Population data to measure mortality reductions produced by organized cancer screening: analyze with care

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JSM

2015-08-09

Dedication

HARVARDgazette

Campus & Community > Obituaries

HSPH's Marvin Zelen dies at 87

Was considered a 'tremendous force' in biostatistics

November 19, 2014 | Editor's Pick

Photo by Shaina Andelman

Harvard Professor Marvin Zelen was noted for developing the statistical methods and study designs that are used in clinical cancer trials, in which experimental drugs are tested for toxicity, effectiveness, and proper dosage.

HSPH Communications

Professor Marvin Zelen of the Department of Biostatistics at the Harvard T.H. Chan School of Public Health (HSPH) died on Nov. 15 after a battle with cancer. He was 87.

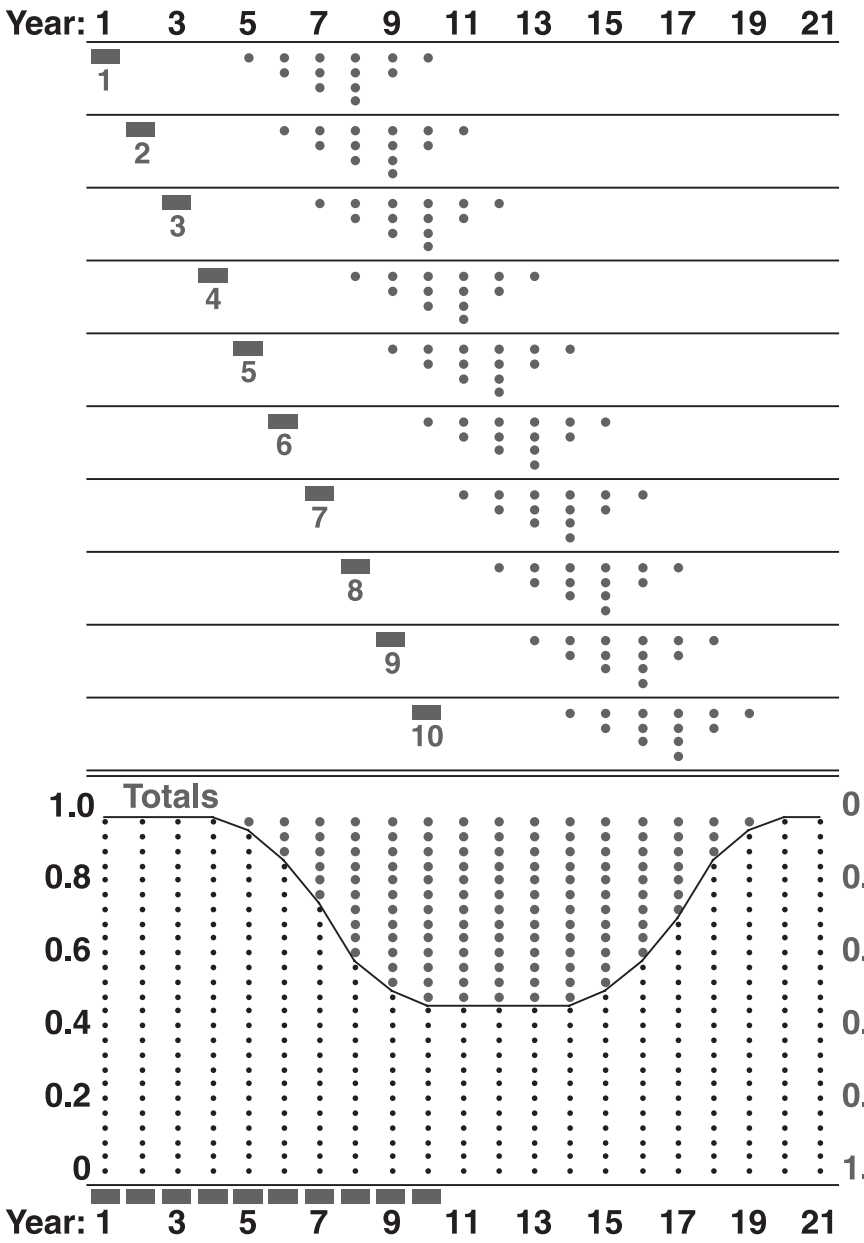
Outline

- Screening is different from prevention/treatment
- Bathtub-shaped Hazard Ratio function
- Breast Cancer Screening with Mammography:
  21st century (non-experimental) population-based studies
- Avoiding underestimates: examples from Norway & Ireland
- **It's all about TIMING – and the Lexis diagram helps !!**

Ways in which cancer screening differs from prevention/treatment

- Prevention aims to stop cancer from ever developing
- Treatment combats it once it becomes apparent
- Screening: pursuit of earlier diagnosis
  - disease not necessarily present at 1st screen.. must repeat
  - benefits not immediate, but delayed, & time-limited
  - in screening: no screening comparisons, if screening works as intended, mortality hazard rates are non-proportional

Bathtub-shaped Hazard Ratio function



<— deaths averted by screen 1

<— deaths averted by screen 2

...

<— deaths averted by screen 10

Figure (after Miettinen et al. 2002.) is from Hanley JA. Analysis of Mortality Data From Cancer Screening Studies: Looking in the Right Window. *Epidemiology, Vol 16, 2005*, pp 786-790.

See also. Liu Z at al. J Med Screening. 2013.

???

Magnitude of reductions being achieved with contemporary mammography

Estimates from (non-experimental) population-based studies

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]

[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.

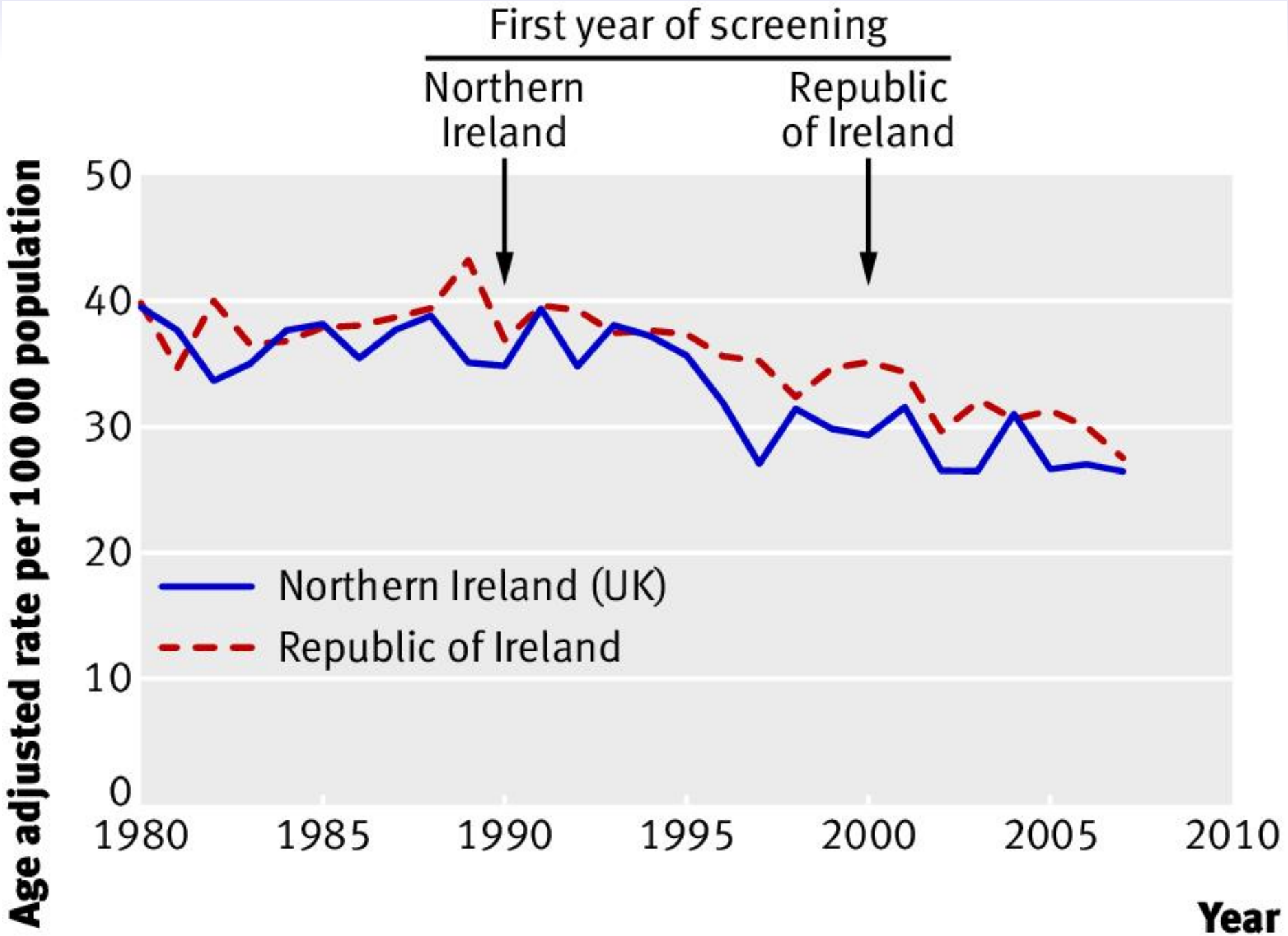
Setting Three country pairs (Northern Ireland (United Kingdom) *v* Republic of Ireland, the Netherlands *v* Belgium and Flanders (Belgian region south of the Netherlands), and Sweden *v* Norway).

