Measuring the mortality reductions produced by Irish and Danish breast-cancer screening programs

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Dundalk, 2019-05-15

OUTLINE

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- Data: populations that introduced screening programs

Best studies: use date of diagnosis to emulate RCT

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Cancer Registry: EXCLUDE WOMEN DIAGNOSED BEFORE PROGRAM BEGAN

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Original Article

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

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

J Med Screen
2015, Vol. 22(1) 20–27

DOI: 10.1177/0969141314563632
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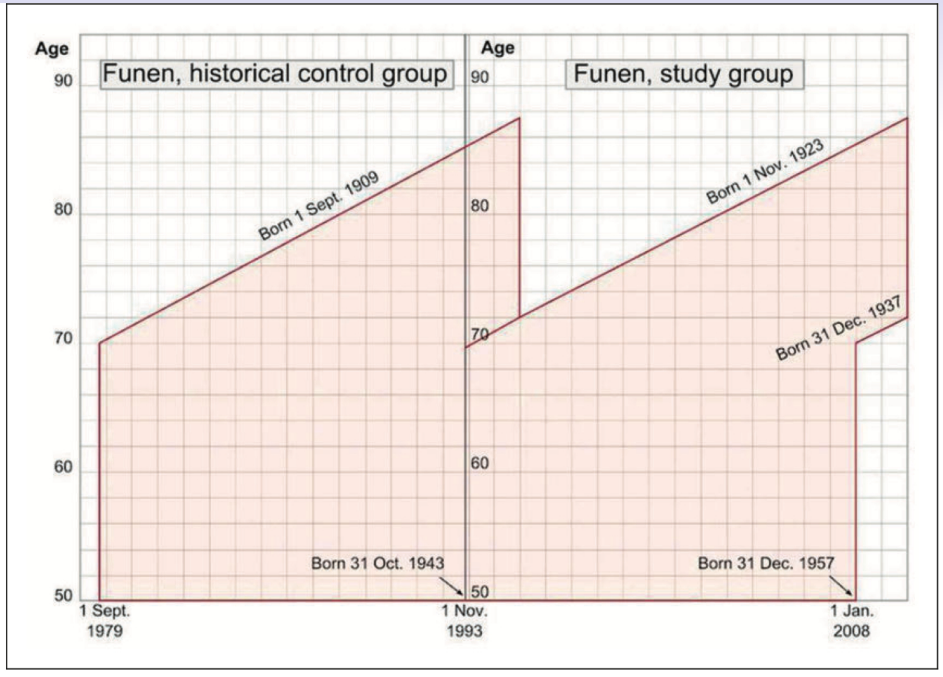
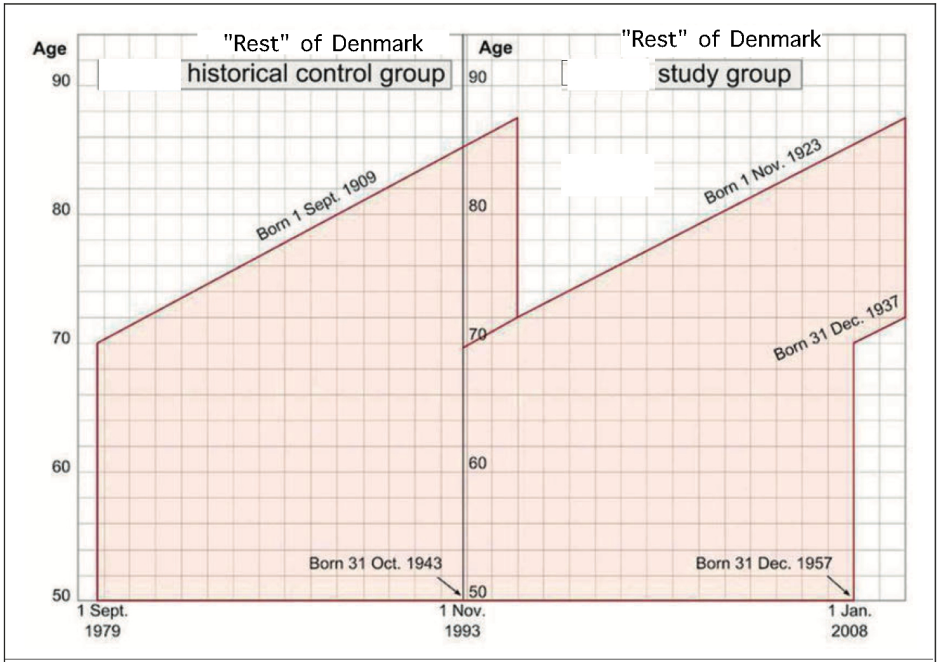
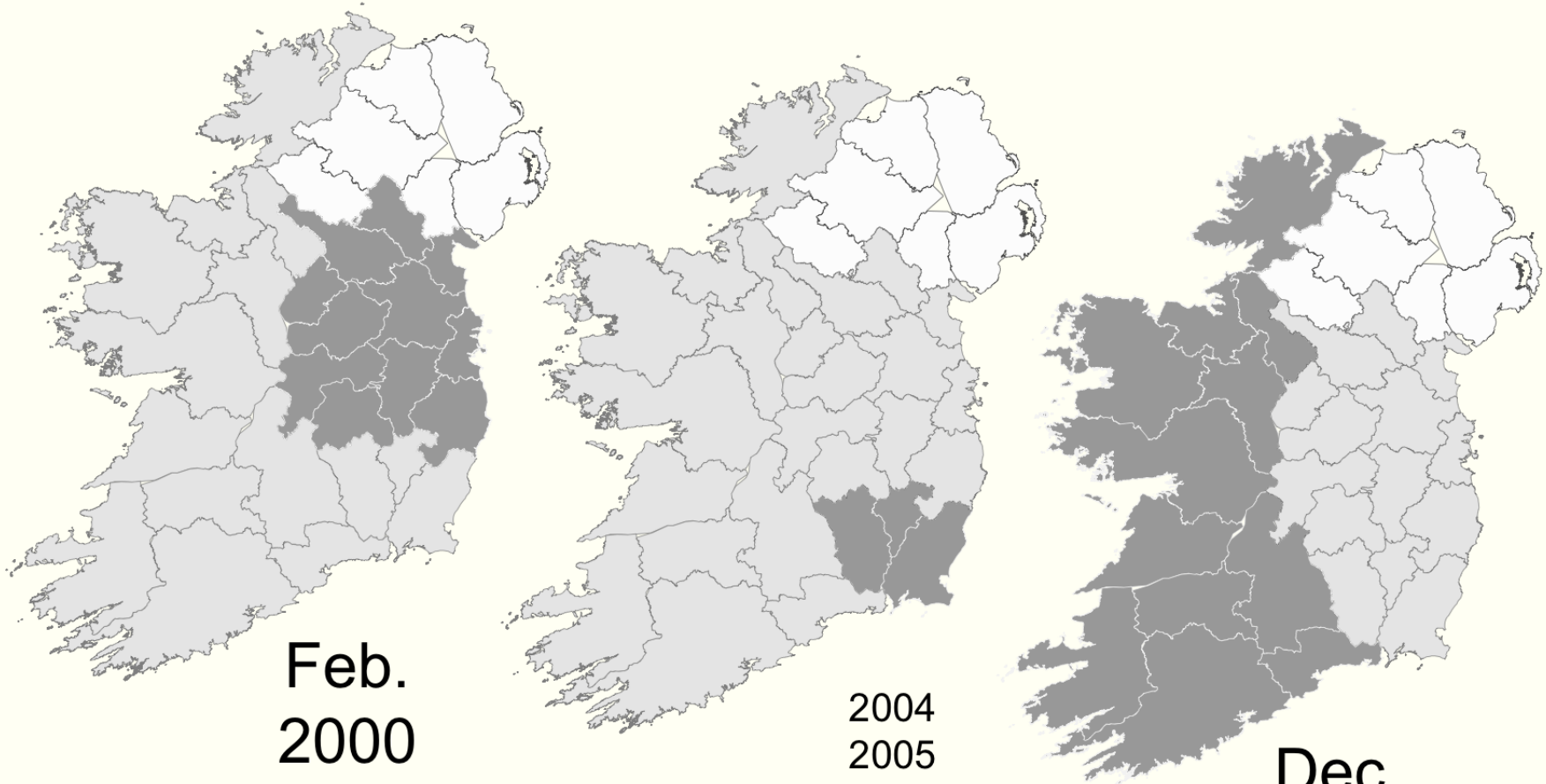
FUNEN ↓ 1993





‘REST’ ↑ 1993



BreastCheck invitations every 2 years to women aged 50-64

RESULTS

traditional
1-number summaries

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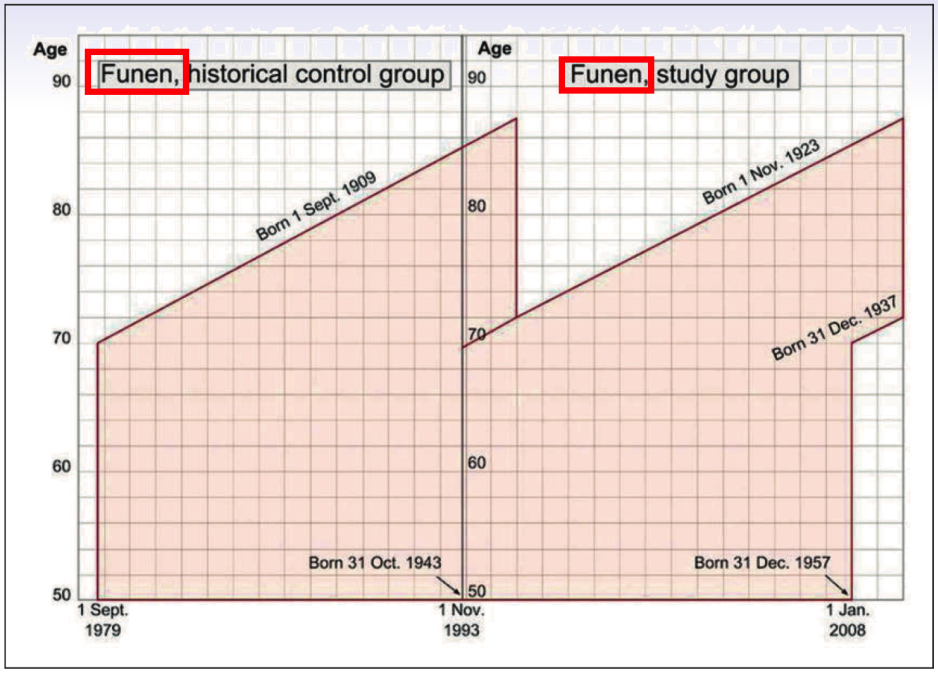
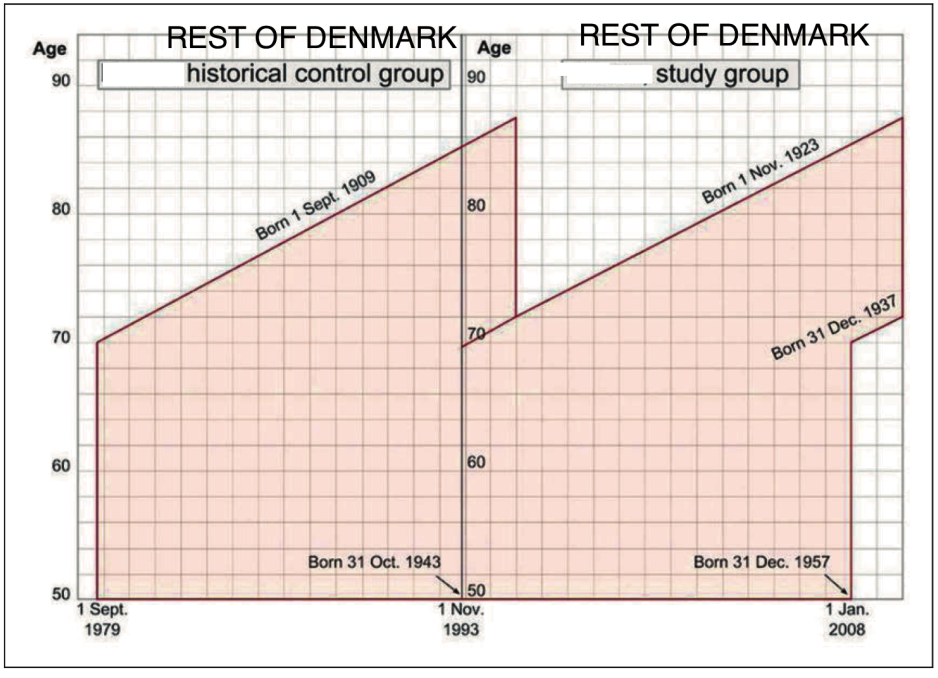
traditional
1-number summaries
(proportional hazards model)


