HOW BIG ARE THE REAL MORTALITY REDUCTIONS PRODUCED BY CANCER SCREENING?

WHY DO SO MANY TRIALS REPORT ONLY 20%?

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McGill University, Montréal, Québec, CANADA

(SSC-sponsored) JSM Invited Session
Montréal
Aug 7, 2013

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  (v) focus on the parameters that describe impact of 1 round of screening

Outline

- The mortality reductions produced by a screening regimen: what payers want to know
- European Randomized Study of Screening for Prostate Cancer
  [and Göteborg portion of this study]
- Data-analysis practice in other cancer screening trials
- How to stop a screening RCT at a 20% mortality reduction? [Theorem]
- A way ahead?

What payers would like to know...

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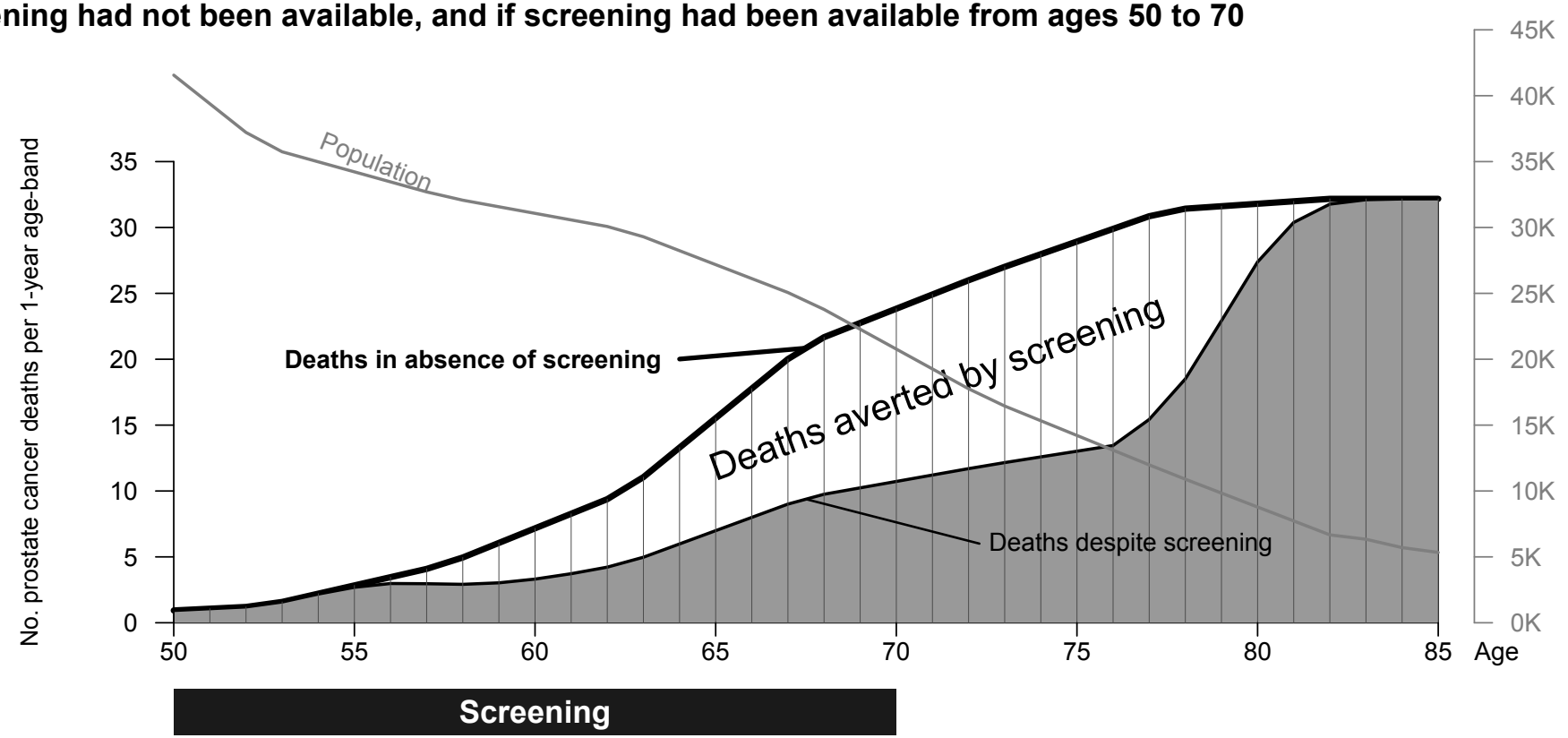

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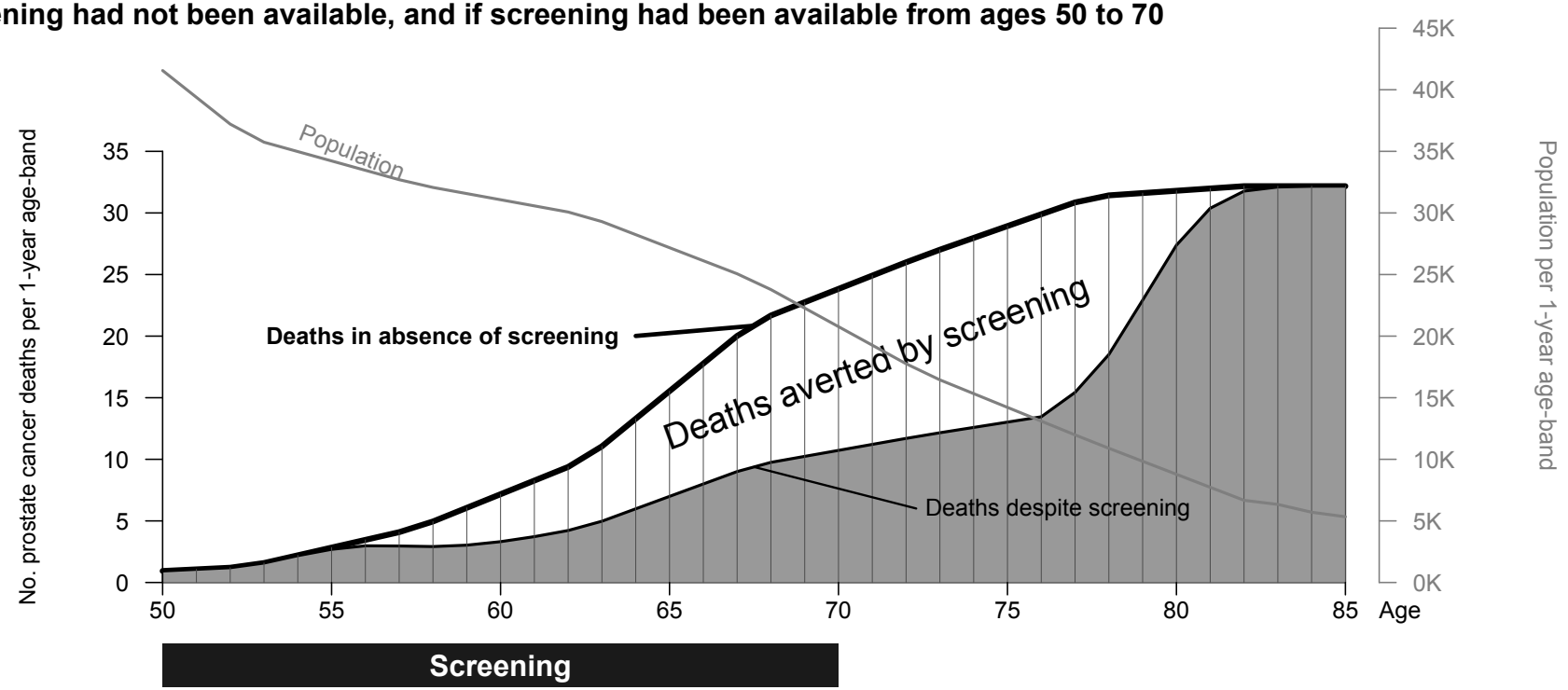
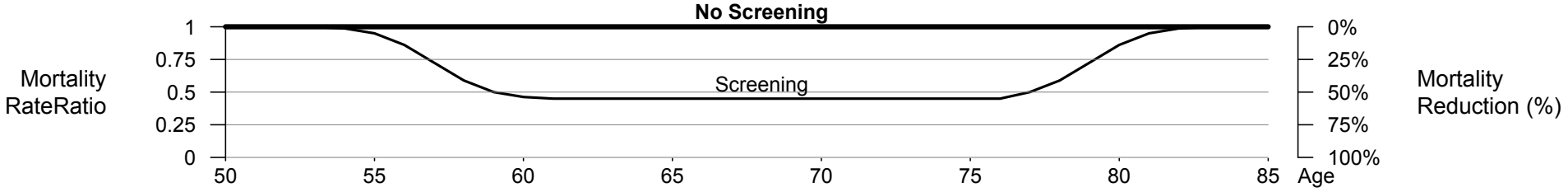


(b) The corresponding age-specific prostate cancer mortality rate ratios



Can they obtain these (or asymptote) from published reports?

Screening & Prostate-Ca Mortality in Randomized European Study ("ERSPC" nejm2009.04)

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As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. (...) The adjusted **rate ratio** for death from prostate cancer in the screening group was **0.80** (95% CI, 0.65 to 0.98; P=0.04).

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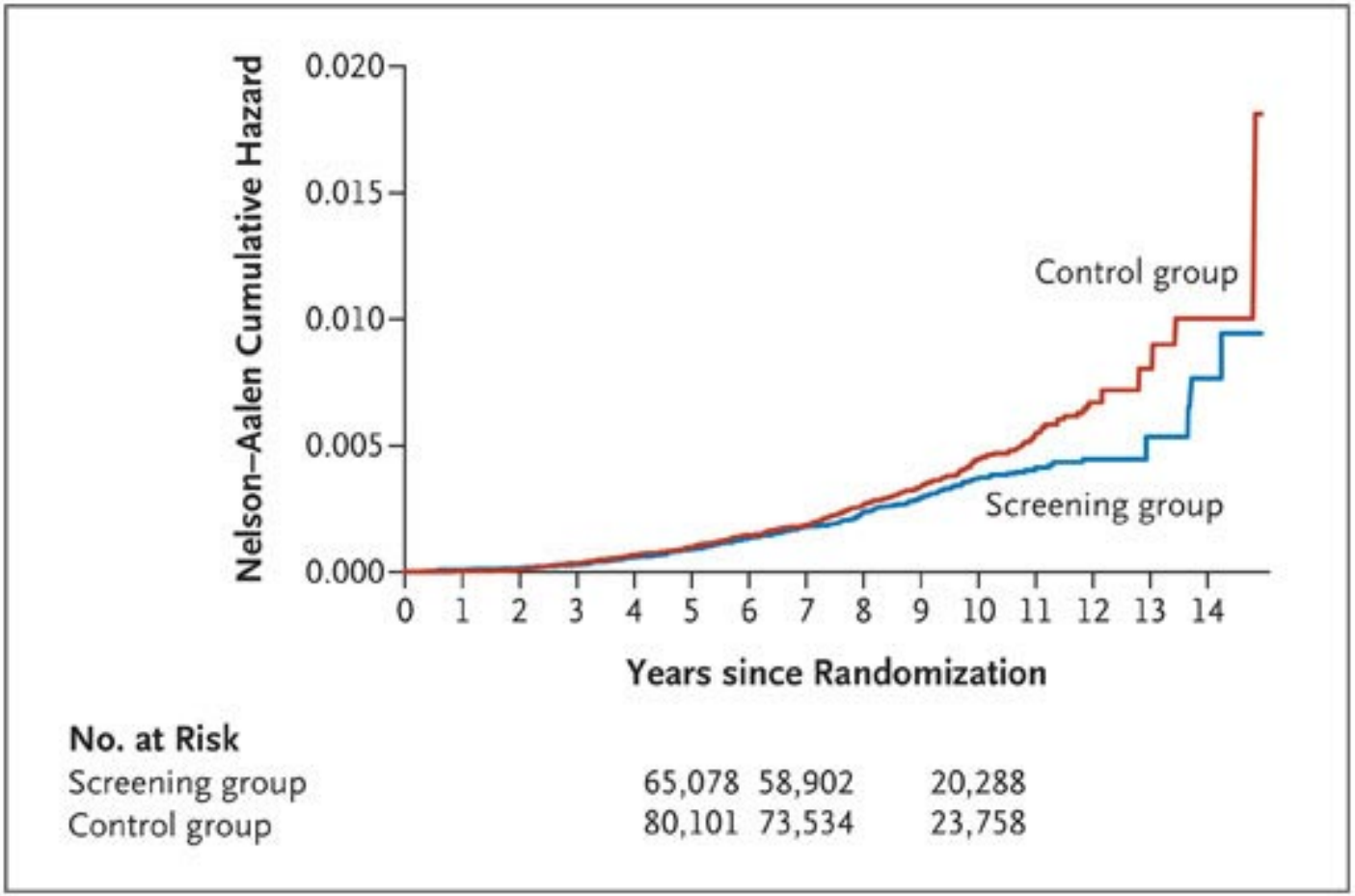
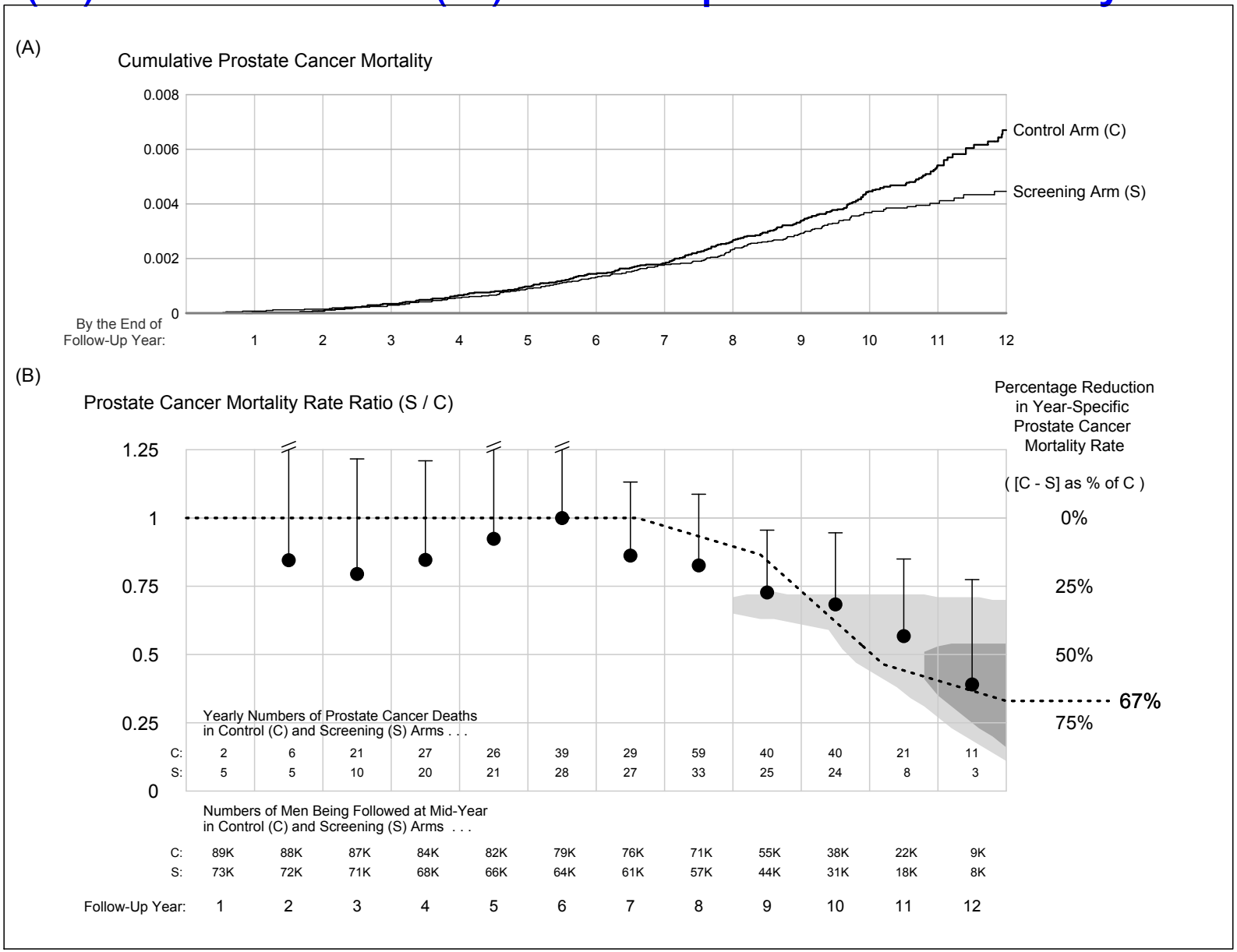


RE-ANALYSIS OF ERSPC DATA
using
year-specific prostate cancer mortality ratios

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



Hanley, *J Medical Screening*, 2010.

Göteborg randomised population-based prostate-cancer screening trial

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Methods In December, 1994, 20 000 men born between 1930 and 1944, randomly sampled from the population register, were randomised by computer in a 1:1 ratio to either a screening group invited for PSA testing every 2 years (n=10 000) or to a control group not invited (n=10 000). Men in the screening group were invited up to the upper age limit (median 69, range 67–71 years) and only men with raised PSA concentrations were offered additional tests such as digital rectal examination and prostate biopsies. The primary endpoint was prostate-cancer specific mortality, analysed according to the intention-to-screen principle. The study is ongoing, with men who have not reached the upper age limit invited for PSA testing. This is the first planned report on cumulative prostate-cancer incidence and mortality calculated up to Dec 31, 2008. This study is registered as an International Standard Randomised Controlled Trial ISRCTN54449243.

