# Underestimation of Mortality Reductions in Cancer Screening Studies:

# Prostate, Breast, Colon and [???] Lung

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# Outline

- The mortality reductions produced by a screening regimen: what payers want to know
- European Randomized Study of Screening for Prostate Cancer
- Data-analysis practice: studies of screening for breast, colon & lung ca.
- How to stop a screening RCT at a 20% mortality reduction? [Theorem]
- The way ahead

# What payers would like to know...

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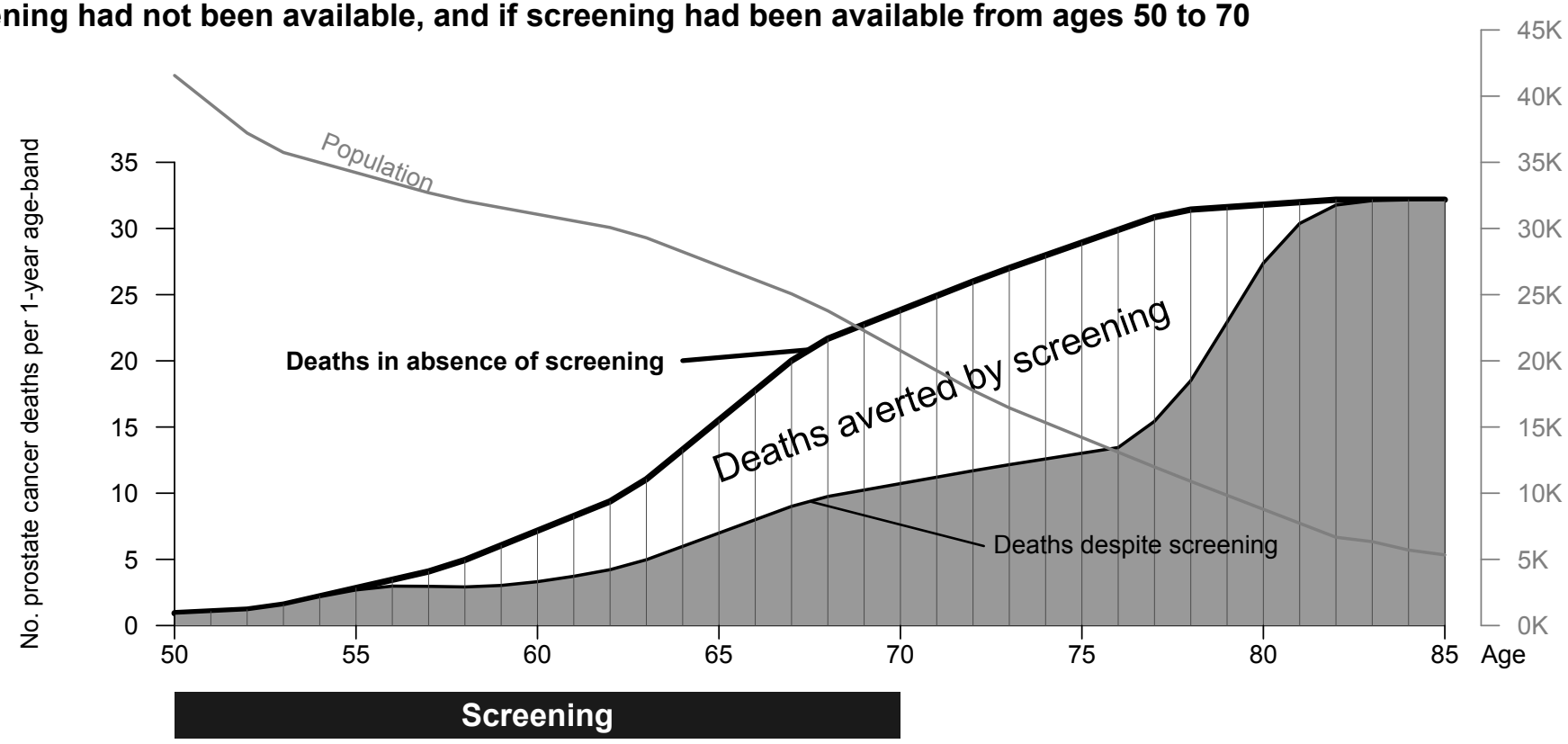
**(a) Age-specific numbers of prostate cancer deaths in a steady state population with a given age-structure, if screening had not been available, and if screening had been available from ages 50 to 70**



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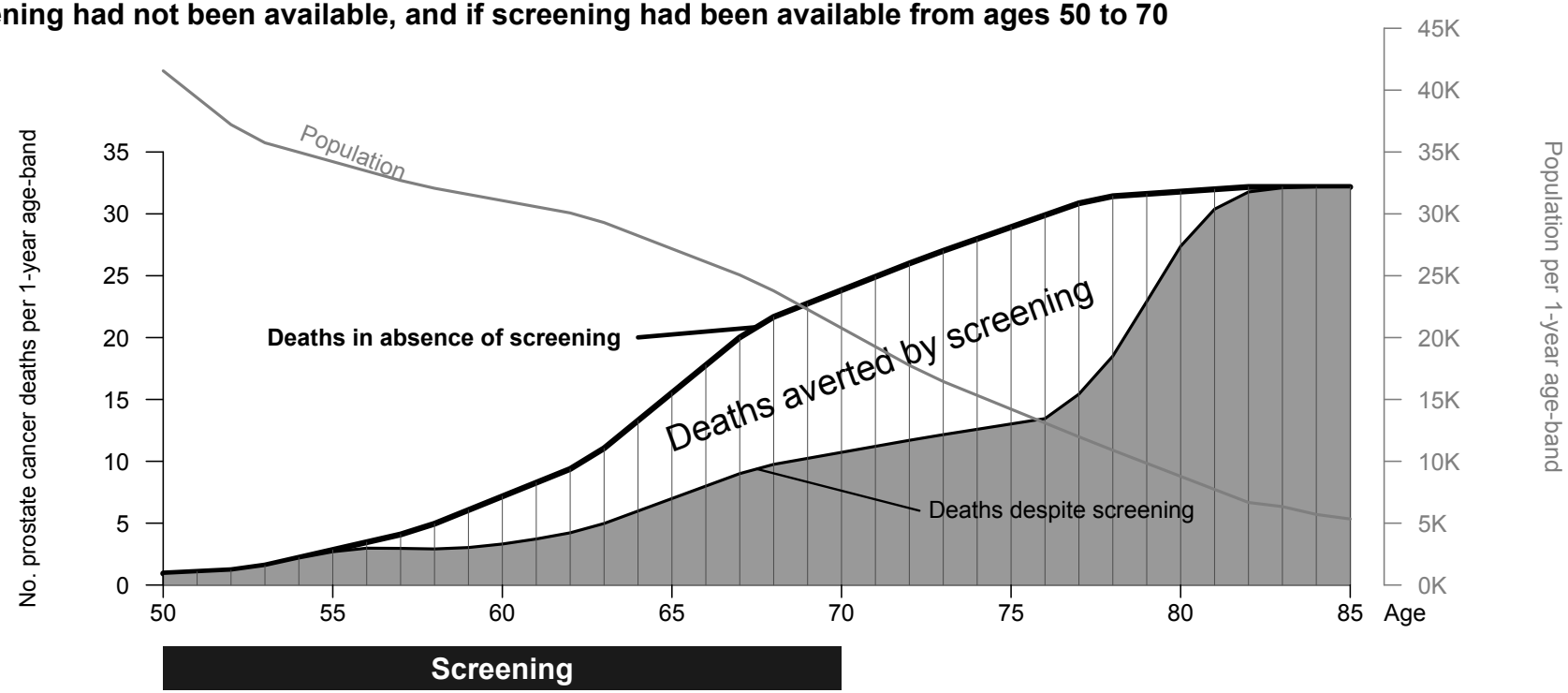
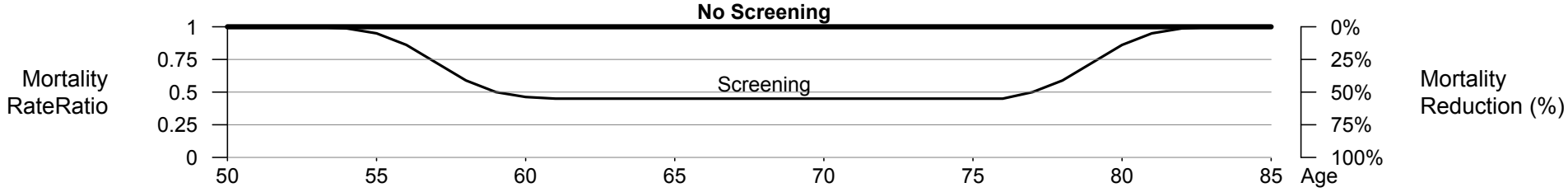



**(b) The corresponding age-specific prostate cancer mortality rate ratios**



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- 2005 RCT: Radical prostatectomy $>$ but $\not>$ watchful waiting in early Pr Ca
- 2009: European Randomized Study of Screening for Pr Ca (ERSPC)

* An Evaluation of benefits, unwanted health effect and costs. http://www.aetmis.gouv.qc.ca/site/home.phtml.

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| **Trial:** / Author: | Québec<br>Labrie | Sweden[1]<br>Sandbloma | Sweden[2]<br>Kjellman | USA<br>Andriole | Europe[†]<br>Schröder |
|---|---|---|---|---|---|
| Began | 1988 | 1987 | 1988 | 1993 | 1991 |
| Last report | 2004 | 2004 | 2009 | 2009 | 2009 |
| No. men $\frac{\textit{Screening arm}}{\textit{Control arm}}$ | $\frac{31{,}000}{15{,}000}$ | $\frac{1{,}500}{7{,}500}$ | $\frac{2{,}400}{24{,}000}$ | $\frac{38{,}000}{38{,}000}$ | $\frac{73{,}000}{89{,}000}$ |
| Frequency of testing | ?1y | 3y | once | 1y $\times$ 6 | 4y* |
| Duration of follow-up (y) | 11 | 15 | 15 | 10 | 9 |
| Screened $\geq$ once | $\frac{24\%}{7\%}$ | $\frac{78\%}{?}$ | $\frac{74\%}{?}$ | $\frac{85\%}{52\%}$ | $\frac{82\%}{??}$ |
| No. Pr Ca deaths | $\frac{153}{75}$ | $\frac{20}{97}$ | $\frac{53}{506}$ | $\frac{92}{82}$ | $\frac{214}{326}$ |

[1] Norrköping [2] Stockholm

† Party-overlapping Göteborg experience, biennial screens, longer follow-up, published separately [Hugosson2010].

* Varied somewhat by country. ? Information not reported.

?? ERSPC-wide estimate not available; by 2006 in Rotterdam portion, 24% had had PSA tested at least once [Kerkhof, 2010]

ORIGINAL ARTICLE

# Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

## ABSTRACT

### BACKGROUND

The European Randomized Study of Screening for Prostate Cancer was initiated in the early 1990s to evaluate the effect of screening with prostate-specific–antigen (PSA) testing on death rates from prostate cancer.

### METHODS

We identified 182,000 men between the ages of 50 and 74 years through registries in seven European countries for inclusion in our study. The men were randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. The predefined core age group for this study included 162,243 men between the ages of 55 and 69 years. The primary outcome was the rate of death from prostate cancer. Mortality follow-up was identical for the two study groups and ended on December 31, 2006.

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Schröder at the Erasmus Medical Center, P.O. Box 2040, Rotterdam 3000 CA, the Netherlands, or at secr.schroder@erasmusmc.nl.

*Members of the European Randomized Study of Screening for Prostate Cancer (ERSPC) are listed in the Appendix.

This article (10.1056/NEJMoa0810084) was published at NEJM.org on March 18, 2009.

N Engl J Med 2009;360:1320-8.

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"PSA-based screening reduced the rate of death from prostate cancer by 20%."

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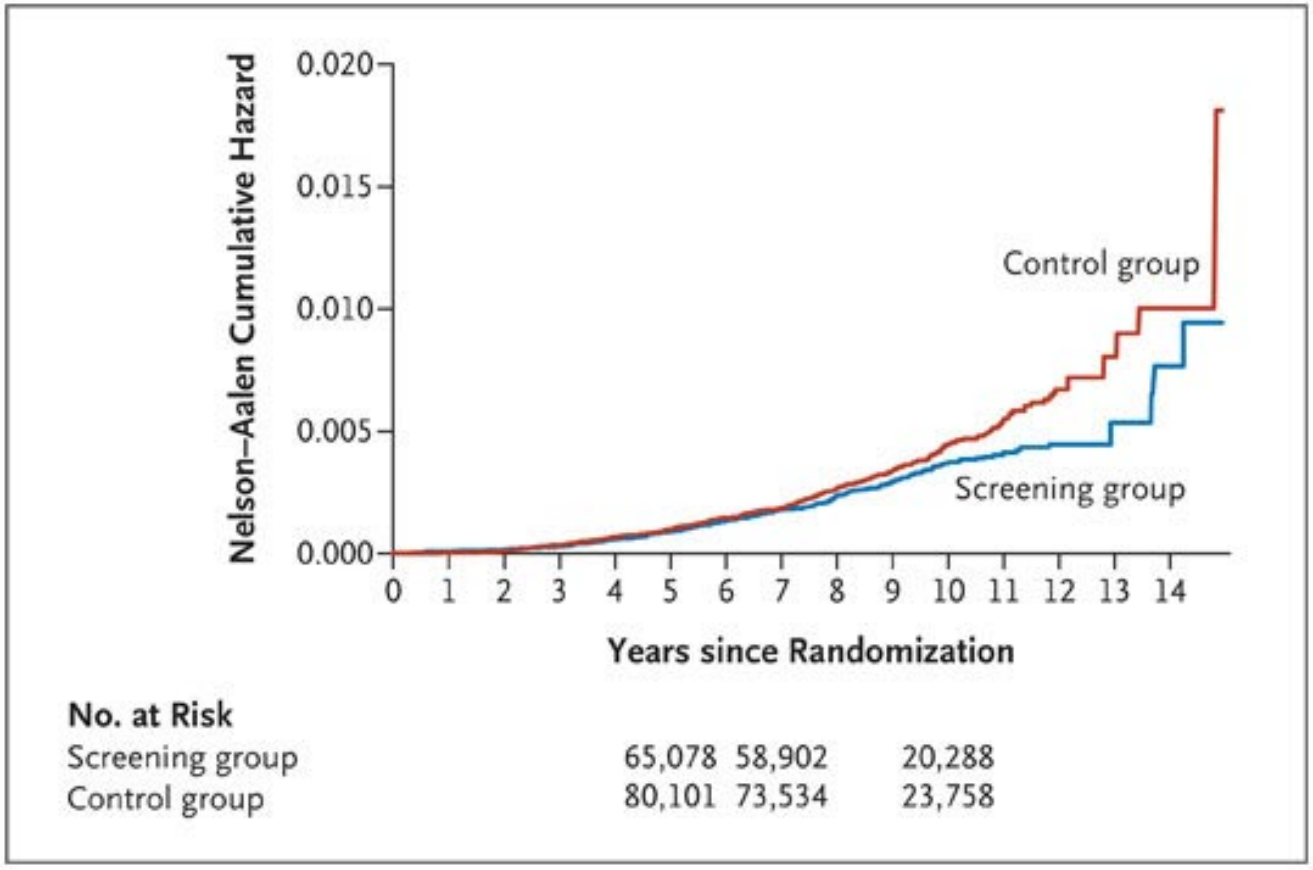


As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate cancer. The **adjusted rate ratio** for death from prostate cancer in the screening group was **0.80** (95% CI, 0.65 to 0.98; P=0.04). The Nelson-Aalen method was used for the calculation of cumulative hazard.

