Cancer ‘screening’: principles, programs, performance

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Epidemiology Seminar Series
McGill University
2019-10-21

www.biostat.mcgill.ca/hanley/screening

OUTLINE

- Principles
- Programs
- Estimands `https://www.latin-is-simple.com/en/vocabulary/verb/3691/`
  ~~unprincipled 1-number answers based on proportional hazards model~~

How many screening tests have you undergone?

https://www.uptodate.com/contents/screening-tests-in-children-and-adolescents

https://www.merckmanuals.com/en-ca/professional/pediatrics/health-supervision-of-the-well-child/screening-tests-for-infants,-children,-and-adolescents

https://www.canada.ca/en/indigenous-services-canada/services/first-nations-inuit-health/health-care-services/nursing/clinical-practice-guidelines-nurses-primary-care/pediatric-adolescent-care/chapter-3-pediatric-prevention-health-maintenance.html#a224

https://www.newbornscreening.on.ca

https://www.chudequebec.ca/patient/maladies,-soins-et-services/m-informer-sur-les-soins-et-services/programme-quebecois-de-depistage-neonatal-sanguin.aspx

https://naitreetgrandir.com/fr/etape/0_12_mois/developpement/nouveau_ne/fiche.aspx?doc=naitre-grandir-bebe-nouveau-ne-test-depistage

Broader meanings of ‘screening’

the verb ‘to screen’: (OED link)

I. To protect, conceal, or divide, and related senses

II. To sieve, filter; to evaluate, analyse. [9 and 11]

III. To project on to or display on a screen, and related senses.

Phrasal verbs
With adverbs in specialized senses. to screen out

a. To obtain, remove, or separate (something, esp. impurities or unwanted material) from a substance, mixture, etc., using a large sieve or other filter. Cf. sense 9a.

b. To identify, select, exclude, or remove by means of screening (screening n. 8). Cf. sense 12.

1931 Milbank Memorial Fund Q. Bull. 9 135/2 A test of the entire group by tuberculin – to screen out those with significant tuberculous infection.

1968 International Herald Tribune 3 Sept. 7/3 The FBI has improved its methods of screening out inaccurate reporting.

2007 Independent 26 Feb. 30/3 Cracking down on bars and clubs which fail to screen out underage drinkers, often closing them down by court order for weeks at a time.

……

Medical concept of screening: Stedman’s Medical Dictionary; Miettinen et al., 2019

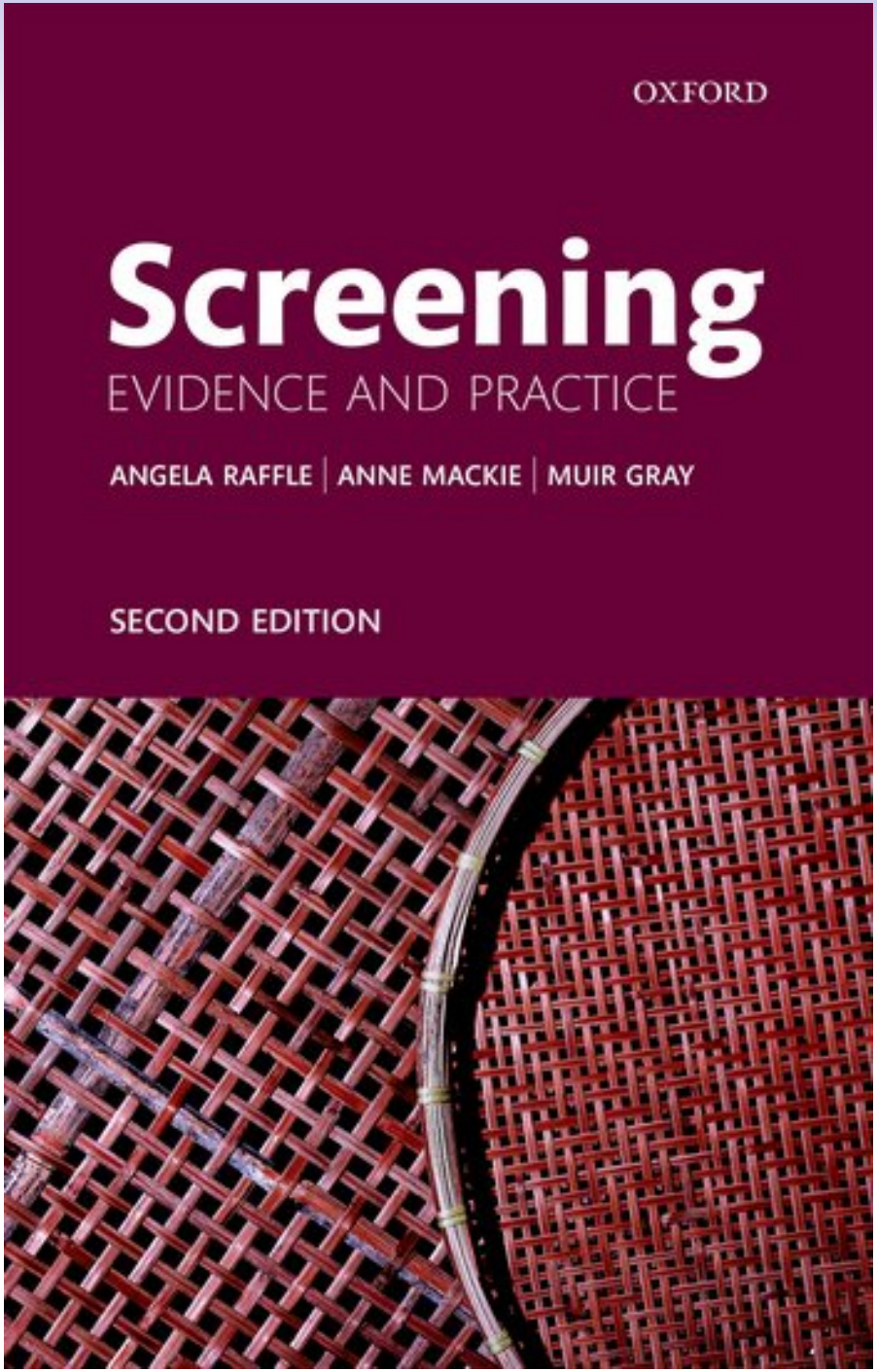
TEXTBOOK: Screening in Chronic Disease. Alan Morrison

1992 Edition
https://books.google.ca/books/about/Screening_in_Chronic_Disease.html?id=HSoQAQAAMAAJ&redir_esc=y

Early detection, or screening, is a common strategy for controlling chronic disease, but little information has been available to help determine which screening procedures are worthwhile, and how often, or to whom, they should be applied. This book presents the epidemiological methods that can be used to answer such questions. The book focuses on the description and measurement of changes in the natural history of disease brought about by early detection and treatment. Valid methods for assessing the usefulness of screening in reducing morbidity and mortality are emphasized and both ...

1985 Edition https://mcgill.on.worldcat.org/oclc/11030220 and https://www.amazon.ca/Screening-Chronic-Disease-Alan-Morrison/dp/0195035054

This timely book presents the epidemiologic methods that can be used to determine when screening procedures are indicated, focusing on how to describe and measure changes in the natural history of disease brought on by early treatment, lead time, and prognostic selection. The author explains how to assess the usefulness of screening in reducing morbidity and mortality, and provides thorough descriptions of the experimental and case-control approaches. "An intelligent account of the role ...



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eBook: https://oxfordmedicine-com.proxy3.library.mcgill.ca/view/10.1093/med/9780198805984.001.0001/med-9780198805984

Preface

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.

Unfortunately, many screening services either have been introduced on the basis of inadequate evidence that they do more good than harm at reasonable cost or, even if introduced on good evidence, are managed so badly that the efficacy demonstrated in research is not translated into effectiveness in practice. This results in a waste of resources and in harm to those individuals who accept the offer of screening.

Clinicians' and public health practitioners' viewpoints on screening

A **clinician** is faced with a patient in front of them suffering advanced disease. They inevitably think 'if only this person had been tested 10 years ago they could have had intervention before symptoms and they would be well.' Screening seems an obvious thing to do.

A **public health practitioner** is faced with a population in front of them – imagine the crowd at a vast festival, for example. They are searching for the needle in the haystack – the tiny number of people who can be found at the moment of opportunity for altering the course of disease. Yet everyone must be tested and nobody must be harmed.

Therefore the public health physician, who does not have a time machine to travel back in time and intervene in that one future patient, is more cautious about screening. [RMM Box 2.3]

“Key events for screening...”:

- Two reports were published, both in 1968. One was from the Nuffield Provincial Hospitals Trust (1968) the other from the World Health Organization (Wilson and Jungner 1968). These began the process of questioning some of the accepted beliefs about screening.
- Two randomized control trials were established, one at Kaiser Permanente in 1964 (Friedman et al. 1986), the other in south-east London in 1967 (South-East London Study Group 1977), with the aim of measuring the impact of (the) periodic examination on mortality rates, on general health, and on use of health services.

The Nuffield Provincial Hospitals Trust (1968)

bacteriuria in pregnancy	breast cancer	iron deficiency anaemia	deafness in childhood	diabetes mellitus
glaucoma	cervical cancer	phenylketonuria	pulmonary tuberculosis	rhesus haemolytic disease of newborn.

Their conclusion: **six** of the ten programmes they examined were 'seriously deficient', meaning that it was not possible to say whether the screening programmes did more good than harm. Even for the **four** that did have valid evidence (deafness, phenylketonuria, tuberculosis, and rhesus haemolytic disease), the authors found important gaps in the available information. The overall conclusion, summarized in the Preface, was:

> *public funds can be, and it seems may already have been, diverted from fields of certain benefit to procedures which are not proved and possibly harmful*
>
> *Nuffield Provincial Hospitals Trust (1968) p. viii.*

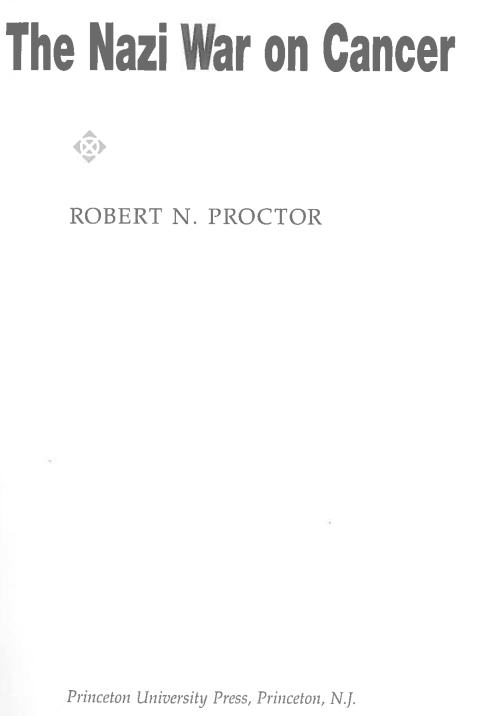
Wilson and Jungner's 'guides to planning case finding'

Wilson and Jungner reviewed most of the specific conditions for which screening programmes had been claimed to bring benefit, and found problems with almost all of them. They set out ten tentative principles, which they called 'guides to planning case finding'. We have listed these ten principles, as they appear in the original 1968 publication.

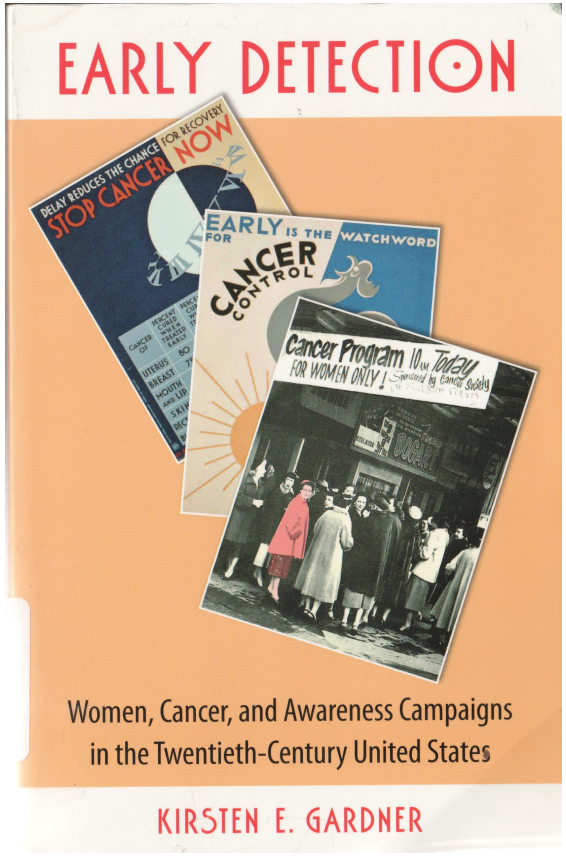
'Guides to planning case-finding' [Max Wilson and Gunnar Jungner (1968) pp. 26 - 27]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a 'once and for all' project.

Early Detection of Cancer – Early On

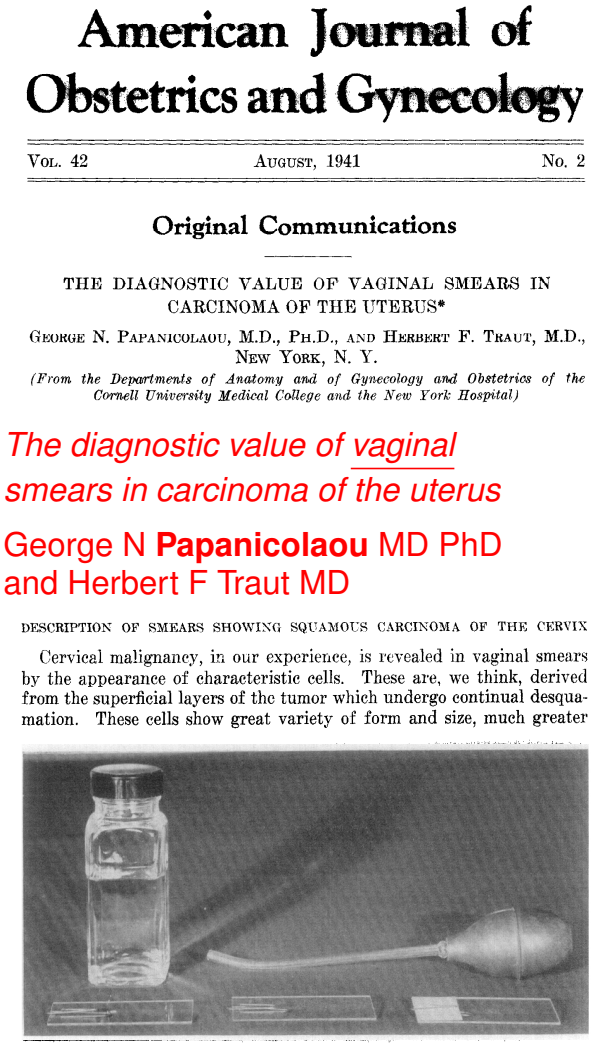


Ch. 2. Early Detection & Mass Screening
Ch. 4. Occupational Carcinogenesis
Ch. 5. The Nazi Diet
Ch. 6. The Campaign against Tobacco [incl. 1939 'case-control' study by Franz Müller]



1913: American Society for the Control of Cancer formed [out of American Gynecological Society]

1940s: American Cancer Society



The diagnostic value of vaginal smears in carcinoma of the uterus

George N **Papanicolaou** MD PhD and Herbert F Traut MD

1945: cervical smears, Ayre spatula

Cancer Screening: Technologies, Trials

Organ	Technology	Major Trials
Uterine Cervix	'Pap', HPV	
Female Breast	Physical exam, mammography, MRI	US(NYC), Sweden, Canada, UK
Neuroblastoma	urine [catecholamine metabolites]	(Japan), Quebec['89.05.01-'94.04.30] Germany
Colon	FOBT, FIT, -scopy	Minnesota, UK, PLCO
Prostate	DRE, PSA	Quebec, Sweden, PLCO, ERSPC
Lung	X-Ray, CT	Mayo Clinic, PLCO, NLST, NELSON
Ovary	serumCA125, transvaginal ultrasound	PLCO, UKCTOCS
Pancreas, Thyroid Skin, Mouth, . . .		

Benefits and harms
(& the role of time)

"*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)

Large variation in reports of 'the good' because first principles of screening have been ignored

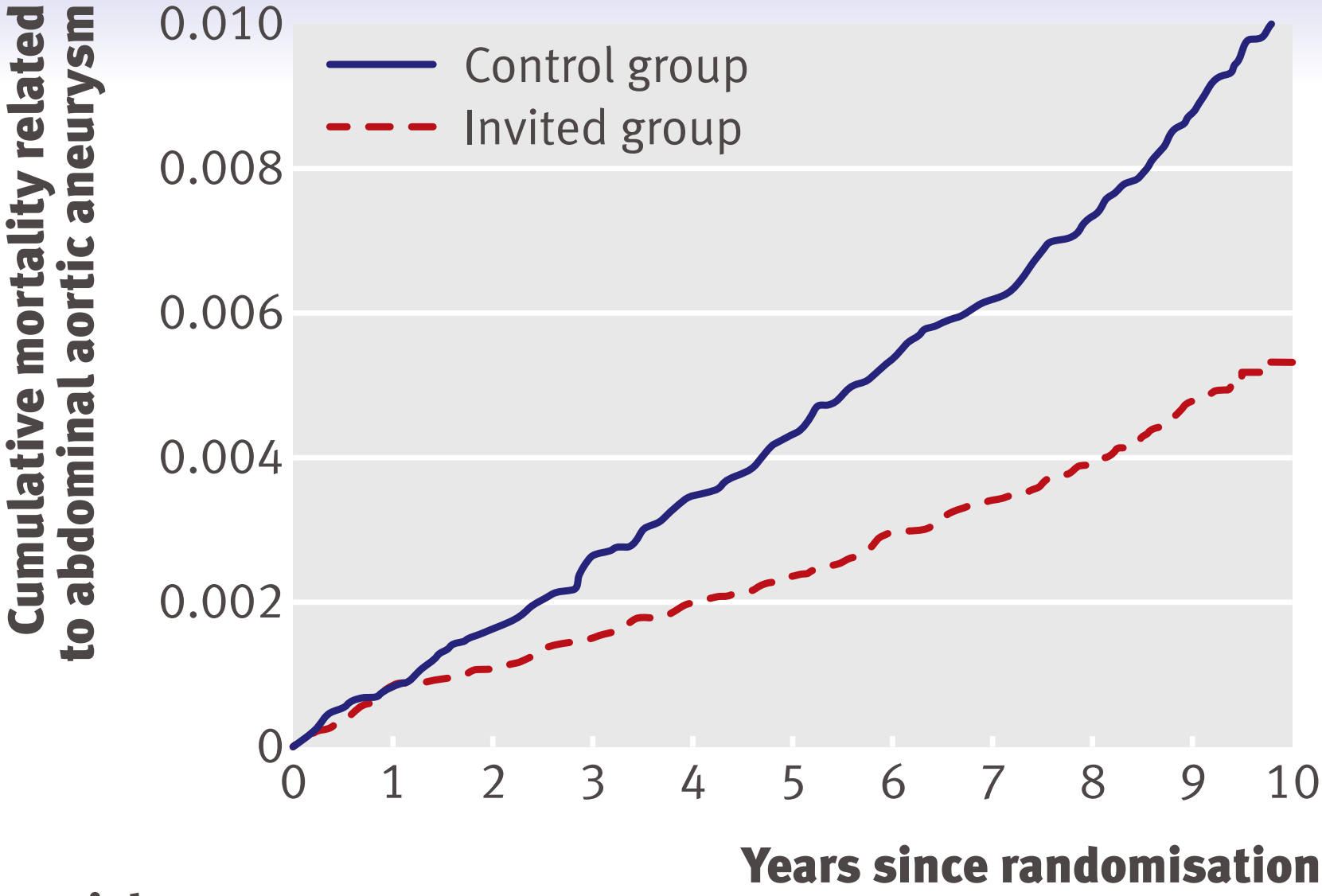
- **Time** (early detection) — e.g.: trials
- **Who** might benefit (early detection) – e.g.: populations