Findings In each group, 48 men were excluded from the analysis because of death or emigration before the randomisation date, or prevalent prostate cancer. In men randomised to screening, 7578 (76%) of 9952 attended at least once. During a median follow-up of 14 years, 1138 men in the screening group and 718 in the control group were diagnosed with prostate cancer, resulting in a cumulative prostate-cancer incidence of 12·7% in the screening group and 8·2% in the control group (hazard ratio 1·64; 95% CI 1·50–1·80; p<0·0001). The absolute cumulative risk reduction of death from prostate cancer at 14 years was 0·40% (95% CI 0·17–0·64), from 0·90% in the control group to 0·50% in the screening group. The rate ratio for death from prostate cancer was 0·56 (95% CI 0·39–0·82; p=0·002) in the screening compared with the control group. The rate ratio of death from prostate cancer for attendees compared with the control group was 0·44 (95% CI 0·28–0·68; p=0·0002). Overall, 293 (95% CI 177–799) men needed to be invited for screening and 12 to be diagnosed to prevent one prostate cancer death.

Interpretation This study shows that prostate cancer mortality was reduced almost by half over 14 years. However, the risk of over-diagnosis is substantial and the number needed to treat is at least as high as in breast-cancer screening programmes. The benefit of prostate-cancer screening compares favourably to other cancer screening programs.

Hugosson et al. Lancet Oncol. 2010 Aug;11(8):725-32. Epub 2010 Jul 2.

Mortality Results

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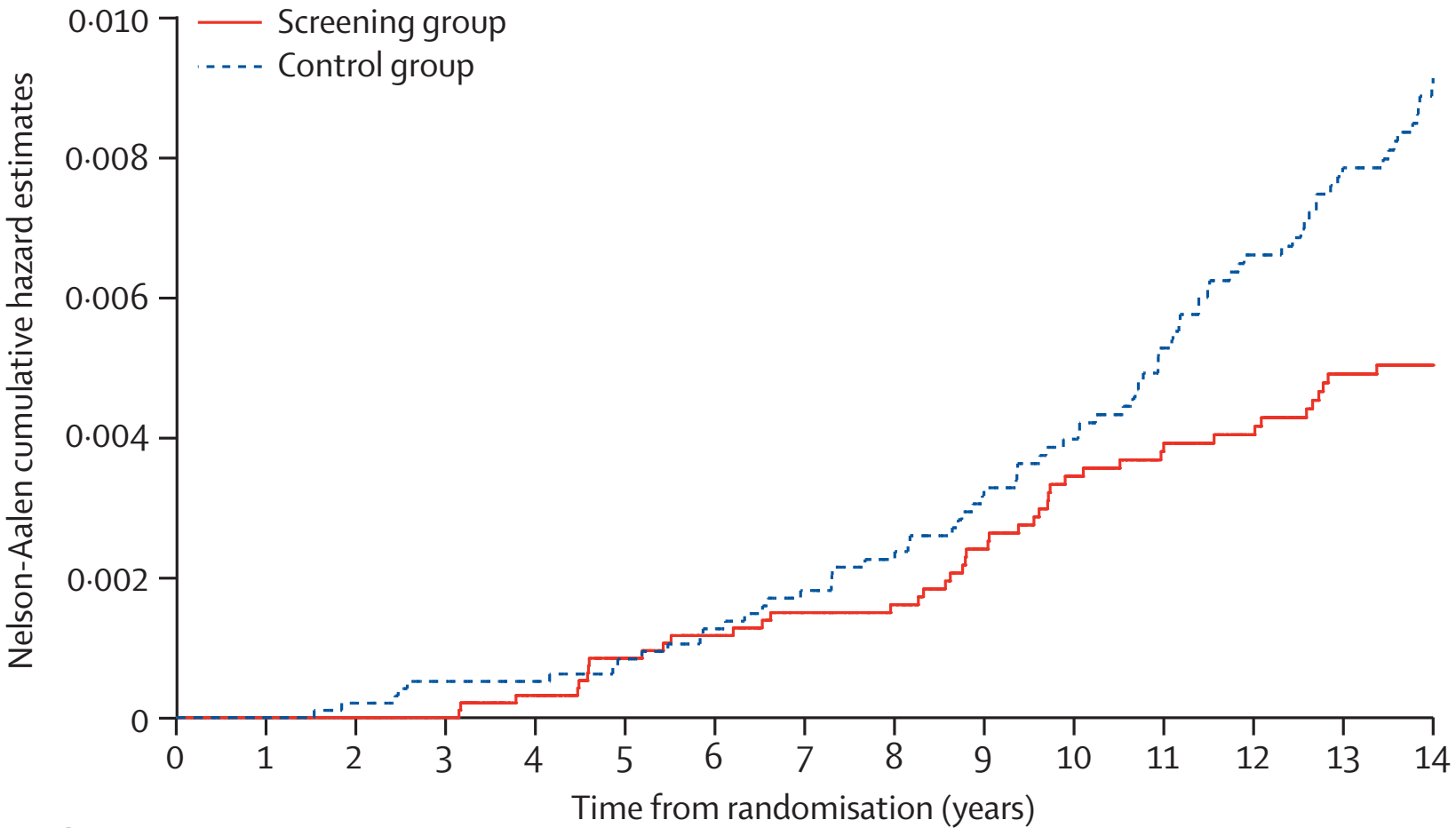

Number at risk

Screening group	9952	9333	8585	7746
Control group	9952	9345	8580	7755

***Figure 3*: Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates**

YEARLY numbers of Pr Ca Deaths in Control and Screening groups

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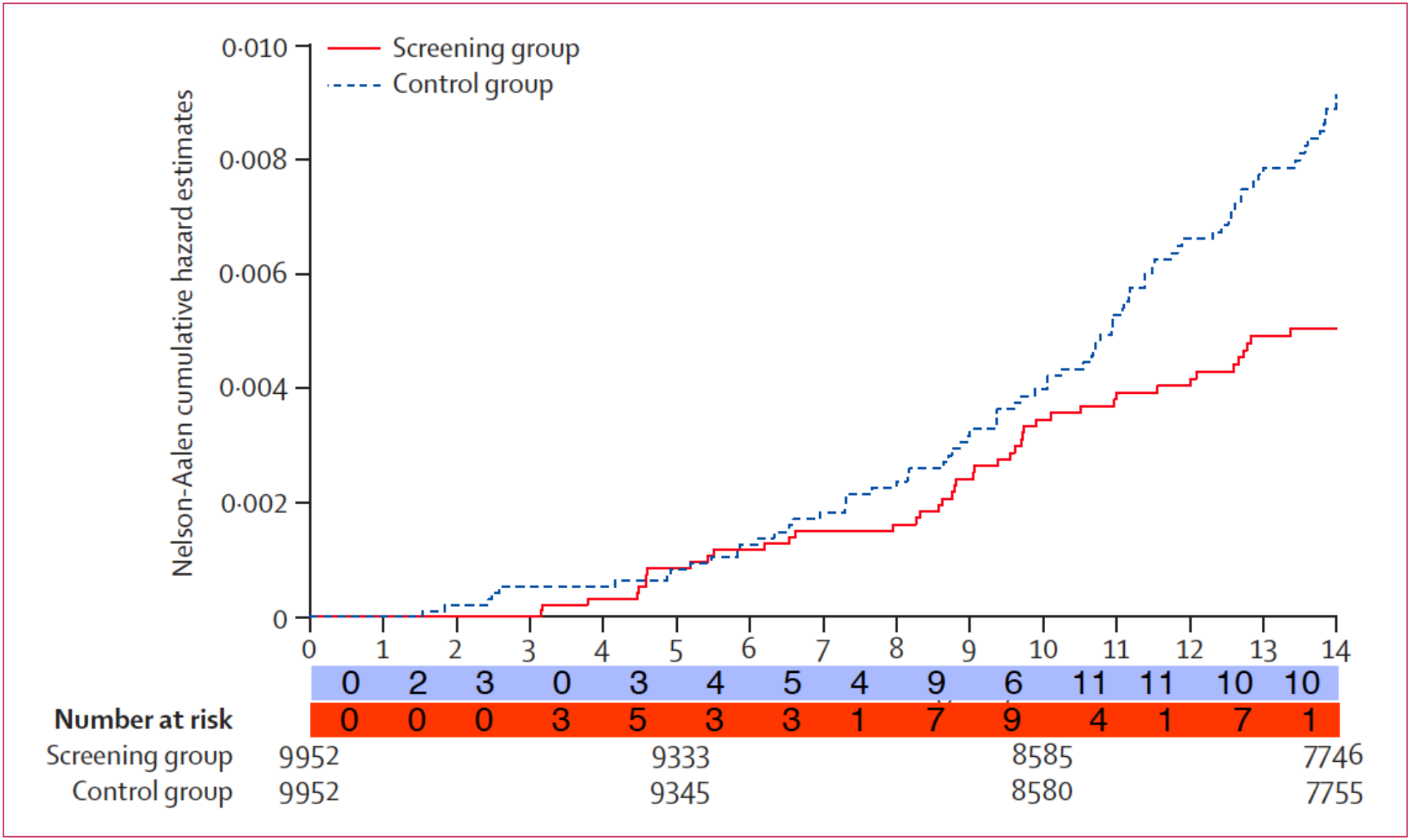

Figure 3: **Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates**

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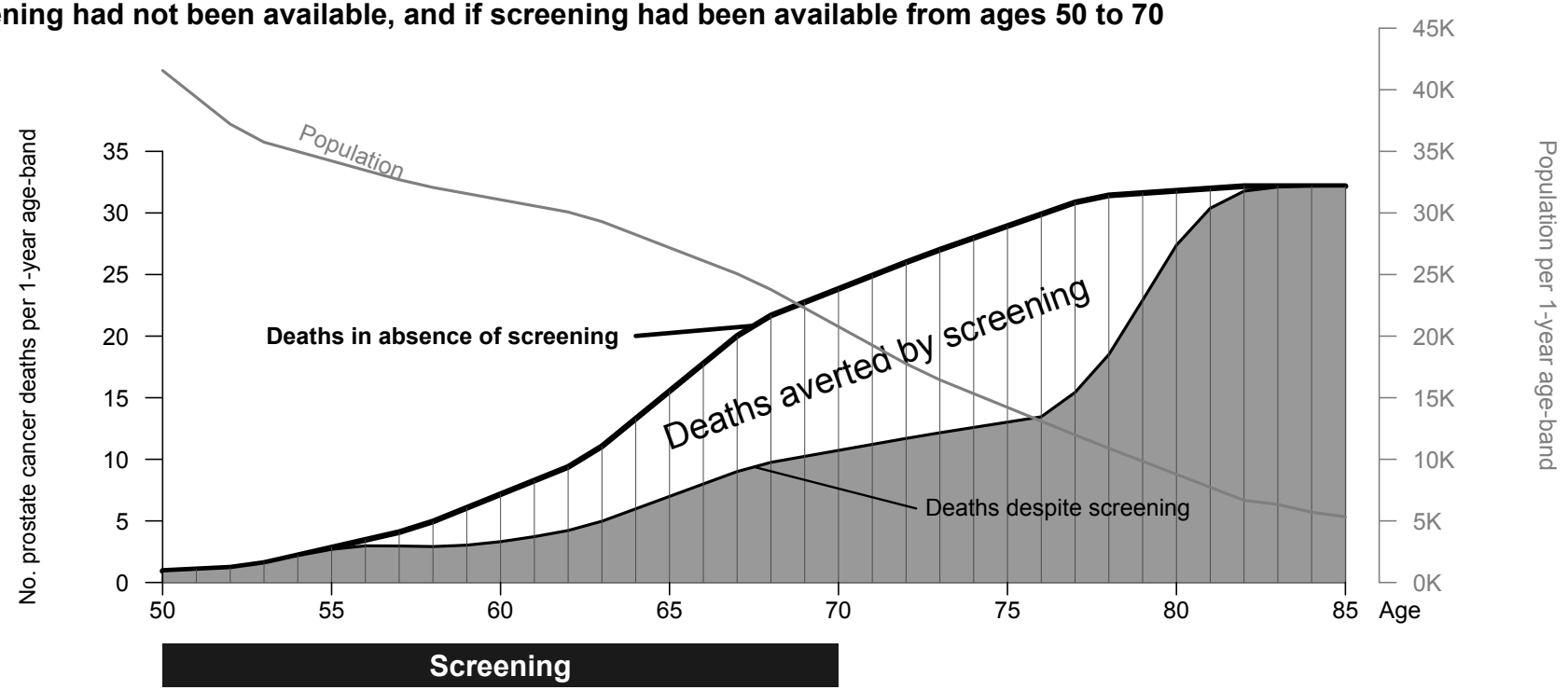

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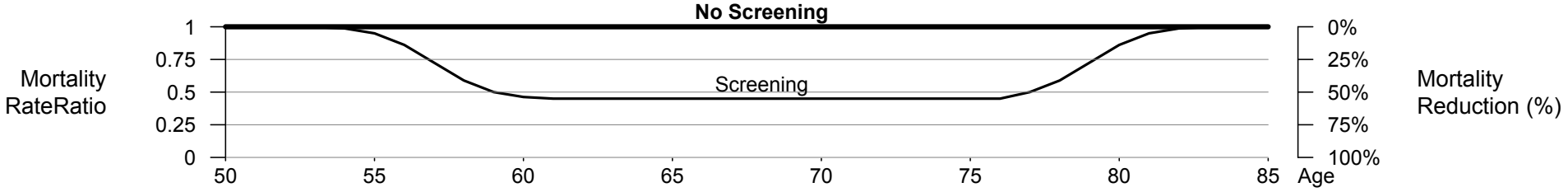

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- Hanley, Liu, Strumpf, Dendukuri, McGregor.
  "No.s of breast cancer deaths averted by mammography screening".
  (Response to Canadian Task Force on Preventive Health Care)
  ... manuscript under review at Canadian J Public Health
- Hanley JA, Z Liu Z, McGregor M. The [ratio of] benefits [to] harms of breast cancer screening. Letter re the Report The Independent UK Panel on Breast Cancer Screening (Lancet Nov 17, 2012)

LUNG CANCER

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What was reported (NEJM Aug 4, 2011) ...

Follow-up Year:	1	2	3	4	5	6	7	ALL
Screens	↑	↑	↑					
X-ray Arm:								442
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Year-specific data extracted from graph in that report ...

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CT Arm:	31	57	67	84	72	42	3	
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Further year-specific numbers essential to measure impact of 3 rounds of screening.

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A UNIVERSAL CONSTANT IN SCREENING TRIALS?

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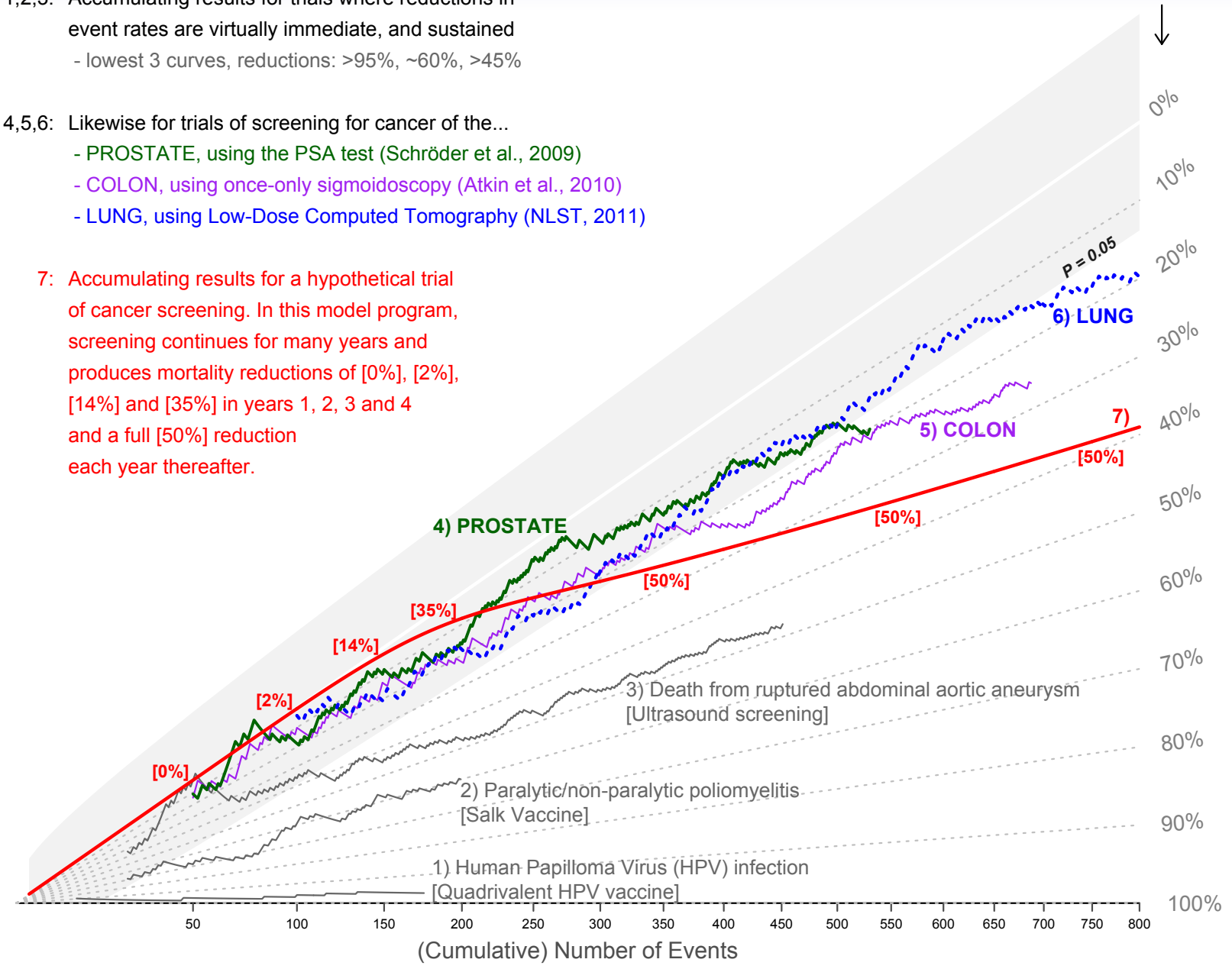
- when in f-up time events occurred (*'time-specific'* rates) ?

