Cancer Screening: Evidence, Opinion and Fact
Dialogue on Cancer April 2018

Ruth Etzioni
Fred Hutchinson Cancer Research Center
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 come from?

- Clinical trials of cancer screening
- Population trends in cancer cases and deaths 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
- RP: radical prostatectomy
- RT: radiation therapy
- RT+ADT: radiation therapy with hormone therapy

Breast Cancer: Adjuvant chemotherapy
- Adjuvant chemotherapy

Graphs showing trends in treatment percentages over time.
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

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 deaths in screen and control groups

**ERSPC**
- 20% reduction

**PLCO**
- No reduction

**European trial**
- Screening group
- Control group

**US trial**
- Screening group
- Control group
Prostate cancer screening trials
*Cumulative deaths in screen and control groups*

**ERSPC**
20% reduction

**European trial**

**PLCO**
No reduction

**US trial**

Pinsky et al, Cancer 2018
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.
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

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

3. *Observational studies of cancer screening are prone to bias*
   - Those who choose to get screening may have a different innate risk of disease

4. *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 KITTENSTEIN

In the United States, prostate cancer is the most common cancer among men and the second leading cause of cancer death. The American Cancer Society recommends annual screening for men over the age of 50, but many men are hesitant to undergo the test due to concerns about its potential side effects.

A recent study published in the Journal of the American Medical Association found that the PSA test can lead to unnecessary treatment for men who do not have prostate cancer. The study followed 162,000 men for an average of 11 years and found that those who had a PSA test in the first year of the study had a higher rate of death from other causes than those who did not have a test.

The study's lead author, Dr. Mark Schröder, said that the results indicate that the PSA test may be doing more harm than good. "The PSA test is not a perfect test," he said. "It can lead to unnecessary treatment, which can be dangerous for some men."

The study's findings have led some doctors to recommend that men consider whether they want to undergo the PSA test. Dr. Schröder said that men should discuss the risks and benefits of the test with their doctors and make an informed decision about whether to undergo it.

"It's important for men to understand that the PSA test is not a one-size-fits-all solution," he said. "We need to individualize the test and consider each man's risk profile and personal goals."
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>Tissue</th>
<th>Overdiagnosis Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>60%</td>
</tr>
<tr>
<td>Breast</td>
<td>30%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>90%</td>
</tr>
<tr>
<td>Skin</td>
<td>90%</td>
</tr>
<tr>
<td>Lung</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

BY MELINDA BECK

A growing number of experts argue that the zeal of 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 from the abovementioned types of studies

- 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

2. Clinical trials are the most reliable sources of evidence about screening benefit

3. Prostate cancer screening saves very few lives – 0 to 1 lives per 1000 men

4. The Canadian mammography trial shows breast cancer screening is not beneficial

5. Breast cancer screening doesn’t work because advanced-stage incidence has not gone down

6. 30% of breast cancers and 60% of prostate cancers are overdiagnosed

7. Ovarian cancer screening doesn’t work

8. New blood-based screening tests are going to solve all of our problems
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 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

Control group

Intervention group

Percent reduction in mortality

ERSPC  21%

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](image)

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.
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 with biopsy referral?
- Was there screening in the control group?
- What were the treatments available?
- **Were the two groups treated similarly?**

**Timing**
- Screening, biopsy and treatment technologies
 Trial duration and screening benefit: Prostate cancer

### 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>Rate per 1000 Person-Yr</td>
<td>Rate per 1000 Person-Yr</td>
</tr>
<tr>
<td></td>
<td>no.</td>
<td>Person-Yr</td>
<td>Rate per 1000 Person-Yr</td>
<td>no.</td>
</tr>
<tr>
<td>1–9</td>
<td>189</td>
<td>608,852</td>
<td>0.31</td>
<td>274</td>
</tr>
<tr>
<td>8–9</td>
<td>71</td>
<td>122,867</td>
<td>0.58</td>
<td>118</td>
</tr>
<tr>
<td>10–11</td>
<td>56</td>
<td>97,994</td>
<td>0.57</td>
<td>111</td>
</tr>
<tr>
<td>1–11</td>
<td>245</td>
<td>706,846</td>
<td>0.35</td>
<td>385</td>
</tr>
<tr>
<td>≥12</td>
<td>54</td>
<td>57,387</td>
<td>0.94</td>
<td>77</td>
</tr>
<tr>
<td>Total</td>
<td>299</td>
<td>764,233</td>
<td>0.39</td>
<td>462</td>
</tr>
</tbody>
</table>

