

# Measuring the mortality reductions in prostate (& other) cancer screening studies

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## Outline

- Recent media coverage of prostate cancer (Pr Ca) screening
- 1995 CETS (Québec) Report
- 2004 ACP Report
- 2005 RCT: Radical prostatectomy vs. watchful waiting in early Pr Ca
- European Randomized Study of Screening for Pr Ca (ERSPC)
- Re-analysis of ERSPC data
- Methodologic issues applicable to all screening studies

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# Prostate Cancer Screening: recent media coverage

NPR, Oct 21, 2009

[A Rethink On Prostate and Breast Cancer Screening](#)

Time, Oct 23, 2009

[Rethinking the benefits of breast and prostate cancer screening](#)

Globe and Mail, Feb 8, 2010

[Prostate cancer dilemma](#)

New York Times Mar 10, 2010

[The Great Prostate Mistake](#)

cyberpresse.ca: 13 mars 2010

[Cancer de la prostate: le test de détection remis en doute](#)

BMJ Mar 17, 2010

[Is the tide turning against the test?](#)

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AN EVALUATION OF BENEFITS, UNWANTED HEALTH EFFECTS AND COSTS. SYNTHESIS. Montreal: CETS, [1995](#).

## CONCLUSIONS

a) From the perspective of Quebec's public health-care system, the health gains which might result from prostate cancer screening are too uncertain and, if there are any, too slight to justify the adverse health effects and the cost that it would entail. This is equally true for an organized comprehensive screening program as it is for such screening as presently takes place in the context of case finding.

b) From the perspective of the individual, every man who considers having his PSA measured should be made fully aware of the potential important consequences of this test and the interventions that ensue therefrom. The personal decision should be made with discernment and in consultation with a physician after carefully weighing the uncertain chances of better survival with a radical prostatectomy against the better known chances of significant adverse health effects associated with this operation.

## American College of Physicians, 2004

- There is no direct evidence that prostate cancer screening decreases mortality.
- There is good evidence that prostate-specific antigen (PSA) screening can detect early-stage cancer but inconclusive evidence that early detection improves health outcomes.
- The large discrepancy between prostate cancer diagnoses and deaths indicates that some, and probably most, tumors detected by screening are clinically unimportant.
- Screening for prostate cancer with PSA is associated with frequent false-positives which leads to unnecessary biopsies and patient anxiety and increases the risk for complications.

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### Radical prostatectomy vs. watchful waiting in early prostate cancer

#### RCT by Scandinavian Prostate Cancer Group Study

**2005:** During a median of 8.2 years of follow-up, 83 men in the surgery group and 106 men in the watchful-waiting group died ( $P=0.04$ ). In 30 of the 347 men assigned to surgery (8.6 percent) and 50 of the 348 men assigned to watchful waiting (14.4 percent), death was due to prostate cancer.

**CONCLUSIONS:** Radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression. The absolute reduction in the risk of death after 10 years is small, but the reductions in the risks of metastasis and local tumor progression are substantial.

**2008:** At 12 years, 12.5% of the surgery group and 17.9% of the watchful waiting group had died of prostate cancer.

## Screening for Prostate Cancer:

### U.S. Preventive Services Task Force Recommendation Statement, 2008

- Current evidence is insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75 years (I statement).
- Do not screen for prostate cancer in men age 75 years or older (Grade D recommendation).

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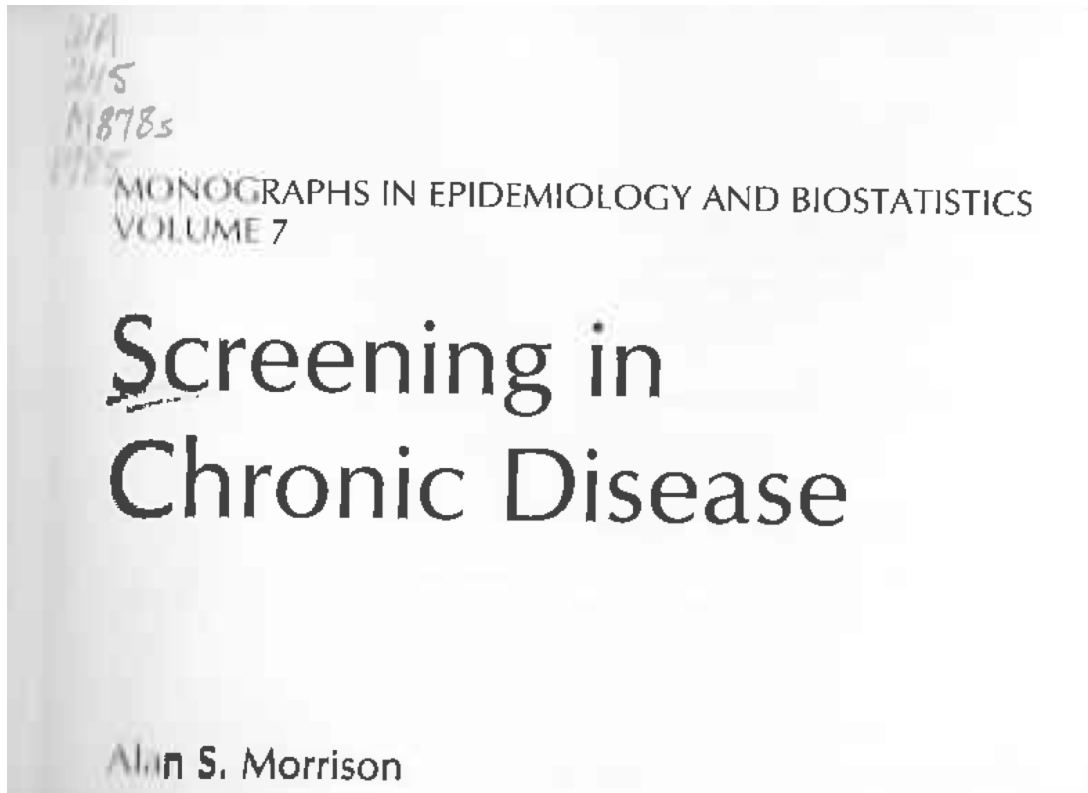
### RCTs of Screening for Prostate Cancer