Percentage Reduction in Average Event Rate, if data are analyzed after indicated no. of events

1,2,3: Accumulating results for trials where reductions in event rates are virtually immediate, and sustained
- lowest 3 curves, reductions: >95%, ~60%, >45%

4,5,6: Likewise for trials of screening for cancer of the...
- PROSTATE, using the PSA test (Schröder et al., 2009)
- COLON, using once-only sigmoidoscopy (Atkin et al., 2010)
- LUNG, using Low-Dose Computed Tomography (NLST, 2011)

7: Accumulating results for a hypothetical trial of cancer screening. In this model program, screening continues for many years and produces mortality reductions of [0%], [2%], [14%] and [35%] in years 1, 2, 3 and 4 and a full [50%] reduction each year thereafter.



PLANS

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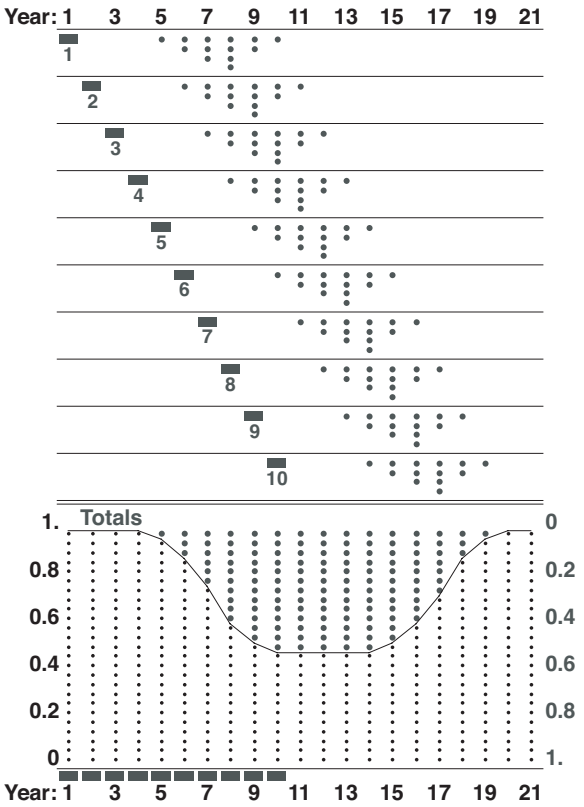

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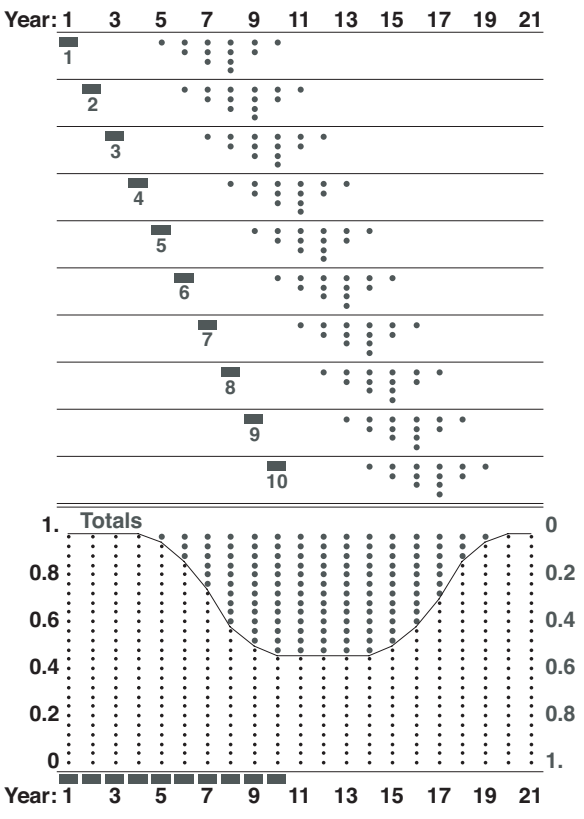

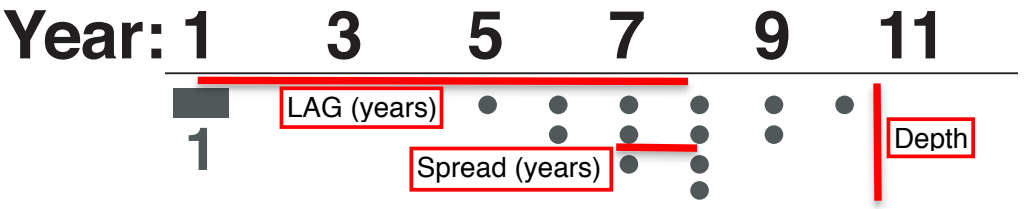

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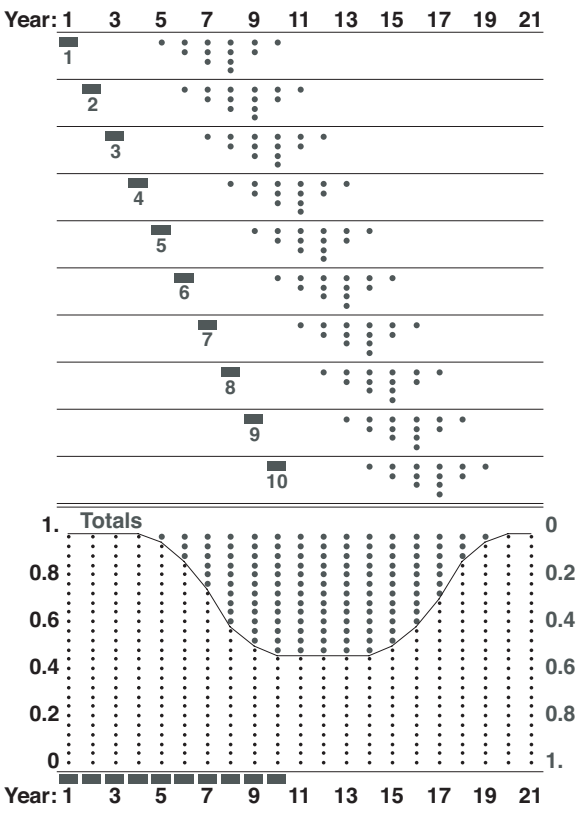

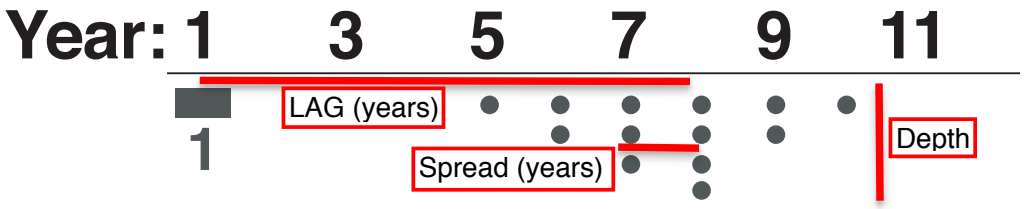

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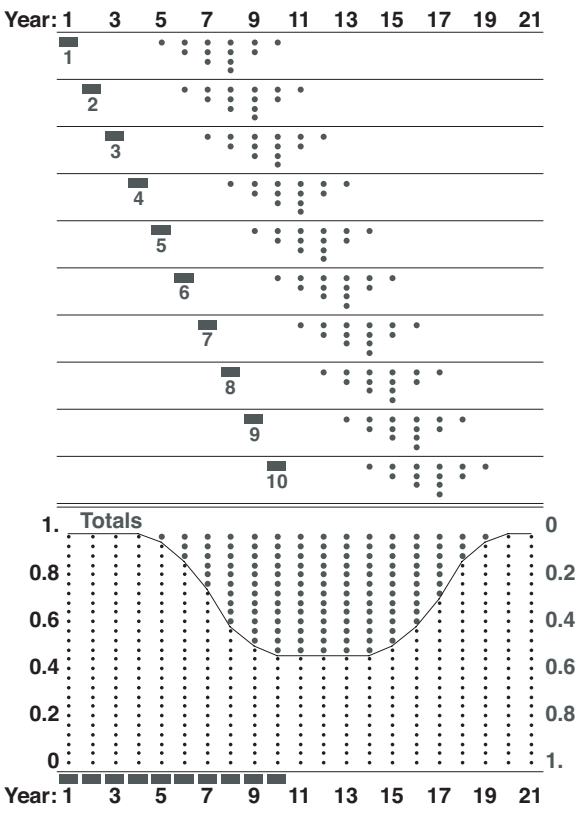

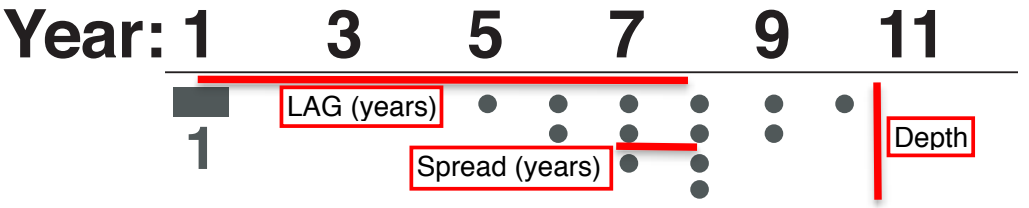

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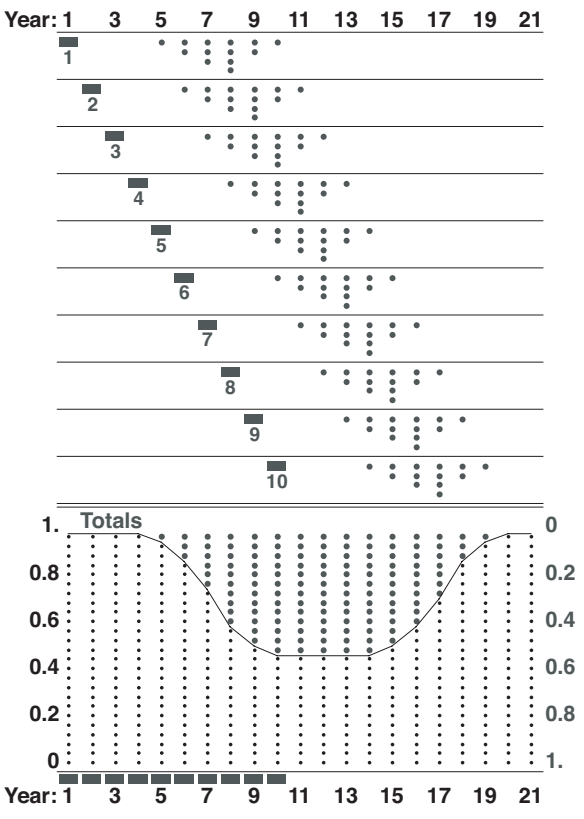

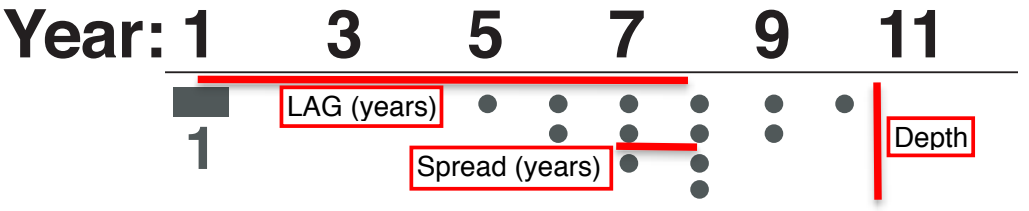

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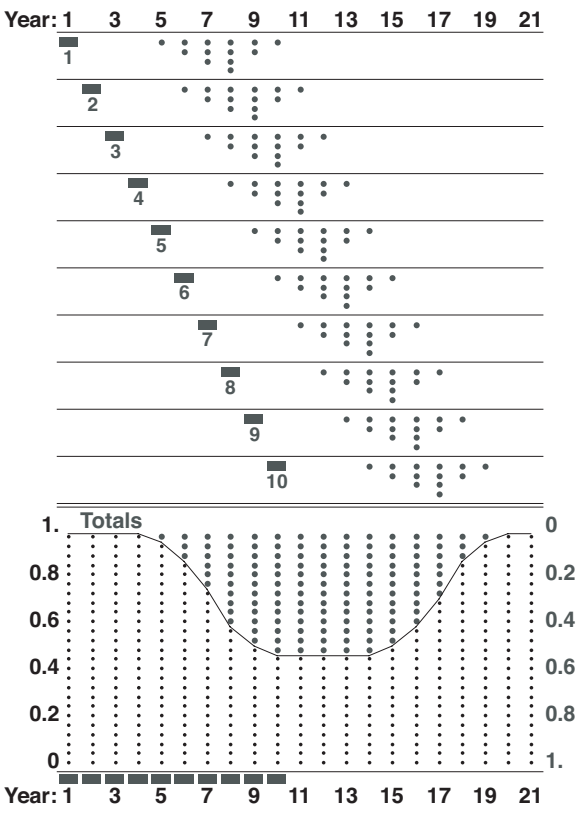

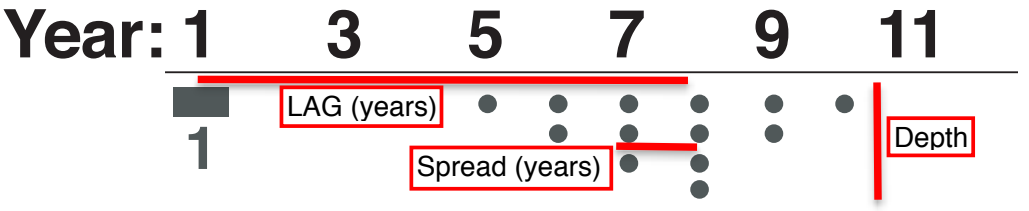

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- Design matrix: 1 row per y-a-s ‘cell’

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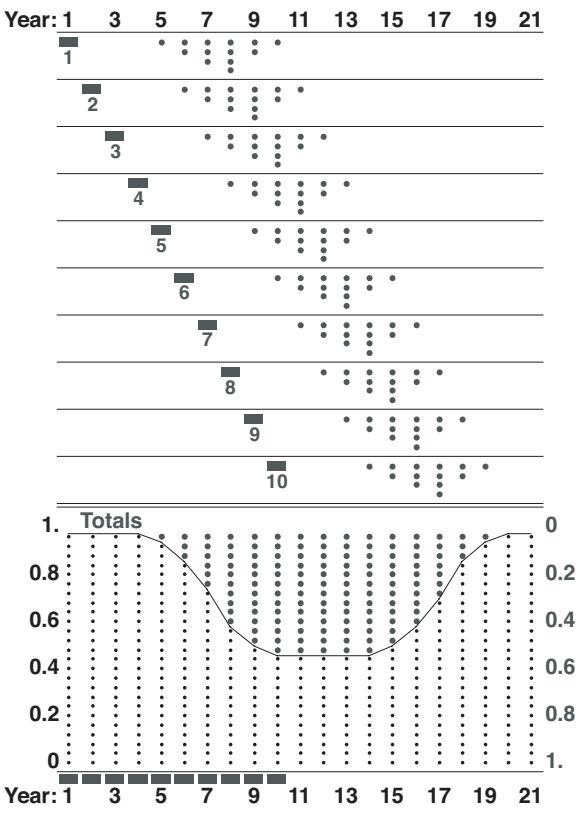

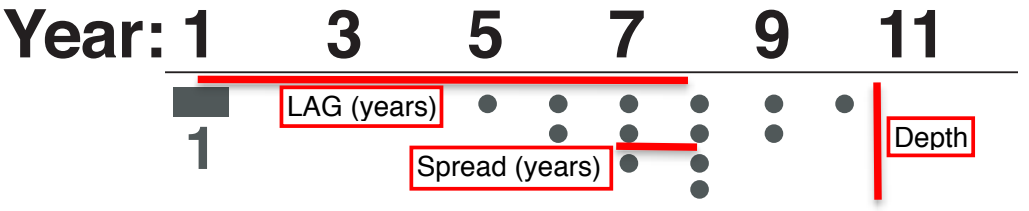

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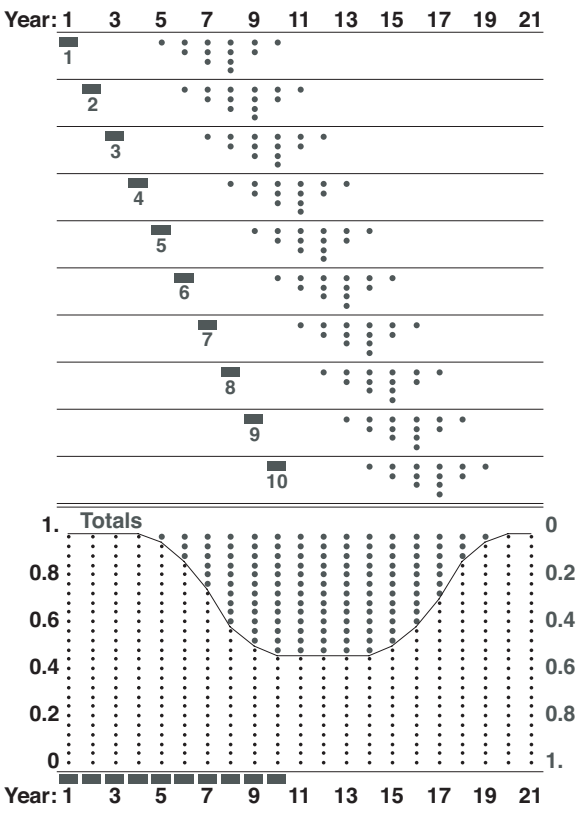