NEJM, March 2009.

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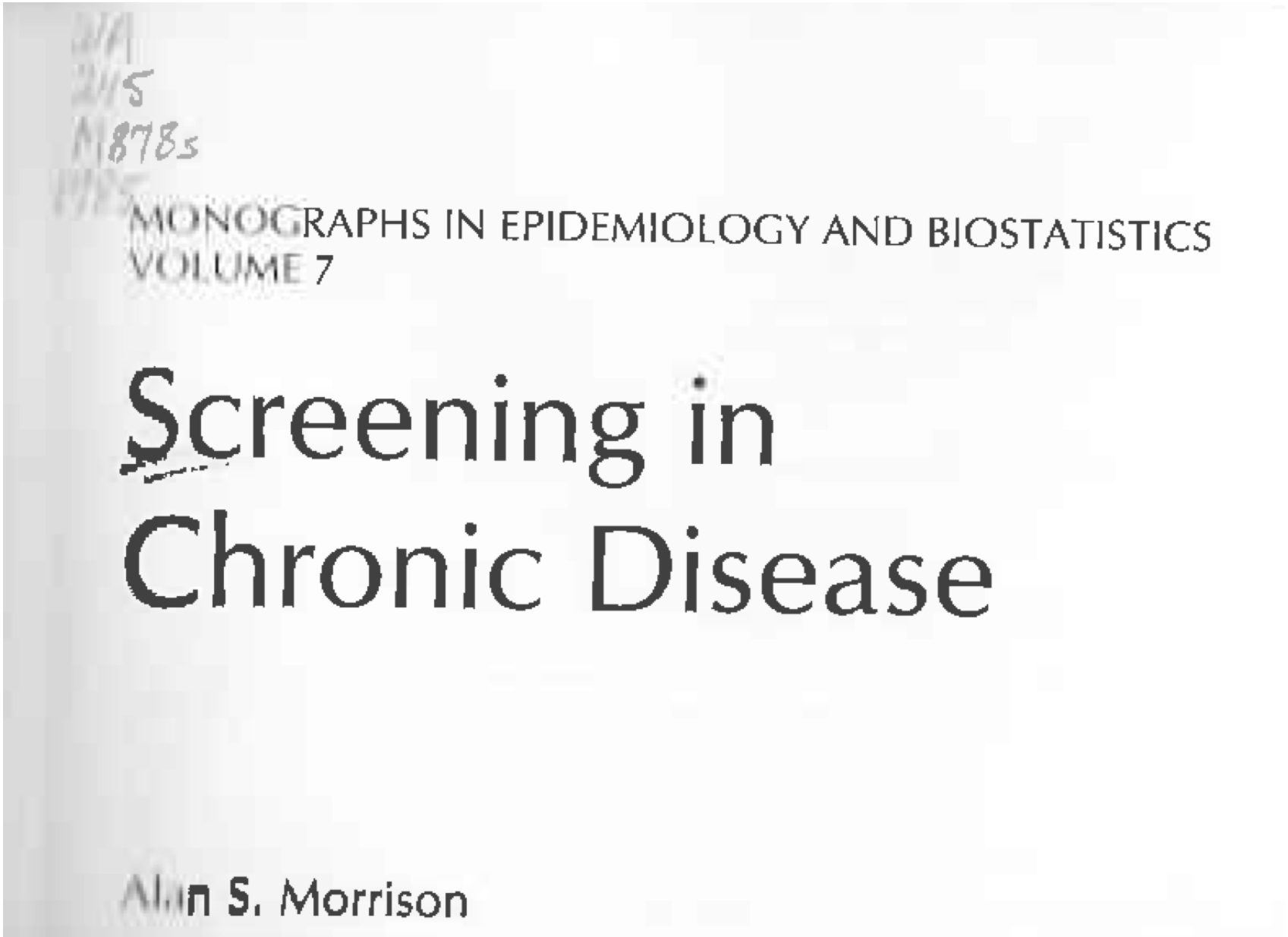

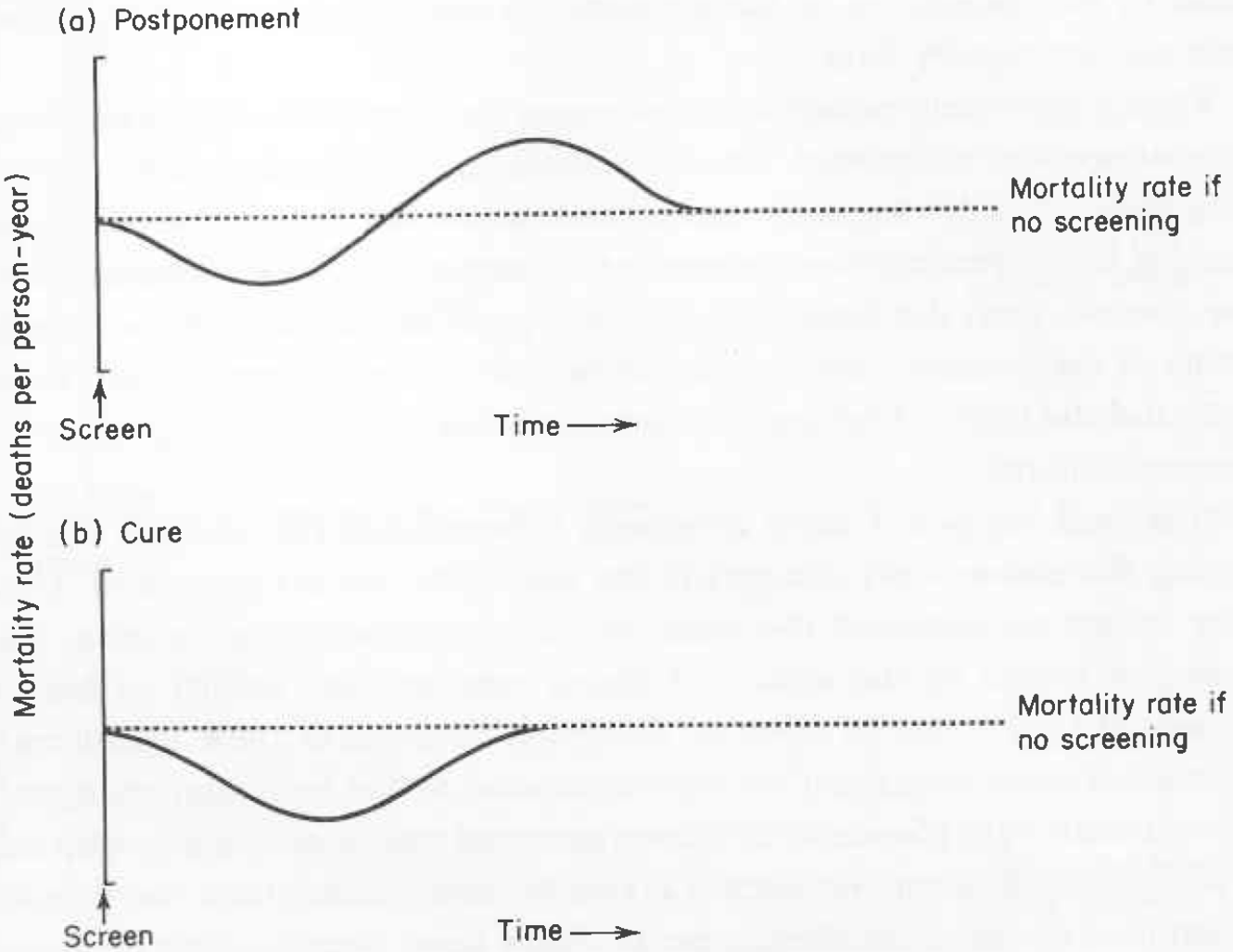


**Figure 2-5.** Changes in the disease-specific mortality rate brought about by postponement of death and by "cure" of screen-detected cases.

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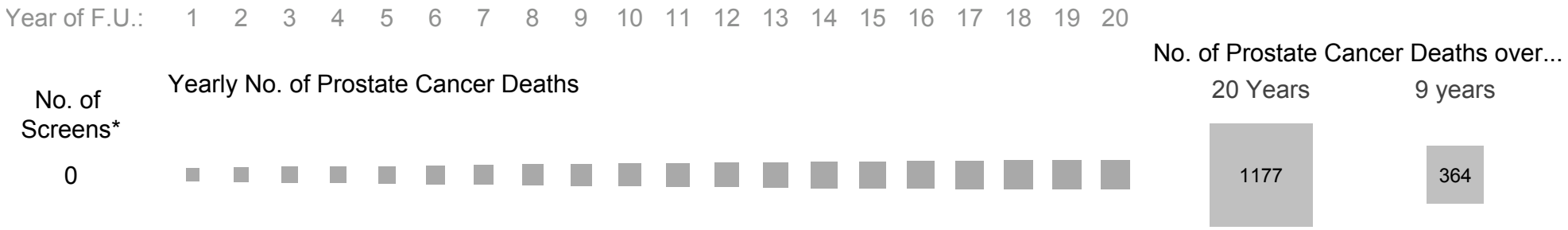
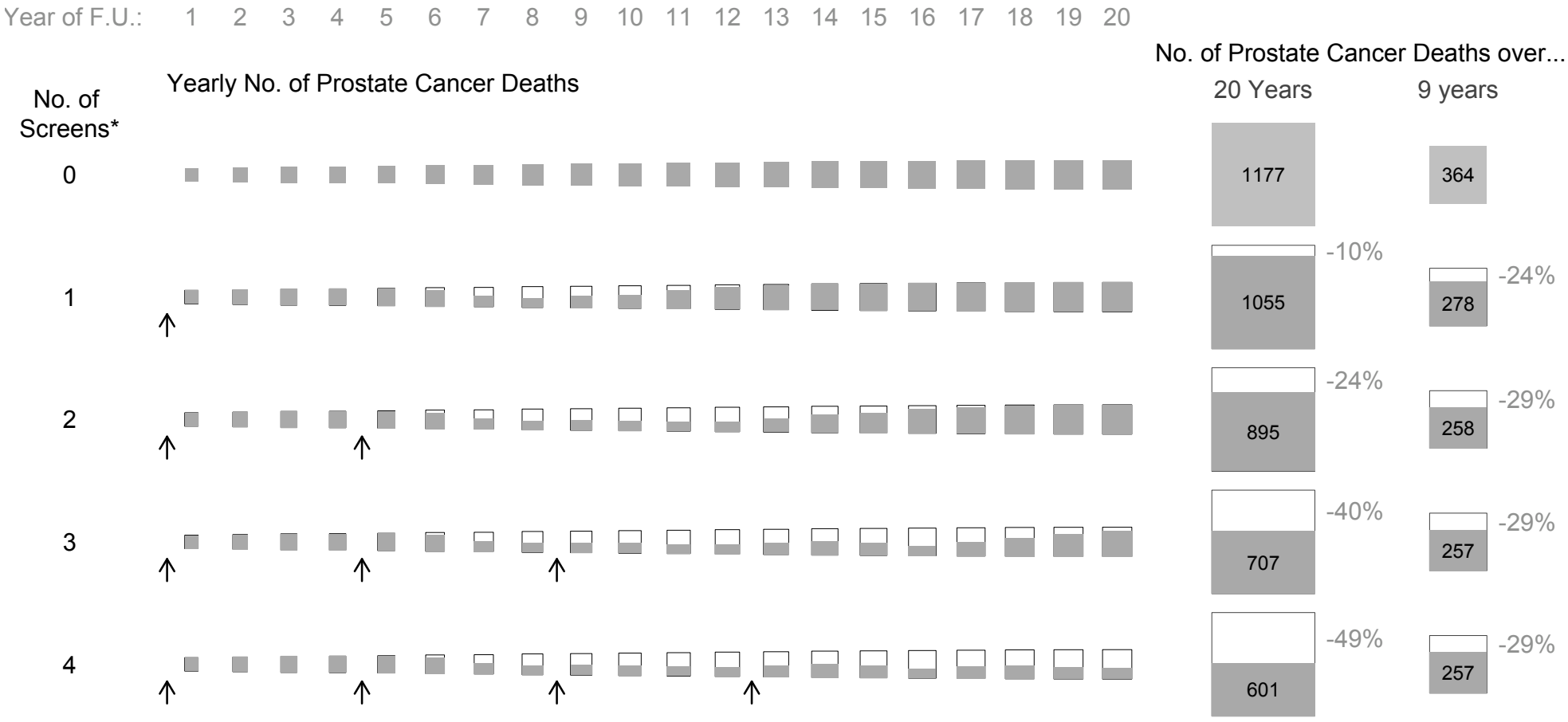
**HYPOTHETICAL DATA**

# Cumulative & Year-specific results, if screen 0 times [HYPOTHETICAL]




[over these 20 years, approx. 65,000 men would die of other causes]

