Evidence, opinion and fact in cancer screening and prevention

Ruth Etzioni PhD
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Cancer screening and prevention
Where does evidence about cancer screening and prevention come from?

1. Clinical trials
2. Cancer trends
3. Observational studies
Where does evidence about cancer screening and prevention come from?

1. Clinical trials

   *DO NOT ALWAYS AGREE*

2. Cancer trends

3. Observational studies
Ten 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.\(^3\) RR = relative risk. Malmo II is excluded because follow-up of about 13 years was not available; the Swedish Two County (Kopparberg and Ostergotland) and Canada I and II trials are split into their component parts; the Edinburgh trial is included because of severe imbalances between randomised groups. Weights are from random-effects analysis.
European prostate cancer screening trial

Cumulative deaths in screen and control groups

20% reduction
US prostate cancer screening trial
Cumulative deaths in screen and control groups

Screening group
Control group

0% reduction
UK prostate cancer screening trial

*Cumulative deaths in screen and control groups*

![Graph showing cumulative deaths in screen and control groups with a 9% reduction in the screening group.](image-url)
Where does evidence about cancer screening and prevention come from?

1. Clinical trials
2. Cancer trends *HAVE MULTIPLE EXPLANATIONS*
3. Observational studies
Breast and prostate cancer mortality in the US

1990-2010
43% drop

1990-2010
34% drop

screening starts

Screening starts
Prostate and breast cancer treatment trends

Prostate Cancer
Increase in curative treatment

Breast Cancer
Increase in adjuvant chemotherapy

Conservative management

RP: radical prostatectomy
RT: radiation therapy
ADT: hormone therapy
Colorectal cancer incidence in young people

The New York Times

Colon and Rectal Cancers Rising in Young People
Where does evidence about cancer screening and prevention come from?

1. Clinical trials
2. Cancer trends
3. Observational studies

FACTORS OTHER THAN THE ONES STUDIED MAY ACTUALLY EXPLAIN THE RESULTS
Plan for today

• Review some opinions and facts about cancer screening and prevention
• In each case
  • Explain the basis for the observation
  • Decide whether it is defensible or not
• Objectives
  • Learn about pitfalls when evaluating cancer screening and prevention
  • Come away better equipped to read about screening and prevention
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 doesn’t save lives
4. Breast cancer screening doesn’t work because advanced-stage incidence is flat
5. 30% of breast cancers and 60% of prostate cancers are overdiagnosed
6. Ovarian cancer screening doesn’t work
7. New blood-based screening tests are going to solve all of our problems
8. Excess body weight causes cancer
9. Alcohol consumption increases your chance of getting breast and some other cancers
10. Women with dense breasts have a greater risk of getting breast cancer
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 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)
A fact 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 the most reliable sources of evidence about screening benefit
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

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

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

**Timing of the trial**
- Screening, biopsy and treatment technologies available
- Follow-up duration
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>1–9</td>
<td>189</td>
<td>274</td>
<td>0.31</td>
<td>0.37</td>
</tr>
<tr>
<td>8–9</td>
<td>71</td>
<td>118</td>
<td>0.58</td>
<td>0.78</td>
</tr>
<tr>
<td>10–11</td>
<td>56</td>
<td>111</td>
<td>0.57</td>
<td>0.92</td>
</tr>
<tr>
<td>1–11</td>
<td>245</td>
<td>385</td>
<td>0.35</td>
<td>0.44</td>
</tr>
<tr>
<td>≥12</td>
<td>54</td>
<td>77</td>
<td>0.94</td>
<td>1.16</td>
</tr>
<tr>
<td>Total</td>
<td>299</td>
<td>462</td>
<td>0.39</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Y 1-9: 15% reduction
Y10-11: 38% reduction
"Trial duration and timing of analysis matter greatly."
An ovarian cancer screening trial

**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)
3. Prostate cancer screening doesn’t save lives
Prostate cancer trials: key differences in execution

<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 for 5 years</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>Only 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>

Prostate cancer trials: more similar than they appear

PSA screening as conducted in the trials reduced prostate cancer mortality by 25-32% compared with no screening

Tsodikov et al, Annals of Internal Medicine 2018
For men who are weighing the pros and cons of prostate cancer screening, a new study strengthens the evidence that testing can reduce deaths from this cancer, something two earlier large landmark clinical trials appeared to reach different conclusions about.

Despite ongoing debate over the value of prostate cancer screening, a new review says it can indeed reduce a man’s risk of dying from the disease.