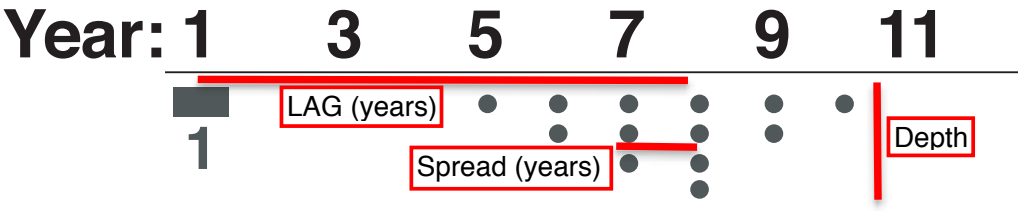

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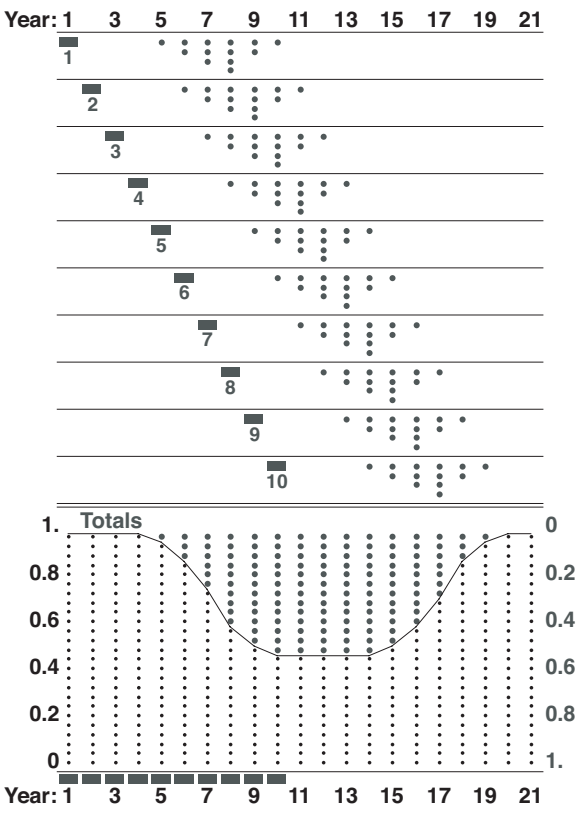

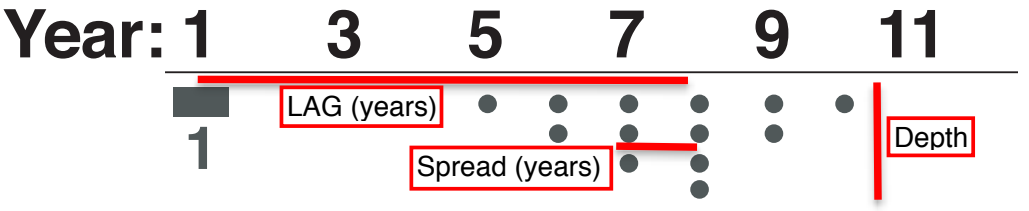

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- **USE**: project mort. reductions due to a screening regimen

Mortality deficits produced by 1 or more rounds of screening

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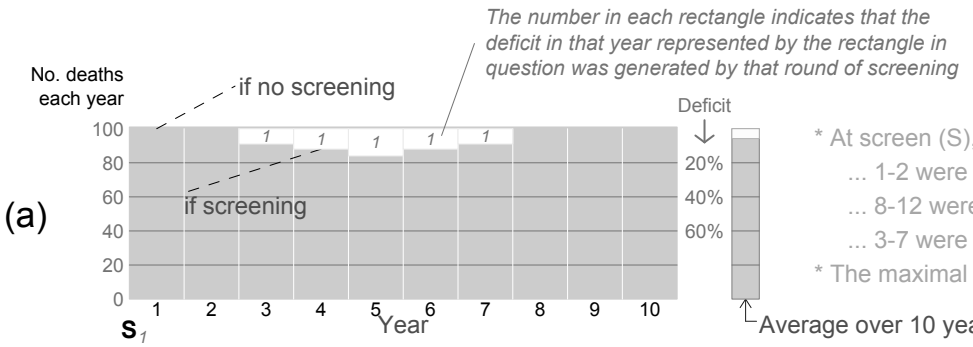
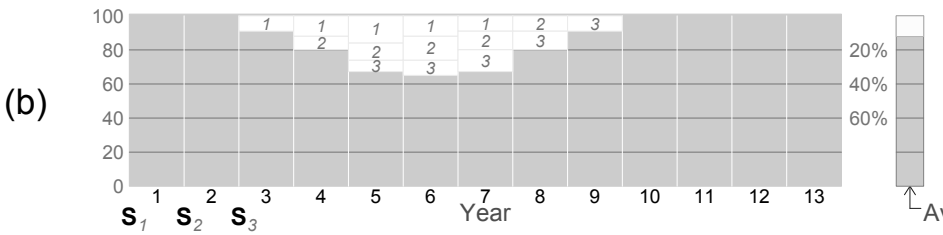
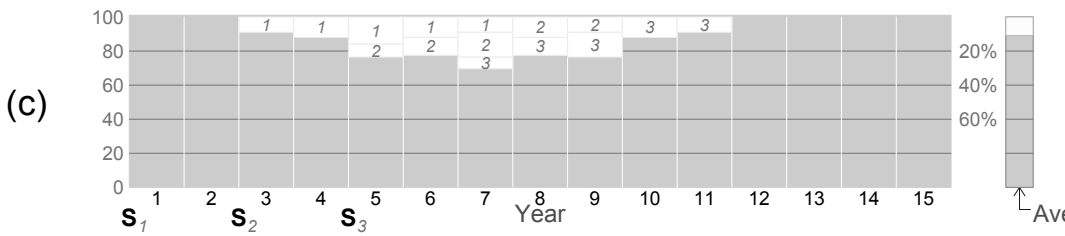


Description/remarks

* At screen (S), most/some cancers that -- S absent -- would have proved fatal in years
  ... 1-2 were probably screen-detectable, but already incurable [null mortality deficit];
  ... 8-12 were probably curable, but still undetectable [null mortality deficit];
  ... 3-7 were probably screen-detectable, and curable [some mortality deficits].
* The maximal mortality deficit produced by 1 round of screening is in year 5.



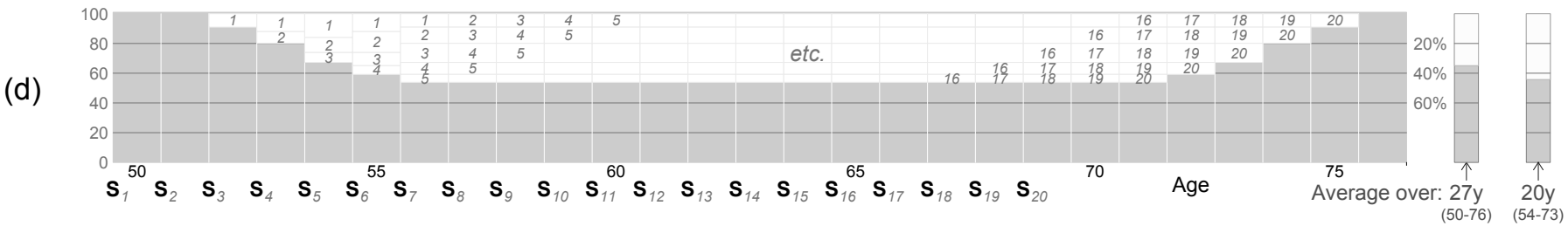
* 3 rounds of screening, 1 year apart, produce greater mortality deficits over a more prolonged time-window.
  [numbers in rectangles indicate deficits generated by successive rounds]
* The maximal mortality deficit, in year 6, is SMALLER THAN those produced by SUSTAINED screening: see asymptote in (d) below.



* 3 rounds of screening, 2 years apart, produce deficits shallower than those in (b), but extending over a wider time-window.

* The maximal mortality deficit, in year 7, would be achieved again in years 9, 11, ... if there were more than 3 such rounds.

Mortality deficits produced by once-a-year screening for 20 years, beginning when women reach 50, and ending when they reach 69



Observed breast cancer mortality deficits in 5 Mammography Trials

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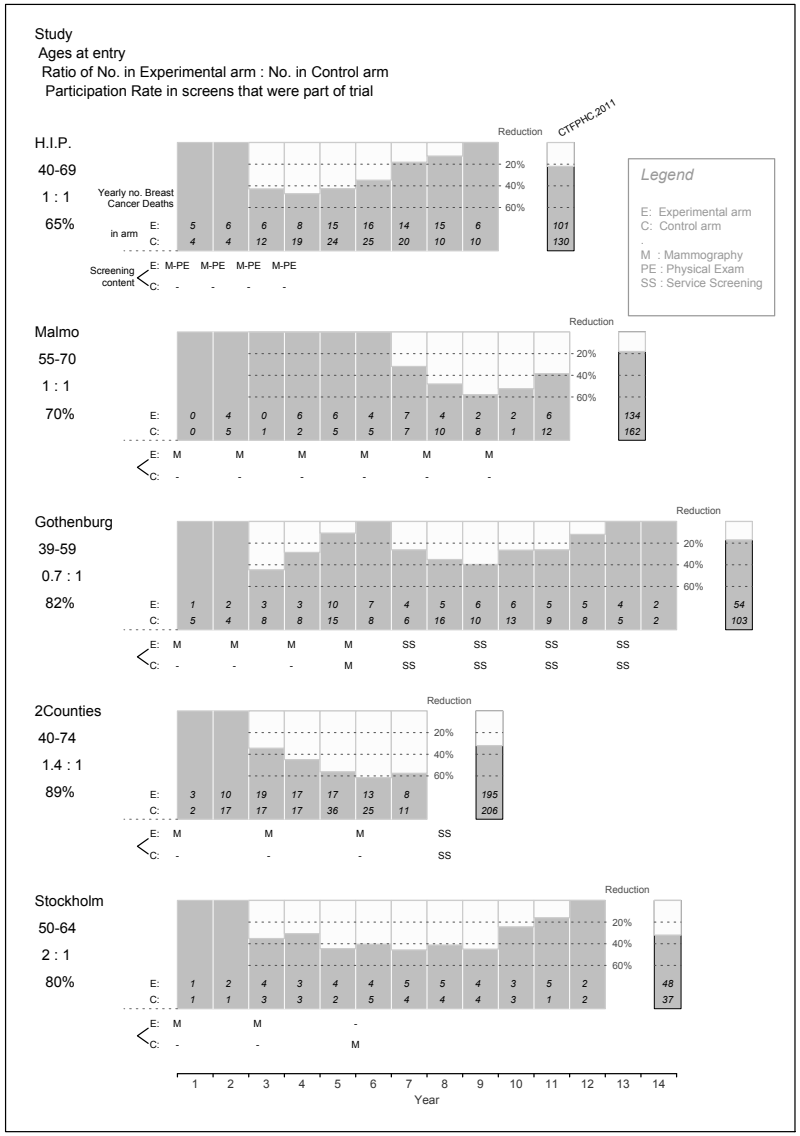

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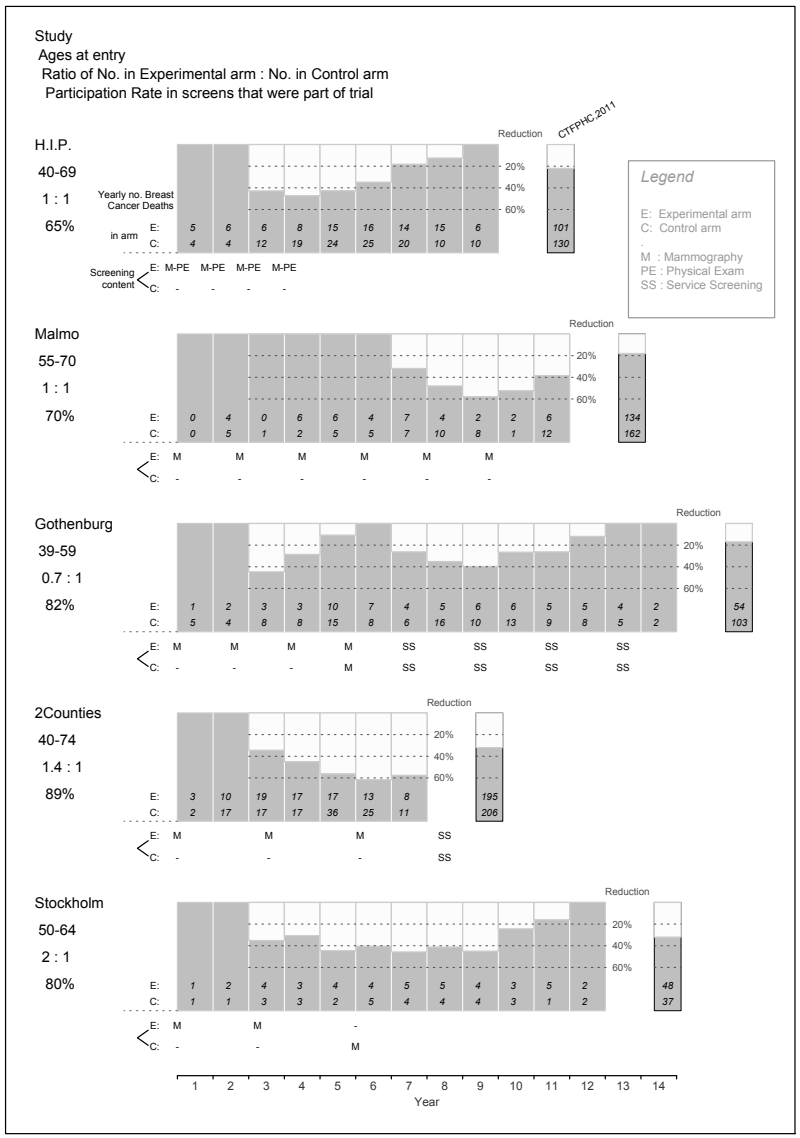

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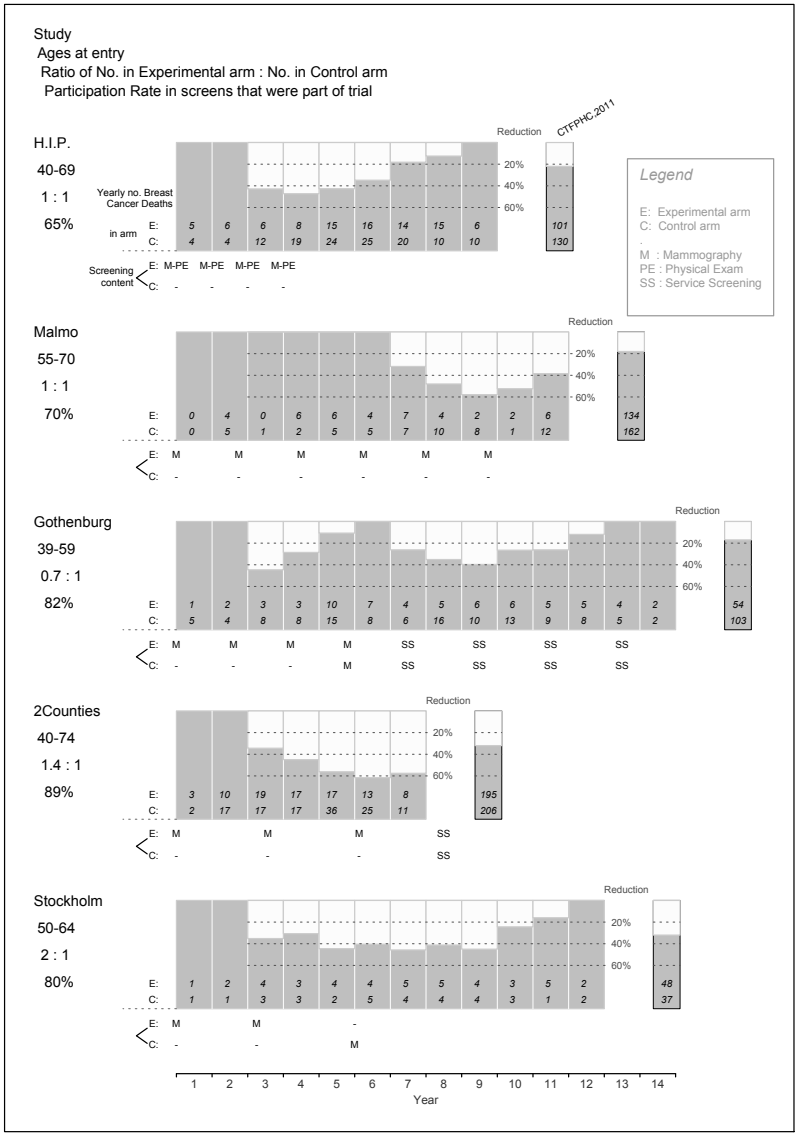

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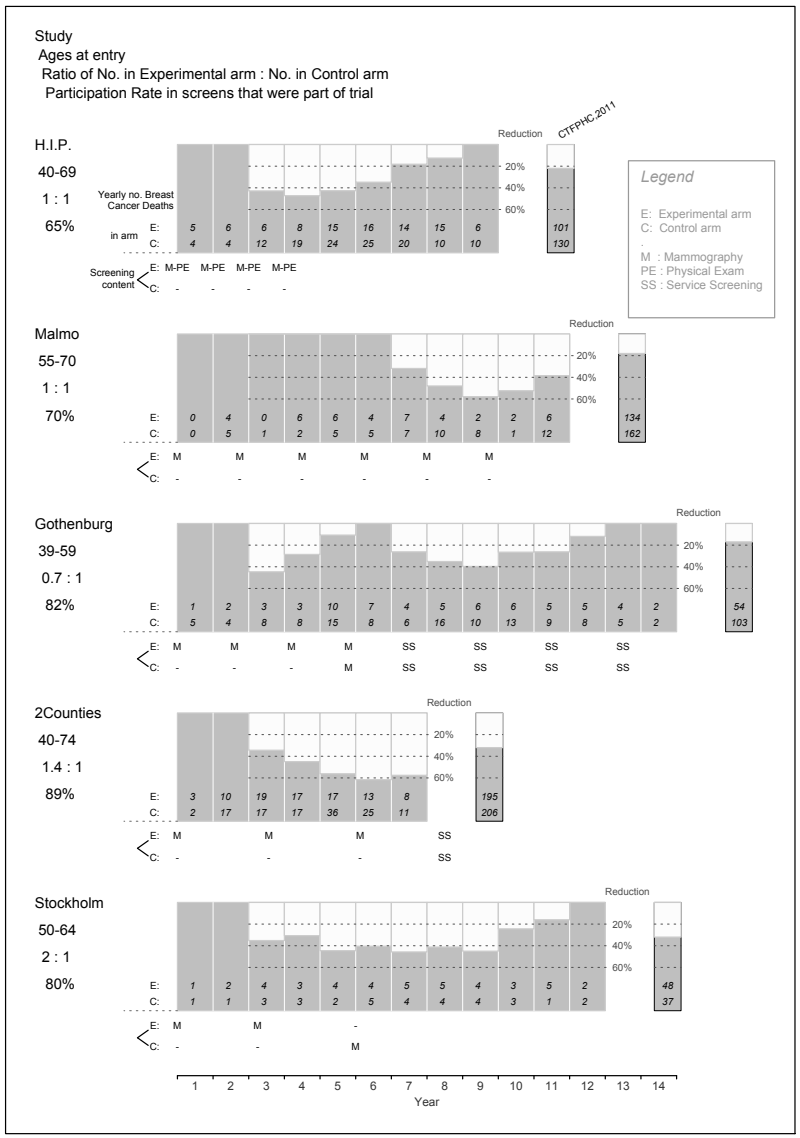

