Underestimation of Mortality Reductions in Cancer Screening Studies:
Prostate, Breast, Colon and [???] Lung

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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...

(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.

Deaths in absence of screening

Deaths despite screening

Deaths averted by screening

Population

No. prostate cancer deaths per 1-year age-band

Population per 1-year age-band

Age

WebFigure 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.
They could arrive at these numbers if they had...

(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

WebFigure 2. Age-specific numbers of prostate cancer deaths and prostate cancer mortality rate ratios.

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Can they obtain them from published reports?

- 1995 CETS (Québec) Report*: uncertain benefit / certain harms
- 2005 RCT: Radical prostatectomy  > but  < watchful waiting in early Pr Ca
- 2009: European Randomized Study of Screening for Pr Ca (ERSPC)

### In all, 5 RCTs of Screening for Prostate Cancer

<table>
<thead>
<tr>
<th>Trial:</th>
<th>Québec</th>
<th>Sweden(^1)</th>
<th>Sweden(^2)</th>
<th>USA</th>
<th>Europe(^\dagger)</th>
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<tr>
<td>Author:</td>
<td>Labrie</td>
<td>Sandbloma</td>
<td>Kjellman</td>
<td>Andriole</td>
<td>Schröder</td>
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<tr>
<td>No. men</td>
<td>31,000</td>
<td>1,500</td>
<td>2,400</td>
<td>38,000</td>
<td>73,000</td>
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<td>7,500</td>
<td>24,000</td>
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<td>89,000</td>
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<tr>
<td>Frequency of testing</td>
<td>?1y</td>
<td>3y</td>
<td>once</td>
<td>1y × 6</td>
<td>4y*</td>
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<tr>
<td>Duration of follow-up (y)</td>
<td>11</td>
<td>15</td>
<td>15</td>
<td>10</td>
<td>9</td>
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<tr>
<td>Screened ≥ once</td>
<td>24% / 7%</td>
<td>78% / ?</td>
<td>74% / ?</td>
<td>85% / 52%</td>
<td>82% / ??</td>
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<tr>
<td>No. Pr Ca deaths</td>
<td>153 / 75</td>
<td>20 / 97</td>
<td>53 / 506</td>
<td>92 / 82</td>
<td>214 / 326</td>
</tr>
</tbody>
</table>

\(^1\) Norrköping \(^2\) Stockholm

\(^\dagger\) 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]
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*

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

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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.
“During a median follow-up of 9 years, the prostate cancer mortality rate ratio in the screening group, as compared with the control group, was **0.80** (95% confidence interval [CI], 0.65 to 0.98; adjusted P=0.04). The absolute risk difference was 0.71 death per 1000 men.”

Number Needed... to **Screen**: 1410; to **Treat**: 48

“The analysis of men who were actually screened during the first round (excluding subjects with noncompliance) provided a rate ratio of **0.73** (95% CI, 0.56 to 0.90).”

**CONCLUSIONS**

“PSA-based screening reduced the rate of death from prostate cancer by 20%.”
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.
Expected ‘Response function’: Guidance from 1985 textbook

Screening in Chronic Disease

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

in 100,000 men
(average age at entry: 62 years)

if screened using PSA test

0, 1, 2, 3, or 4 times,

tests 4 years apart

and followed for (9) 20 years

HYPOTHETICAL DATA
Cumulative & Year-specific results, if screen 0 times  

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

No. of Screens*  
0  

Yearly No. of Prostate Cancer Deaths  

Year of F.U.: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20  

No. of Prostate Cancer Deaths over...  
20 Years  1177  
9 years  364  

* Each arrow indicates the timing of a screen for prostate cancer.
Cumulative & Year-specific results, if screen 0,1,...,4 times, q 4y

No. of Screens*

0 1 2 3 4

Year of F.U.: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20

Yearly No. of Prostate Cancer Deaths

No. of Prostate Cancer Deaths over...

20 Years 9 years

1177 364

1055 -10% 278 -24%

895 -24% 258 -29%

707 -40% 257 -29%

601 -49% 257 -29%

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

[HYPOThETICAL]
**B) Year-specific Rate Ratios & Percent Reductions**

![Diagram showing year-specific rate ratios and percent reductions.]