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

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)

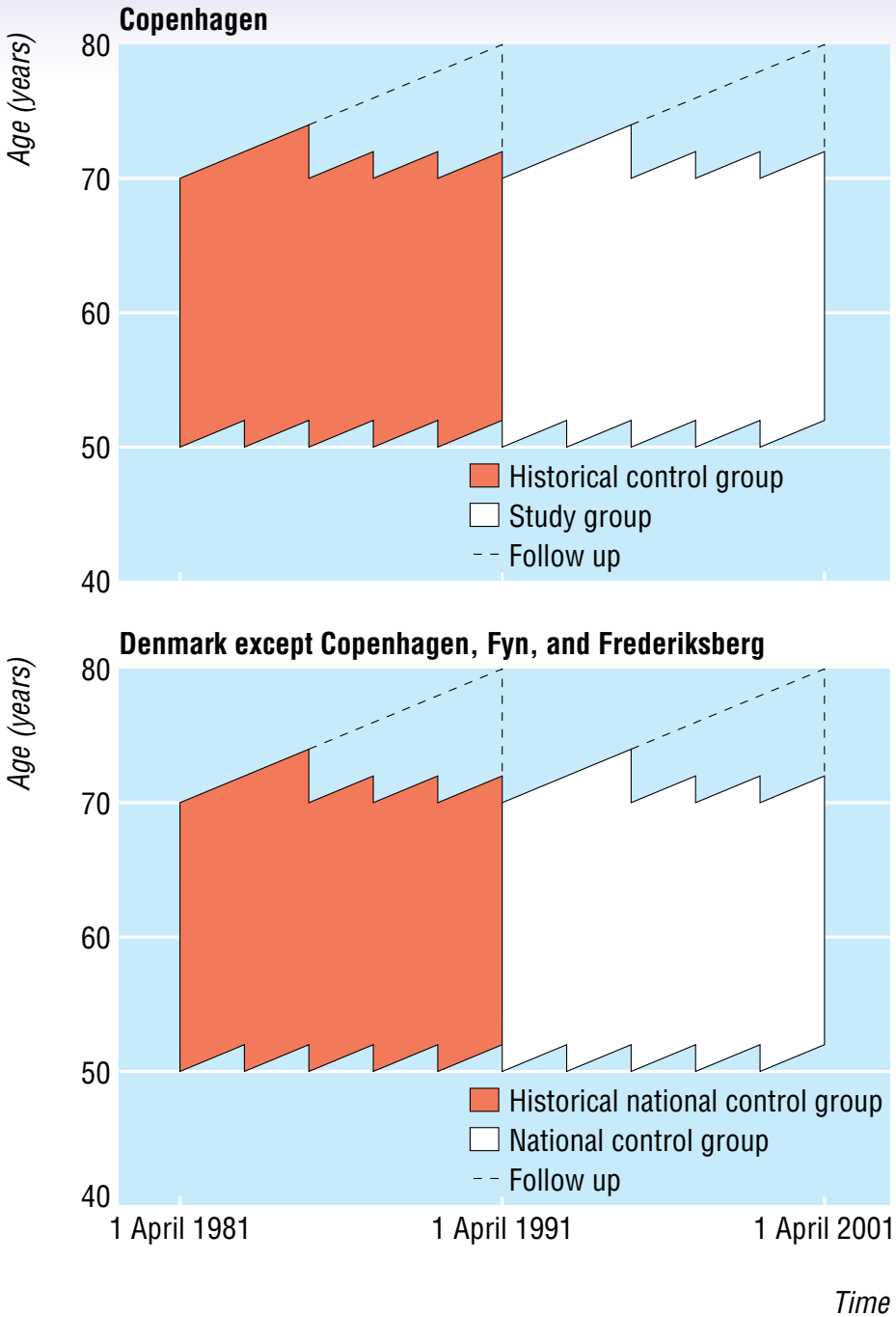
HOW TO conduct population-based studies

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



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

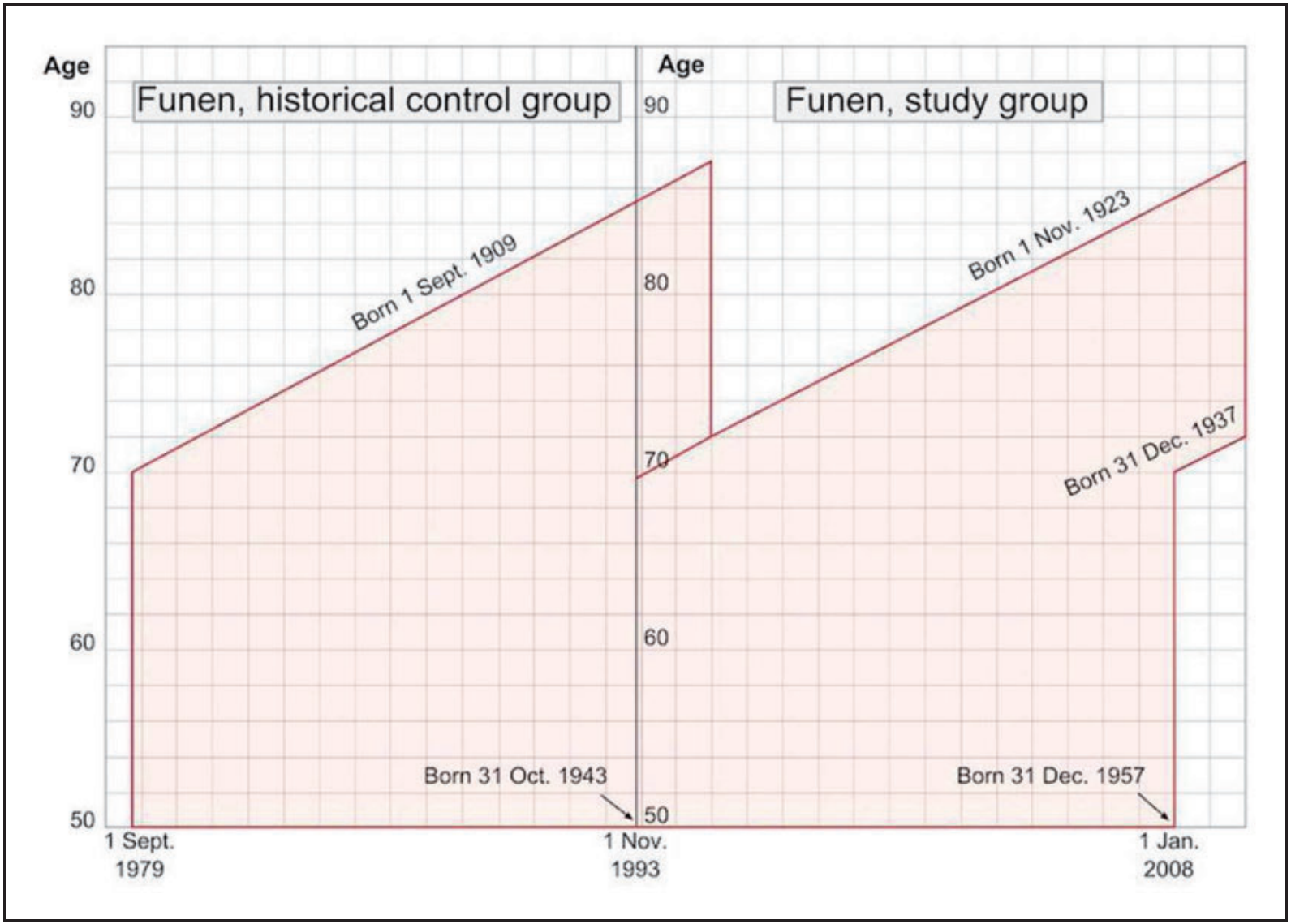
i.e., they focused on women who were eligible for the program, or would have been, had it been available in that region or at that time.

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

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Accepted for publication 20 June 2012

Norway

Diluted estimate of impact

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 23, 2010 VOL. 363 NO. 13

Effect of Screening Mammography on Breast-Cancer Mortality in Norway

Mette Kalager, M.D., Marvin Zelen, Ph.D., Frøydis Langmark, M.D., and Hans-Olov Adami, M.D., Ph.D.

Screening program was started in one region in 1996 and expanded to all 6 regions during subsequent 9 years.