Trial:	Québec	Sweden <sup>1</sup>	Sweden <sup>2</sup>	USA	Europe
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)	$\frac{24\%}{7\%}$	$\frac{78\%}{7\%}$	$\frac{74\%}{7\%}$	$\frac{85\%}{52\%}$	$\frac{82\%}{7\%}$
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

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Expected 'Response function': Guidance from 1985 textbook



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34 Screening in Chronic Disease

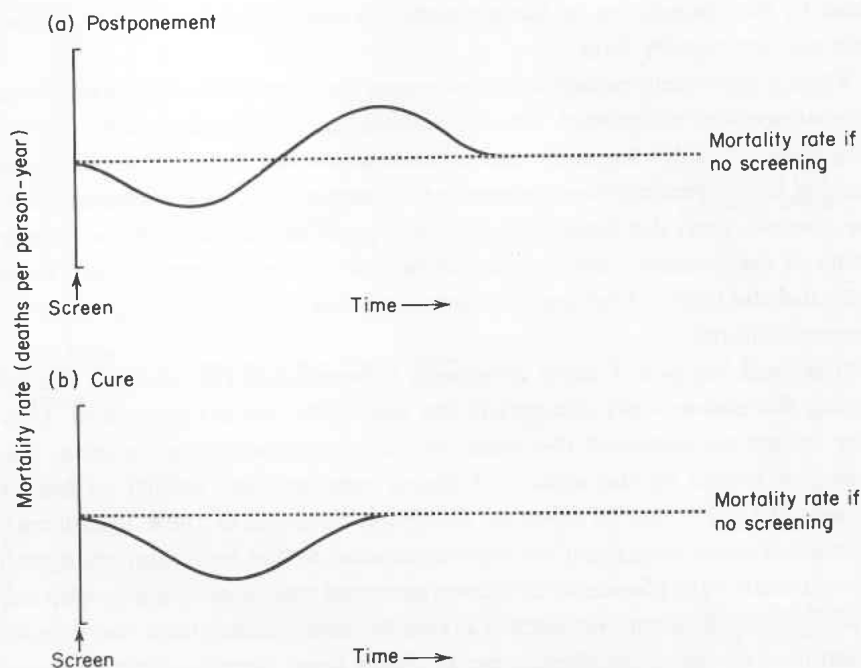
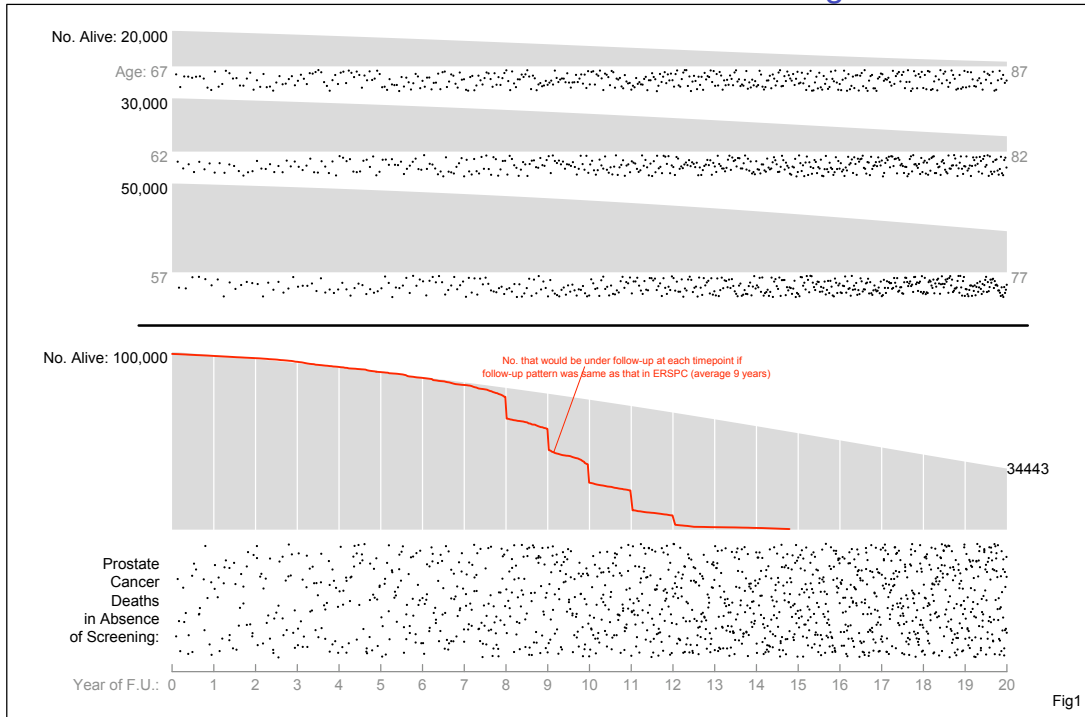