Age
Funen, historical control group
Born 1 Sept. 1909
Born 31 Oct. 1943
1 Sept. 1979
1 Nov. 1993
Age
Funen, study group
Born 1 Nov. 1923
Born 31 Dec. 1937
Born 31 Dec. 1957
1 Jan. 2008
90
80
70
60
50


Age
REST OF DENMARK
historical control group
Born 1 Sept. 1909
Born 31 Oct. 1943
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Age
REST OF DENMARK
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Born 1 Nov. 1923
Born 31 Dec. 1937
Born 31 Dec. 1957
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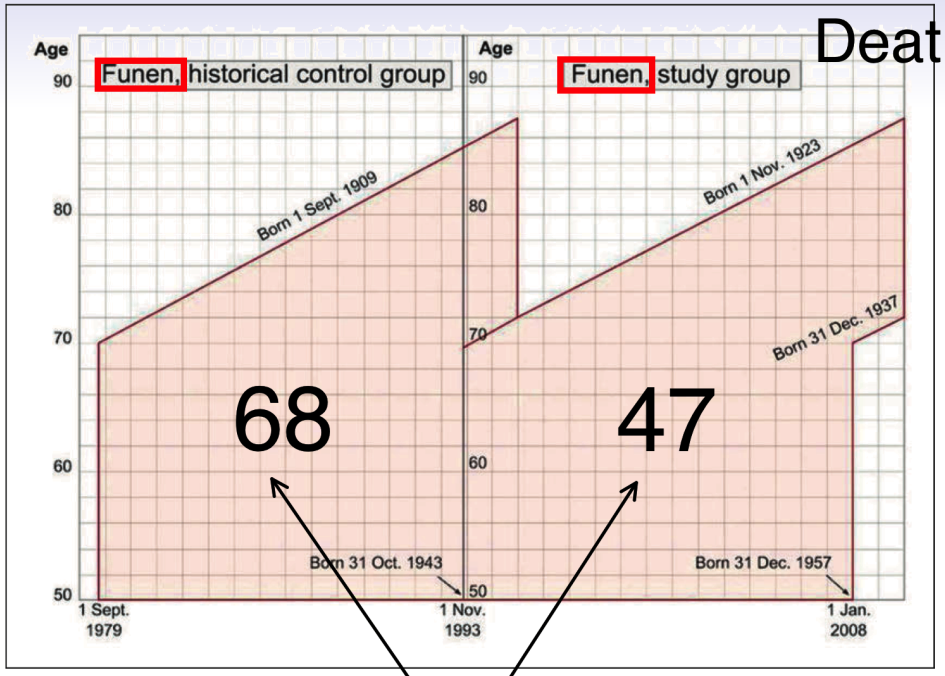
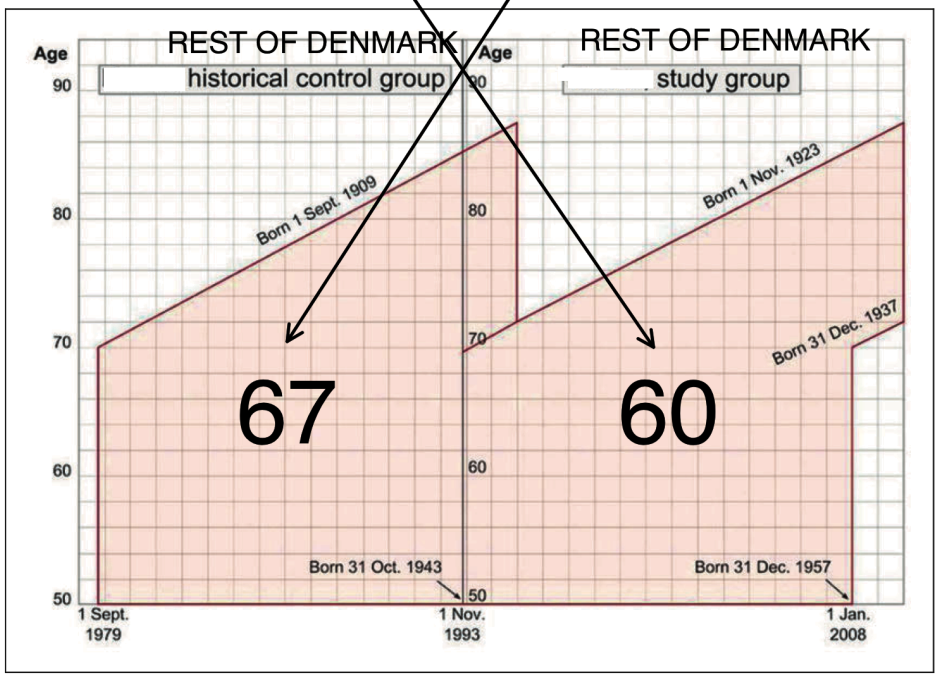
90
80
70
60
50

(8 x Funen)

Deaths per 100,000 WY





22% reduction

↑

HR = 0.78

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.
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OPEN ACCESS

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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

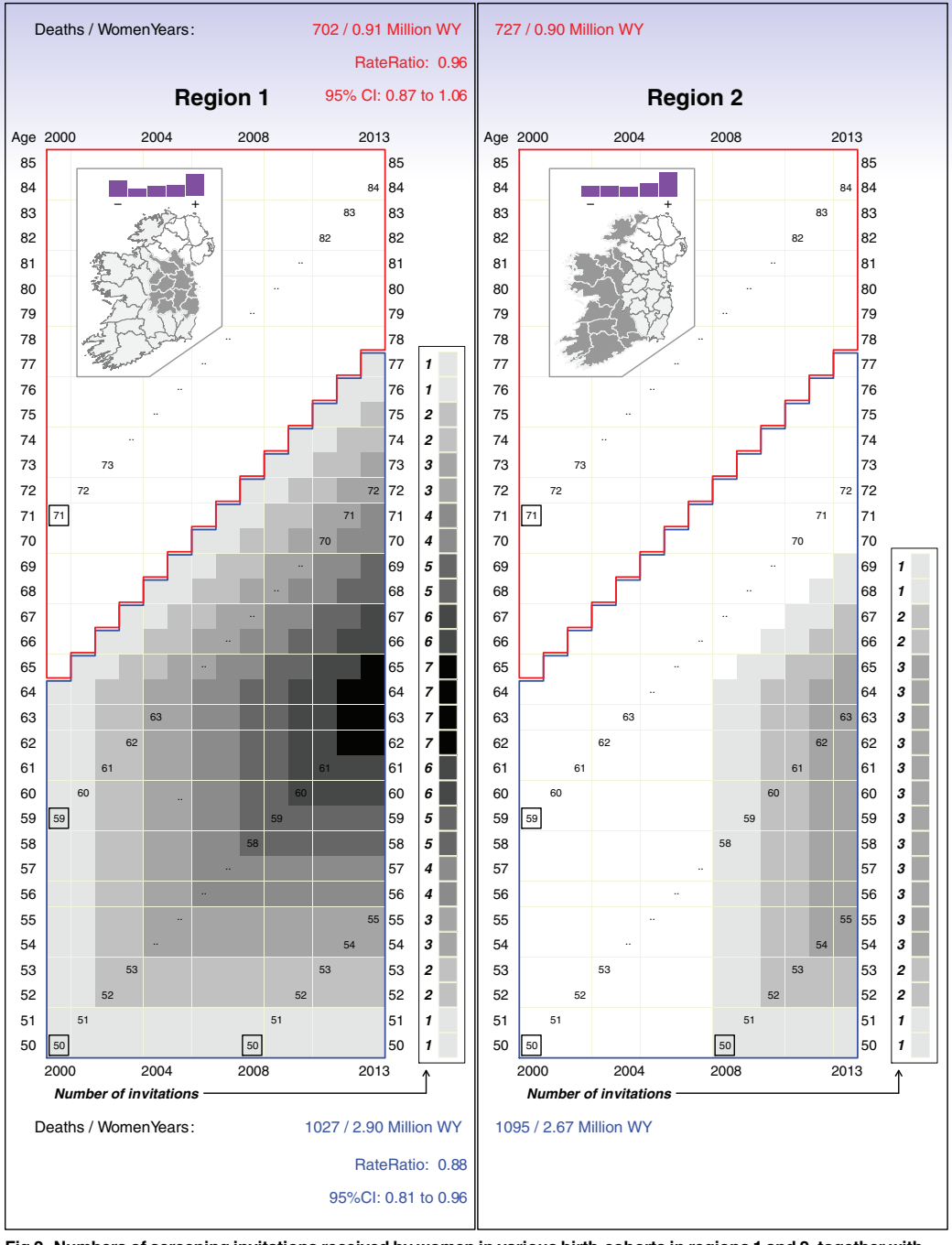


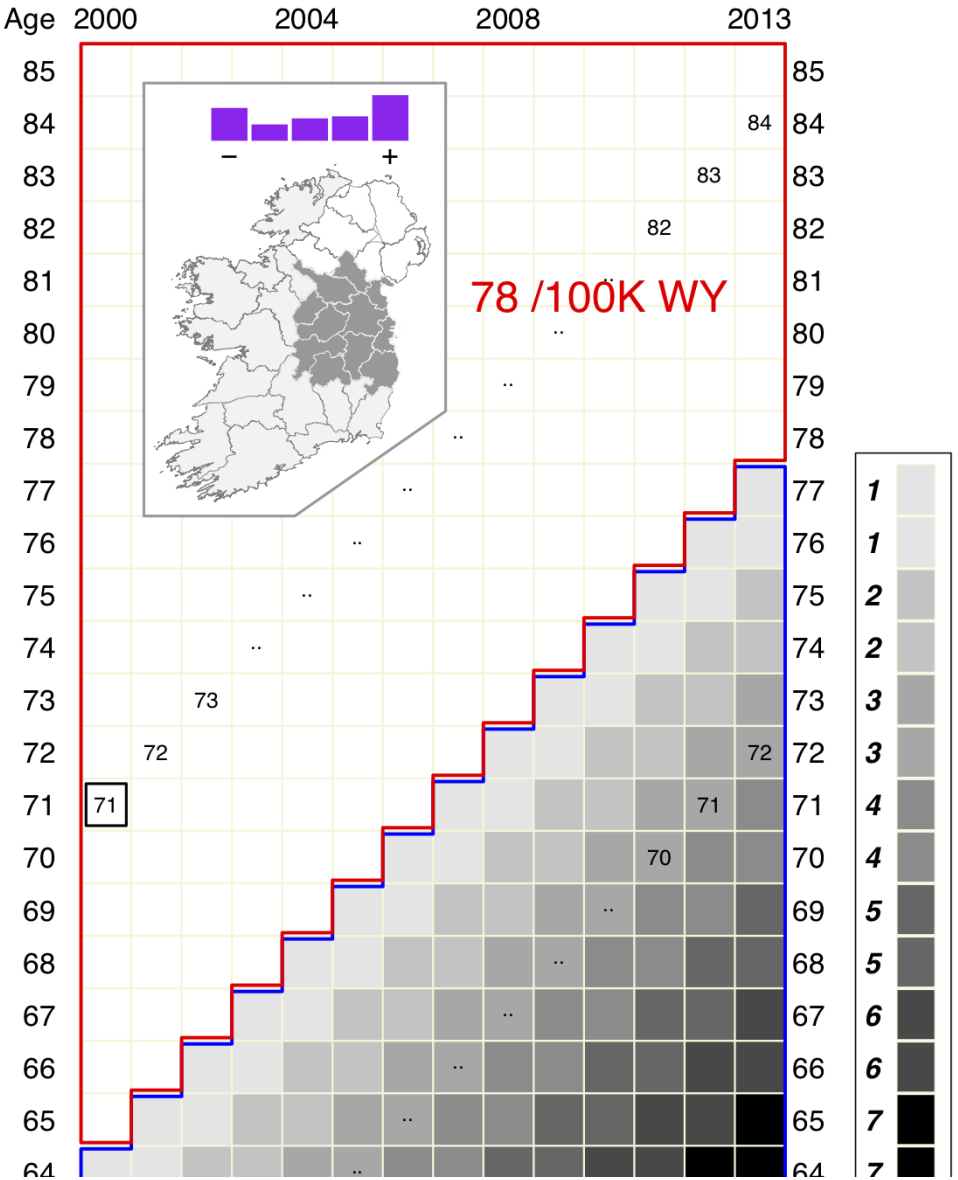
Fig 2. Numbers of screening invitations received by women in various birth-cohorts in regions 1 and 2, together with mortality rates and their ratios. Insets show the extent of each region, and (in purple) the fractions of those aged 50–85 in each quintile of the deprivation index, with '-' denoting 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