Women between the ages of 50 and 69 years were offered screening mammography every 2 years.

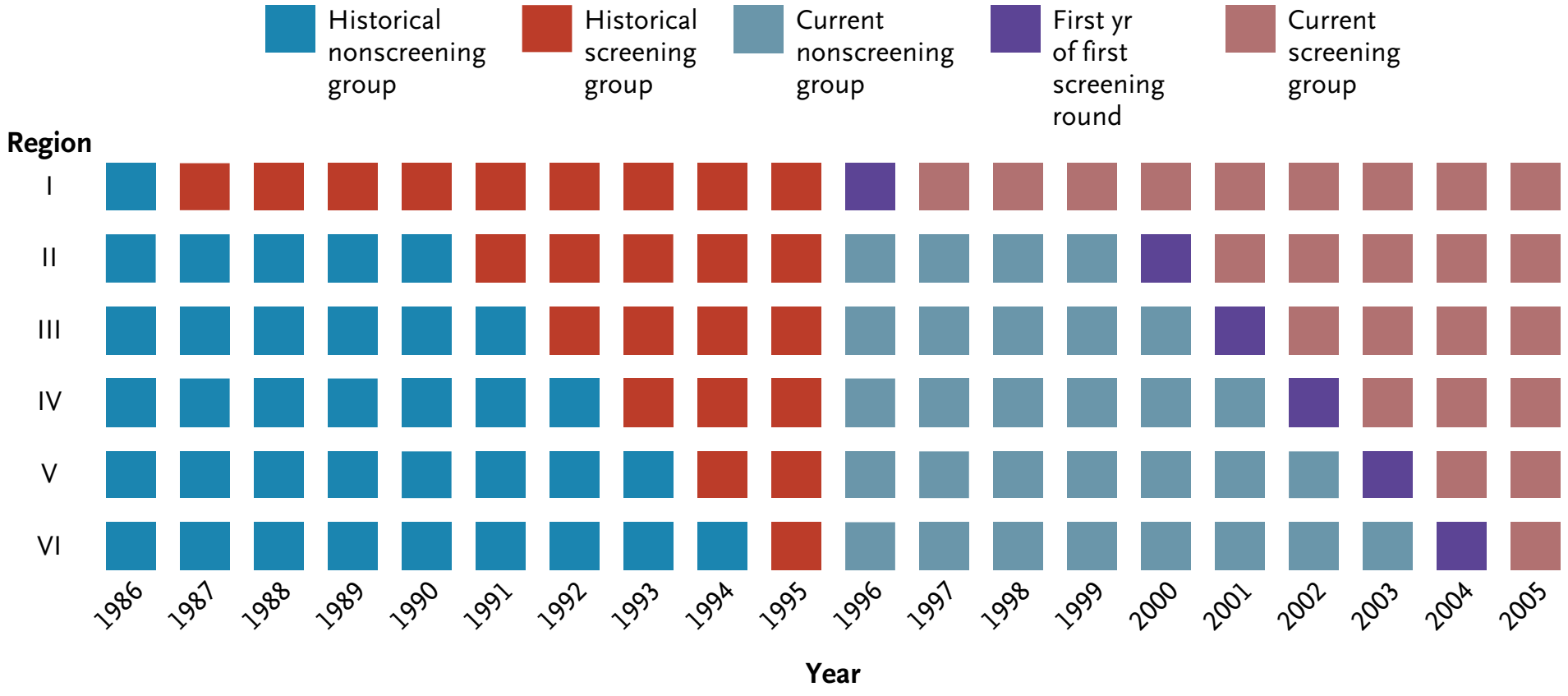


Figure 1. The Four Study Groups, According to Region and Year.

The 19 counties were grouped into six regions according to the date of introduction of the screening program, which was implemented throughout the country in a staggered fashion, starting in 1996. The screening group consisted of women who received a diagnosis of breast cancer after the introduction of the screening program. The nonscreening group consisted of women living in regions where screening was not offered in the same calendar period that screening was offered in other regions. The historical study groups consisted of women residing in the 19 counties in the 10-year period before screening was offered. A screening round lasted for 2 years, and the first year of the first round was included in both the screening and nonscreening groups (purple).

Double-difference: adjust for concomitant improvements in treatment

Table 1. Rates of Death from Breast Cancer, According to Study Group and Age.*

Age Group and Mortality Data	Nonscreening Groups		Screening Groups		Difference		
	Historical Group	Current Group	Historical Group	Current Group	Nonscreening Groups†	Screening Groups‡	Nonscreening Groups vs. Screening Groups§
50–69 Yr							
No. of deaths	494	396	555	423			
No. of person-yr	1,898,989	1,866,741	2,197,469	2,337,323			
No. of deaths/100,000 person-yr	26.0	21.2	25.3	18.1	4.8	7.2	2.4±4.1
Rate ratio for death (95% CI)					0.82 (0.71–0.93)	0.72 (0.63–0.81)	0.10
20–49 Yr							
No. of deaths	238	183	332	267			
No. of person-yr	3,842,740	4,030,443	5,134,212	5,357,163			
No. of deaths/100,000 person-yr	6.2	4.5	6.5	5.0	1.7	1.5	–0.2±4.4
Rate ratio for death (95% CI)					0.73 (0.63–0.92)	0.77 (0.65–0.90)	–0.04
70–84 Yr							
No. of deaths	429	386	623	465			
No. of person-yr	1,101,019	1,173,624	1,349,967	1,318,004			
No. of deaths/100,000 person-yr	39.0	32.9	46.1	35.3	6.1	10.8	4.7±6.9
Rate ratio for death (95% CI)					0.84 (0.74–0.97)	0.76 (0.68–0.86)	0.08

* Only women between the ages of 50 and 69 years were invited to participate in screening mammography. All women in this group were also eligible for treatment by the multidisciplinary teams that are part of the screening program.

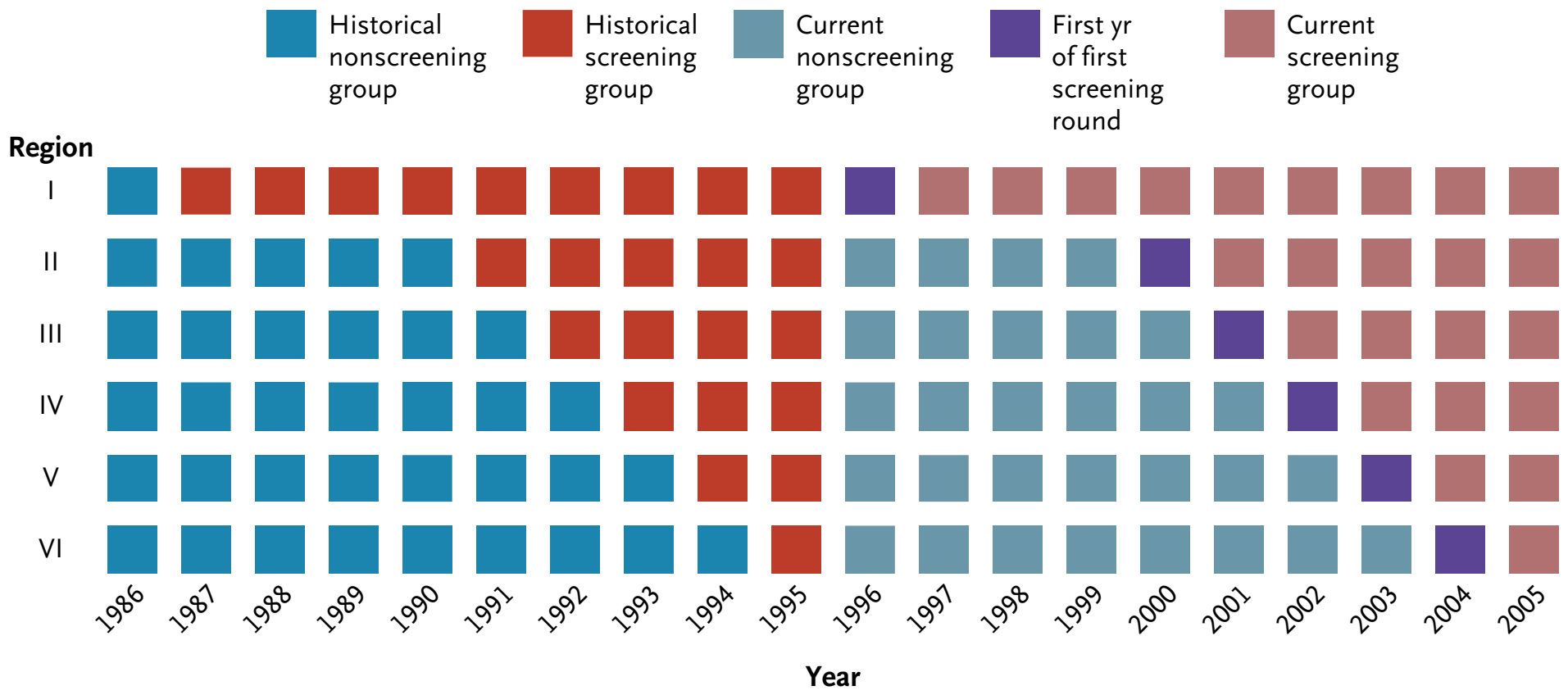
† For the nonscreening groups, the value shown is the difference between the rate of death in the historical group and that in the current group. This difference represents changes in mortality over time as a result of increased breast-cancer awareness, improved therapy, and more sensitive diagnostic tools.

