Estimating the mortality reduction produced by each round of cancer screening

James A. HANLEY

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XXVIII International Biometrics Conference
Victoria, British Columbia, Canada
2016-07-14

draft July 5

Dedication

Biometrika 1969

On the theory of screening for chroni

BY M. ZELEN

State University of New York at Buffalo

AND M. FEINLEIB

National Institutes of Health

Biometrika 1997

Planning clinical trials to evaluate early detection p

BY PING HU AND MARVIN ZELEN

Division of Biostatistics, Dana Farber Cancer Institute, 44 Binney Str
Massachusetts 02115, U.S.A.

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Biometrics 2008

Mortality Modeling of Early Detection H

Sandra J. Lee* and Marvin Zelen

Harvard School of Public Health and the Dana-Farber Cancer
Boston, Massachusetts 02115, U.S.A.

HARVARD gazette

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: non-proportional hazards, in 2 time scales

bathtub-shape HR function,

generated from 2 parameters of a

Canadian model,

fitted to Danish breast cancer data.

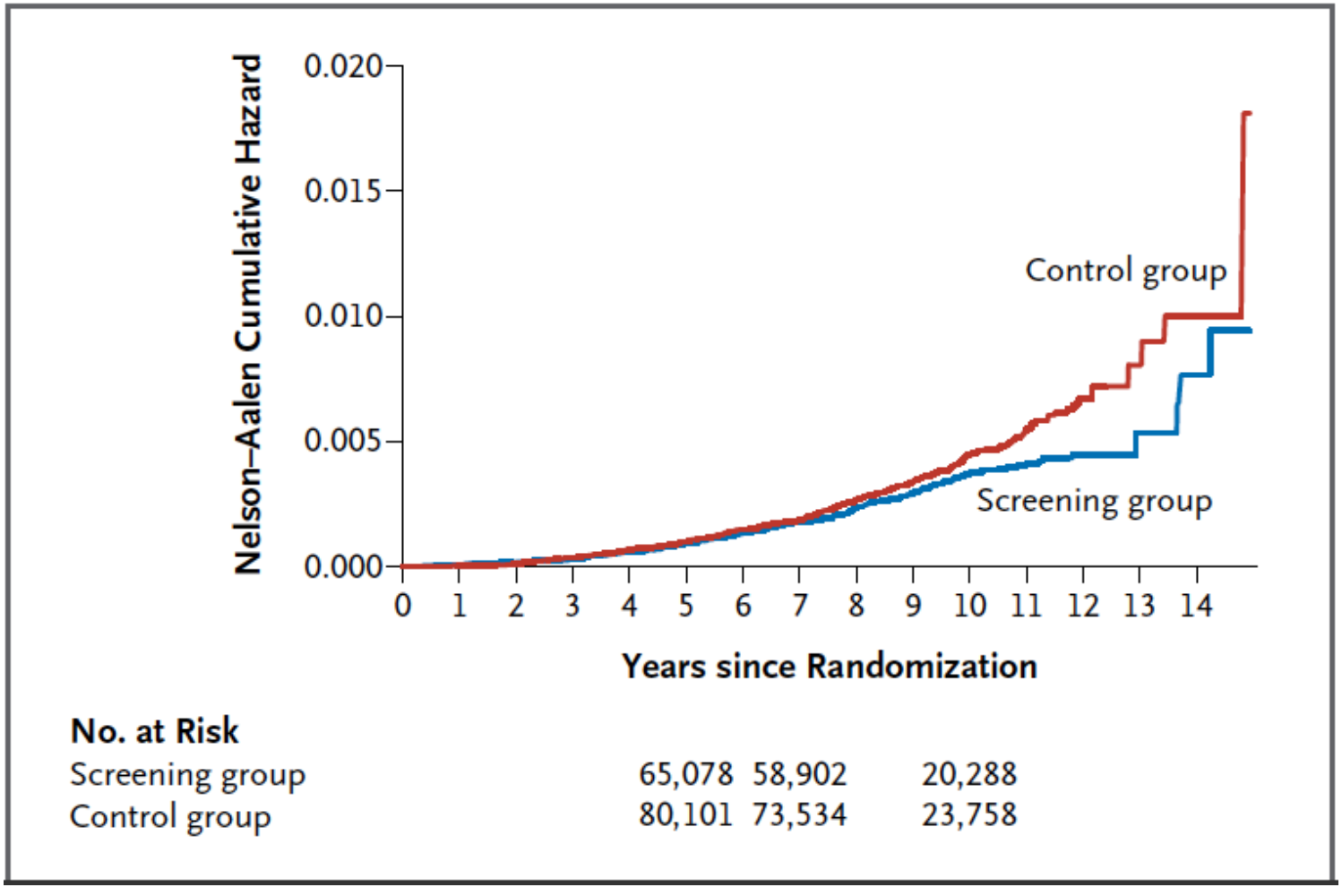
Mortality Reductions due to cancer screening are **DELAYED**

PROSTATE CANCER SCREENING
is a striking example

Screening & Prostate-Ca Mortality in Randomized European Study ’92-’08 (“ERSPC” nejm2009.04)

8.8 years mean F.U., 214 & 326 deaths: **HAZARD RATIO: 0.80**

“PSA-based screening reduced rate of [pr. ca.] death **by 20%**. ”



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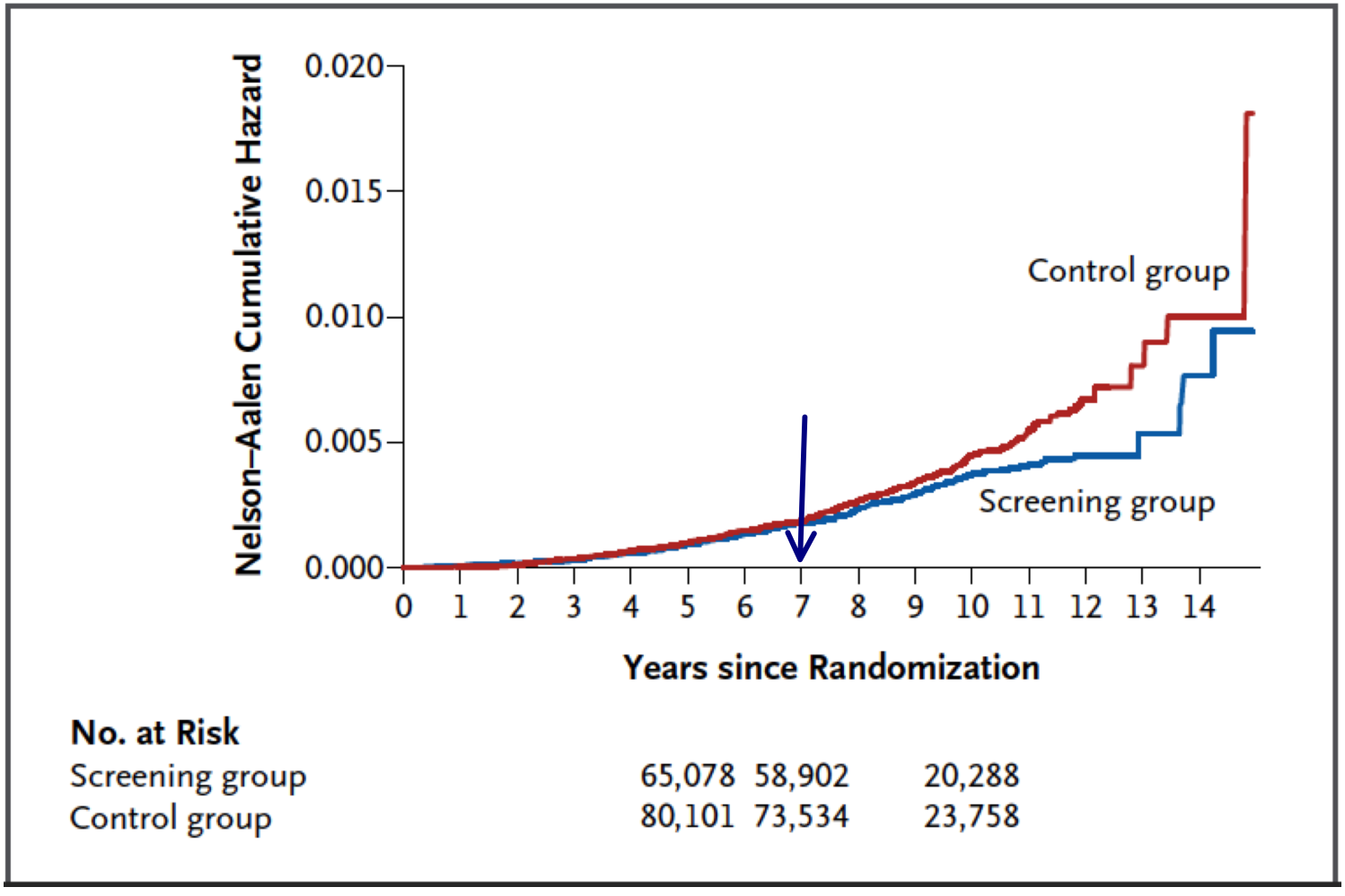
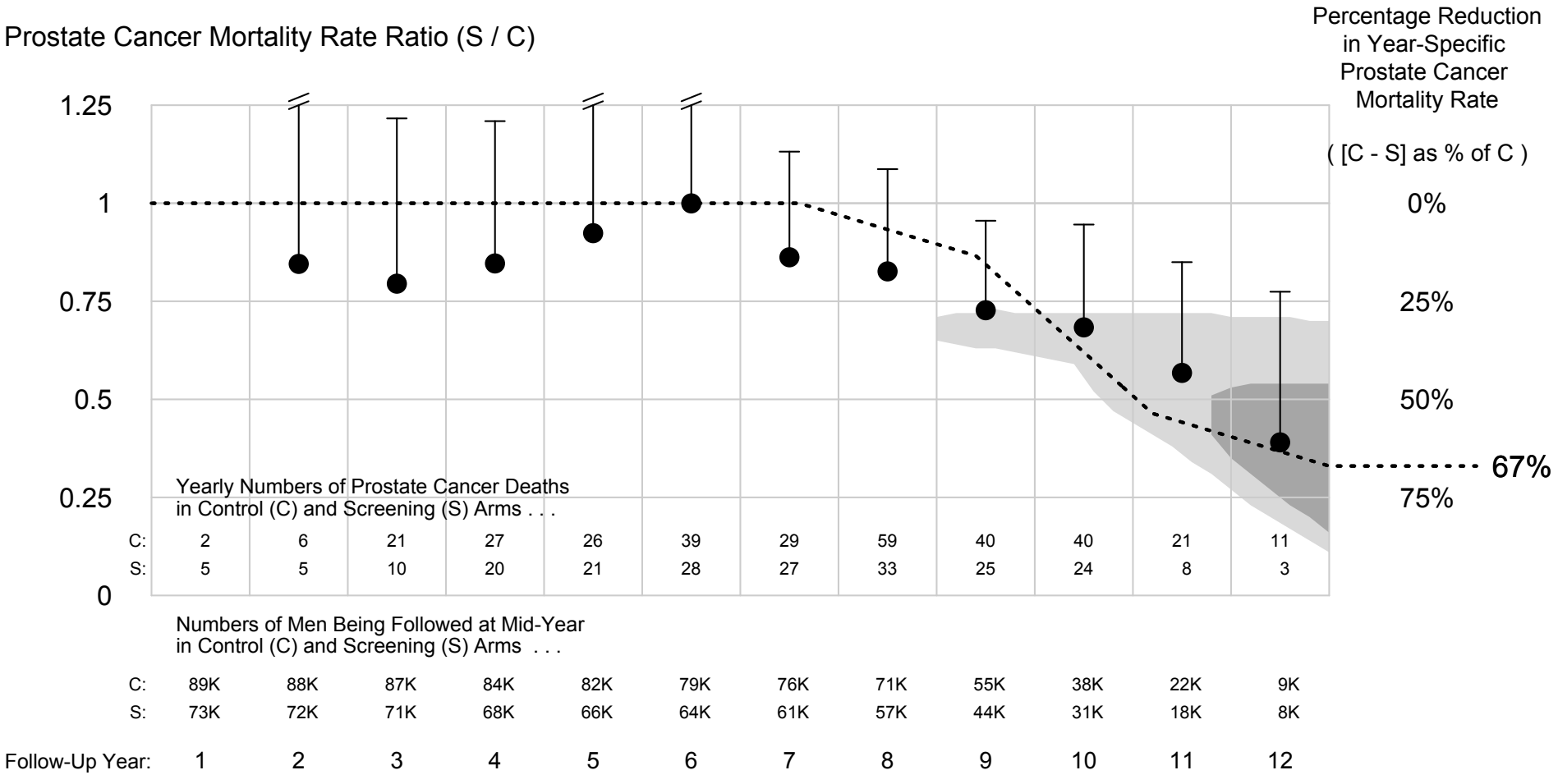


