

## Screening Absent

In a population of a given size (a),  
the numbers of prostate cancers that would...  
(c) come to clinical attention and  
(e) ultimately prove fatal despite treatment at that time.

The remaining number (c minus e) would not prove fatal,  
either because of the treatment received at that time (c minus d)  
or because the men died of other causes before their cancers could  
have proved fatal (d minus e).

The cancer mortality impact of a screening program is limited to  
the 'otherwise fatal' cancers, i.e., circle (e).

(a) No. men in Population

## Screening Present

In the same size population (a),  
the numbers of prostate cancers that would...  
(b) come to attention clinically or because of screening and  
(f) ultimately prove fatal despite the earlier detection and treatment program.

The remaining number (b minus f) would not prove fatal,  
specifically because of the earlier treatment (e-f),  
or because they would in any event have been curable at the time  
the cancer would have presented clinically, (c minus d) ,  
or because the men died of another causes (b minus d).

**The percentage reduction in cancer mortality  
specifically due to the screening program is  $100 \times (e-f)/e$ .**

**The additional number of cancers needed to be diagnosed  
in order to avert one cancer death is  $(b-c)/(e-f)$ .**

(b) No. cancers Diagnosed

(c) No. cancers Diagnosed

(d) No. cancers Fatal If Not Treated

(e) No. cancers Fatal Despite Treatment

**Deaths averted by treatment at time of clinical presentation**

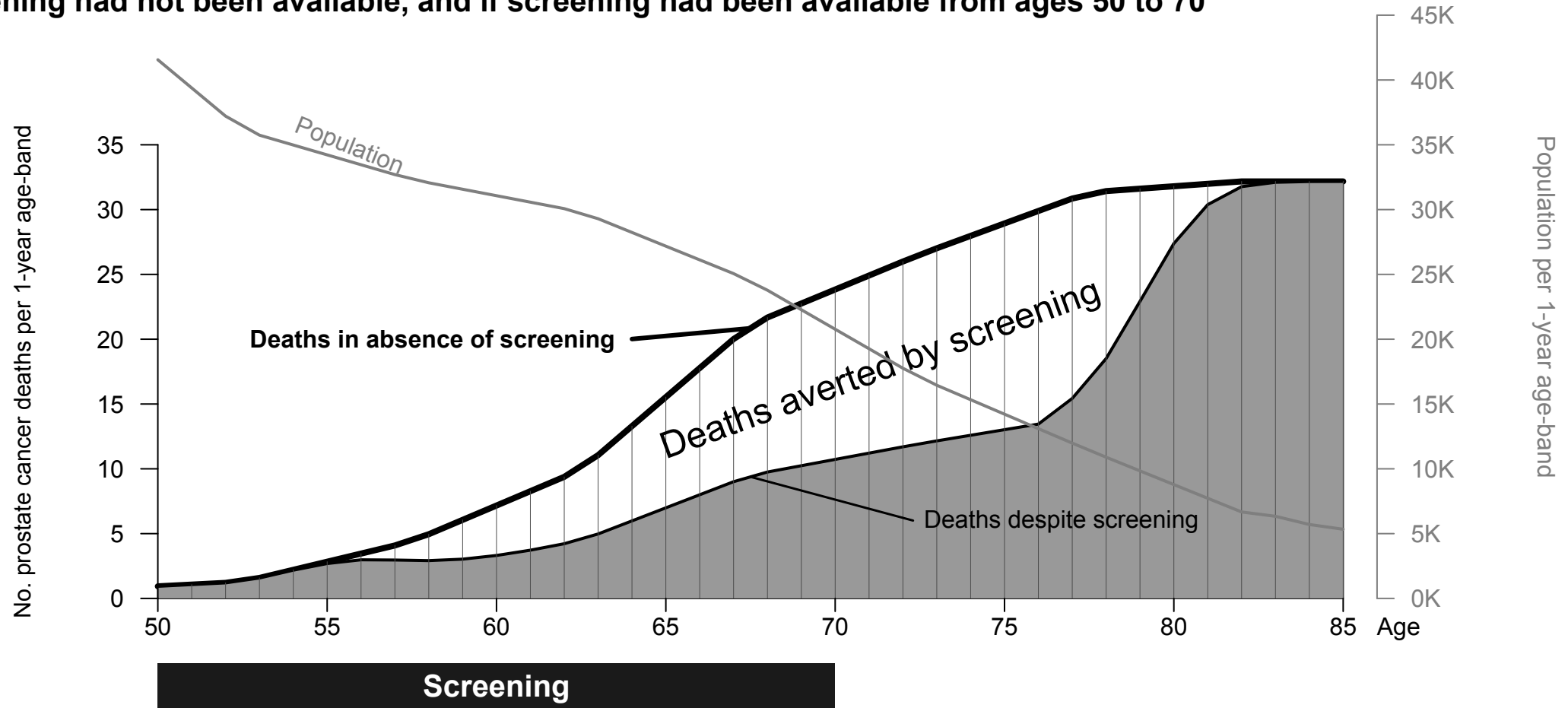
(d) No. cancers Fatal If Not Treated

(f) No. cancers Fatal Despite Treatment

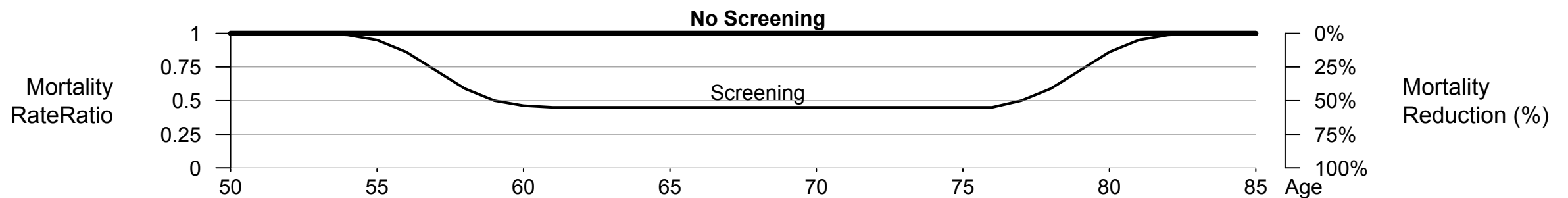
**Deaths averted by earlier detection and treatment**

