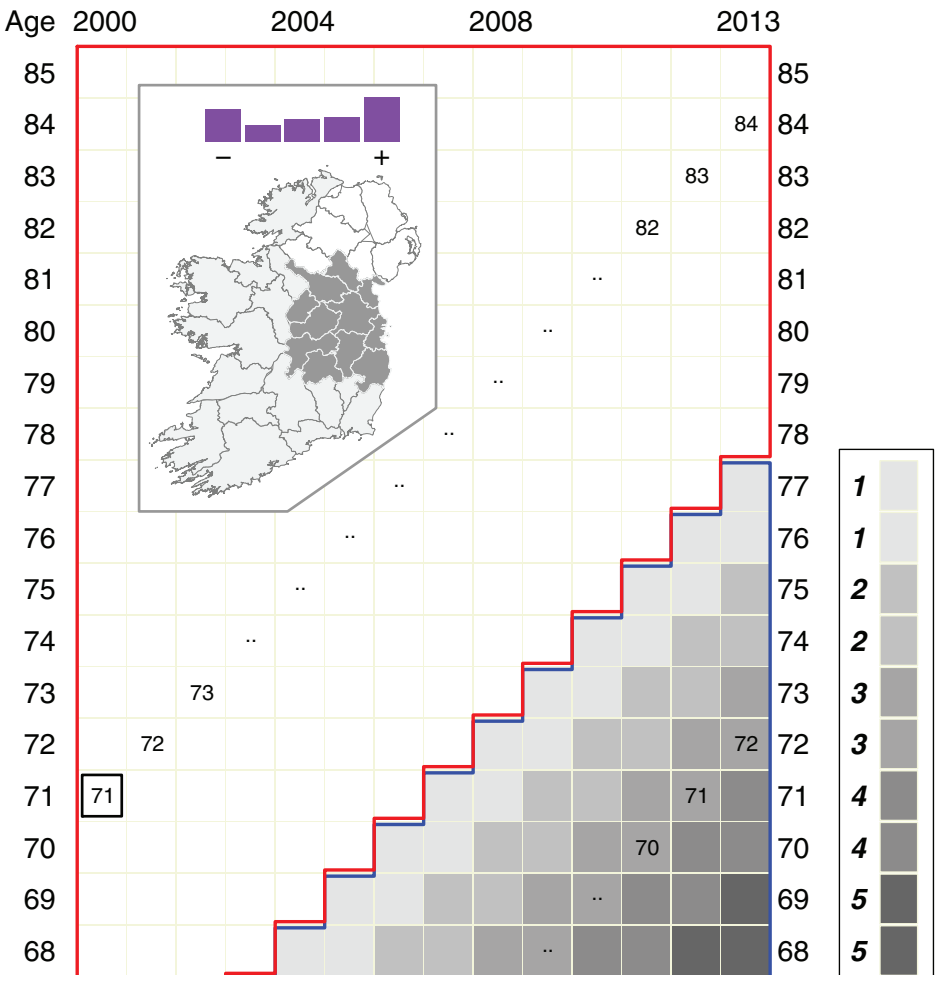
Fig 2. Numbers of screening invitations received by women in various birth-cohorts in regions 1 and 2, together with mortality rates and their ratios. Insets show the extent of each region, and (in purple) the fractions of those aged 50–85 in each quintile of the deprivation index, with '-' denoting the least and '+' the most deprived. For each birth cohort, the numbers of screening invitations received by the end of the indicated years are indicated by squares ranging in colour from white (0) to black (7), and the numbers received by the end of 2013 are shown to the right of their last follow-up year. The *Region 1 vs. Region 2*