# 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]

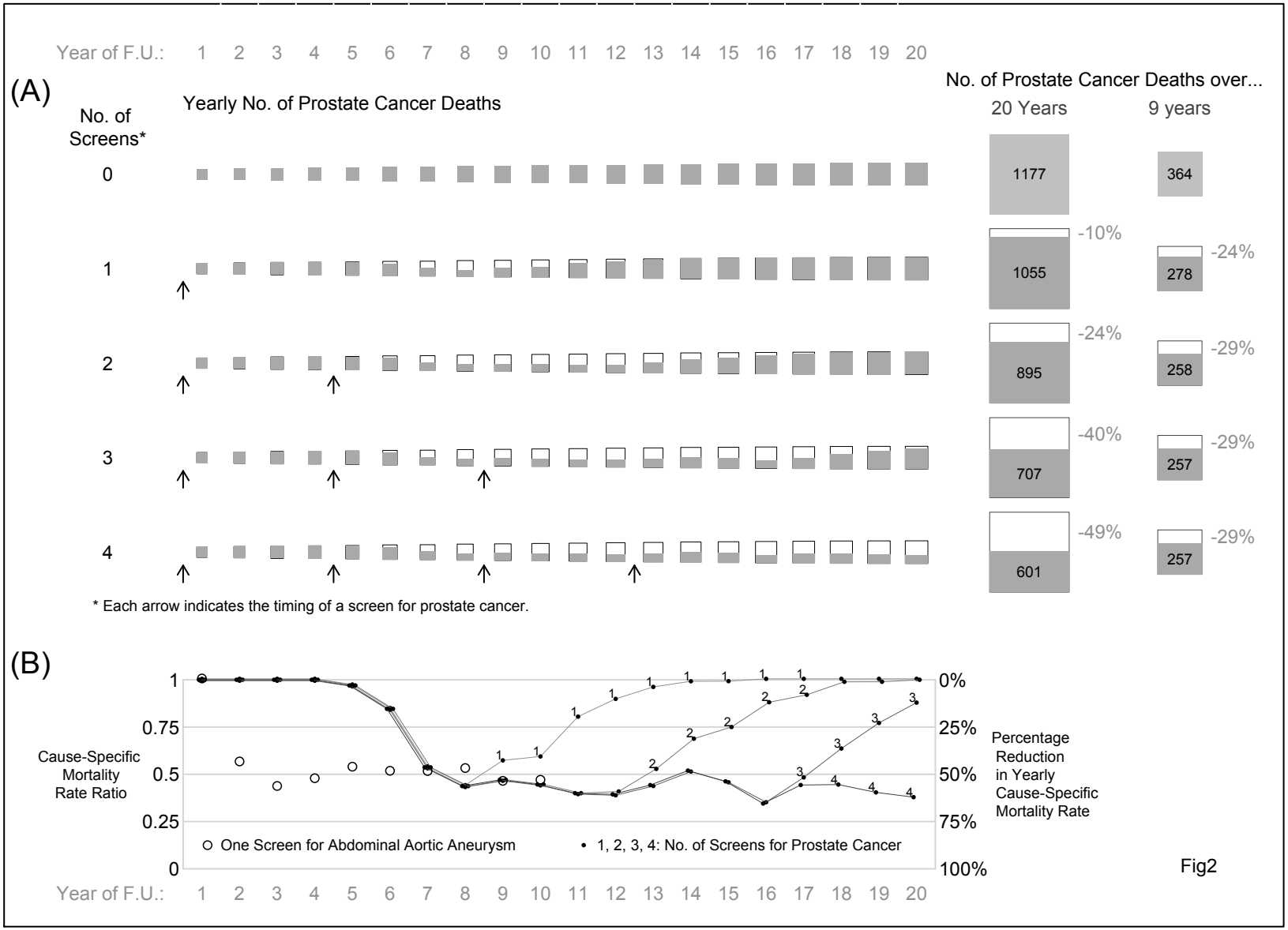



Fig2

# RE-ANALYSIS OF ERSPC DATA

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  - pdf file containing Fig 2 $\rightarrow$ encapsulated postscript (eps) file format;
  - eps file $\rightarrow$ exact information (co-ordinates of line segments and dots) that statistical program, Stata, had used to draw two Nelson- Aalen cumulative hazard curves. eps file contained exact co-ordinates of each of 89,308 and 72,837 line segments or dots, one per man.
  - horizontal/vertical co-ordinates of each segment/dot $\rightarrow$ exact numbers of men being followed at each point in follow-up time, and thus at exact times of the vertical steps in curves (pr ca deaths).
  - size of step $\times$ number being followed $\rightarrow$ number of prostate cancer deaths at each time point
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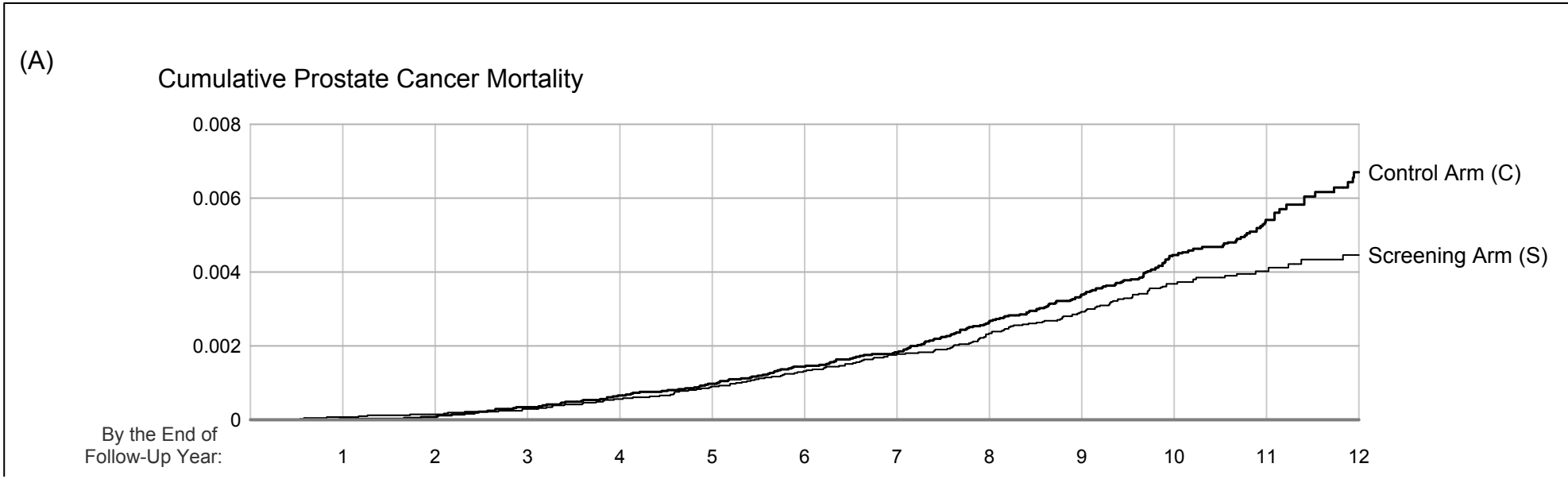
- Smooth curve for rate ratio function (data bins 0.2 y wide).

# Year-specific prostate cancer mortality ratios



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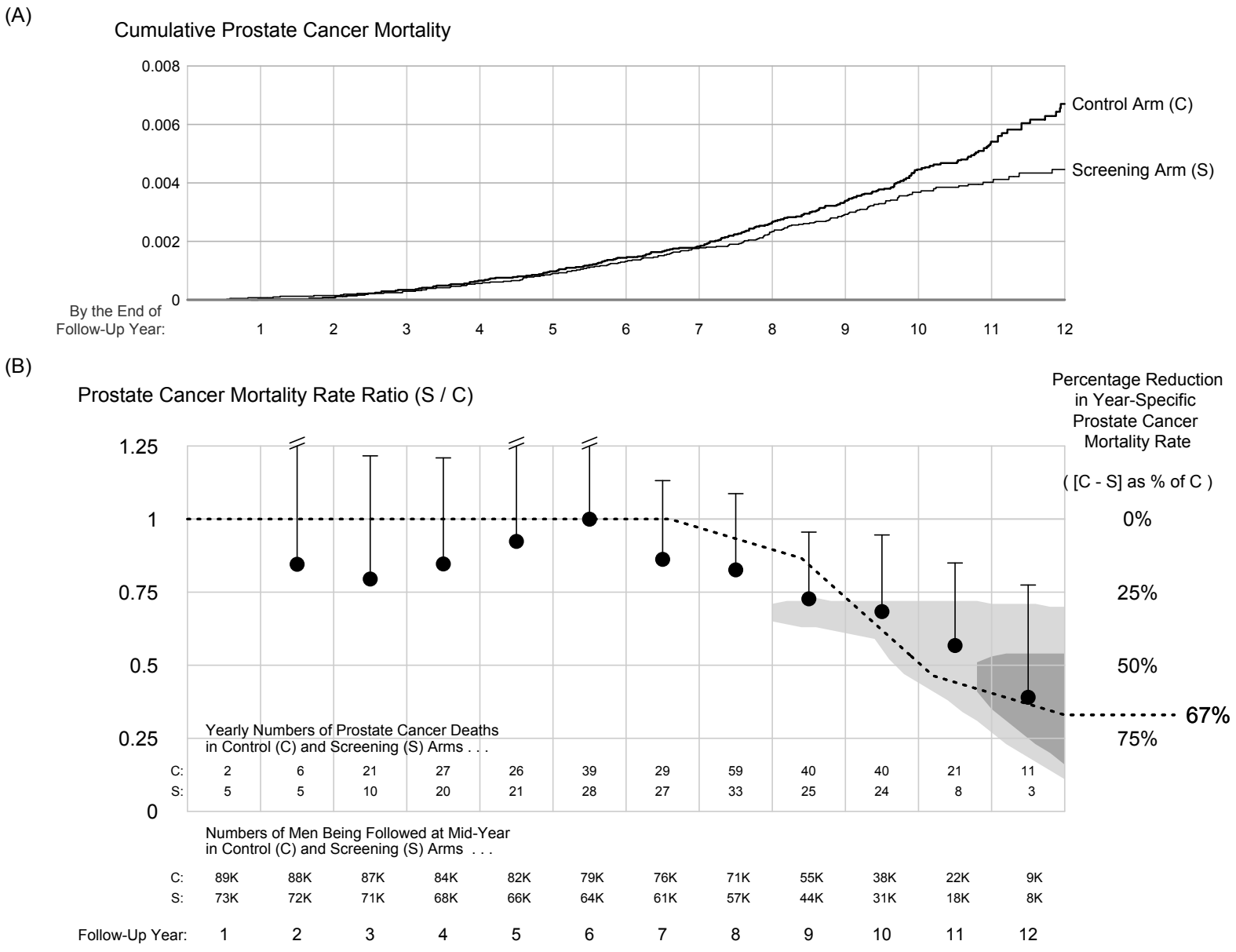

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- Numbers of deaths are not sufficient to establish its timing and magnitude more precisely. (Data cutoff: Dec 2006)

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- Prostate cancer deaths from **2007 onwards crucial to more precisely measure** the reduction achieved.

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  - data themselves inform us about two critical parameters that determine 'response curve' (i.e., **timing** & **extent** of prostate cancer mortality reduction caused by screening).

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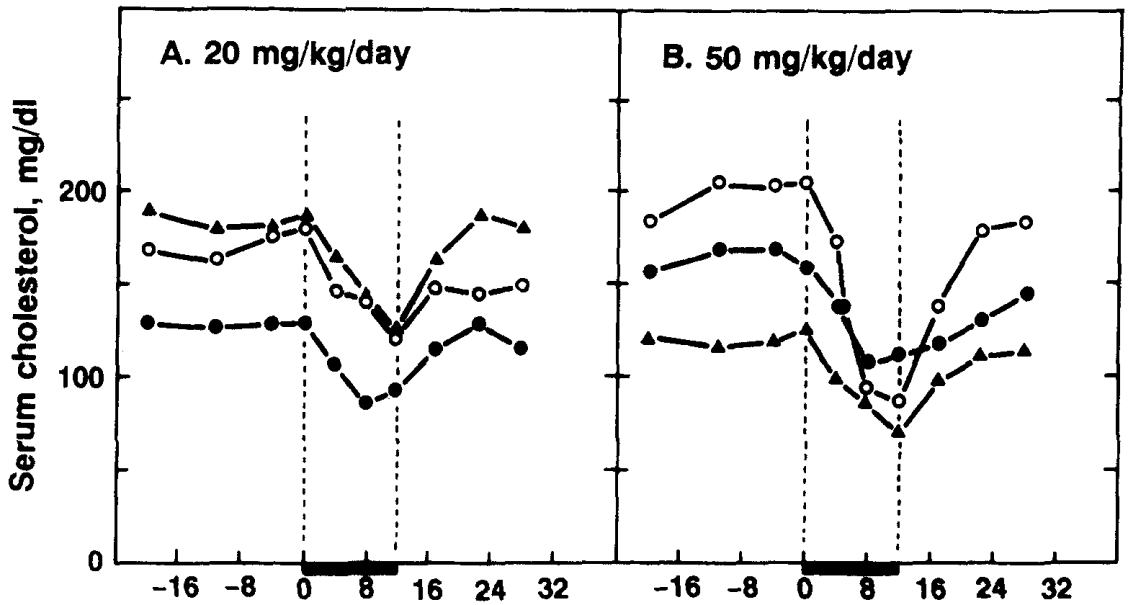

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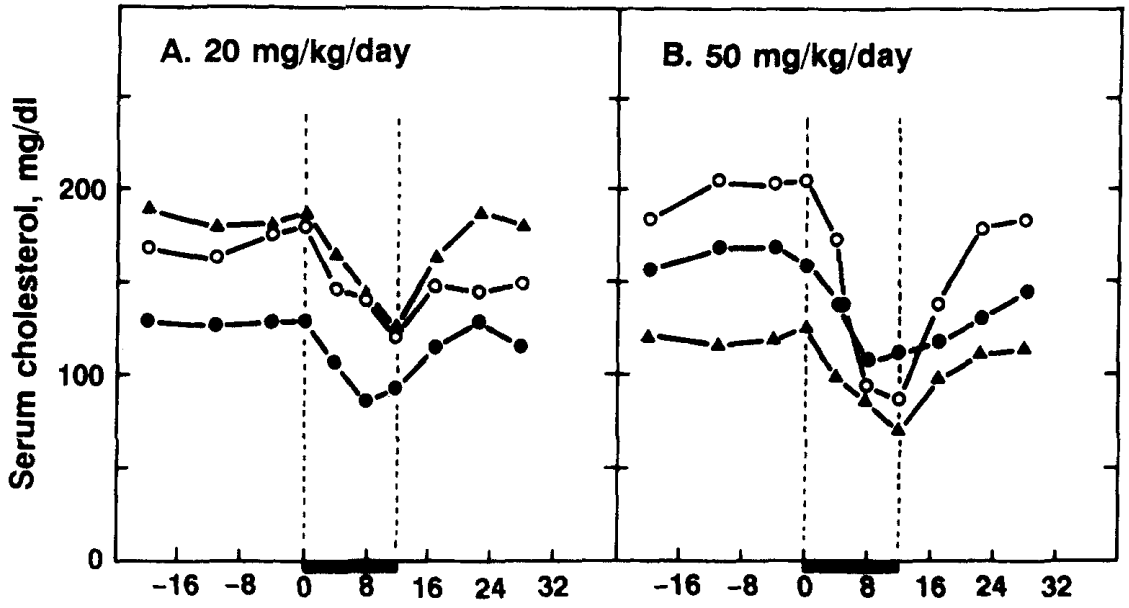
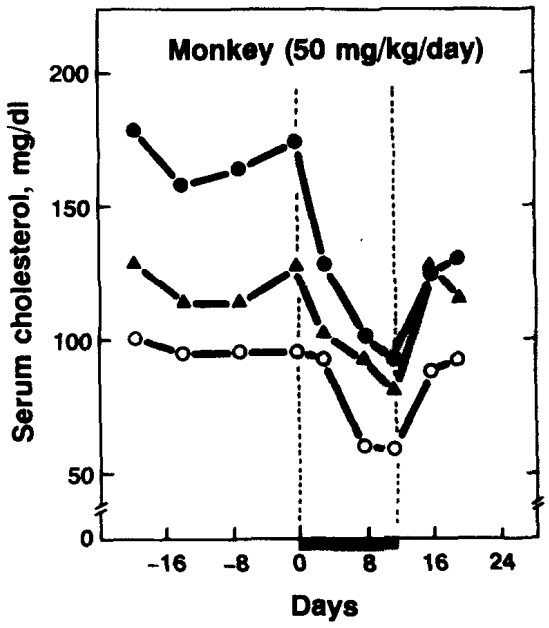