RE-ANALYSIS OF ERSPC DATA
using
year-specific prostate cancer mortality ratios

Year-specific mortality ratios



Hanley, *J Medical Screening*, 2010.

SCREENING for COLON CANCER

Later, if time

SCREENING for BREAST CANCER

???

Magnitude of reductions being achieved with contemporary mammography

Estimates from (non-experimental) population-based studies of staggered introductions

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

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

****

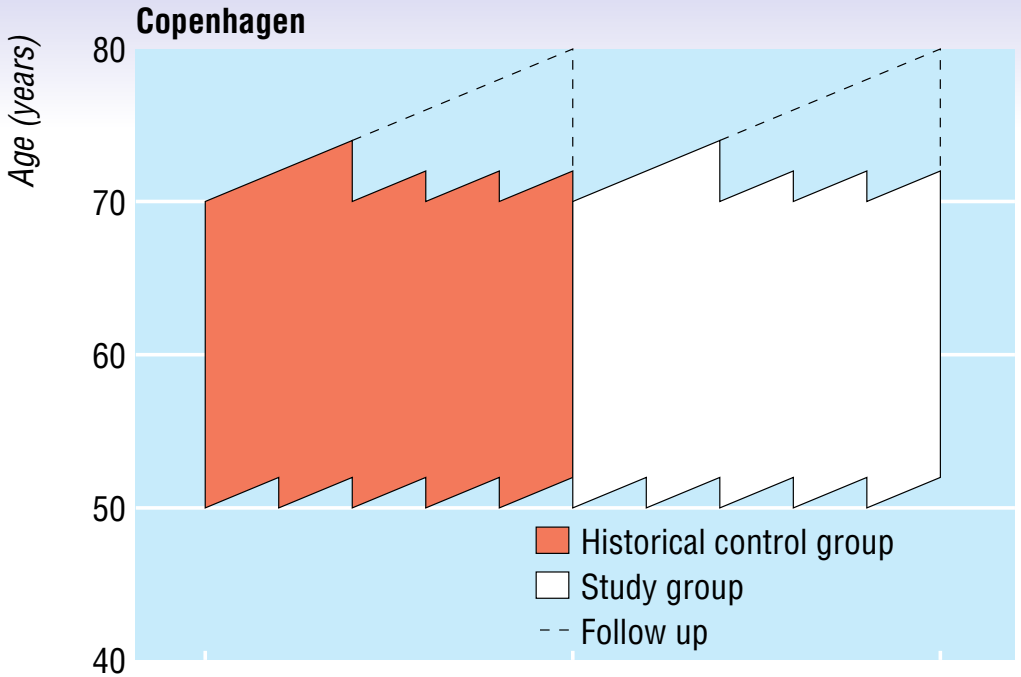
in FUNEN

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

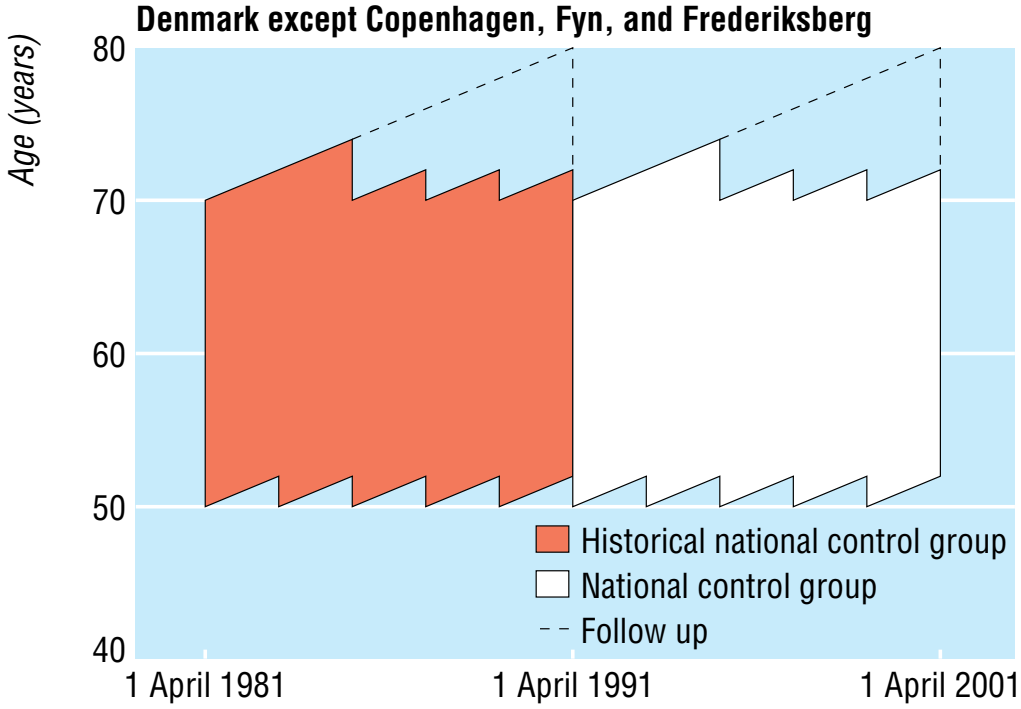
J Med Screen
2015, Vol. 22(1) 20–27

DOI: 10.1177/0969141314563632
msc.sagepub.com
SAGE

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

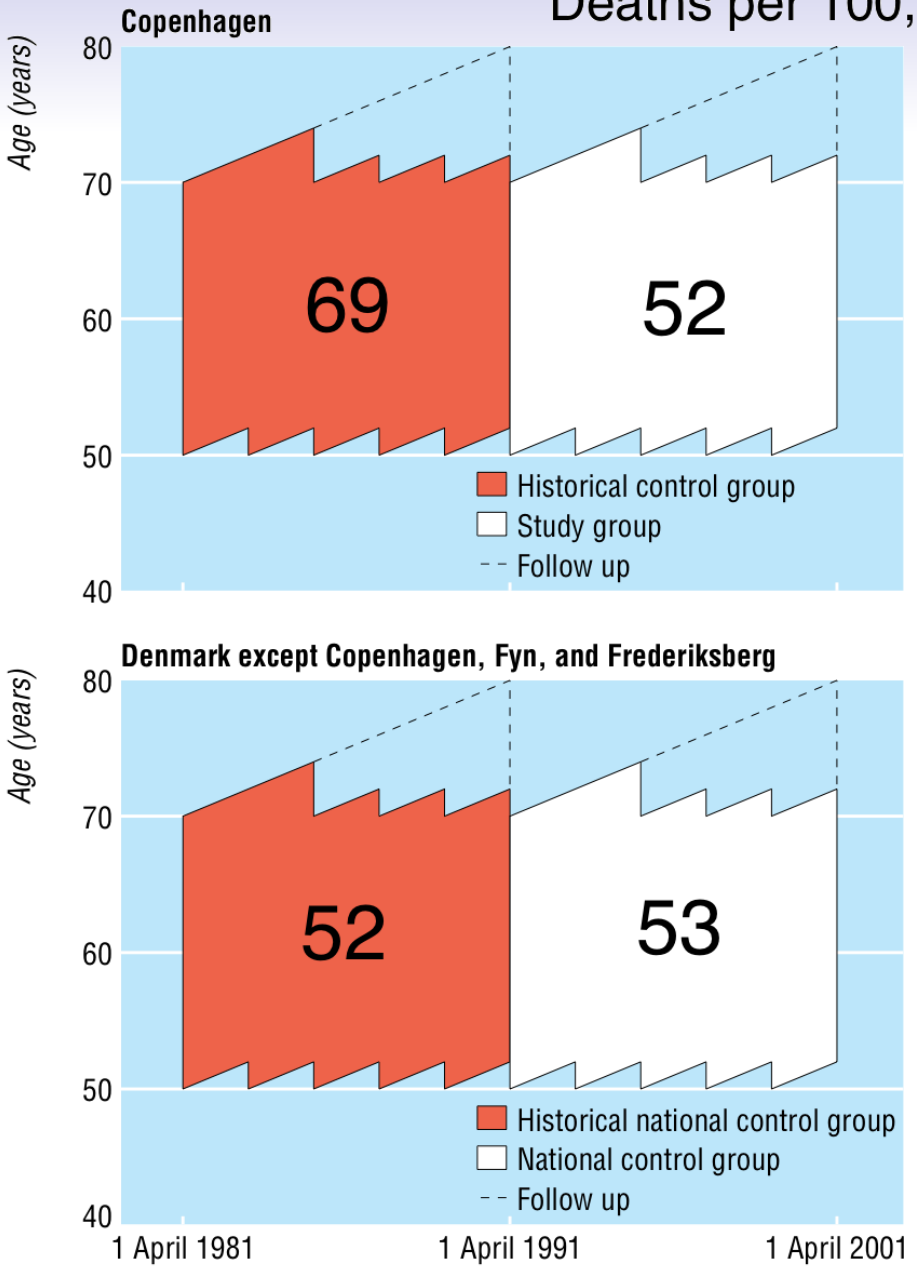


Copenhagen

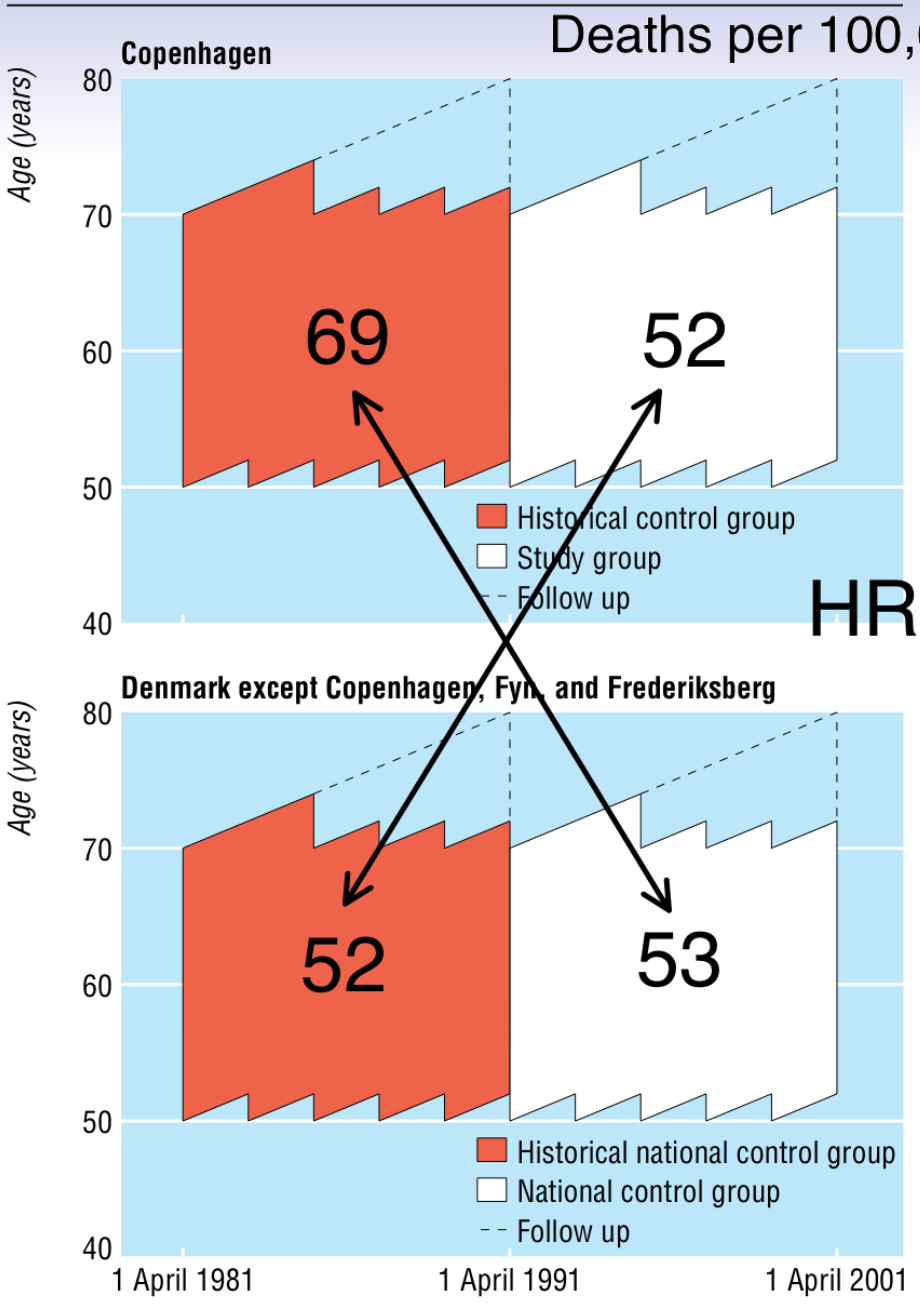


Rest of Denmark (10 x)