Results & Conclusions

The rate of death was reduced by 7.2 deaths per 100,000 person-years in the screening group as compared with the historical screening group (rate ratio, 0.72; and by 4.8 deaths per 100,000 person-years in the nonscreening group as compared with the historical nonscreening group (rate ratio, 0.82; for a relative reduction in mortality of 10% in the screening group. Thus, the difference in the reduction in mortality between the current and historical groups that could be attributed to screening alone was 2.4 deaths per 100,000 person-years, or a third of the total reduction of 7.2 deaths.

The availability of screening mammography was associated with a reduction in the rate of death from breast cancer, but the screening itself accounted for only about a third of the total reduction.

Time-insensitivity DILUTES estimated impact.



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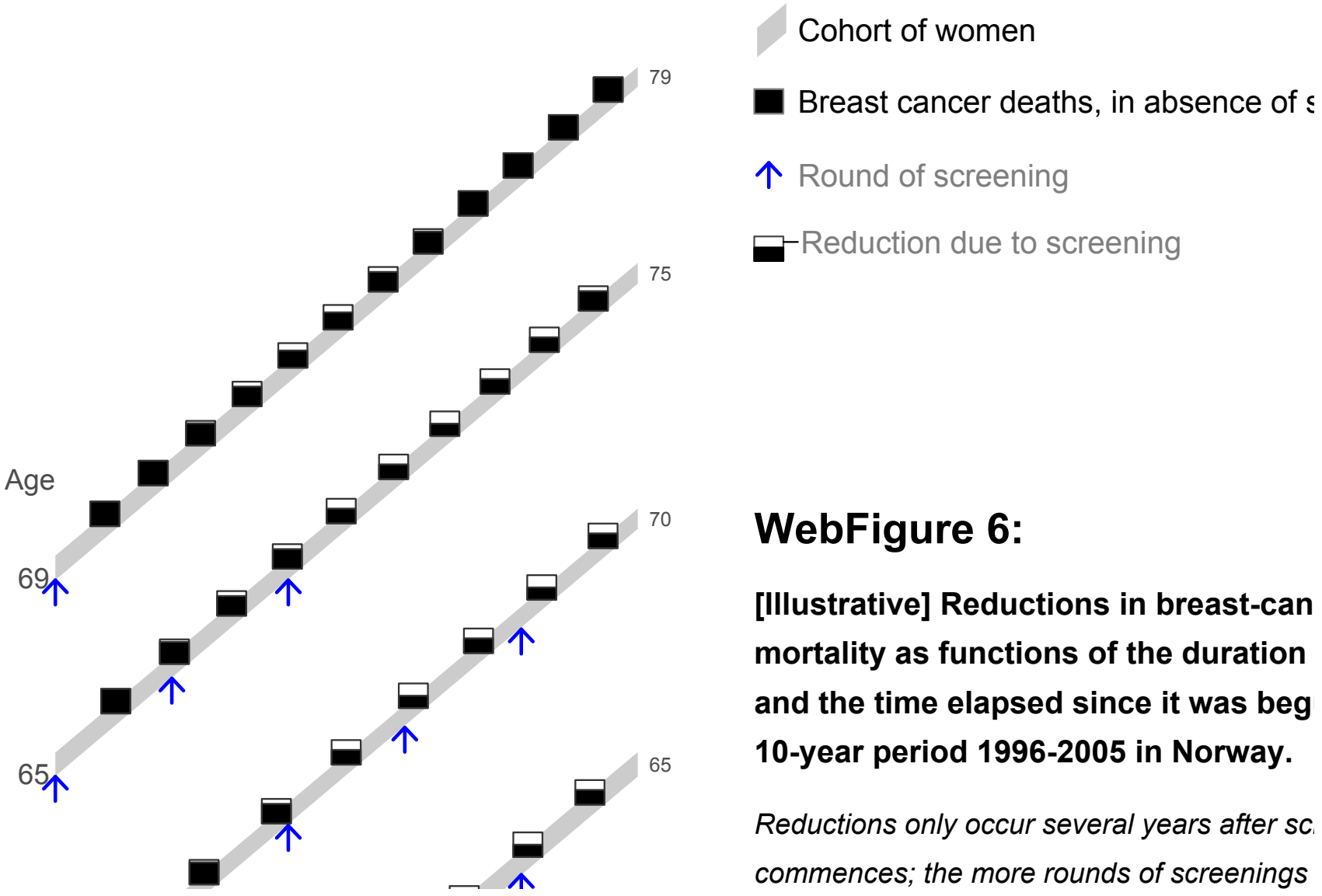
Age-insensitivity DILUTES estimated impact



WebFigure 6:

[Illustrative] Reductions in breast-can mortality as functions of the duration and the time elapsed since it was beg 10-year period 1996-2005 in Norway.

Reductions only occur several years after sc commences; the more rounds of screenings

Hanley JA. *Epidemiologic Reviews*, 2011

Avoiding dilution, & improving precision

BMJ 2014;348:g3701 doi: 10.1136/bmj.g3701 (Published 17 June 2014)

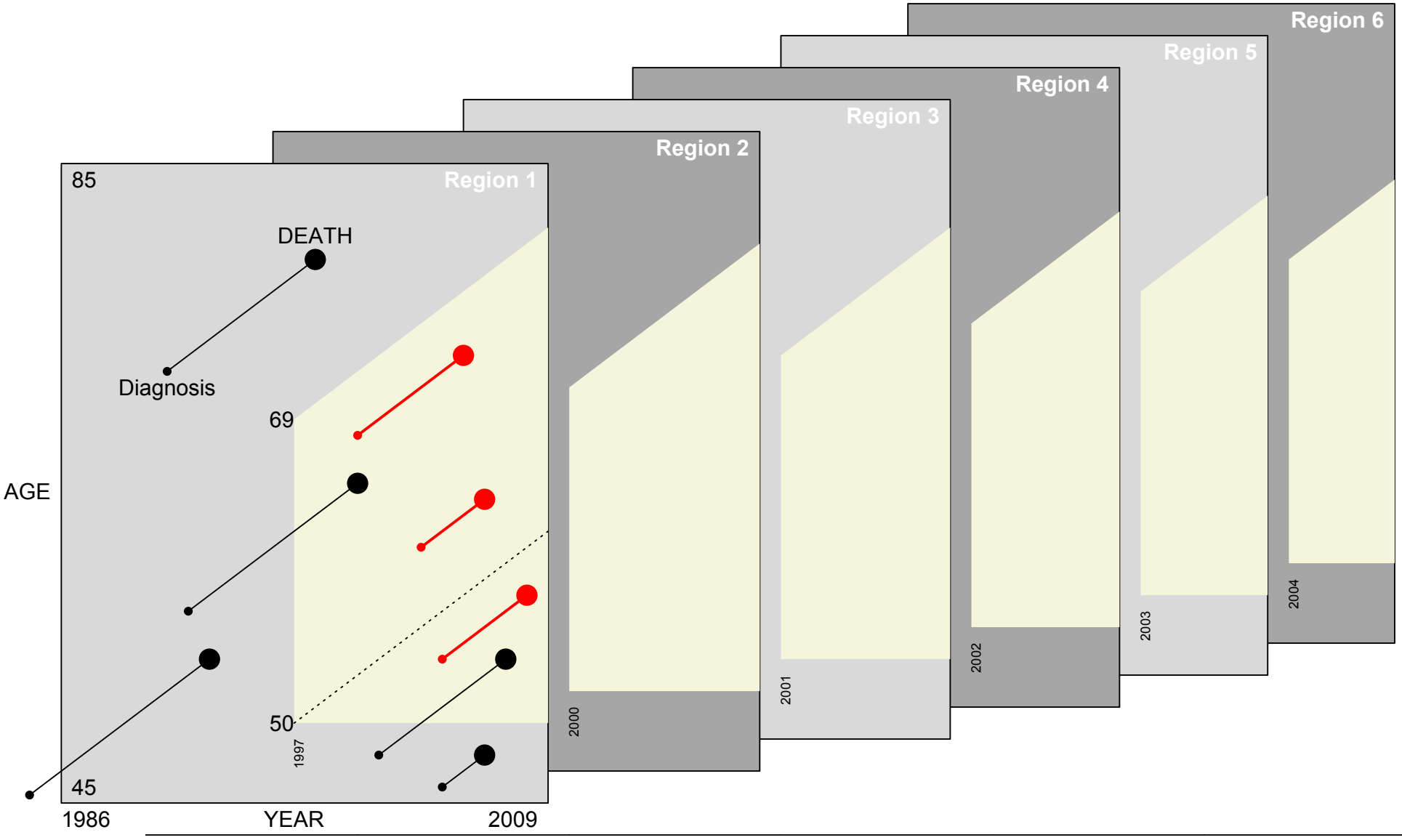
NORWAY

RESEARCH

Modern mammography screening and breast cancer mortality: population study

Harald Weedon-Fekjær *researcher*[1 2 3], Pål R Romundstad *professor of epidemiology*[1], Lars J Vatten *professor of epidemiology*[1 4]