**Web Figure 1. Schematic representation of the numbers of prostate cancers (as areas of circles) that would be detected and that would prove fatal in a given population over a given timescale in the absence of a screening program (left), and if a screening program had been in place for some portion of that timescale (right). Each cancer that ultimately did prove fatal did so because it was detected after some 'critical point' [Hutchison, 1960] and because the man did not die of another cause in the meantime; treatment before that critical time point would have averted the fatality.**

**(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**



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

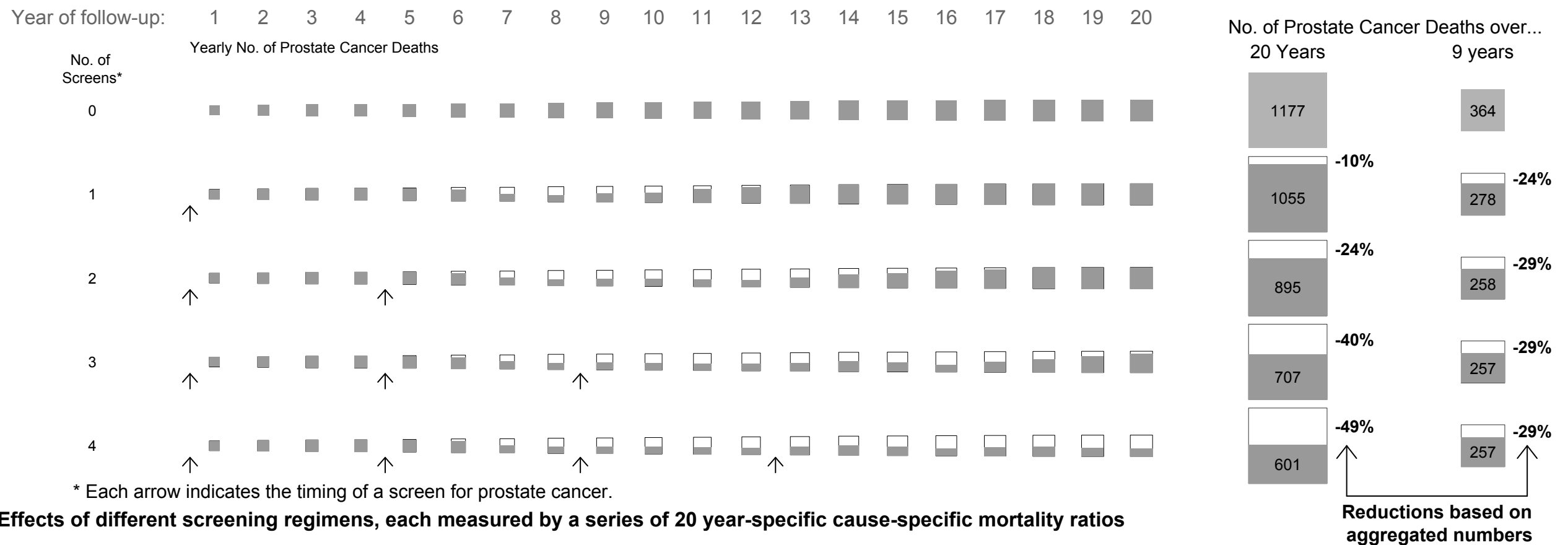


**Web Figure 2. Age-specific numbers of prostate cancer deaths and prostate cancer mortality rate ratios.**

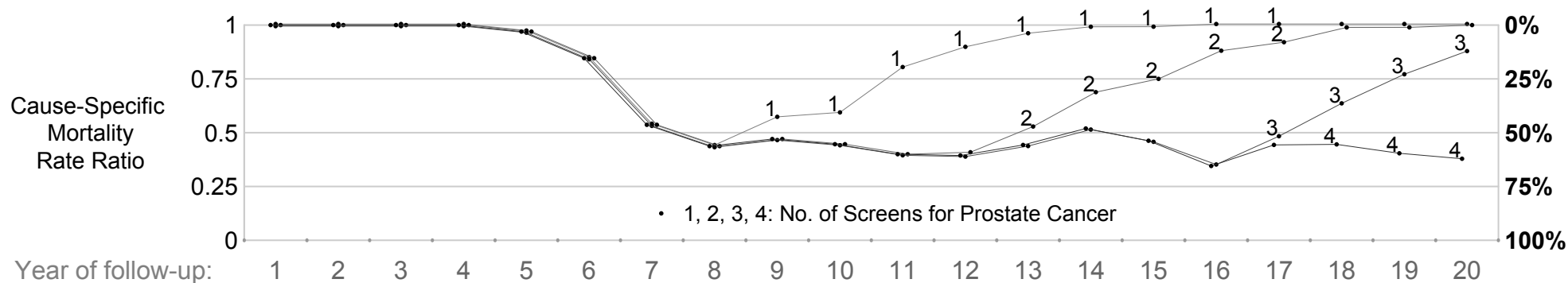
Age-specific numbers from Quebec in the early 1990s are used to represent the (steady-state) annual numbers of prostate cancer deaths in the absence of screening. The numbers of annual deaths that there would have been in these same population had a screening program been available [from when men reach the age of 50 until they turn 70] are hypothetical. Note that these two sets of numbers are age-specific, not cumulative – they decrease if the age range is extended past 85 – and merely reflect the exponential rise in prostate cancer death rates with age.