Time-pattern in reduction(s) in rates

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

↓ virtually immediate, and sustained

✓1-number summary from PH model

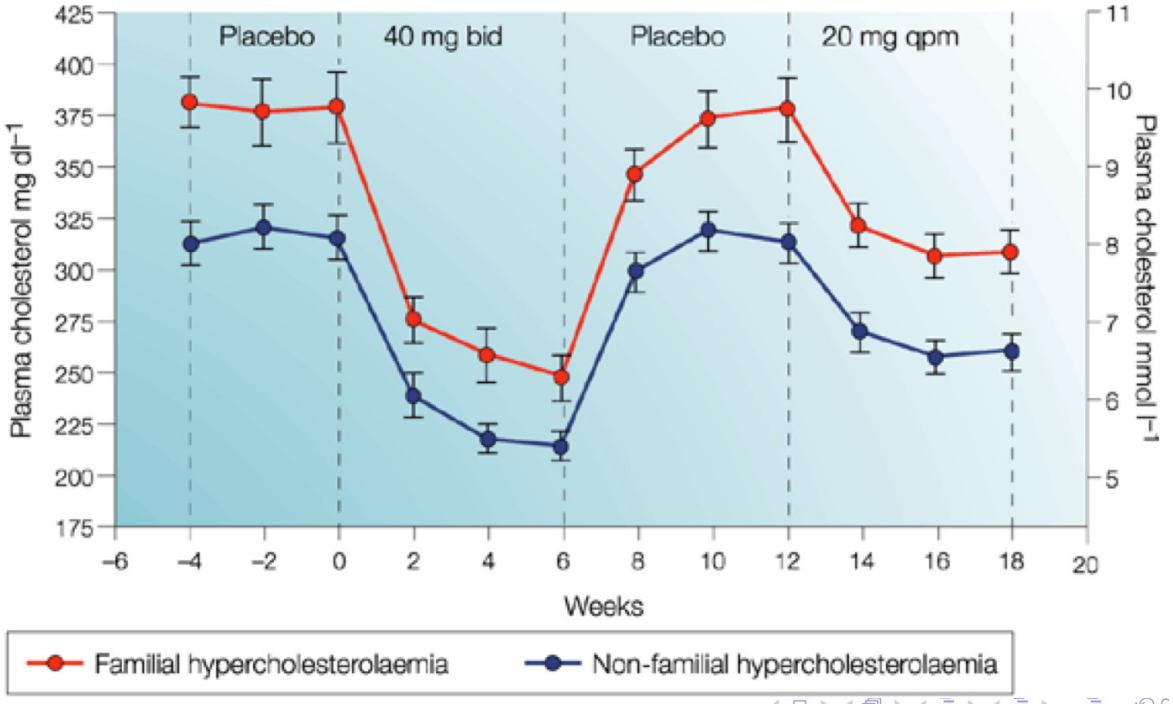


Men at risk

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

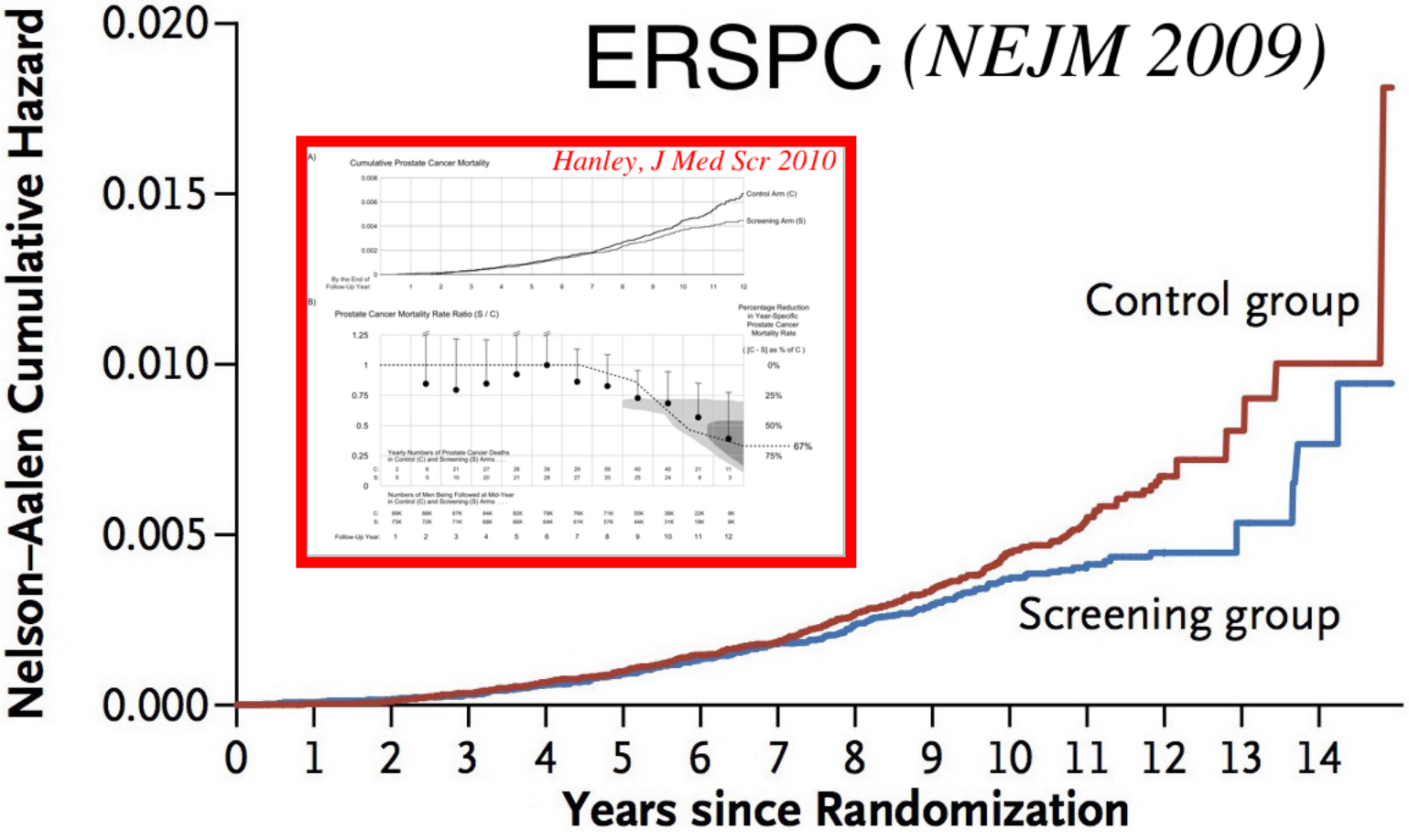
Time-pattern in reduction(s) in rates/levels

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



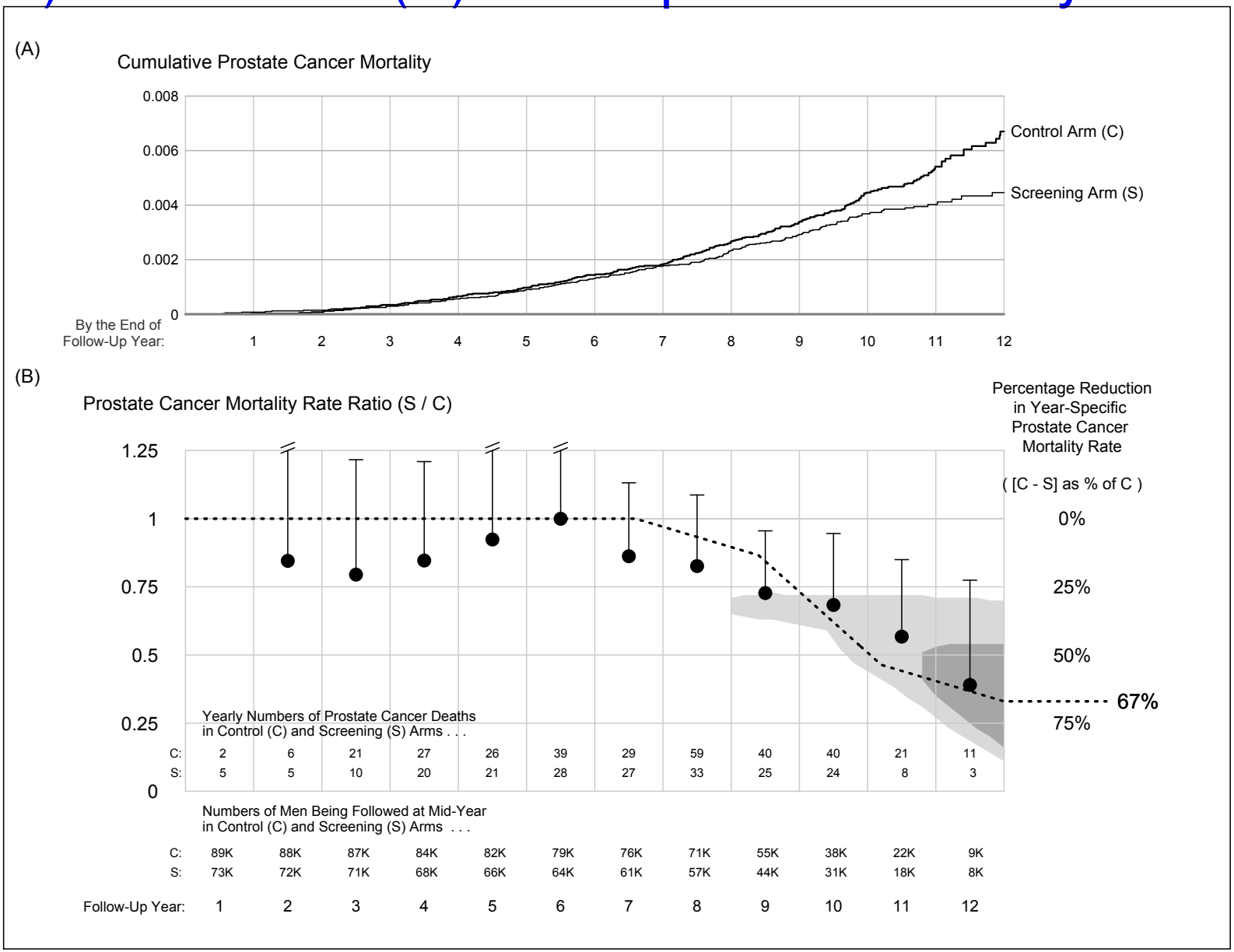
↓ **disappears when agent removed**

PROSTATE cancer screening: a '1-number' reduction



"Average f.-up: 8.8y. **Rate ratio** for death from prostate cancer in screening group:' **0.80** → '**AVERAGE**' reduction of **20**%."

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



Hanley, *J Medical Screening*, 2010.

FOBT screening for COLON cancer – Minnesota Trial 1976-2008

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

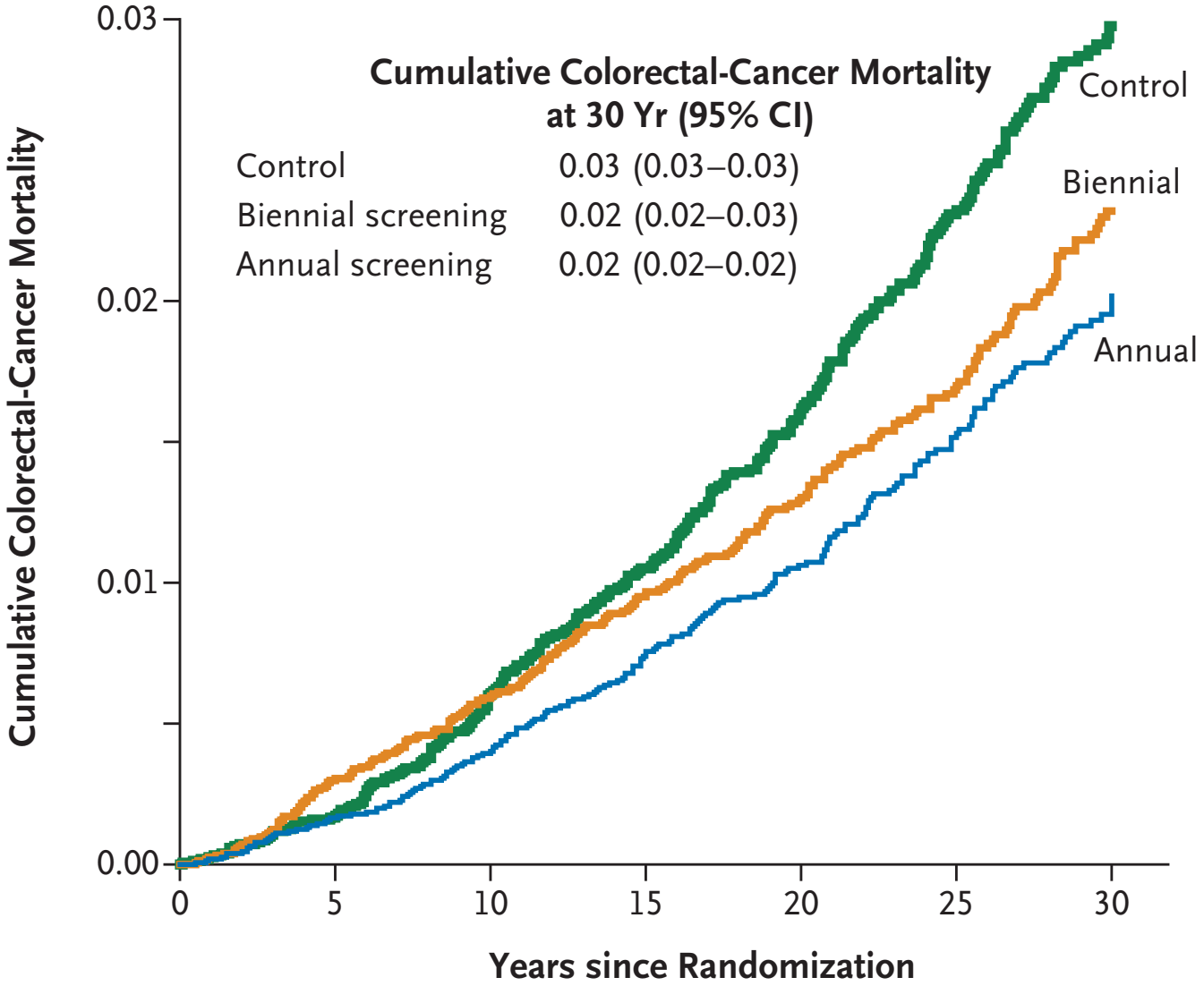
FOBT screening for COLON cancer – Minnesota Trial 1976-2008

RESULTS

Through 30 years of follow-up, 33,020 participants (70.9%) died. A total of 732 deaths were attributed to colorectal cancer: 200 of the 11,072 deaths (1.8%) in the annual-screening group, 237 of the 11,004 deaths (2.2%) in the biennial-screening group, and 295 of the 10,944 deaths (2.7%) in the control group. Screening reduced colorectal-cancer mortality (relative risk with annual screening, 0.68; 32% onfidence interval [CI], 0.56 to 0.82; relative risk with biennial screening, 0.78; 22% , 0.65 to 0.93) through 30 years of follow-up. No reduction was observed in all-cause mortality (relative risk with annual screening, 1.00; 95% CI, 0.99 to 1.01; relative risk with biennial screening, 0.99; 95% CI, 0.98 to 1.01). The reduction in colorectal-cancer mortality was larger for men than for women in the biennial-screening group (P=0.04 for interaction).

CONCLUSIONS

The effect of screening with fecal occult-blood testing on colorectal-cancer mortality persists after 30 years but does not influence all-cause mortality. The sustained reduction in colorectal-cancer mortality supports the effect of polypectomy. (Funded by the Veterans Affairs Merit Review Award Program and others.)



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

Radiologists as Statisticians & vice versa

Figure 1. *Rep. Alexander Pirnie, R-NY, draws the first capsule in the lottery drawing held on Dec. 1, 1969. The capsule contained the date. Sept. 14.*

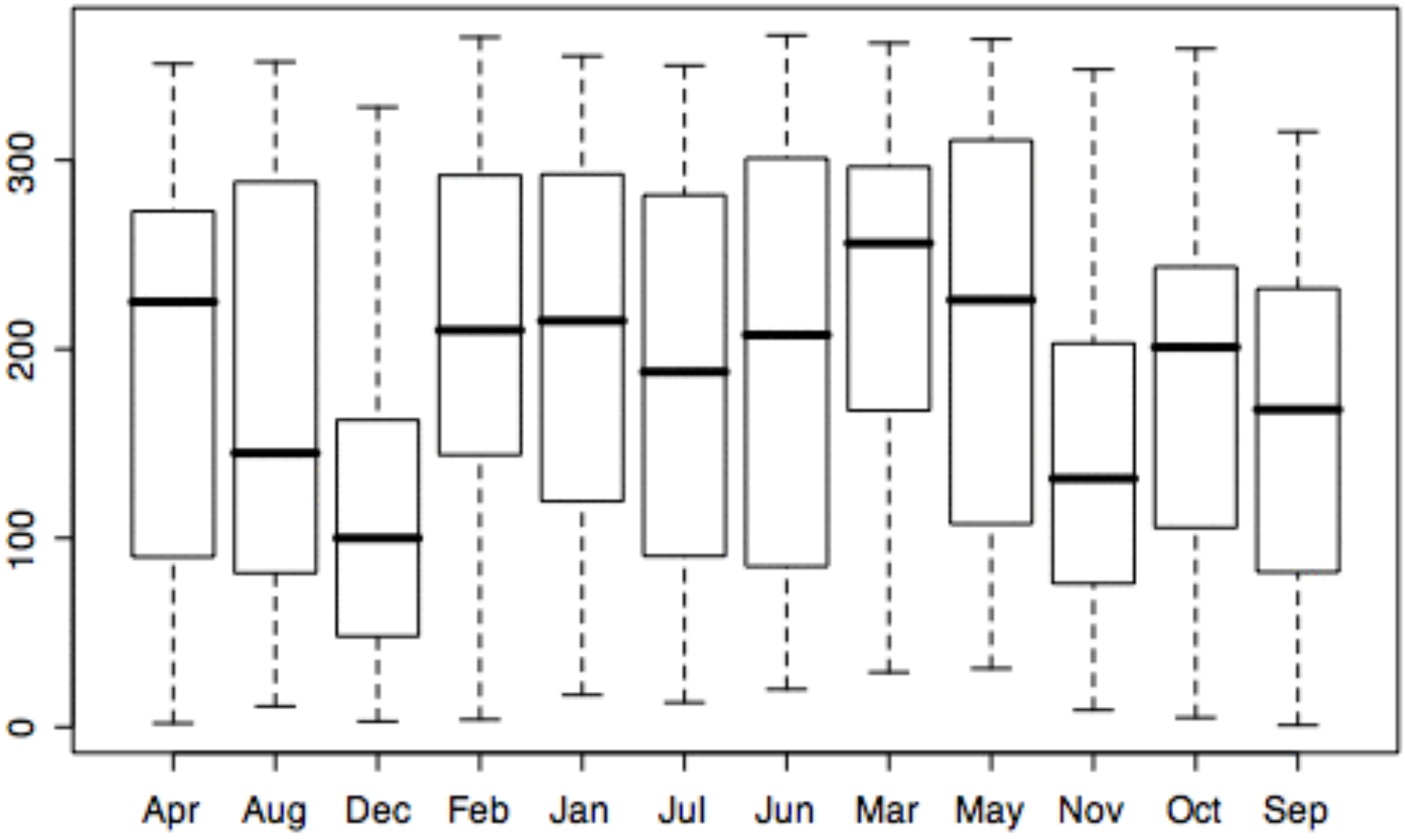


Figure 4. Side-by-side boxplots of draft numbers for each month.