3 monkeys at 50



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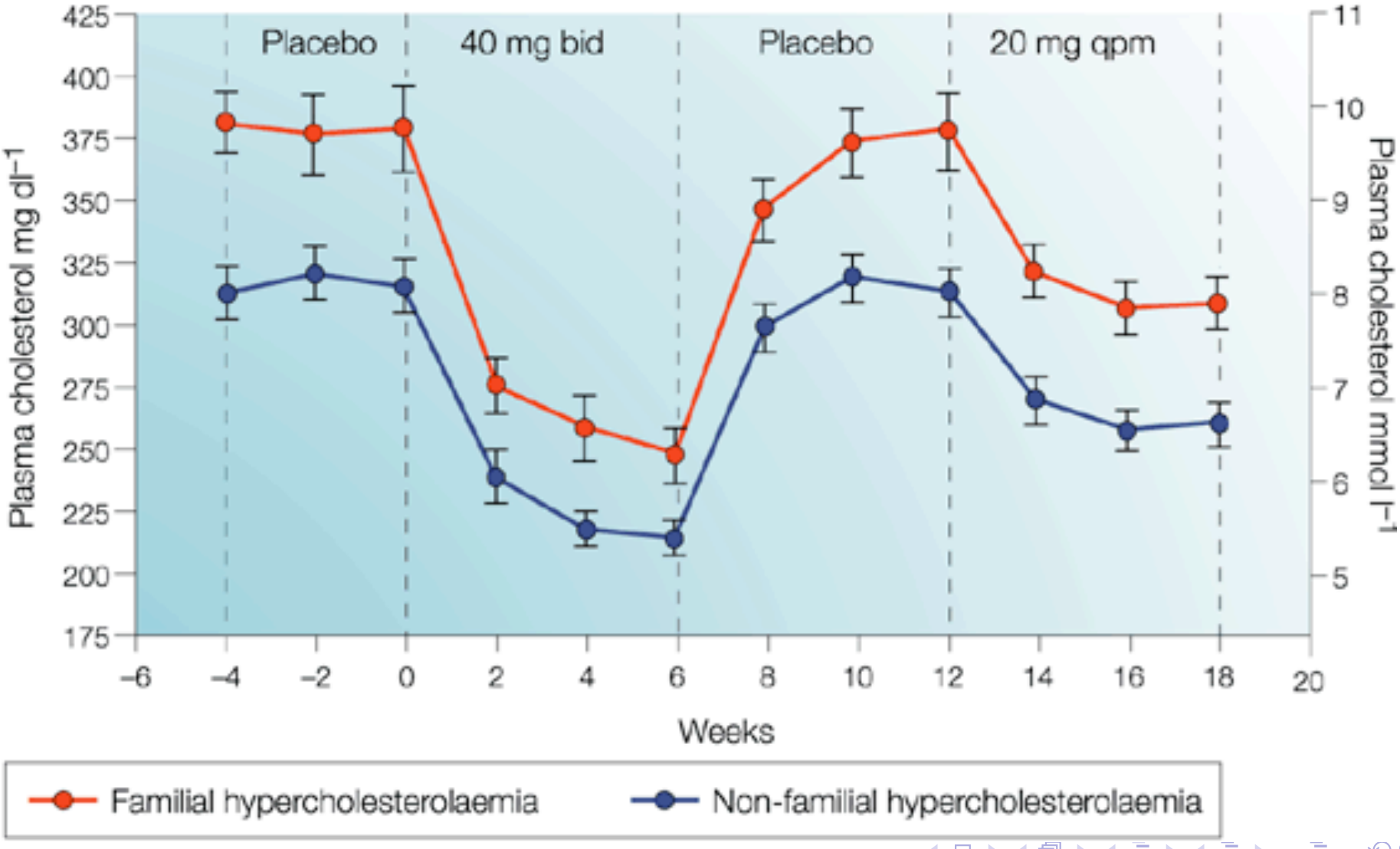

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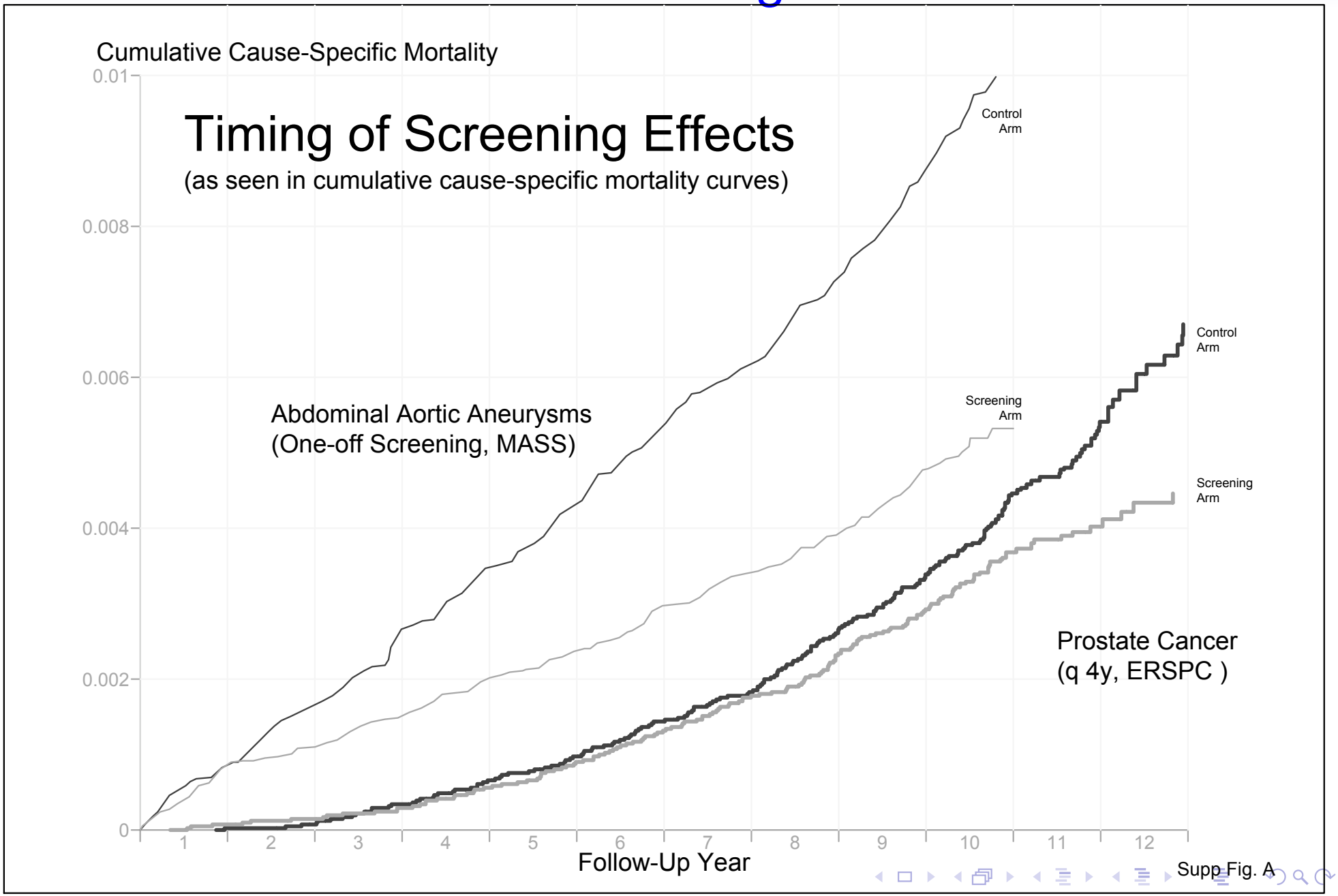


Supp Fig. A

# BREAST CANCER

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- IN EVERY INSTANCE: REDUCTION UNDER-ESTIMATED

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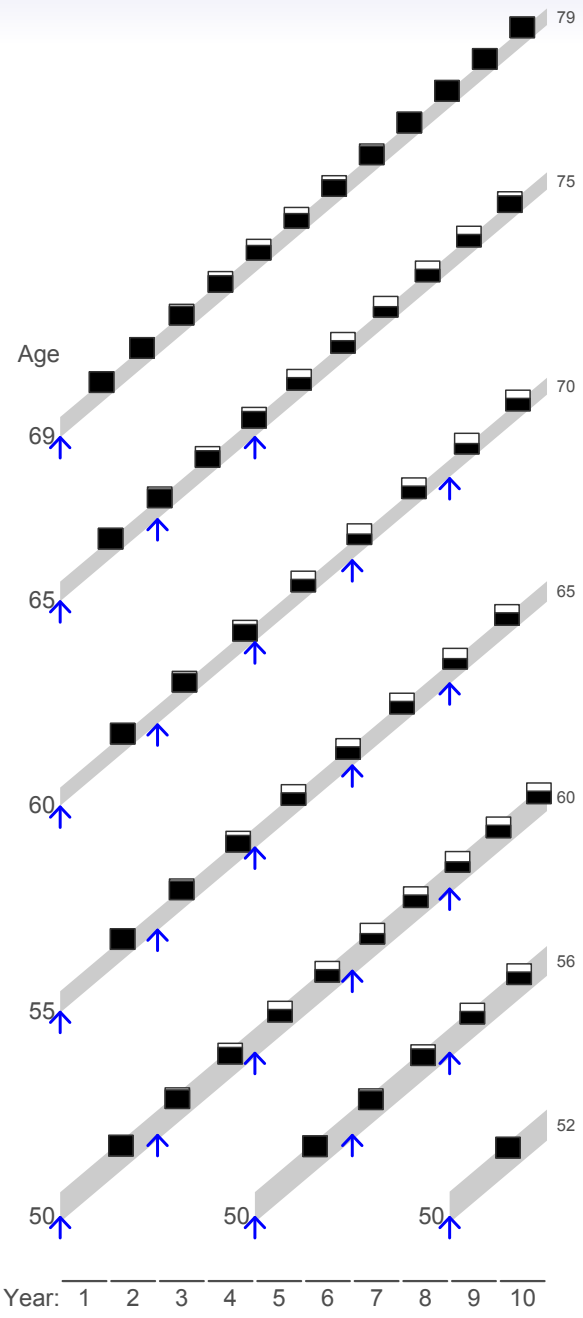


**WebFigure 6:**

**[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.**

COLON CANCER:

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excerpts from JH's 2005 and 2011 reviews

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CLINICAL REVIEWS

# Cochrane Systematic Review of Colorectal Cancer Screening Using the Fecal Occult Blood Test (Hemoccult): An Update

Paul Hewitson, B.A. (Hons), M.MSc,[1] Paul Glasziou, M.B.B.S., Ph.D., F.A.F.P.H.M., F.R.A.C.G.P.,[2] Eila Watson, B.Sc., Ph.D.,[3] Bernie Towler, M.B.B.S. M.PH.,[4] and Les Irwig, M.B.B.Ch., Ph.D., F.F.P.H.M.[5]

[1]*Department of Primary Health Care,* [2]*Centre for Evidence Based Medicine, Department of Primary Health Care, University of Oxford, Oxford, United Kingdom;* [3]*School of Health and Social Care, Oxford Brookes University, Oxford, United Kingdom;* [4]*Department of Health and Aging Services, Macarthur, Australia; and* [5]*Screening and Test Evaluation Program, School of Public Health, University of Sydney, Sydney, Australia*

**BACKGROUND: AND AIMS:** Reducing mortality from colorectal cancer (CRC) may be achieved by the introduction of population-based screening programs. The aim of the systematic review was to update previous research to determine whether screening for CRC using the fecal occult blood test (FOBT) reduces CRC mortality and to consider the benefits, harms, and potential consequences of screening.

**METHODS:** We searched eight electronic databases (Cochrane Library, MEDLINE, EMBASE, CINAHL, PsychINFO, AMED, SIGLE, and HMIC). We identified nine articles describing four randomized controlled trials (RCTs) involving over 320,000 participants with follow-up ranging from 8 to 18 yr. The primary analyses used intention to screen and a secondary analysis adjusted for nonattendance. We calculated the relative risks and risk differences for each trial, and then overall, using fixed and random effects models.

**RESULTS:** Combined results from the four eligible RCTs indicated that screening had a 16% reduction in the relative risk (RR) of CRC mortality (RR 0.84, 95% confidence interval [CI] 0.78–0.90). There was a 15% RR reduction (RR 0.85, 95% CI 0.78–0.92) in CRC mortality for studies that used biennial screening. When adjusted for screening attendance in the individual studies, there was a 25% RR reduction (RR 0.75, 95% CI 0.66–0.84) for those attending at least one round of screening using the FOBT. There was no difference in all-cause mortality (RR 1.00, 95% CI 0.99–1.02) or all-cause mortality excluding CRC (RR 1.01, 95% CI 1.00–1.03).

**CONCLUSIONS:** The present review includes seven new publications and unpublished data concerning CRC screening using FOBT. This review confirms previous research demonstrating that FOBT screening reduces the risk of CRC mortality. The results also indicate that there is no difference in all-cause mortality between the screened and nonscreened populations.