[1]Department of Public Health, Norwegian University of Science and Technology, 7491 Trondheim, Norway; [2]Oslo Center for Biostatistics and Epidemiology, Department of Biostatistics, University of Oslo, Oslo, Norway; [3]Oslo Center for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Oslo, Norway; [4]Harvard School of Public Health, Department of Epidemiology, Boston, MA, USA


Region 6
Region 5
Region 4
Region 3
Region 2
Region 1
85
DEATH
Diagnosis
69
50
45
AGE
1997
2000
2001
2002
2003
2004
1986
YEAR
2009

Breast cancer mortality rates in women who were invited to screening (intention to screen)

vs.

in women who were not invited,

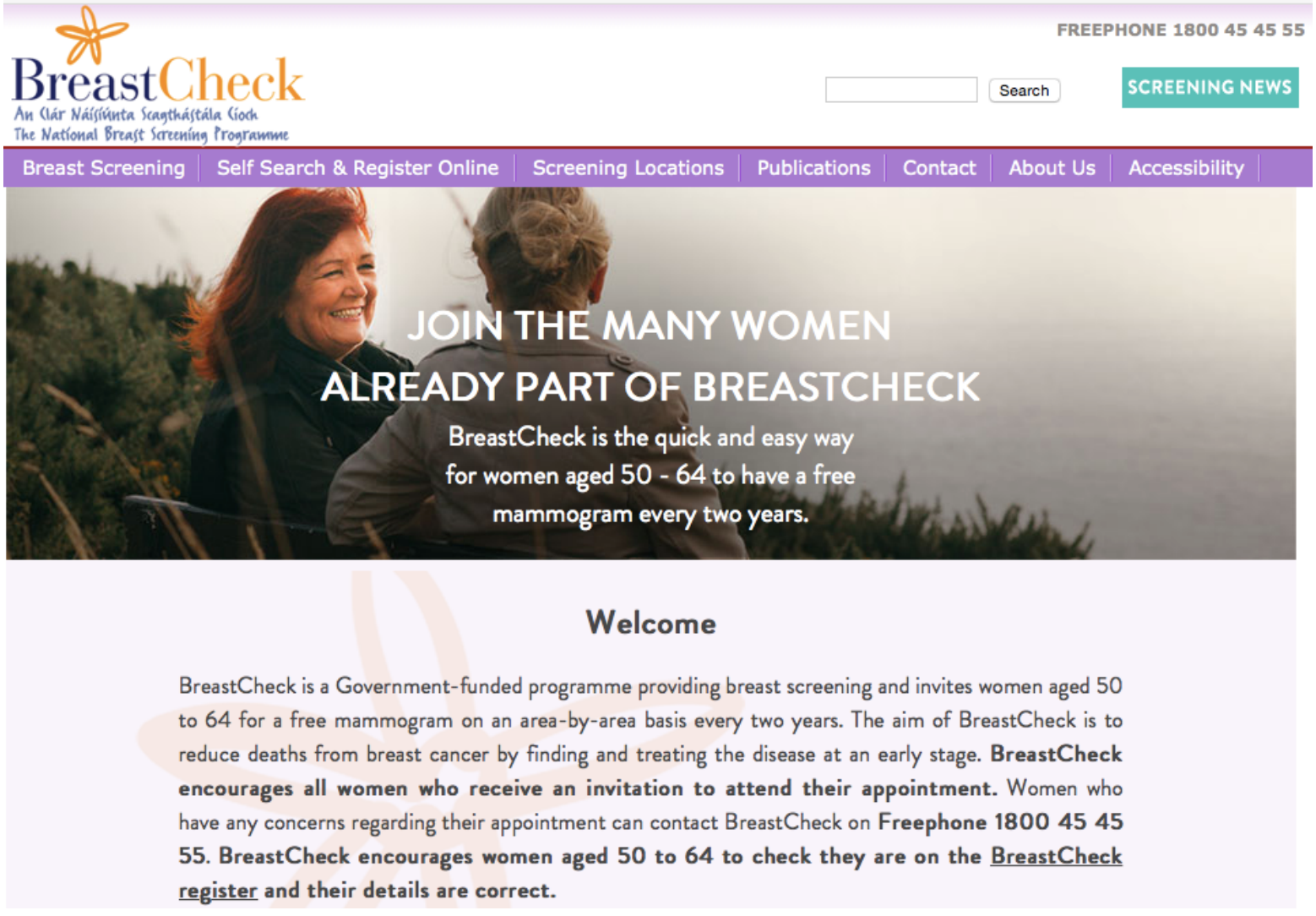
with a clear distinction between cases of breast cancer diagnosed before (without potential for screening effect) and after (with potential for screening effect) the first invitation for screening.

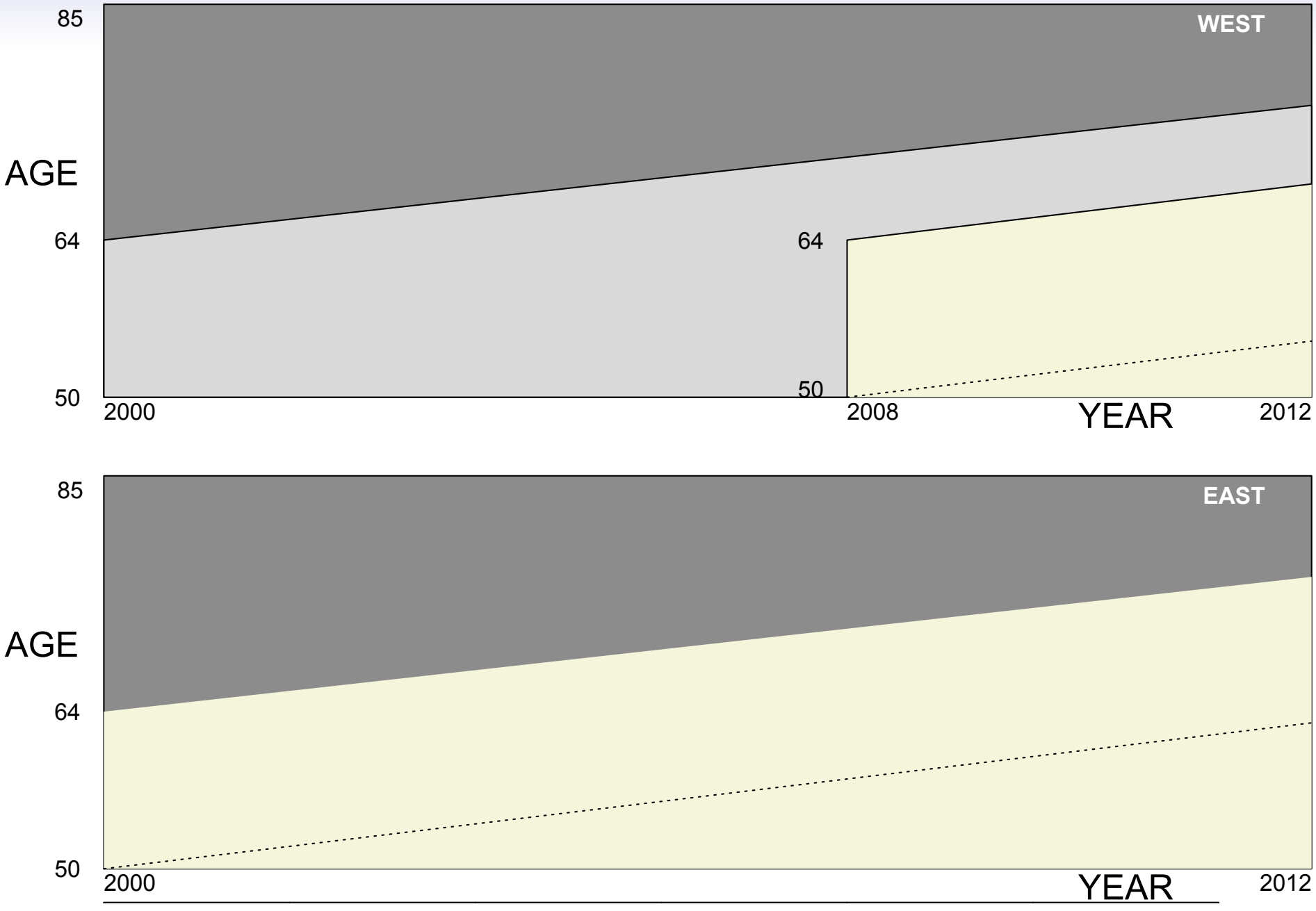
[$\approx$ 35 term] model included county as a factor, and natural splines to allow for non-linear variations in age, period, and cohort effects.

