Three thoughts to begin

1. Cancer screening is a good idea in principle
   • Detect cancers early while still curable

2. Cancer screening is controversial in practice
   • Evidence about harm/benefit is uncertain

3. Cancer screening is complicated
   • Standard ways of evaluating evidence don’t always work and can mislead
Where does evidence about cancer screening benefit and harm come from?

- Clinical trials of cancer screening
- Population trends in cancer deaths before and after screening
- Population trends in cancer incidence before and after screening
- Observational/epidemiologic studies
Why is cancer screening controversial?

1. Population trends reflect other improvements in cancer control
   - Primary treatment trends
   - Disease monitoring and new treatments for recurrent disease
   - Supportive care for cancer patients
Breast and prostate cancer mortality in the US

1990-2010
43% drop

1990-2010
34% drop
Prostate and breast cancer treatment trends

Prostate Cancer: Primary treatment

- Conservative management
- RP: radical prostatectomy
- RT: radiation therapy
- RT+ADT: radiation therapy + hormone therapy

Breast Cancer: Adjuvant chemotherapy

- Various chemotherapy regimens:
  - Multiagent chemotherapy only
  - Tamoxifen only
  - Both

RP: radical prostatectomy
RT: radiation therapy
ADT: hormone therapy
1. **Population trends reflect other improvements in cancer control**
   - Primary treatment trends
   - Disease monitoring and new treatments for recurrent disease
   - Supportive care for cancer patients

2. **Clinical trials of screening are not always consistent**
   - In prostate cancer two trials give two seemingly different answers
   - Many breast screening trials, some with no benefit
Prostate cancer screening trials

Cumulative death rate in screen and control groups

**ERSPC**
- 20% reduction

**PLCO**
- No reduction

**European trial**
- Control group
- Intervention group

**US trial**
- Control group
- Intervention group
Breast cancer screening trials

Relative reduction in risk of death in screened group

Figure 1: Meta-analysis of breast cancer mortality after 13 years of follow-up in breast cancer screening trials
Adapted from the Cochrane Review. RR=relative risk. Malmö II is excluded because follow-up of about 13 years was not available; the Swedish Two County (Kopparberg and Östergötland) and Canada I and II trials are split into their component parts; the Edinburgh trial is excluded because of severe imbalances between randomised groups. Weights are from random-effects analysis.
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   – In prostate cancer two trials give two seemingly different answers
   – Many breast screening trials, some with no benefit

3. People are worried about harms of screening like overdiagnosis
   – Does cancer screening lead to diagnosis of harmless tumors?
Can the Prostate-Test Be Hazardous to Your Health?

By LARRY KATZENSTEIN

F

For millions of American men over age 50, the Prostate Specific Antigen blood test for detecting prostate cancer has become a routine part of their annual checkup. If they don’t ask for it, their doctors often recommend it. But there are serious concerns about the test’s usefulness and whether the treatment for prostate cancer may be harming more lives than it saves.

Despite a recent barrage of high-profile endorsements for the test by Arnold Palmer and H. Norman Schwarzkopf, among others, not one major medical or public-health group endorses the screening. And in recent years, most of the groups that have evaluated the test either oppose its use for routine screening, or do not recommend it. These include the National Cancer Institute, the American College of Physicians, the American College of Preventive Medicine and the United States Preventive Services Task Force.

The American Cancer Society, which once endorsed the screening, changed its stance in 1997 and now recommends that the Prostate Specific Antigen test, also known as P.S.A., be offered annually to men 50 and older, who should be given information about the risks and benefits of treatment should cancer be found.

Even the American Urological Association, whose members are among the most enthusiastic advocates of P.S.A. testing, now endorses the new American Cancer Society policy.

Dr. Gabriel Feldman, the society’s national director of prostate and colorectal cancer control, calls the P.S.A. “the most controversial medical test in the country right now.”