Figure 2-5. Changes in the disease-specific mortality rate brought about by postponement of death and by "cure" of screen-detected cases.



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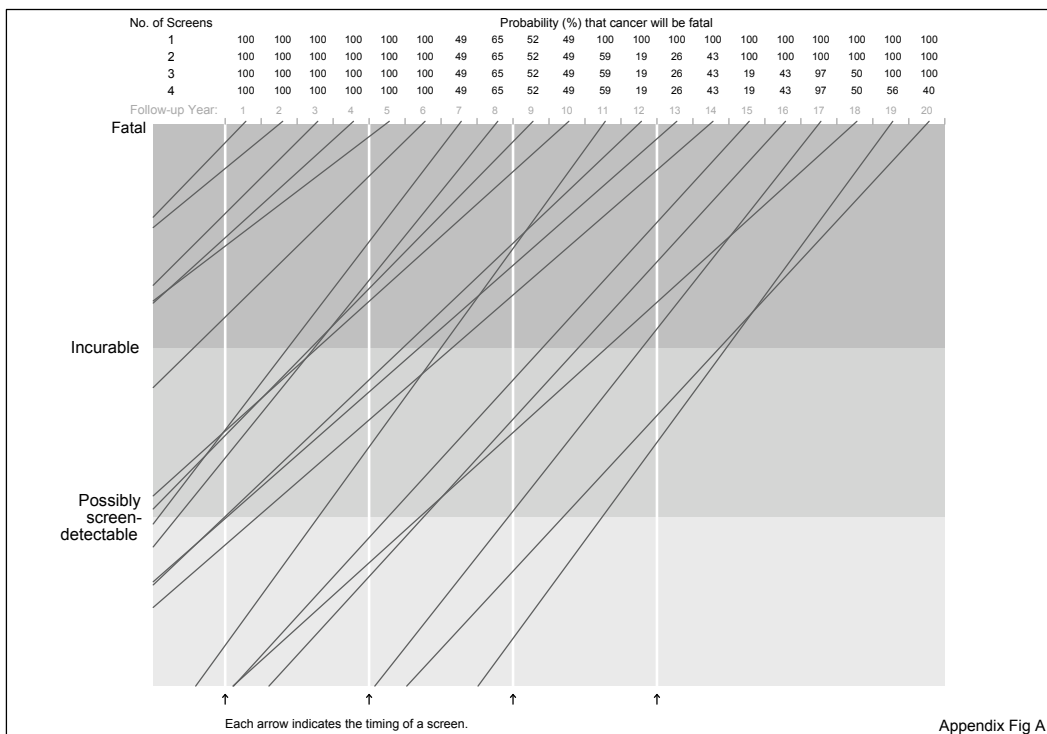
## Numbers of Pr Ca deaths under a 0-screening scenario



Based on actual population experience in province of Québec in early 1990's, with ave. age-at-entry same as, and rates scaled to match actual prostate cancer mortality to date, in control arm of ERSPC.