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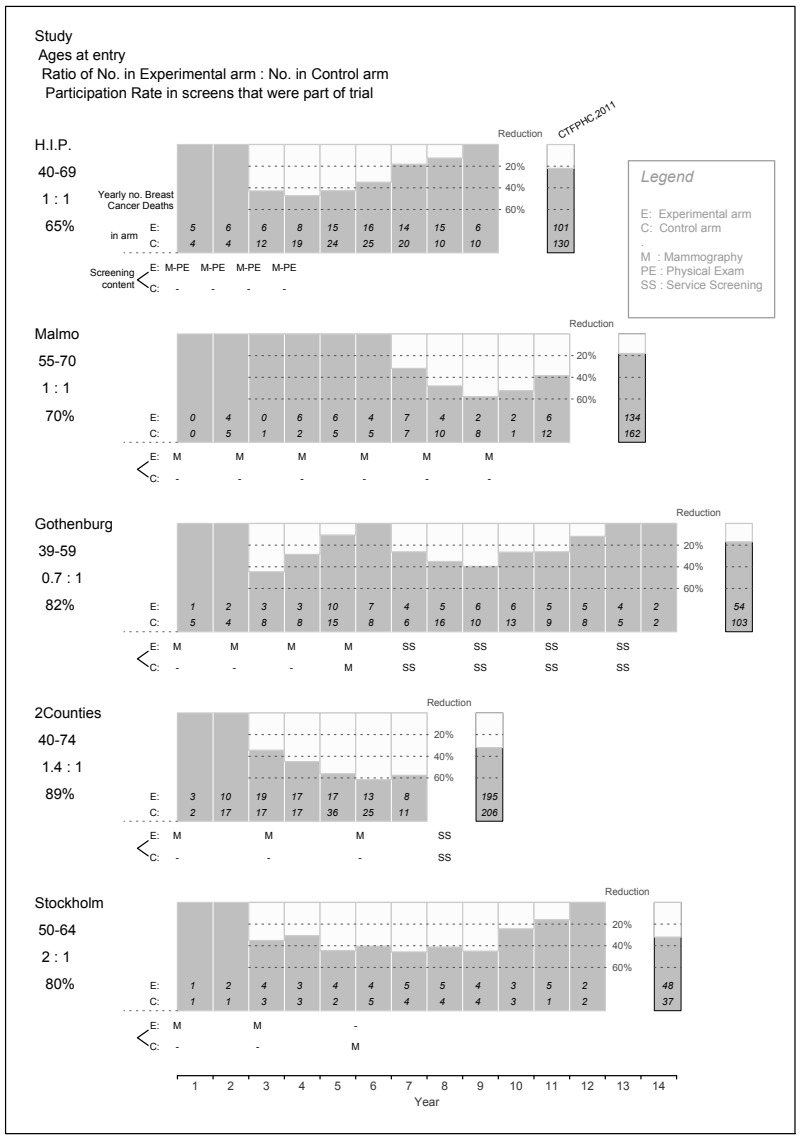

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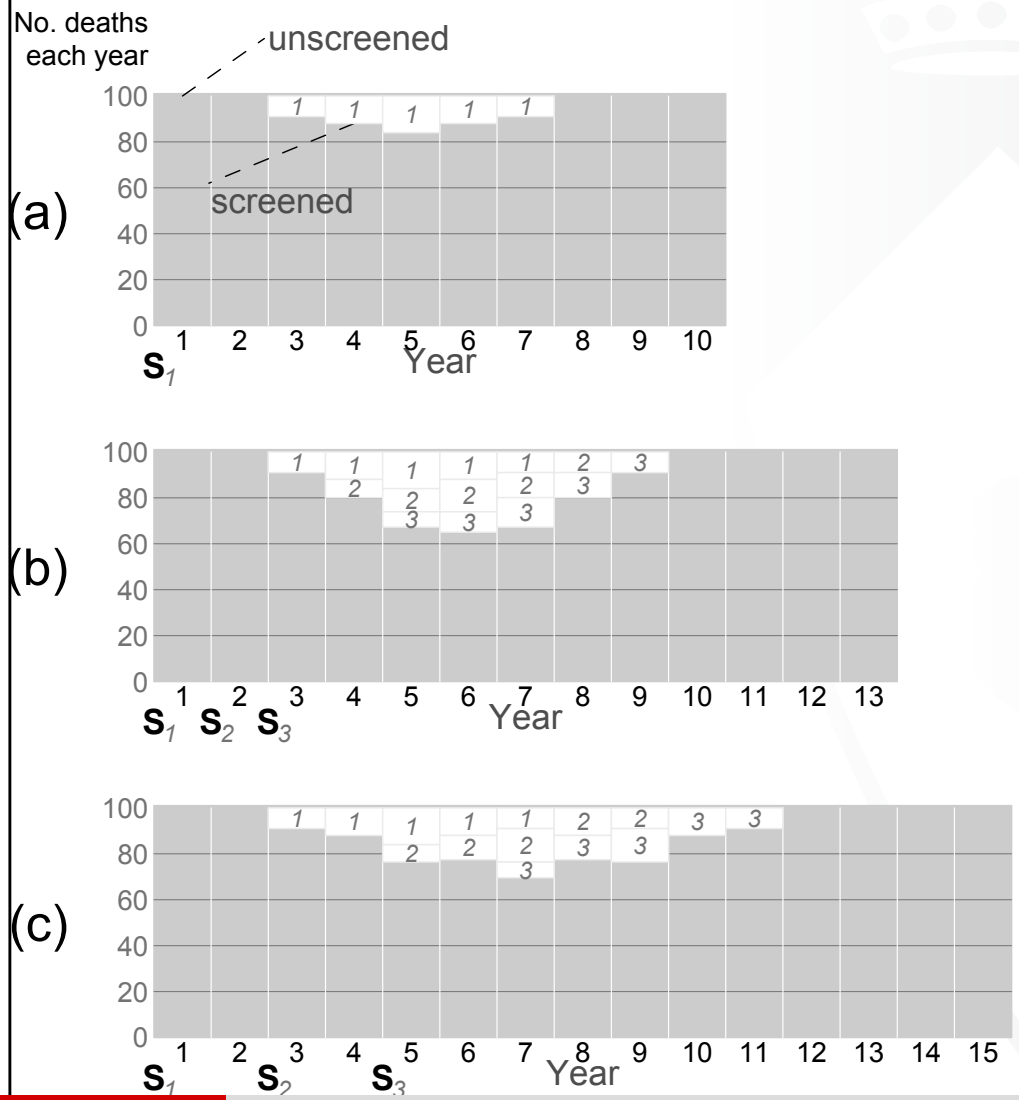
A round-by-round approach?



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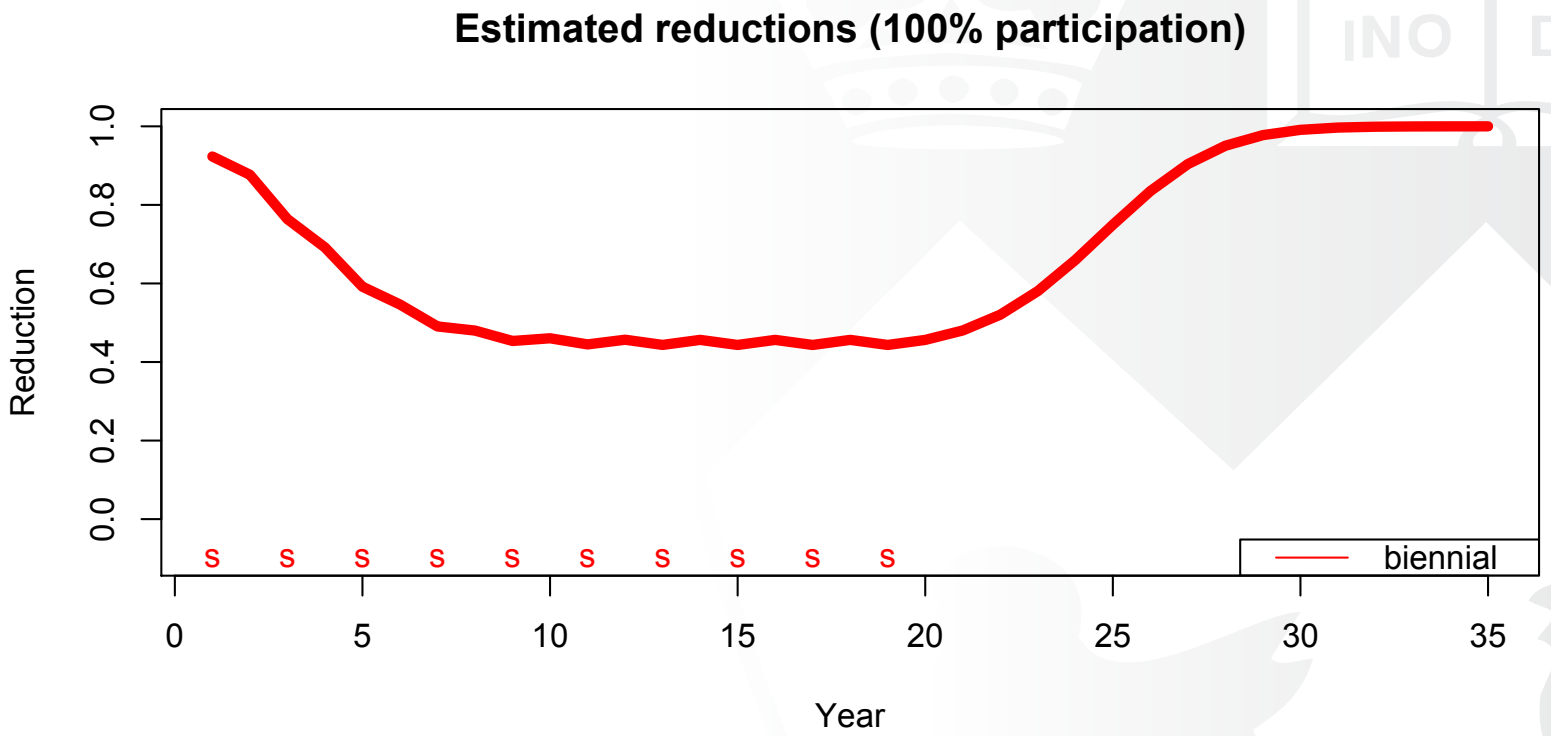

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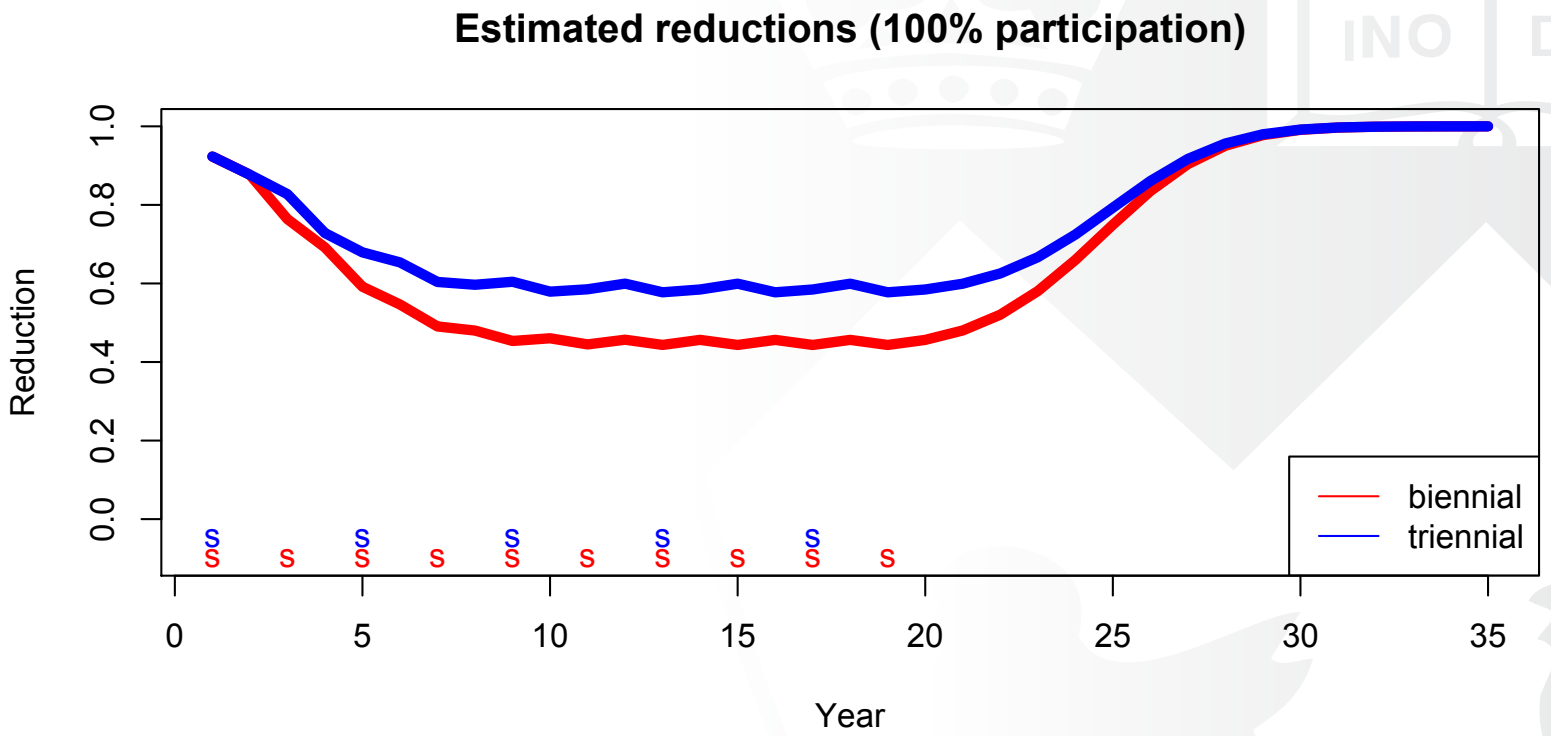

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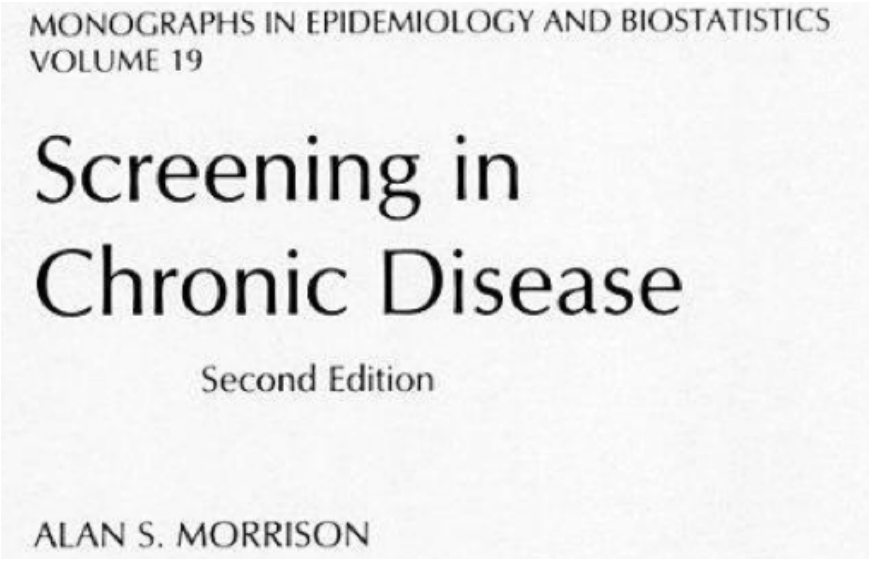

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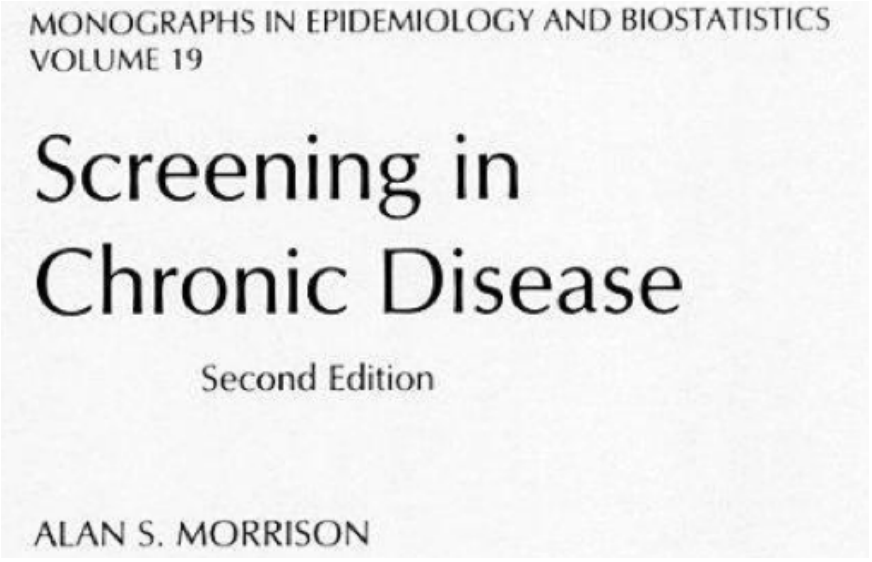