Deaths / WomenYears: 702 / 0.91 Million WY

RateRatio: 0.96

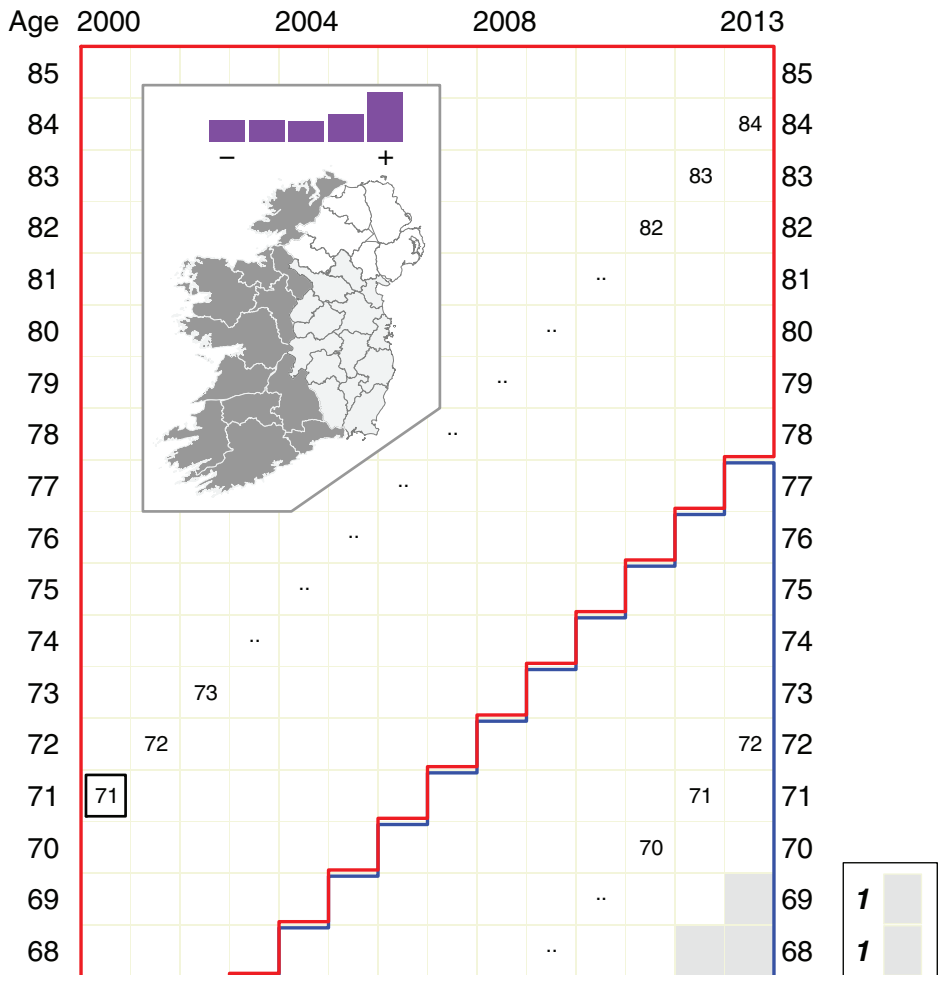