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## Probability[cancer proves fatal] under 1-screen, ... 4-screens scenarios



Impact of screening, repeated every 4 years, on individual "otherwise fatal" cancers, i.e., cancers that would subsequently prove fatal if they were detected 'clinically' – even if treated at that time. Vertical axis: cancer "stage"

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

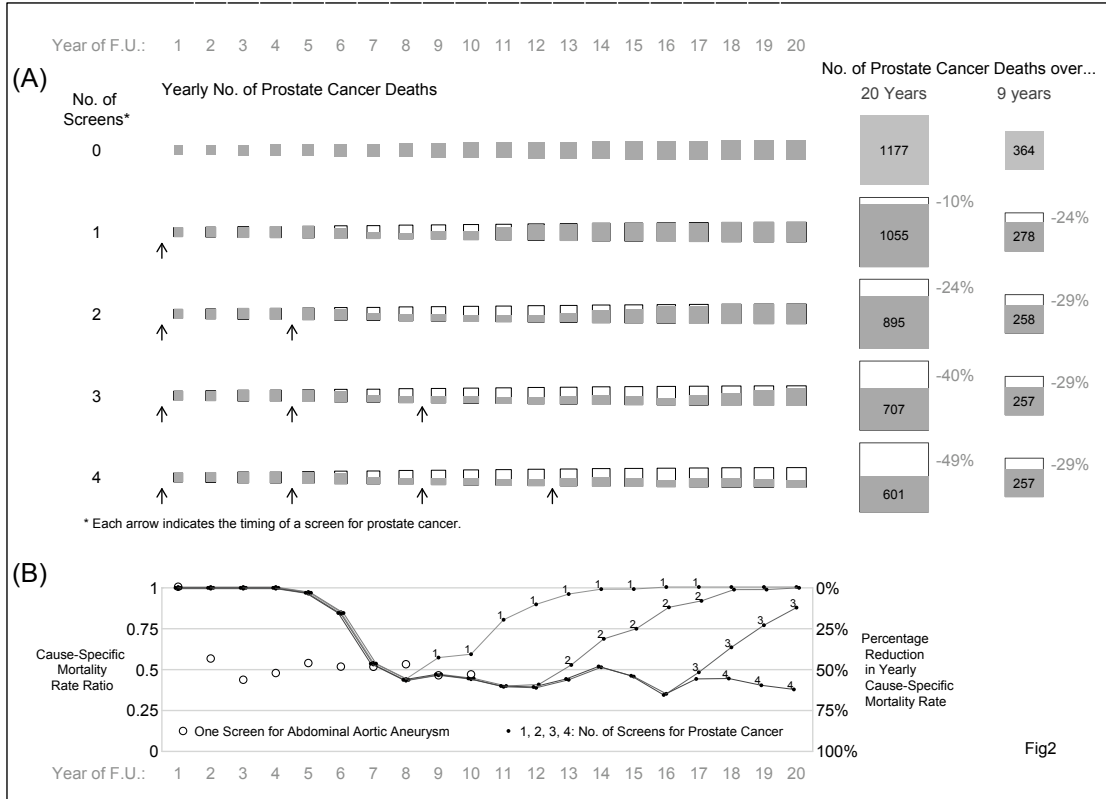
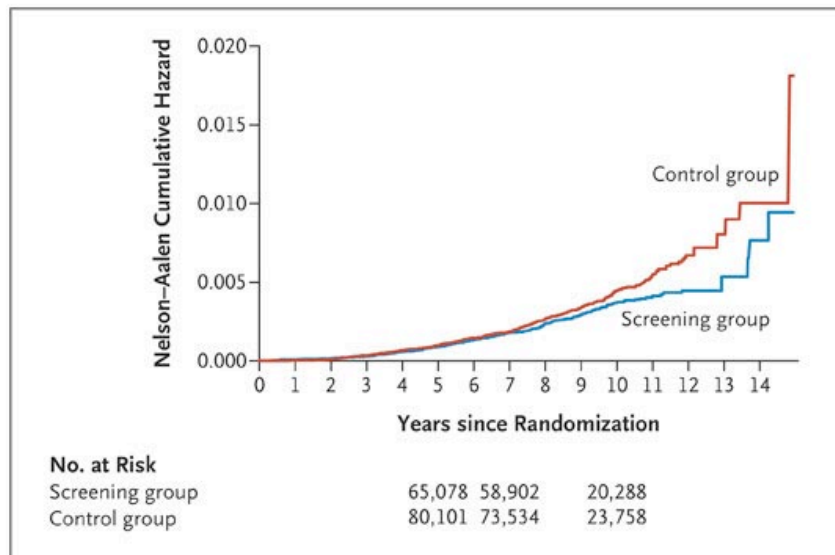