Y 1-9: 15% reduction

Y 10-11: 38% reduction

Schroder et al, NEJM 366: 981-990, 2012
“Trial duration and timing of analysis matter greatly.”
Prostate cancer: Three screening trials

<table>
<thead>
<tr>
<th></th>
<th>ERSPC</th>
<th>PLCO</th>
<th>CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening interval</td>
<td>4 years (most centers) 2 years (Sweden)</td>
<td>Annual</td>
<td>One screen at start of trial</td>
</tr>
<tr>
<td>Screening on control arm</td>
<td>Infrequent</td>
<td>74% at least one test 50% tested each year</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Compliance with screening</td>
<td>Relatively good</td>
<td>Relatively good</td>
<td>36% of eligible men were screened</td>
</tr>
<tr>
<td>Compliance with biopsy</td>
<td>80%</td>
<td>40%</td>
<td>85%</td>
</tr>
</tbody>
</table>

ERSPC and PLCO trials are more similar than they seem

- Compare incidence of prostate cancer on each arm of each trial with a common baseline (no screening)

- “Earliness of detection” expressed as a Mean Lead Time
  - Similar for the two PLCO arms, greater for ERSPC screened than ERSPC control arm
  - Lines up exactly with ordering of disease-specific mortality on each arm

- Earliness of detection on screened arms of ERSPC and PLCO trials implies mortality reduction of 25-32% when compared with no screening
3. Prostate cancer screening saves 0 to 1 lives per 1000 men screened
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.

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
  - Only 40% biopsied within one year of abnormal screen

PSA screening uptake in the US
(Source: Mariotto et al, 2007)
One life saved: ERSPC trial

**Relative benefit**: Deaths in screened group divided by deaths in control group

\[ A/B \]

**Absolute benefit**: Deaths in 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 – about 5 per 1000 at the time of the analysis
One life saved: ERSPC trial

**Relative benefit:** $21\% = (1 - A/B)$
- Among men who would have died of prostate cancer without screening about one fifth were saved by screening
  - Lives saved among those who would have died without screening

**Absolute benefit:** 1 death per 1000 = $(B - A) / (\text{size of screened group})$
- Because the risk of death without screening was 5 per 1000
- One-fifth reduction means we are saving one person
  - Lives saved among men entering the screening program
Trial versus population: short vs long term

11 year follow-up

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>Difference</td>
<td>1</td>
</tr>
</tbody>
</table>

20% difference

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>

20% difference
The latest from USPSTF on prostate cancer screening

“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”
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...
RESEARCH

Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial

Anthony B Miller professor emeritus, Claus Wall data manager, Cornelia J Baines professor emerita, Ping Sun statistician, Teresa To senior scientist, Steven A Narod professor

1Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario M5T 3M7, Canada; 2Women’s College Research Institute, Women’s College Hospital, Toronto, Ontario M5G 1N8, Canada; 3Child Health Evaluative Services, The Hospital for Sick Children, Toronto, Ontario, Canada

Abstract

Objective To compare breast cancer incidence and mortality up to 25 years in women aged 40-59 who did or did not undergo mammography screening.

Design Follow-up of randomised screening trial by centre coordinators, the study’s central office, and linkage to cancer registries and vital statistic databases.