Early tumor detection using the prostate-specific antigen (PSA) blood test lowers a man’s risk of prostate cancer death by 25 percent to 32 percent, the new analysis of two major trials of PSA testing found.
4. 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

Autier P et al,
JCO 2009 Dec 10
Breast Cancer Screening in Denmark
A Cohort Study of Tumor Size and Overdiagnosis

March 7 2017
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?
True background trend increasing?
5. 30 percent of breast cancers and 60 percent of prostate cancers are overdiagnosed
JOURNAL REPORT

HEALTH CARE

THE WALL STREET JOURNAL

Monday, September 15, 2014

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   Breast   Thyroid   Skin   Lung
60%       30%      90%       90%     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 RECK

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.

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 detected breast cancers—38%

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.
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
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

*Two ways to estimate overdiagnosis*

- Lead time approach – first calculate the lead time then infer overdiagnosis
- Excess incidence – incidence with minus incidence without screening
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

Incidence in women 40 and older
By calendar year and stage

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 – 31% of all cancers

In 2008, 31% of breast cancers were overdiagnosed.
Questioning the background trend
Trends in Testicular Cancer Incidence

Trends in younger men do not match trends in older men.
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); MD Anderson Cancer Center (Thyroid); American Academy of Dermatology (Skin); JAMA Internal Medicine (Lung)

Early cancer 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 later-stage ones, other experts argue that zealous screening too often leads to overtreatment. They call for changing the way we even talk about the disease.
Screening and Prostate-Cancer Mortality in a Randomized European Study

Prostate cancer incidence in ERSPC

- **Screened arm (Screen-detected)**: 8.2% (5.8%)
- **Control arm**: 4.8%
- **Excess**: 8.2% - 4.8% = 3.4%
- **Excess/screen-detected**: 3.4/5.8 = 58%

*Schroeder et al*  
*NEJM 2009*  
*Prostate cancer incidence in ERSPC*
The problem with excess incidence in the ERSPC

- What we know
  Cases diagnosed during the trial reflect cases that would have been diagnosed both during and after the trial in the absence of screening

- Continued screen trial stops counting cases in the screen and control groups at the same time!
The problem with excess incidence in the ERSPC

In this setting cumulative excess incidence will always be greater than zero even if there is NO overdiagnosis!
So how many prostate cancers are overdiagnosed?

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean lead time (years)</th>
<th>Overdiagnosis (percent of screen detected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telesca Biometrics 2008</td>
<td>4.6 (white men)</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>6.8 (black men)</td>
<td>34%</td>
</tr>
<tr>
<td>Draisma JNCI 2009</td>
<td>5.9</td>
<td>28%</td>
</tr>
<tr>
<td>Gulati CEBP 2012</td>
<td></td>
<td>4% age 50-54 with high grade, high PSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70% age 75-79 with low grade, low PSA</td>
</tr>
</tbody>
</table>

All estimates based on prostate cancer incidence in the US assuming incidence would have been flat without PSA.
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 lead time from incidence trends
  • Infer overdiagnosis rates based on lead time
  • Sensitive to modeling assumptions
  • Data inadequate to get sharp estimates if we allow that some cancers don’t progress

• Our best estimate at this time:
  • About 10-15% of cancers detected
  • Likely higher for DCIS cases

Annals of Internal Medicine
Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies
Jeane S. Mandelblatt, MD; Natasha K. Stout, PhD; Cyide B. Schechter, MA, MD; Jereen J. van den Broek, MS; Diana L. Miglioretti, PhD; Martin Krapcho, BS; Amy Trentham-Dietz, PhD, MS; Diego Munoz, PhD, MS; Sandra J. Lee, ScD; Donald A. Berry, PhD; Nicolien T. van Ravesteyn, PhD; Oguzhan Aлагوز, PhD; Karla Kerlikowske, MD; Anna N.A. Tosteson, ScD; Aimee M. Noor, MPH; Amanda Hoeflken, MPH; Yajiong Chang, DrPH, MS, MPH; Eveline A. Heijnsdijk, PhD; Gary Chisholm, MS; Xuelin Huang, PhD; Hui Huang, MS; Mehmet Ali Ergun, MSc; Ronald Gangnon, PhD; Brian L. Sprague, PhD; Sylvia Plevritis, PhD; Eric Feuer, PhD; Harry J. de Koning, MD, PhD; and Kathleen A. Cronin, PhD, MPH

2016
6. 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

Summary
Background Ovarian cancer has a poor prognosis, with just 40% of patients surviving to establish the effect of early detection by screening on ovarian cancer mortality.

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

• It is likely that those women diagnosed early had shorter lead times than those referred later
7. New blood-based screening tests are going to solve all of our problems
The sensitivities ranged from 69 to 98% for the detection of five cancer types for which there are no screening tests available...