Fig2

## Actual ERSPC experience



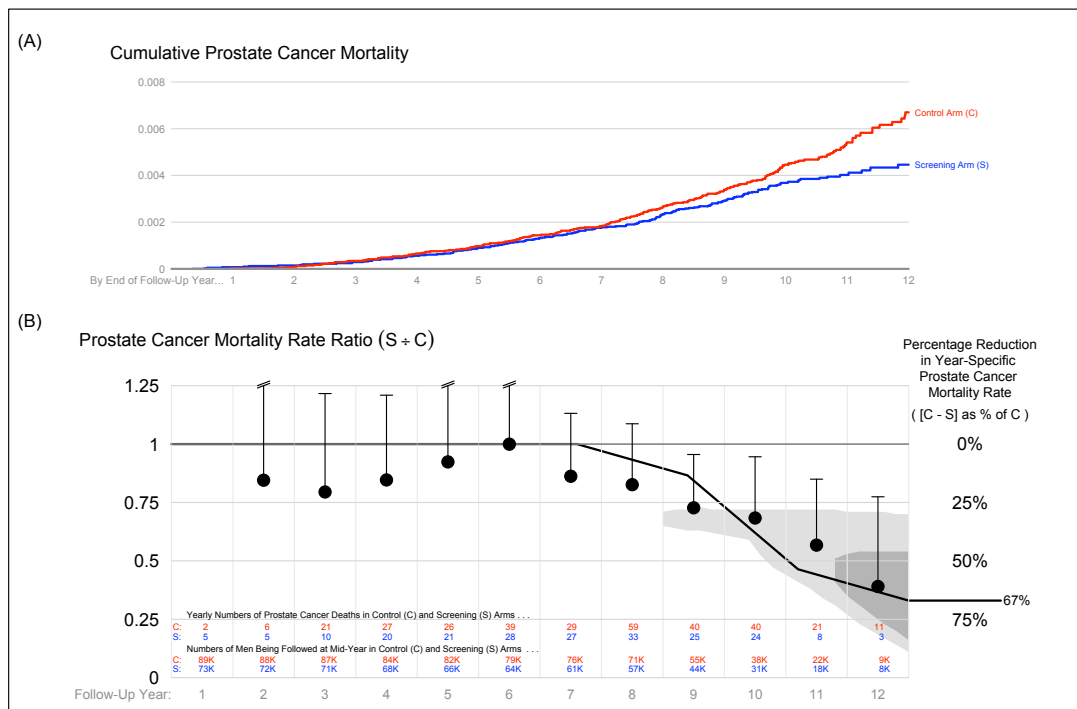
**Fig 2: Cumulative Risk of Death from Prostate Cancer.** As of December 31, 2006, with an average follow-up time of 8.8 years, there were 214 prostate-cancer deaths in the screening group and 326 in the control group. Deaths that were associated with interventions were categorized as being due to prostate 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 Nelsen-Aalen method was used for the calculation of cumulative hazard.

# RE-ANALYSIS, with emphasis on time-specificity

- **Year-by-year mortality rate ratios**
  - pdf file containing Fig 2 → encapsulated postscript (eps) file format;
  - eps file → 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 → 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 → number of prostate cancer deaths at each time point
  - Numbers aggregated by year (each of 1st 12 ) and study arm → counts listed in new Figure.
- **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).

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## Year-specific prostate cancer mortality ratios



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## Interpretation

- After an expected delay (data indicate  $\approx 7$  years), the prostate mortality reductions that become evident in years 9 and beyond are statistically significant and considerably greater than the reported 20% reduction in the rate of prostate cancer deaths.
- The best (ML) estimate is that, although the rate ratio became non-null starting at  $\approx 7$  years, the steady state reduction has not yet been reached: the point estimate so far is a sustained 67% reduction (80%CI 30% to 89%) beginning at year 12.
- Numbers of deaths are not sufficient to establish its timing and magnitude more precisely. (Data cutoff: Dec 2006)

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## Implications - substantive

- '**Downsides**' of PSA-based prostate cancer screening: well documented and long since agreed upon.
- Even if screening could achieve a sustained reduction of 67%, (or even 77 or 87%!) the very low prostate mortality rates in the control group means that the **small absolute reductions** will be achieved at an unacceptable cost. (So far, only 326 or 0.36% of the 89,353 men in control group have died of prostate cancer; number will approximately triple by follow-up year 20.)
- 'Upsides': 5 RCTs; 23 years; 321,000 men; 10 countries average f.-u. ranging from 7-15 years.
  - 4 have virtually no resolving power.
  - **ERSPC**: much larger  $\Delta$  in screening activity b/w 2 arms  $\rightarrow$  considerably greater **resolving power**.
  - Must measure signal in f.-u. window where probably strongest  $\rightarrow$  collect **additional data**.
- Casual reader of ERSPC report **should not conclude** that best we can expect from PSA screening is a reduction in prostate cancer mortality of **20%**.
- Re-analysis: if screening is carried out for several years, and if **f.-u. pursued into window where reduction in mortality becomes manifest**, reduction to be seen there will be **50-60%**.
- ERSPC report published March 2009, but **f.-u. ended in Dec 2006**, just when pattern had begun to emerge. **Not possible to put precise statistical bounds** on this reduction.
- Prostate cancer deaths from **2007 onwards crucial to more precisely measure** the reduction achieved.