- **Year of F.U.:** 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20

- **(A) No. of Screens**
  - 0
  - 1
  - 2
  - 3
  - 4

- **Yearly No. of Prostate Cancer Deaths**

- **No. of Prostate Cancer Deaths over 20 Years**
  - 1177
  - 1055
  - 895
  - 601

- **No. of Prostate Cancer Deaths over 9 Years**
  - 364
  - 278
  - 258
  - 257

- **Percentage Reduction in Yearly Cause-Specific Mortality Rate**
  - 100%
  - 75%
  - 50%
  - 25%
  - 0%

- **(B) Yearly No. of Prostate Cancer Deaths**

- **No. of Screens for Abdominal Aortic Aneurysm**
  - 1

- **Year of F.U.:** 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20

* Each arrow indicates the timing of a screen for prostate cancer.
RE-ANALYSIS OF ERSPC DATA
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 × 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).
Year-specific prostate cancer mortality ratios

Cumulative Prostate Cancer Mortality

(A) Cumulative Prostate Cancer Mortality

By the End of Follow-Up Year:

0 0.002 0.004 0.006 0.008

1 2 3 4 5 6 7 8 9 10 11 12

Control Arm (C)

Screening Arm (S)
Year-specific prostate cancer mortality ratios

(A) Cumulative Prostate Cancer Mortality

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

Percentage Reduction in Year-Specific Prostate Cancer Mortality Rate

- Control Arm (C)
- Screening Arm (S)

Yearly Numbers of Prostate Cancer Deaths in Control (C) and Screening (S) Arms...

- Numbers of Men Being Followed at Mid-Year in Control (C) and Screening (S) Arms...

Follow-Up Year: 1 2 3 4 5 6 7 8 9 10 11 12
Interpretation

- After an expected delay (data indicate \(\approx 7\) years), the prostate cancer 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)
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** would be achieved at what some people would consider to be an unacceptable cost. (So far, only 326 or 0.36% of the 89,353 men in control group have died of prostate cancer; the 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 Δ in screening activity b/w 2 arms → considerably greater **resolving power**.
  - Must measure signal in f.-u. window where probably strongest → 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.
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).
Data-analysis using proportional hazards (ph) model: no place in cancer screening programs!

- **Time-specific analysis** (non-proportional hazards model) necessary to accommodate *delayed* mortality reductions (unless screening program doesn’t reduce mortality at all)
- **Screening for abdominal aneurysms**: immediate and sustained reduction in mortality from ruptured aneurysms; difference in cumulative, or average mortality (ph model) captures full benefit of screening.
- Need to **distinguish** between interventions with immediate and delayed effects.
- Data from all trials of cancers screening need to be re-analyzed.
**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?

- METRIC: nadir or (ideally) asymptote of response curve
Timing of cholesterol reductions produced by statins

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

A. 20 mg/kg/day

B. 50 mg/kg/day

3 monkeys at 50

Monkey (50 mg/kg/day)
Timing of cholesterol reductions produced by statins

Humans

[Graph showing the timing of cholesterol reductions produced by statins in humans. The graph compares the effects of placebo and statin treatments on plasma cholesterol levels over 20 weeks.]
The loneliness of the long-distance trialist

Timing of Screening Effects
(as seen in cumulative cause-specific mortality curves)

Abdominal Aortic Aneurysms
(One-off Screening, MASS)

Prostate Cancer
(q 4y, ERSPC)

Cumulative Cause-Specific Mortality
Follow-Up Year

Supp Fig. A
BREAST CANCER
Data-analysis: 1977-2010

- 1977/85 (HIP study): Shapiro/Morrison sensitive to time since start/end of screening
- 1985 (year 7 of Swedish 2-County Trial): “significant 30% reduction in mortality; control group invited to screening”
- 2000 (Meta-analysis): Gøtzsche et al. ignored time (and intensity/duration of screening)
- 2002 (Malmö data): Miettinen et al.: time-specific data bring out true signal
- Organized Population-based Screening Programs
  - Copenhagen, England, Norway, Sweden 40-49
  - Insensitive to timing (calendar, age) of mortality reductions
- IN EVERY INSTANCE: REDUCTION UNDER-ESTIMATED
Paraphrase of (refused) letter to NEJM re 2010 analysis of data from Norway