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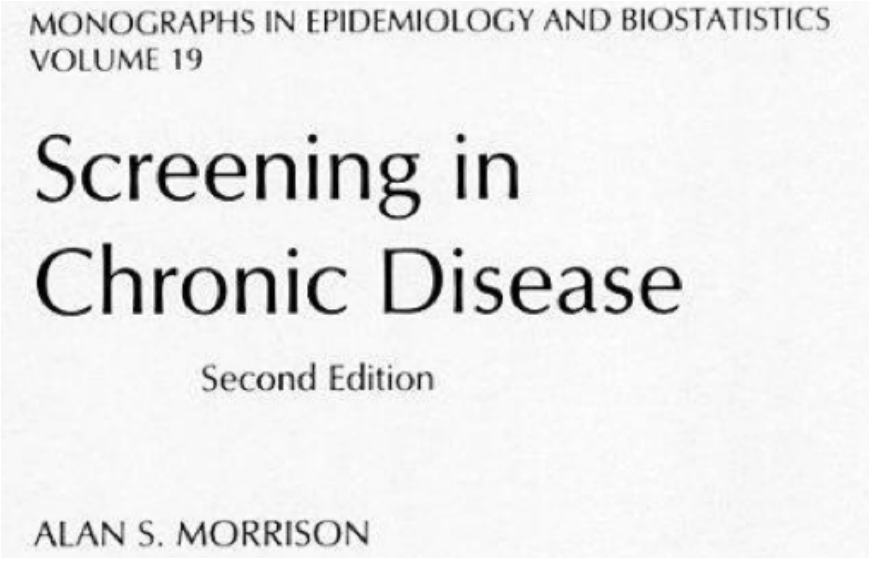

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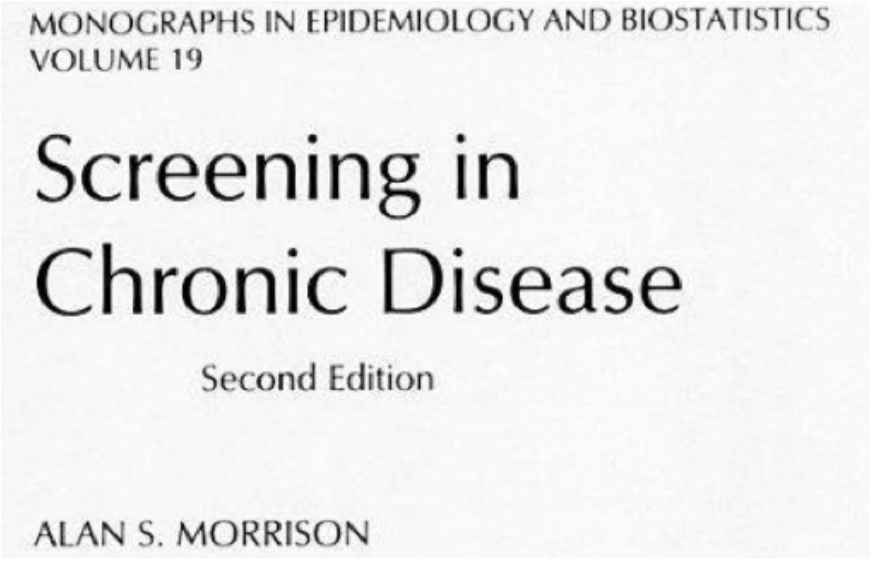

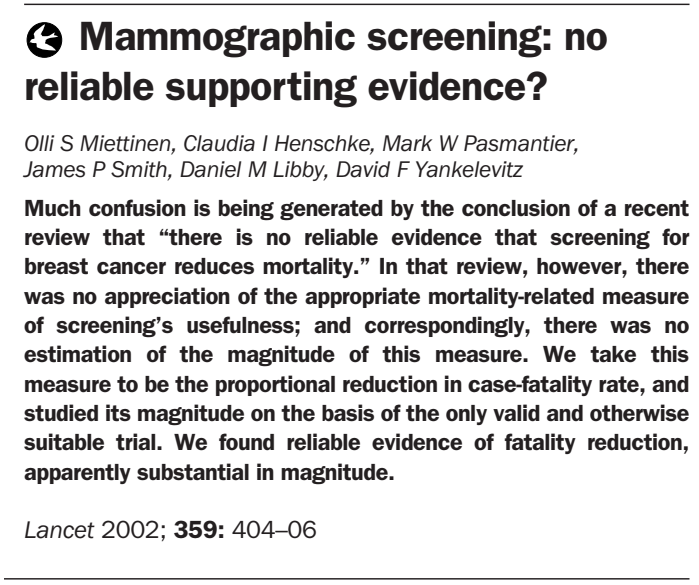

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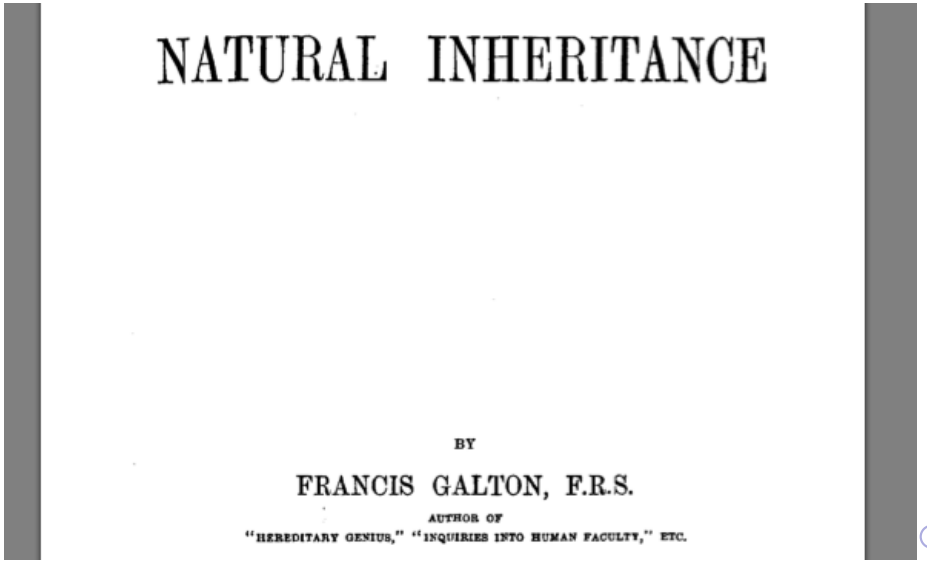

NATURAL INHERITANCE

BY

FRANCIS GALTON, F.R.S.

AUTHOR OF

"HEREDITARY GENIUS," "INQUIRIES INTO HUMAN FACULTY," ETC.

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James.Hanley@McGill.CA

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

→ **r e p r i n t s / talks**

Some References

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

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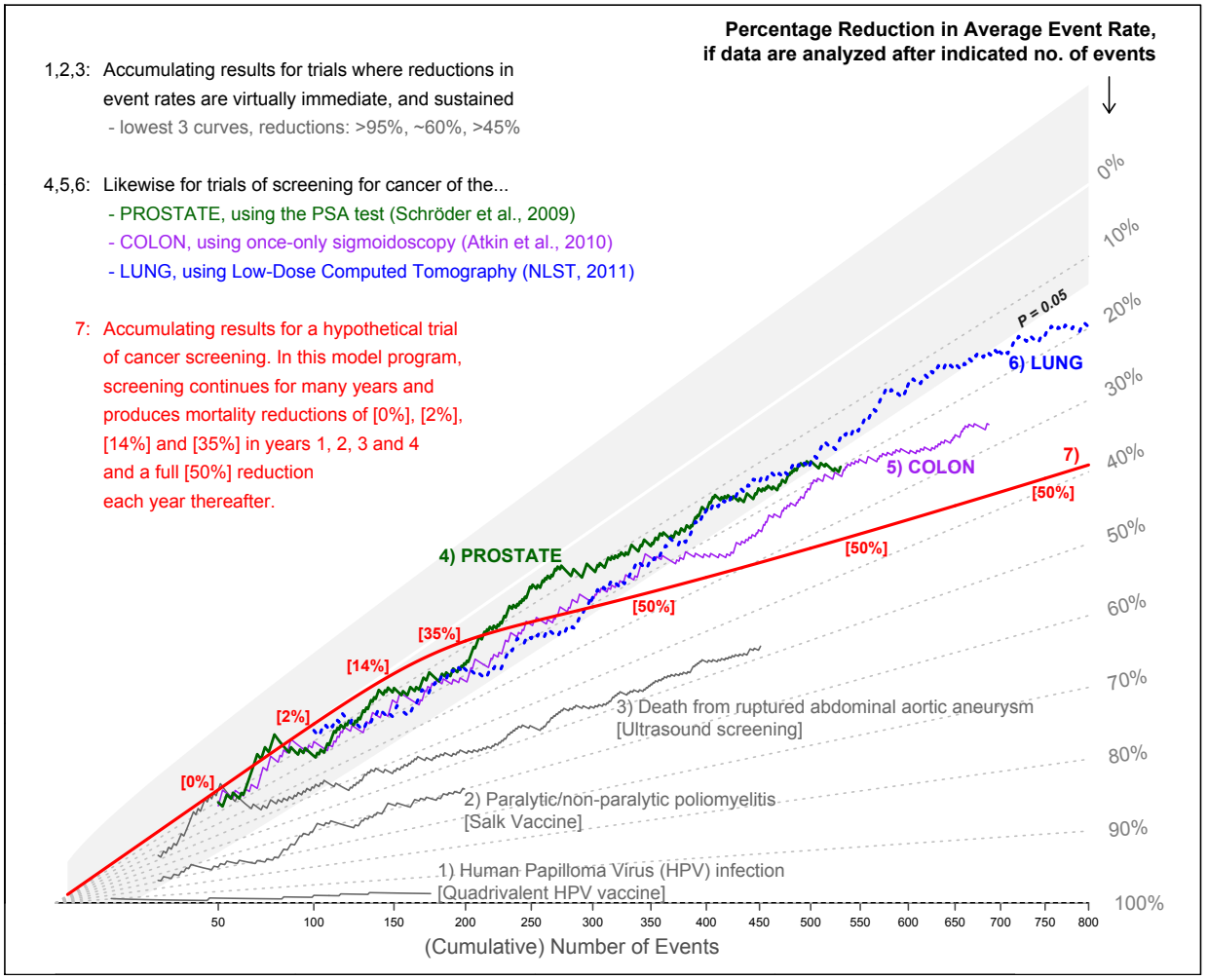
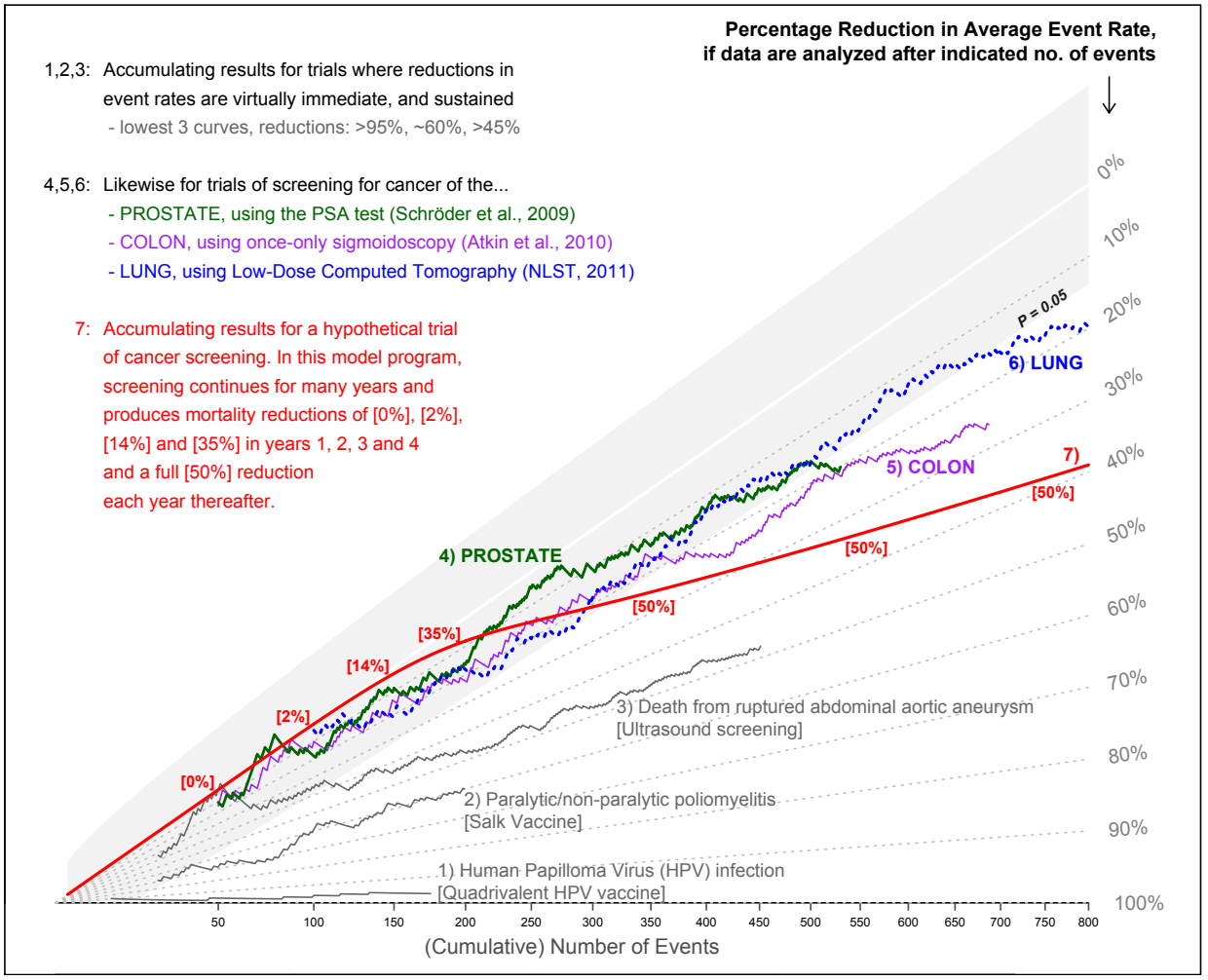
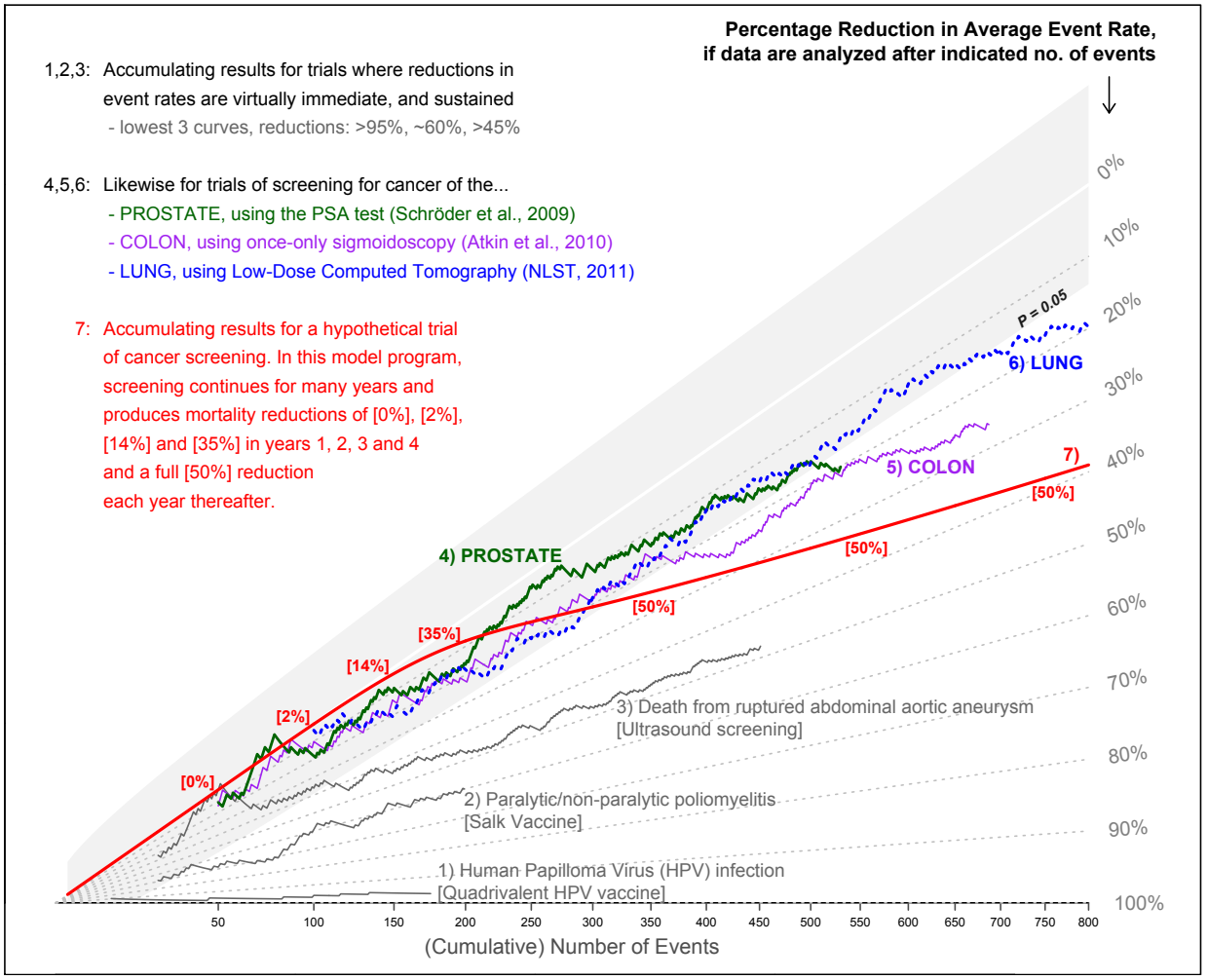
    to
  - 24, 18 years after last screen.