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# Implications - Methodologic

## Time-specificity...

- **Avoids dilution** caused by averaging
  - 7 years of (expected) non-reductions with
  - 5 years of progressively larger reductions
- With current data, **imprecise estimates**: fixable.
- Follows **intention to treat** principle
- With **objective** curve-fitting...
  - **avoid need to “pre-specify” when** reduction reaches steady state
  - **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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## Only an ineffective cancer screening program can yield proportional hazards

- **Time-specific** analysis only necessary when effect of intervention is **delayed**, as in case of Pr Ca screening.
- Screening for abdominal aneurysms produces an **immediate and sustained reduction** in mortality from ruptured aneurysms; **cumulative** mortality, in this case, **fully captures benefit** of screening.
- Results of a program of screening competitive athletes for potentially lethal cardiovascular abnormalities: further striking example of shape of the ‘response function’ with time, and the **role of screening intensity** in this.
- Recognition of **difference between interventions with immediate and delayed effects** should prompt similar re-analyses of data from trials of screening in other cancers, and similar analyses in yet-to-be reported cancer screening trials.

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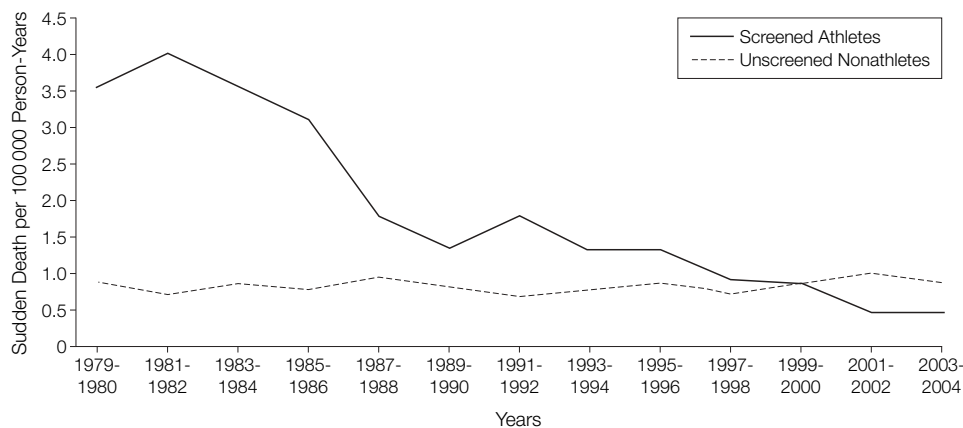
## IMPLICATIONS: data-analysis, meta-analyses, public health

- ‘Response Curve’ in any one RCT is a function of the number and timing of screens [& compliance]
- Time-specificity in data-analysis is paramount
- No common parameter (response curve) to meta-analyze: trials not uniform w.r.t. number and timing of screens
- REAL Q: reduction with SUSTAINED SCREENING ?
- How about using nadir of response curve ?

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## Role of time and screening intensity

**Figure.** Annual Incidence Rates of Sudden Cardiovascular Death in Screened Competitive Athletes and Unscreened Nonathletes Aged 12 to 35 Years in the Veneto Region of Italy (1979-2004)