The rate ratio graph in panel (b) is modeled after Figure 2-5(b) in Morrison and is designed to illustrate (from left to right) its three features: the time-lag until the deaths averted by screening become apparent, the 20 years of full benefit that follow – after this lag -- the 20 years of screening, and the disappearance of the effect (i.e., a reversion to late-age mortality rates in the unscreened scenario) at some point after the last age at which men are screened.

**(a) Effects of different screening regimens, each measured by a single (overall) cause-specific mortality ratio calculated from aggregated (cumulative) number of deaths**



**(b) Effects of different screening regimens, each measured by a series of 20 year-specific cause-specific mortality ratios**



**Web Figure 3. Effect of screening, measured by one overall cause-specific mortality ratio versus by separate year-specific cause-specific mortality ratios.**

**A single-number measure of effect of a screening regimen with sustained effects is misleading if there is inadequate follow-up (cf. the 'over 9 years' vs. 'over 20 years' summary in last row of Panel (a)). Unlike the single-number reductions in panel (a), the series of time-specific mortality rate ratios in panel (b) are not subject to the artifacts caused by an arbitrarily selected duration of follow-up.**

Panel (a): The top row shows hypothetical yearly and overall numbers of expected prostate cancer deaths if 100,000 men, average age 61, were followed for 20 years, or until they died of another cause, under a non-screening scenario (row '0', with the numbers represented by the areas of the squares). Each subsequent row represents a screening scenario, and shows the corresponding numbers under that scenario (rows, '1' to '4', shaded portions of the squares). The expected numbers alive at various follow-up times under the no-screening scenario were calculated from vital statistics data, while the numbers of prostate cancer deaths were calculated from a model for screening [Hanley, 2005]. The numbers of deaths in the 'over 9 years' column are the numbers of prostate cancer deaths that would be observed if these hypothetical data were analyzed an average of 9 years after the start of follow-up (as in the European Randomized Study of Screening for Prostate Cancer [ERSPC]). This panel emphasizes that the timing and extent of the reductions in prostate cancer mortality are (i) modulated by the number and spacing of the screens (ii) diluted and obscured if a single measure based on the deaths over the entire period of follow-up is used and (iii) further diluted if follow-up ends before the full mortality reductions become apparent.

Panel (b): Timing of effects of different screening activities as measured quantitatively by yearly prostate cancer mortality rate ratios (inputs to these are the same hypothetical data as in Panel A). These yearly rate ratios are not systematically affected by the duration of follow-up. They provide a comprehensive and unbiased measure of the timing and extent of the reductions in prostate cancer mortality. They also show the steady-state reduction that would become apparent, after a suitable delay, in a sustained-screening scenario.

**Web Table 1.** Reported trials of prostate cancer screening

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

<sup>1</sup>Norrköping      <sup>2</sup>Stockholm

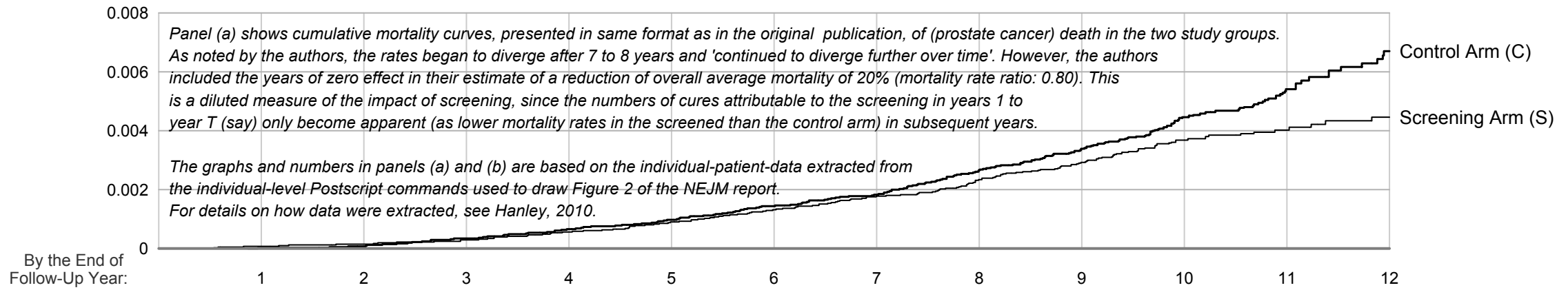
† Party-overlapping Göteborg experience, biennial screens, longer follow-up, published separately [Huggeson2010].

\*Varied somewhat by country. ? Information not reported.