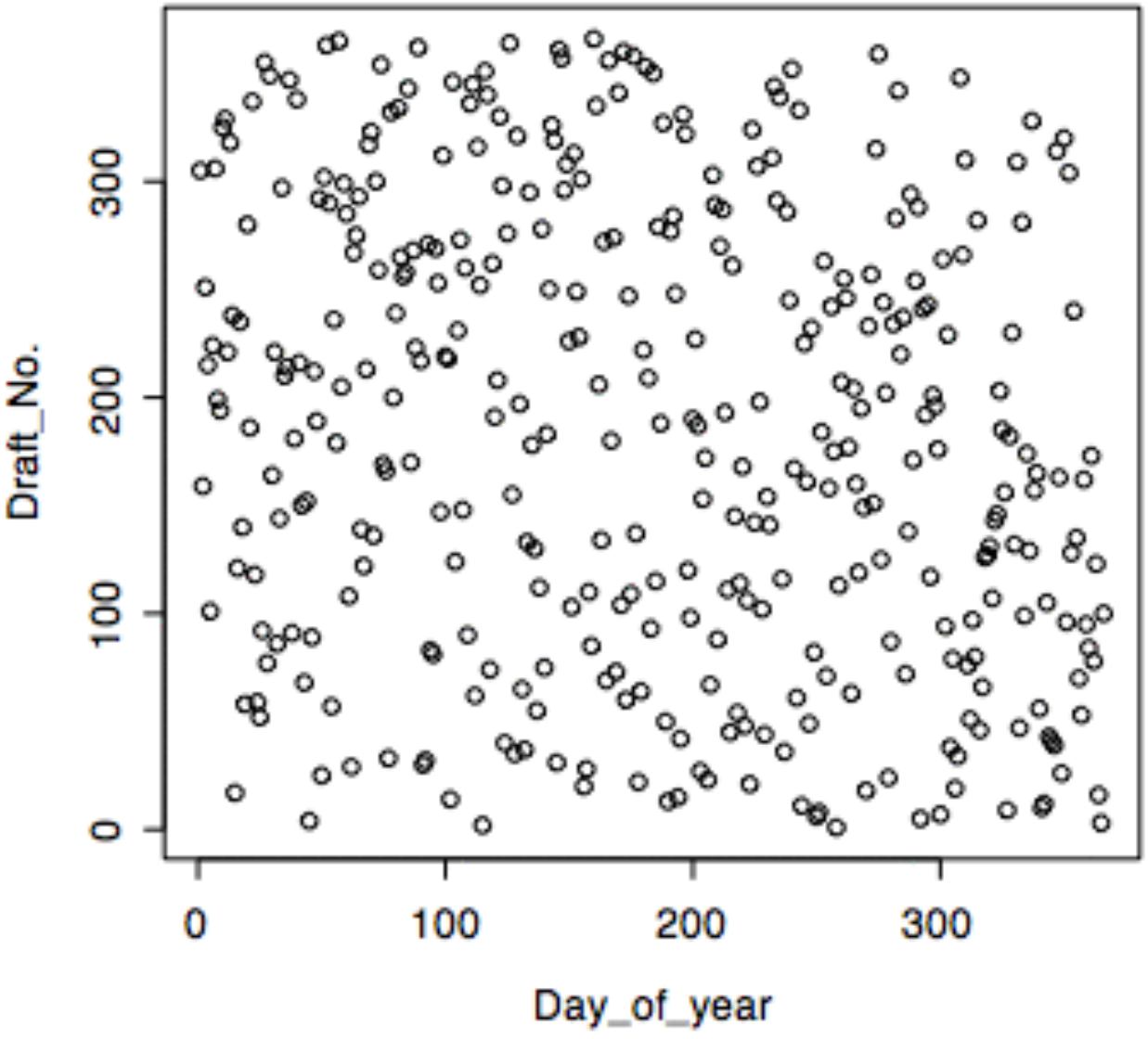


Figure 2. A scatterplot of ***Draft_No.*** *versus* ***Day_of_year****.*

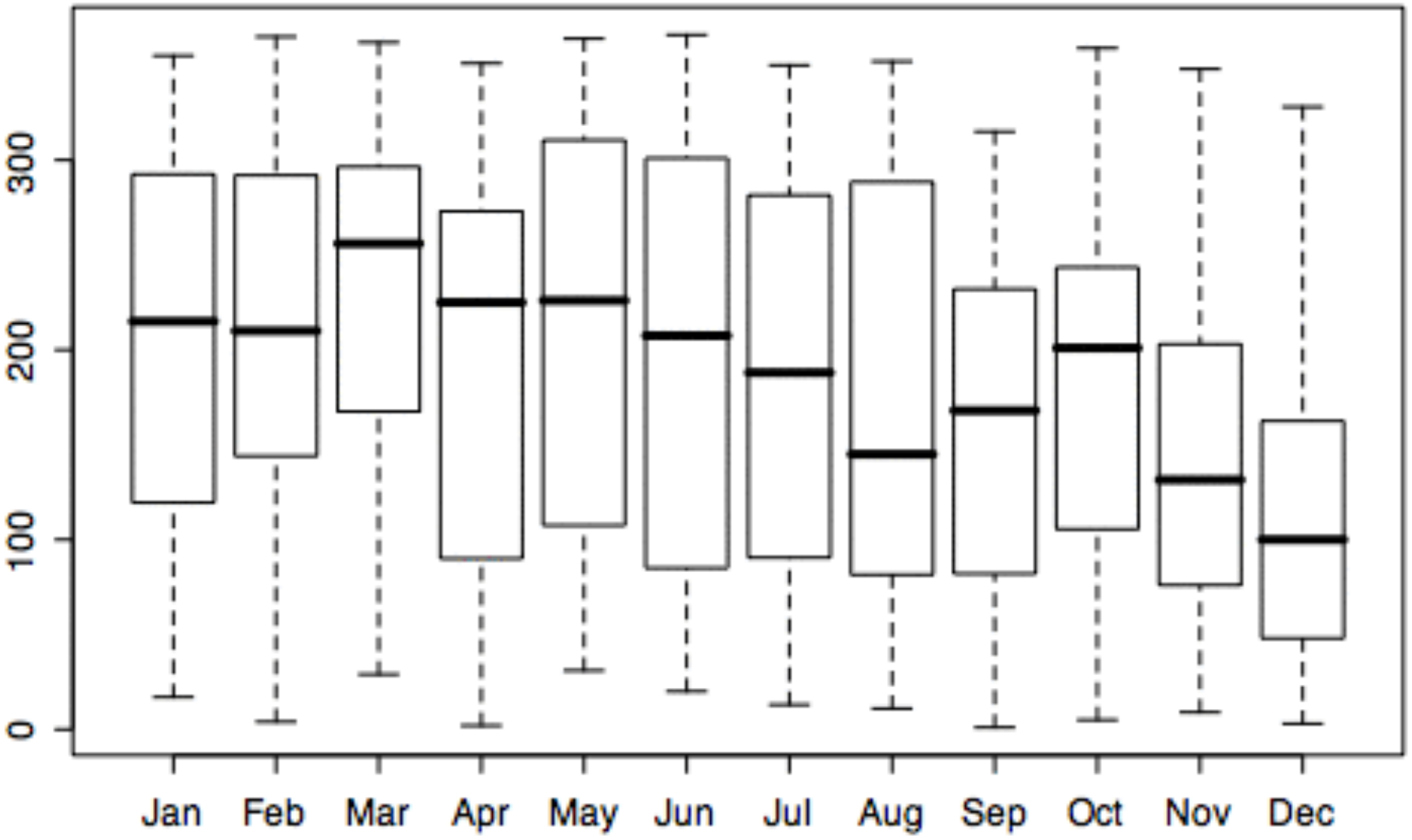


Figure 6. Side-by-side boxplots of draft numbers sorted by month.

Cartoon from David Moore's book Statistics: Concepts and Controversies

http:www.biostat.mcgill.ca/hanley/c678/vietnam.pdf

Statisticians Charge Draft Lottery Was Not Random
By DAVID E. ROSENBAUM Special to The New York Times
New York Times (1857-Current file); Jan 4, 1970; ProQuest Historical Newspapers The New York Times
pg. 66

Statisticians Charge Draft Lottery Was Not Random

By DAVID E. ROSENBAUM
Special to The New York Times

WASHINGTON, Jan. 3—The new draft lottery is being challenged by statisticians and politicians on the ground that the selection process did not produce a truly random result.

The challenge was taken up by the courts this week when a Federal district judge in Wisconsin, James Doyle, agreed to hear a test case on the lottery.

"It may become necessary," the judge warned, "to accept the consequences." By that he meant a new drawing.

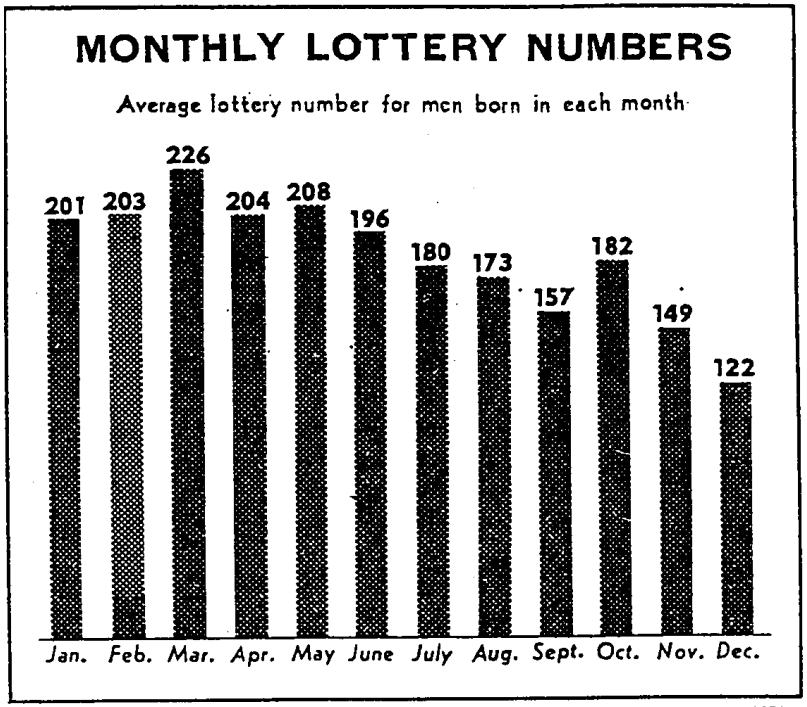
The attacks on the system of selection come at a time when hundreds of thousands of young men have been assigned a spot in the draft sequence and when the first men are about to be inducted under the new lottery.

They threaten to undermine public confidence in the draft and provide an issue for Congressional hearings on the draft scheduled to begin early this year.

New Drawing Ruled Out

A knowledgeable White House official said this week that "discussions that the lottery was not random are purely speculative." He added that there was "no possibility" that there would be another drawing.

The Selective Service official who conducted the lottery Dec. 1 said, "An effort was made to make the thing as fair as



Averages were obtained by adding up total of lottery numbers for month and dividing by number of days in the month. A random system could be expected to produce an average number of 183 or 184 in every month. The lower the number, the better the chances of being drafted.

lection process is 100,000 to 1.

Two graduate students at the University of Wisconsin, David Stodolsky and Carol Falender, believe the probability is 50,000 to 1.

Statisticians at other universities have arrived at similar results.

and February capsules were thoroughly mixed.

The same process was followed with each subsequent month, counting the capsules into the empty side of the box and then pushing them with the divider into the capsules of the previous months.

sules 11 times, the February capsules 10 times and so on, with the November capsules intermingled with others only twice and the December ones only once.

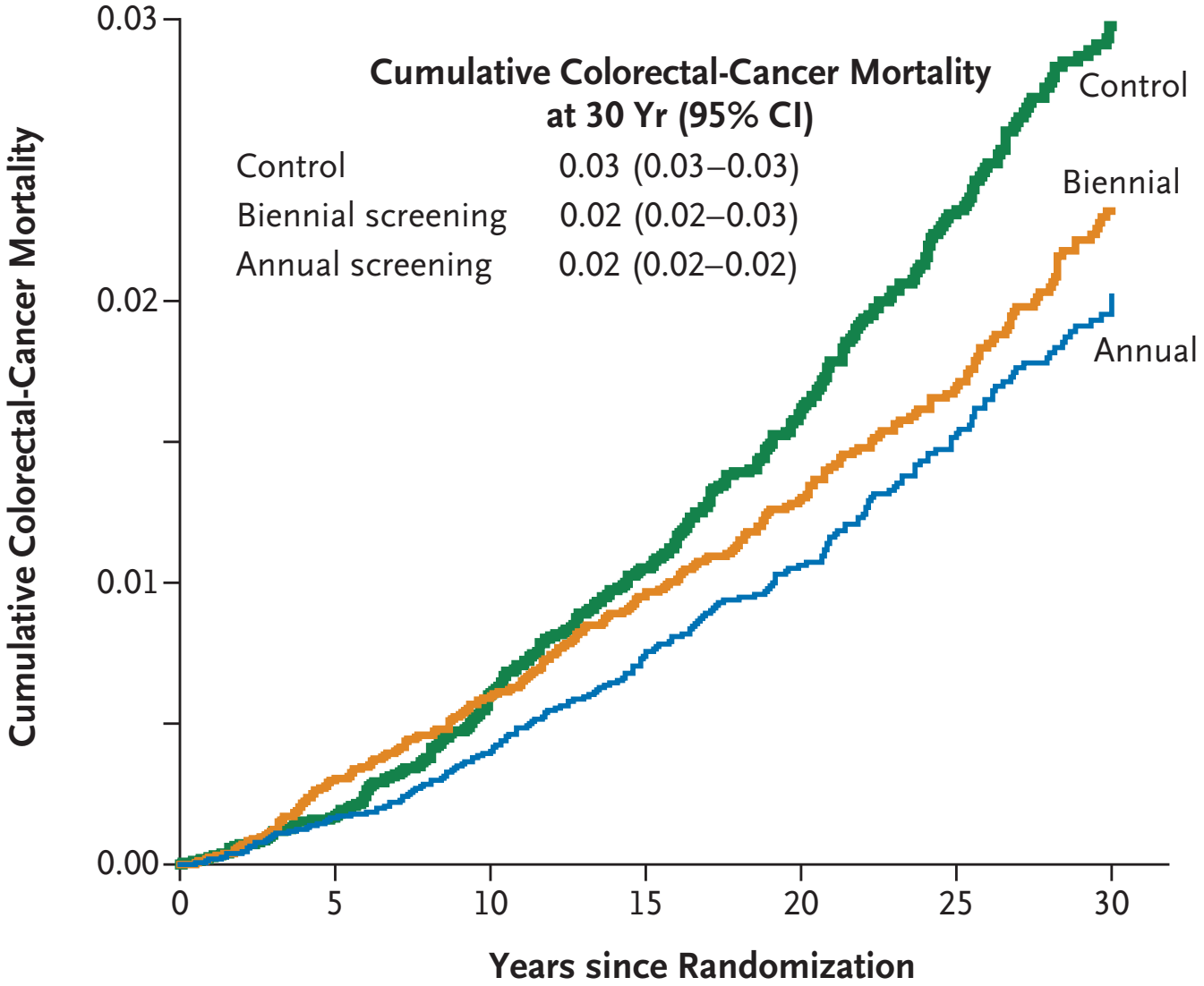
The box was then shut, and Colonel Fox shook it several times. He then carried it up three flights of stairs, a process that Captain Pascoe says further mixed the capsules.

The box was carried down the three flights shortly before the drawing began. In public view, the capsules were poured from the black box into the two-foot-deep bowl.

Captain Pascoe said he did not know which end of the box he poured from. If he poured from the end where the capsules with the early months had been repeatedly shoved, these capsules might have fallen to the bottom of the bowl. Conversely, if he poured from the other end, the later months could have fallen to the bottom. This assumes that the shoving and shaking procedure did not adequately mix the capsules.

Once in the bowl, the capsules were not stirred. The last draft lottery, in 1940, was conducted entirely differently. But officials remembered that when the capsules were stirred then, some of them broke.

The persons who drew the capsules last month generally picked ones from the top, although once in a while they would reach their hand to the



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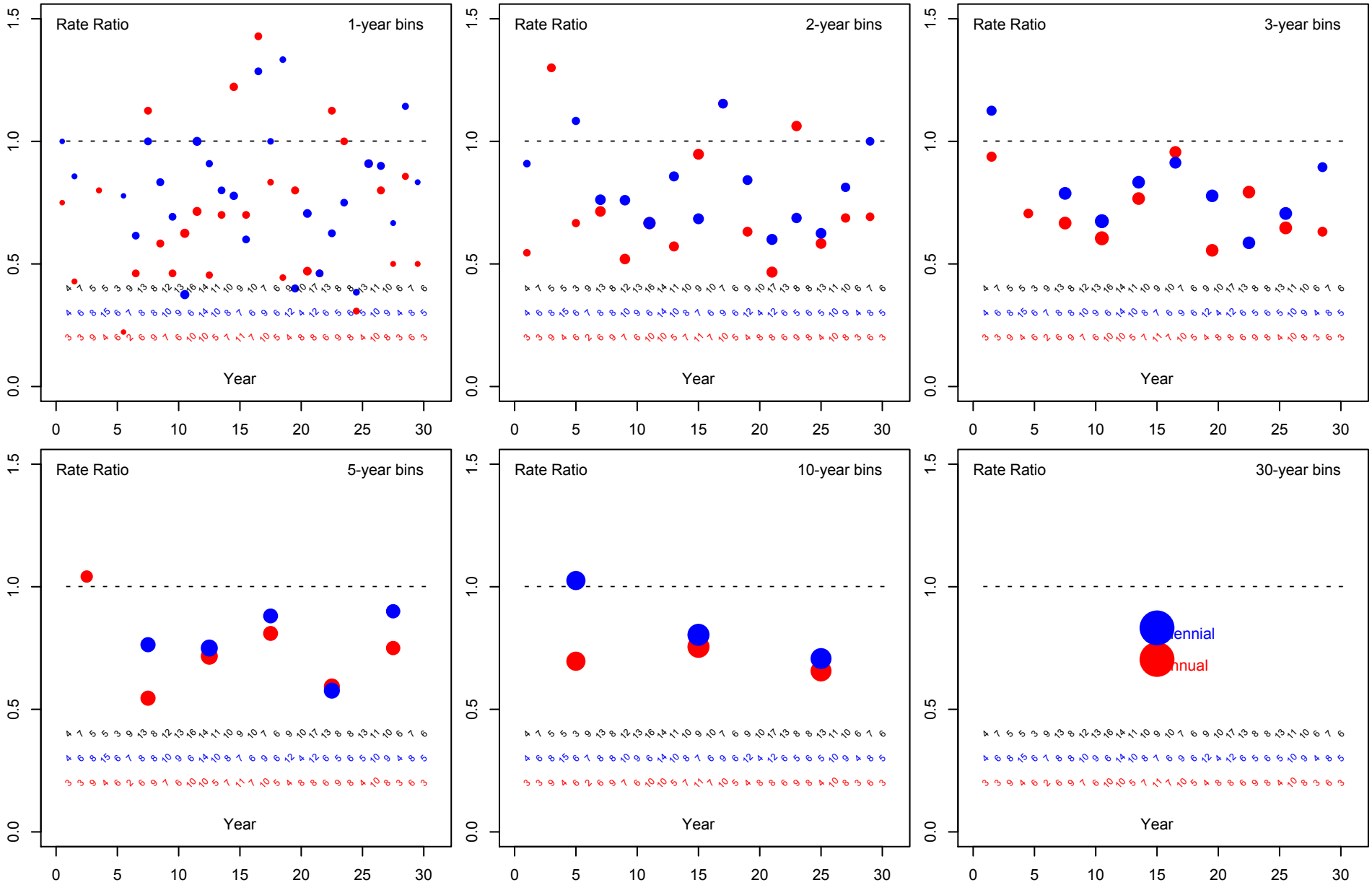
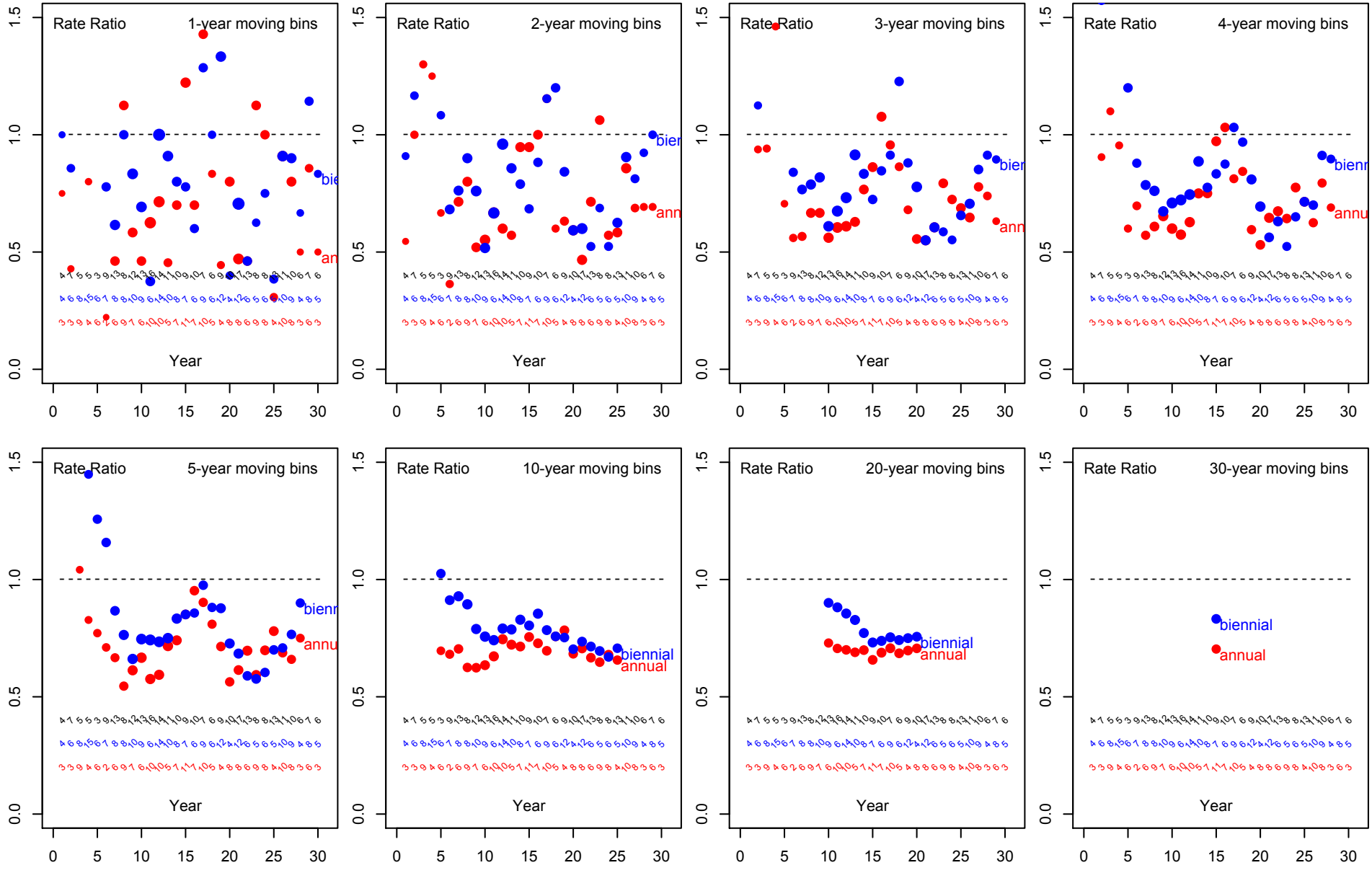
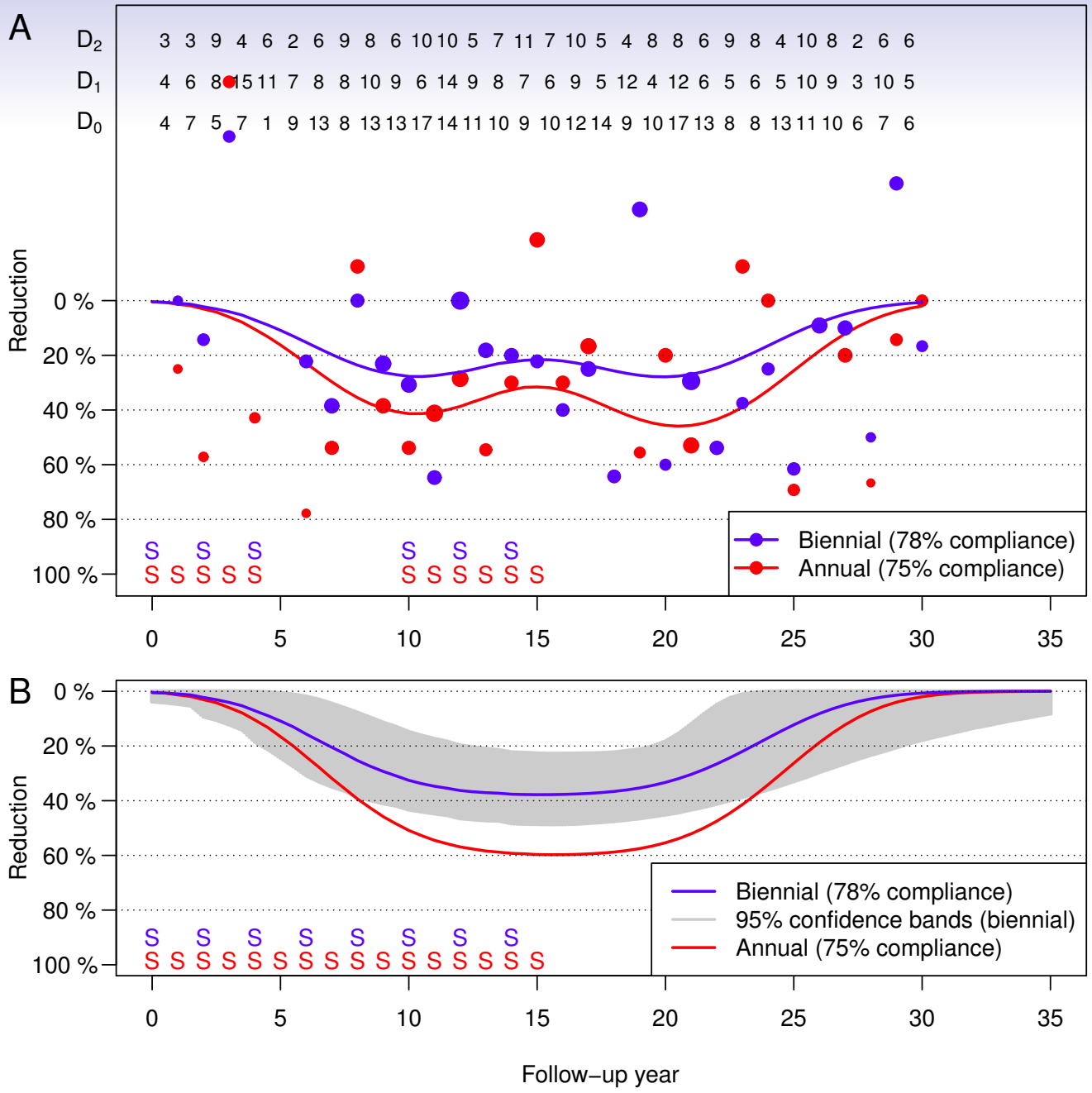
Time-**split** versus time-**lumped** Rate Ratios