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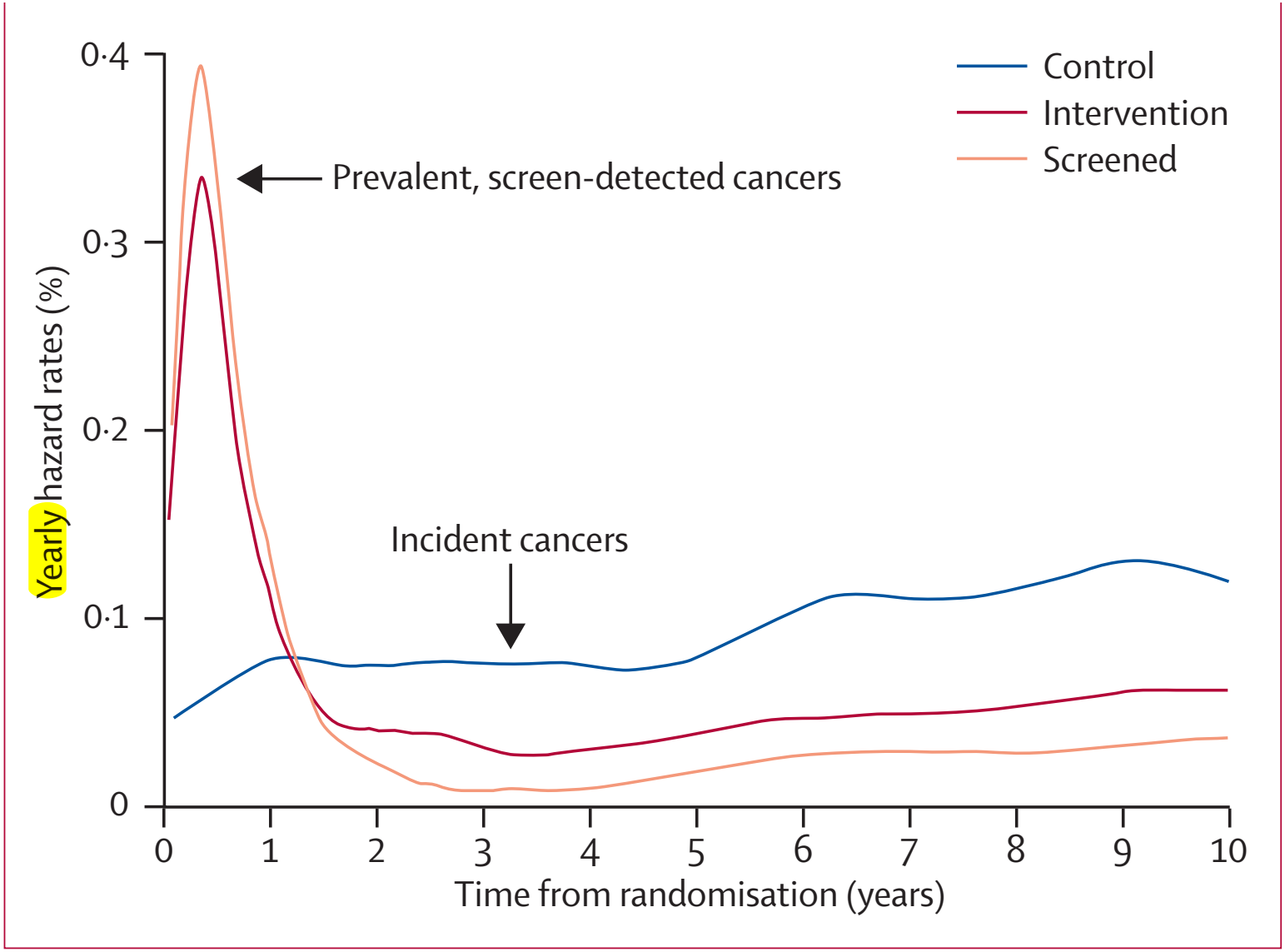


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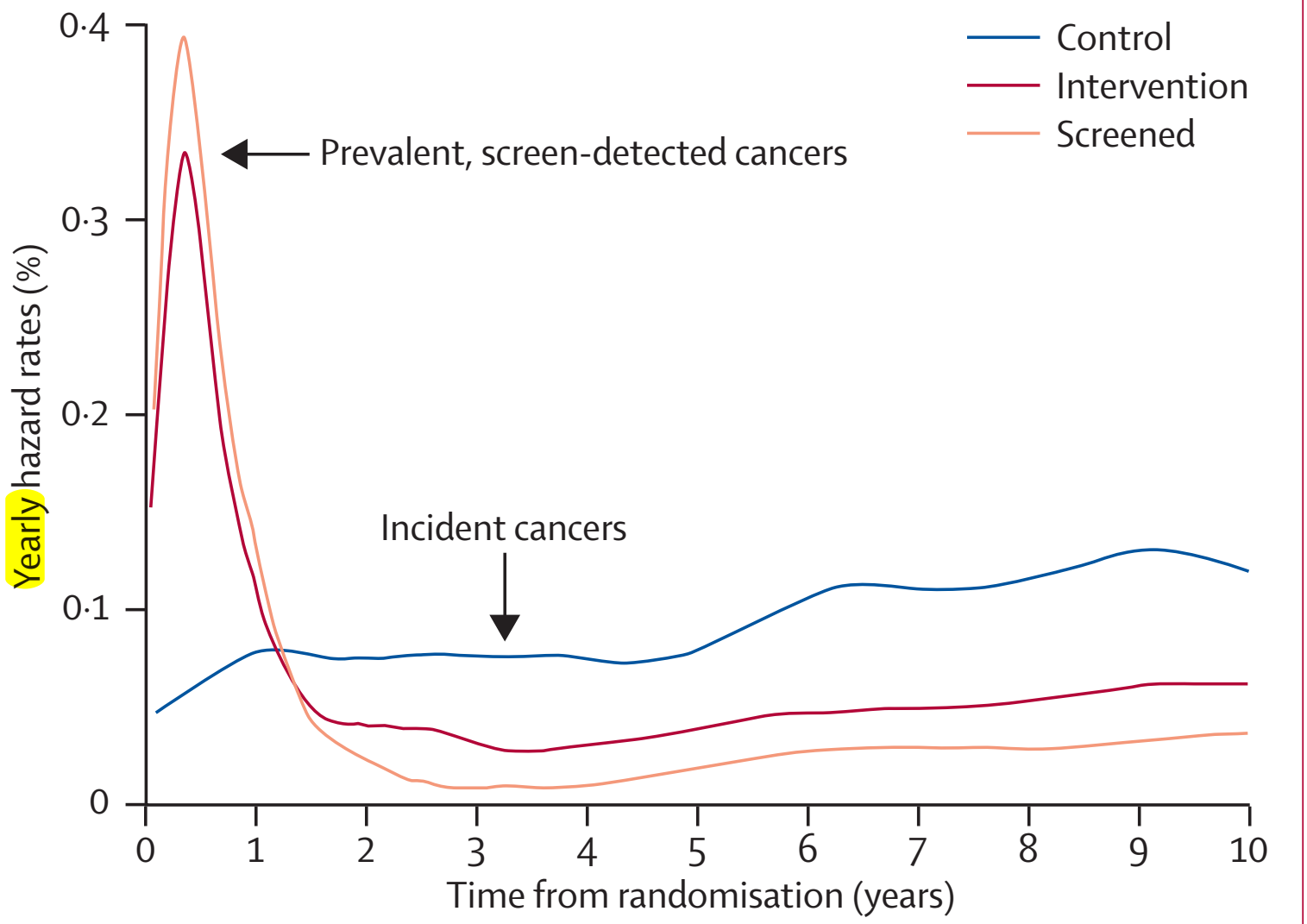


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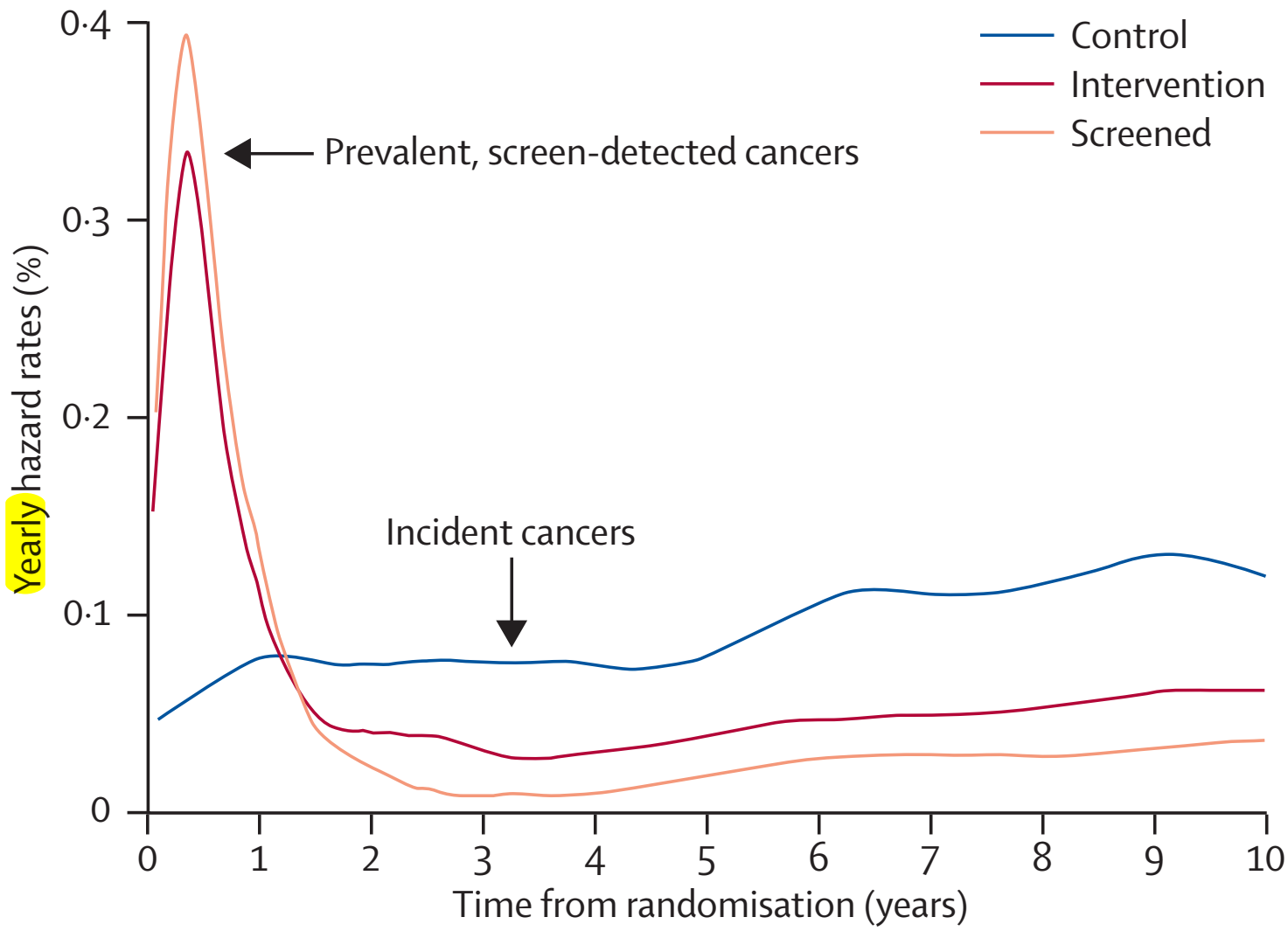


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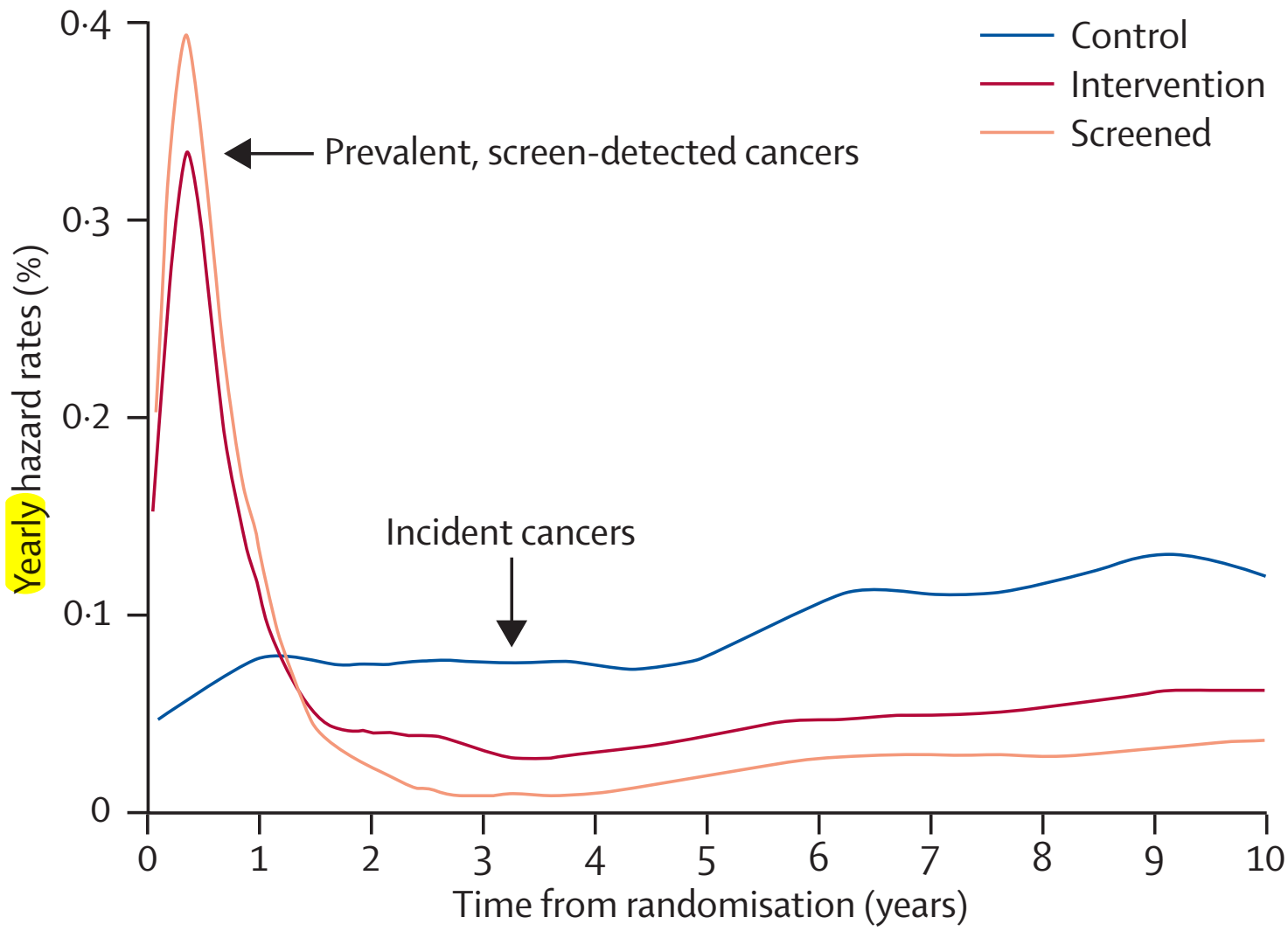


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  *to determine whether three annual screenings with low-dose helical computerized tomography (LDCT) reduces [sic] mortality from lung cancer*

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  *Screening of people at high-risk for lung cancer with low dose CT significantly reduces lung cancer death: 20% fewer lung cancer deaths [ACR]*

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# National Lung Screening Trial (NLST)

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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 |
| **CXR** | 143,363.5 | 442 | 308.3 | | | |

# Timing of the ‘deficit’ of (442-354=) 88 deaths

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20% MORTALITY REDUCTION

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A UNIVERSAL CONSTANT IN SCREENING TRIALS?

