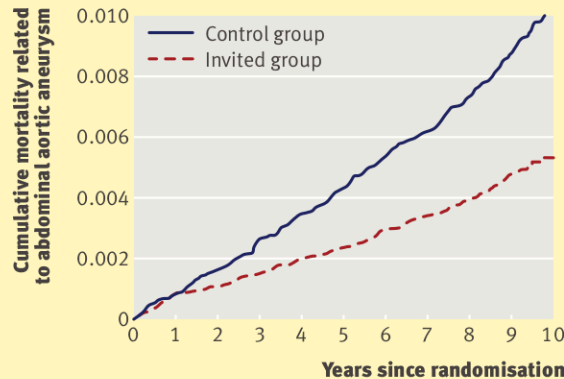


Rate Reductions: time-pattern

NOT SAME as if using ... to ↓ (risk of) ...

- ADULT CIRCUMCISION: (HIV).
- VACCINATION: (MEASLES, POLIO, ..),
- Ultrasound SCREENING: (AAA rupture)

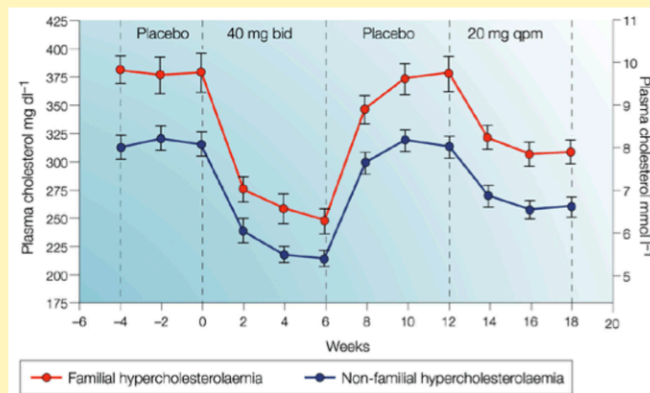


Men at risk

Control group	33 887	32 103	29 992	27 664	25 000	13 242
Invited group	33 883	32076	30 101	27 860	25 388	13 385

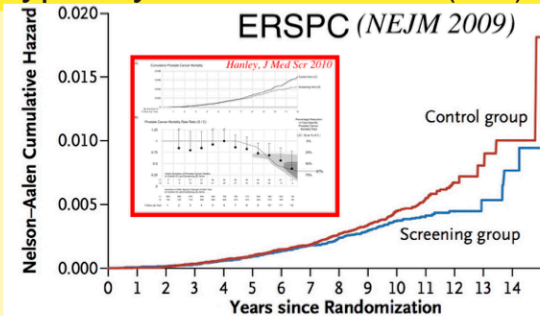
↓ virtually immediate, and sustained

- BLOOD THINNERS: (STROKE/MI)
- STATINS: LDL CHOLESTEROL

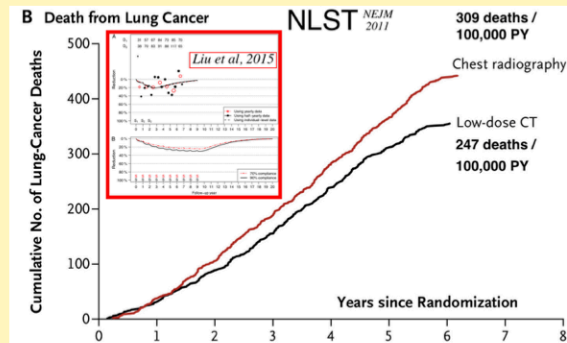


↓ disappears when agent removed

Typically: 1 Hazard Ratio(HR)



“Average f.-up: 8.8y. Rate ratio for death from prostate cancer in screening group: 0.80.”



With **sustained** screening, the steady-state mortality reduction would be more than the 20% observed after just the 3 trial rounds.

Some time **after screening ceases, mortality rates revert** to those in unscreened, e.g., as in the 30 y. FOBT trial [next column]. Baker calls this dilution “post screening noise.” Nor should there be mortality deficits in the 21st year if lung cancer screening lasted just 6 years.