Introduction

Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available. Overall, 22% (100/468) of screen detected invasive breast cancers were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who resolved mammography screening in the trial.
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>Screening period (5 years)</td>
<td>Cases</td>
<td>666</td>
</tr>
<tr>
<td></td>
<td>Deaths (over 25 y)</td>
<td>180</td>
</tr>
<tr>
<td>Entire study period (25 years)</td>
<td>Cases</td>
<td>3250</td>
</tr>
<tr>
<td></td>
<td>Deaths (over 25 y)</td>
<td>500</td>
</tr>
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The Canadian Trial

- A stop-screen trial comparing
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- 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

- 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
Breast Cancer Screening in Denmark
A Cohort Study of Tumor Size and Overdiagnosis

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

Cancers larger than 2cm

screening areas

non-screening areas
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:

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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.
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
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
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: 0.4% per year

Trends in younger men do not match trends in older men.
What if we could get a better background trend?

Denmark provides a natural experiment

- Organized screening program (Ages 50-69) began in some areas in 1991-1994
- 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
Estimates of overdiagnosis from the Danish study

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 screen-detected cases
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.
The Latest Study On Breast Cancer Overdiagnosis Fails To Persuade

Yesterday's health news delivered another paper slamming mammography. A report out of Denmark uses statistics to show that overdiagnosis is incredibly frequent. An

“It’s simply not valid to cherry-pick findings of non-randomized studies to support one’s views.”
What about clinical trials of screening?

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

*Most 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:

- **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

IT’S TIME TO RETHINK EARLY CANCER DETECTION

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 a double-edged sword.

While it’s clear that early-stage cancers are more treatable than those detected later, the widespread use of screening tests means many cancers are found before they have the potential to cause harm—some even before they are truly cancerous. This practice has led some experts to call for changes in how we think about cancer risk and detection.

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

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 30 years didn’t have cancer after all.

Overdiagnosis—the detection of tumors that aren’t likely to cause harm—is a hot topic in other cancers as well. A growing volume of studies estimate that as many as 90% of recently diagnosed breast cancers—18%


Ductal carcinoma in situ is the early, non-invasive 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.
Screening and Prostate-Cancer Mortality in a Randomized European Study

Prostate cancer incidence in ERSPC

“Cumulative Excess incidence; Continued-screen trial”

<table>
<thead>
<tr>
<th></th>
<th>Cumulative Incidence at 9 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened arm (Screen-detected)</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 excess incidence from trials like the ERSPC

- **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!**
So how many prostate cancers are overdiagnosed?

**Lead Time and Overdiagnosis in Prostate-Specific Antigen Screening: Importance of Methods and Context**

Gerrit Draisma, Ruth Etzioni, Alex Tsodikov, Angela Mariotto, Elisabeth Wever, Roman Gulati, Eric Feuer, Harry de Koning

<table>
<thead>
<tr>
<th>Overdiagnosed cases as percent of</th>
<th>MISCAN</th>
<th>FHCRC</th>
<th>UMICH</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases detected</td>
<td>18.6</td>
<td>11.9</td>
<td>8.6</td>
</tr>
<tr>
<td>Screen-detected cases</td>
<td>42.0</td>
<td>28.0</td>
<td>22.9</td>
</tr>
</tbody>
</table>

*JNCI 2009*
So how many breast cancers are overdiagnosed?

- We still don’t have a clear answer
  - Estimates based on excess incidence are generally inflated
- Some statistical modeling studies
  - Try to learn about latent preclinical duration and lead time from incidence trends
  - Infer overdiagnosis rates based on lead time
  - Sensitive to modeling assumptions
  - Data inadequate to get sharp estimates

- Our best estimate at this time:
  - About 10-15% of cancers detected
- Likely much higher for DCIS cases
7. Ovarian cancer screening doesn’t work
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

MMS: Multi-modal screening using CA-125
USS: ultrasound screening

MMS uses ROCA algorithm – learns by observing serial CA125 trajectories over time

15% reduction in risk of ovarian cancer death in MMS arm compared to no screening (p=0.1)
Understanding the UKTOCS trial

ROCA (Risk Of CAncer) algorithm

- Triages women to diagnostic follow-up on the basis of their evolving CA-125 trajectories
- Takes time to classify a woman into high-risk or normal-risk and to refer to biopsy
- Incidence pattern shows that expected excess incidence in screened group only emerges after 7 years