The specificity of CancerSEEK was greater than 99%
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

Excitement about liquid biopsies for early detection of rare cancers but
• Tests need to be extremely specific – almost not false positive tests
• 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

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
8. Excess body weight causes cancer
Excess weight and cancer risk

Body Fatness and Cancer — Viewpoint of the IARC Working Group

Proportion of Cancer Cases Attributable to Excess Body Weight by US State, 2011-2015

Farhad Islami, MD, PhD; Ann Goding Sauer, MSPH; Susan M. Gapstur, PhD; Ahmedin Jemal, DVM, PhD

Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk
A Secondary Analysis of the Women’s Health Initiative Randomized Clinical Trials

Excessive Weight Gain, Obesity, and Cancer Opportunities for Clinical Intervention

Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults
Excess weight and cancer risk

• Many studies point to an association between excess weight and cancer risk
• Several cohort studies have long-term information on BMI and cancer
  • Women’s Health Initiative
  • Nurses Health Study
  • Cancer Prevention Study II
• Studies differ in timing of BMI measurements
  • Concurrent with diagnosis
  • Prior to diagnosis

<table>
<thead>
<tr>
<th>Cancer Site or Type</th>
<th>Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus: adenocarcinoma</td>
<td>4.8 (3.0–7.7)</td>
</tr>
<tr>
<td>Gastric cardia</td>
<td>1.8 (1.3–2.5)</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1.3 (1.3–1.4)</td>
</tr>
<tr>
<td>Liver</td>
<td>1.8 (1.6–2.1)</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>1.3 (1.2–1.4)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.5 (1.2–1.8)</td>
</tr>
<tr>
<td>Breast: postmenopausal</td>
<td>1.1 (1.1–1.2)§</td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>7.1 (6.3–8.1)</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.1 (1.1–1.2)</td>
</tr>
<tr>
<td>Kidney: renal-cell</td>
<td>1.8 (1.7–1.9)</td>
</tr>
</tbody>
</table>
All of these studies are observational

• Studies show association but not causation
  • Excess weight affects estrogens and insulin but more research needed

• Other factors not accounted for may explain finding
  • Health seeking behaviors may differ by BMI
  • Screening tests may have different performance by BMI

• Story is likely more complicated than it appears
  • But there is a tendency to oversimplify
The disturbing links between too much weight and several types of cancer

Being obese and overweight — long implicated in heart disease and diabetes — has been associated in recent years with an increased risk of getting at least 13 types of cancer, including stomach, pancreatic, colorectal and liver malignancies, as well as postmenopausal breast cancer.

Most alarming, young people, who as a group are heavier than their parents, are developing weight-related malignancies, including colorectal cancer, at earlier ages than previous generations, experts say.
Can increasing BMI explain colorectal cancer trends in younger cases?

Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry

Hyuna Sung, Rebecca L. Siegel, Philip S. Rosenberg, Ahmedin Jemal

• Studied 12 “obesity-related cancers” and 18 other cancers
• For 6 of 12 “obesity-related cancers” estimated incidence was increasing at younger ages
  • Multiple myeloma, colorectal, uterine, kidney, gallbladder, pancreas
• For 5 of the 6, estimated incidence was also increasing at older ages
  • All except colorectal
“Sung and colleagues did not comment on why only some obesity-related cancers, and not all 12, showed temporal trends of markedly rising younger adult incidence, or why some obesity-related cancers appeared to have declining rather than increasing incidence in the older age groups. Such observations could reflect varying influences of other risk factors across such cancer types and age groups, and warrant further investigation.”
9. Alcohol consumption increases your chance of getting breast and some other cancers
Alcohol and cancer risk

• Many studies point to an association between drinking and cancer risk
• Recent studies have shown an increase in risk even with very modest intake
• Some biological basis for the link
• Questions about
  • Which is the best measure of alcohol consumption?
  • What is the timing that matters most?

Some alcohol-related cancers

- Liver
- Esophagus
- Throat
- Breast
- Colorectal
Could increased alcohol consumption at younger ages explain colorectal cancer trends?
All of these studies are observational

• All of these studies are observational
• Alcohol consumption is usually self-reported
  • Many people understate their alcohol intake
  • Reports of modest intake could reflect higher consumption
• Have to balance effect of alcohol on cancer risk with effect on general health
  • Positive effects of modest intake on cardiovascular disease
  • Known beneficial effects of red wine
Review

1. Most screen-detected cases are not saved by screening  T F
2. Clinical trials are the most reliable sources of evidence about screening benefit  T F
3. Prostate cancer screening doesn’t save lives  T F
4. Breast cancer screening doesn’t work because advanced-stage incidence is flat  T F
5. 30% of breast cancers and 60% of prostate cancers are overdiagnosed  T F
6. Ovarian cancer screening doesn’t work  T F
7. New blood-based screening tests are going to solve all of our problems  T F
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