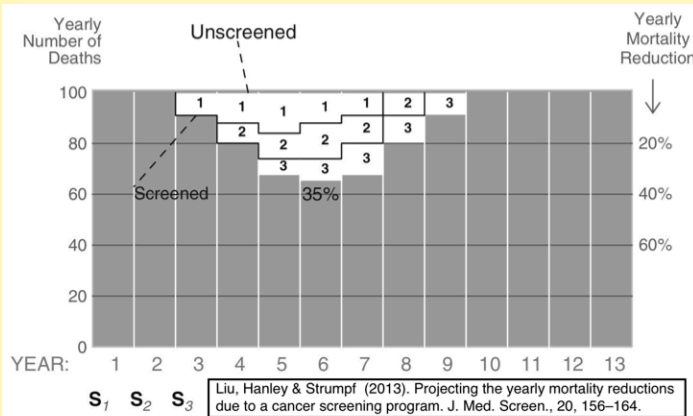
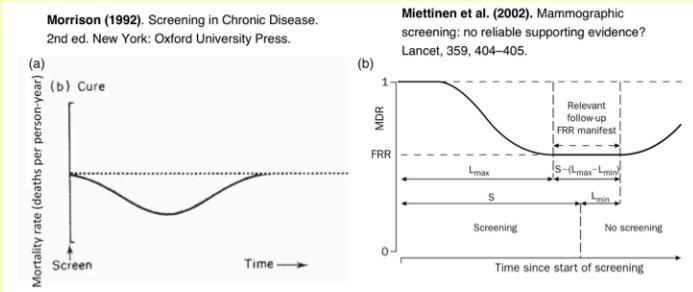
Bottom Line (1)

The unprincipled 1-number hazard-ratio (HR) measure ignores **1. how many screens, 2. when the last screen was, 3. when follow-up ended or 4. when mortality deficits are expected to manifest.**

First Principles

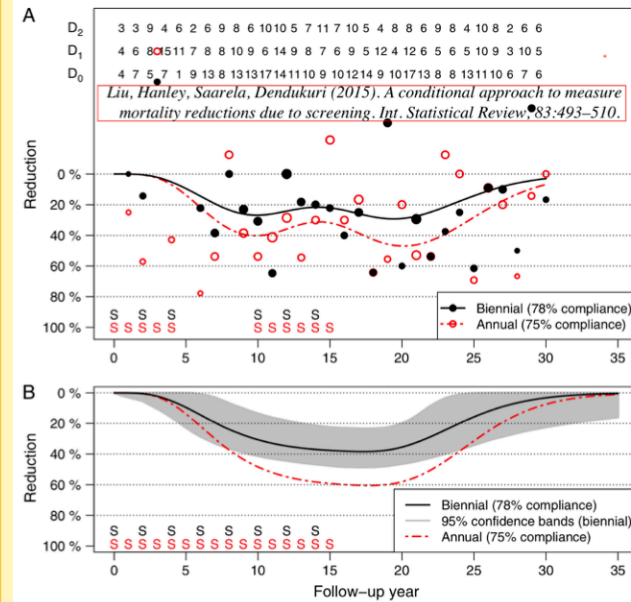
Screening: pursuit of **earlier Dx (& earlier Tx)**.
 Because of the **Detectability : Curability trade-off**, the course of many cancers, 'otherwise' fatal at $T = t$, is not altered by screen at $T = 0$. They are too early/late to be detected/cured.
Mortality deficits manifest after some delay, and disappear at some point after last screen.

Principles → HR function

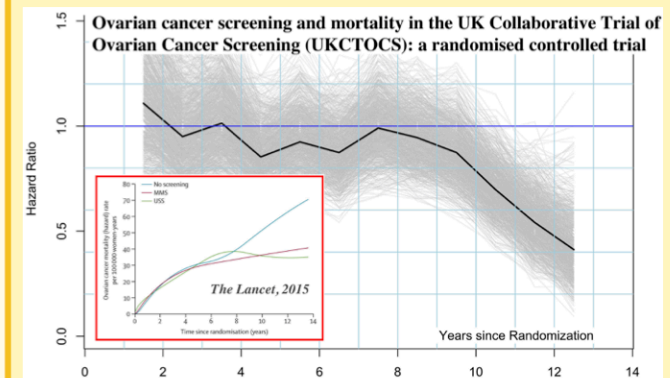


The **depth & duration** of the mortality deficits produced by 3 screenings. In women screened from 50-69, deficits would reach their max. at \approx age 56 & maintain this level for many age-bins.