95% CI: 0.87 to 1.06

Region 1



727 / 0.90 Million WY

Region 2



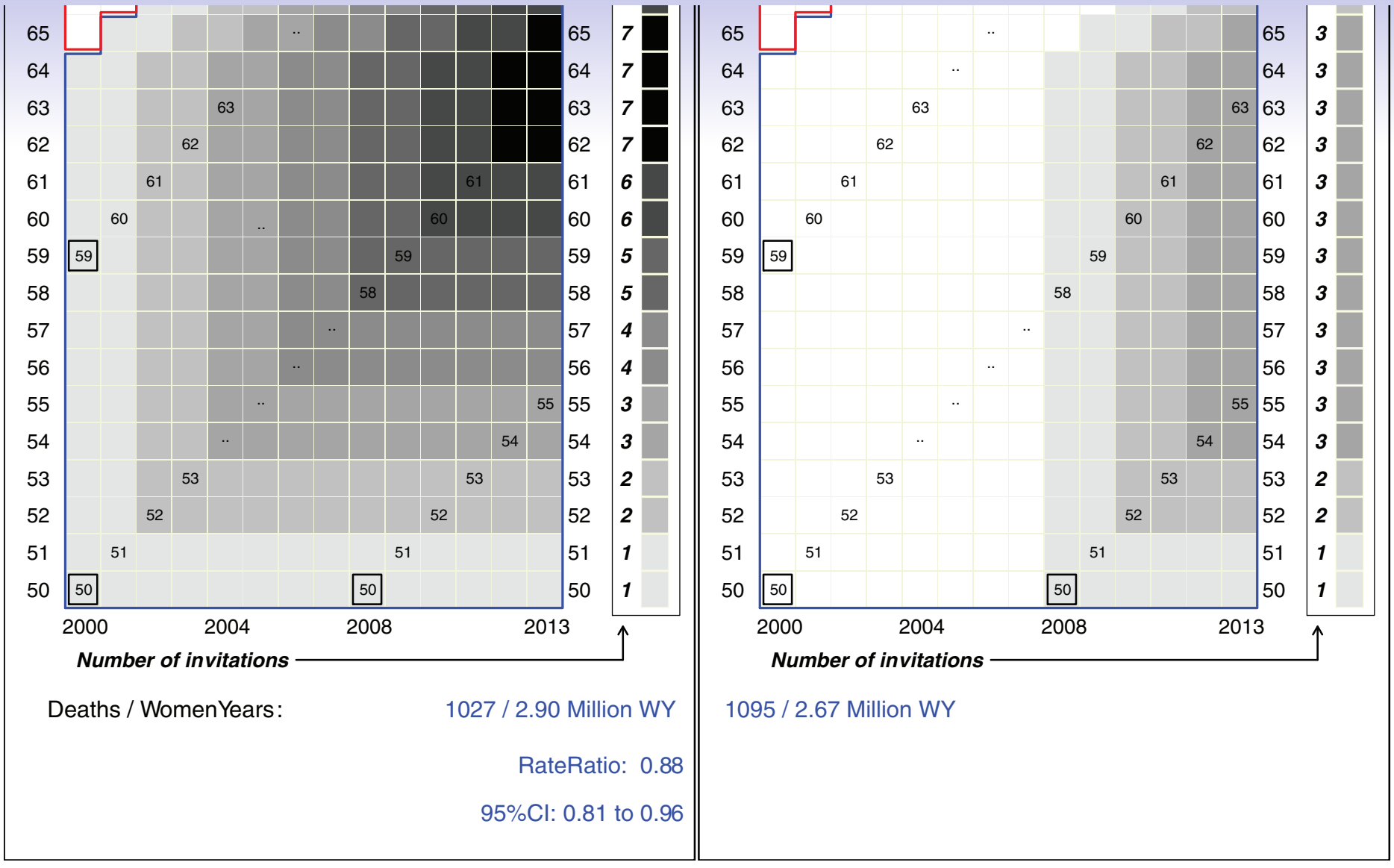