Time-**split** versus time-**lumped** Rate Ratios





Liu, PhD Biostatistics, McGill 2014; International Statistical Review 2015.

MAMMOGRAPHY (BREAST CANCER)

POPULATION DATA

Best studies: try to emulate RCT

Cancer Registry: EXCLUDE WOMEN DIAGNOSED BEFORE PROGRAM BEGAN

Original Article

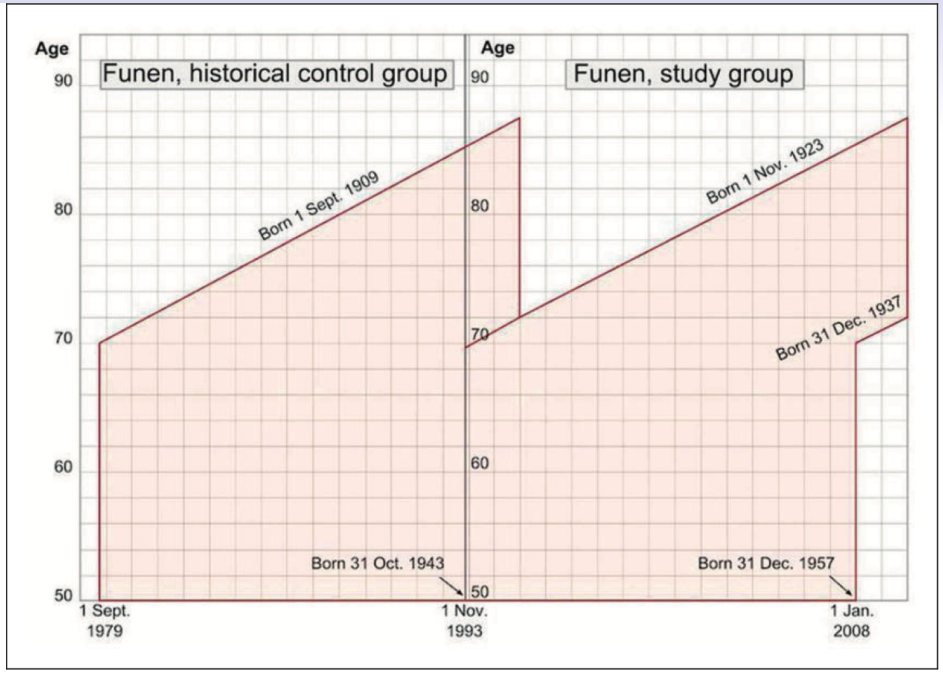
Decline in breast cancer mortality: How much is attributable to screening?

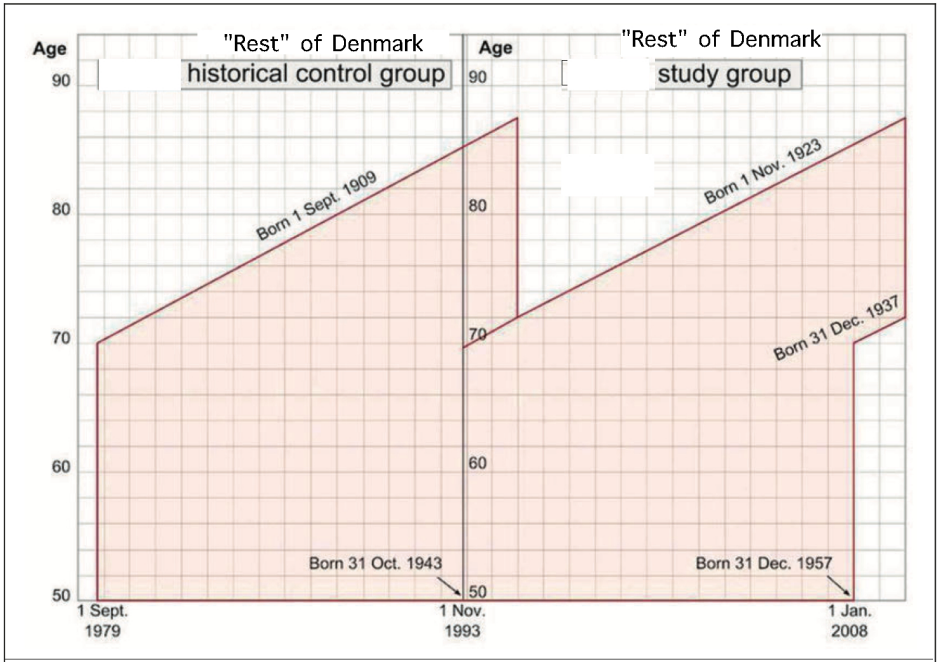
Sisse Helle Njor[1], Walter Schwartz[2], Mogens Blichert-Toft[3] and Elsebeth Lynge[1]

J Med Screen
2015, Vol. 22(1) 20–27

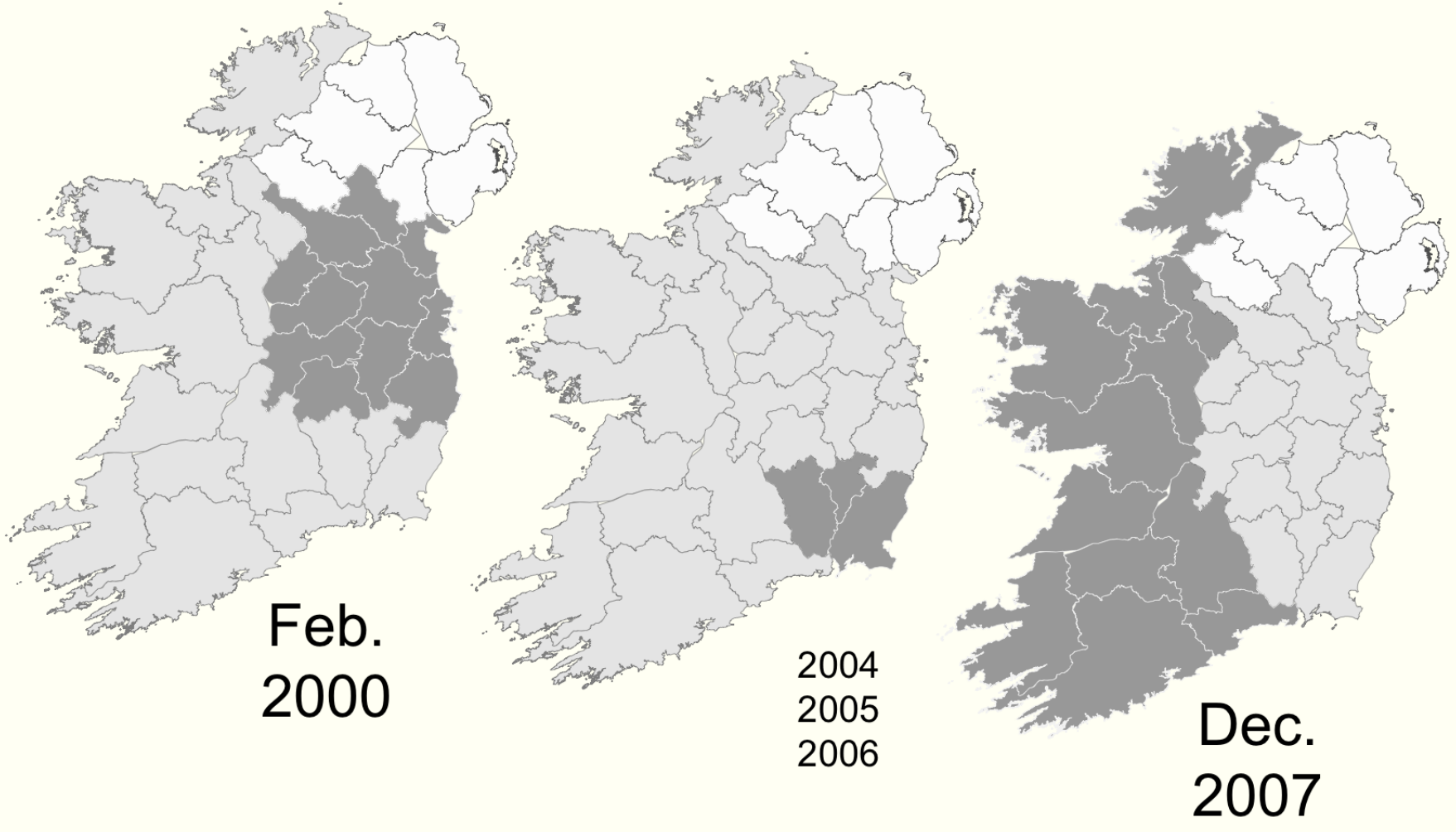
DOI: 10.1177/0969141314563632
msc.sagepub.com
SAGE

FUNEN ↓ 1993





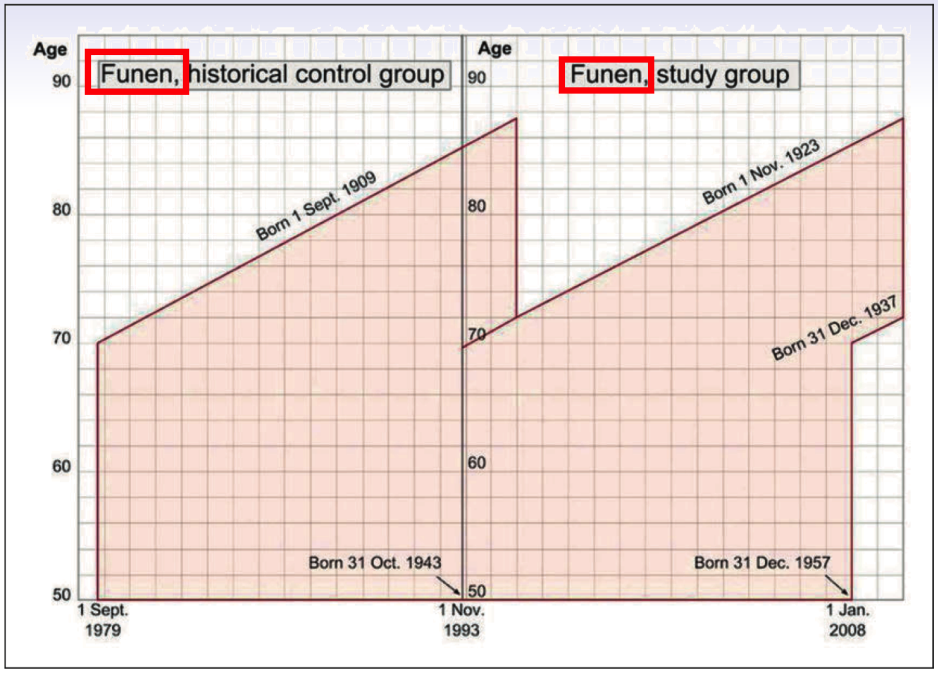
'REST' ↑ 1993

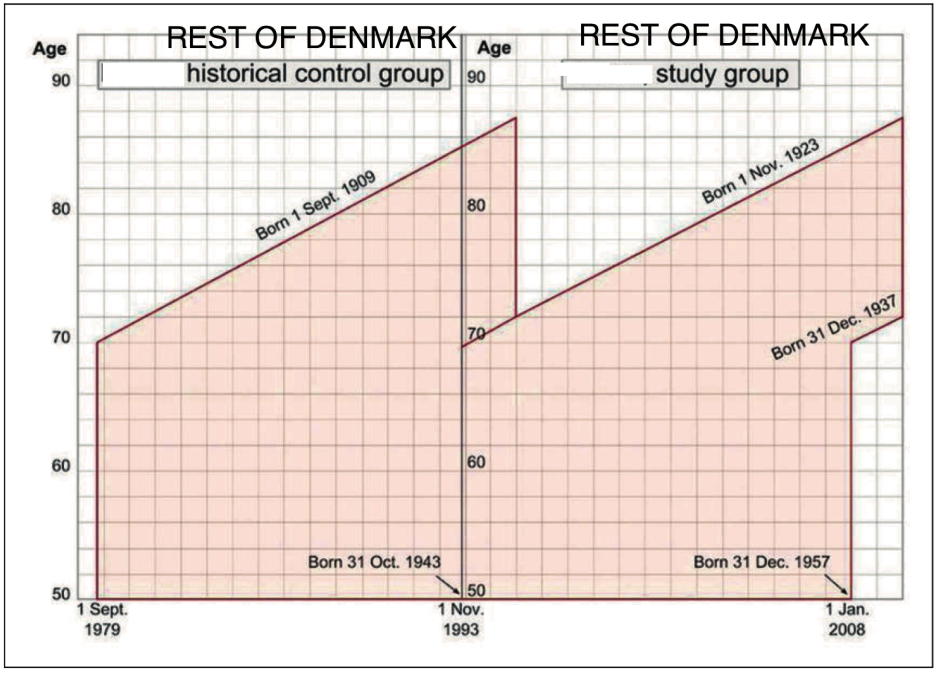


BreastCheck invitations every 2 years to women aged 50-64

RESULTS

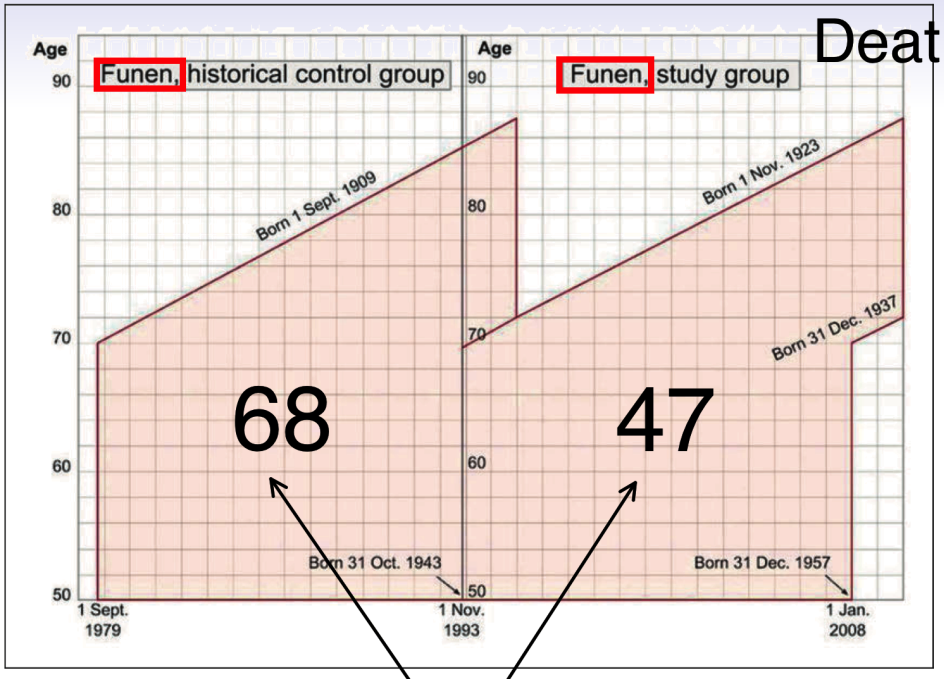
traditional
1-number summaries
(proportional hazards model)

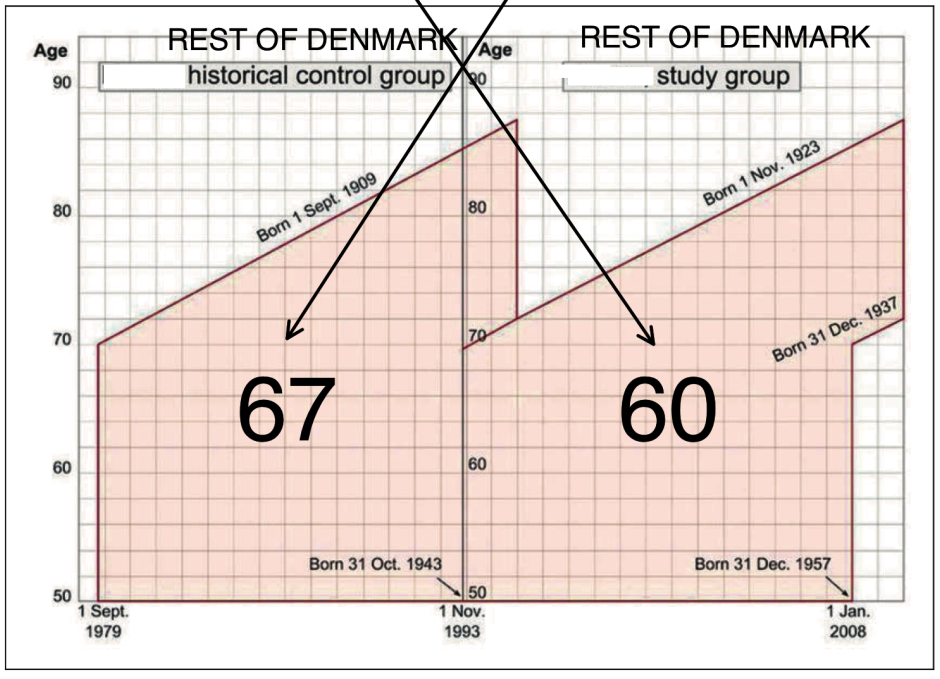

Age
Funen, historical control group
Born 1 Sept. 1909
Born 31 Oct. 1943
1 Sept. 1979
1 Nov. 1993
Age
Funen, study group
Born 1 Nov. 1923
Born 31 Dec. 1937
Born 31 Dec. 1957
1 Jan. 2008
90
80
70
60
50


Age
REST OF DENMARK
historical control group
Born 1 Sept. 1909
Born 31 Oct. 1943
1 Sept. 1979
1 Nov. 1993
Age
REST OF DENMARK
study group
Born 1 Nov. 1923
Born 31 Dec. 1937
Born 31 Dec. 1957
1 Jan. 2008
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☯]

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OPEN ACCESS

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Editor: Sabine Rohrmann, University of Zurich, SWITZERLAND

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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