FOBT Screening. HR function



Ovarian Cancer. HR function

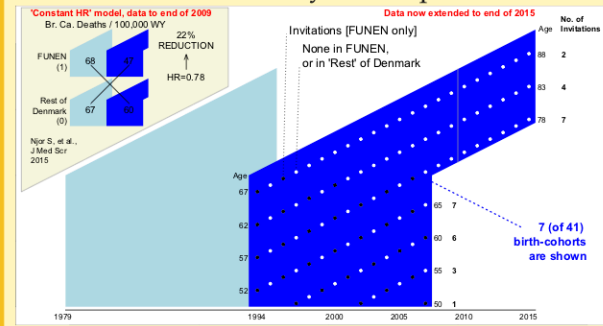


Bottom Line (2)

IT'S ABOUT TIME: to not just recognize the importance of the HR function & its determinants, but to use them in data analysis

Pop'lⁿ Mammography Programs

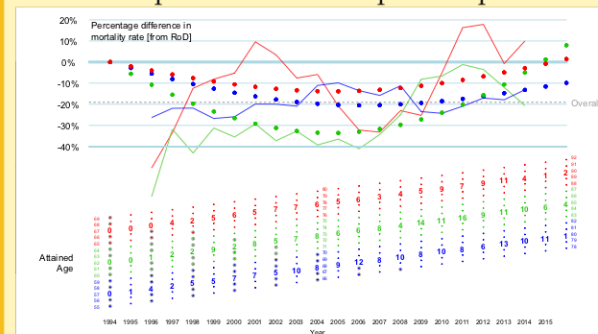
- Norway (NEJM): Some counties only in 2nd or 6th year, too short for full impact to manifest. (cf. Hanley, Epi Reviews , 2011)
- Funen, Denmark: 22 years' experience.



Funen-'RoD' differences in Rates

Average, and followup-year-specific, differences in breast cancer mortality, in 3 birth cohorts, each 5 years wide (color-coded). In modified Lexis diagram in bottom panel, grey circles indicate invitations to those Funen women who attained the indicated ages in the years indicated. Numbers are numbers of deaths from breast cancer in the 3 age-bands. Percentage differences in upper panel:

- . Dotted line: age-year-matched M-H 'average'.
- . 3 lines: age-matched M-H year-specific.
- . 3 smooth patterns: cohort-specific spline fits.



Effects of 1,2,3, ... , 7 screens

Data for, and fitting of, HR model

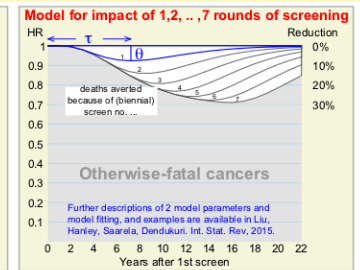
Year[y]	Age[a]	No. Deaths	D ₀	D ₁	PY ₀	PY ₁	Person Years (Design' Matrix)	Invitation History (Design' Matrix)	PY ₁	How many years earlier
2014	87	11	1	16,827	2,101	20	18			
2013	81	24	3	17,034	2,227	19	17	15	13	
2012	75	18	1	19,788	2,491	17	15	13	11	9 7 5
etc.	etc.

$D_1 + D_0 = D$ fixed $\rightarrow D_1 \sim \text{Binomial}(D, \pi)$

with

$\pi = \text{HR}_{ay} \times \text{PY}_1 / (\text{HR}_{ay} \times \text{PY}_1 + 1 \times \text{PY}_0)$

$\text{HR}_{ay} = \prod_{\text{Age} \leq \text{AgeAIS}} \text{Prob. not helped by screen at age AIS}$



Fitted Percentage Reductions

Fitted reductions (%) based on parameters ($\hat{\tau}$, $\hat{\theta}$) of model for effect of 1 round of screening, and on the variations in numbers of invitations.

Fitted Percent Differences ('Reductions')

The relatively small number of events in the screened population makes it difficult to show that the 2-parameter model fits significantly better than the prevailing (but un-principled) constant-hazard-ratio (proportional-hazards) model.

Age	1995	1997	1999	2001	2003	2005	2007	2009	2011	2013	2015
68.69	0	2	4	6	7	8	7	7	6	5	4
66.67	0	2	4	8	11	15	18	21	23	25	26
64.65	0	2	4	8	11	15	18	21	23	25	26
62.63	0	2	4	8	11	15	18	21	23	25	26
60.61	0	2	4	8	11	15	18	21	23	25	26
58.59	0	2	4	8	11	15	18	21	23	25	26
56.57	0	2	4	8	11	15	18	21	23	25	26
54.55	0	2	4	8	11	15	18	21	23	25	26
52.53	0	2	4	8	11	15	18	21	23	25	26
50.51	0	2	4	8	11	15	18	21	23	25	26

The fitted model assumes the same 2 parameter values for both the initial ('prevalence') and follow-up screens, and for all ages at the first screen.

With sufficient data, it could readily be extended to allow these to vary.

THE BOTTOM LINE

- This first principles model can use RCT or population data to pursue more realistic measures of mortality reductions, and better inputs for cost effectiveness calculations.
- To more precisely measure reductions due to mammography, we wish to collaborate with those already holding suitable population data.