Will appear in:

*Epidemiologic Reviews*, 2011

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 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.
COLON CANCER:

excerpts from JH’s 2005 and 2011 reviews
Fecal Occult Blood testing: U.S. RCT

Biennial screening:

- Re-analyses, which focused on Year-specific data: had biennial screening not been interrupted, there would be:
  - $\approx 40\%$ sustained reduction in new cancers and
  - $\approx 40\%$ in cancer mortality

- Original report:
  - based on cumulative data
  - ignored 5-year hiatus and 2 waves of delayed reductions
  - 18% reduction in new cancers
  - 21% reduction in cancer mortality
CLINICAL REVIEWS

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

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

BACKGROUND: 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.
This Cochrane review of 4 RCTs...

Given the different

- random allocation methods (volunteers vs. all)
- tests (rehydrated vs. non-rehydrated)
- numbers of rounds of screening (2, 6, 6, 9)
- participation rates (60% - 80%)
- lengths of follow-up (12, 16, 17, 18 years)
- time-specific rate ratios

more meaningful if displayed 4 separate rate ratio time curves.

UK trial: \(\% \downarrow\) in cancer mortality in each of the years 2-15:

5, 17, 15, 23, 17, 23, 23, 16, 15, 6, 4, -2, 1, 2.

13\% \downarrow\) in cancer mortality over entire f-up period (median 12y) was given weight of 40\% in meta-analysis.

Swedish trial: 16\% \downarrow\) over 15.5 years; screens: 0 & 1.7 years.
Once-only flexible sigmoidoscopy (U.K. trial)

Figure 3: Smoothed yearly hazard rates for distal cancer (rectum and sigmoid colon).

Explicitly discussed the non-applicability of proportional hazards model.

31% mortality reduction based on cumulative mortality.

Cancers of proximal and distal colon were... separated for incidence rates, conflated for mortality rates.
LUNG CANCER
Mayo Lung Project (chest x-ray & sputum cytology)

- Enrollment: 1971-1976; negative on ‘prevalence’ screen; screening every 4 mo. for 6 years (vs., on enrollment, recommendation to receive annual chest x-ray & sputum cytology).
  
  Would 24-year follow up "allow for a reduction in lung cancer mortality to be observed?"

- ALL lung cancer deaths, from those in year...
  - 1, before impact could become evident, to
  - 24, 18 years after last screen.
National Lung Screening Trial (NLST)

- Enrollment: August 2002 - March 2004
  3 annual screens: low-dose helical CT (vs. standard chest X-ray).

Primary scientific goal:

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

- Press Releases, November 2010:

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

  An interim analysis of the study’s primary endpoint, reported to the DSMB on October 20, 2010, revealed a deficit of lung cancer deaths in the LDCT arm, and the deficit exceeded that expected by chance, even allowing for the multiple analyses conducted during the course of the trial. Data presented at previous meetings of the DSMB did not meet the requirements for statistical significance with respect to the primary endpoint. [NCI(US)]
Table 3: Interim Analysis of Primary Endpoint Reported on October 20, 2010

<table>
<thead>
<tr>
<th>Trial Arm</th>
<th>Person years (py)</th>
<th>Lung cancer deaths</th>
<th>Lung cancer mortality per 100,000 py</th>
<th>Reduction in lung cancer mortality (%)</th>
<th>Value of test statistic</th>
<th>Efficacy boundary</th>
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<tr>
<td>LDCT</td>
<td>144,097.6</td>
<td>354</td>
<td>245.7</td>
<td>20.3</td>
<td>−3.21</td>
<td>−2.02</td>
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<tr>
<td>CXR</td>
<td>143,363.5</td>
<td>442</td>
<td>308.3</td>
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Timing of the ‘deficit’ of (442-354=) 88 deaths