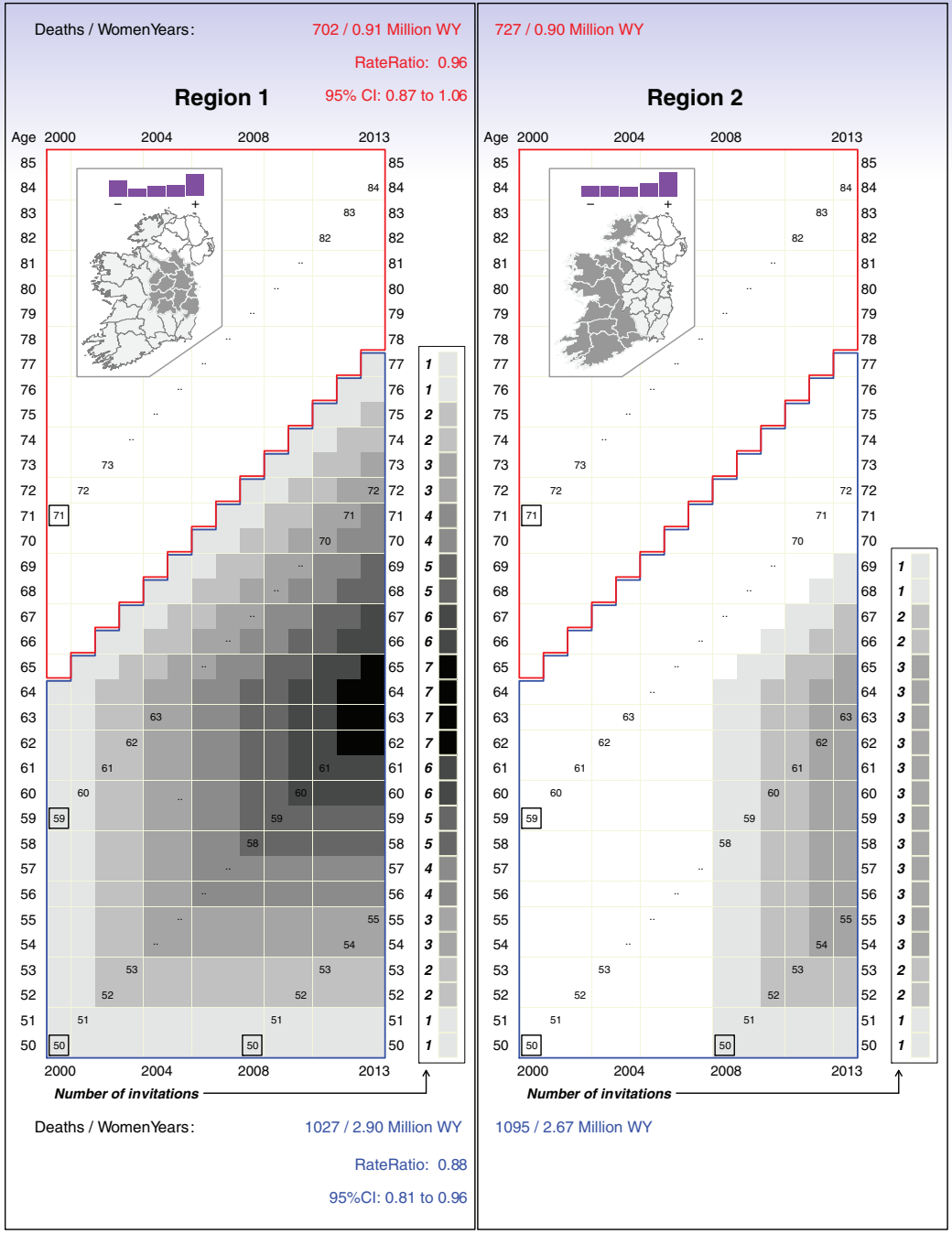


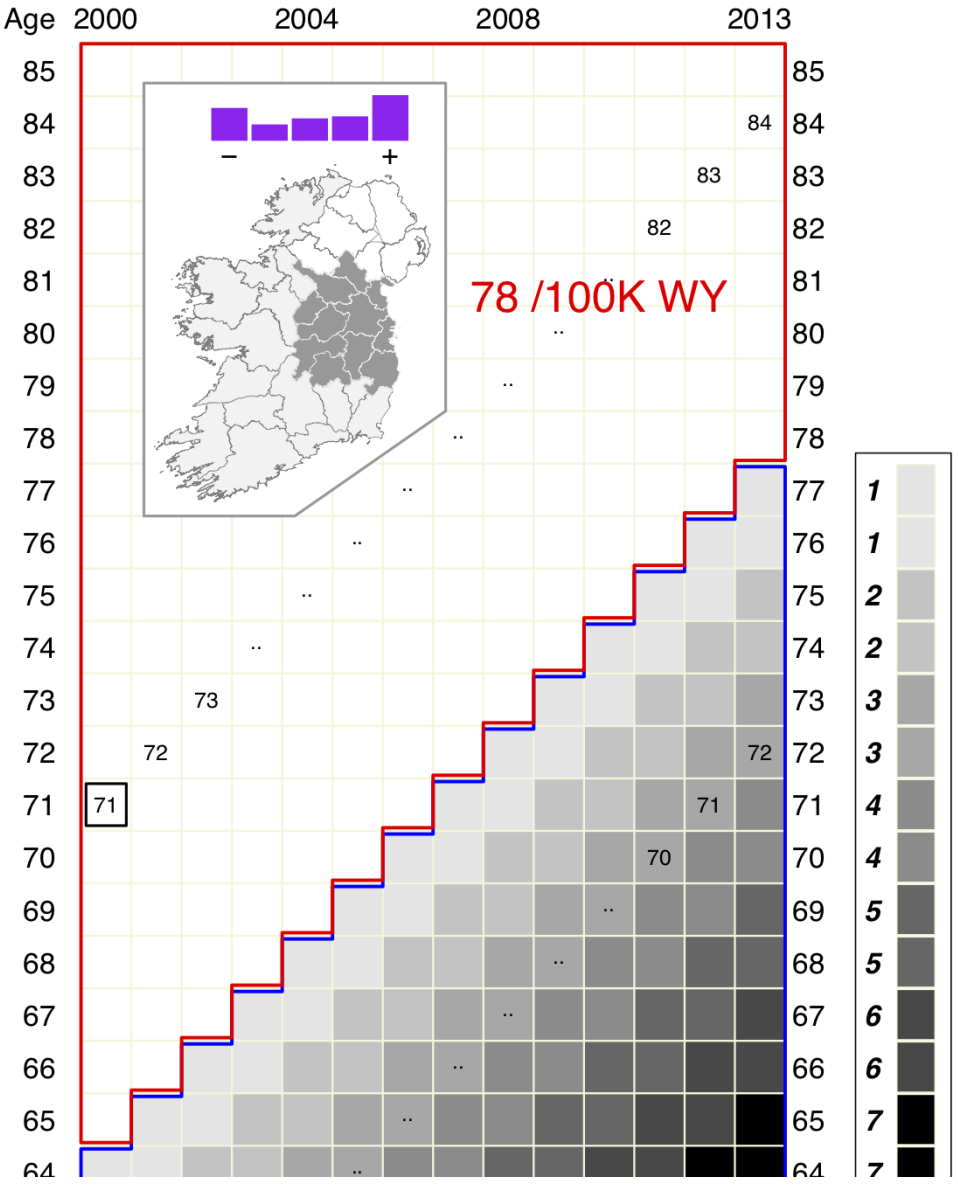
Fig 2. Numbers of screening invitations received by women in various birth-cohorts in regions 1 and 2, together with mortality rates and their ratios. Insets show the extent of each region, and (in purple) the fractions of those aged 50–85 in each quintile of the deprivation index, with '-' denoting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

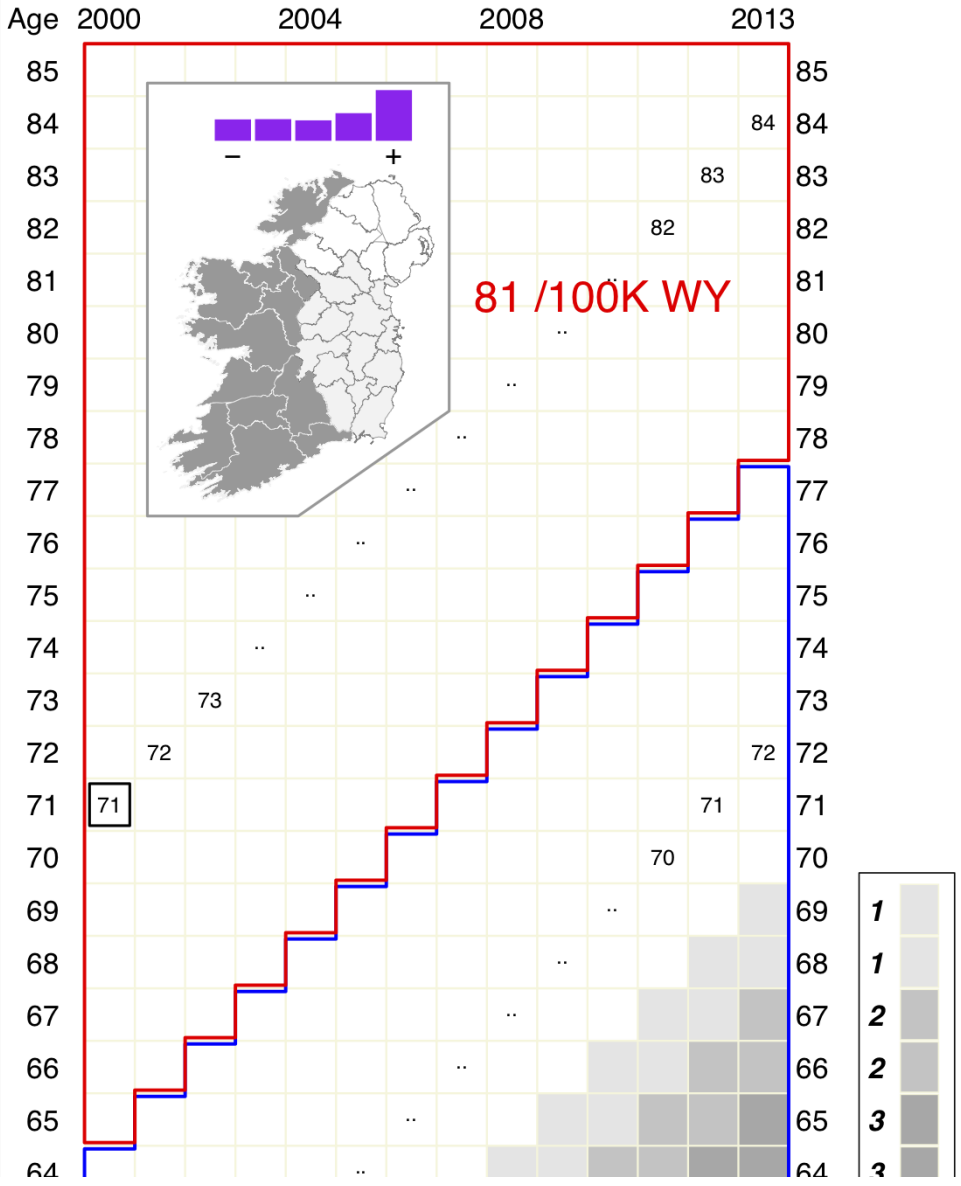
95% CI: 0.87 to 1.06

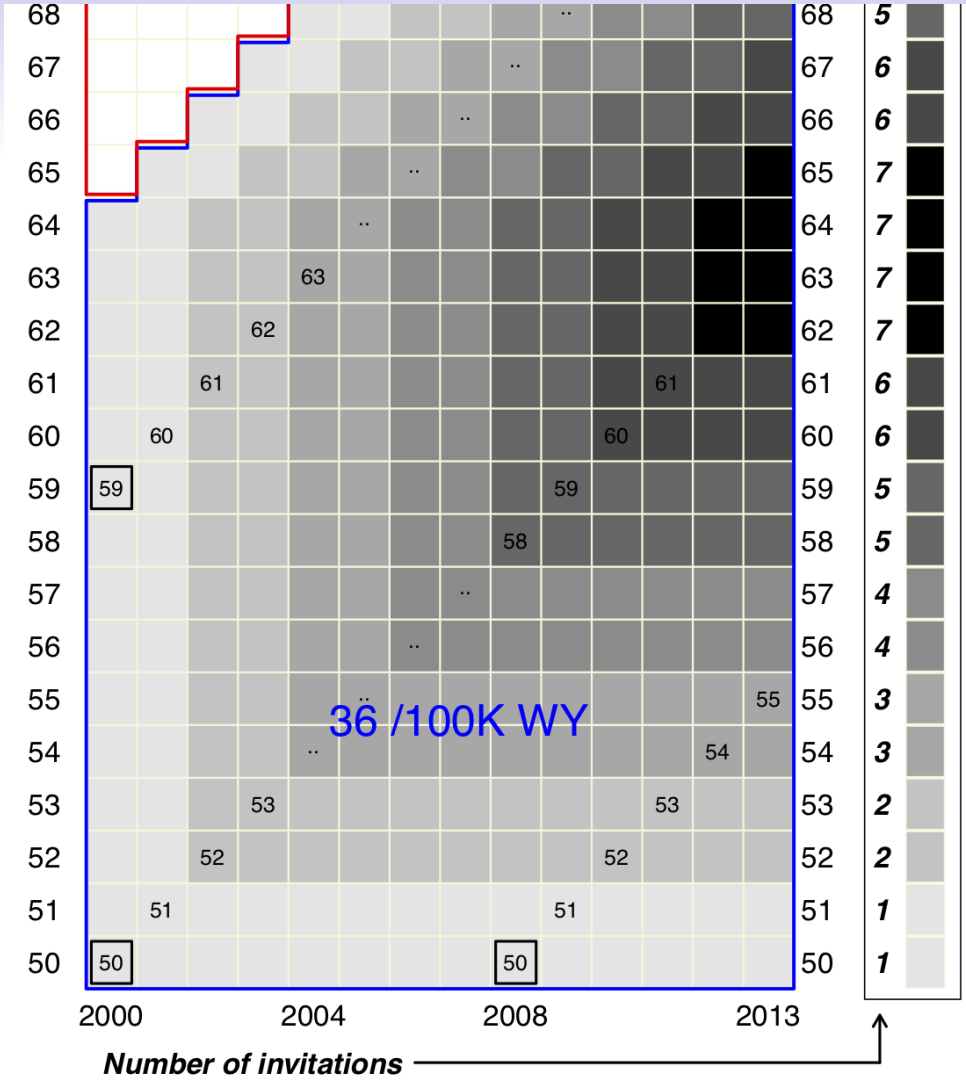
Region 1

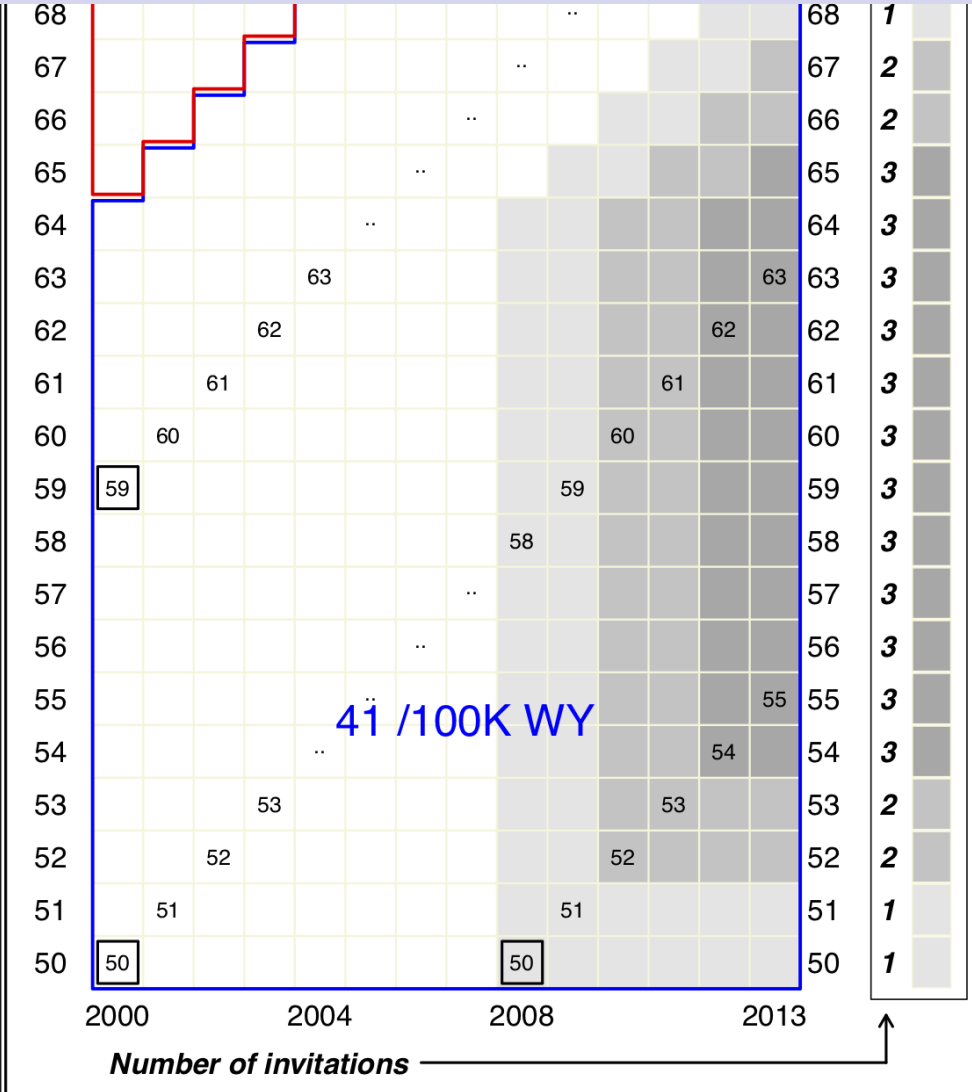


727 / 0.90 Million WY

Region 2







Deaths / WomenYears : 1027 / 2.90 Million WY

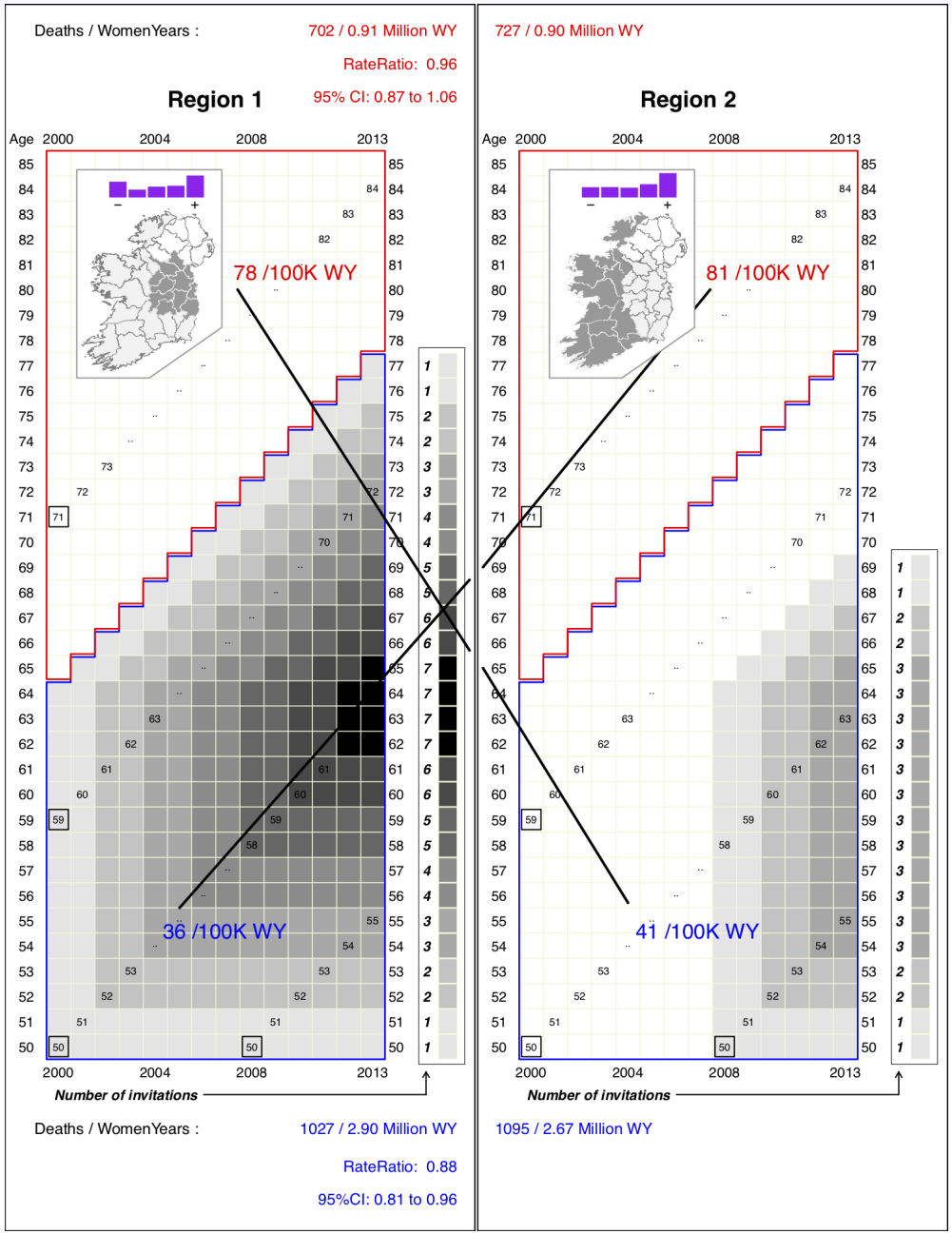
1095 / 2.67 Million WY

RateRatio: 0.88

95%CI: 0.81 to 0.96

HR = 0.91

(9% Δ)