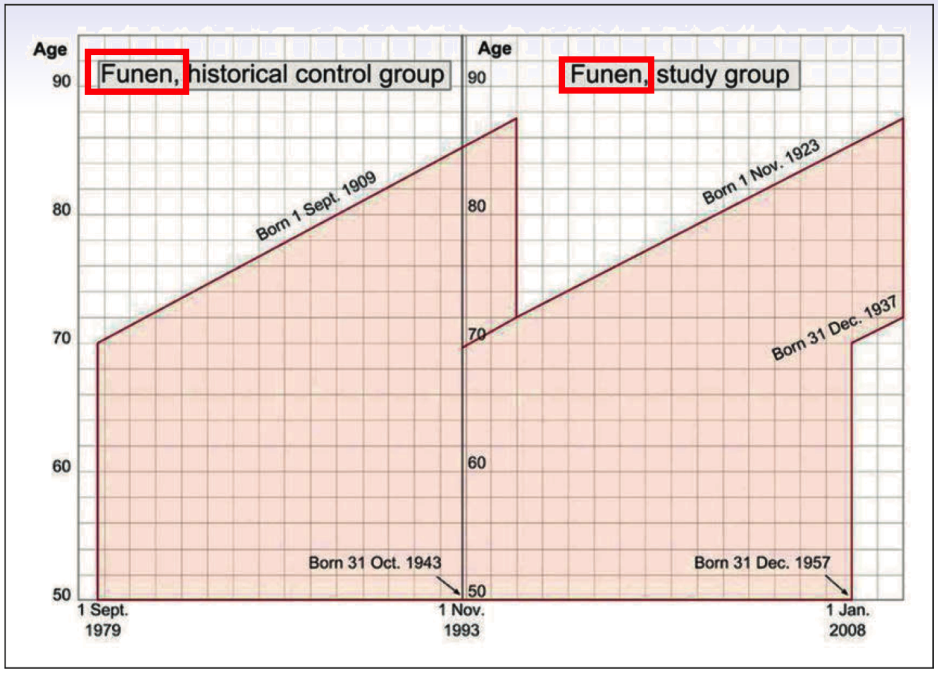
Deaths per 100,000 WY

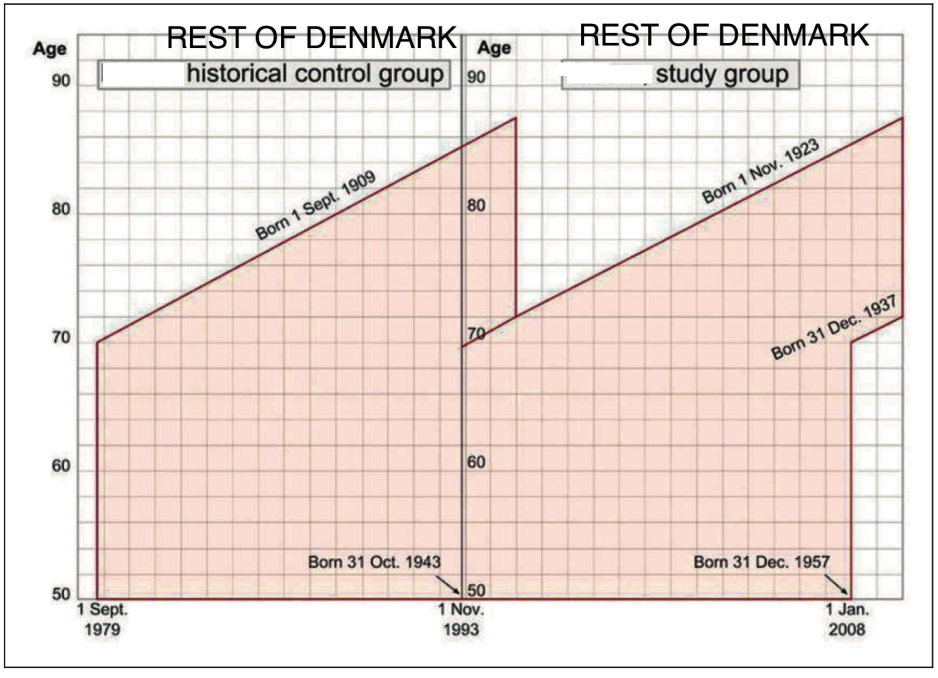


Deaths per 100,000 WY



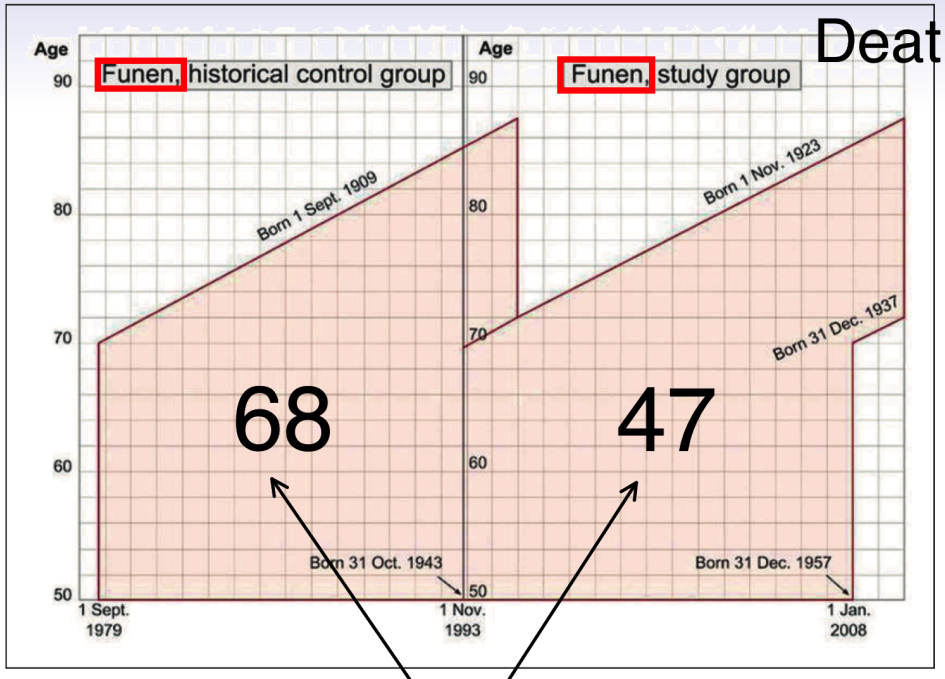
HR = 0.75

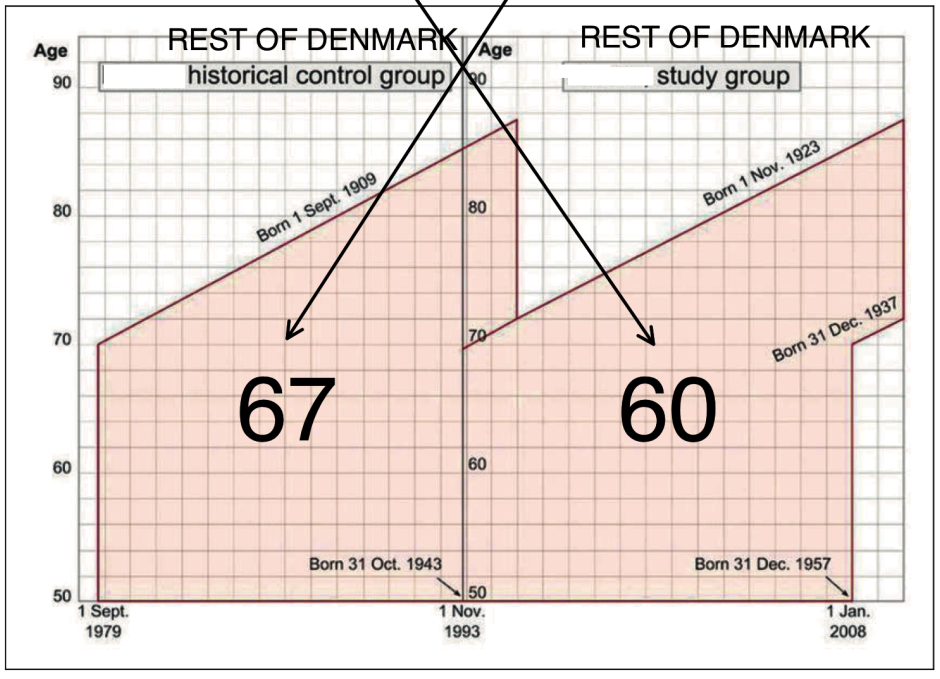

Age
Funen, historical control group
Born 1 Sept. 1909
Born 31 Oct. 1943
1 Sept. 1979
1 Nov. 1993
Age
Funen, study group
Born 1 Nov. 1923
Born 31 Dec. 1937
Born 31 Dec. 1957
1 Jan. 2008
90
80
70
60
50


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

Review of European studies

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

Table 1 Incidence-based breast cancer mortality studies with expected mortality estimated from women not yet invited

Reference	Country, region and age group for study group	Person years, study group	Person years, comparison group	Accrual period	Follow-up Period	Years of screening	Individual data on cases	Individual data on all women	Relative risk, invited to screening	95% Confidence interval
Accrual period = follow-up time for breast cancer deaths										
Hakama *et al.* (1997)[3]	Finland, two-third of municipalities, 50–64 y	89,893*	68,862*	1987–1992	1987–1992	≤6 y	Yes	Yes	0.76	0.53–1.09
Anttila *et al.* (2002)[4]	Finland, Helsinki, 50–59 y	161,400	155,400	1986–1997	1986–1997, average 10 y	1986–1997, average 10 y	Yes	No	0.81†	0.62–1.05
Accrual period<follow-up time for breast cancer deaths										
Paci *et al.* (2002), EJC[6]	Italy, Florence, 50–69 y	254,890	NA	1990–1996	1990–1999‡	1990–1996	Yes	No	0.81§	0.64–1.01

NA, not applicable, y, years
*Number of women at baseline
†Adjusted for difference in prescreening age
‡Follow-up time not equally distributed in invited cohort and non-invited cohort
§Not adjusted for lead time

Table 2 Incidence-based breast cancer mortality studies with expected mortality estimated from regional and historical comparison group(s)

Reference	Country, region and age group for study group	Person years, study group	Person years, comparison group(s)*	Accrual period	Follow-up period	Years of screening	Individual data on cases	Individual data on all women	Relative risk, invited to screening	95% Confidence interval
Accrual period = follow-up time for breast cancer deaths										
Olsen *et al.* (2005)[7]	Denmark, Copenhagen, 50–69 y	430,823	634,244, 4,396,417, 4,055,004	1991–2001	1991–2001	1991–2001	Yes	Yes	0.75	0.63–0.89
Sarkeala *et al.* (2008)[8]	Finland, eight municipalities, 50–69 y†	228,527	256,548, NR, NR	1992–2003	1992–2003	1992–2003	Yes	No	[0.69]	NR
Accrual period<follow-up time for breast cancer deaths										
Jonsson *et al.* (2001)[11]	Sweden, seven counties in south, 50–69 y	2,036,000	2,046,000, 1,296,000, 1,265,000	1979–1986/ 1980–1987 depending on county	Accrual period + 4 y	7 y 1979–1986/ 1980–1987	Yes	No	0.87‡	NR
Jonsson *et al.* (2003)[12]	Sweden, Gävleborg, 40–64 y	885,000	2,581,000, 957,000, 2,650,000	1974–1984/ 1979–1989 depending on county	Accrual period + time until end 1998	10 y 1974–1984/ 1979–1989	Yes	No	0.82§,**	0.71–1.05
Parvinen *et al.* (2006)[13]	Finland, Turku, 55–69 y	204,896	549,331, 199,329, 618,415	1987–1997	Accrual period + 4 y	11 y 1987–1997	Yes	No	0.75††	0.49–1.14
Jonsson *et al.* (2007)[14]	Sweden, two counties in north, 50–69 y	707,742	539,184‡‡, NR, NR	1989–1996	Accrual period + time until end 2001	7 y 1989–1996	Yes	No	0.84§§	NR
Age at diagnosis<age at breast cancer death										
Kalager *et al.* (2010)[10]	Norway, all, 50–69 y	2,337,323	2,197,469, 1,866,741, 1,898,989	1996–2005	1996–2005	1996–2005	Yes	No	[0.88]***	[0.73–1.05]***
Kalager *et al.* (2010) – re-analysis long follow-up	Norway, four counties, 50–69 y	1,430,069	1,371,444, 459,362, 443,685	1996–2005	1996–2005, Max 10 y	1996–2005	Yes	No	0.81	0.62–1.05
Kalager *et al.* (2010) – re-analysis short follow-up	Norway, 15 counties, 50–69 y	907,254	826,025, 1,407,379, 1,455,304	2000–2005	2000–2005 Max 2–6 y†††	2000–2005	Yes	No	0.99	0.71–1.37

NR, not reported, y, years

[ ] calculated by the authors based on reported data

*In the order: historical, regional and regional–historical comparison group

†Reduction in breast cancer mortality when screening women aged 50–69 years was compared with screening women aged 50–59 years

‡With adjustment for inclusion bias

§Estimate with a conservative adjustment for lead time

**Using neighbouring counties as control group

††Turku compared with Tampere is claimed to be the best estimate of a screening effect as there is no interaction between region and time in this comparison

‡‡Regional comparison group

§§Calculated from Table 4, Jonsson *et al.* 2007. The estimate is hereafter as described in the article, decreased by 2% to adjust for lead-time bias. This provides a conservative adjustment for lead time

***Reported by authors as the difference between the relative risks for the non-screening and screening areas, respectively. 82% reduction − 72% reduction = 10% reduction (95% confidence interval −4 to 24) [11]