Some objections to the screening involve errors. The test fails to detect prostate cancer in 1 in 4 men who have the disease (false-negative results), and as many as two-thirds of the men tested receive false-positive results, meaning that biopsies and other follow-ups fail to confirm the cancer finding. A P.S.A. score above four micrograms of antigen per milliliter of serum usually prompts follow-up tests.

But the main reason so many groups oppose P.S.A. screening is the lack of evidence that early detection actually improves a man’s chances of surviving prostate cancer. “That’s the big secret that nobody likes to talk about,” Dr. Feldman said.

A discovery of cancer through P.S.A. testing usually leads to treatment, Dr. Feldman said. But we don’t have any conclusive evidence that surgery or other aggressive treatment make any difference in the long term in helping men live longer or better,” he said. “Instead, we are going completely on intuition.”

Dr. Feldman contrasts prostate cancer with breast cancer, where clinical studies have proven that regular mammograms result in early detection and treatment that can save lives.

Dr. Feldman added that radical prostatectomy, the principal treatment for prostate cancer, causes 30 percent to 50 percent of all patients to become impotent for at least some period of time. Radiation, the other form of aggressive treatment, can cause similar side effects as well as other complications, he added. There is also some risk: approximately 1 percent of patients who undergo a radical prostatectomy die from it.

The P.S.A. detects prostate cancers 10 to 15 years earlier than was possible with the digital rectal exam. But because of the nature of prostate cancer — it is overwhelmingly a disease that afflicts elderly men and is usually very slow-growing — the early warning is often meaningless.

The prostate gland, the size of a walnut, is located in front of the rectum and beneath the bladder. The gland produces the fluid portion of semen and secretes prostate-specific antigen, a protein that is pumped into the bloodstream in higher-than-normal amounts by cancerous cells.

While it is not uncommon for a few cancer cells to develop when men are in their 30’s or 40’s, these cells typically divide so slowly that tumors are rare in men younger than 50. After that, prostate cancer becomes increasingly common: men in their 60’s and 70’s have a 1-in-4 chance of being diagnosed with prostate cancer; a man living to 100 is almost certain to develop it.

But again, given prostate cancer’s long-term growth, most older men will die of other causes, like heart disease or stroke. Hence the adage that most prostate cancer patients die with their disease rather than from it. Moreover, the P.S.A. test cannot pinpoint three faster growing tumors for which early treatment might make a difference.

Still, the P.S.A. test continues to have strong advocates, not the least of whom are patients who have had surgery and never experienced a recurrence. They are usually convinced that P.S.A. testing has prolonged their lives, if not saved them. Indeed, in some cases the test may have done just that.

And urologists, who in general treatment doesn’t work, why are we using the P.S.A. to look for tumors?”

To underscore their argument, critics of the P.S.A. point to studies showing that prostate cancer screening has little effect on the mortality rates. In a 1991 study in the journal Cancer, Dr. Otto Brawley, a medical oncologist and epidemiologist at the National Cancer Institute, calculated new prostate cancer cases per 100,000 men and prostate cancer deaths per 100,000 men in nine regions of the United States from 1974 through 1994. Not surprisingly, regions screened most intensively for prostate cancer (the Seattle-Portland Sound area, for example) had a much higher incidence of the cancer than regions screening the least (Connecticut, for one).

Mortality rates, however, were basically identical for all nine regions — and actually slightly higher in the Seattle-Portland Sound area. Dr. Brawley cites similar findings from a recent study comparing the United States with Britain. “I believe prostate cancer screening probably does save some lives,” Dr. Brawley said, “but I can prove through studies like these that it ruins some lives.”