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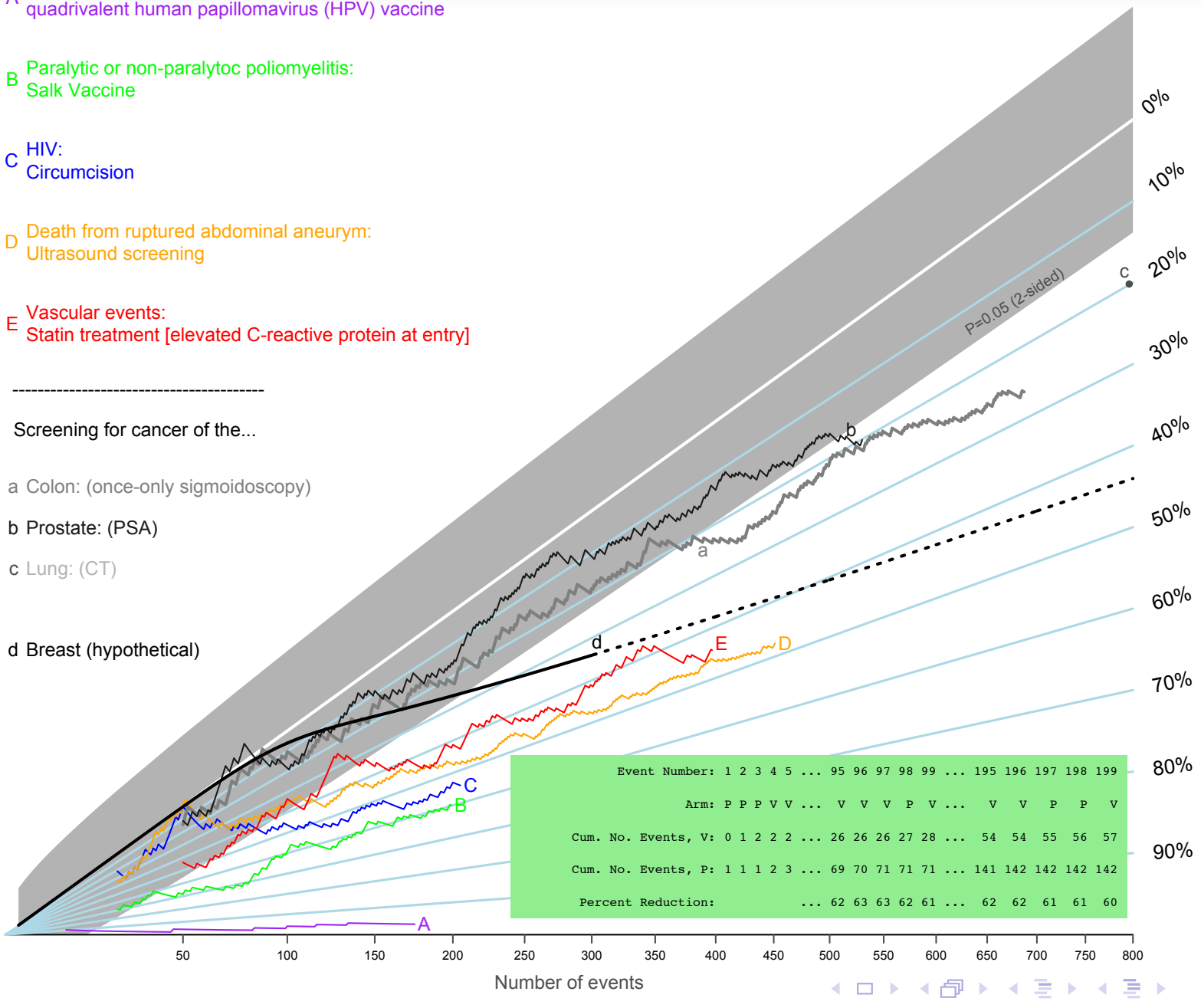
- when in f-up time events occurred (*'time-specific'* rates) ?


(i) Percentage Reduction in AVERAGE Event Rate
(if data analyzed after indicated no. of events)
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Screening for cancer of the...
a Colon: (once-only sigmoidoscopy)
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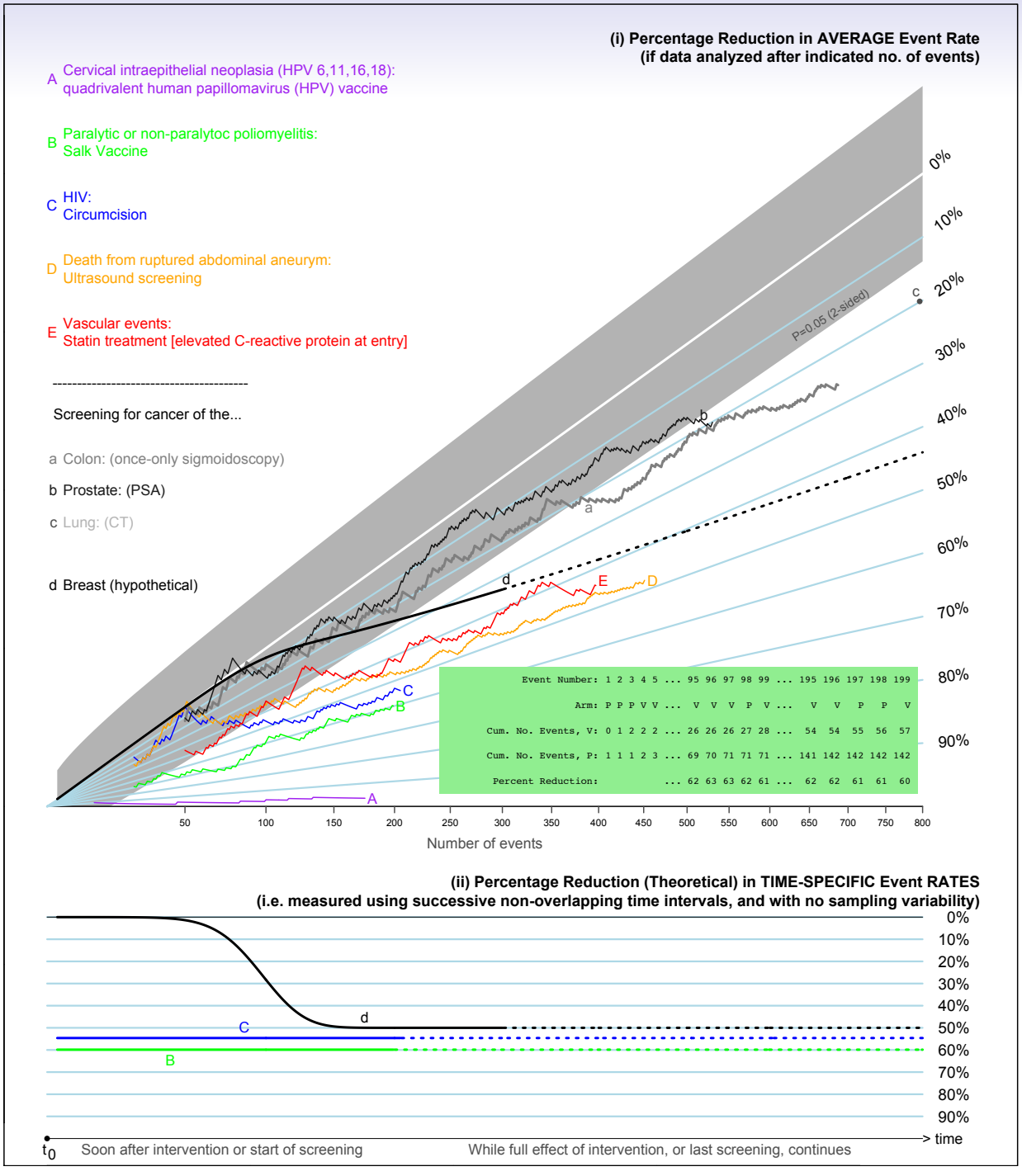
d Breast (hypothetical)
P=0.05 (2-sided)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
Event Number: 1 2 3 4 5 ... 95 96 97 98 99 ... 195 196 197 198 199
Arm: P P P V V ... V V V P V ... V V P P V
Cum. No. Events, V: 0 1 2 2 2 ... 26 26 26 27 28 ... 54 54 55 56 57
Cum. No. Events, P: 1 1 1 2 3 ... 69 70 71 71 71 ... 141 142 142 142 142
Percent Reduction: ... 62 63 63 62 61 ... 62 62 61 61 60
50 100 150 200 250 300 350 400 450 500 550 600 650 700 750 800
Number of events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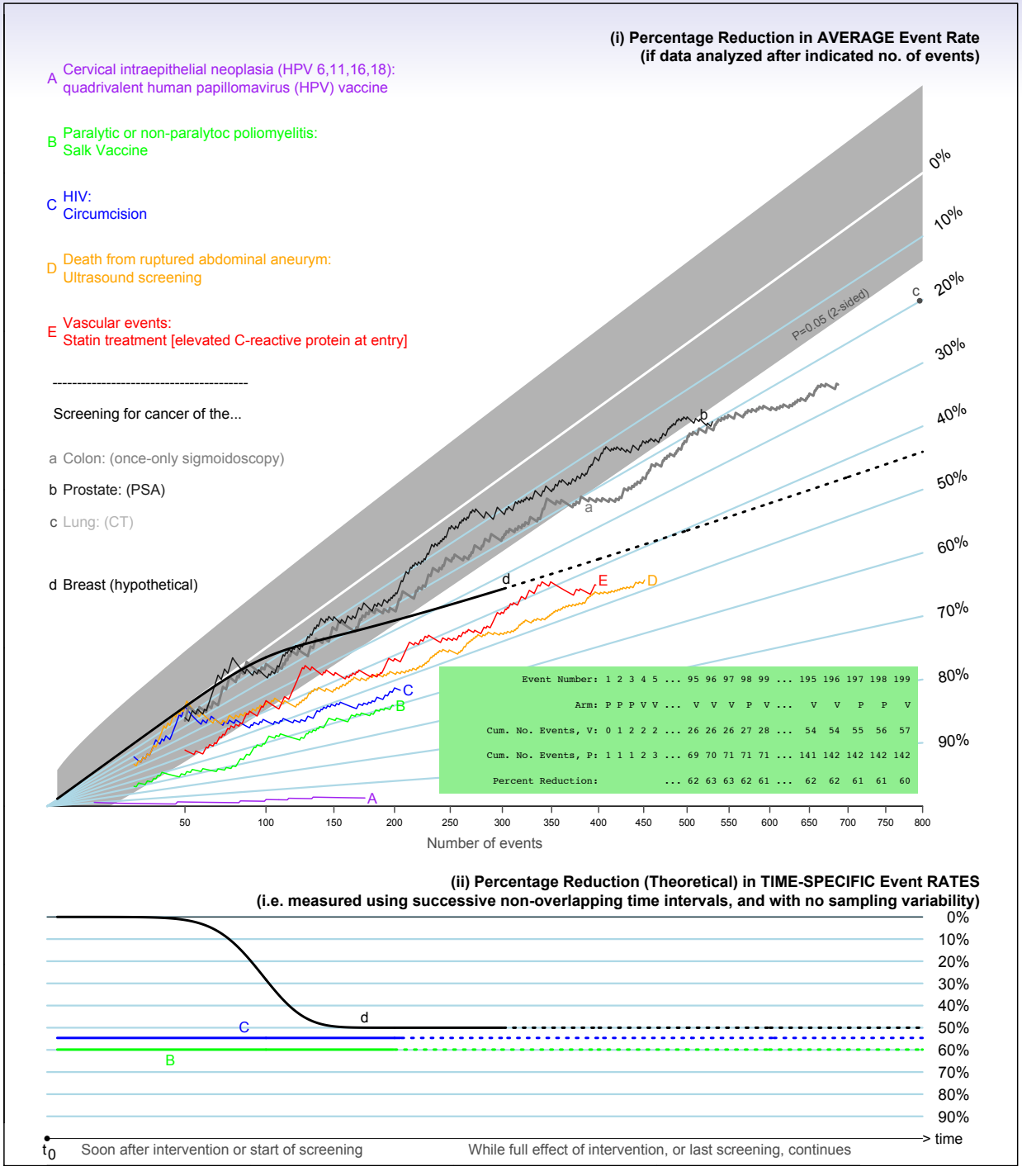
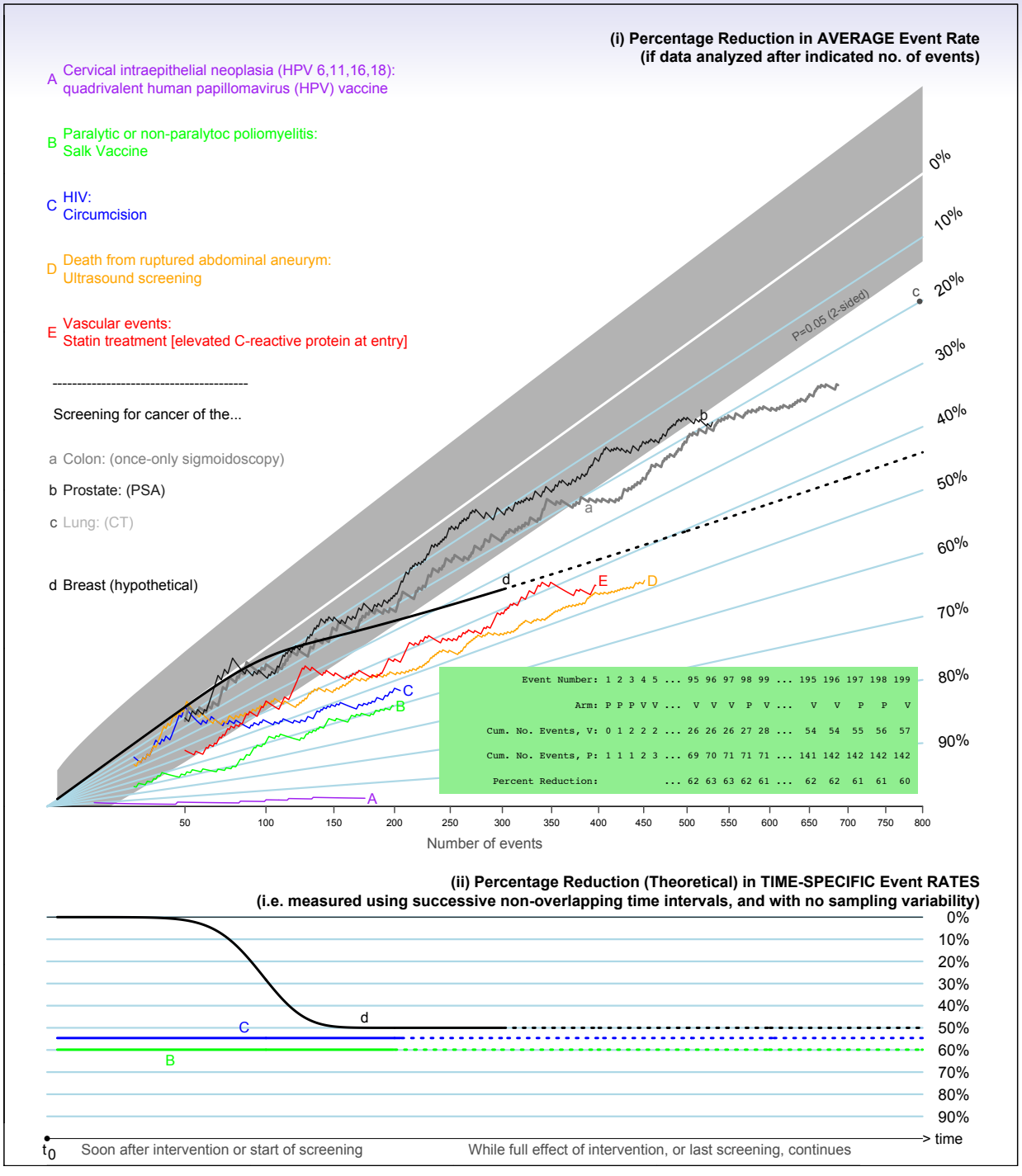
(ii) Percentage Reduction (Theoretical) in TIME-SPECIFIC Event RATES
(i.e. measured using successive non-overlapping time intervals, and with no sampling variability)
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
time
t0
Soon after intervention or start of screening
While full effect of intervention, or last screening, continues