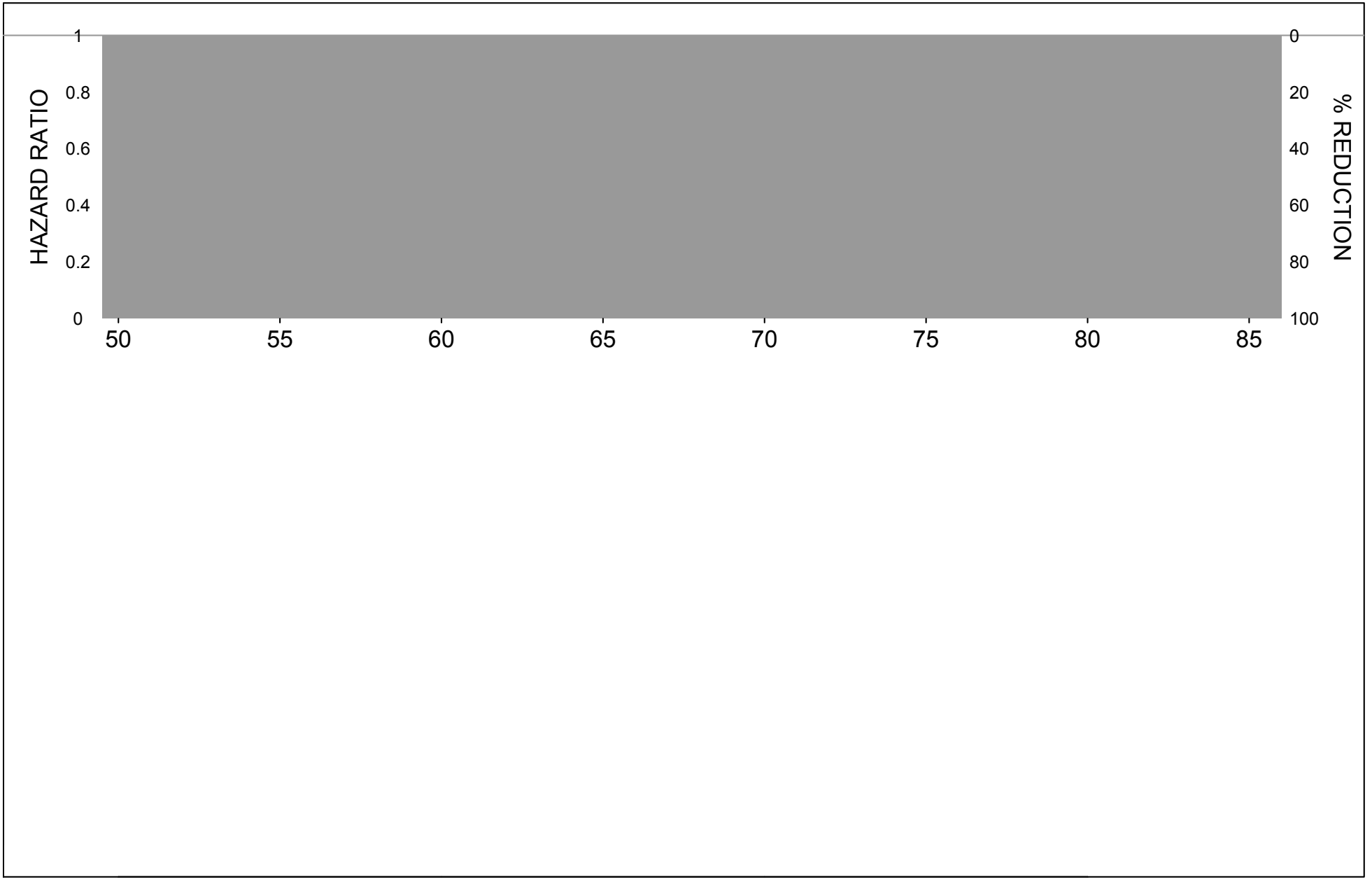
†††Length of follow-up depending on county

Table 3 Incidence-based breast cancer mortality studies with expected mortality estimated from historical comparison group and non-participants*

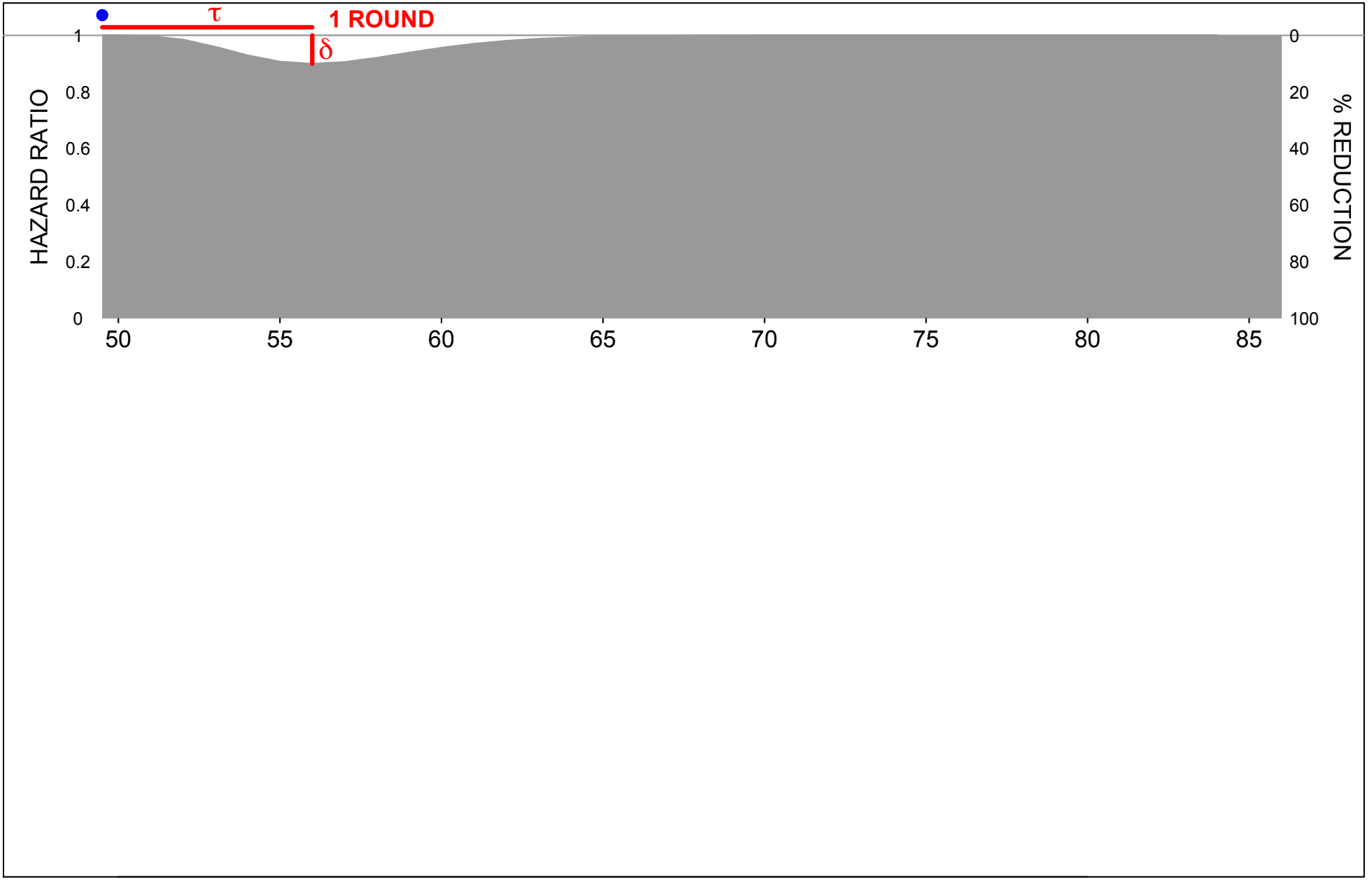
Reference	Country, region and age group for study group	Person years, Study Group	Person years, comparison group	Accrual period	Follow-up period	Years (y) of screening	Individual data on cases	Individual data on all women	Relative risk, invited to screening	95% Confidence interval
Accrual period = follow-up time for breast cancer deaths										
Tabar *et al.* (2001)[15]	Sweden, two-county, 40–69 y	1,100,931	1,213,136	1988–1996	1988–1996 study: 9 y, Comparison: 10 y	Max 9 y	Yes	No	0.52†	0.43–0.63
Duffy *et al.* (2002)‡[16]	Sweden, Dalarna+, Gävleborg, 40–69 y	1,797,819	1,823,057	1978–1997/ 1984–1998 depending on county	1978–1997/ 1984–9198 depending on county	Max 20/ 15 y§ depending on county	Yes	No	0.68**,†††	0.60–0.77
Duffy *et al.* (2002)‡‡[16]	Sweden, five counties, 40–69 y	2,017,511	1,870,007	1989–1998 or part of it depending on county	1989–1998 or part of it depending on county	Max 5–10 y depending on county	Yes	No	0.82**,†††	0.72–0.94
Ascunce *et al.* (2007)§§[17]	Spain, Navarra, 45–65 y***	[293,000]	[289,000]	1991–2001	1997–2001	Max 11 y	Yes	No	0.58	0.44–0.75
Sarkeala *et al.* (2008)[8]	Finland, eight municipal, 50–69 y†††	228,527	NR	1992–2003	1992–2003	Max 12 y	Yes	No	0.72	0.51–0.97
Sarkeala *et al.* (2008)[9]	Finland, 260 municipal, 50–69 y†††,‡‡‡	2,731,268	NR	1992–2003	1992–2003 average 9.8 y	Max 12 y	Yes	No	0.78	0.70–0.87
SOSSEG, (2006)*[18]	Sweden, 13 areas, 40–69 y§§§	7,542,833	7,265,841	1980–1901 or part of it depending on area	Accrual period†††	Max 11–22 y depending on area	Yes	No	0.73****	0.69–0.77
Accrual period<follow-up time for breast cancer deaths and age at diagnosis<age at breast cancer death										
Anttila *et al.* (2008)[19]	Finland, 410 municipal., 50–64 y	3,118,700	NR	1992–1996	1992–2003	Max 5 y	Yes	No	0.89††††	0.81–0.98

NR, not reported, Y, years
[ ] calculated by the authors based on reported data
*Only the estimates from the two Sarkeala articles are based on data from non-participants
†Estimated for invited women adjusted for selection bias in actually screened women. Crude relative risk (RR): 0.50; adjusted RR: 0.52
‡All Swedish counties with >10 years screening
§Fifteen years in one county and 20 years in one county
**Adjusted for lead time when relevant due to screening in prescreening area
††Expected mortality only estimated based on historical comparison group
‡‡All Swedish counties with ≤10 years screening
§§Not completely incidence-based mortality study, as 9% of the breast cancer deaths in the study group had a breast cancer diagnose prior the first invitation to screening
***Deaths among women aged 50–69 years
†††Deaths among women aged 60–79 years
‡‡‡Of whom all were invited at ages 50–59, 40% at aged 60–64 and 20% at aged 65–69
§§§As an exception, the accrual period was five years shorter than the follow-up period for one of the 13 areas
****The expected mortality in the absence of screening estimated exclusively from the historical comparison group
††††Estimated from the historical comparison group and age groups not subjected for service screening