A recent study of men living near the Mayo Clinic in Minnesota has added more force to the debate. The Journal of Urology this month published a report by researchers who analyzed prostate cancer deaths in Ginoset, Minn., from 1886 to 1997. They found
Fatal Retraction

Not all cancers are lethal—despite the fear the name evokes. Although doctors often can’t tell for certain which individual tumors are destined to be deadly, a growing number of studies suggest that many found at early stages may be so slow-growing they are unlikely to be fatal. Some recent estimates of this ‘overdiagnosis’ rate in common cancers:

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Prostate</th>
<th>Breast</th>
<th>Thyroid</th>
<th>Skin</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (%)</td>
<td>60%</td>
<td>30%</td>
<td>90%</td>
<td>90%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Sources: American Cancer Society (Prostate); New England Journal of Medicine (Breast); The BMJ (Thyroid); American Academy of Dermatology (Skin); JAMA Internal Medicine (Lung)

The Wall Street Journal

It’s Time to Rethink Early Cancer Detection

A growing number of experts argue that zealous screening too often leads to overtreatment. They call for changing the way we even talk about the disease.
Plan for today

▪ Review some commonly cited “facts and figures” about cancer screening

▪ In each case
  – Explain the basis for the observation
  – Decide whether it is defensible or not

▪ Objective
  – Learn some of the pitfalls when evaluating screening harms and benefits
  – Come away better equipped to read and critique media reports about screening
1. MOST SCREEN-DETECTED CASES ARE NOT SAVED BY SCREENING
“The truth is that most women who find breast cancer as a result of regular screening have not had their lives saved by the test.”
Breast cancer screening

Q: How many women would have had a diagnosis of breast cancer without screening?
A: 9% (based on old SEER data)

Q: How many women will die of breast cancer without screening:
A: About 3%

Q: If screening benefit is 20% reduction in breast cancer death, how many women will have their lives saved by screening?
A: About 0.6% (NOTE: this is less than 1%)

Q: How many women will be diagnosed with breast cancer with screening?
A: About 12.5% (based on SEER data from 2011-2013)
The facts of screening

“The truth is that most women who find breast cancer as a result of regular screening have not had their lives saved by the test.”

THIS STATEMENT IS TRUE

But does it justify the headline?
2. CLINICAL TRIALS ARE RELIABLE SOURCES OF EVIDENCE ABOUT SCREENING BENEFIT
Prostate cancer: Two screening trials

ERSPC PLCO

Percent reduction in mortality
ERSPC 21%
PLCO 0%

Lives saved per 1000 screened
ERSPC 1
PLCO 0

Breast cancer: Eight screening trials

**Figure 1:** Meta-analysis of breast cancer mortality after 13 years of follow-up in breast cancer screening trials

Adapted from the Cochrane Review. \(^5\) RR=relative risk. Malmö II is excluded because follow-up of about 13 years was not available; the Swedish Two County (Kopparberg and Östergötland) and Canada I and II trials are split into their component parts; the Edinburgh trial is excluded because of severe imbalances between randomised groups. Weights are from random-effects analysis.
Why so much variability?

**Trial design and analysis**
- Continuous-screen or stop-screen
- Duration of follow-up

**Screening protocol**
- Ages, intervals, cutoffs

**Compliance, contamination, treatment**
- Did screening group attend and comply?
- Was there screening in the control group?
- Were the two groups treated similarly?