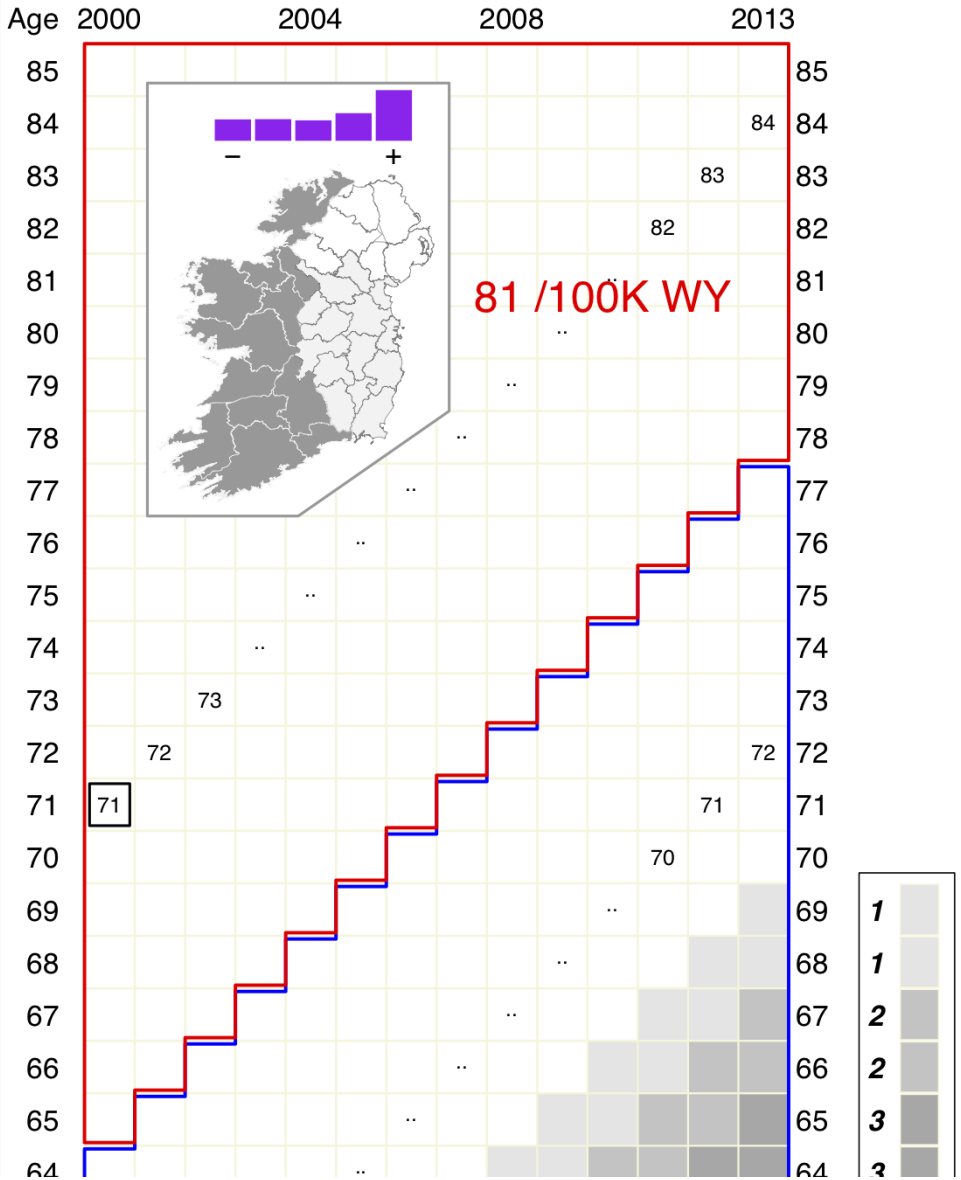
95% CI: 0.87 to 1.06

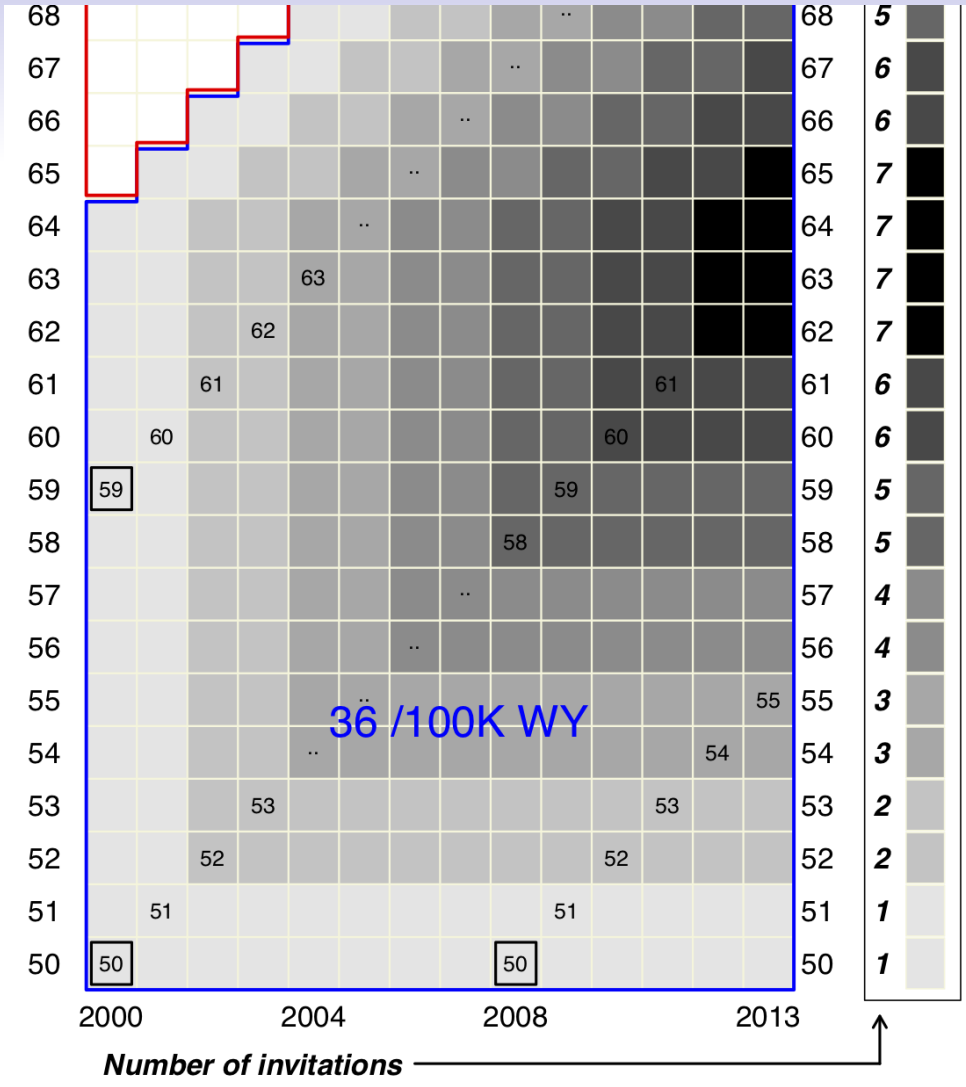
Region 1

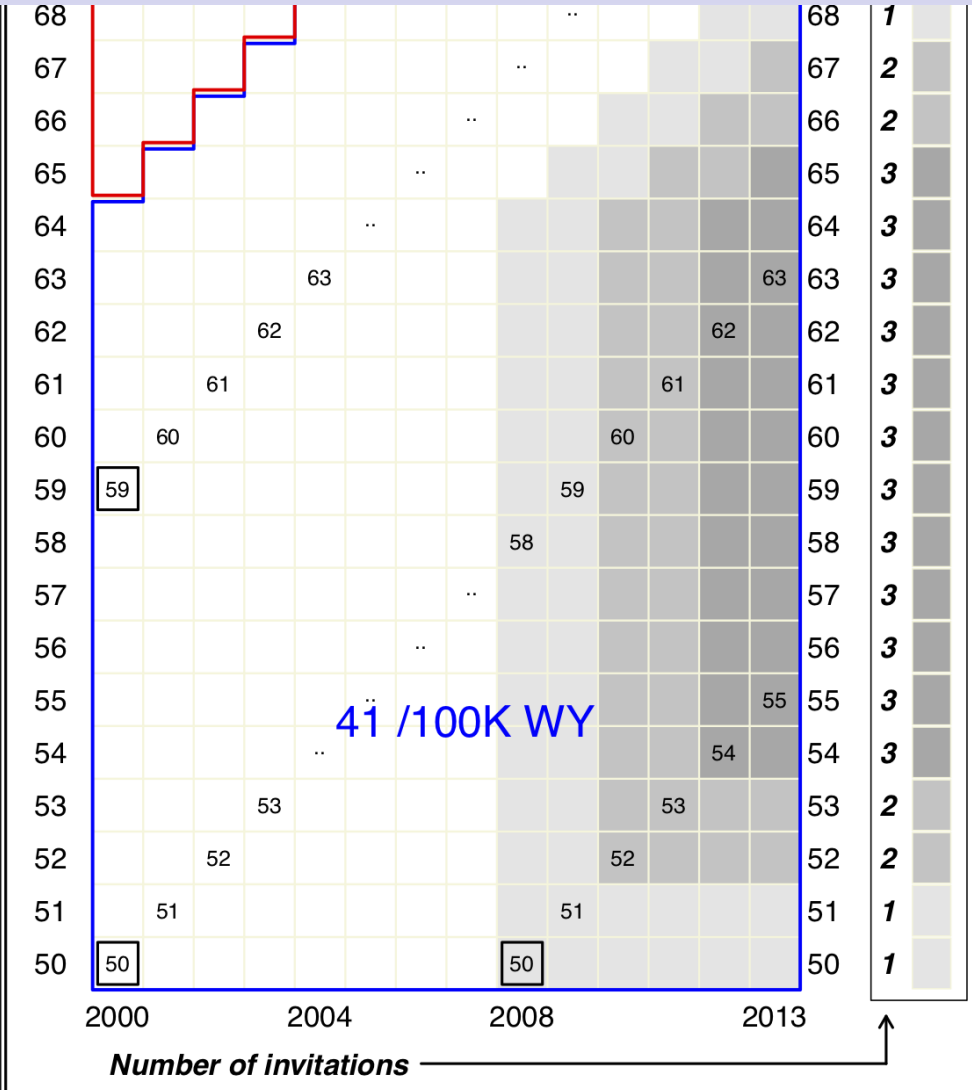


727 / 0.90 Million WY

Region 2







Deaths / WomenYears : 1027 / 2.90 Million WY

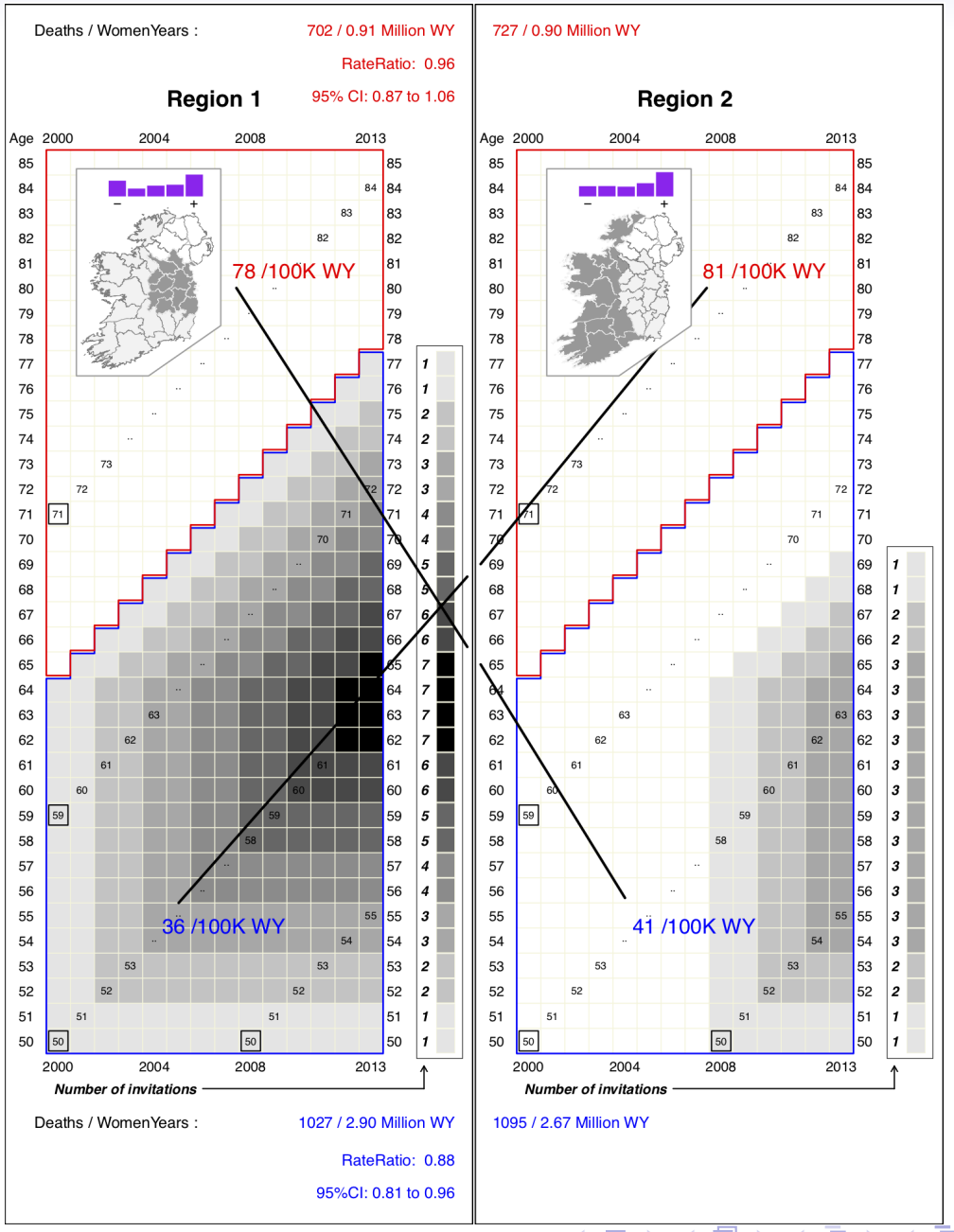
1095 / 2.67 Million WY

RateRatio: 0.88

95%CI: 0.81 to 0.96

HR = 0.91

(9% Δ)


Deaths / WomenYears :
702 / 0.91 Million WY
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Region 1
727 / 0.90 Million WY
Region 2
Age 2000 2004 2008 2013
78 /100K WY
81 /100K WY
36 /100K WY
41 /100K WY
Number of invitations
Deaths / WomenYears :
1027 / 2.90 Million WY
1095 / 2.67 Million WY
RateRatio: 0.88
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RESULTS

Hazard-Ratio (% Reduction) Functions over Lexis-Space

DENMARK

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

SCREENING

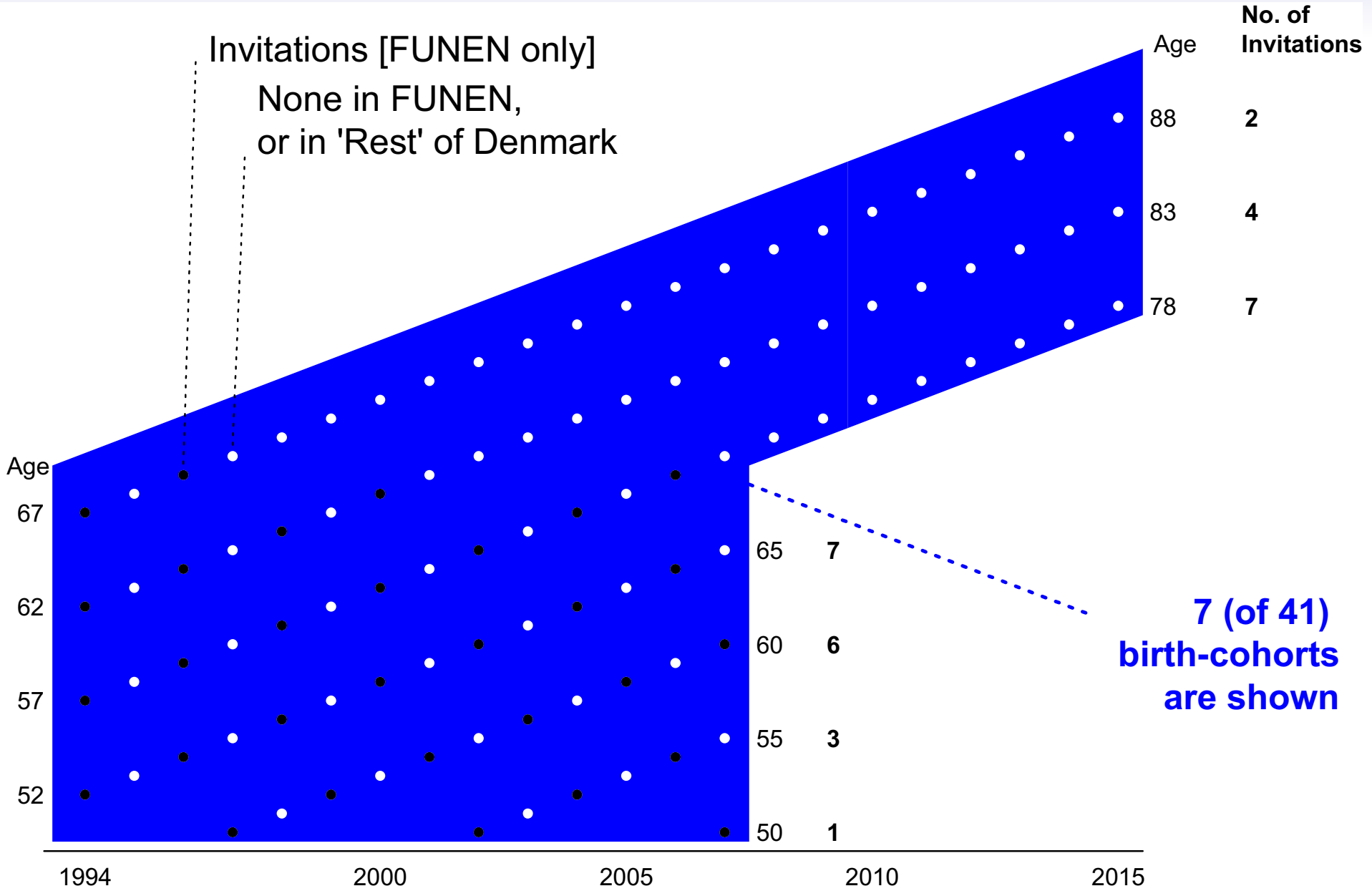
Disaggregating the mortality reductions due to cancer screening: model-based estimates from population-based data

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

BASIC IDEA IN (2 parameter) MODEL

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- Think of a population without a program, and the women who died of breast cancer in a certain year.