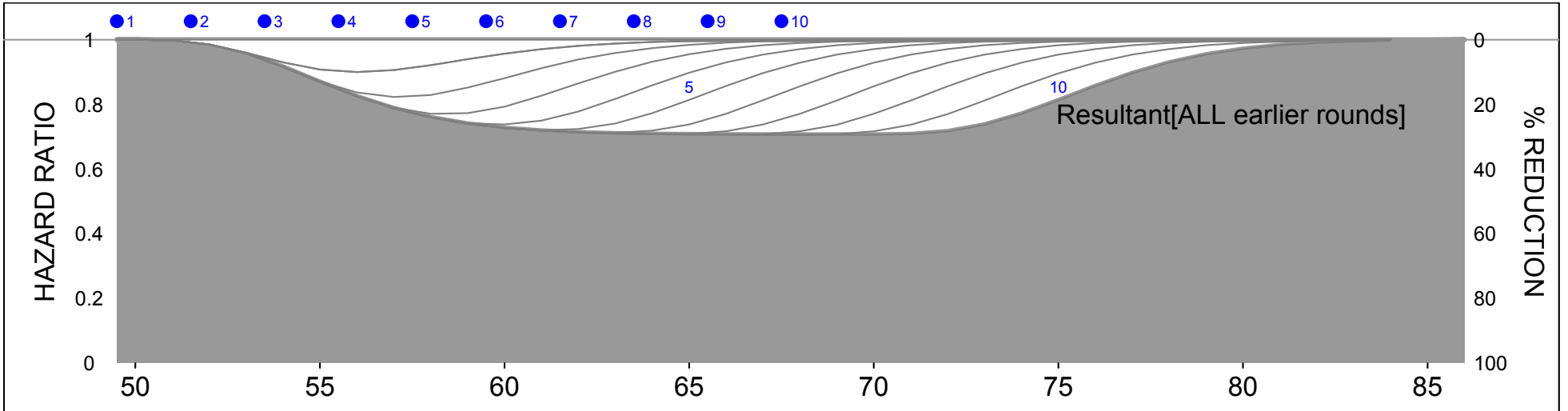
1-D time-pattern of mortality deficits (HRs) if NO screening: age 50 onwards



MODEL for 1-D time-pattern of mortality deficits (HRs) if ● round



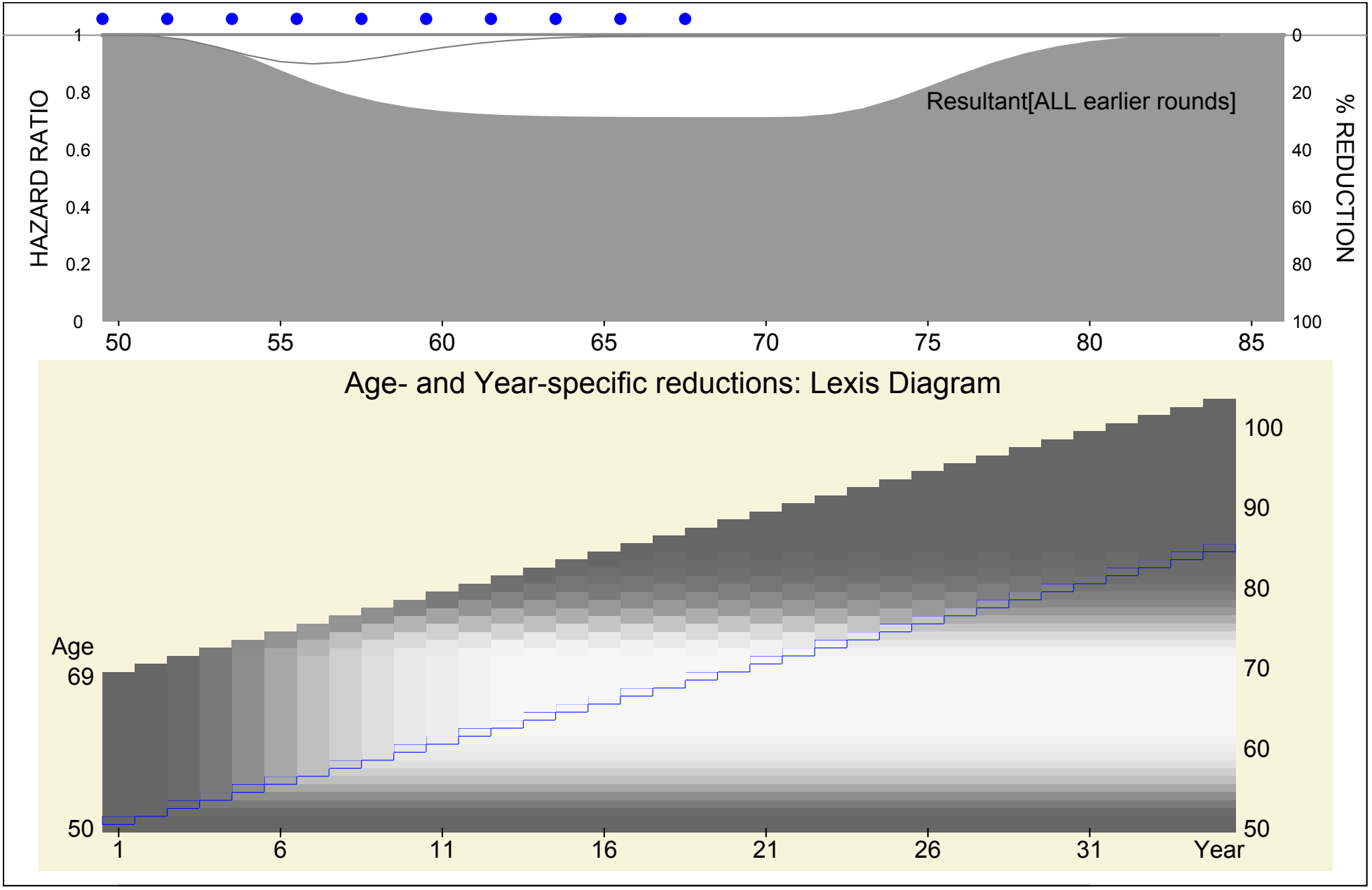
MODEL for 1-D HR pattern if ● ● ● ● ● ● ● ● ● ● rounds