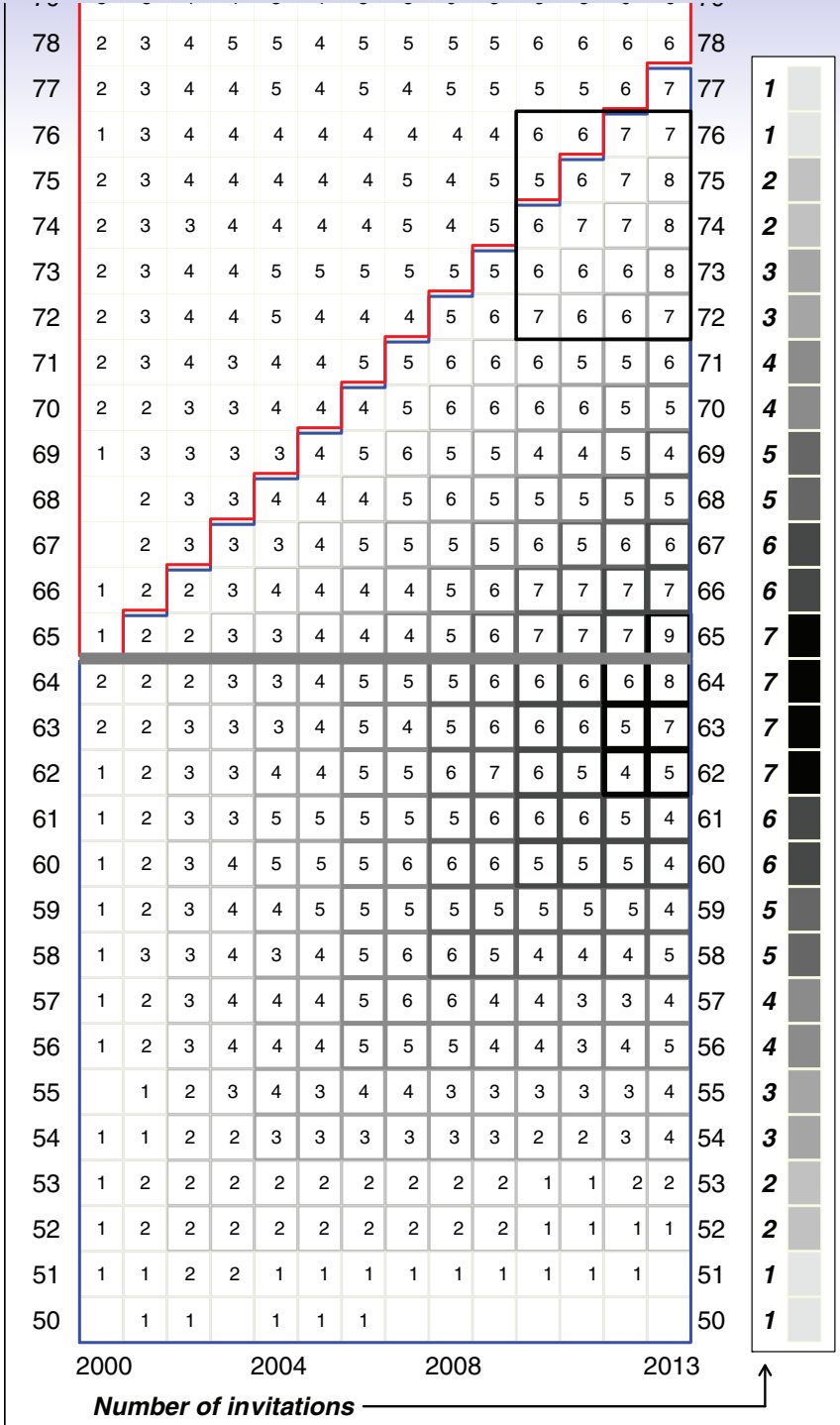
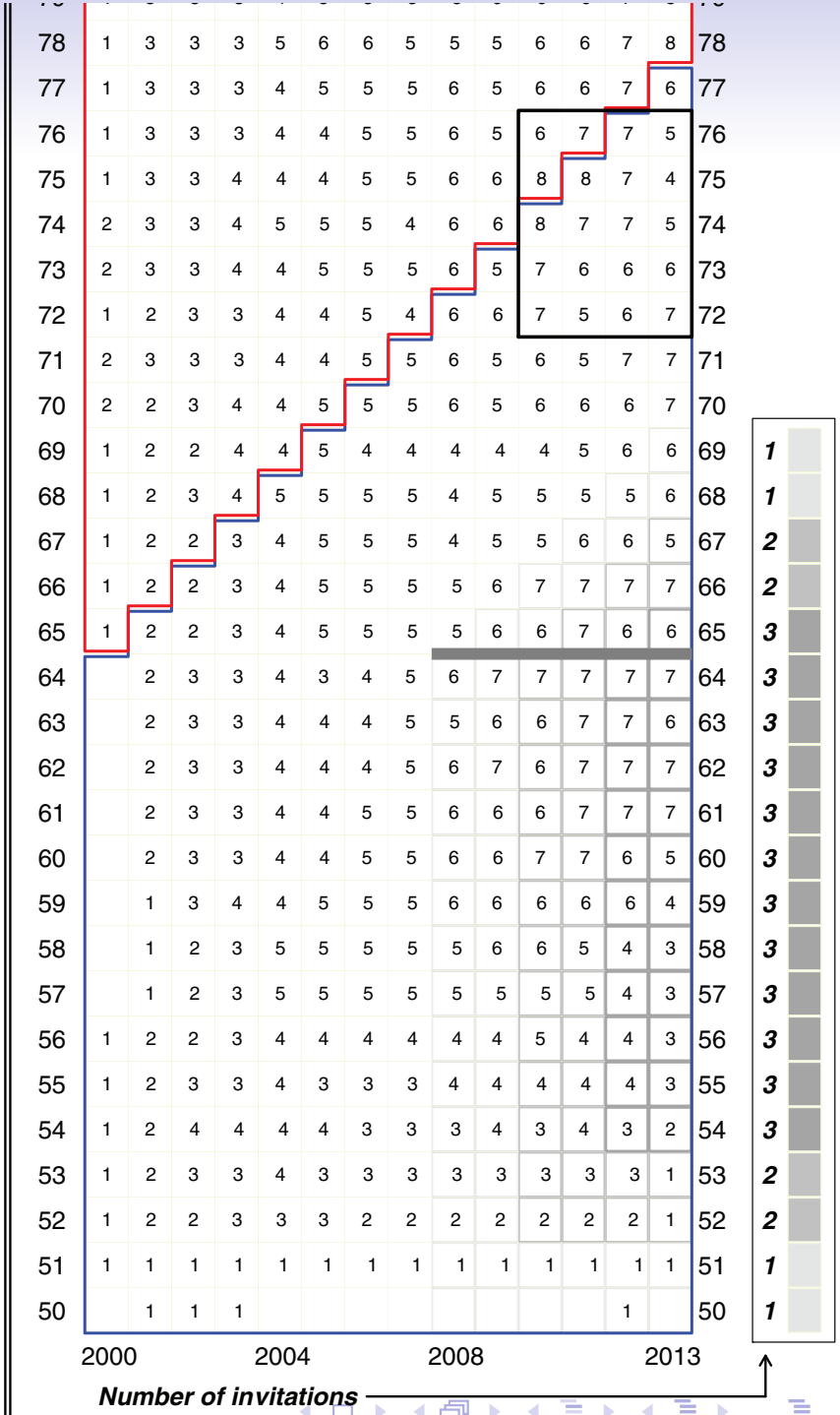