BASIC IDEA IN (2 parameter) MODEL

- Think of a population without a program, and the women who died of breast cancer in a certain year.
- If these women could have been offered JUST ONE SCREEN in one of the years before they were diagnosed,

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- which year would have been optimal?

BASIC IDEA IN (2 parameter) MODEL

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- If these women could have been offered JUST ONE SCREEN in one of the years before they were diagnosed,
- which year would have been optimal?

  what % of them would have had their deaths averted because of the earlier detection and treatment that resulted from that earlier detection?

(b) Data for, and fitting of, HR model

Year[y]	Age[a]	No. Deaths D_0	No. Deaths D_1	Person Years PY_0	Person Years PY_1	Invitation History ('Design' Matrix): How many years earlier
2014	87	11	1	16,827	2,101	20 18
2013	81	24	3	17,034	2,227	19 17 15 13
2012	75	18	1	19,788	2,491	17 15 13 11 9 7 5
etc.	..	..	.	..,...	.,...	etc.

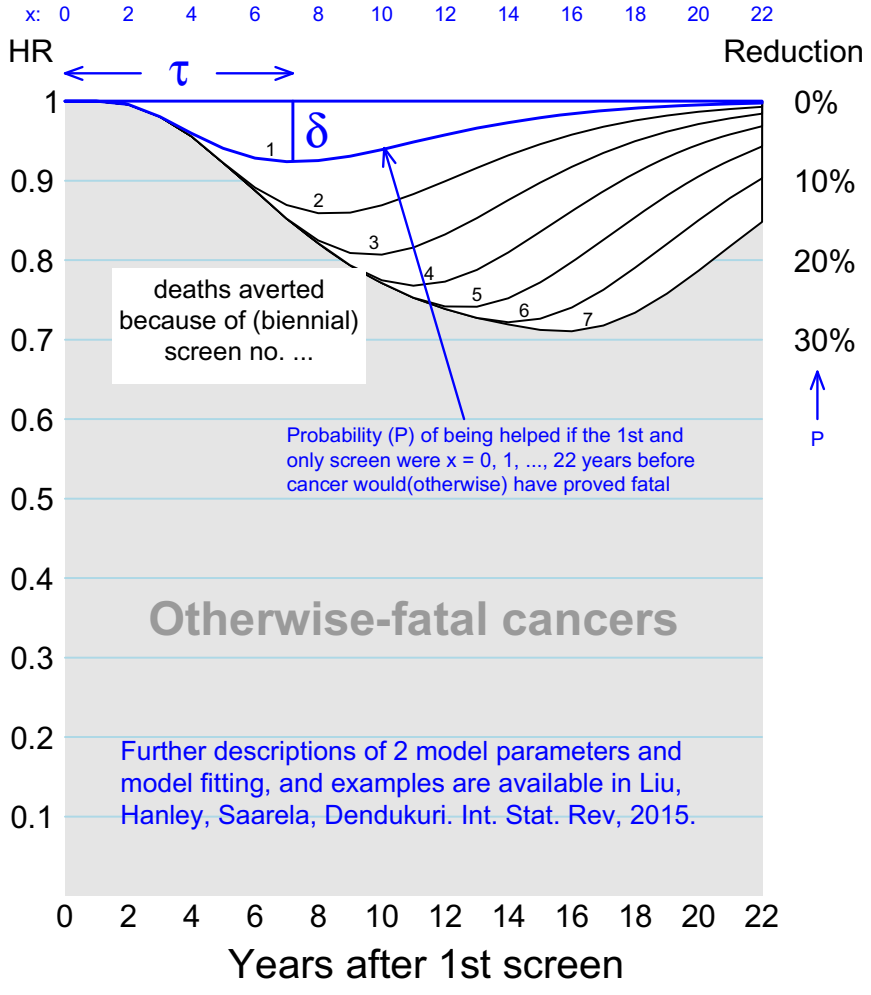
$$D_1 + D_0 = D \text{ fixed} \rightarrow D_1 \sim \text{Binomial}(D, \pi)$$