**Timing**
- Screening, biopsy and treatment technologies
Prostate-Cancer Mortality at 11 Years of Follow-up

<table>
<thead>
<tr>
<th>Study Years</th>
<th>Screening Group</th>
<th>Control Group</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths from Prostate Cancer</td>
<td>Deaths from Prostate Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no.</td>
<td>Rate per 1000 Person-Yr</td>
<td>no.</td>
<td>Rate per 1000 Person-Yr</td>
</tr>
<tr>
<td>1–9</td>
<td>189</td>
<td>0.31</td>
<td>274</td>
<td>0.37</td>
</tr>
<tr>
<td>8–9</td>
<td>71</td>
<td>0.58</td>
<td>118</td>
<td>0.78</td>
</tr>
<tr>
<td>10–11</td>
<td>56</td>
<td>0.57</td>
<td>111</td>
<td>0.92</td>
</tr>
<tr>
<td>1–11</td>
<td>245</td>
<td>0.35</td>
<td>385</td>
<td>0.44</td>
</tr>
<tr>
<td>≥12</td>
<td>54</td>
<td>0.94</td>
<td>77</td>
<td>1.16</td>
</tr>
<tr>
<td>Total</td>
<td>299</td>
<td>0.39</td>
<td>462</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Schroder et al, NEJM 366: 981-990, 2012
Trial duration and timing of analysis matter greatly.
3. PROSTATE CANCER SCREENING SAVES 0 TO 1 LIVES PER 1000 MEN
There is **adequate evidence** that the benefit of PSA screening and early treatment ranges from 0 to 1 prostate cancer deaths avoided per 1000 men screened.

- **PLCO** “0”
- **ERSPC** “1”

Note: Figures cited are “absolute benefit”
Zero lives saved: The PLCO trial

- PLCO trial began in 1993
- Not a comparison of screening versus no screening
- Many men on control arm screened
  - 74% at least once
  - 50% each year
- Poor compliance with biopsy recommendations
  - 40% biopsied within one year of abnormal screen

PSA screening uptake in the US
(Source: Mariotto et al, 2007)
**Relative benefit**: Deaths in screened group divided by deaths in the control group

\[ \frac{A}{B} \]

**Absolute benefit**: Deaths in the control group minus deaths in the screened group

\[ B - A \]
Relative benefit: Deaths in screened group divided by deaths in the control group

\[ \frac{A}{B} \]

Absolute benefit: Deaths in the control group minus deaths in the screened group

\[ B - A \]

For a given relative benefit, absolute benefit depends critically on
- Trial duration/timing of analysis
- Baseline mortality without screening
One life saved: ERSPC

Relative mortality reduction: \(21\% = (1 - \frac{A}{B})\)

- Among men who would have died of prostate cancer without screening roughly one fifth were saved by screening
  → Reduction among those who would have died without screening

Absolute mortality reduction: \(1 \text{ death per 1000} = \frac{(B - A)}{1000}\)

- Because the risk of death without screening was 5 per 1000
- One-fifth reduction means we are saving one person
  → Reduction among those entering the screening program
Absolute mortality: trial versus population

Short term versus long term

11-year follow-up (ERSPC)

Prostate cancer deaths per 1,000 men invited in core age group after 11 years:

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5</td>
</tr>
<tr>
<td>Screening</td>
<td>4</td>
</tr>
<tr>
<td>Absolute Difference</td>
<td>1</td>
</tr>
<tr>
<td>NNS</td>
<td>1000</td>
</tr>
</tbody>
</table>
Absolute mortality: trial versus population

11 year follow-up

Prostate cancer deaths per 1,000 men invited in core age group after 11 years:

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<td>5</td>
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<tr>
<td>Screening</td>
<td>4</td>
</tr>
<tr>
<td>Difference</td>
<td>1</td>
</tr>
</tbody>
</table>

Long-term follow-up (SEER)

Prostate cancer deaths per 1,000 men invited starting at age 40 or 50 over lifetime:

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
</tr>
<tr>
<td>Screening</td>
<td>24</td>
</tr>
<tr>
<td>Difference</td>
<td>6</td>
</tr>
</tbody>
</table>
4. THE CANADIAN TRIAL SHOWS THAT MAMMOGRAPHY SCREENING IS NOT BENEFICIAL
One of the largest and most meticulous studies of mammography ever done, involving 90,000 women and lasting a quarter-century, has added powerful new doubts about the value of the screening test for women of any age.

