Underestimation of Mortality Reductions in Cancer Screening Studies:

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

James A. Hanley

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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 cancer

• 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

Screening

Mortality

Rate Ratio

Mortality Reduction (%)

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.
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.

<table>
<thead>
<tr>
<th>Age</th>
<th>Deaths in absence of screening</th>
<th>Deaths averted by screening</th>
<th>Deaths despite screening</th>
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<tr>
<td>85</td>
<td>7</td>
<td>7</td>
<td>0</td>
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</table>

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

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Can they obtain them from published reports?

- 1995 CETS (Québec) Report: uncertain benefit / certain harms
- 2004 Amer. Coll. Physicians Report: likewise; 'overdiagnosis'
- 2005 RCT: Radical prostatectomy > but ≯ watchful waiting in early Pr Ca
- 2009: European Randomized Study of Screening for Pr Ca (ERSPC) ∗
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- 2009: European Randomized Study of Screening for Pr Ca (ERSPC)

In all, 5 RCTs of Screening for Prostate Cancer
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>
</tr>
</thead>
<tbody>
<tr>
<td>Author:</td>
<td>Labrie</td>
<td>Sandbloma</td>
<td>Kjellman</td>
<td>Andriole</td>
<td>Schröder</td>
</tr>
<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>15,000</td>
<td>7,500</td>
<td>24,000</td>
<td>38,000</td>
<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>
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</tr>
<tr>
<td>Screened ≥ once</td>
<td>24%</td>
<td>78%</td>
<td>74%</td>
<td>85%</td>
<td>82%</td>
</tr>
<tr>
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<td>7%</td>
<td>?</td>
<td>?</td>
<td>52%</td>
<td>??</td>
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<tr>
<td>No. Pr Ca deaths</td>
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<td>20</td>
<td>53</td>
<td>92</td>
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<tr>
<td></td>
<td>75</td>
<td>97</td>
<td>506</td>
<td>82</td>
<td>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*

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.


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%.
“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.”
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ERSPC Results and “Conclusions”

“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.”

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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 Nelson-Aalen method was used for the calculation of cumulative hazard. NEJM, March 2009.
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
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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.
Cumulative and Year-specific Mortality...
Cumulative and Year-specific Mortality...

in 100,000 men

(average age at entry: 62 years)
Cumulative and Year-specific Mortality...

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

if screened using PSA test
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,
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
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
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  

<table>
<thead>
<tr>
<th>Year of F.U.</th>
<th>No. of Screens*</th>
<th>Yearly No. of Prostate Cancer Deaths</th>
<th>No. of Prostate Cancer Deaths over...</th>
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<td></td>
<td>0</td>
<td>1177</td>
<td>20 Years</td>
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<td></td>
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<td>364</td>
<td>9 years</td>
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</table>

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

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

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 Screens:
1
2
3
4

Yearly No. of Prostate Cancer Deaths

* Each arrow indicates the timing of a screen for prostate cancer.
(B) Year-specific Rate Ratios & Percent Reductions

[Fig 2]

(A) Yearly No. of Prostate Cancer Deaths

<table>
<thead>
<tr>
<th>Year of F.U.</th>
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<th>2</th>
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</tr>
</tbody>
</table>

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

(B) Percentage Reduction in Yearly Cause-Specific Mortality Rate

| Year of F.U.: | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|--------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| 0 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.25 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.5 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 0.75 |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 1    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

One Screen for Abdominal Aortic Aneurysm
1, 2, 3, 4: No. of Screens for Prostate Cancer

Fig 2
RE-ANALYSIS OF ERSPC DATA
emphasis on time-specificity
emphasis on time-specificity

- Year-by-year mortality rate ratios
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 (prostate cancer 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.
emphasis on time-specificity

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• Moving averages to reduce the statistical noise (deaths in moving 3-year intervals)
emphasis on time-specificity

• Year-by-year mortality rate ratios
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• 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

By the End of Follow-Up Year:

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

0 0.002 0.004 0.006 0.008

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)

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

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Control (C)</th>
<th>Screening (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
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Numbers of Men Being Followed at Mid-Year in Control (C) and Screening (S) Arms...

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Percentage Reduction in Year-Specific Prostate Cancer Mortality Rate

- **0%**
- **25%**
- **50%**
- **67%**
- **75%**
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.

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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 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 $\Delta$ 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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- 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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Timing of cholesterol reductions produced by statins

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

![Graph showing cholesterol levels over time for 20 mg/kg/day and 50 mg/kg/day](image-url)
Timing of cholesterol reductions produced by statins

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

3 monkeys at 50
Timing of cholesterol reductions produced by statins

Humans
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The loneliness of the long-distance trialist
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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
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”

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• Copenhagen, England, Norway, Sweden 40-49

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Paraphrase of (refused) letter to NEJM re 2010 analysis of data from Norway

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.
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Will appear in:

Epidemiologic Reviews, 2011
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COLON CANCER:
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excerpts from JH’s 2005 and 2011 reviews
Fecal Occult Blood testing: U.S. RCT

Re-analyses, which focused on year-specific data: had biennial screening not been interrupted, there would be:

- ≈ 40% sustained reduction in new cancers
- ≈ 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
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- **Re-analyses**, which focused on *Year-specific data*: had biennial screening not been interrupted, there would be:
  - ≈ 40% sustained reduction in *new cancers* and
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- Original report:
  - based on cumulative data
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  - 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, Centre 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)

more meaningful if displayed 4 separate rate ratio time curves.