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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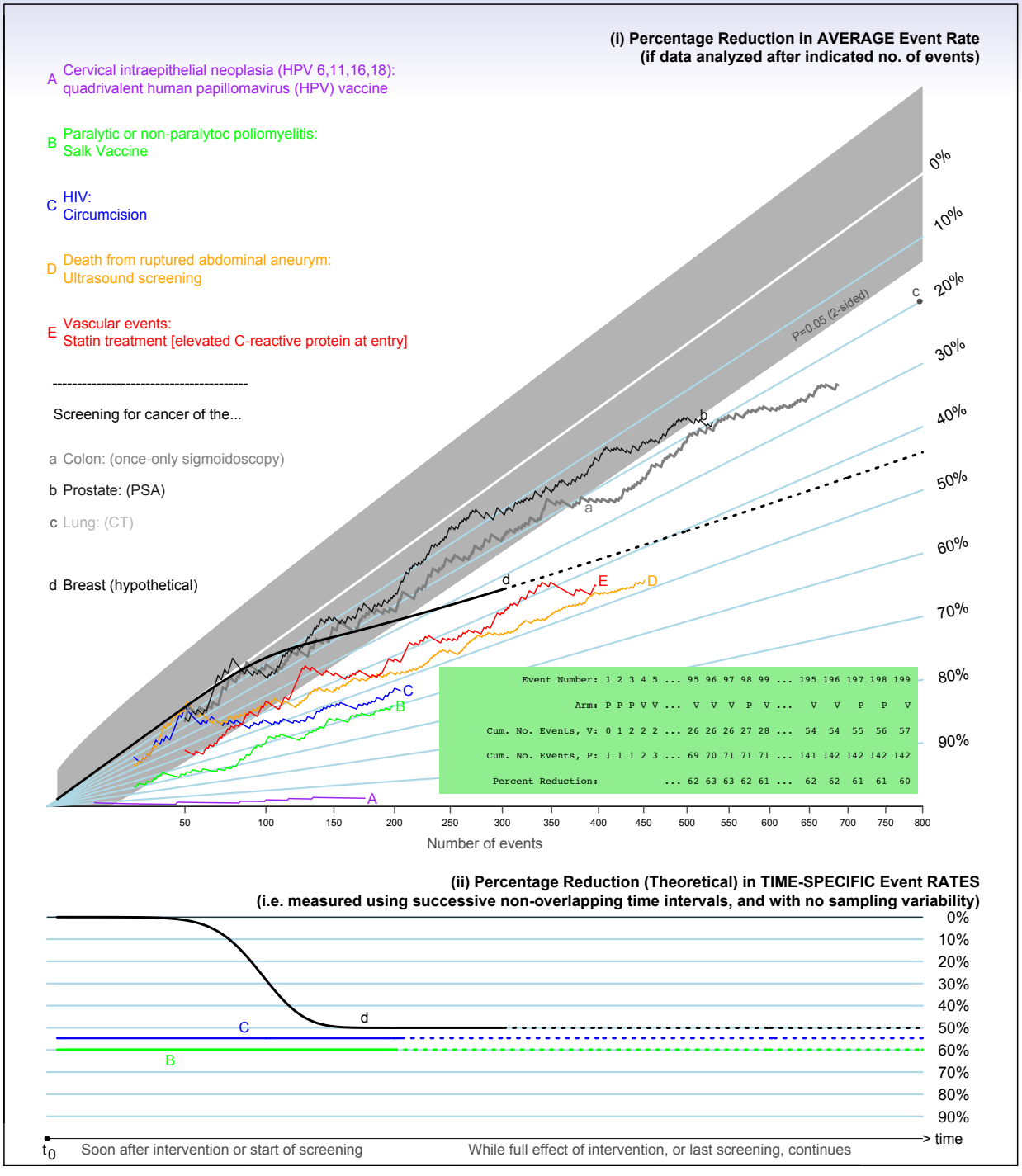


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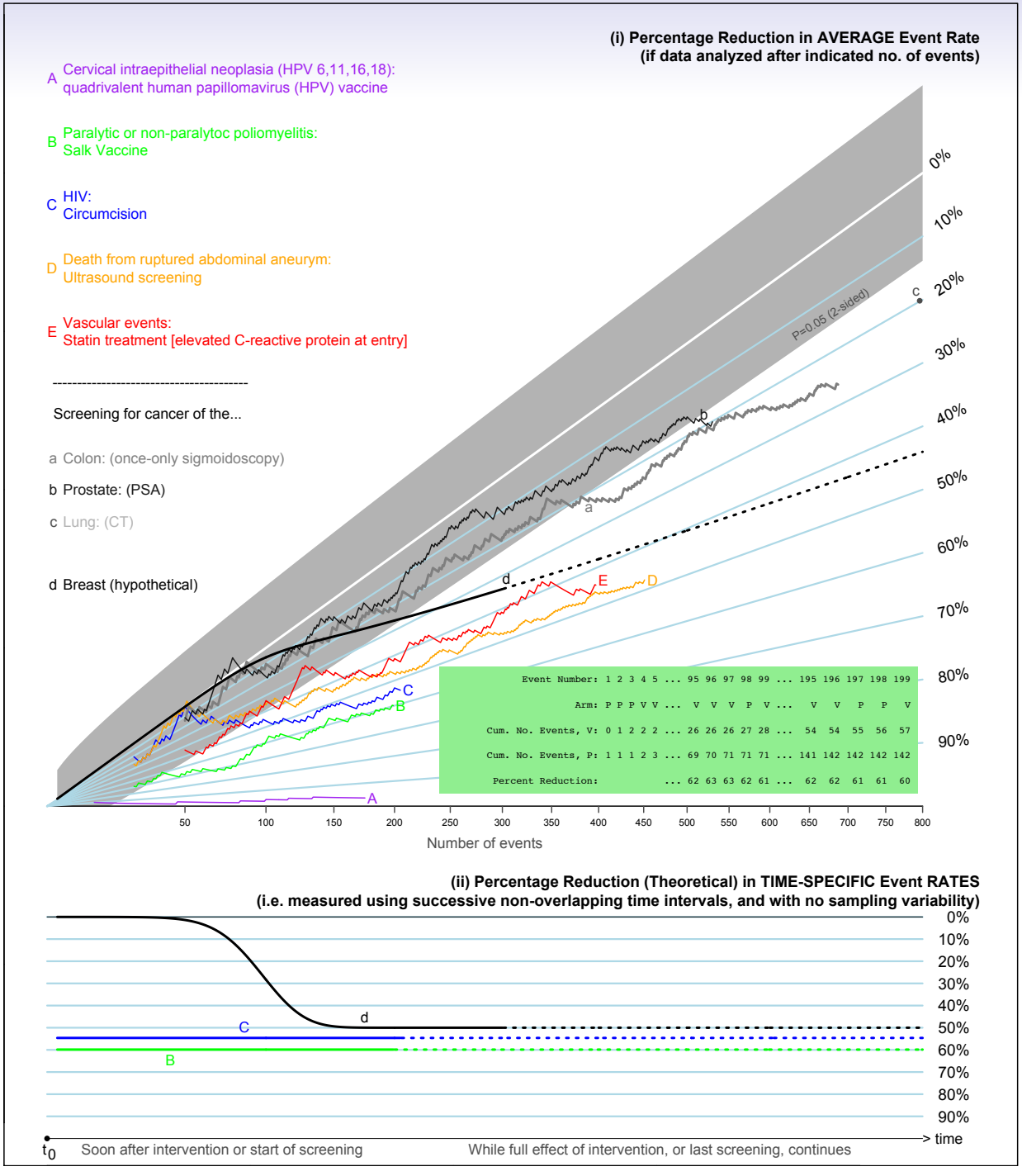


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The seemingly-universal 20% reduction is an artifact of prevailing data-analysis methods and stopping rules.

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.

# PLANS

# Data and Methods, Parameters, their Use

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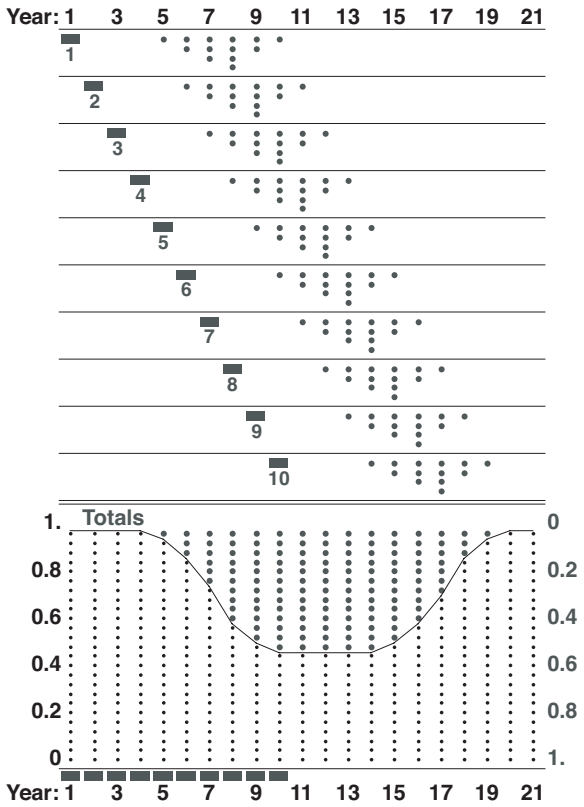

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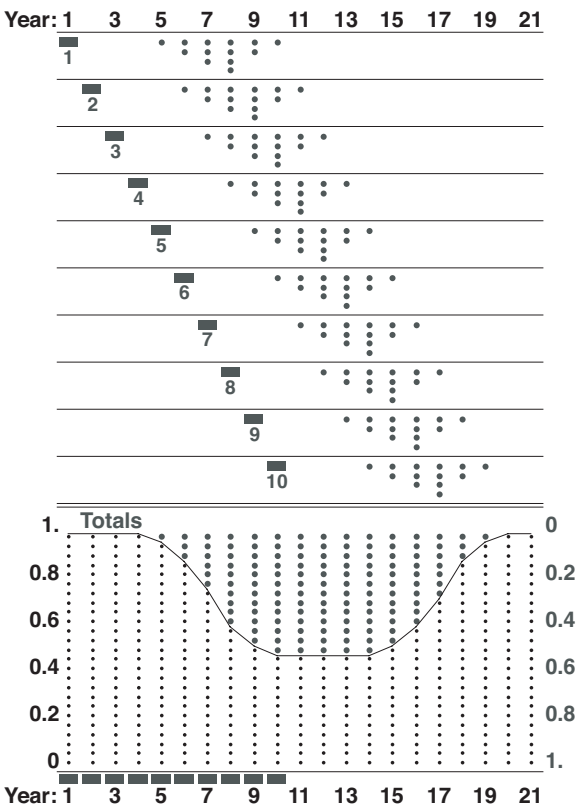


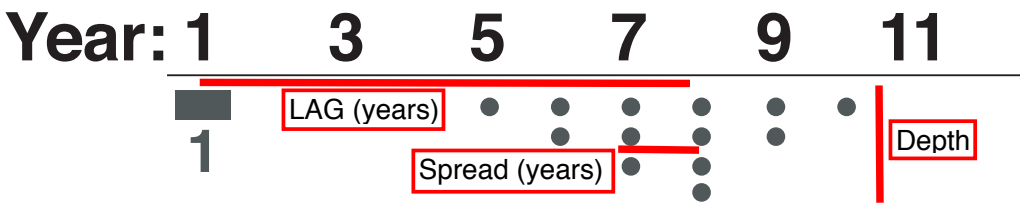

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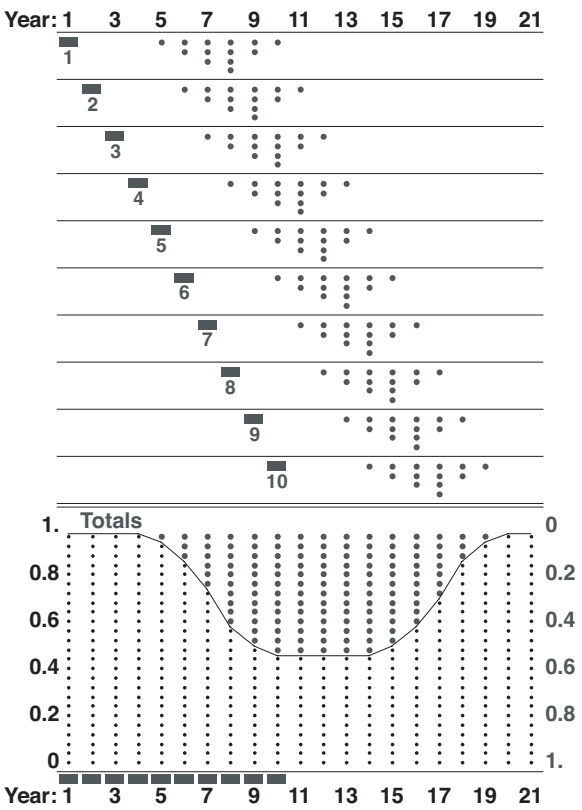