with

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

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

(a) Model for impact of 1,2, .. ,7 rounds of screening



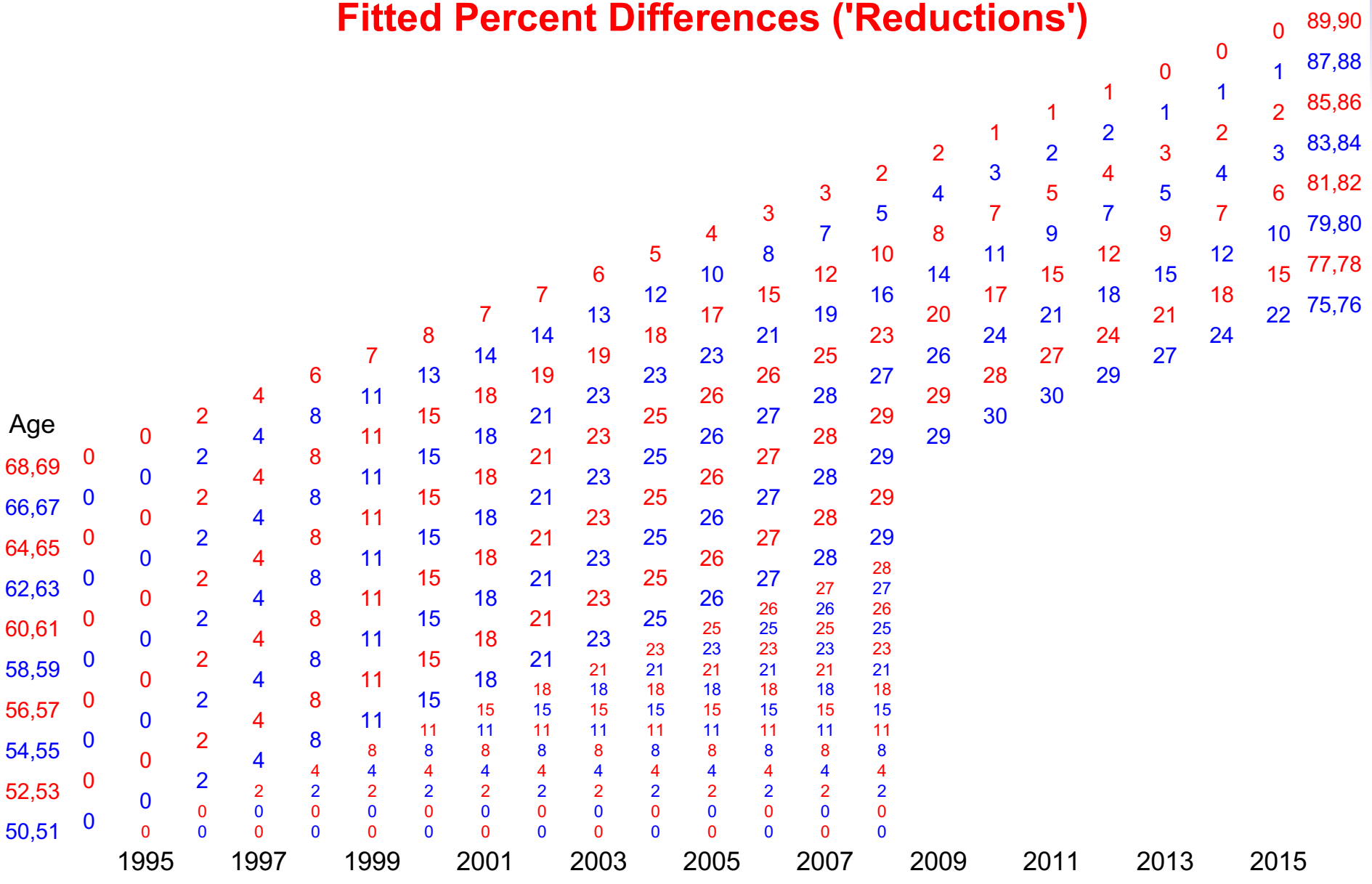
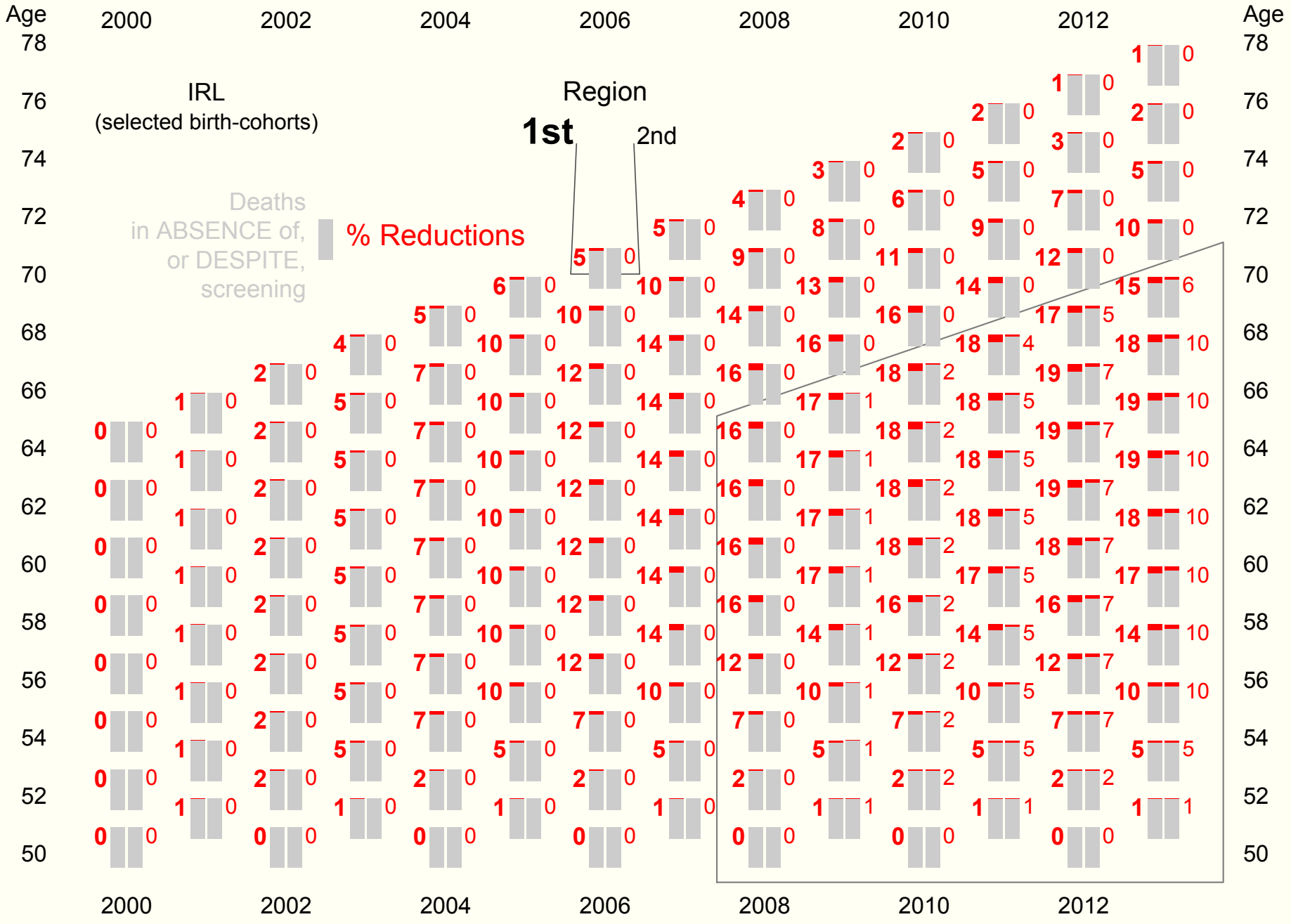


Fig. 4 For each birth cohort, the age-and year-specific fitted percentage reductions in breast cancer mortality. They were derived from the Maximum Likelihood estimates of the two model parameters (maximum probability of being helped by a single round of screening 8 years previously: 9%) and the number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

IRELAND


Age
2000
2002
2004
2006
2008
2010
2012
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
IRL
(selected birth-cohorts)
Region
1st
2nd
Deaths
in ABSENCE of,
or DESPITE,
screening
% Reductions

Our Model ... in more detail (written/video)

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Webpage: screening

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

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Methods

`http://www.biostat.mcgill.ca/hanley/screening/section2.mov`

Applications: (TRIALS) Lung Cancer; Colon Cancer

`http://www.biostat.mcgill.ca/hanley/screening/section3.mov`

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  - Plan to use between-country rather than within-country contrasts, but
  - (by modelling, rather than registries) first remove numbers of cases that could not have benefitted from the program.

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Hanley, J.A. Hannigan, A., O'Brien, K. (2017). Mortality reductions due to mammography screening: Contemporary population-based data. *PLoS ONE*, **12(12): e0188947.**.

Hanley, J.A., Njor S.H. (2018). Disaggregating the mortality reductions due to cancer screening: model-based estimates from population-based data. *Eur J Epidemiology*, **33**, pp. 465 – 472.

WEB PAGE

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

or Google "James Hanley McGill screening"

FUNDING

Canadian Institutes of Health Research
2011-2019

FUNDING

Canadian Institutes of Health Research
2011-2019

Economic and Social Research Institute (Ireland)
1969

https://www.esri.ie/people/james-hanley

Loneliness of Long-Distance (non-)Experimentalist

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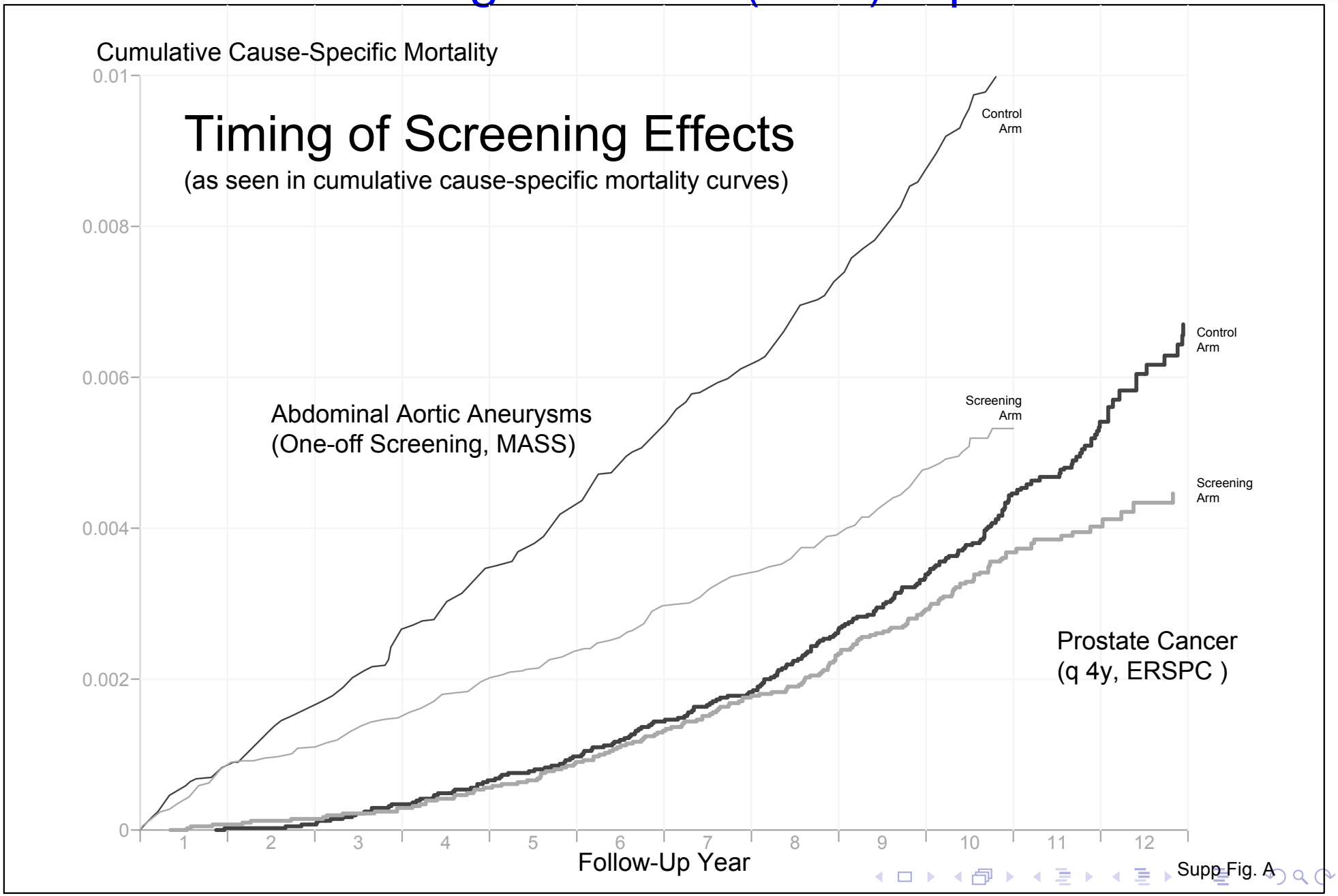

Supp Fig. A

Why do statisticians commonly limit their inquiries to Averages?