Fig 2. Numbers of screening invitations received by women in various birth-cohorts in regions 1 and 2, together with mortality rates and their ratios. Insets show the extent of each region, and (in purple) the fractions of those aged 50–85 in each quintile of the deprivation index, with '-' denoting the least and '+' the most deprived. For each birth cohort, the numbers of screening invitations received by the end of the indicated years are indicated by squares ranging in colour from white (0) to black (7), and the numbers received by the end of 2013 are shown to the right of their last follow-up year. The *Region 1 vs. Region 2*


2000
2004
2008
2013
Number of invitations


2000
2004
2008
2013
Number of invitations

European Journal of Epidemiology
https://doi.org/10.1007/s10654-017-0339-7

SCREENING

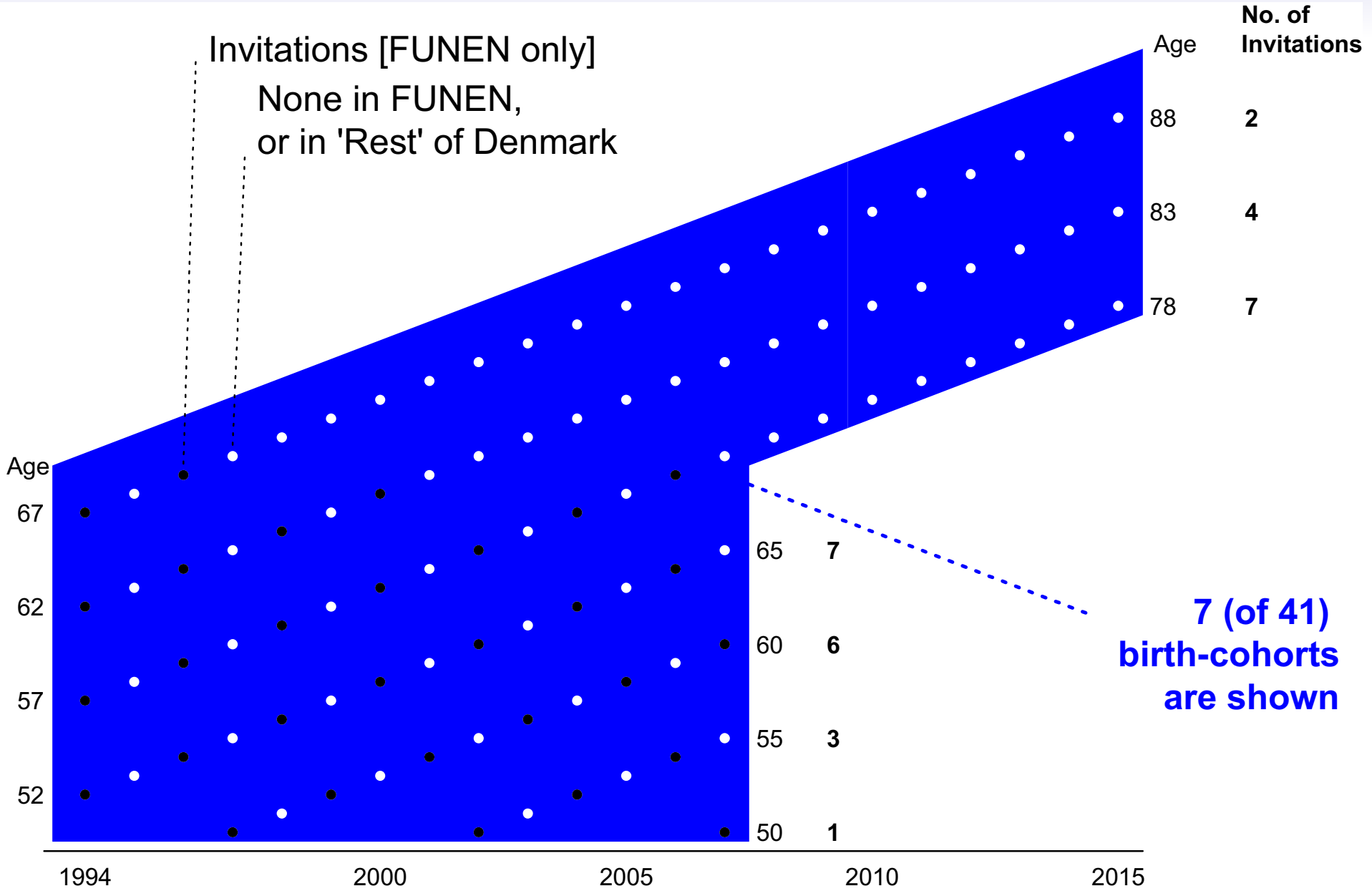
Disaggregating the mortality reductions due to cancer screening: model-based estimates from population-based data

James Anthony Hanley[1] · Sisse Helle Njor[2,3]

Received: 25 July 2017 / Accepted: 28 November 2017

Abstract

The mortality impact in cancer screening trials and population programs is usually expressed as a single hazard ratio or percentage reduction. This measure ignores the number/spacing of rounds of screening, and the location in follow-up time of the averted deaths vis-a-vis the first and last screens. If screening works as intended, hazard ratios are a strong function of the two Lexis time-dimensions. We show how the number and timing of the rounds of screening can be included in a model that specifies what each round of screening accomplishes. We show how this model can be used to disaggregate the observed reductions (i.e., make them time-and screening-history specific), and to project the impact of other regimens. We use data on breast cancer screening to illustrate this model, which we had already described in technical terms in a statistical journal. Using the numbers of invitations different cohorts received, we fitted the model to the age- and follow-up-year-specific numbers of breast cancer deaths in Funen, Denmark. From November 1993 onwards, women aged 50–69 in Funen were invited to mammography screening every two years, while those in comparison regions were not. Under the