Percentage Reduction in Average Event Rate,
if data are analyzed after indicated no. of events
1,2,3: Accumulating results for trials where reductions in event rates are virtually immediate, and sustained
- lowest 3 curves, reductions: >95%, ~60%, >45%
4,5,6: Likewise for trials of screening for cancer of the...
- PROSTATE, using the PSA test (Schröder et al., 2009)
- COLON, using once-only sigmoidoscopy (Atkin et al., 2010)
- LUNG, using Low-Dose Computed Tomography (NLST, 2011)
7: Accumulating results for a hypothetical trial of cancer screening. In this model program, screening continues for many years and produces mortality reductions of [0%], [2%], [14%] and [35%] in years 1, 2, 3 and 4 and a full [50%] reduction each year thereafter.
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
P = 0.05
6) LUNG
5) COLON
7)
[50%]
[50%]
[50%]
4) PROSTATE
[35%]
[14%]
[2%]
[0%]
3) Death from ruptured abdominal aortic aneurysm
[Ultrasound screening]
2) Paralytic/non-paralytic poliomyelitis
[Salk Vaccine]
1) Human Papilloma Virus (HPV) infection
[Quadrivalent HPV vaccine]
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
(Cumulative) Number of Events



If **intervention continues over time to deflect the same % of events**, an estimate of the % reduction, based on the total number events in more (person)-time will be more precise



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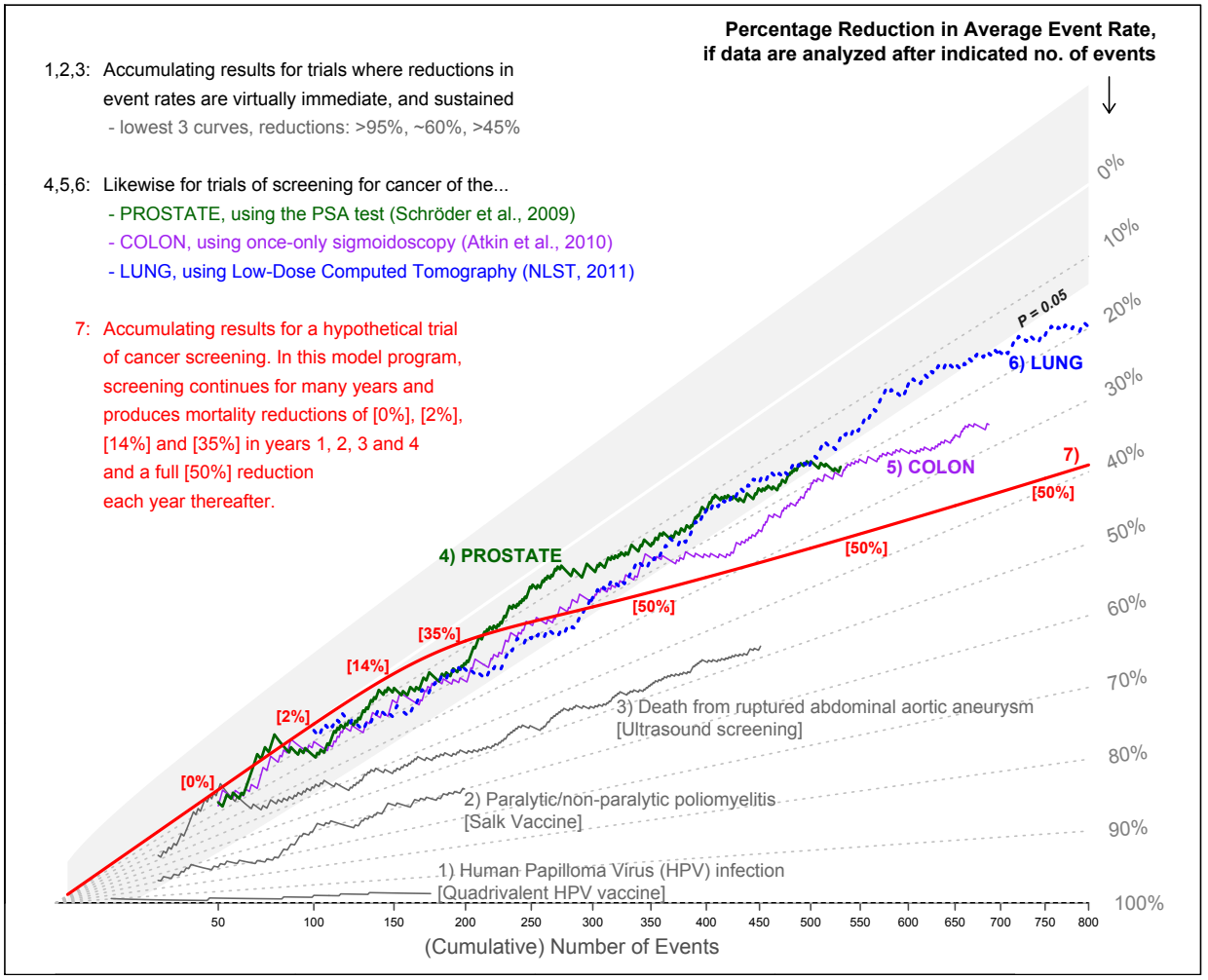
Mortality reductions from cancer screening manifest distally. Enrolling and following more people for short length of time yields a more precise UNDERestimate.



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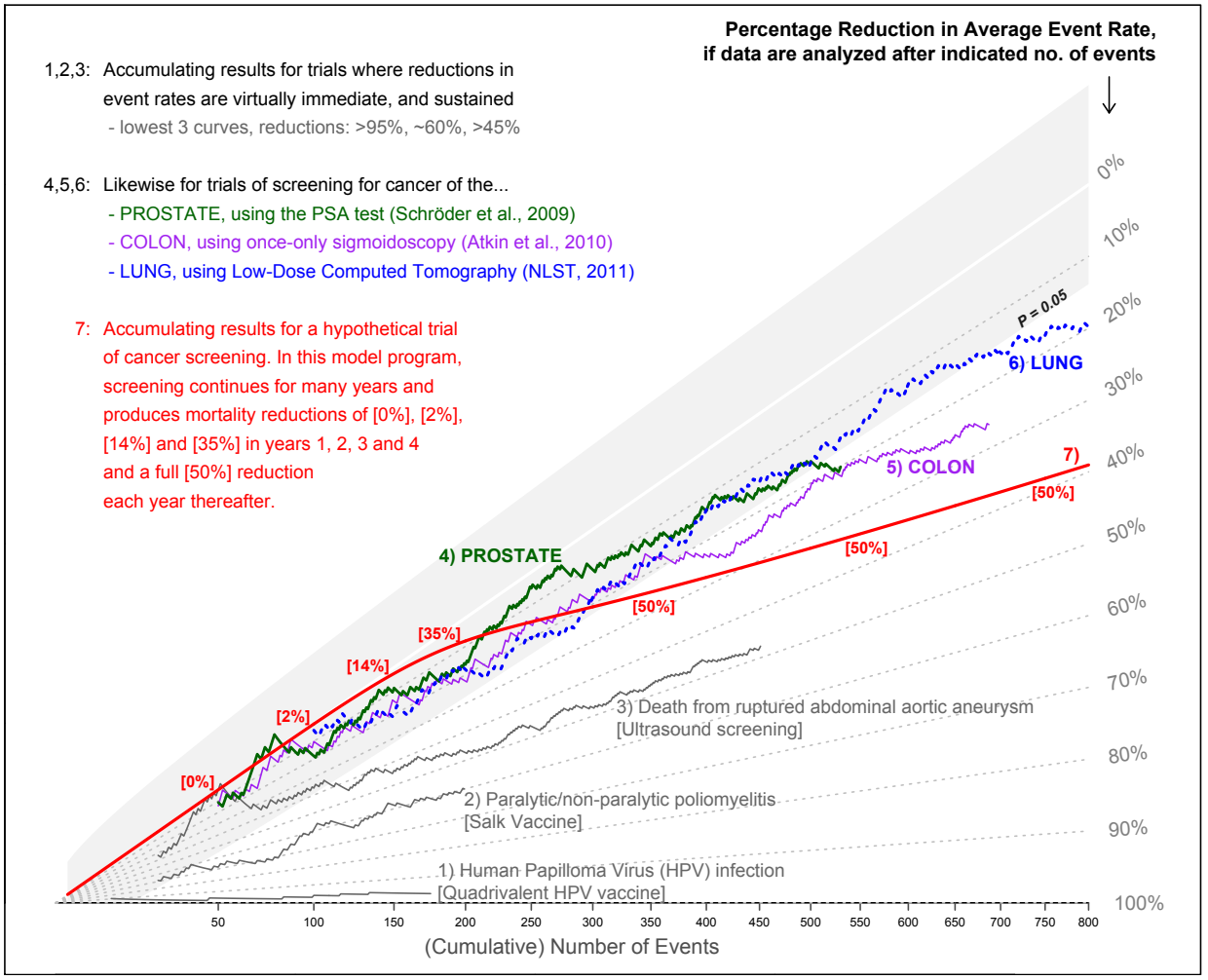

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The seemingly-universal 20% reduction is an artifact of prevailing data-analysis methods and stopping rules.

If use all data from time screening commences, the first % reduction which was statistically different from zero does not answer the question of interest to payers.

The loneliness of the long-distance trialist

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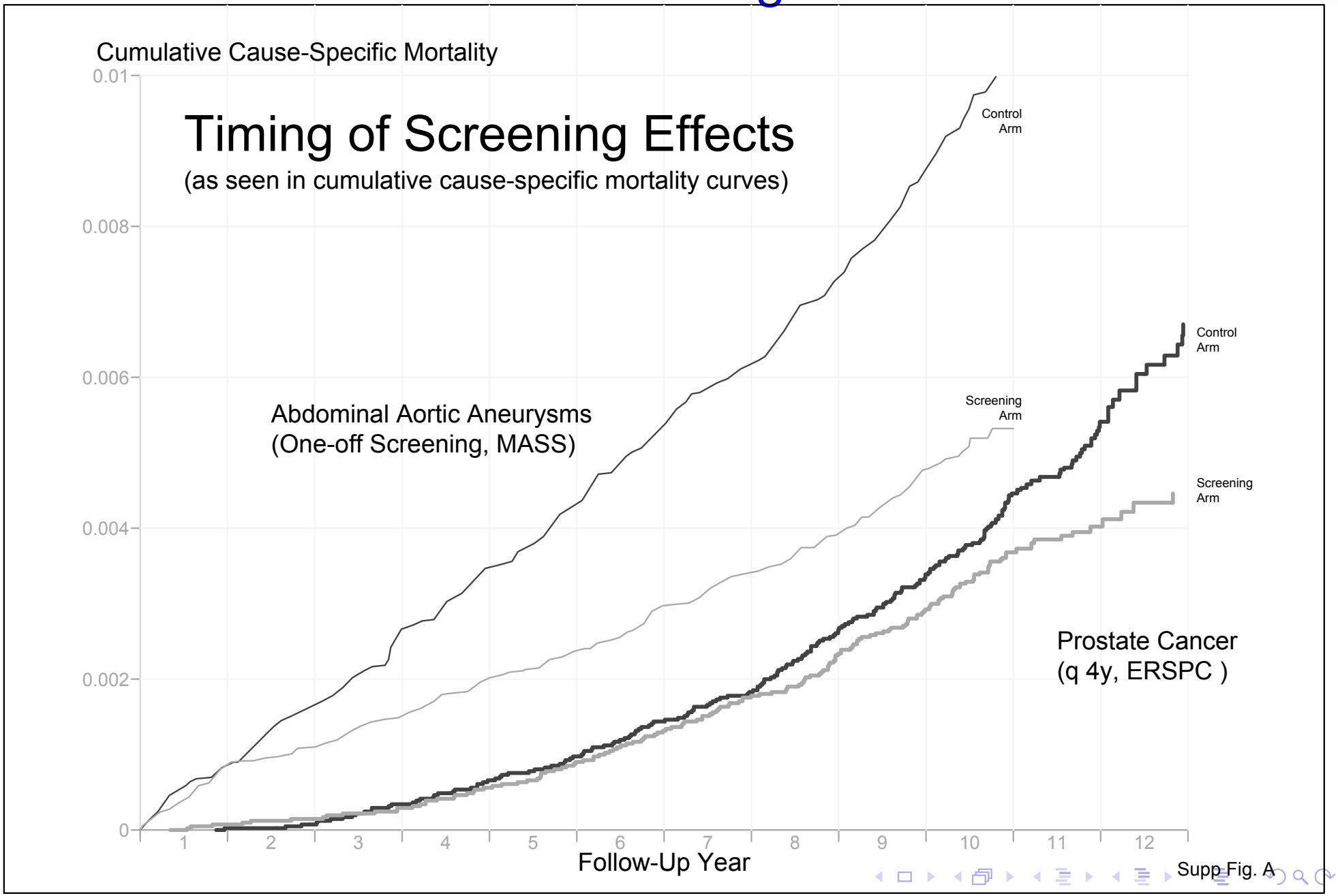
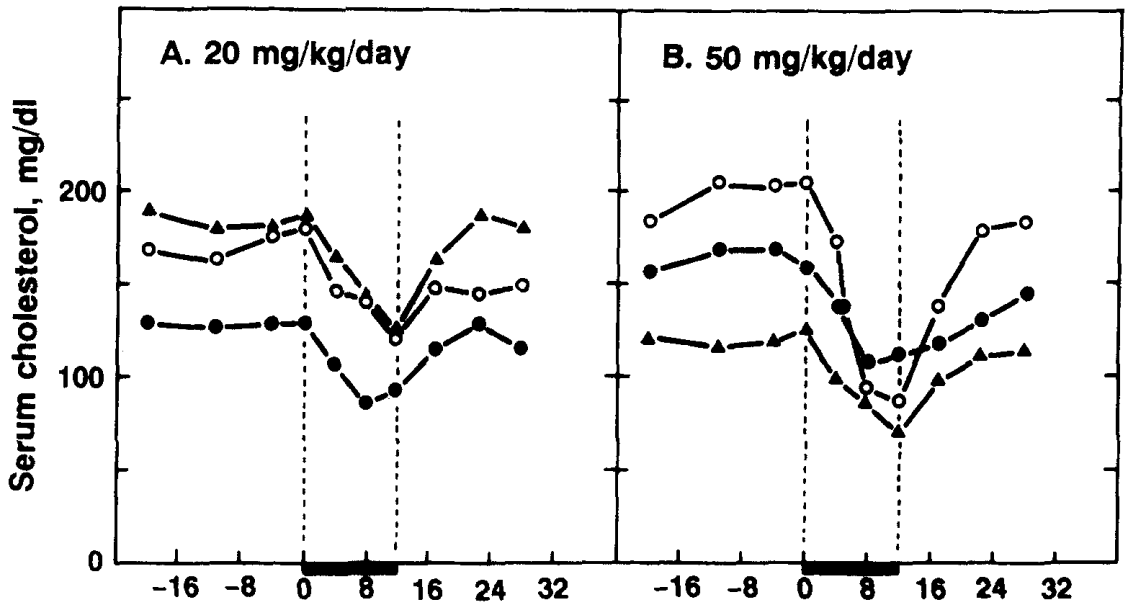


Supp Fig. A

Timing of cholesterol reductions produced by statins

Timing of cholesterol reductions produced by statins

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



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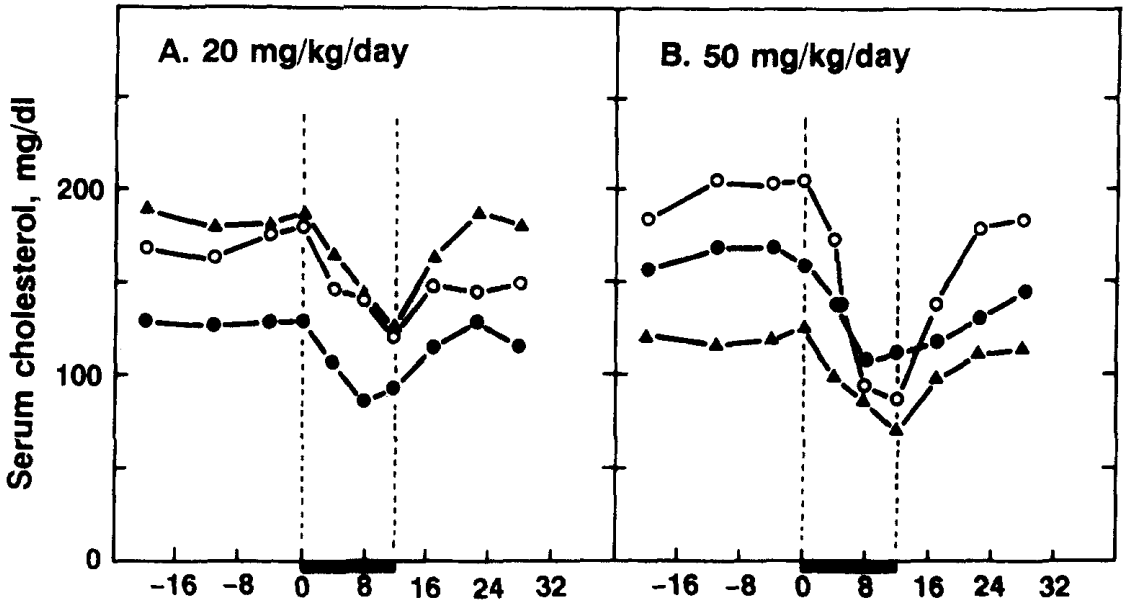
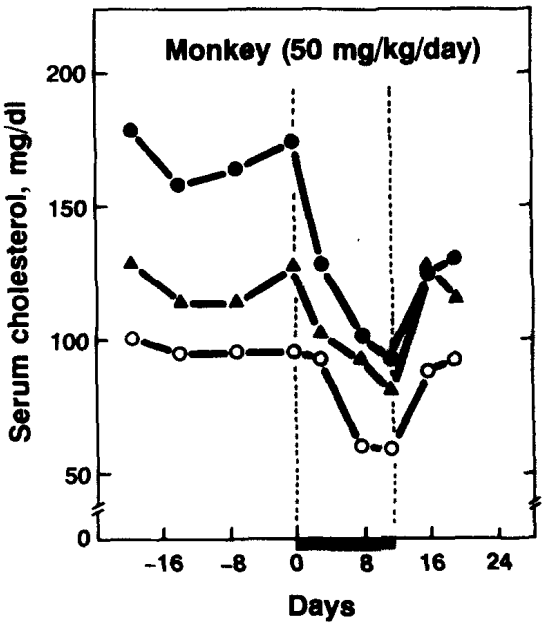