Graph showing ovarian cancer mortality rate per 100,000 women-years over time since randomisation (years).
8. New blood-based screening tests are going to solve all of our problems
Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen, 1,2,3,4,5 Lu Li, 6 Yuxuan Wang, 1,2,5,4 Christopher Thoburn, 3 Bahman Afsari, 7 Ludmila Danilova, 7 Christopher Douville, 1,2,3,4 Ammar A. Javed, 8 Fay Wong, 1,3,4 Austin Mattox, 1,2,3,4 Ralph. H. Hruban, 3,4,9 Christopher L. Wolfgang, 9 Michael G. Goggins, 3,4,9,10,11 Marco Dal Molin, 4 Tian-Li Wang, 5,9 Richard Roden, 3,9 Alison P. Klein, 3,4,12 Janine Ptak, 1,2,3,4 Lisa Dobbins, 1,3,4 Joy Schaefer, 1,3,4 Natalie Silliman, 1,2,3,4 Maria Popoli, 1,3,4 Joshua T. Vogelstein, 12 James D. Browne, 14 Robert E. Schoen, 15,16 Randall E. Brand, 15 Jeannie Tie, 17,18,19,20 Peter Gibbs, 17,18,19,20 Hui-Li Wong, 17 Aaron S. Mansfield, 21 Jin Jen, 22 Samir M. Hanash, 23 Massimo Falconi, 24 Peter J. Allen, 25 Shibin Zhou, 1,3,4 Chetan Bettegowda, 1,3,4 Luis A. Diaz Jr., 1,3,4 Cristian Preda, 1,3,4 Bert Vogelstein, 1,2,3,4,† Anne McCall

Earlier detection is key to reducing deaths caused by cancer. For those patients with late-stage cancers, surgery is often the only option to slow the progression of cancer and can detect eight common cancers (lung, prostate, breast, colon, stomach, ovary, pancreas, and esophagus) for which there are no screening tests available. The sensitivity of CancerSEEK was greater than 99% for the detection of five cancer types for which there are no screening tests available... The specificity of CancerSEEK was greater than 99%: only 7 of 812 healthy controls scored positive. In addition, CancerSEEK localized the cancer to a small number of anatomic sites in a median of 83% of the patients.
Sensitivity and specificity

- Sensitivity is the ability of the test to pick up a cancer if it is there
- Specificity is the ability of the test to not pick up a cancer if it is not there
- If the condition is rare is it enough to have a pretty **sensitive** and **specific** test?

- Cases with + test result
- Non cases with + test result

**ALL CASES**

Individuals with + results

Only 50% have disease

One of two biopsies is unnecessary!

*Rarest cancers need extremely high specificity e.g. 99.6% for ovarian cancer!*
Promise and challenge of liquid biopsies for early detection

- Much excitement about liquid biopsies for early detection of rare cancers
  - Tests need to be extremely specific
  - Even a test that performs reasonably well may not be useful for population screening
  - In early disease setting may not be enough circulating tumor DNA

- Same DNA mutations span multiple cancers
  - May be challenging to localize the cancer
  - Pan-cancer test sounds nice but does it make sense?

- Confirmatory diagnostics for very early cancers need to be developed
  - May not be able to visualize the tumor even if can localize it
Critiques of CancerSEEK study

Study not properly designed to address value for early detection

- Cases had already been diagnosed with cancer – not an early detection setting
- Cases stage I-III, only 40% of stage I patients detected by test; report cites overall 70%
- Unclear where control samples were from and whether they had been handled similarly to cases
Review

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. Ovarian cancer screening doesn’t work   T   F
8. New blood-based screening tests are going to solve all of our problems   T   F
Take home messages

- 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 judgements – beware the byline

- That overdiagnosis exists is a fact
  - Most studies of overdiagnosis are biased and give inflated results
  - Overdiagnosis does not mean a test is not efficacious

- Even the most efficacious test will not save all lives
  - Historic bar for efficacy – 20-30% reduction in disease-specific deaths (not all-cause deaths)
  - The absolute number of lives saved per 1000 screened is limited by the number of deaths without screening