Deaths / WomenYears :
702 / 0.91 Million WY
RateRatio: 0.96
95% CI: 0.87 to 1.06
Region 1
78 /100K WY
36 /100K WY
Deaths / WomenYears :
1027 / 2.90 Million WY
RateRatio: 0.88
95%CI: 0.81 to 0.96
727 / 0.90 Million WY
Region 2
81 /100K WY
41 /100K WY
1095 / 2.67 Million WY
Age
2000
2004
2008
2013
Number of invitations

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

DENMARK

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

SCREENING

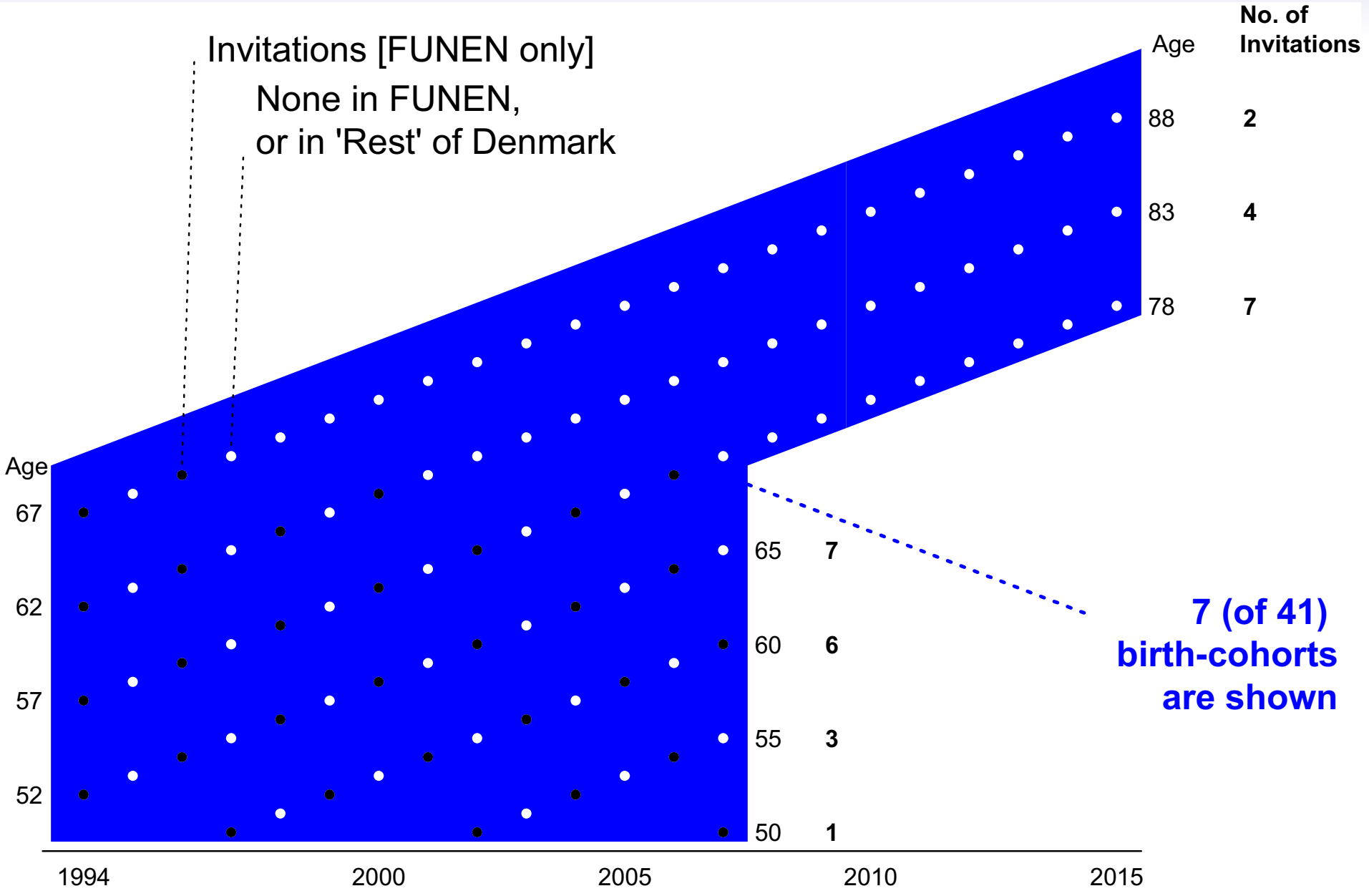
Disaggregating the mortality reductions due to cancer screening: model-based estimates from population-based data

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

- 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,
- 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.

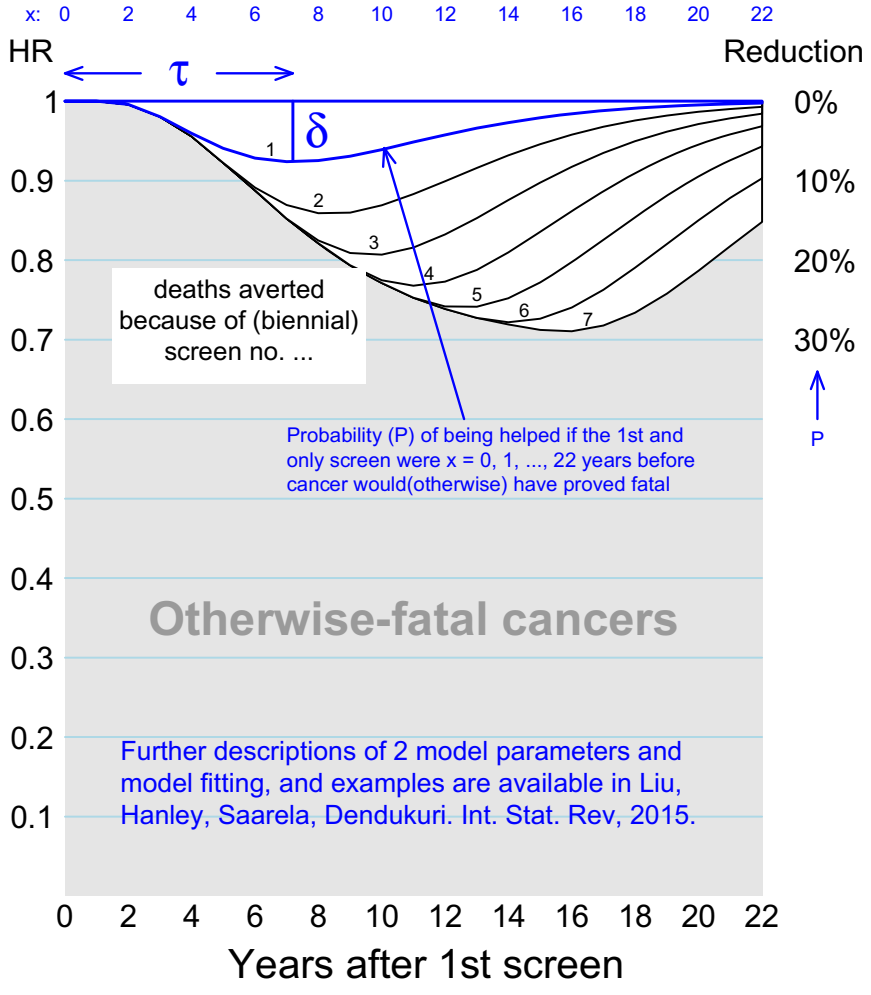
$$D_1 + D_0 = D \text{ fixed} \rightarrow D_1 \sim \text{Binomial}(D, \pi)$$

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



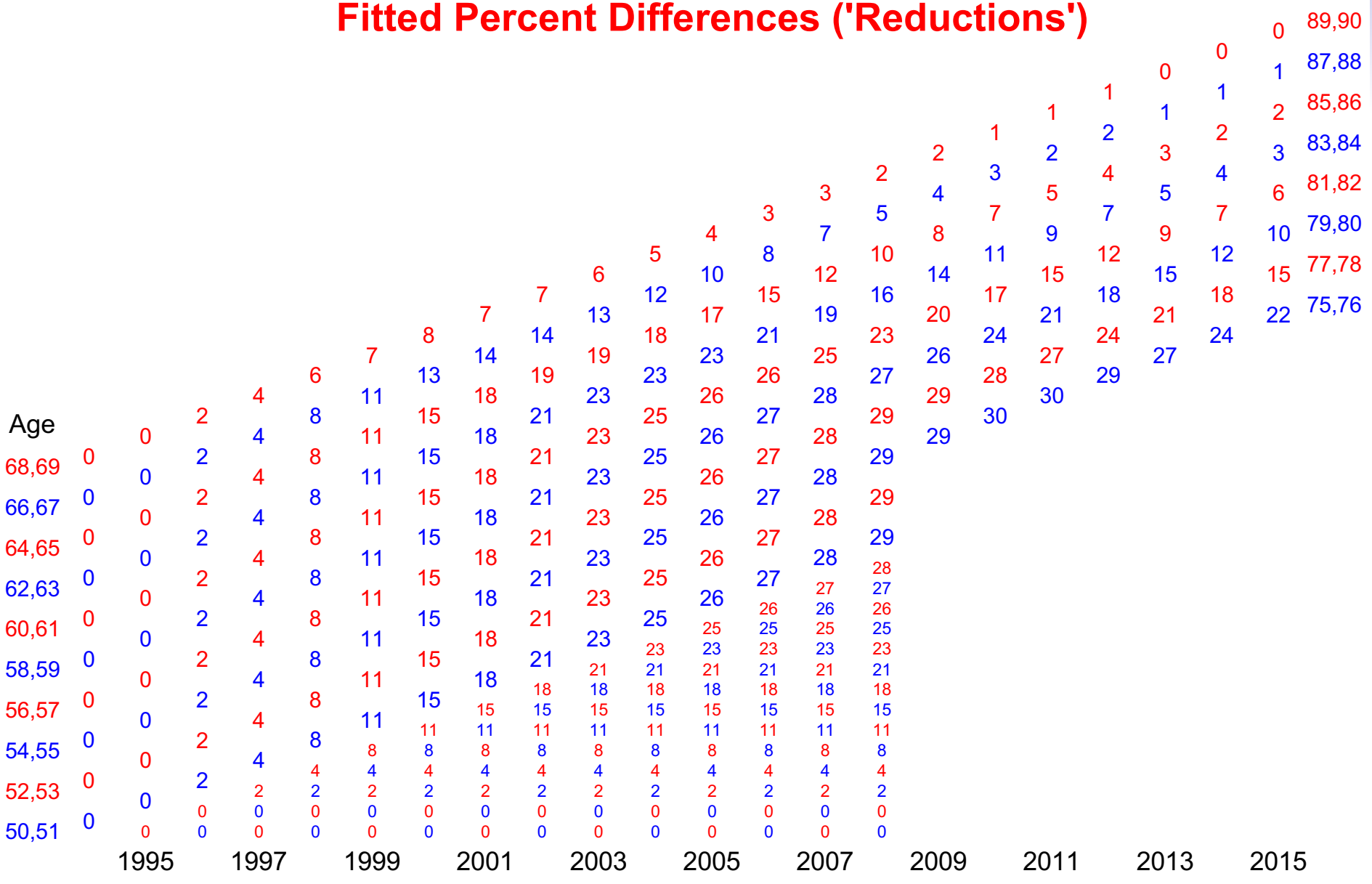
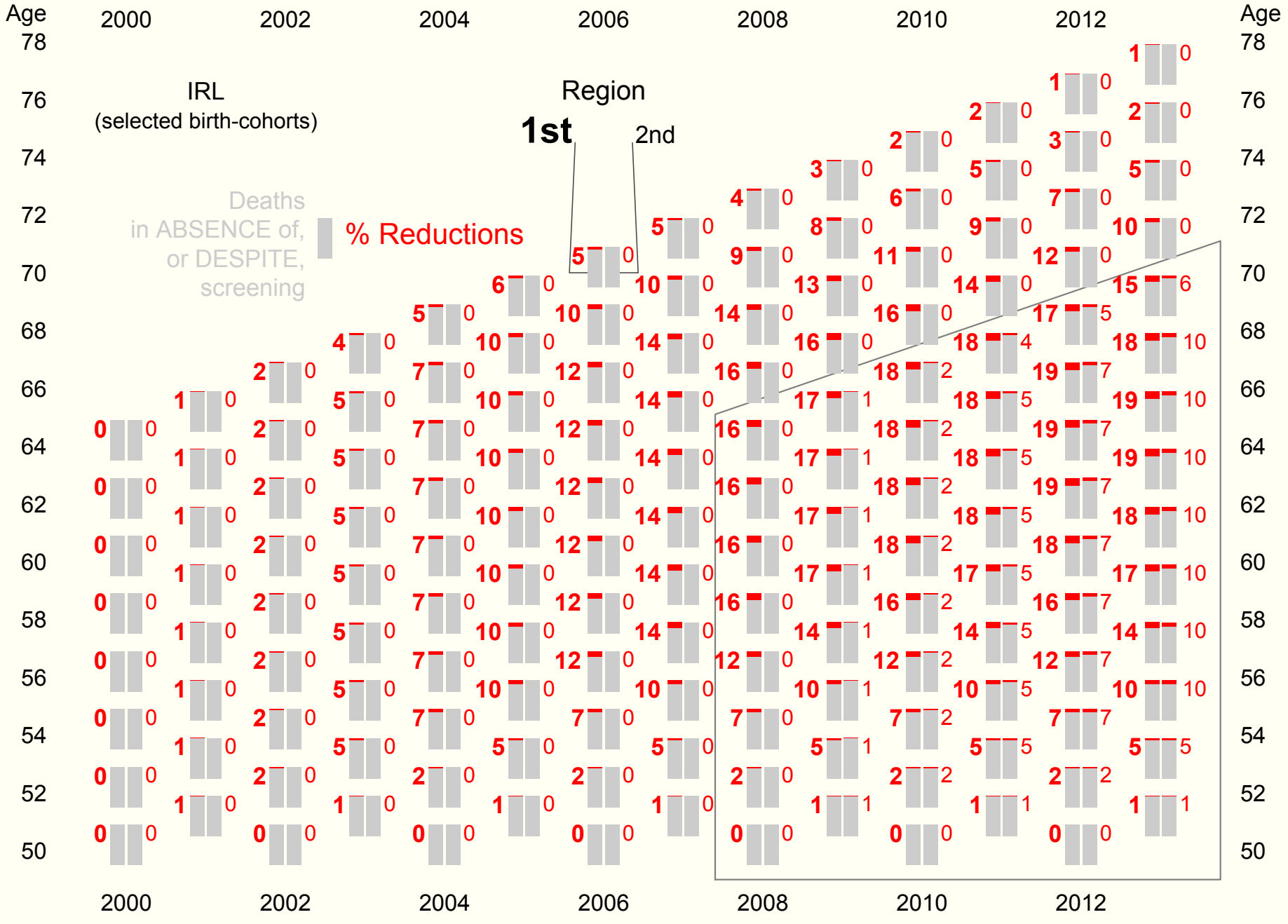


Fig. 4 For each birth cohort, the age-and year-specific fitted percentage reductions in breast cancer mortality. They were derived from the Maximum Likelihood estimates of the two model parameters (maximum probability of being helped by a single round of screening 8 years previously: 9%) and the number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

Webpage: screening

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

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`

SUMMARY

- **Societal**: delayed returns vs. upfront investments, harm
- **Data analysis:** respect cancer screening principles: ~~1-number~~ $\rightarrow$ HR function, based on interpretable parameters, over Lexis space
- **Breastcheck:** "$\downarrow$ mortality from breast cancer by 20% in ten years"

  Steady state: invited from 50 onwards, followed to (say) 85, when full benefits of all invitations have been expressed, and HR reverts to 1. Estimand: depth & extent of the full bathtub-shaped HR curve.
- **Invitations, not screenings:** Reductions averaged over those who did/did not participate. Ones for those who did are presumably higher.
- **Future work**: Data to fit HR functions are hard to come by. WHO has year-and-age-specific breast cancer mortality data from 20-30 countries that introduced national mammography screening programs, starting at different times .
  - 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.

WEB PAGE

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

or Google "James Hanley McGill screening"

FUNDING

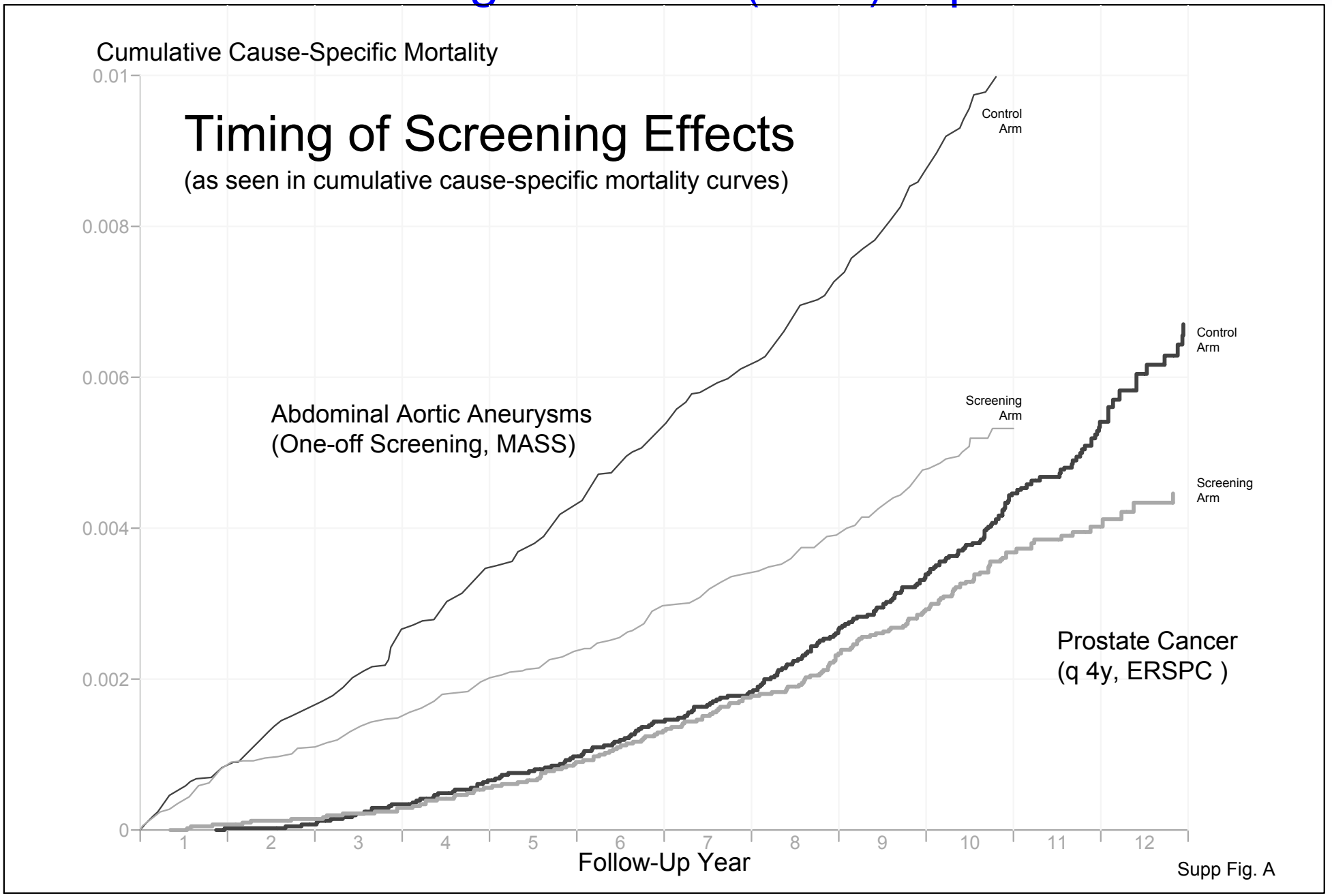
Canadian Institutes of Health Research
2011-2019

Economic and Social Research Institute (Ireland)
1969

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

extra

Loneliness of Long-Distance (non-)Experimentalist



Supp Fig. A

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.”

Cancer of the uterine cervix

1939: Papanicolaou began collaboration with gynaecologist and pathologist, Herbert F. Traut, and gynaecologist, Andrew Marchetti. All women admitted to the obstetrical and gynaecological service at the New York Hospital routinely underwent a vaginal smear. Findings included the astounding discovery that cancers unsuspected in asymptomatic women, and undemonstrable by biopsy, could be detected by use of the vaginal smear.

Link: Papanicolaou GN, Traut HF. The diagnostic value of vaginal smears in carcinoma of the uterus. Am J Obstet Gynecol 1941

Monograph "Diagnosis of Uterine Cancer by the Vaginal Smear" containing drawings of the various cells seen in patients with no disease, inflammatory conditions and pre-clinical and clinical carcinoma.