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F. Galton, Natural Inheritance, 1889.

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Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if its mountains could be thrown into its lakes, two nuisances would be got rid of at once.”

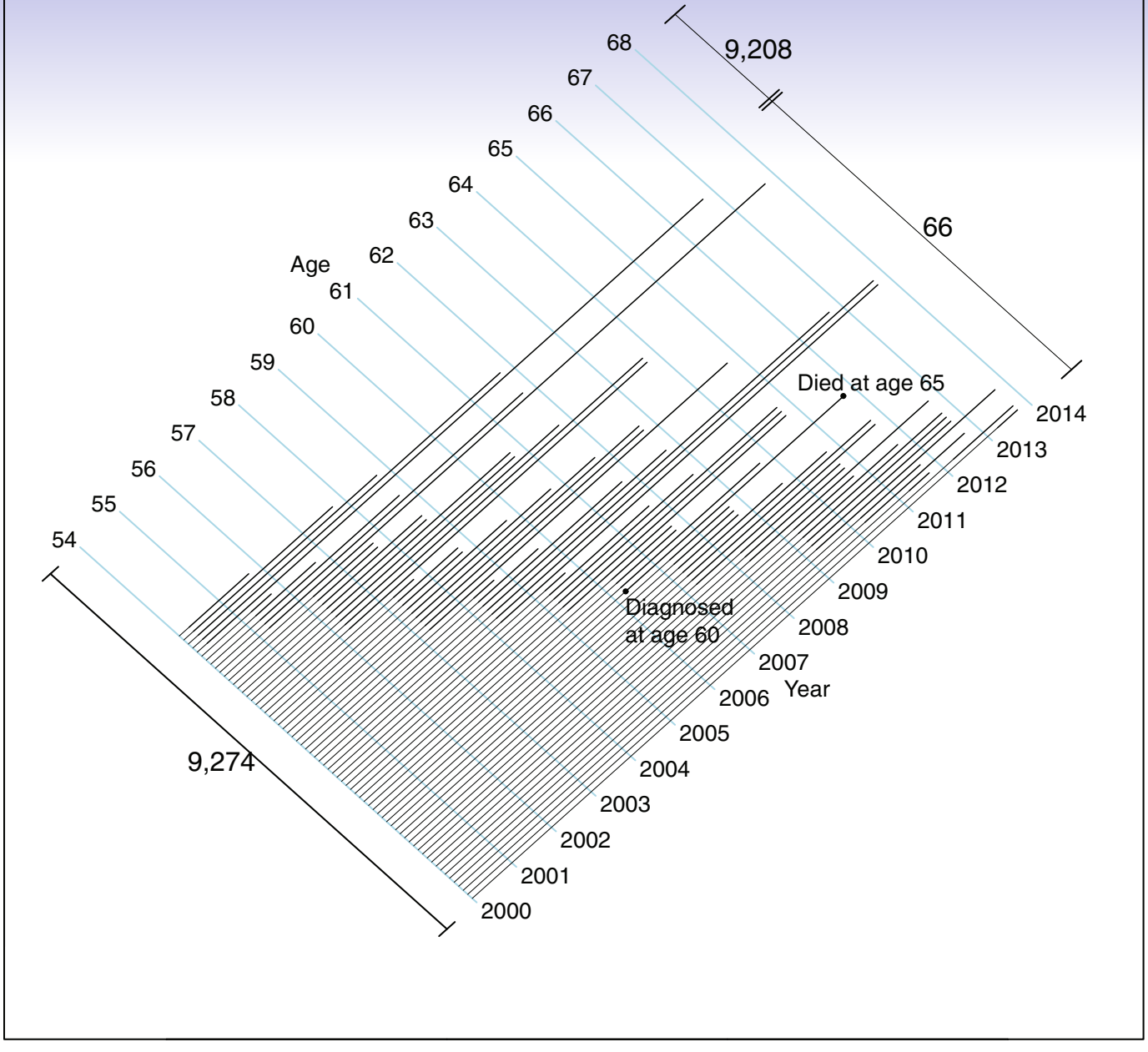

Fig 1. The ages when they were diagnosed with, and died of, breast cancer: 66 women in one selected cohort in region 2. Some 9,274 women, aged 54 in the year 2000, followed to the end of 2013. This cohort received just two screening invitations, at ages 62 and 64, too late to alter the course of these 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

OVERLOOKED PRINCIPLES

OVERLOOKED PRINCIPLES

How not to conduct population-based studies

OVERLOOKED PRINCIPLES

How not to conduct population-based studies

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]

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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.

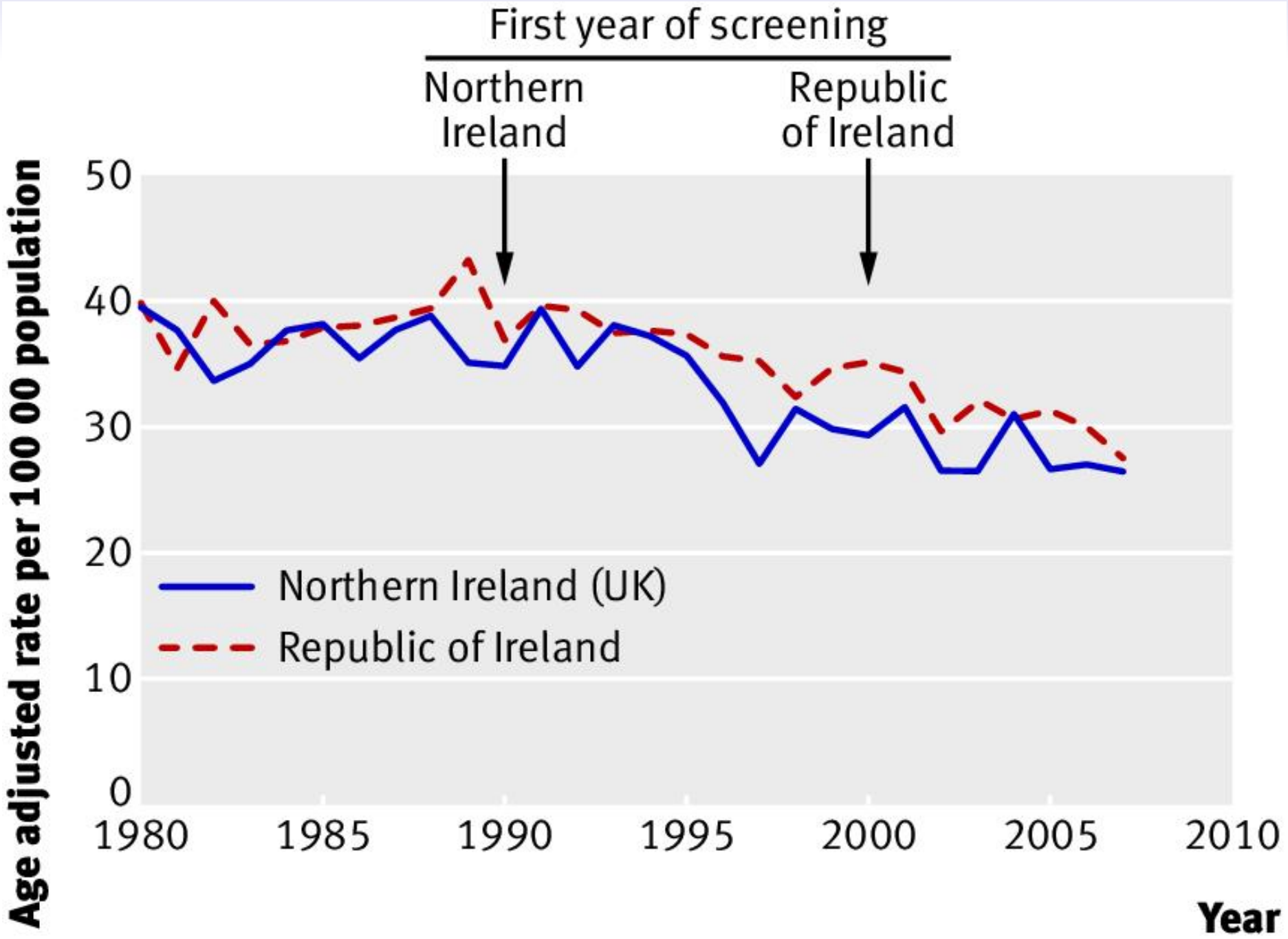
Setting Three country pairs (Northern Ireland (United Kingdom) *v* Republic of Ireland, the Netherlands *v* Belgium and Flanders (Belgian region south of the Netherlands), and Sweden *v* Norway).

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

This big-data approach dilutes the measured impact

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1. **WHO?** Most of the breast cancer deaths in Northern Ireland in the early 1990s involved cancers that had been diagnosed before the screening was introduced.