Invitations [FUNEN only]
None in FUNEN,
or in 'Rest' of Denmark
Age
No. of Invitations
88 2
83 4
78 7
Age
67
62
57
52
65 7
60 6
55 3
50 1
7 (of 41) birth-cohorts are shown
1994
2000
2005
2010
2015

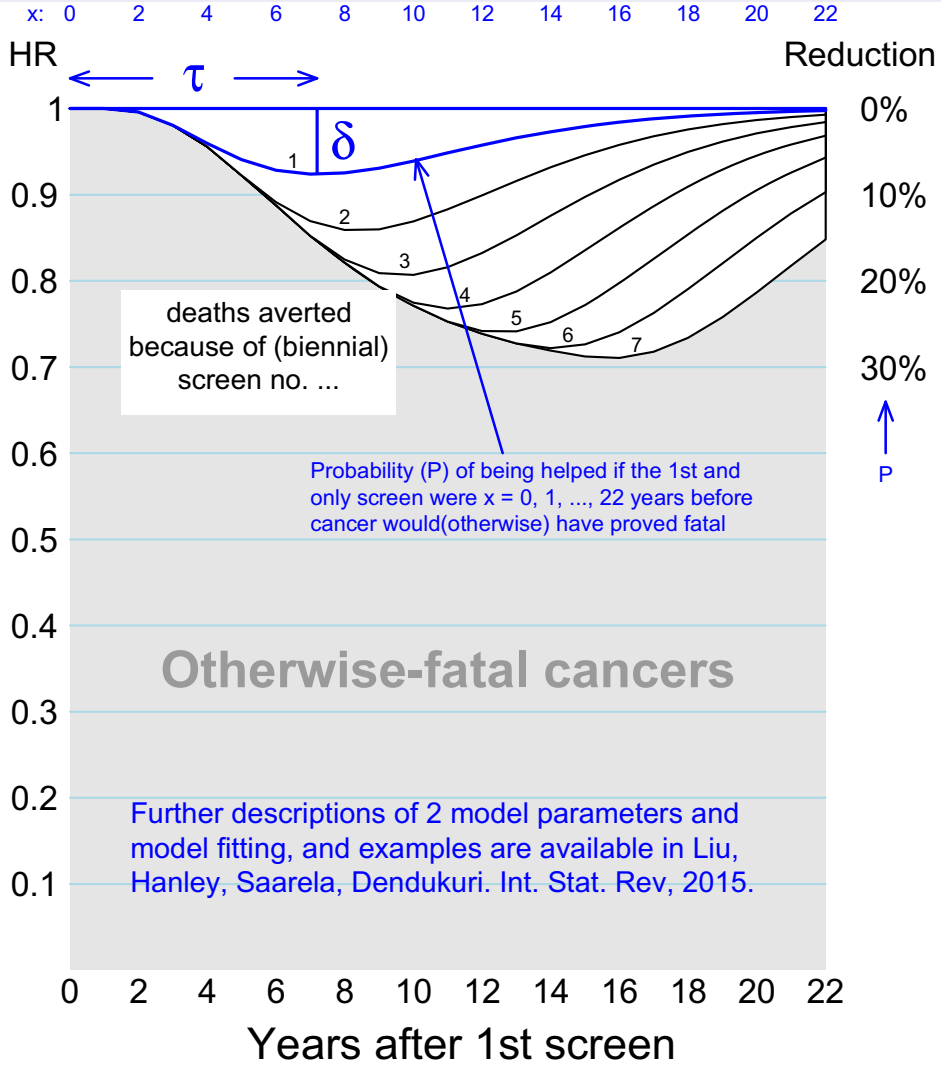
	No. Deaths		Person Years		Invitation History ('Design' Matrix)
Age[a]	D_0	D_1	PY_0	PY_1	How many years earlier
87	11	1	16,827	2,101	20 18
81	24	3	17,034	2,227	19 17 15 13
75	18	1	19,788	2,491	17 15 13 11 9 7 5
..	..	.	..,...	.,...	etc.