It found that the death rates from breast cancer and from all causes were the same in women who got mammograms and those who did not. And the screening had harms: One in five cancers found with mammography and treated was not a threat to the woman’s health and did
The Canadian trial

• A stop-screen trial comparing
  – Mammography+CBE with CBE alone or usual care
  – Screening for 5 years with 25-year follow-up

• Analysis options:
  1. Compare breast cancer deaths in the two groups over the entire follow-up period
  2. Compare breast cancer deaths restricted to cases diagnosed in the two groups during the screening period
**Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial**

<table>
<thead>
<tr>
<th>Analysis options</th>
<th>Screen arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening period (5 years)</strong></td>
<td>Cases</td>
<td>666</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>180</td>
</tr>
<tr>
<td><strong>Entire study period (25 years)</strong></td>
<td>Cases</td>
<td>3250</td>
</tr>
<tr>
<td></td>
<td>Deaths</td>
<td>500</td>
</tr>
</tbody>
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The Canadian Trial

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  1. Compare breast cancer deaths in the two groups over the entire follow-up period
  2. Compare breast cancer deaths restricted to cases diagnosed in the two groups during the screening period

• Each of these is problematic
  1. *Dilution of effect from cases diagnosed in both groups after the screening period*
  2. *Non-comparable groups with more cases in the screening group than in the control group*
5. BREAST CANCER SCREENING DOESN’T WORK BECAUSE ADVANCED-STAGE INCIDENCE HAS NOT GONE DOWN
No reduction observed in the population over time.
Stage shift under screening Breast cancer trials

Advanced Breast Cancer and Breast Cancer Mortality in Randomized Controlled Trials on Mammography Screening

Philippe Autier, Clarisse Héry, Jari Haukka, Mathieu Boniol, and Graham Byrnes

Autier P et al, JCO 2009 Dec 10
Cancers larger than 2cm
No reduction observed in the population over time

- Changes in technology for identifying advanced disease?
- Greater availability of imaging and surgery to stage new cases
- Changes in medical record and registry coding practices?
6. 30 PERCENT OF BREAST CANCERS AND 60 PERCENT OF PROSTATE CANCERS ARE OVERDIAGNOSED
Fatal Retraction

Not all cancers are lethal—despite the fear the name evokes. Although doctors often can’t tell for certain which individual tumors are destined to be deadly, a growing number of studies suggest that many found at early stages may be so slow-growing they are unlikely to be fatal. Some recent estimates of this ‘overdiagnosis’ rate in common cancers:

- **Prostate**: 60%
- **Breast**: 30%
- **Thyroid**: 90%
- **Skin**: 90%
- **Lung**: 18%

Sources:
- American Cancer Society (Prostate)
- New England Journal of Medicine (Breast)
- The BMJ (Thyroid)
- American Academy of Dermatology (Skin)
- JAMA Internal Medicine (Lung)
- The Wall Street Journal

Ductal carcinoma in situ is an early, noninvasive form of breast cancer in which abnormal cells (the small dark spots) are confined to milk ducts. Experts think only about 20% of cases would eventually become invasive cancer, but virtually all are treated with surgery and radiation.

It’s Time to Rethink Early Cancer Detection

A growing number of experts argue that zealous screening too often leads to overtreatment. They call for changing the way we even talk about the disease.
What is overdiagnosis?

Detection of cancers that would never have been diagnosed without screening

- Cancers that are slow growing or non-progressive
- Cancers that arise in individuals with short life expectancy

An overdiagnosed cancer is an excess case of cancer

- Can we estimate overdiagnosis by excess incidence in screened versus unscreened individuals?
Thirty percent of breast cancers overdiagnosed

- Compare incidence observed with incidence expected in absence of screening
- Expected incidence based on trend observed in women under 40
- Attribute all excess cases to overdiagnosis

Bleyer and Welch NEJM 2012

Incidence in women 40 and older
By calendar year and stage
Thirty percent of breast cancers overdiagnosed

- Compare incidence observed with incidence expected in absence of screening
- Expected incidence based on trend observed in women under 40
- Attribute all excess cases to overdiagnosis

**NEJM 2012**
Questioning the background trend
Questioning the background:
Trends in Testicular Cancer Incidence

Trends in younger men do not match trends in older men.