3 monkeys at 50



Timing of cholesterol reductions produced by statins

Humans

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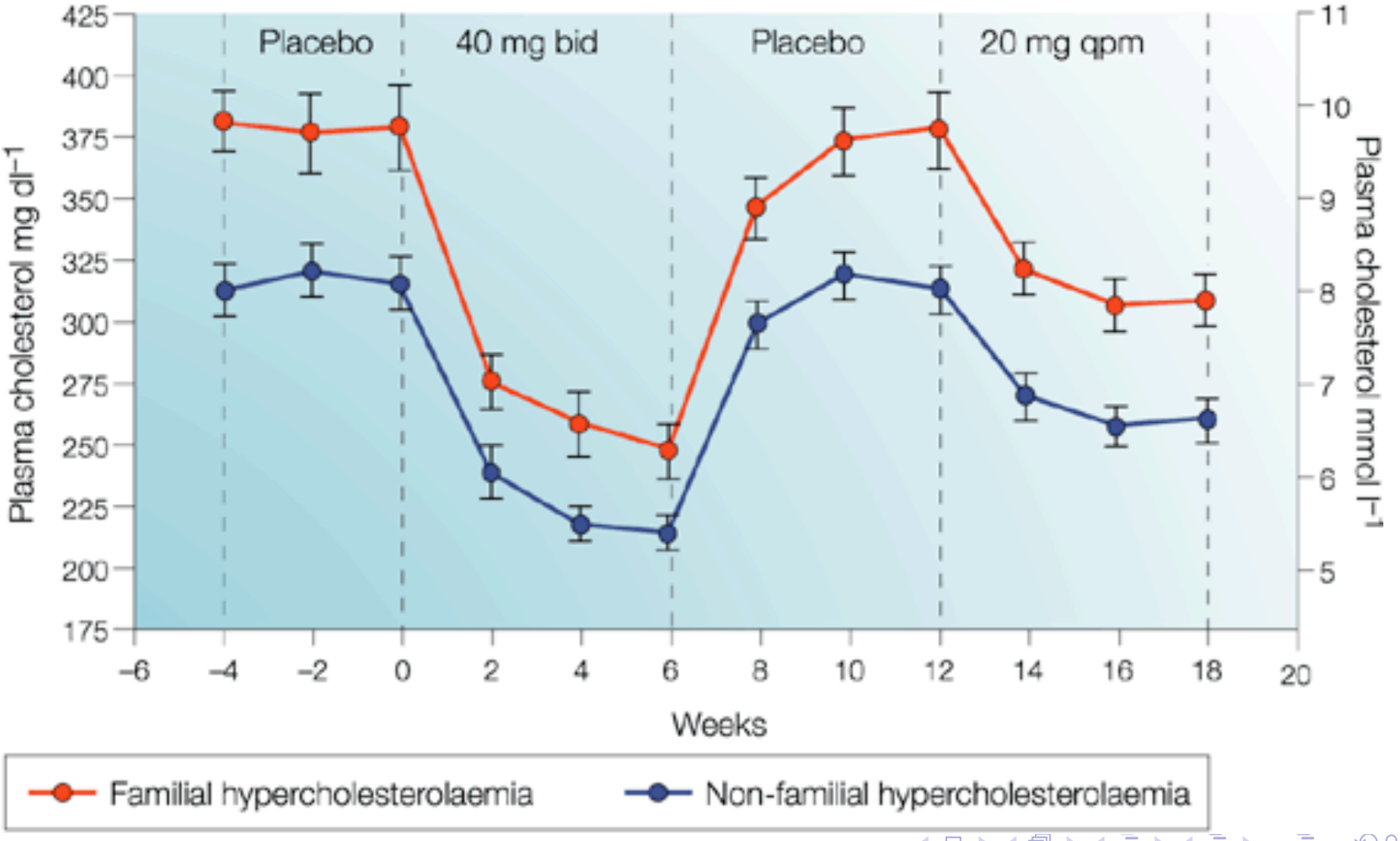
Humans



Cumulative vs. Year-specific Mortality...

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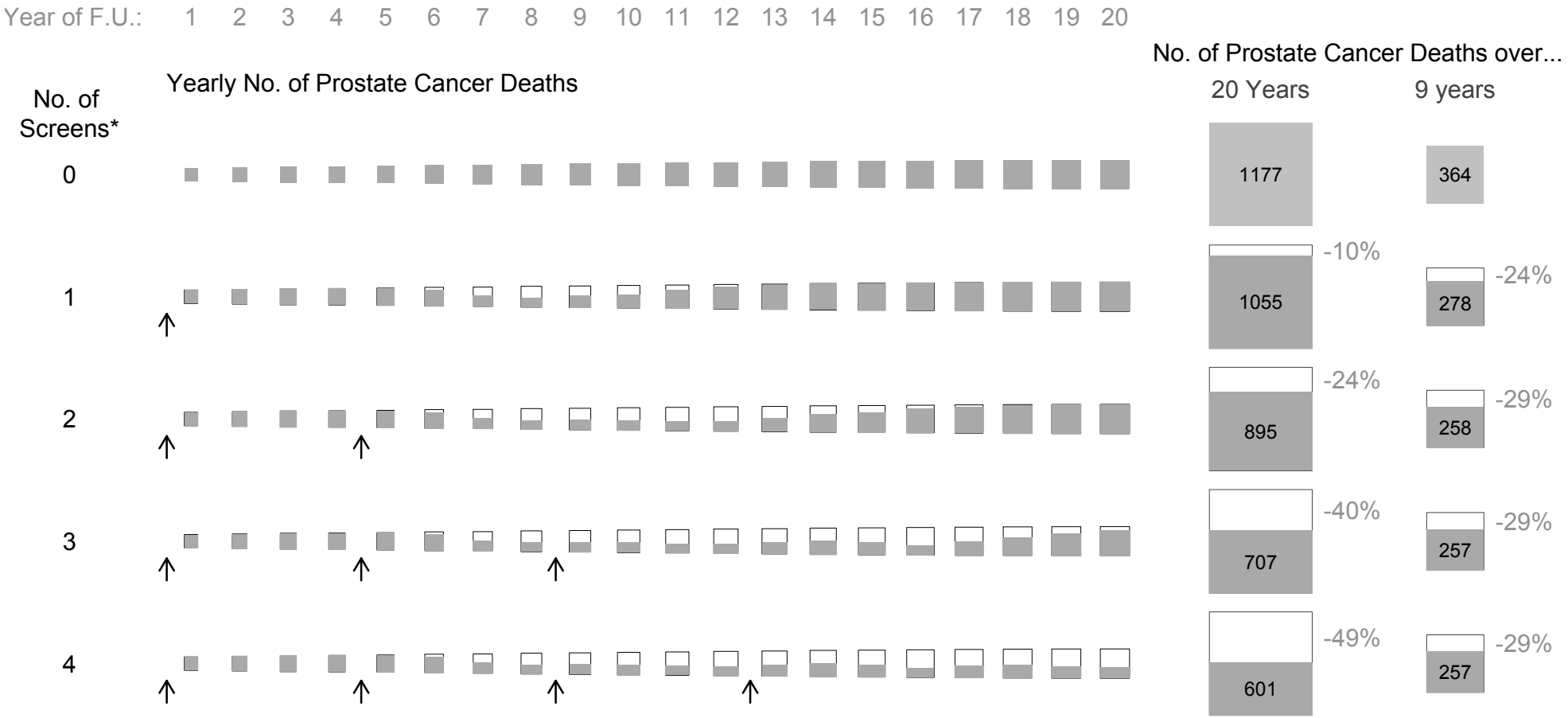
HYPOTHETICAL DATA

Cumulative & Year-specific results, if screen 0,1,...,4 times, q 4y [HYPOTHETICAL]



* Each arrow indicates the timing of a screen for prostate cancer.

(B) Year-specific Rate Ratios & Percent Reductions [HYPOTHETICAL]

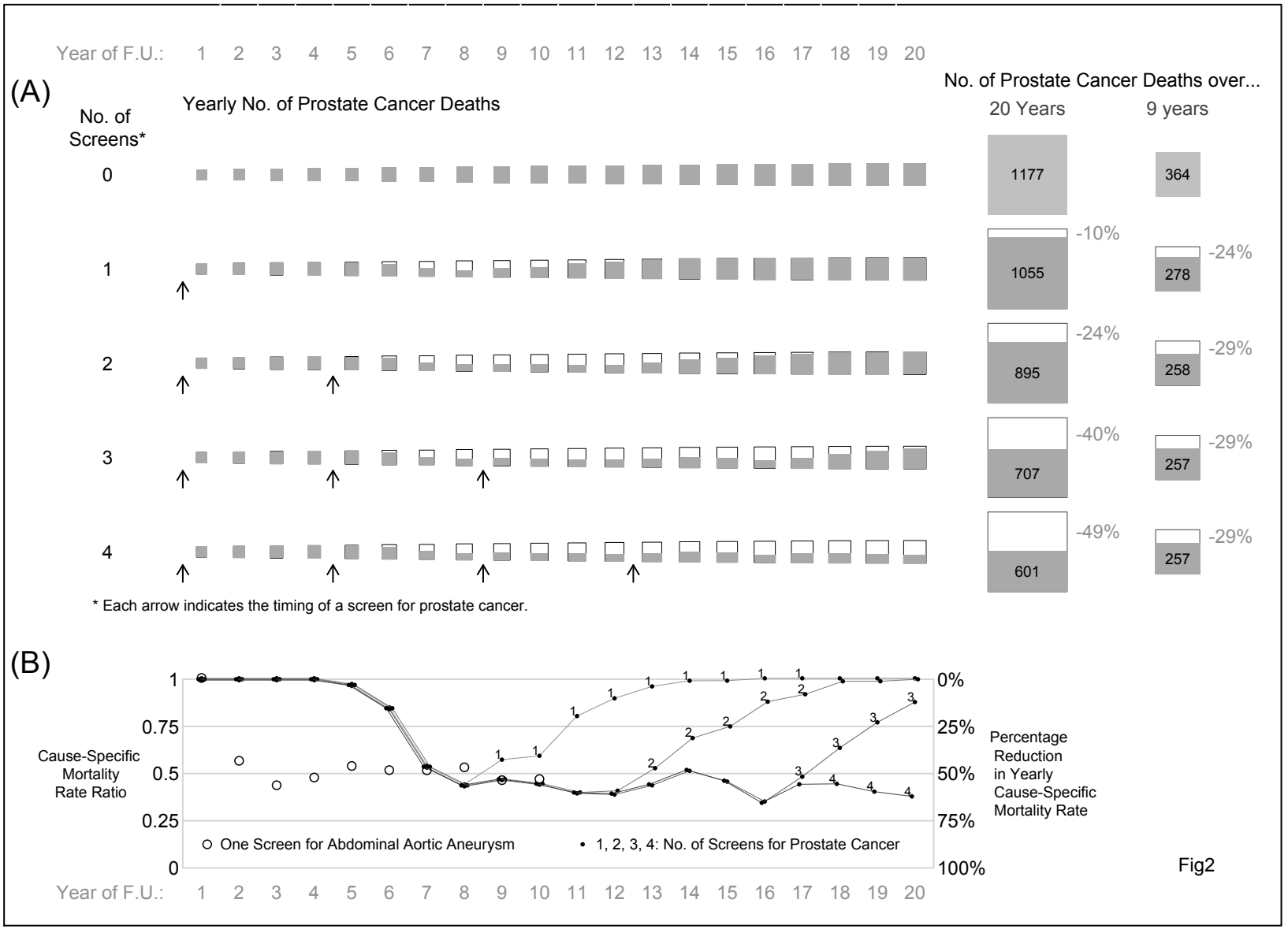


Fig2

Norway - 'before-after' study

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 1996 and expanded geographically during the subsequent 9 years.

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

Results & Conclusions

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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.

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Time-insensitivity: not exclusive to RCT reports

Paraphrase of (refused)
letter by JH to NEJM re
2010 analysis of data from
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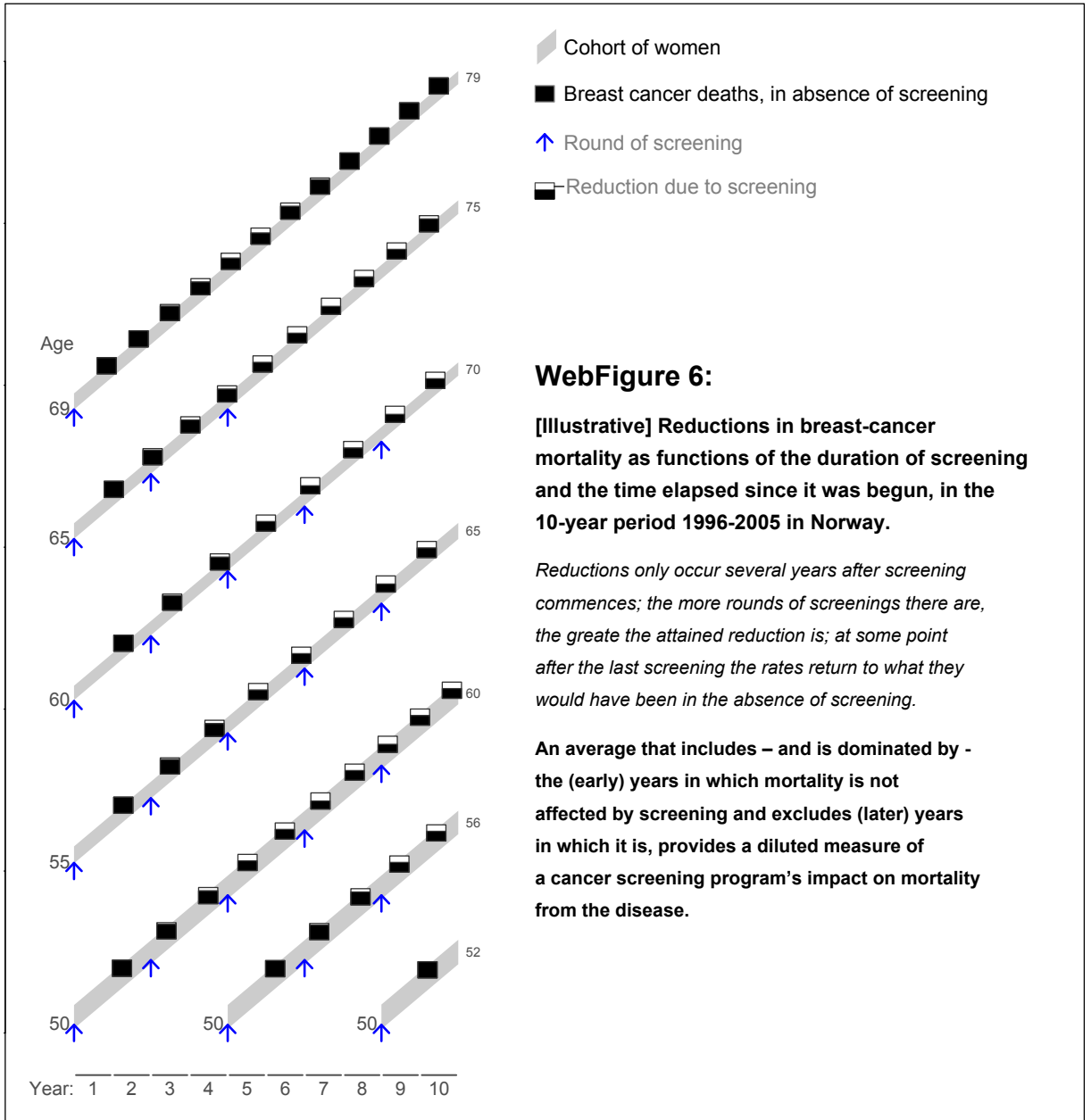

WebFigure 6:

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

Reductions only occur several years after screening commences; the more rounds of screenings there are, the greate the attained reduction is; at some point after the last screening the rates return to what they would have been in the absence of screening.

An average that includes – and is dominated by - the (early) years in which mortality is not affected by screening and excludes (later) years in which it is, provides a diluted measure of a cancer screening program's impact on mortality from the disease.

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- Moving averages* to reduce the statistical noise (deaths in moving 3-year intervals)
- Smooth curve for rate ratio function (data bins 0.2 y wide).

---

* cf. Miettinen et al. 2002

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ACR Imaging Network: Press Release

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Table 3: Interim Analysis of Primary Endpoint Reported on October 20, 2010

Trial Arm	Person years (py)	Lung cancer deaths	Lung cancer mortality per 100,000 py	Reduction in lung cancer mortality (%)	Value of test statistic	Efficacy boundary
LDCT	144,097.6	354	245.7	20.3	–3.21	–2.02
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