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

(a)

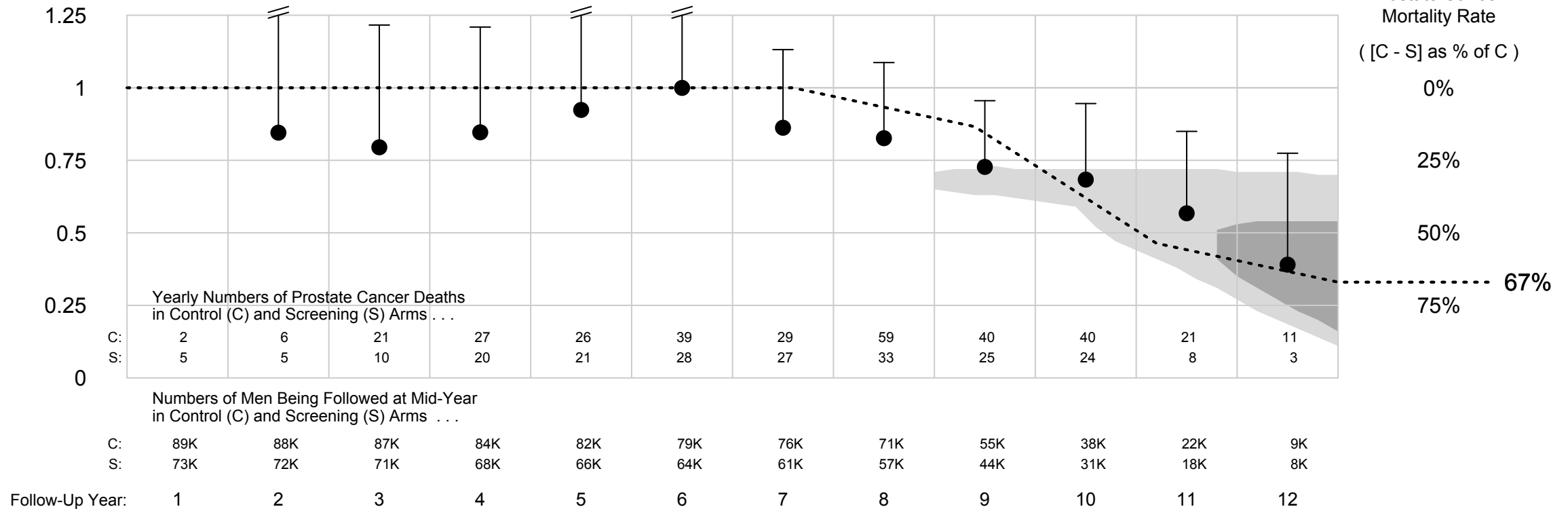
### Cumulative Prostate Cancer Mortality



(b)

### Prostate Cancer Mortality Rate Ratio (S / C)

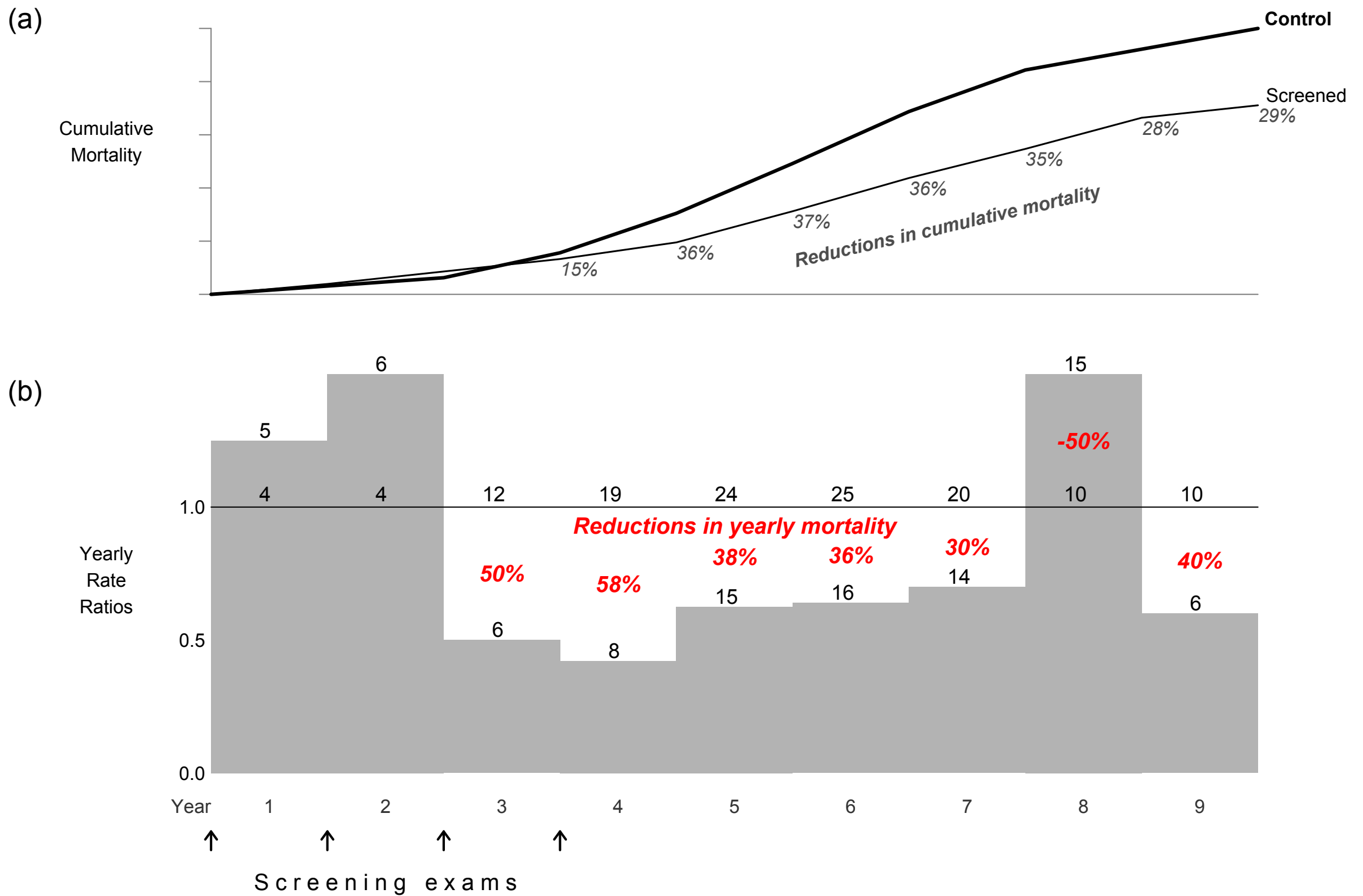
Percentage Reduction in Year-Specific Prostate Cancer Mortality Rate ([C - S] as % of C)