Ages < 50 y
- 2.8% per year

Ages ≥ 50 y
- 0.7% per year
- 0.4% per year
What if we can get a better background trend?

Denmark provides a natural experiment

- Organized screening program (Ages 50-69) began in some areas in 1991-1994 and not in others
- Study compares incidence trends in screening versus non-screening areas
- Concludes screening not associated with a decline in advanced (> 2cm) cancer
- Different methods of estimating overdiagnosis frequency
Breast Cancer Screening in Denmark
A Cohort Study of Tumor Size and Overdiagnosis

Karsten Juhl Jørgensen, MD, DrMedSci; Peter C. Gøtzsche, MD, MSc; Mette Kalager, MD, PhD*; and Per-Henrik Zahl, MD, DrMedSci*

Before screening started
Screening start years
AGE 50-69

Non-screened areas
Screened areas
Estimates of overdiagnosis

Method 1: tries to account for the relatively lower incidence of advanced cancers in the screening areas and includes older women

- 9.9% invasive
- 16.4% invasive plus DCIS

Method 2: does not account for the relatively lower incidence of advanced cancers in the screening areas

- 38% invasive
- 48% invasive plus DCIS

Both methods: overdiagnosis is expressed relative to cases that would be detected without screening, not as a fraction of all diagnosed cases
Mammograms Aren’t Perfect, American Cancer Society Top Doc Says

by MAGGIE FOX

It's time to admit that mammograms are not perfect and that doctors are treating women who don't need treatment for breast cancer, the American Cancer Society's top doctor said Monday after yet another study showed breast cancer screening leads to so-called over diagnosis.

The new study found that as many as a third of women in Denmark diagnosed with breast cancer through mammograms either didn't have malignant cancer, or had slow-growing tumors that didn’t need immediate treatment.

“The numbers match those found in other studies that cast doubt on whether mammograms actually reduce the risk of dying from breast cancer. A 2012 study published in the New England Journal of Medicine that found that as many as a third of cancers detected through routine mammograms may not be life threatening.”
What about clinical trials of screening?

**Screening trials should be ideal for estimating overdiagnosis**
- Concurrent control group

**Screening trials do not generally produce unbiased estimates**
- Depends on design (stop-screen or continuous-screen)
- Depends on measure used (cumulative or annual incidence)
- Depends on timing of the estimation procedure – need to wait
Fatal Retraction

Not all cancers are lethal—despite the fear the name evokes. Although doctors often can't tell for certain which individual tumors are destined to be deadly, a growing number of studies suggest that many found at early stages may be so slow-growing they are unlikely to be fatal. Some recent estimates of this ‘overdiagnosis’ rate in common cancers:

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<th>Lung</th>
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IT'S TIME TO RETHINK EARLY CANCER DETECTION

A growing number of experts argue that zealous screening too often leads to overtreatment. They call for changing the way we even talk about the disease.

BY MELINDA BECK

EARLY DETECTION HAS long been seen as a powerful weapon in the battle against cancer. But some experts now see it as double-edged sword.

While it's clear that early-stage cancers are more treatable than late-stage ones, some leading cancer researchers argue screening for prostate and breast cancer is done too much, and that there is no evidence it actually improves survival rates.

Gleason score of 6 or below "benign lesions"—although others note that that would mean half of the men treated for prostate cancer in the past 20 years didn't have cancer after all.