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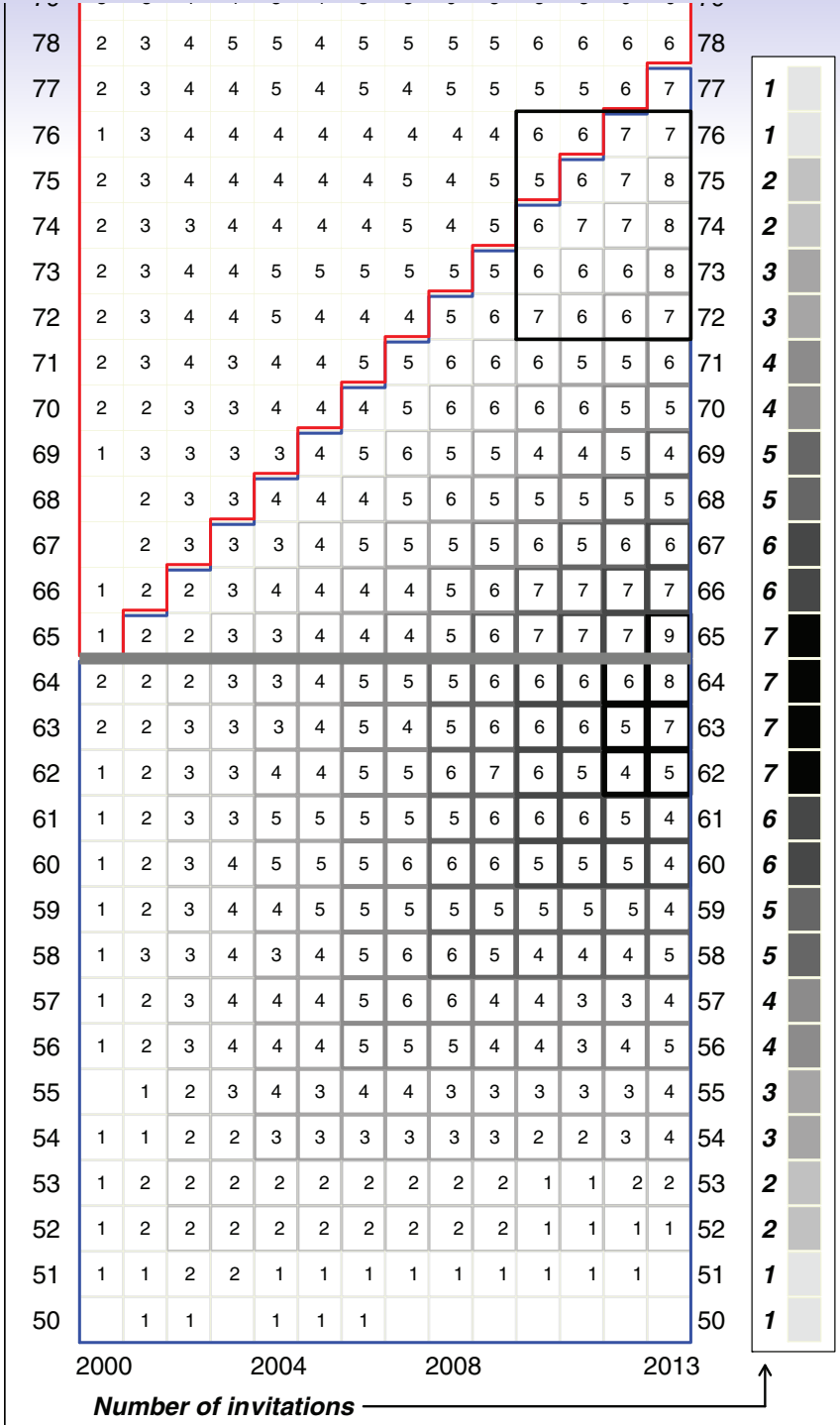
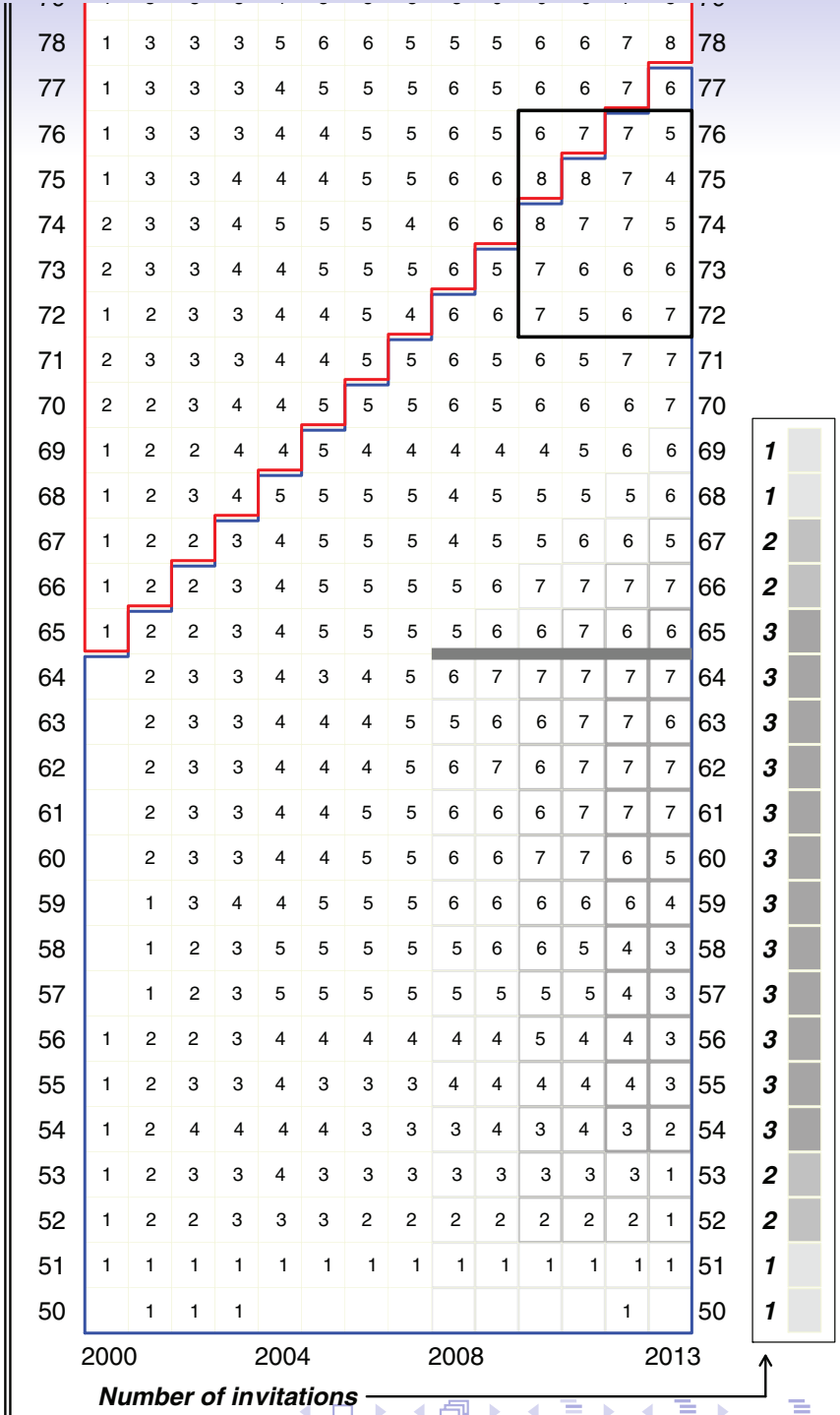
1. **WHO?** Most of the breast cancer deaths in Northern Ireland in the early 1990s involved cancers that had been diagnosed before the screening was introduced. These women could not have been helped by the program.
2. **WHEN?** Because of the 'detectability vs. curability' tradeoff, mortality deficits produced by cancer screening become evident only after some delay.
3. **HOW MUCH?** The closer to the upper screening age when the program began, the smaller the number of invitations received


2000
2004
2008
2013
Number of invitations


2000
2004
2008
2013
Number of invitations

From PLOS article

A synthesis in 2012 of the highest quality quasi-experimental studies – all based on incidence-based data – put the 'best estimate' of breast cancer mortality reduction produced by European service mammography screening programmes at 26% [6]. One contribution to this estimate were the D1 = 223 and D1 = 438 breast cancer deaths in the 10 years after/before screening was introduced to Copenhagen [1]. These two counts were the biggest component of the width of the confidence interval (D_1 = 223, D_0 = 2,333, D_1' = 438; D_0' = 2,123). Since the review, two additional data points have been added. The data from Norway, with 1,175 deaths in the 4 to 14 years after screening was introduced in the different counties, yielded a point estimate of 28% with the width of the CI determined by D_1 = 1,175 and D_0 = 8,996 [6]. The other data point was from the Funen area of Denmark with an estimate of 22% based on the 14 years after/before screening was introduced (D_1 = 416; D_0 = 566; D_1' = 4,246; D_0' = 4,111) [2].

From PLOS article

The numbers of screening invitations issued to women in these areas followed the same pattern as on the left half of our Fig 2. No area had yet reached the steady state where every cohort had been invited since age 50, up until age 69, and followed until the full benefits of these screens – expected to be centred on the ages 55 to 75 or so – had been expressed. Thus the estimated reductions measure only a portion of what will be achieved in steady state, and each area provides a different portion: for example, in the Copenhagen [1] and Funen [2] studies, which relied on ?time-shifts? of 10 and 14 years respectively, the maximum number of invitations were only 5 and 7 respectively, and many cohorts had had far fewer.

From PLOS article

What is different about these newest, Irish data, and how should the observed 9% difference between the regions involved in the two phases thus far be interpreted? The first difference is that the close to 50:50 sample size ratio in the two regions makes for a small variance (D_1 = 1,027; D_0 = 1,095 D_1' = 702; D_0' = 727). The second is that the correction in the double difference involves contemporary (post year 2000 only) rather than historical data. The closeness of the background rates in the women who were too old for the screening program reduces the risk of mixing mortality differences produced by screening and ones caused by regional differences in quality of care. Third, the Republic of Ireland is one of the few EU countries to have limited screening to women aged 50–64, rather than to those aged 50?69 as recommended by the Council of the European Union [21] (the program will now be extended to include all women from 50?69 by 2021).

From PLOS article

The 9% regional difference seen thus far in Ireland measures how much of an advantage women in Region 1 have achieved thus far (i.e. in the 14 years) over their Region 2 counterparts (or their own counterfactuals) by having had access to organized screening almost 8 years sooner. The full effect in Region 1 (when all cohorts have received all 8 invitations, from age 50 to 64) could eventually be estimated indirectly if Region 2 had delayed its introduction, not for 8, but for say 20?25 years. Given our inexact knowledge as to the timing of the delayed cancer screening dividends, it is not possible to precisely extrapolate from the estimated 9% achieved this far with a lead of 8 years, to an estimate based on a (hypothetical) phase 1 lead of 20?25 years. However, one might extrapolate from the differences seen with the 10 and 14 year leads in the two Danish studies, as long as one allows for the shorter ?age-reach? of the Irish program (and its inability to avert most of the deaths that occur in women aged from the early 70s onwards). One should also allow for the initial phase 1 challenges in achieving full coverage and a 21?27 month cycle. Based on all of these considerations, it seems reasonable to project that had the Region 1 lead been 20?25 years, their advantage over Region 2 in these years would have been close to 20% – the remit of the program [13].

From PLOS article

When magnified by a factor of 100/70 so that it refers to the benefit of full participation in region 1, the projection is closer to 30%.

From PLOS article

The observed 9% difference that drives these estimates might have been attenuated by the phase 1 start up challenges, and by greater opportunistic screening in Region 2?prompted by awareness of the program in Region 1, and paid for by private health insurance. But this is offset by the possibly greater access to treatment in Region 1 pre 2008, when treatment pathways were linked to the screening programme. Centres of clinical excellence for cancer treatment were more common post 2008.

From PLOS article

In addition to reporting the first 21st century-only screening data thus far, this paper highlights an important but neglected principle in the analysis of cancer screening data. The effects of cancer screening are not like those of adult circumcision, where the resulting protection against HIV acquisition is immediate and lifelong, or one-time screening for abdominal aortic aneurysms [22], where the full benefits are already evident in year 2, and persist for at least a decade. To estimate the full effects of this activity/intervention, a difference of a year or two between starting phase 1 and 2 would have been more than adequate; to directly see the full mortality effects of eight rounds of every second year screening, a lead of perhaps 20?25 years is necessary.

From PLOS article

The central role of timing and the difference in outlook between therapeutics and screening is further exemplified in the question of extending mammography screening from the ages of 50?64 to 50?69. When considering the implications of the last screening invitation being at age 69 rather than at age 64, it is more instructive to work backwards. Suppose that, in the absence of screening, a cancer had proved fatal at age 74; if there had been just one opportunity to screen for that cancer, at what age would it have been optimal to do so? What if there had been more than one? The patterns in Fig 2 and the raw data in Fig 3 illustrate why mortality data related to cancer screening, whether derived from old trials or newer quasi-experimental studies, need to be very carefully considered. Few analyses or meta-analyses to date have considered these core screening questions: how long after the beginning of screening do the mortality deficits manifest themselves? How long after the cessation of screening do the mortality deficits disappear? In each trial, how many rounds were there and how long was the follow-up? In light of these, what does a single average data from trials of varying screening duration and varying follow-up periods mean? And to whom does it apply?

From PLOS article

The reductions produced by cancer screening cannot be summarized using a single number (the remit of the BreastCheck program was ?reducing mortality from breast cancer by 20% in ten years?), but must be arrayed in time along both of the dimensions used in these Figs. Moreover, the cells must not be grouped merely by horizontal age-bands, as is commonly done. Women must also be followed, along the diagonals of the Lexis diagram, into subsequent age-bands. The good that screening at age 64 does only becomes apparent (as a mortality deficit) in subsequent age bands. These principles should be used to interpret not just these latest data from Ireland, but all of the trial and population data to date.