Results During 15 193 034 person years of observation (1986-2009), deaths from breast cancer occurred in 1175 women with a diagnosis after being invited to screening and 8996 women who had not been invited before diagnosis. After adjustment for age, birth cohort, county of residence, and national trends in deaths from breast cancer, the mortality rate ratio associated with being invited to mammography screening was 0.72 (95% confidence interval 0.64 to 0.79). To prevent

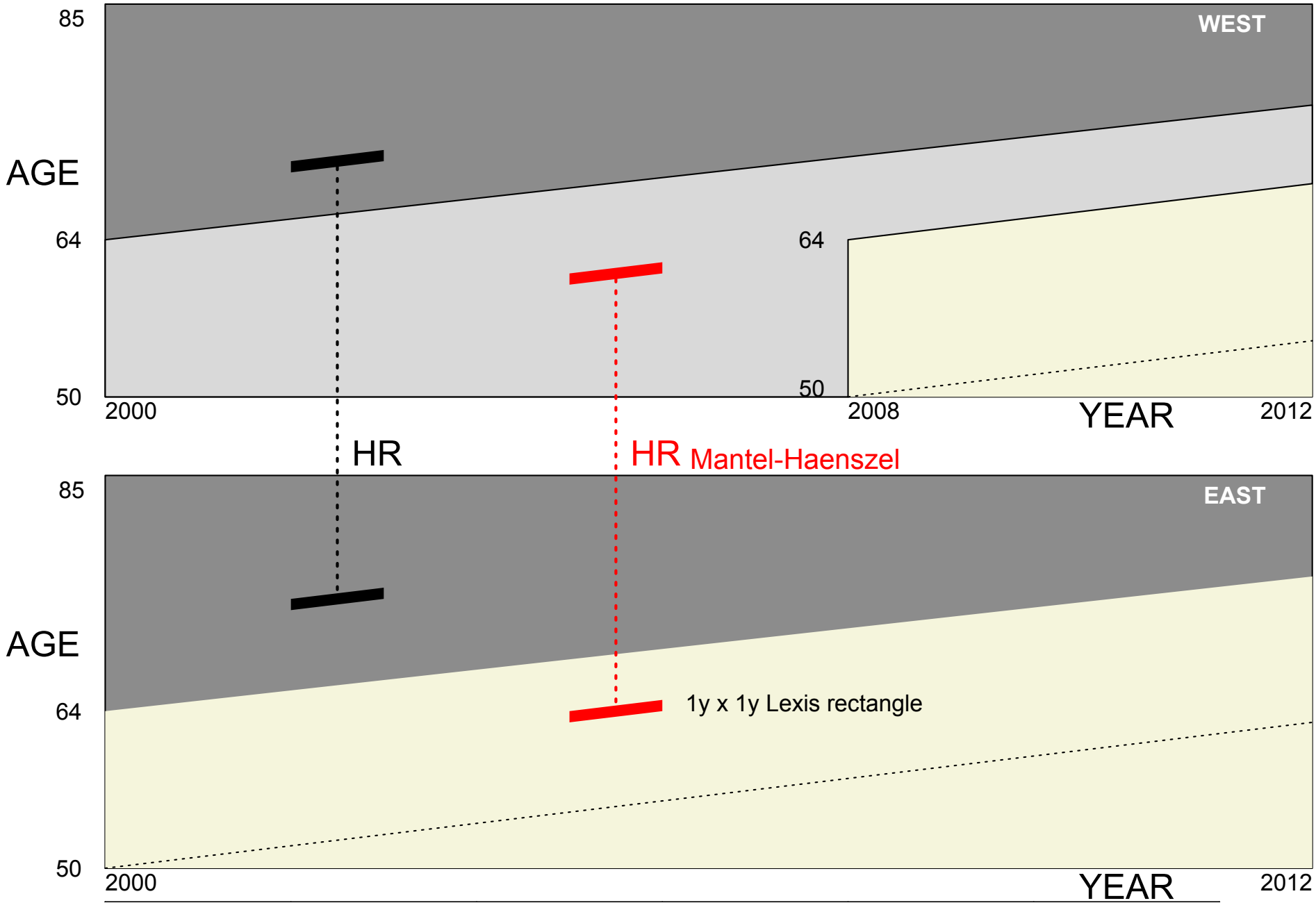
28% REDUCTION

IRELAND


BreastCheck
An Clár Náisiúnta Scagthástála Cioch
The National Breast Screening Programme
FREEPHONE 1800 45 45 55
Search
SCREENING NEWS
Breast Screening
Self Search & Register Online
Screening Locations
Publications
Contact
About Us
Accessibility
JOIN THE MANY WOMEN
ALREADY PART OF BREASTCHECK
BreastCheck is the quick and easy way
for women aged 50 - 64 to have a free
mammogram every two years.
Welcome
BreastCheck is a Government-funded programme providing breast screening and invites women aged 50 to 64 for a free mammogram on an area-by-area basis every two years. The aim of BreastCheck is to reduce deaths from breast cancer by finding and treating the disease at an early stage. **BreastCheck encourages all women who receive an invitation to attend their appointment.** Women who have any concerns regarding their appointment can contact BreastCheck on **Freephone 1800 45 45 55. BreastCheck encourages women aged 50 to 64 to check they are on the BreastCheck register and their details are correct.**


WEST
85
AGE
64
50
64
50
2000
2008
YEAR
2012
EAST
85
AGE
64
50
2000
YEAR
2012

2 age- & year-matched EAST:WEST contrasts

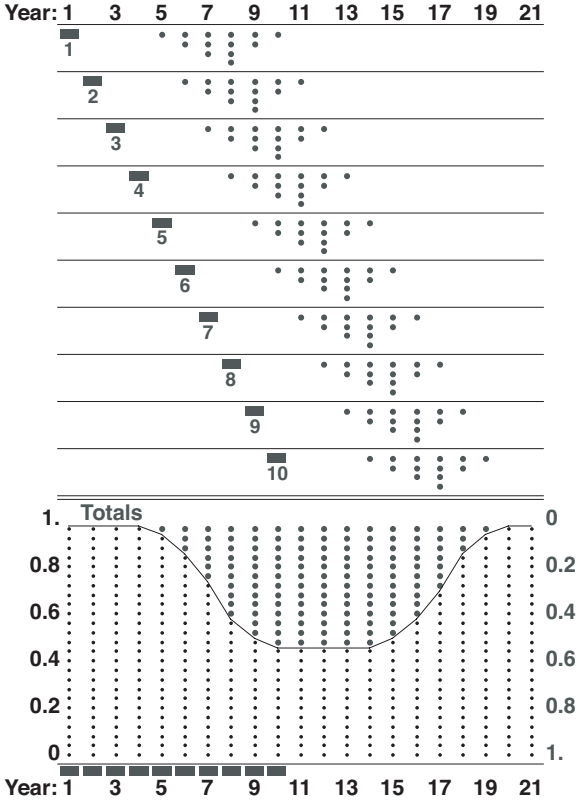


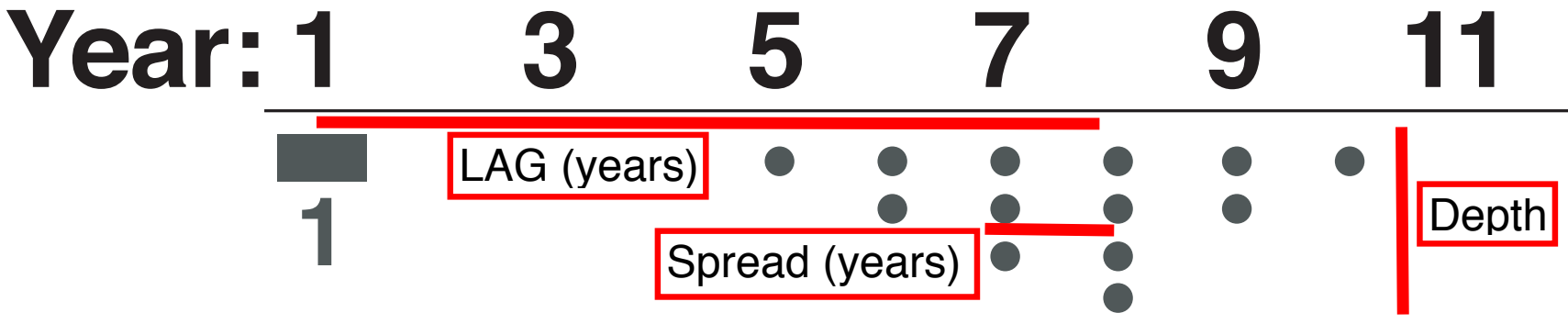
Incorporating NO. & TIMING of Screens

Estimate impact of (each) single round of screening:

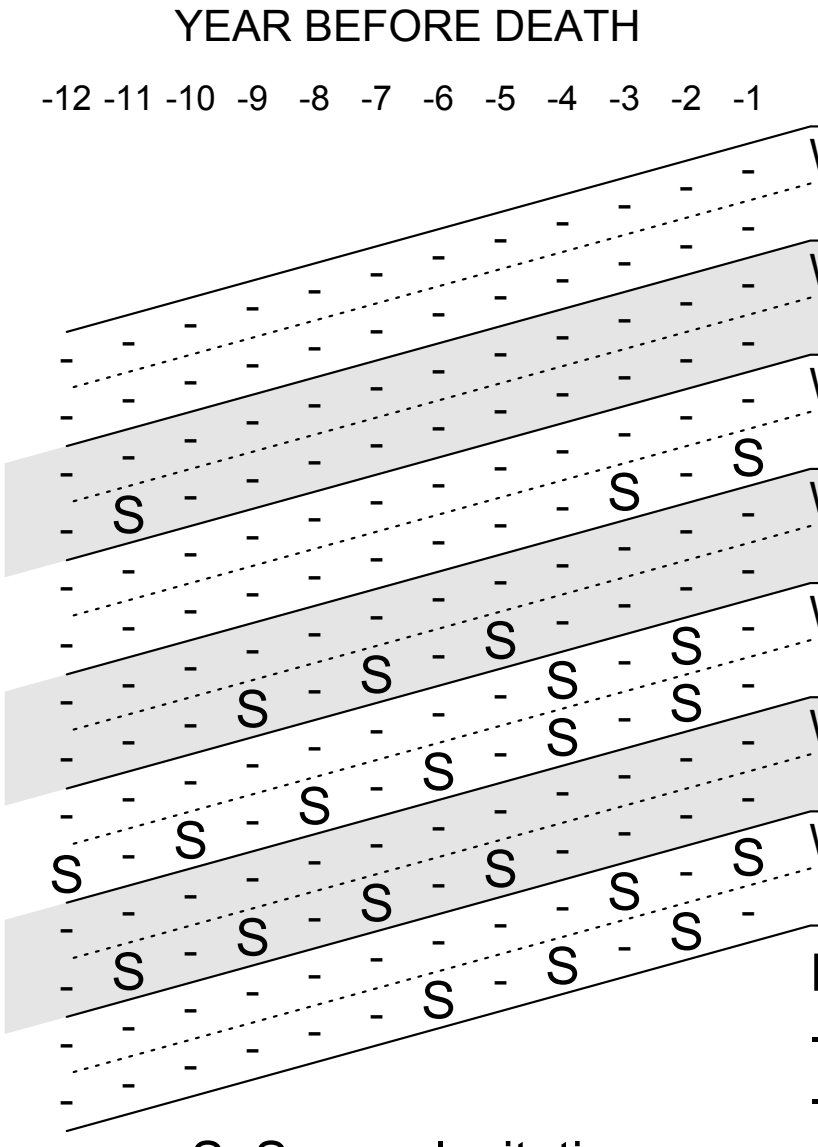
Liu, Hanley, et al. parametrization, in RCT context, easily extended to population-based studies

Single-Round Model and its 3 Parameters





Design Matrix, Mortality Data, Parameter Fitting



	AGE	YEAR	No. Deaths
WEST	80	2003	2
EAST	80	2003	5
WEST	75	2011	7
EAST	75	2011	5
WEST	64	2003	5
EAST	64	2003	2
WEST	68	2009	4
EAST	68	2009	2
WEST	62	2012	6
EAST	62	2012	3
WEST	68	2011	4
EAST	68	2011	5
WEST	56	2011	5
EAST	56	2011	2

} Binomial

S: Screen Invitation

Binomial P = function of
- Region, Relative Population Sizes,
- NUMBER & TIMING of Screens
- IMPACT of each ROUND of SCREENING
- Participation Rate

Some References

1. Miettinen OS, Henschke CI, Pasmantier MW, et al. Mammographic screening: no reliable supporting evidence? *Lancet* 2002;359:404-406. and http://image.thelancet.com/extras/1093web.pdf.
2. * Hanley JA. Analysis of Mortality Data From Cancer Screening Studies: Looking in the Right Window. *Epidemiology* 2005; 16: 786-790.
3. * Hanley JA. CANNeCTIN Clinical Trials Methodology Seminar Series. Videoconference April 9, 2010. Slides: http://www.cannectin.ca/ . Video: Archived Events, http://webcast.otn.ca/
4. * Hanley JA. Mortality reductions produced by sustained prostate cancer screening have been underestimated. Journal of Medical Screening. *J Medical Screening* 2010;17:147-151.
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6. * Liu Z, Hanley JA, Strumpf EC. Projecting the yearly mortality reductions due to a cancer screening programme. *Journal of Medical Screening*. 2013; 20(3): 156-64. doi:10.1177/0969141313504088
7. Weedon-Fekj$\frac{3}{4}$r, et al. Modern mammography screening and breast cancer mortality: population study BMJ 2014;348:g3701 doi: 10.1136/bmj.g3701 (Published 17 June 2014)
8. * Liu Z, Hanley JA, Saarela O, Dendukuri N. A conditional approach to measure mortality reductions due to screening. 2015: *International Statistical Review*

* `http:www.medicine.mcgill.ca/epidemiology/hanley/`
(reprints/talks)

FUNDING, CO-ORDINATES, DOWNLOADS

Natural Sciences and Engineering Research Council of Canada

Le Fonds québécois de la recherche sur la nature et les technologies

Canadian Institutes of Health Research (2011-2015)

.....

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http://www.mcgill.ca/epi-biostat-occh/grad/biostatistics/

EXTRA SLIDES

Why do statisticians commonly limit their inquiries to Averages?

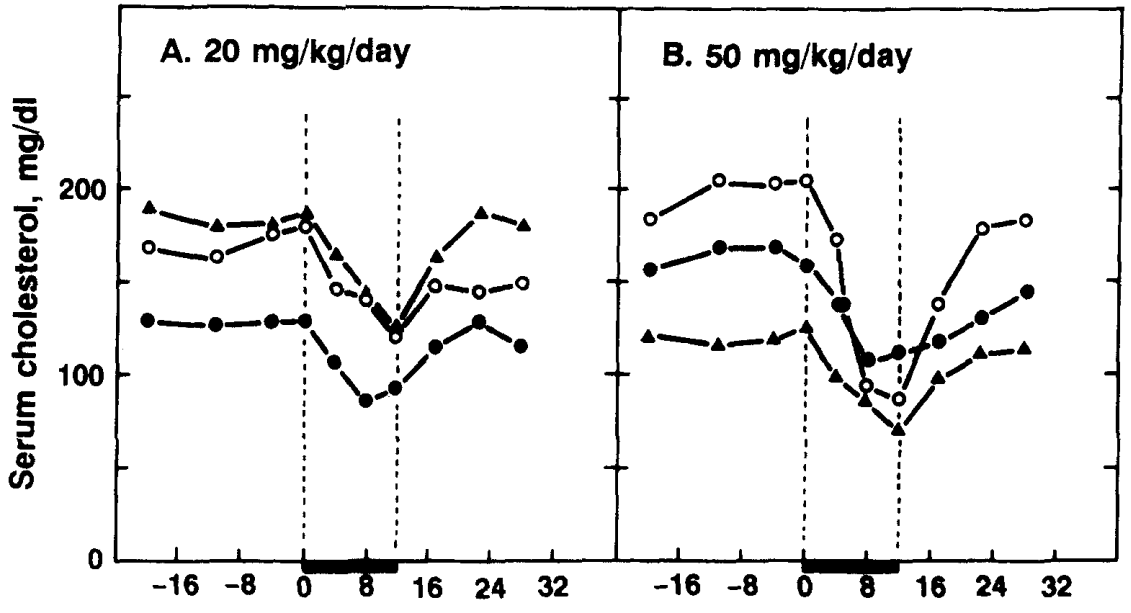
F. Galton, Natural Inheritance, 1889.

“It is difficult to understand why statisticians commonly limit their inquiries to Averages, and do not revel in more comprehensive views.