$D_1 + D_0 = D$ fixed $\rightarrow D_1 \sim \text{Binomial}(D, \pi)$

with

$\tau = HR_{ay} \times PY_1 / (HR_{ay} \times PY_1 + 1 \times PY_0)$

$HR_{ay} = \prod_{AgeAtS<a}$ Prob.not.helped.by.screen.at.age.AgeAtS



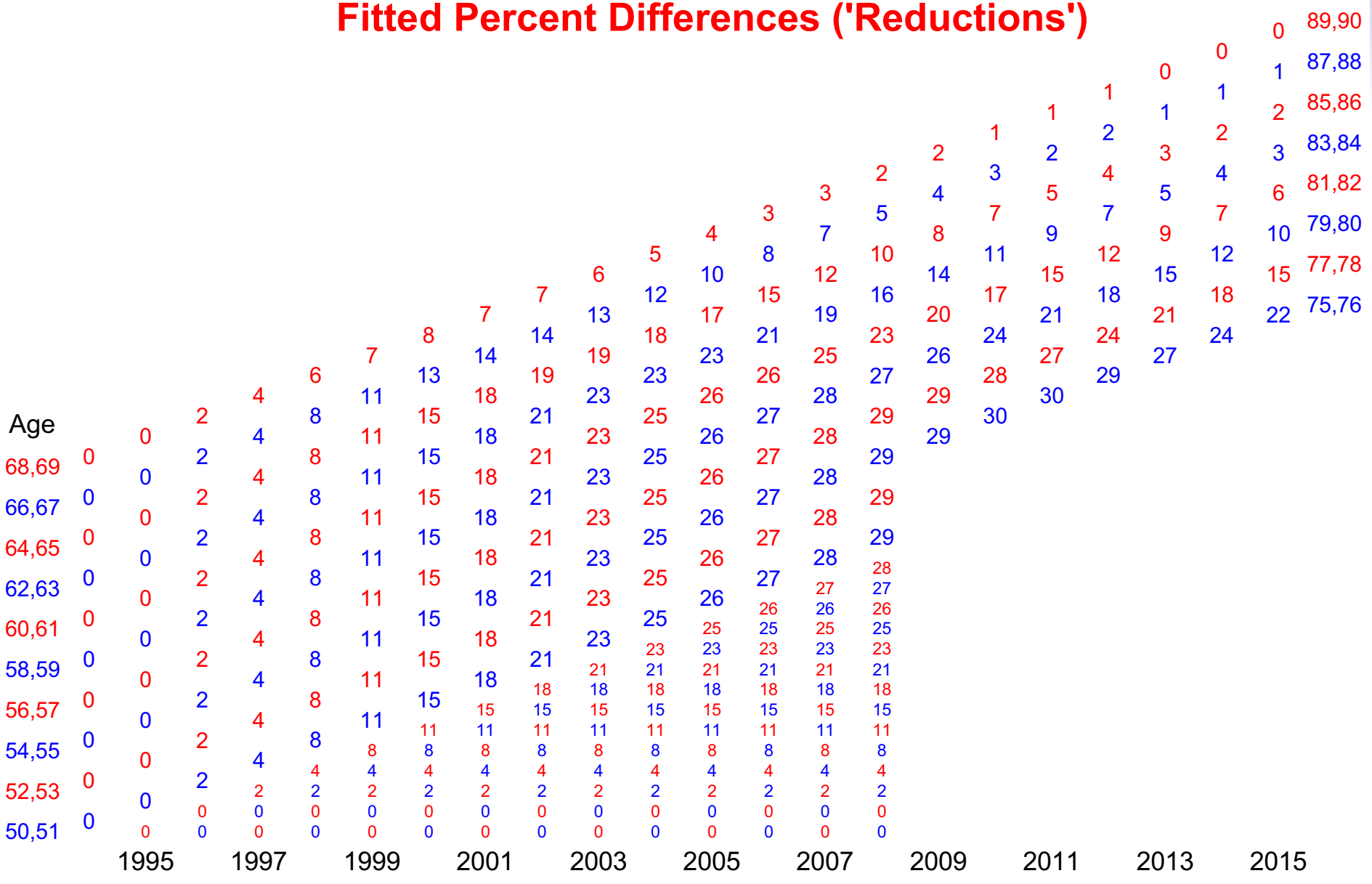


Fig. 4 For each birth cohort, the age-and year-specific fitted percentage reductions in breast cancer mortality. They were derived from the Maximum Likelihood estimates of the two model parameters (maximum probability of being helped by a single round of screening 8 years previously: 9%) and the number and timing of the preceding screening invitations

DOWNLOADS / FUNDING

http://www.biostat.mcgill.ca/hanley

or Google "James Hanley McGill"

CIHR

Reductions EVENTUALLY CEASE:

30-year follow-up in Minnesota Trial

Reductions EVENTUALLY CEASE:

30-year follow-up in Minnesota Trial

Long-Term Mortality after Screening for Colorectal Cancer

Aasma Shaukat, M.D., M.P.H., Steven J. Mongin, M.S., Mindy S. Geisser, M.S., Frank A. Lederle, M.D., John H. Bond, M.D., Jack S. Mandel, Ph.D., M.P.H., and Timothy R. Church, Ph.D.