### Web Figure 4. Comparison of prostate cancer mortality rates in 2 arms of European Randomized Study of Screening for Prostate Cancer.

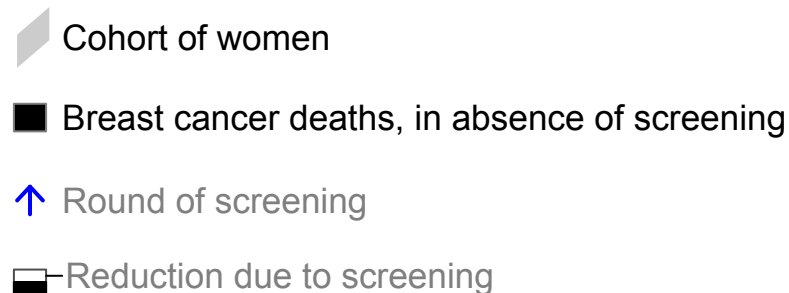
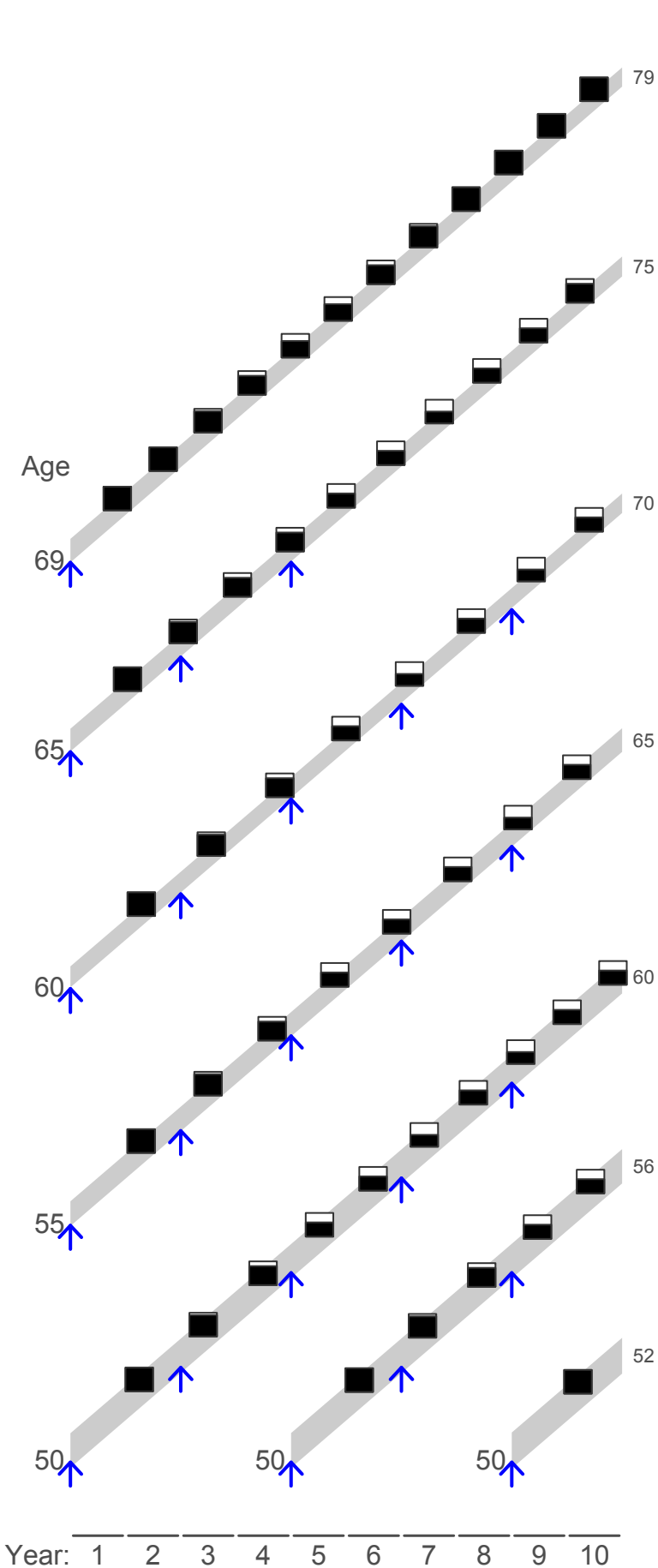
Panel (b) shows the yearly prostate cancer mortality rate ratios, used for re-analysis. These are designed to measure the timing and extent of the prostate cancer mortality reduction in subsequent years as a result of the screening in years 1 to T. Each rate ratio was calculated by dividing the observed rate of prostate cancer deaths in the screening arm by the corresponding rate in the control arm. The rate ratio shown above a given year is based on the data for that year together with the data in the years immediately preceding and following it. The upper ends of the vertical lines denote the upper 95% confidence limits of the percentage reductions in prostate cancer mortality, which are greater than 0% in the 3-year intervals centered on years 9 and beyond. The dotted line, with an asymptote of 67%, beginning at 12 years, was fitted using the method of Maximum Likelihood. The two shaded regions represent the 50% and 80% confidence regions for these two parameters. The 80% CI associated with the 67% asymptote, derived from the vertical range of the lighter grey region at 12 years, is 30% to 89%.