Overdiagnosis—the detection of tumors that aren't likely to cause harm—is now a hot topic in other cancers as well. A growing volume of studies estimate that as many as 30% of invasive breast cancers 18%
## Prostate cancer incidence in ERSPC

<table>
<thead>
<tr>
<th></th>
<th>Cumulative Incidence at 9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened arm</td>
<td>8.2% (5.8%)</td>
</tr>
<tr>
<td>Control arm</td>
<td>4.8%</td>
</tr>
<tr>
<td>Excess</td>
<td>8.2% - 4.8% = 3.4%</td>
</tr>
<tr>
<td>Excess/screen-detected</td>
<td>3.4/5.8 = 58%</td>
</tr>
</tbody>
</table>

*Schroder et al*  
*NEJM 2009*
The problem with cumulative excess incidence in continued-screen trials

- **What we know**
  - Cases detected under screening
  - Represent cases that would have arisen during AND after the trial
  - Corresponding cases in the absence of screening

- **What we do**
  - Take cases detected under screening
  - Subtract the cases on the control group that arose during the trial
  - Corresponding cases in the absence of screening

- If there is no overdiagnosis this approach will still yield a positive result!
This is much less problematic in stop-screen trials

- When you stop screening (but keep following), you give cases in the control group a chance to “catch up”

- If there is no overdiagnosis, the difference between the cumulative incidence in the screened and control groups will eventually go to zero
One of the largest and most meticulous studies of mammography ever done, involving 90,000 women and lasting a quarter-century, has added powerful new doubts about the value of the screening test for women of any age.

It found that the death rates from breast cancer and from all causes were the same in women who got mammograms and those who did not. And the screening had harms: One in five cancers found with mammography and treated was not a threat to the woman’s health and did

20% of cancers overdiagnosed
7. FOR EVERY LIFE SAVED BY PROSTATE SCREENING 48 MEN ARE OVERDIAGNOSED
The European Study showed a small decline in death rates but also found that 48 men would need to be treated to save one life. That’s 47 men, who in all likelihood can no longer function sexually or stay out of the bathroom for long ...
“During a median follow-up of 9 years, the rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80. The absolute risk difference was 0.71 deaths per 1000 men. This means that 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer.

Schroder et al, NEJM 2009 April
Number Needed to Detect

- NND is a harm-benefit measure
  \[
  \text{NND} = \frac{\text{fraction overdiagnosed}}{\text{fraction whose life is saved}}
  \]

- Calculation of NND in the ERSPC
  \[
  \text{NND} = \frac{\text{fraction overdiagnosed}}{\text{ABSOLUTE BENEFIT}}
  \]

- NND of 48 to 1 is an overestimate
- A more accurate estimate is more like 5 to 1!
“After a median follow-up of 11 years, the relative reduction in the risk of death from prostate cancer in the screening group was 21% (rate ratio 0.79). The absolute reduction in mortality in the screening group was 1.07 deaths per 1000 men. To prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and **37 (additional) cancers would need to be detected.**”
Conclusions

- Evidence about cancer screening harms and benefits can be hard to fathom
  - Trials may not be as unequivocal as we would hope

- Both investigators and reporters have opinions
  - Media tends to oversimplify and impose unwarranted judgements – beware the byline

- That overdiagnosis exists is a fact
  - Most studies of overdiagnosis are subject to bias
1. Most screen-detected cases are not saved by screening  T  F
2. Clinical trials are the most reliable sources of evidence  T  F
3. Prostate cancer screening saves 0 to 1 lives per 1000 men  T  F
4. The Canadian trial shows breast cancer screening is not beneficial  T  F
5. Breast cancer screening doesn’t work because advanced-stage incidence has not gone down  T  F
6. 30% of breast cancers and 60% of prostate cancers are overdiagnosed  T  F
7. For every life saved by prostate cancer screening 48 men are overdiagnosed  T  F
“The change in recommendations was brought about by several developments, including additional follow-up data from a European trial that found a slightly smaller number of deaths as well as fewer cases of cancer spreading among men who were screened”
"For every 1000 men offered screening... over the course of 10 to 15 years, three cancers will be prevented from spreading, and one to two deaths of prostate cancer will be prevented"
Thank you!

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- Lurdes Inoue

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- Eric Feuer

Cancer Intervention and Surveillance Modeling Network