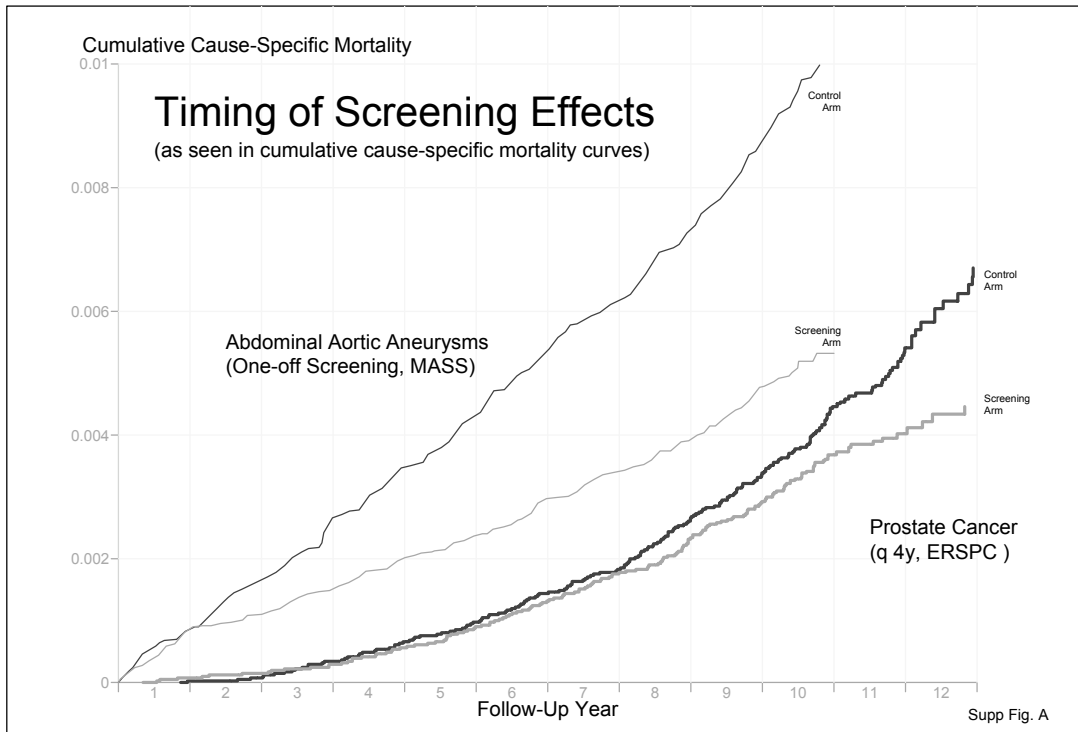


During the study period, the annual incidence of sudden cardiovascular death decreased by 89% in screened athletes ( $P$  for trend  $<.001$ ). In contrast, the incidence rate of sudden cardiovascular death did not demonstrate consistent changes over time in unscreened nonathletes.

**Trends in Sudden Cardiovascular Death in Young Competitive Athletes After Implementation of a Preparticipation Screening Program.** D Corrado, ... , G Thiene. JAMA. 2006;296:1593-1601.

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# The loneliness of the long-distance trialist

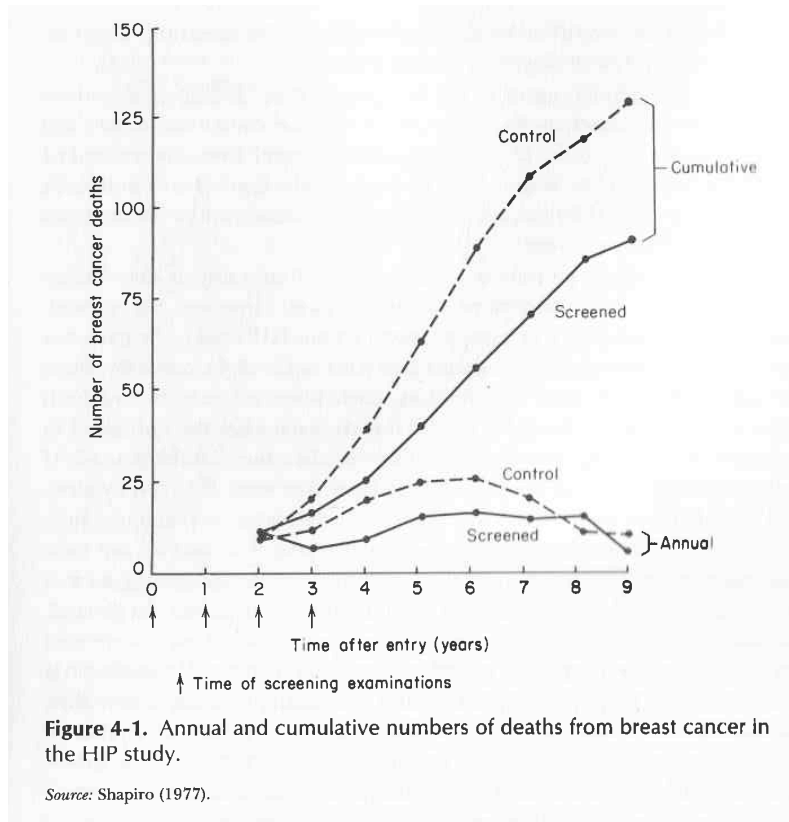


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## Acknowledgments

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## RCT of mammography, begun 1963, data to 1975



Morrison's graph of

original (cumulative) data

year-specific data

## 👁️ Mammographic screening: no reliable supporting evidence?

Olli S Miettinen, Claudia I Henschke, Mark W Pasmantier,  
James P Smith, Daniel M Libby, David F Yankelevitz

**Much confusion is being generated by the conclusion of a recent review that “there is no reliable evidence that screening for breast cancer reduces mortality.” In that review, however, there was no appreciation of the appropriate mortality-related measure of screening’s usefulness; and correspondingly, there was no estimation of the magnitude of this measure. We take this measure to be the proportional reduction in case-fatality rate, and studied its magnitude on the basis of the only valid and otherwise suitable trial. We found reliable evidence of fatality reduction, apparently substantial in magnitude.** }