The results of the re-analysis using time-specific rate ratios indicate that the cures attributable to the screening in study year 't' only begin to become statistically apparent by year 't+7 and later. They also indicate that of those in the control arm who died (or will die) of prostate cancer in years 8-12 of the study, possibly as many as half of them would not have died of prostate cancer had they been offered the program. The 25% - 60% reductions seen in years 8-12 of the study suggest a much greater numbers of cures attributable to the screening in year 1 to year T than the single overall 20% figure reported in the original article. Further follow-up data are required to make a precise estimate.



**Web Figure 5. Reductions in breast cancer mortality, as measured by yearly [ panel (b) ] and cumulative [ panel (a) ] breast-cancer mortality ratios. Illustration using breast cancer screening data analyzed in Morrison (1985).**

The yearly numbers of deaths in the control group are shown in black along the horizontal straight line in panel (b) ; the yearly numbers in the screened group are shown in black above the rectangles representing the yearly mortality ratios.

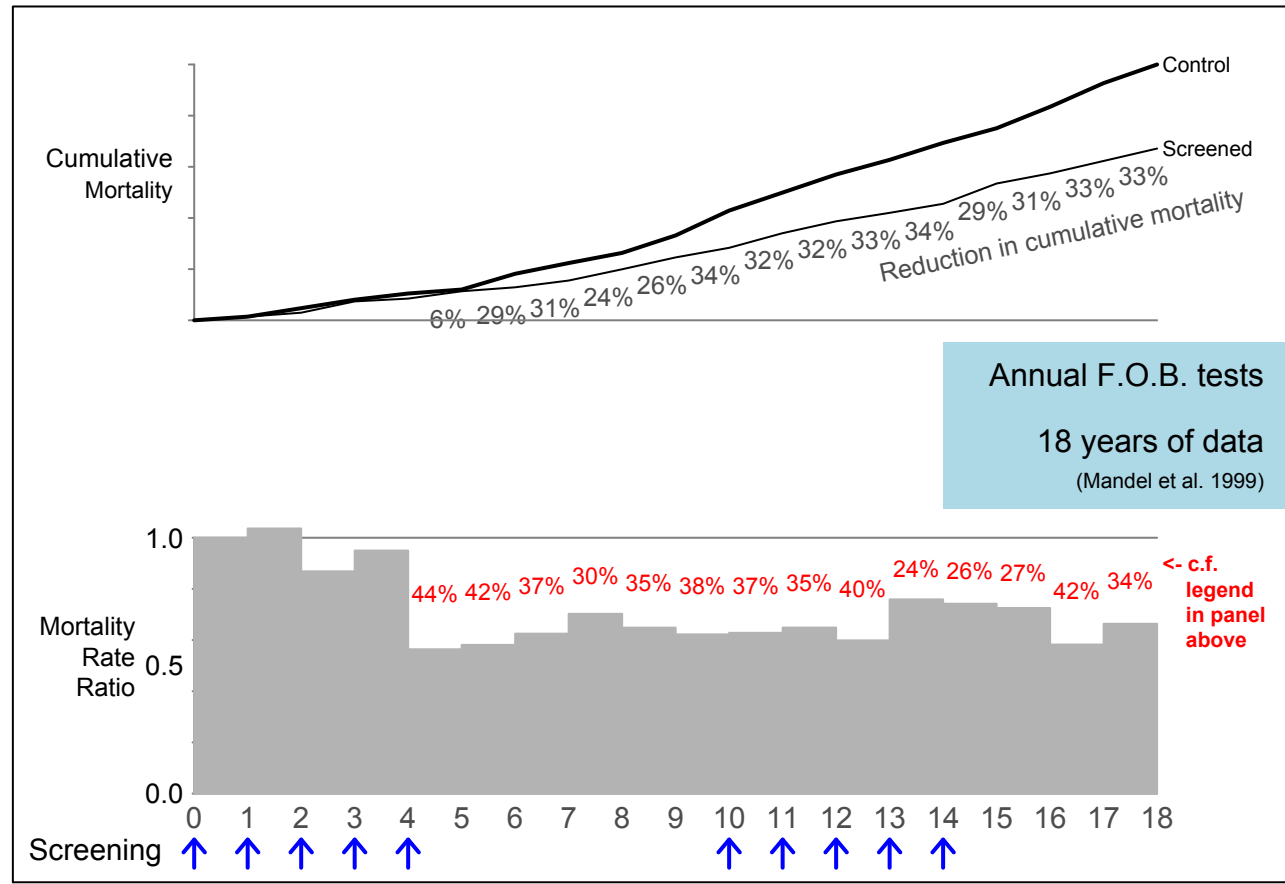
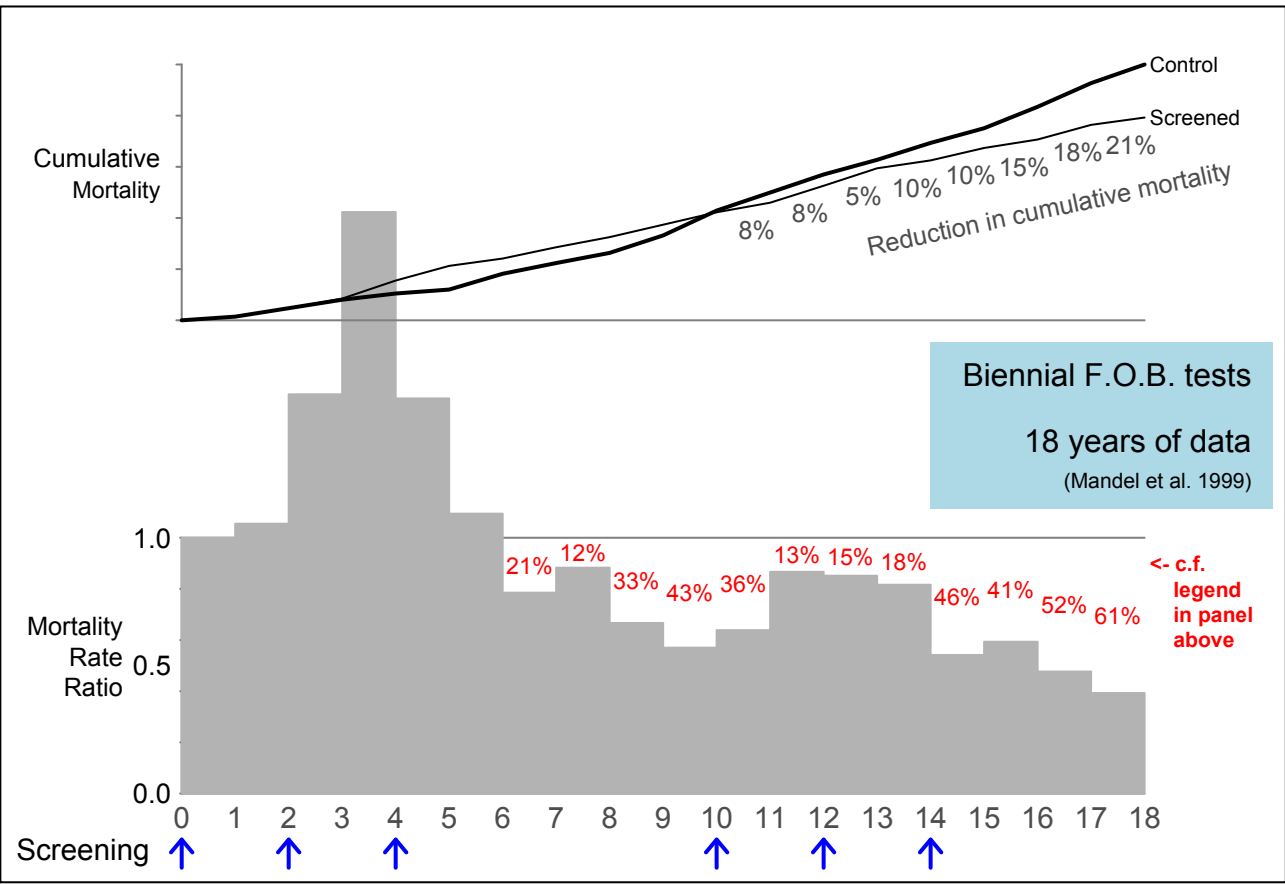
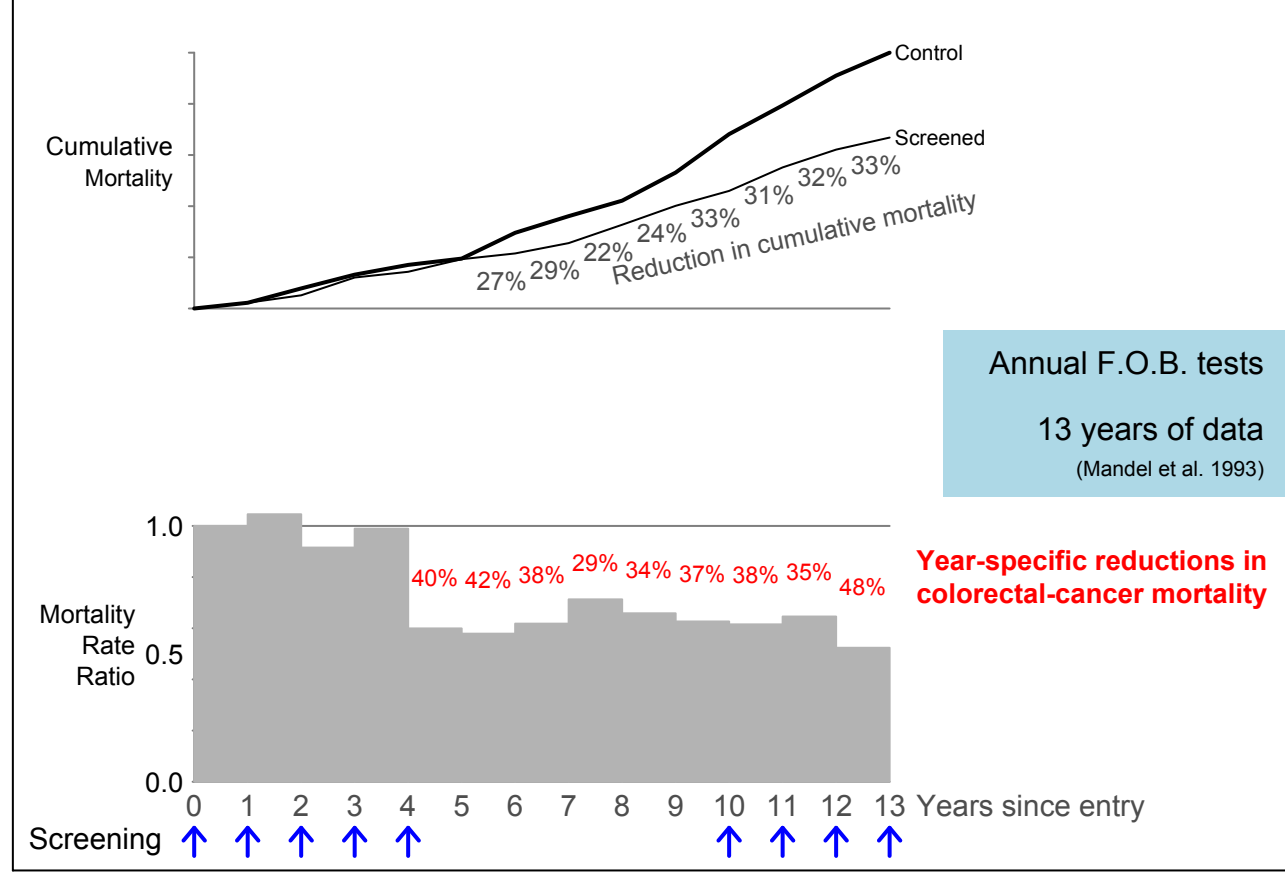
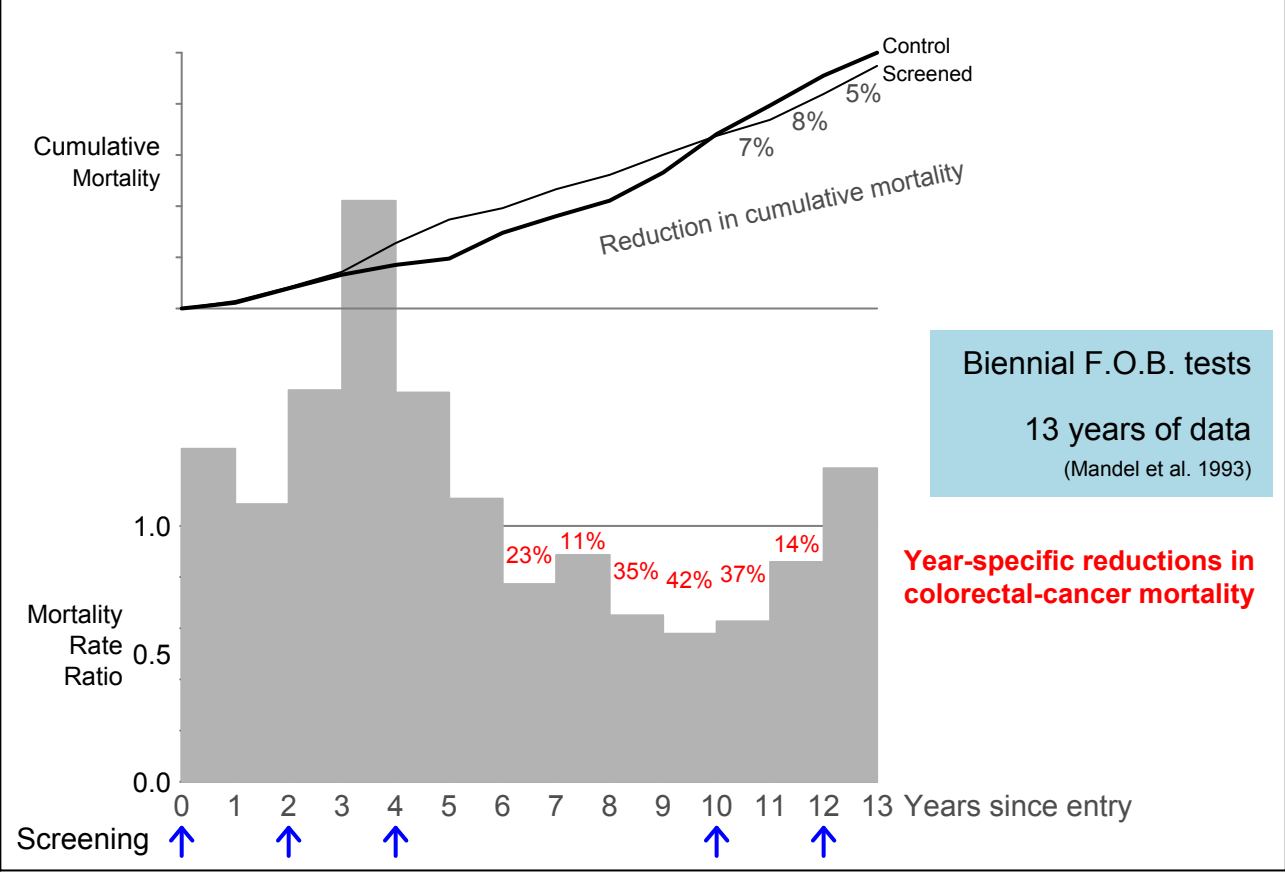


## Web Figure 6.

**[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 greater 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.**



**Web Figure 7. Reductions in colorectal-cancer mortality as measured by cumulative versus year-specific mortality rates**