Link: eponyms-and-names-in-obstetrics-and-gynaecology

Link: Ayre, James Ernest (1910-1974) Ayre's Spatula

Link: A Simple Office Test for Uterine Cancer Diagnosis. CMAJ 1944

Link: Ayre%27s_spatula [Wiki]

Link: https://www.eurocytology.eu/en/course/1119

Link: The History of Cervical Screening I: The Pap. Test. Shaw; J Soc Ob GynCan 2000
Link: Mortality from cancer of uterus in Canada and its relationship to screening for cancer of cervix. Miller, 1977
Link: The Annual Pap Test: A Dubious Policy Success. Foltz and Kelsey. 1979.
Link: Reduced cervical cancer incidence and mortality in Canada: national data from 1932 to 2006. Dickinson
Link: Nordic countries, Incidence, 1955-2010

Neuroblastoma

Link: A population-based (Quebec) study of the usefulness of screening for neuroblastoma. Lancet, 1996

Link: Screening of infants and mortality due to neuroblastoma. Quebec. NEJM 2002

Link: neuroblastoma screening at one year of age. Germany. NEJM 2002

Link: A Halt to Neuroblastoma Screening in Japan. NEJM 2004

Breast Cancer

Link: Mammography and Beyond: Developing Technologies for the Early Detection of Breast Cancer ("to see today with the eyes of tomorrow": a history of screening mammography) Lerner, 2001

Link: Periodic breast cancer screening in reducing mortality from breast cancer. Shapiro, Strax, Venet. JAMA. 1971.

Link: Screening for breast cancer in Quebec: estimates of health effects and of costs : report to the Ministre de la santé et des services sociaux du Québec by the Conseil d'évaluation des technologies de la santé. Caro, 1990

Link: Is screening for breast cancer with mammography justifiable? Gozsche, Lancet 2000
Link: Mammographic screening: no reliable supporting evidence? Miettinen, et al. Lancet 2002

Link: Measuring Mortality Reductions in Cancer Screening Trials. Hanley. Epi. Reviews 2011.

Link: The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies. Broeders et al. J Med Screen. 2012.

Link: Breast cancer mortality in mammographic screening in Europe: a review of incidence-based mortality studies. Njor et al. J Med Screen. 2012.

Link: Measuring the Mortality Impact of Breast Cancer Screening. Hanley et al. Can J Pub Health 2013

Link: "A spider's web": from The emperor of all maladies: a biography of cancer. Siddhartha Mukherjee. 2010.

Lead-Time Bias & Length-Based Sampling

Link: pages 292-293 of the Emperor of All Maladies: The story of identical twins Hope and Prudence

.....

Link: pages 7-9]Length-biased sampling] in these Class Notes from bios601

Example: Imagine you wished to estimate the mean length of words by sampling words from some text. An application might be the mean length of the words used by Donald Trump and Hillary Clinton in the US presidential debate in 2016.
Here are the files:

`http://www.biostat.mcgill.ca/hanley/screening/transcript.trump.txt`
`http://www.biostat.mcgill.ca/hanley/screening/transcript.clinton.txt`

One way would be print the text file and blindly stick pins in the pages and take as your sample the words you land on.

Another would be to extract the words and put them in a data frame, 1 word per row, like this:

`http://www.biostat.mcgill.ca/hanley/screening/words.trump.all.txt`
`http://www.biostat.mcgill.ca/hanley/screening/words.clinton.all.txt`

and to sample the rows.

Which method gives the more valid estimate?

REFERENCES

Liu, Zhihui (Amy) (2014). Measuring the Mortality Reductions due to Cancer Screening. [PhD Thesis] *McGill University*.

Liu, Z., Hanley JA, Saarela O, Dendukuri, N (2015). A conditional approach to measure mortality reductions due to cancer screening. *International Statistical Review* , **83** pp. 493 – 510.

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.

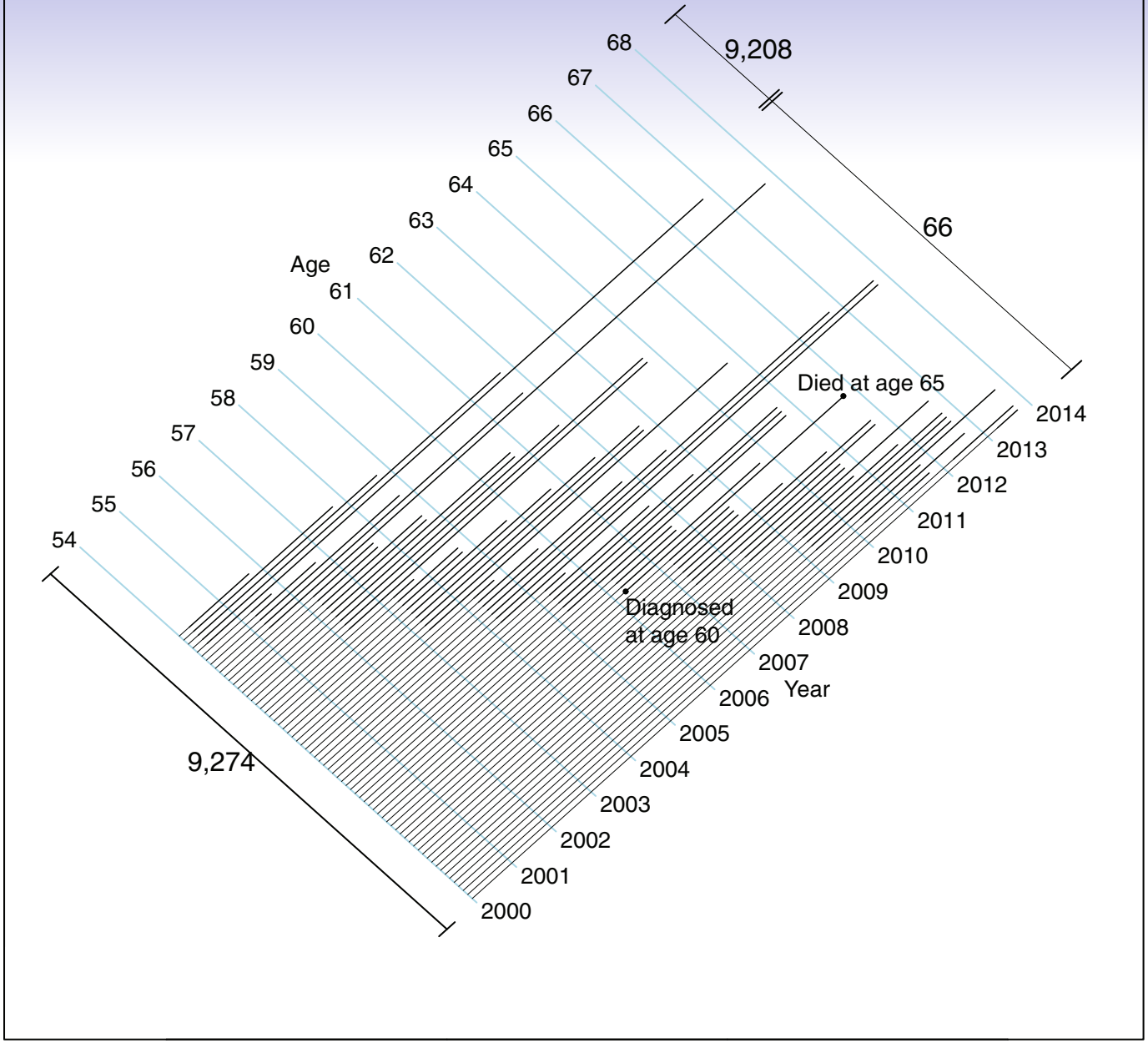


Fig 1. The ages when they were diagnosed with, and died of, breast cancer: 66 women in one selected cohort in region 2. Some 9,274 women, aged 54 in the year 2000, followed to the end of 2013. This cohort received just two screening invitations, at ages 62 and 64, too late to alter the course of these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

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.

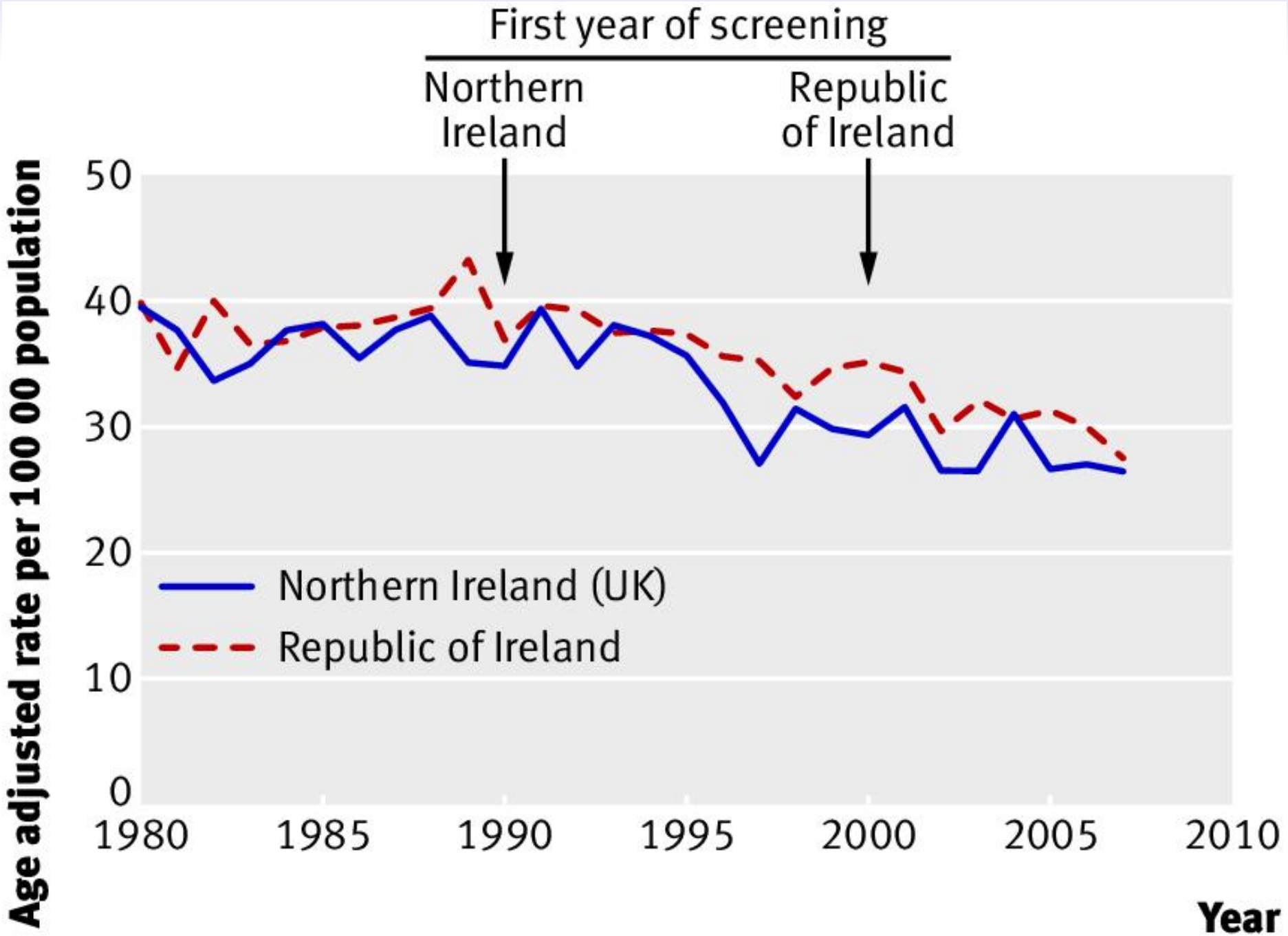
Setting Three country pairs (Northern Ireland (United Kingdom) *v* Republic of Ireland, the Netherlands *v* Belgium and Flanders (Belgian region south of the Netherlands), and Sweden *v* Norway).

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

This big-data approach dilutes the measured impact

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

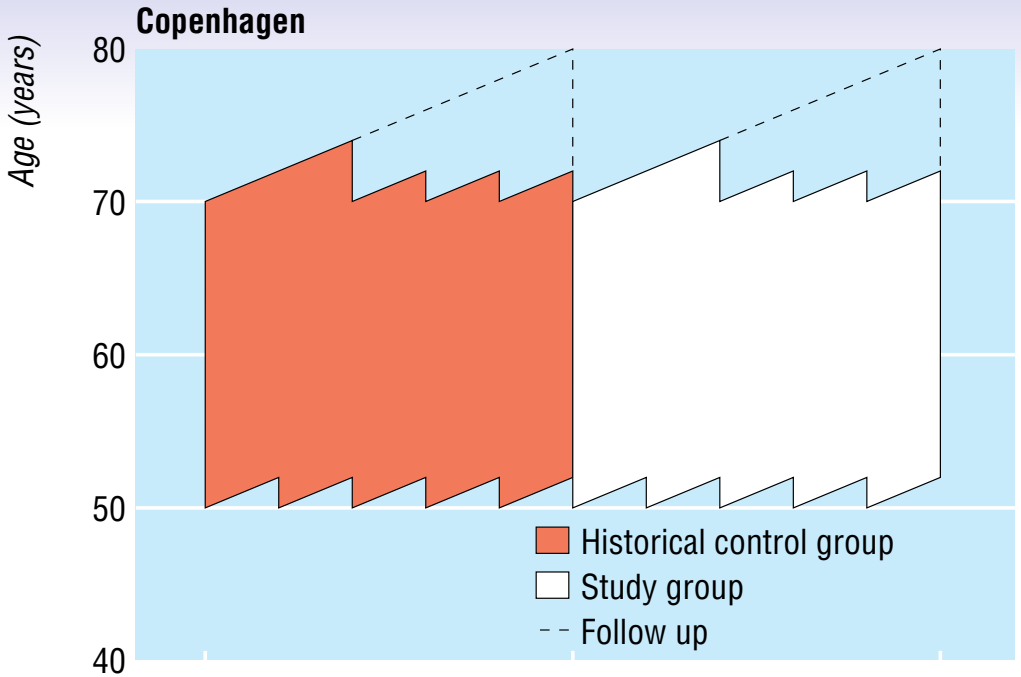
Smaller data: use date of diagnosis to emulate RCT (cancer registry data are required to do this)

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

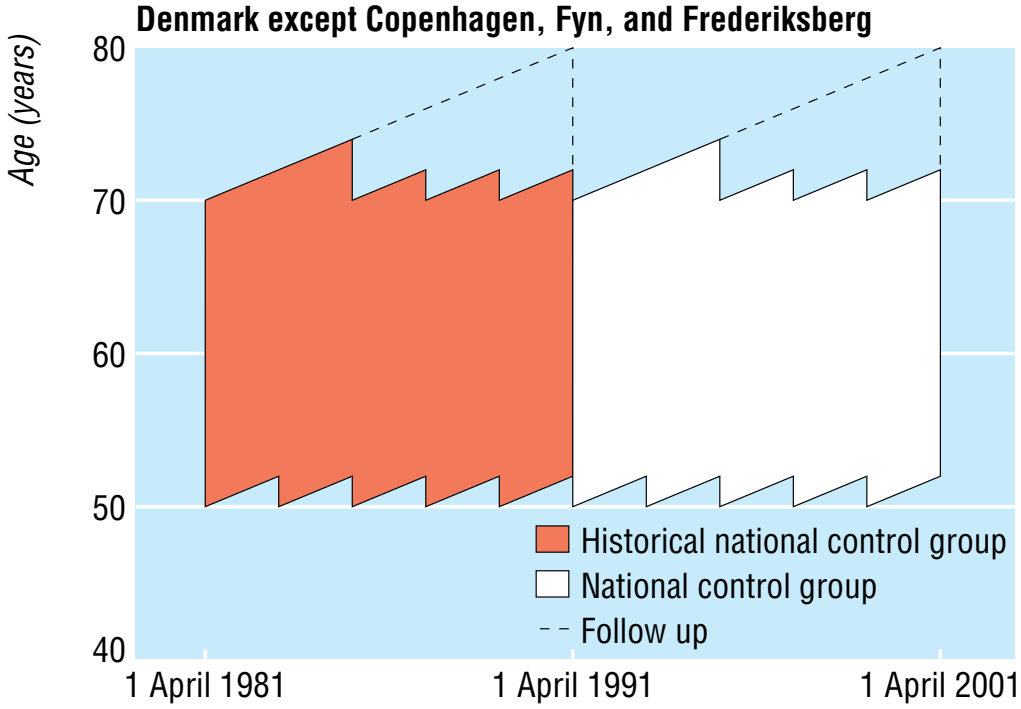
Papers

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

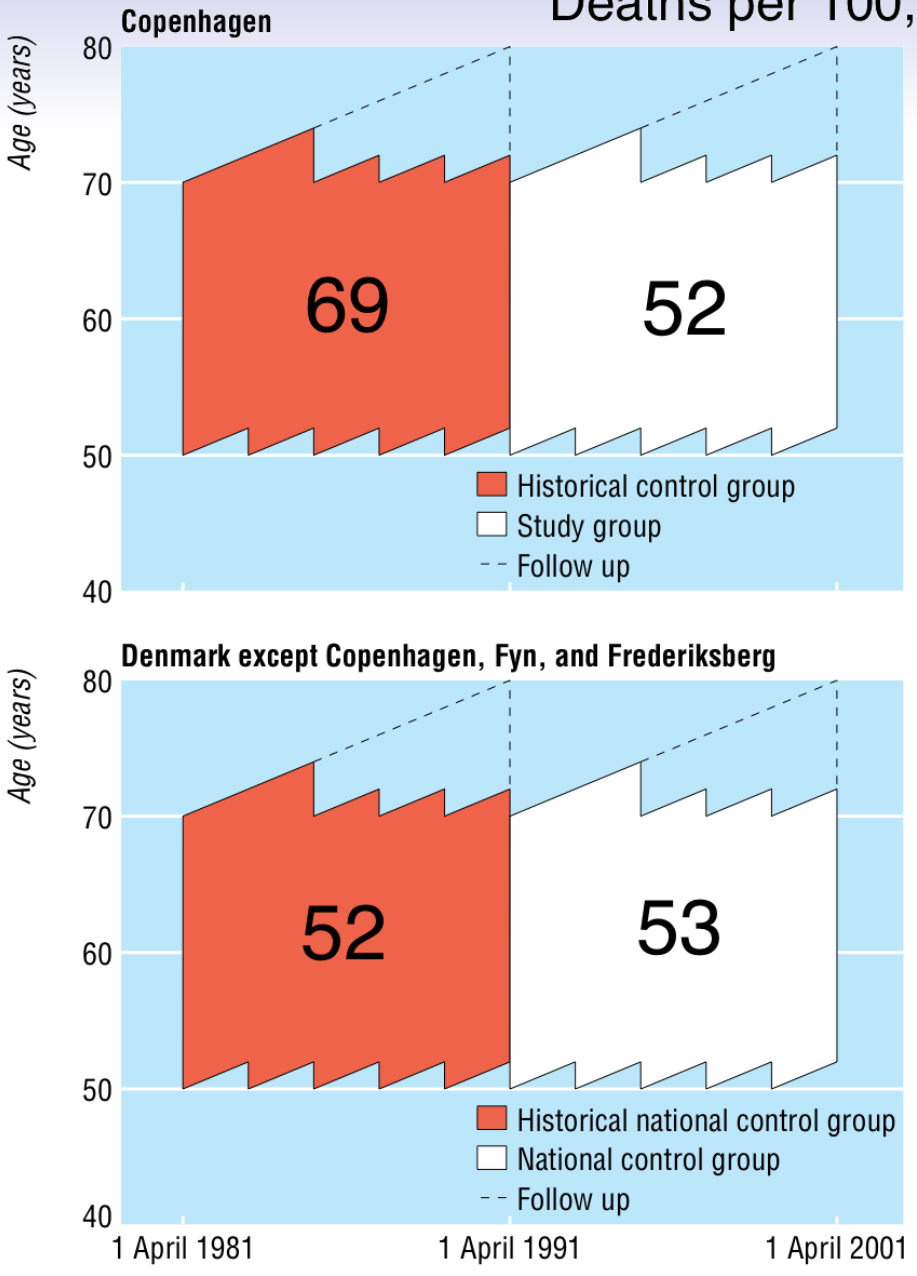


Copenhagen

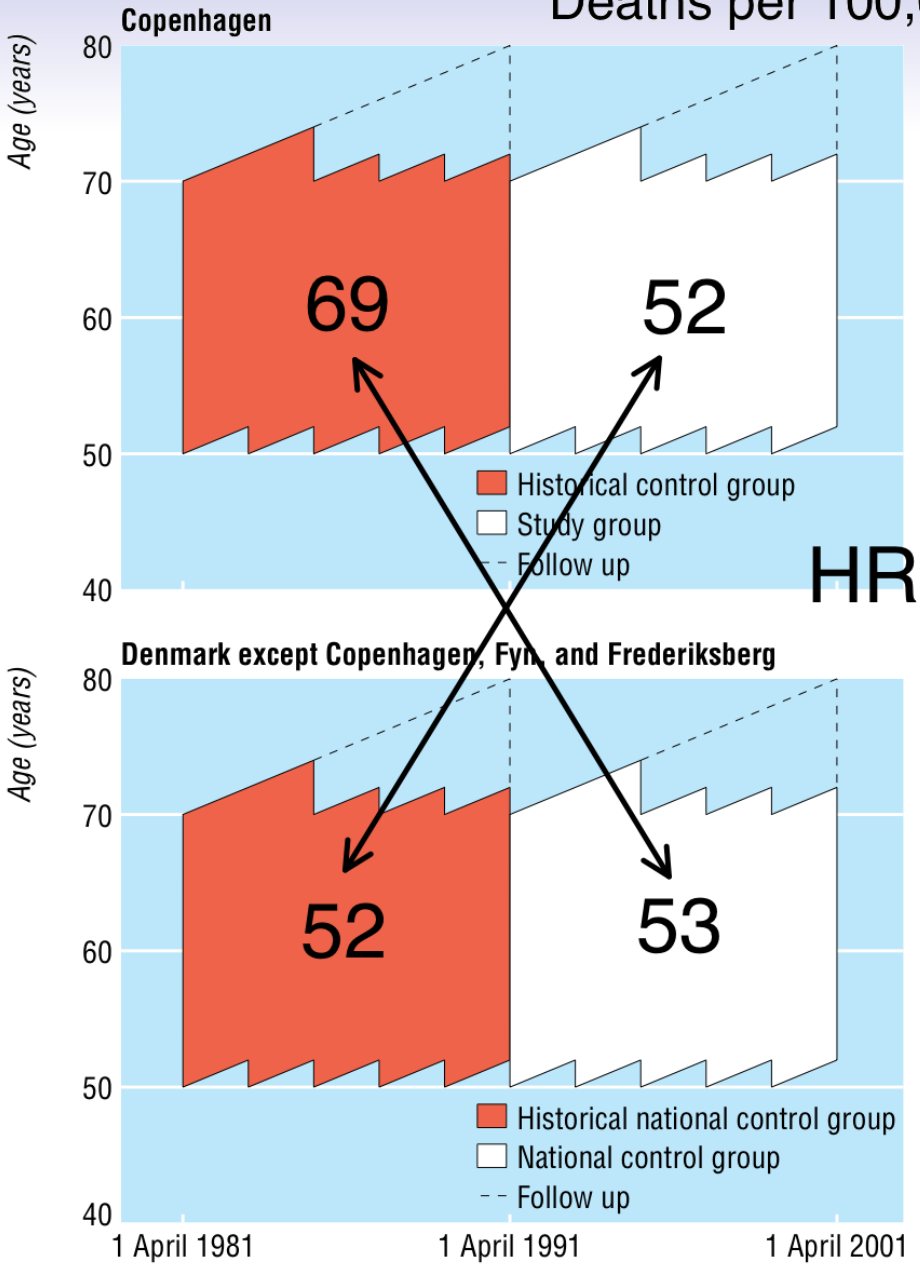


Rest of Denmark (10 x)