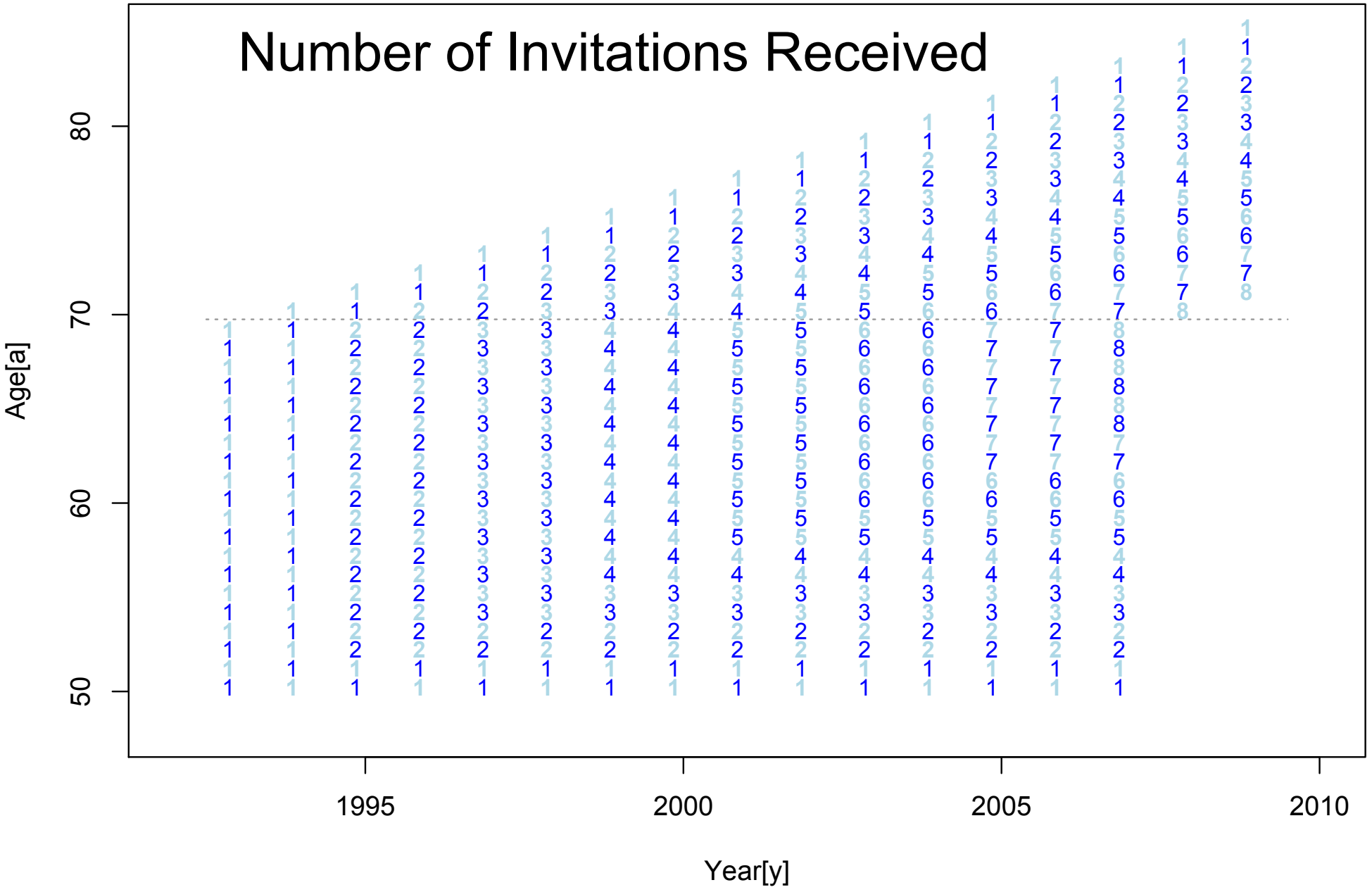
Zhihui (Amy) LIU **PhD Thesis** 2104

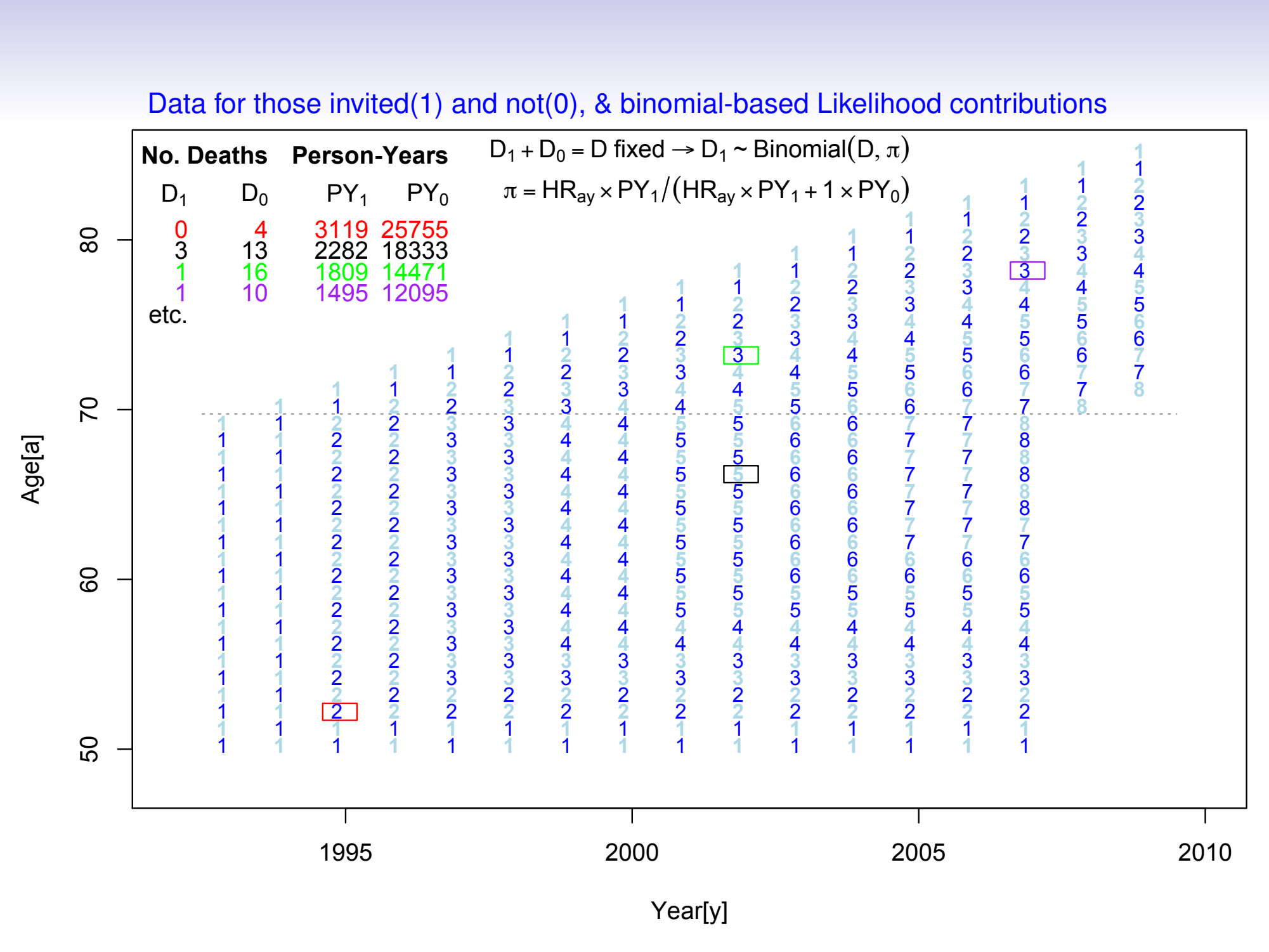
Zhihui (Amy) LIU, James A. Hanley , Olli Saarela and Nandini Dendukuri
A Conditional Approach to Measure Mortality Reductions Due to Cancer Screening
International Statistical Review (2015), 0, 0, 1?18 doi:10.1111/insr.12088

2-D [year-and- age-specific] time-pattern of mortality deficits