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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>38</td>
<td>65</td>
<td>75</td>
<td>82</td>
<td>90</td>
<td>60</td>
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<td>442</td>
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<tr>
<td>?? LDCT arm:</td>
<td>10</td>
<td>36</td>
<td>59</td>
<td>59</td>
<td>56</td>
<td>63</td>
<td>50</td>
<td>21</td>
<td>354</td>
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<td>?? deficit (no.):</td>
<td>0</td>
<td>-2</td>
<td>-6</td>
<td>-16</td>
<td>-26</td>
<td>-27</td>
<td>-10</td>
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<td>-88</td>
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<tr>
<td>?? deficit ( %):</td>
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<td>5%</td>
<td>9%</td>
<td>21%</td>
<td>32%</td>
<td>30%</td>
<td>17%</td>
<td>5%</td>
<td>20%</td>
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<td>?? LDCT arm:</td>
<td>8</td>
<td>30</td>
<td>52</td>
<td>60</td>
<td>66</td>
<td>73</td>
<td>48</td>
<td>17</td>
<td>354</td>
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<td>-8</td>
<td>-13</td>
<td>-15</td>
<td>-16</td>
<td>-17</td>
<td>-12</td>
<td>-5</td>
<td>-88</td>
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<td>?? deficit ( %):</td>
<td>20%</td>
<td>21%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>19%</td>
<td>20%</td>
<td>23%</td>
<td>20%</td>
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<td>?? deficit (no.):</td>
<td>-?</td>
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<td>-?</td>
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<td>-88</td>
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<tr>
<td>?? deficit ( %):</td>
<td>? %</td>
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<td>? %</td>
<td>? %</td>
<td>? %</td>
<td>20%</td>
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20% MORTALITY REDUCTION

A UNIVERSAL CONSTANT IN SCREENING TRIALS?
Reductions in ‘event rates’: 5 ‘prevention’ studies

- Cervical intraepithelial neoplasia (HPV 6,11,16,18): Quadrivalent human papillomavirus (HPV) vaccine
- Paralytic or non-paralytic poliomyelitis: Salk Vaccine
- HIV: (Adult) Circumcision
- Death from ruptured abdominal aneurym: Ultrasound screening
- Vascular events: Statin treatment [elevated C-reactive protein at entry]

**QUESTION:** Shape of $\downarrow (t)$ function, i.e., % Reduction in Rate as function of follow-up time, if rates based on...

- all events up to that point in f-up time? (1 ‘average’ rate)?
- when in f-up time events occurred (’time-specific’ rates)?
A Cervical intraepithelial neoplasia (HPV 6,11,16,18): quadrivalent human papillomavirus (HPV) vaccine

B Paralytic or non-paralytic poliomyelitis: Salk Vaccine

C HIV: Circumcision

D Death from ruptured abdominal aneurym: Ultrasound screening

E Vascular events: Statin treatment [elevated C-reactive protein at entry]

(i) Percentage Reduction in AVERAGE Event Rate (if data analyzed after indicated no. of events)

(ii) Percentage Reduction (Theoretical) in TIME-SPECIFIC Event Rates (i.e. measured using successive non-overlapping time intervals, and with no sampling variability)

Screening for cancer of the...

a Colon: (once-only sigmoidoscopy)

b Prostate: (PSA)

c Lung: (CT)

d Breast (hypothetical)
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.

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

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

- **Data**: completed RCTs of screening for prostate, breast, colon and lung ca; population-based screening programs.

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

  
  \[
  \text{RateRatio}(y, a, s) = \text{sum of reductions from all previous rounds of screening in study } s
  \]

  
  - **Rate ratio in Year \(y\), Age \(a\) in Study \(s\)**
  - **Design matrix**: 1 row per \(y\)-\(a\)-\(s\) ‘cell’
  - **Fit by Max. Likelihood** (binomial model)

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

- A Morrison 1985 textbook on Screening

- O. Miettinen 2002 Lancet article

- J. Caro and M. McGregor


- F. Galton, Natural Inheritance, 1889.
Why do statisticians commonly limit their inquiries to Averages?

“It is difficult to understand why statisticians commonly limit their inquiries to Averages, and do not revel in more comprehensive views.

Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if its mountains could be thrown into its lakes, two nuisances would be got rid of at once.”
FUNDING, CO-ORDINATES, DOWNLOADS

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

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Some References

1. Hanley JA. Mortality reductions produced by sustained prostate cancer screening have been underestimated. Journal of Medical Screening. Fall 2010. [ + Br & Colon Epidemiologic Reviews 2011]