Deaths per 100,000 WY



Deaths per 100,000 WY



HR = 0.75 (25% ↓)

more from Proctor (Germany)

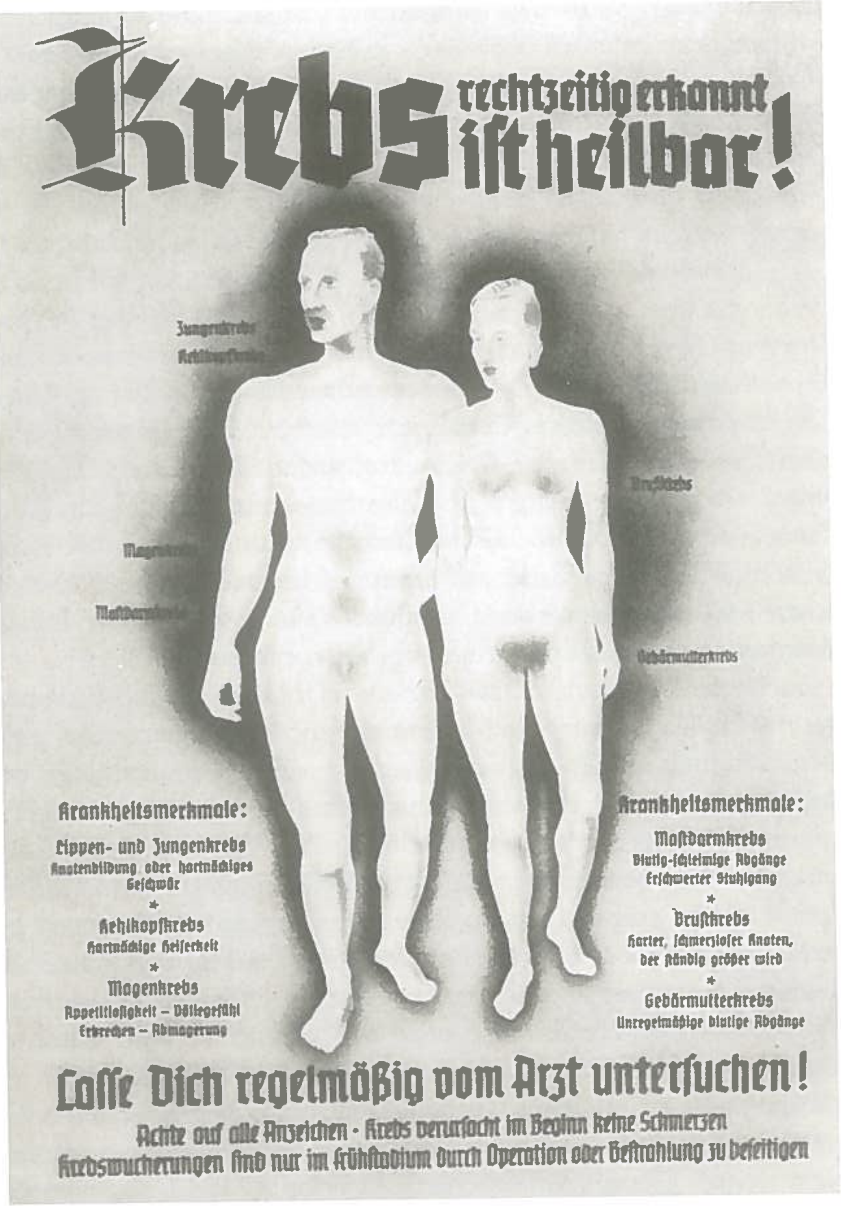


FIG. 1.2. "Cancer can be cured, if detected early!" The Nazis launched mass campaigns to encourage early screening; this poster gives some of the early warning signs for cancer and urges the public to consult their physicians regularly. Source: Friedrich Kortenhaus, "Krebs," in *Deutsches Gold: Gesundes Leben—Frohes Schaffen*, ed. Hans Reiter and Johannes Breger (Munich: Röhrig, 1942), p. 439.

"Cancer can be cured if detected early"

to encourage early detection, sending 1,200 brochures to physicians, plus 1,100 copies of a handbill to midwives advertising the value of early detection. He also published a popular article, printed in every regional newspaper, alerting women to the early signs of the disease and the need for prompt diagnosis. Winter in 1933 celebrated his efforts as "the first organized campaign against cancer."[72]

In the Nazi era, the propaganda designed to encourage (especially) women to consult their physicians was kicked up several notches. Radio and newspaper announcements urged women to submit to annual or even biannual cancer exams, while men were advised to check up on their colons as often as they would check out the engine of their car (see fig. 1.3). "Cancer counseling centers" were established in most German cities, both to popularize the value of early detection and to advise people with cancer of their therapeutic options.[73] Leaflets were also distributed to alert physicians to the value of early detection. Hans Auler helped produce a propaganda film stressing the value of early diagnosis and the curability of cancer; the film's very title (*Jeder Achte*) cautioned that "one in eight" Germans would eventually succumb to cancer[74]—a rhetorical device Rachel Carson would later introduce to American readers.[75] Women were instructed in how to examine their own breasts for cancer (see fig. 1.4; Germans seem to have been the first in the world to take this step (American physicians would not issue comparable instructions until the 1960s).

Hundreds of thousands of women were probed for cancer in this period. In Königsberg alone, 25,000 women had submitted to such exams by 1942, which resulted in the discovery of 129 previously undetected cancers.[76] The massive propaganda for early detection subsided somewhat after 1938, the "peak year" for such propaganda by many accounts. The war put a damper on such efforts, though hopes remained bright in the eyes of some. In a 1942 article on "cancer campaigns of the future," gynecologist Georg Winter looked forward to a time when propaganda (*Aufklärung*) would be combined with mass screening. Radio propaganda was to a play a key role, as was the example of the cured cancer patient ("a patient freed from cancer is a good propagandist"). Physicians

FIG. 1.3. Early detection is as important as care for your car. Middle and bottom captions read: "Every automobile gets a regular checkup; that is obvious. Shouldn't the much more complicated machine of the human body also get regular checkups?" From Kortenhaus, "Krebs," p. 437; first published in the exhibition catalog of the Deutsches Hygiene-Museum, *Kampf dem Krebs*, by Bruno Gebhard (Dresden: Deutscher Verlag für Volkswohlfahrt, 1933), p. 45.

FIG. 1.4. Breast self-examination instruction, circa 1936. The Deutsches Hygiene-Museum in Dresden urged women to examine their breasts to detect tumors at an early stage; Germany's seems to have been the first such campaign anywhere in the world (comparable American campaigns did not begin until thirty years later). Women were also urged to track their menstrual cycles to look for anomalies that might indicate cancer. Top captions read "The Signs of Cancer," and "Breast" and "Uterus." Source: Kortenhaus, "Krebs," p. 431.

Every automobile gets a regular checkup; that is obvious. Shouldn't the much more complicated machine of the human body also get regular checkups?

L: Breast Self-Exam. R: Tracking menstrual cycles (uterus)

would have to learn to combat cancer fear, a special weakness "of the female sex." Winter predicted that cancer physicians of the future would move through the countryside in autos specially equipped with X-ray and other diagnostic equipment, ferreting out uterine and cervical cancers. He also proposed two annual "cancer awareness months," perhaps March and September, during which women would be urged to submit to cancer exams. The campaigns would begin with a barrage of publicity—including lectures, radio announcements, and articles in local newspapers—during which time clinics, hospitals, and counseling stations would gear up for the flood of examinations. Persons found afflicted would immediately be sent to a hospital for treatment, free of charge.[77]

There were many in the German medical community who took this need for early diagnosis quite seriously. A 1939 article in the Viennese medical weekly, by the antitobacco misogynist Robert Hofstätter, argued that all German women over the age of thirty should be required to undergo a semiannual gynecologic cancer exam. Hofstätter reported that a nationwide cancer-screening program of this sort would require a staff of 5,760 physicians at a cost of 35 million reichsmarks per year, a significant but tolerable sum. He also claimed that women who failed to submit to such exams should be punished for placing an extra financial burden on the insurance bureaucracy. Women who refused the exams and chose to "go it alone" were to be awarded only half the normal insurance coverage in the event that they became sick from cancer.[78] Hofstätter, I might note, was not particularly astute when it came to political timing: he joined the Nazi party in August of 1944, only months before the collapse of Nazi rule in Austria. His party number—10,078,751—put him near the last in that long line of infamy.[79]

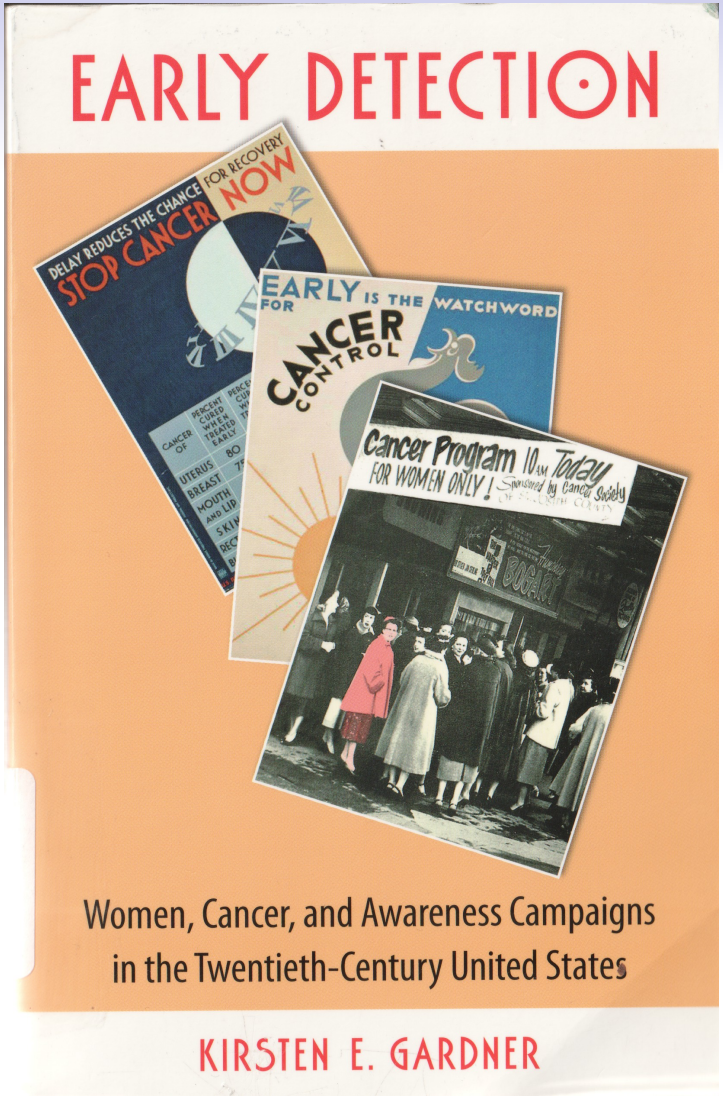
Despite general agreement on the need for screening, opinions differed on the utility of the various techniques to be used. Most radiologists supported the mass use of X-rays, but there were also those—notably Fritz König, head of the Reich Anticancer Committee's science advisory board—who argued that the value of the rays had been exaggerated.[80] There was also a great deal of debate

over the value of colposcopy for cervical cancer screening. At a 1937 meeting in Berlin, a number of gynecologists suggested that the device was superfluous, given that the experienced specialist could identify suspicious cervical changes using only a speculum and the unaided eye. A more common objection was that proper use of the device took a great deal of time. The cervix had to be examined both before and after it was bathed with iodine and acetic acid if precancerous growths were to be detected. In the most commonly expressed view, the colposcope could be profitably used in cases already identified as suspicious but was inappropriate for mass screening.[81]

Criticisms of this sort may be one reason Hinselmann collaborated with Auschwitz physicians in a project to test how well his beloved (and much-hyped) colposcope might serve in detecting cervical cancer at a very early stage. Hinselmann was assisted in this project by Eduard Wirths, the physician-commandant of Auschwitz, who had studied gynecology with Hinselmann. Eduard and his brother, Helmut, a gynecologist colleague of Hinselmann's in Hamburg-Altona, used the colposcope to collect samples of cervical tissues from camp inmates, which were then sent back to Hamburg for examination by Hinselmann and Helmut.[82] The exact purpose of the experiments is not yet clear (postwar testimony suggested Helmut was the instigator), but the studies may have been part of an effort to bolster the reputation of colposcopy for identifying early-stage cancers. The experimenters may have caused the deaths of several Auschwitz inmates, since the entire cervix was generally removed, even in ambiguous cases where cancer was not obvious, causing not infrequent bleeding or infection. After the war, a physician formerly imprisoned in the camp characterized the Hinselmann experiments as equal in brutality to many of the more notorious experiments at the camp.[83]

Nazism was supposed to set the world in motion, to redraw the map of Europe in harmony with the German-imposed "New World Order." The spirit of the times was utopian and millenarian,

more from Gardner (USA)



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1913 American Society for the Control of Cancer formed
1913 What Can We Do about Cancer? *Ladies' Home Journal*

FOR ALL WOMEN

Presented by

THE WOMEN'S FIELD ARMY

of

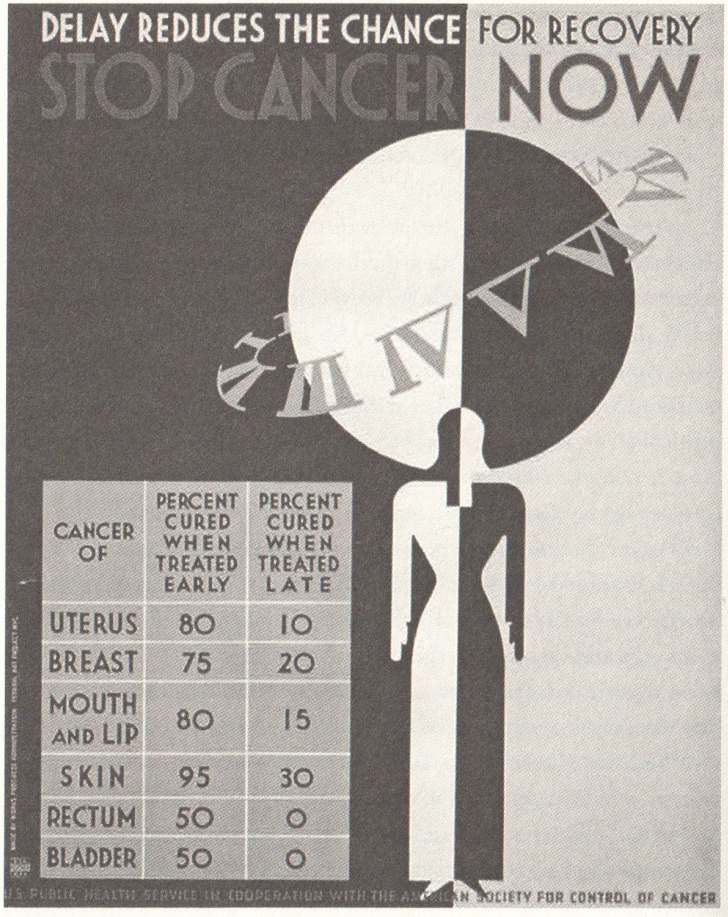
The American Society for the Control of Cancer

Prepared by

THE NEW YORK CITY CANCER COMMITTEE

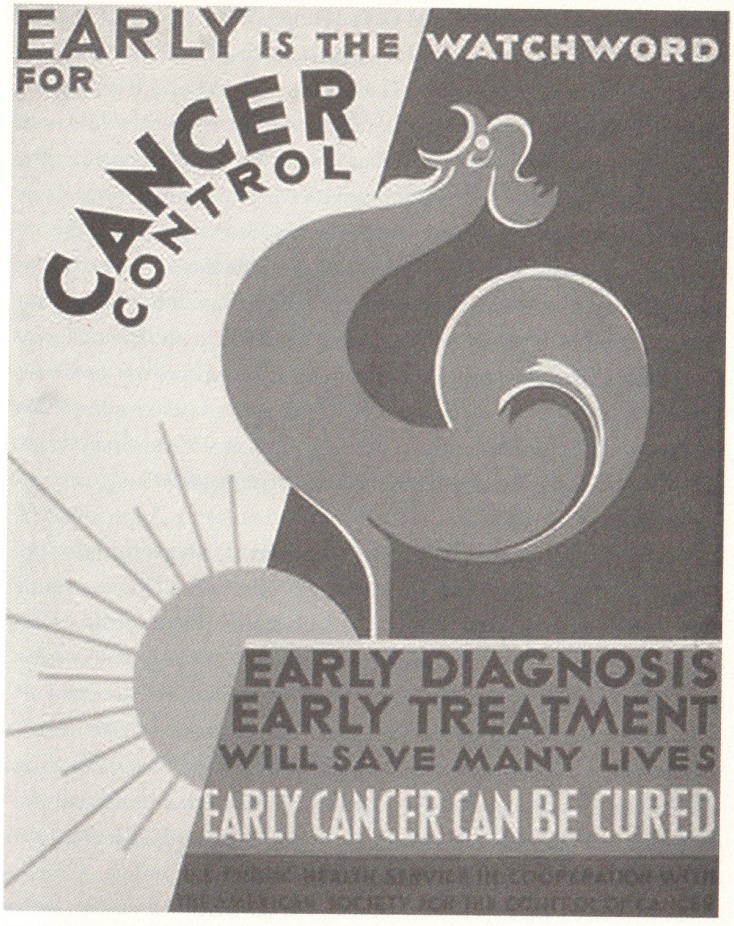
"There *Shall* Be Light!" Front cover of a popular Women's Field Army publication, 1936. (Courtesy of the American Cancer Society)

1936



"Stop Cancer Now." This poster promoted early detection of cancer. It was created by Christopher Denoon in 1938 through the Works Progress Administration. (Library of Congress)

from her mother, who explained, "Mrs. Belter has had cancer and her breasts have been removed." Lasker responded, "What do you mean? Cut off?" When her mother responded affirmatively, Lasker thought, "This shouldn't happen to anybody."[13] Ultimately, Mrs. Belter survived, and the memory encouraged Lasker's belief that cancer



"Early Is the Watchword." This poster taught audiences that early cancer could be cured. It was created by Christopher Denoon in 1938 through the Works Progress Administration. (Library of Congress)

treatment could be effective.[14] In an oral interview conducted in 1976, Lasker still recalled the vividness of her childhood reaction to the disease: "I'll never forget my anger at hearing about this disease that caused such suffering and mutilation and my thinking that something should be done about this."[15]

1938