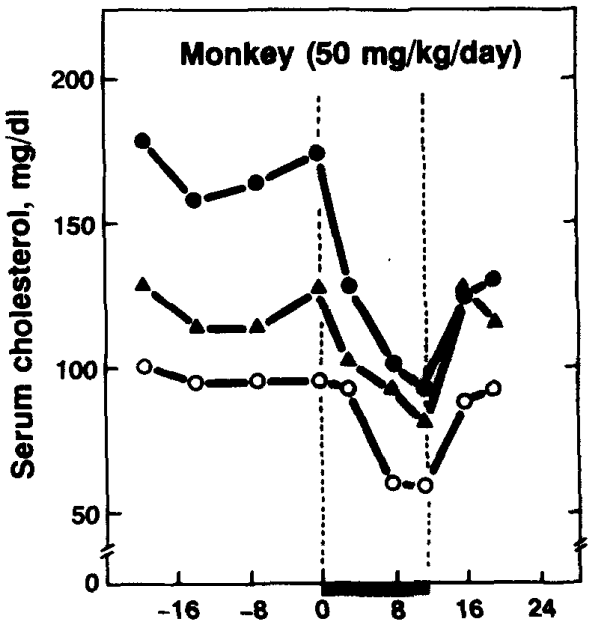
Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if its mountains could be thrown into its lakes, two nuisances would be got rid of at once.”

Timing of cholesterol reductions produced by statins

3 dogs at 20 mg/kg/day; 3 at 50 mg/kg/day

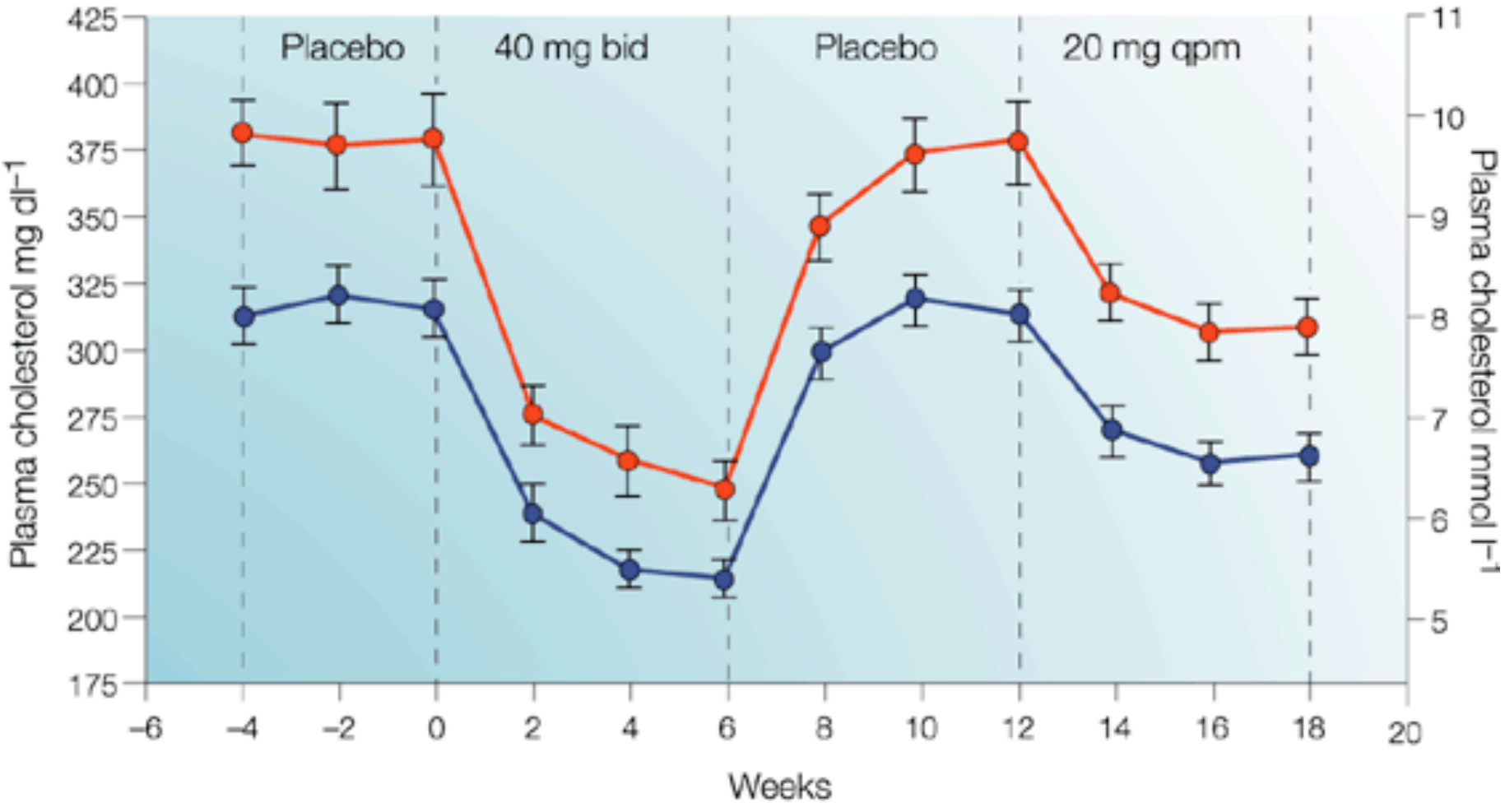


3 monkeys at 50

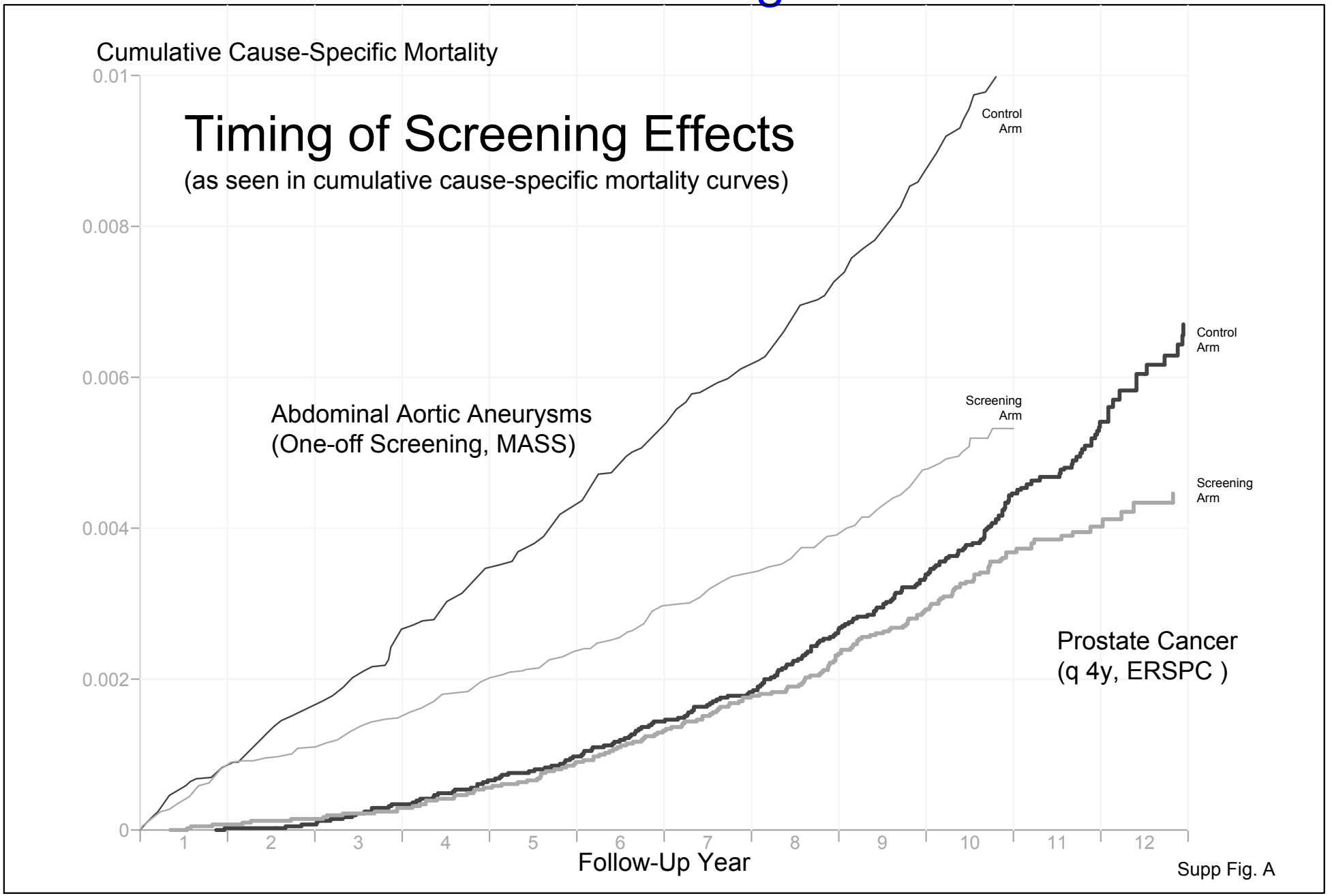


Timing of cholesterol reductions produced by statins

Humans



The loneliness of the long-distance trialist



Supp Fig. A