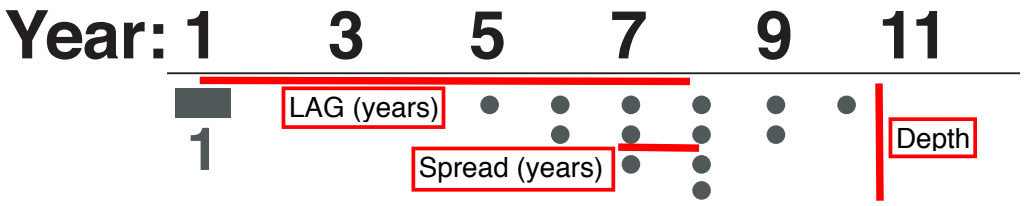


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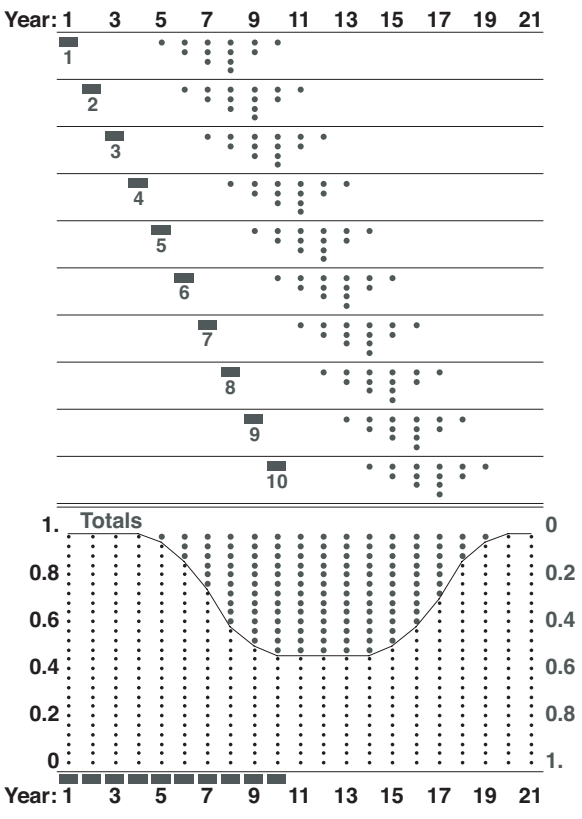


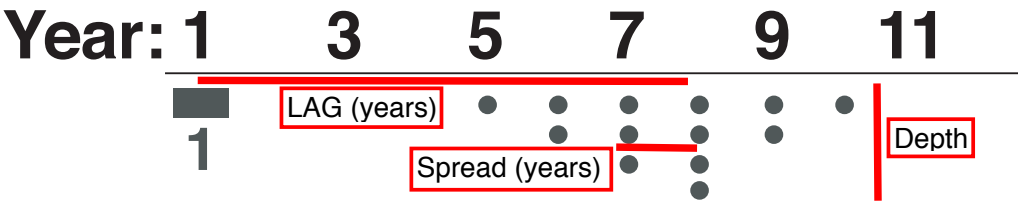


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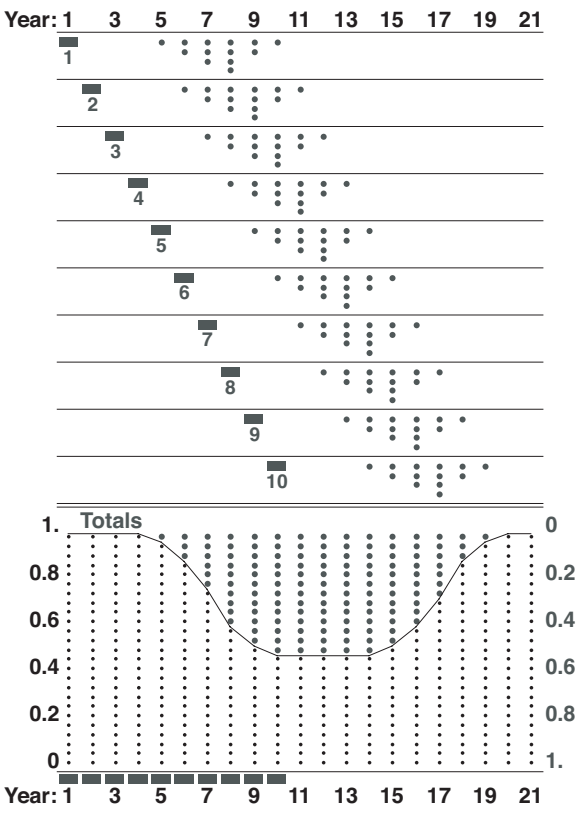


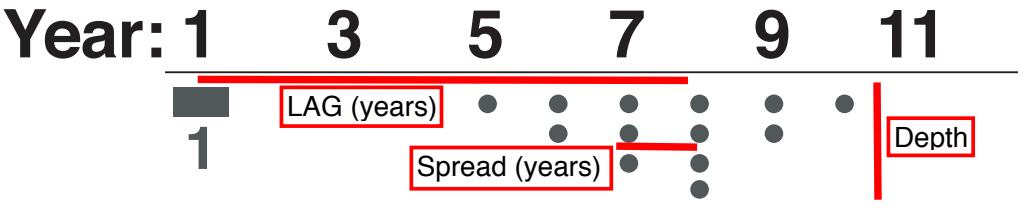


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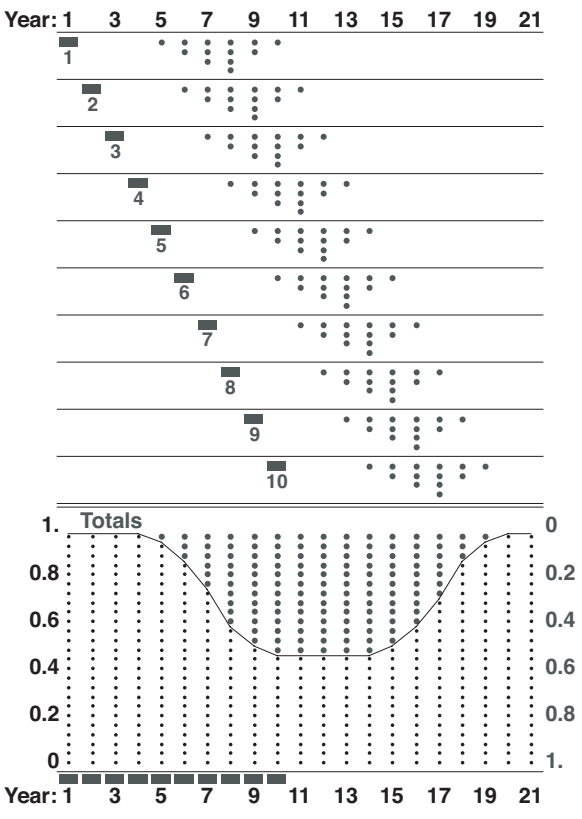


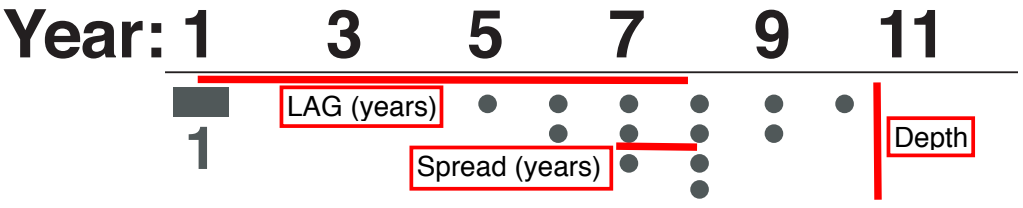


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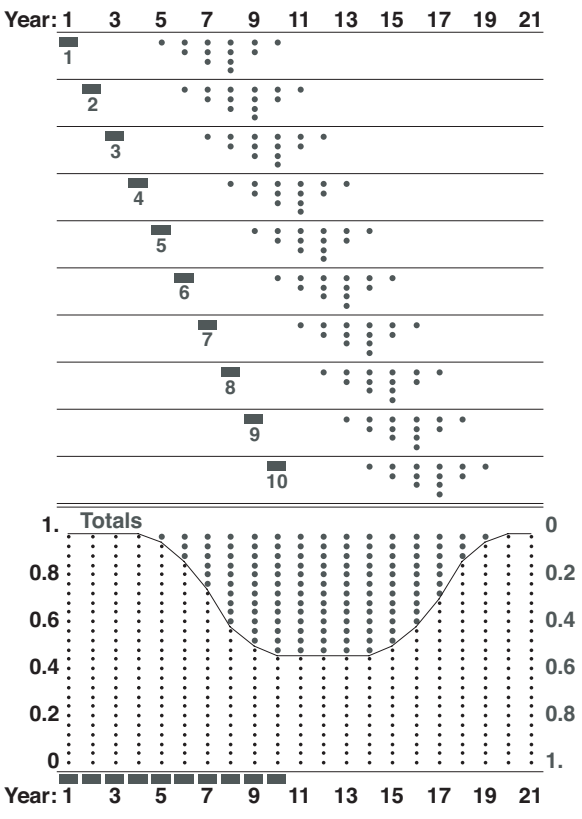


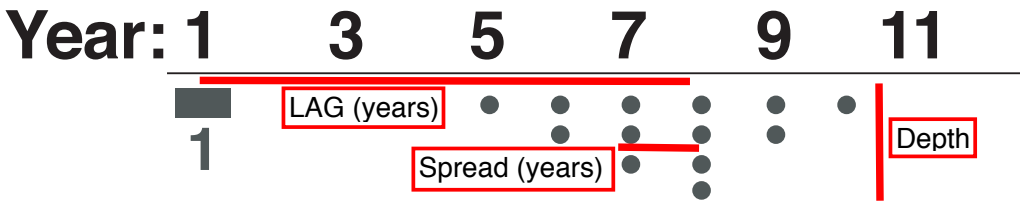


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- $\frac{\text{No. deaths in screening arm}}{\text{No. deaths in 2 arms combined}}$ in each ‘cell’

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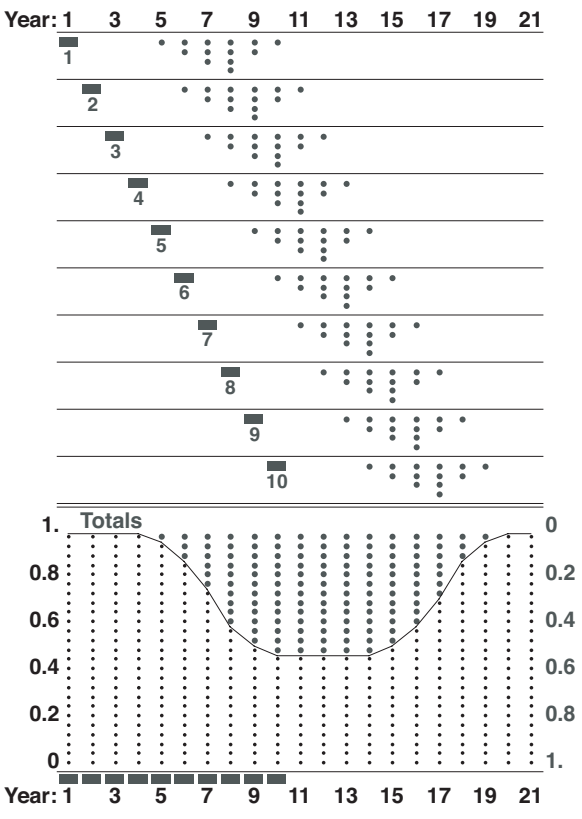
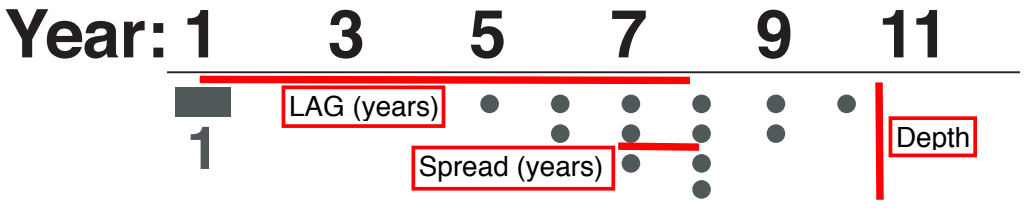
- **3 Parameters** (‘*deliverables*’) and how they will be fitted:




$y$ = years since screening commenced

- Rate ratio in Year $y$, Age $a$ in Study $s$ :

RateRatio($y$, $a$, $s$) =

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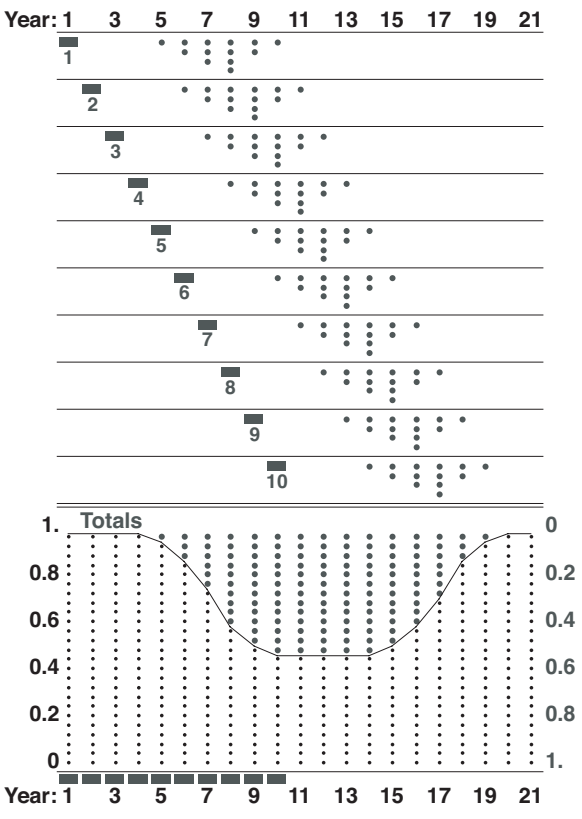


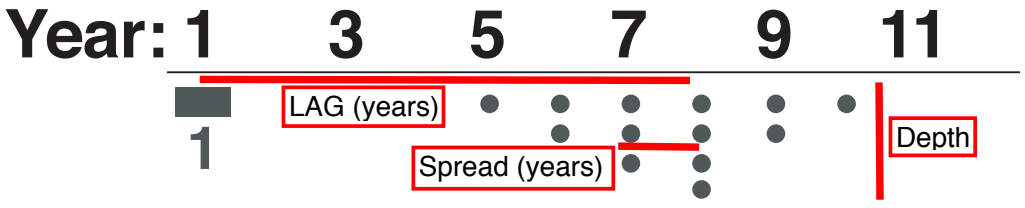


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- **USE**: project mort. reductions due to a screening regimen

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