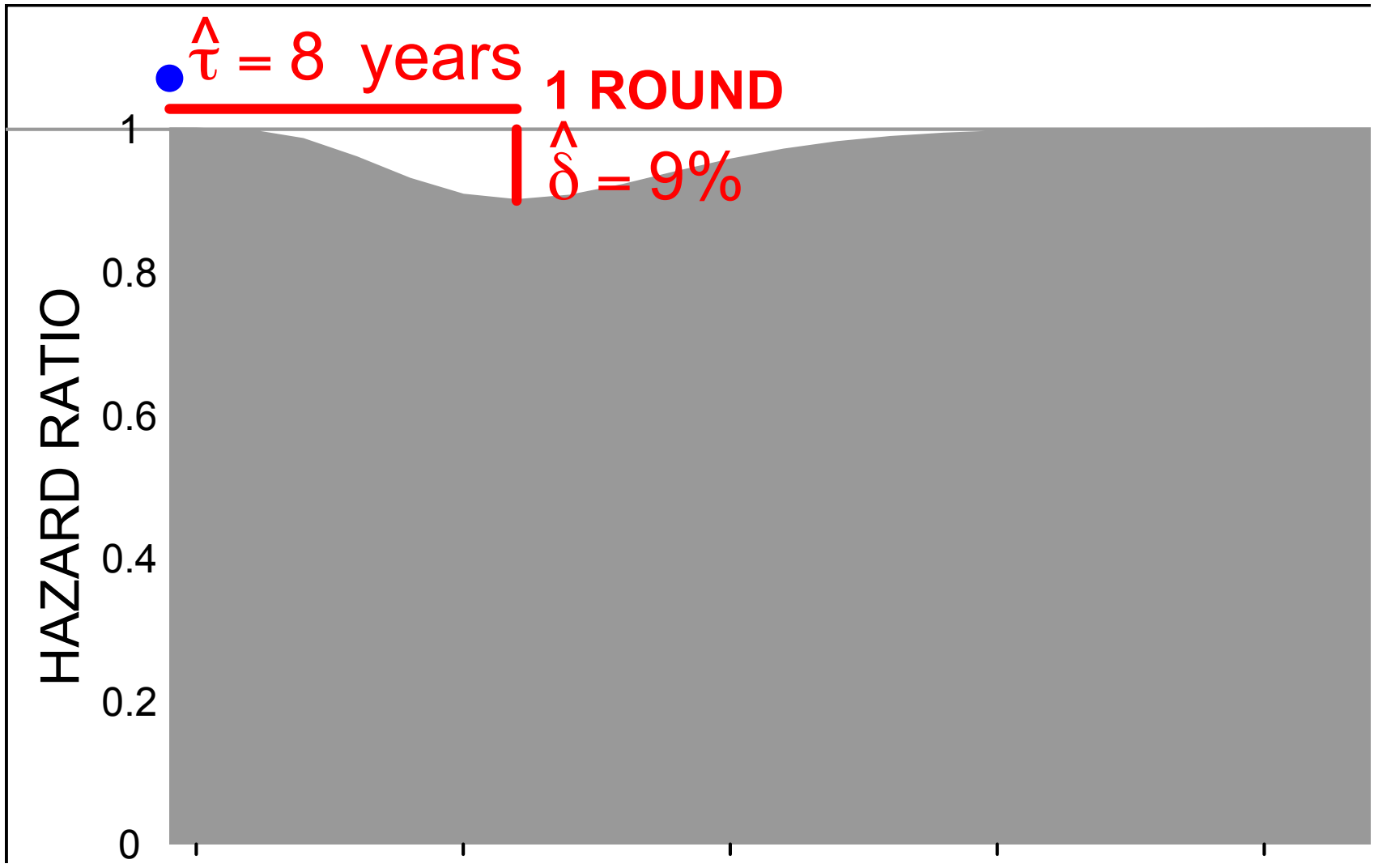


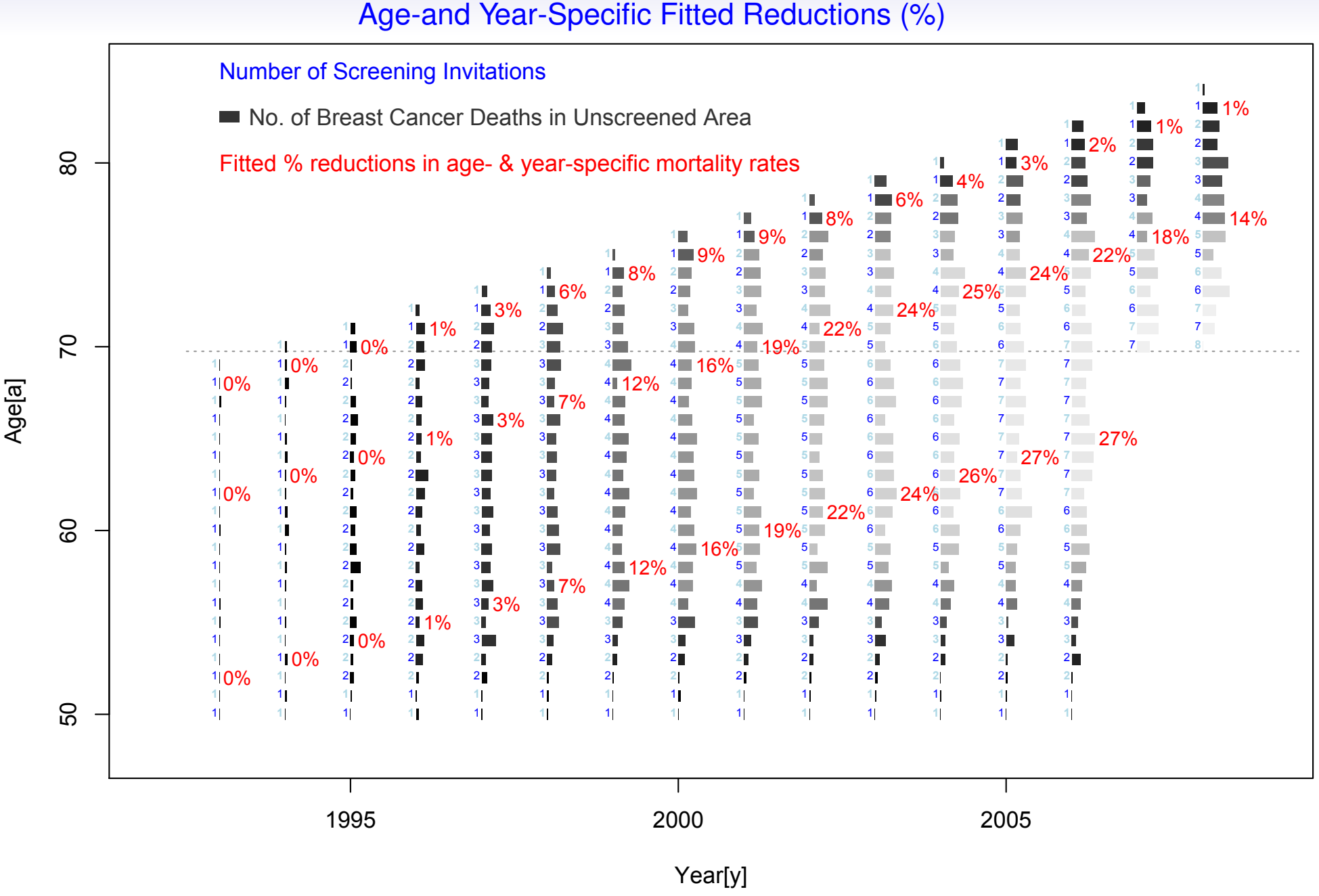
FUNEN birth cohorts




Data for those invited(1) and not(0), & binomial-based Likelihood contributions
No. Deaths
Person-Years
D1 D0 PY1 PY0
0 4 3119 25755
3 13 2282 18333
1 16 1809 14471
1 10 1495 12095
etc.
D1 + D0 = D fixed → D1 ~ Binomial(D, π)
π = HRay × PY1/(HRay × PY1 + 1 × PY0)
Age[a]
50
60
70
80
1995
2000
2005
2010
Year[y]