Smaller data: use date of diagnosis to emulate RCT (cancer registry data are required to do this)

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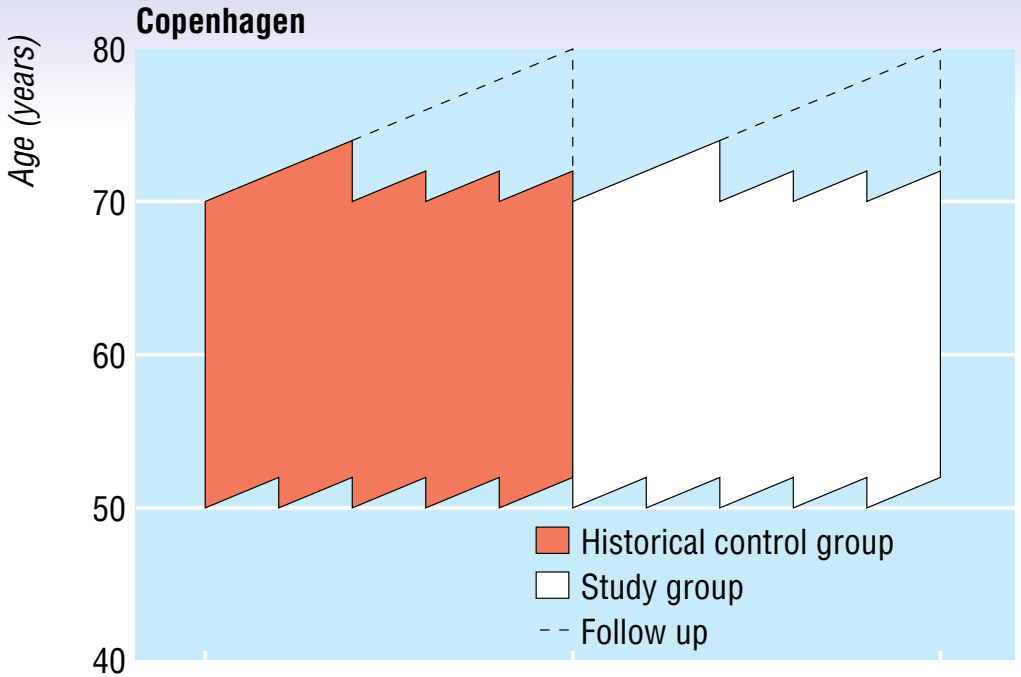
Cite this article as: BMJ, doi:10.1136/bmj.38313.639236.82 (published 13 January 2005)

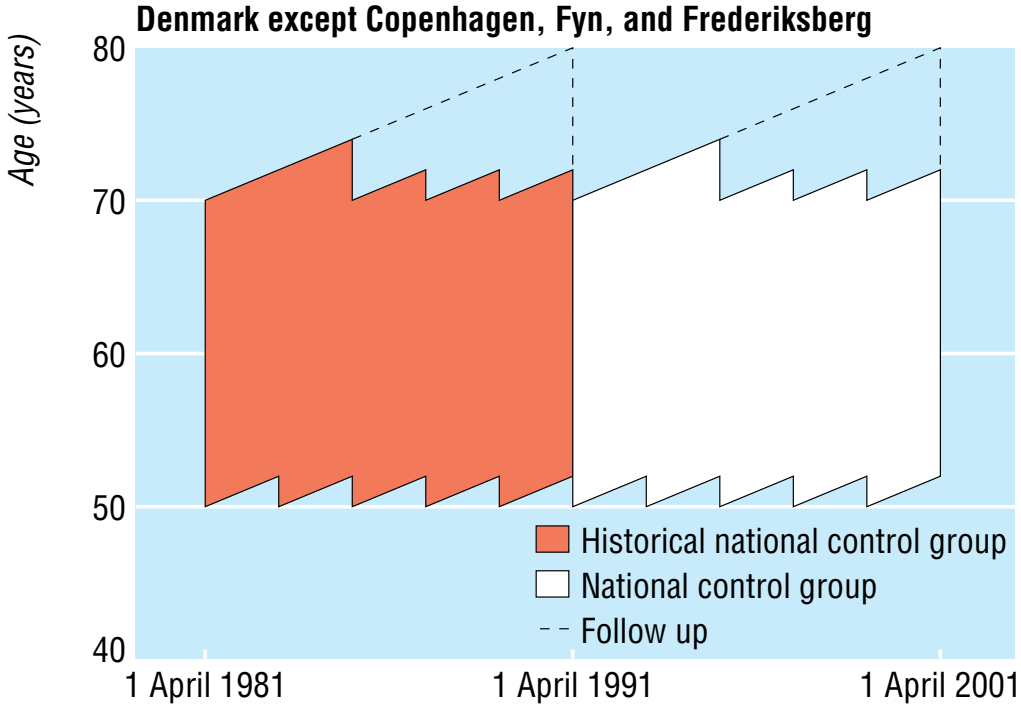
Papers

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

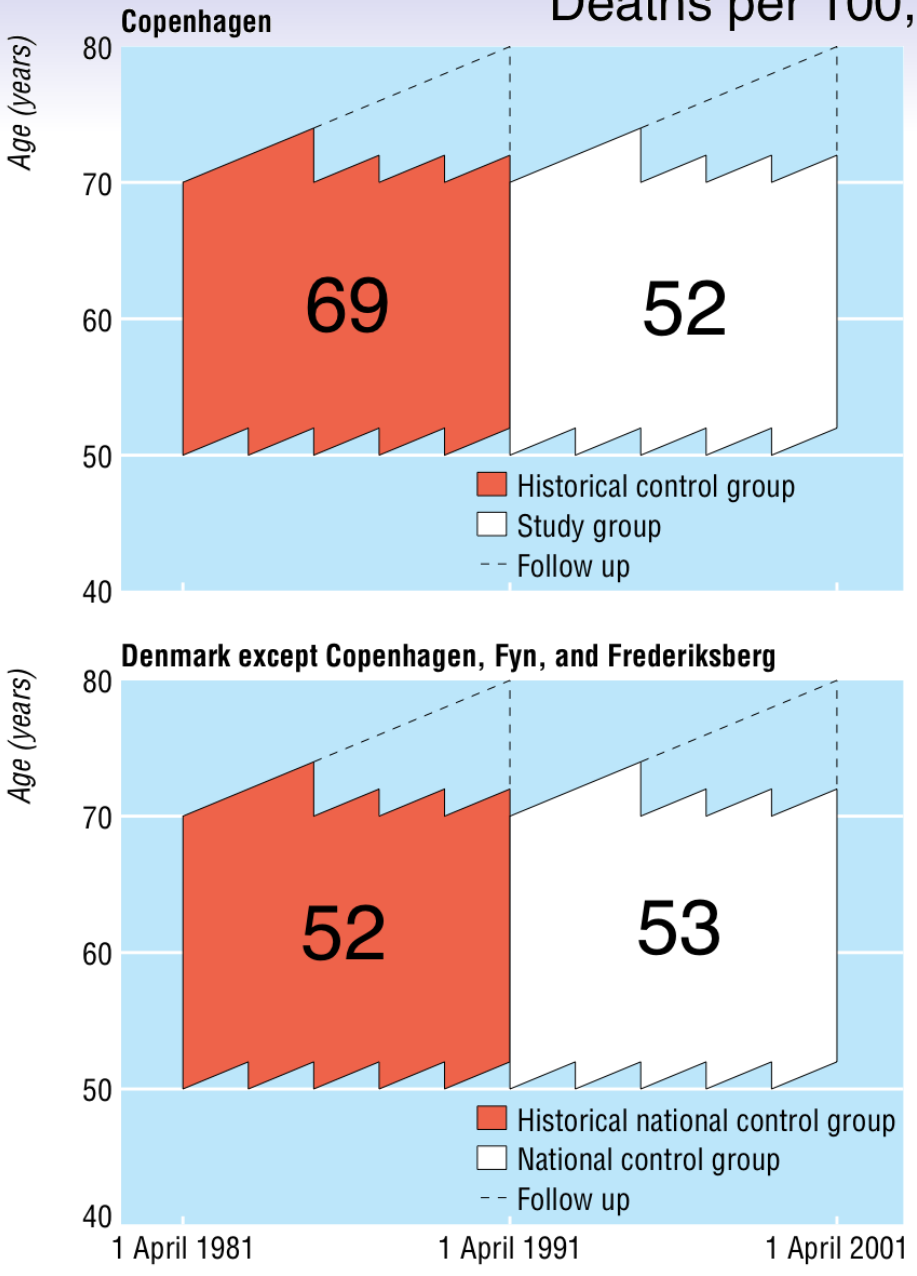


Copenhagen

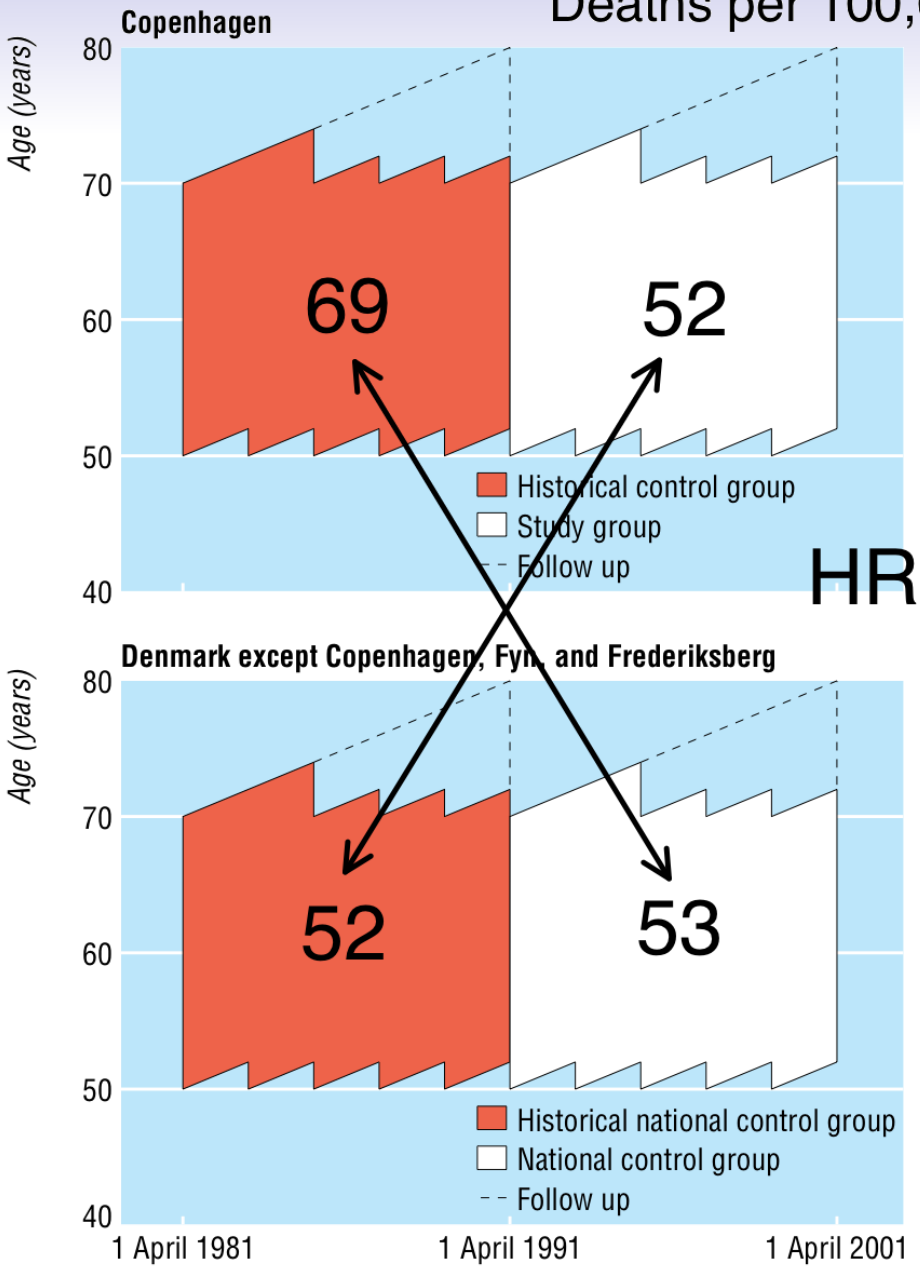


Rest of Denmark (10 x)

Deaths per 100,000 WY



Deaths per 100,000 WY



HR = 0.75 (25% ↓)