UK trial: ↓ 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% ↓ in cancer mortality over entire f-up period (median 12y) was given weight of 40% in meta-analysis.

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

JNCI 2000: "Lung Cancer Mortality in the Mayo Lung Project: Impact of Extended Follow-up"

Would 24-year follow up "allow for a reduction in lung cancer mortality to be observed?"

ALL lung cancer deaths, from those in year...

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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)]
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### Table 3: Interim Analysis of Primary Endpoint Reported on October 20, 2010

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<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>
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<tr>
<td>LDCT</td>
<td>144,097.6</td>
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<td>245.7</td>
<td>20.3</td>
<td>−3.21</td>
<td>−2.02</td>
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<tr>
<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>
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<td>354</td>
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<tr>
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<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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</table>
Timing of the ‘deficit’ of $(442-354=) 88$ deaths

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<td>75</td>
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<td>90</td>
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<tr>
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<td>59</td>
<td>59</td>
<td>56</td>
<td>63</td>
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<td>?? deficit (no.):</td>
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<td>20%</td>
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<tr>
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<th>CXR arm:</th>
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<th>8</th>
<th>ALL</th>
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<td>65</td>
<td>75</td>
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<td>17%</td>
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<td>20%</td>
<td></td>
</tr>
</tbody>
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| Year | LDCT arm: | 8 | 30 | 52 | 60 | 66 | 73 | 48 | 17 | 354 |
| deficit (no.): | -2 | -8 | -13 | -15 | -16 | -17 | -12 | -5 | -88 |
| deficit ( %): | 20% | 21% | 20% | 20% | 20% | 19% | 20% | 23% | 20% |

| deficit (no.): | -? | -? | -? | -? | -? | -? | -? | -? | -88 |
| deficit ( %): | ?% | ?% | ?% | ?% | ?% | ?% | ?% | ?% | 20% |
20% MORTALITY REDUCTION
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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 aneurysm:
- Ultrasound screening

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

QUESTION: Shape of ↓ (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)?
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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)
(i) Percentage Reduction in AVERAGE Event Rate
(if data analyzed after indicated no. of events)

Soon after intervention or start of screening

While full effect of intervention, or last screening, continues

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

---

A Cervical intraepithelial neoplasia (HPV 6,11,16,18):
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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.
If intervention continues over time to deflect the same % of events, an estimate of the % reduction, based on the total number of events in more (person)-time will be more precise.
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PLANS
Data and Methods, Parameters, their Use

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

Parameters (' deliverables '):
1. LAG (years)
2. Depth
3. Spread (years)

\[ y = \text{years since screening commenced} \]

Rate ratio in Year \( y \), Age \( a \) in Study \( s \):

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

Design matrix: 1 row per y-a-s 'cell'

Fit by Max. Likelihood (binomial model)

USE: project mort. reductions due to a screening regimen
Data and Methods, Parameters, their Use

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

<table>
<thead>
<tr>
<th>Year</th>
<th>LAG (years)</th>
<th>Depth</th>
<th>Spread (years)</th>
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<tbody>
<tr>
<td>1</td>
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<td>5</td>
<td>7</td>
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<tr>
<td>15</td>
<td>17</td>
<td>19</td>
<td>21</td>
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</tbody>
</table>

  \[ y = \text{years since screening commenced} \]

  - **Rate ratio in Year** \( y \), **Age** \( a \) in **Study** \( s \):  
    \[
    \text{Rate Ratio}(y, a, s) = \text{sum of reductions from all previous rounds of screening in study} 
    \]

  - **Design matrix**: 1 row per \( y-a-s \) ‘cell’
  - **No. deaths in screening arm**
  - **No. deaths in 2 arms combined in each ‘cell’**
  - **Fit by Max. Likelihood (binomial model)**
  - **USE**: project mort. reductions due to a screening regimen
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  ![Diagram showing data and methods parameters](image)

- Rate ratio in Year $y$, Age $a$ in Study $s$:
  \[
  \text{RateRatio}(y, a, s) = \text{sum of reductions from all previous rounds of screening in study} \\
  \]
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</table>

LAG (years)  Spread (years)  Depth

\[ y = \text{years since screening commenced} \]

- Rate ratio in Year \( y \), Age \( a \) in Study \( s \):
  \[
  \text{RateRatio}(y, a, s) = \sum \text{of reductions from all previous rounds of screening in study s}
  \]

- **Design matrix**: 1 row per y-a-s ‘cell’

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  - No. deaths in 2 arms combined in each ‘cell’

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  - **Year**: 1 3 5 7 9 11
  - **LAG (years)**: 1
  - **Spread (years)**: 1
  - **Depth**: 1

  \[ y = \text{years since screening commenced} \]

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    \[
    \begin{align*}
    \text{No. deaths in screening arm} \\
    \text{No. deaths in 2 arms combined}
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- F. Galton, Natural Inheritance, 1889.
Why do statisticians commonly limit their inquiries to Averages?
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Le Fonds québécois de la recherche sur la nature et les technologies
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http://www.mcgill.ca/epi-biostat-occh/grad/biostatistics/
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]


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