Fitted parameters for Impact of 1 (i.e., Each) Round

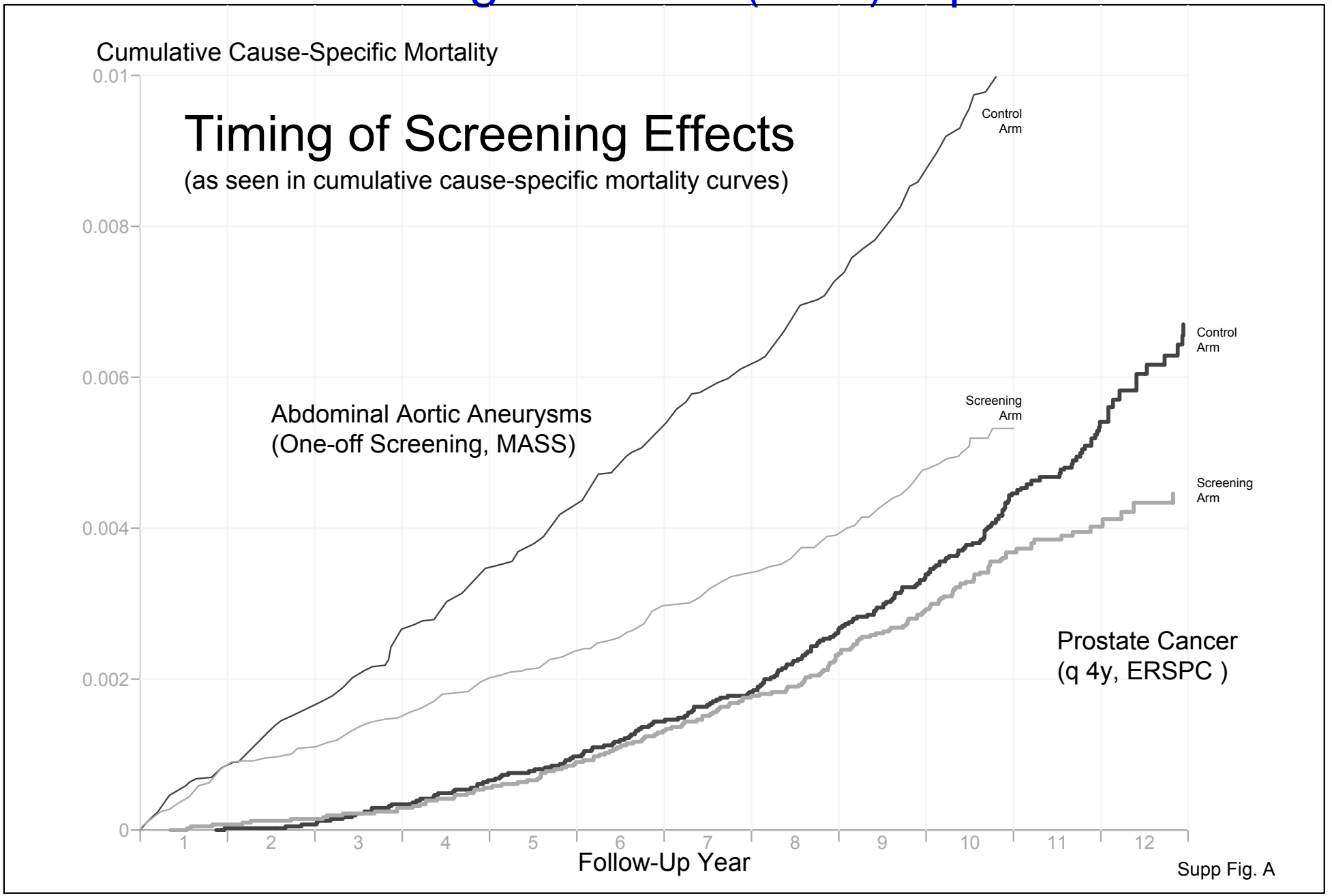



Age-and Year-Specific Fitted Reductions (%)
Number of Screening Invitations
No. of Breast Cancer Deaths in Unscreened Area
Fitted % reductions in age- & year-specific mortality rates
Age[a]
50
60
70
80
1995
2000
2005
Year[y]
0%
1%
2%
3%
4%
6%
8%
9%
12%
16%
19%
22%
24%
25%
26%
27%
18%
14%
7%

WHAT'S NEW & WHAT'S STILL TO DO ?

- We fitted a mortality-reduction (or HR) function that reflects the time-patterns that successful cancer screening is supposed to induce
- First ('prevalent') screen has a different composition, so its impact should be modelled with different parameters than subsequent rounds
- More years of data
- Evaluation of cancer screening is a long-distance activity; impact not easily summarized by a single-number summary

Loneliness of Long-Distance (non-)Experimentalist



Supp Fig. A

DOWNLOADS / FUNDING

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

or Google "James Hanley McGill"

Canadian Institutes of Health Research

A single Hazard Ratio is Appropriate if Reduction is VIRTUALLY IMMEDIATE & ...

- SUSTAINED
  - **Adult circumcision** quickly reduces the risk of **getting HIV** by about 50%; reduced rate is lifelong.
  - **Polio, HPV, ...** Once there is full immunity, **vaccine** protection lasts for decades.

or...

- STOP COUNTING AS SOON AS PROTECTION STOPS
  - **Blood thinners**
  - **beta blockers**

Reductions EVENTUALLY CEASE:

30-year follow-up in Minnesota Trial

Long-Term Mortality after Screening for Colorectal Cancer

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

ABSTRACT

BACKGROUND

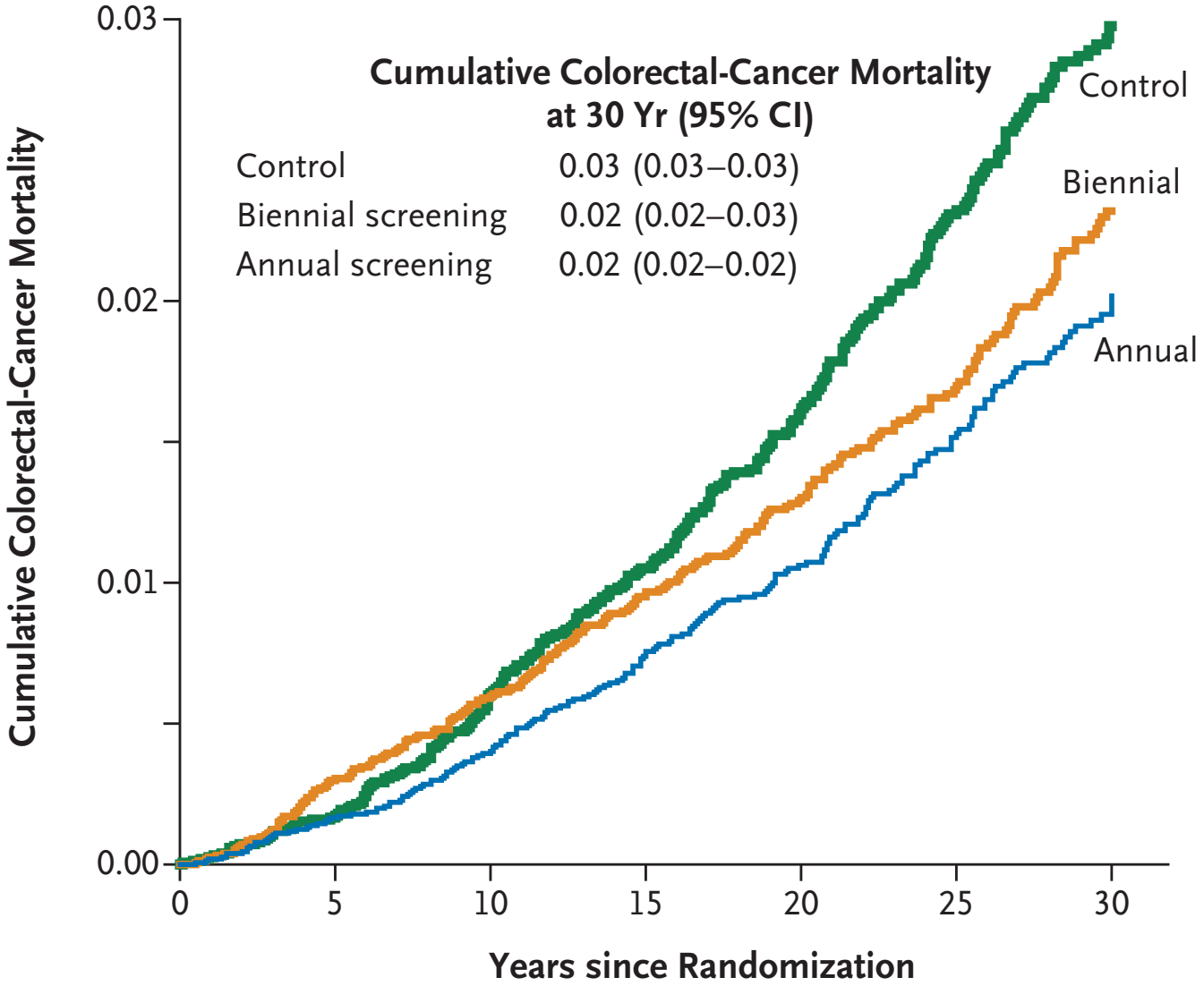
In randomized trials, fecal occult-blood testing reduces mortality from colorectal cancer. However, the duration of the benefit is unknown, as are the effects specific to age and sex.

METHODS

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

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

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



No. at Risk

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

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