*Lancet* 2002; **359**: 404–06

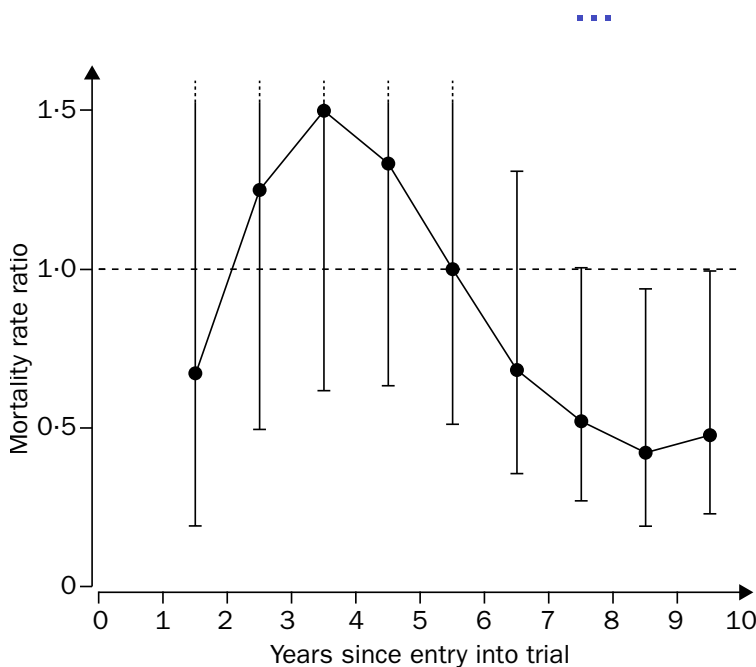
Miettinen's re-analysis of data in Table X of Malmö report

Year	Screened cohort		Control cohort		Rate ratio (95% CI)
	Actual number	Moving average	Actual number	Moving average	
1	0		0		
2	4	1.3	5	2.0	0.7
3	0	3.3	1	2.7	1.2
4	6	4.0	2	2.7	1.5
5	6	5.3	5	4.0	1.3
6	4	5.7	5	5.7	1.0
7	7	5.0	7	7.3	0.7 (0.36–1.31)
8	4	4.3	10	8.3	0.5 (0.27–1.00)*
9	2	2.7	8	6.3	0.4 (0.19–0.94)*
10	2	3.3	1	7.0	0.5 (0.23–0.99)*
11	6†		12†		

\*Based on years 8–11, rate ratio point estimate is  $14/31=0.45$  (95% CI 0.24–0.84). †Some of these deaths (from 1987) probably belong to year 10 or even to year 9.

Table 1: **Number of breast-cancer deaths by year after entry into Malmö study for women 55–69 years of age at entry**

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“Screening in older women seems to have provided for a 100% - 45% = **55% reduction** in case-fatality rate and thereby, after the requisite delay, in cause-specific mortality.”

**Breast-cancer mortality ratio for women at least 55 years of age in the Malmö study**

Shown are point estimates and 95% CI, based on the deaths in the year at issue together with those in the preceding and following years.

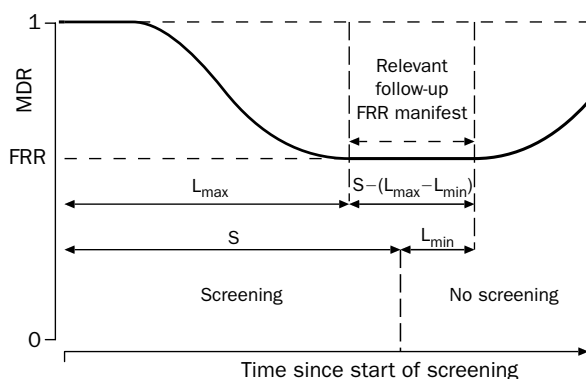
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“Screening in the Canadian study continued for only 3-4 years after study entry, and follow-up stopped at the point at which follow-up in the Malmö study started to show fewer breast-cancer deaths among those screened.

In Malmö, the screening continued throughout the 10-11 years of follow-up. When the duration of screening in a trial that compares screening with no screening (rather than early intervention with late intervention) is too short, nowhere during follow-up does the mortality ratio decline all the way to the case-fatality ratio (which characterises early intervention relative to late intervention).

For the fatality ratio to become fully apparent, in the appropriate interval of follow-up, the duration of screening must exceed the difference between the maximum and the minimum of the time lag from screening-associated early diagnosis to the death in the prevention of which early intervention is essential.”

## Miettinen... schematic



### Follow-up experience in a randomised controlled trial comparing screening for cancer with no screening in respect to cause-specific mortality: interrelations of parameters

At any given point in the follow-up there is a particular mortality density, MD, among the screened and the not screened; for an interval of  $t$  to  $t+dt$ , with  $dC$  cases expected in it,  $MD=dC/Pdt$ , where  $P$  is the size of the population. Contrasting the screened with the not screened, there is the corresponding mortality-density ratio, MDR. This ratio is depicted as a function of time since entry into the trial. The early excess mortality among the screened is not shown, since focus is on the intended result of reduced fatality rate, FR, quantified in terms of fatality-rate ratio, FRR. MDR coincides with FRR in a particular interval of follow-up time if the duration of screening,  $S$ , exceeds the difference between the maximum,  $L_{max}$ , and minimum,  $L_{min}$ , of the time lag from early diagnosis to the death prevented by early intervention but not by late intervention (ie, in the absence of screening).

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**<http://www.biostat.mcgill.ca/hanley>**



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