ABSTRACT

BACKGROUND

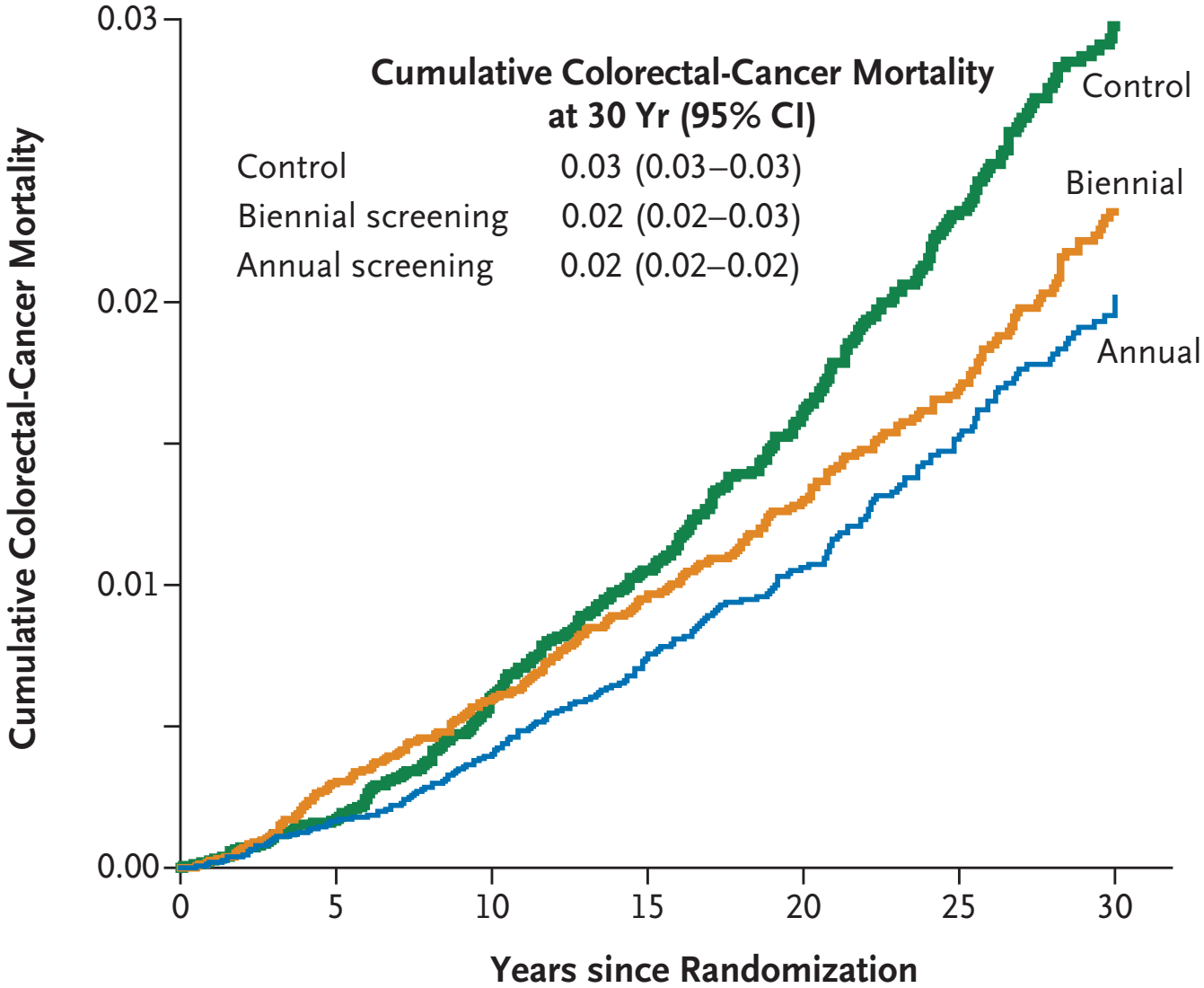
In randomized trials, fecal occult-blood testing reduces mortality from colorectal cancer. However, the duration of the benefit is unknown, as are the effects specific to age and sex.

METHODS

In the Minnesota Colon Cancer Control Study, 46,551 participants, 50 to 80 years of age, were randomly assigned to usual care (control) or to annual or biennial screening with fecal occult-blood testing. Screening was performed from 1976 through 1982 and from 1986 through 1992. We used the National Death Index to obtain updated information on the vital status of participants and to determine causes of death through 2008.

From the Divisions of Gastroenterology (A.S., J.H.B.) and Internal Medicine (F.A.L.), Minneapolis Veterans Affairs Health Care System, and the Department of Medicine, School of Medicine (A.S., F.A.L., J.H.B.), and the Division of Environmental Health Sciences, School of Public Health (S.J.M., M.S.G., T.R.C.), University of Minnesota — both in Minneapolis; and Exponent, Menlo Park, CA (J.S.M.). Address reprint requests to Dr. Shaukat at 1 Veterans Dr., 111-D, Minneapolis, MN 55417.

N Engl J Med 2013;369:1106-14.
DOI: 10.1056/NEJMoa1300720



No. at Risk

Control	14,497	13,103	11,320	9157	6741	4450
Biennial screening	14,635	13,243	11,445	9323	6802	4583
Annual screening	14,658	13,294	11,437	9219	6802	4498