Demystifying Cancer Screening: Science versus Intuition

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National Cancer Institute
Division of Cancer Prevention
In the field of cancer screening, “It is particularly important to be able to sort out what is known versus what makes sense....”

Daniel Wolpaw
Medical Clinics of North America, 1996
Nearly a Century of Enthusiasm for Cancer Screening

"Dr. Bloodgood of Johns Hopkins declares elimination [of cancer] almost sure in early stage."

“Deaths from cancer would be practically eliminated...if persons afflicted sought medical aid immediately upon the discovery of a foreign growth in any part of the body.”
If you haven’t had a mammogram, you need more than your breasts examined.

A mammogram is a safe, low-dose X-ray that can detect breast cancer before there’s a lump. In other words, it could save your life and your breast.

If you’re a woman over 35, be sure to schedule a mammogram. Unless you’re still not convinced of its importance.

In which case, you may need more than your breasts examined.

Find the time.
Have a mammogram.

AMERICAN CANCER SOCIETY
Give yourself the chance of a lifetime.
"It would never happen to me. I've got bigger things to worry about, like homework, friends and all the cute upper classmen."

Rachel Kramer, 14, the day before she was diagnosed with thyroid cancer.

Confidence kills. Thyroid cancer doesn't care how old you are. It can happen to anyone. Including you or your child. That's why it's the fastest increasing cancer in the U.S. Ask your doctor to check your neck. It could save your life.
Levels of Decision Making

Level I: “Would you have this done for yourself or for someone else in your immediate family?”
Influenced by one’s personal experience with the disease and capacity to deal with risk.
Affects few people.

Level II: “What would I recommend to my patient/client?”
Physician making a recommendation for his/her patients.
Influenced by prior experience, but the scientific evidence may play a greater role.
Affects possibly hundreds of people.

Level III: “What would I recommend to the nation, the world?”
Across-the-board recommendations for a population.
Must be based on rigorous assessment of the scientific evidence.
Affects hundreds of thousands, even millions of people.
Core Issues in Screening and Prevention

- It is difficult to make healthy people better off than they already are.

- Strong evidence of benefit is important when putting large numbers of healthy people in harm’s way.
Analytic Framework for Cancer Screening

Persons at Risk ("Healthy") → Screening → Early Cancer Detection → Intermediate Outcomes

- Surgery for cure
- Decreased late stage disease

→ Health Outcomes
- Cancer Mortality
- Overall Mortality
- Quality of Life

→ Societal Outcomes/Trade-Offs
- Healthcare Utilization
- Cost Effectiveness

Adverse Effects of Screening → Adverse Effects of Treatment
Potential Biases in Screening Studies

• Selection Bias
• Lead Time Bias
• Length Bias
Selection Bias

Potential Screenees → Screened

Why Did They Come?
## Healthy Volunteer Effect in the PLCO Trial

<table>
<thead>
<tr>
<th></th>
<th>PLCO Trial (%)</th>
<th>National Health Interview Survey (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>High school/post-high school</td>
<td>51</td>
<td>63</td>
</tr>
<tr>
<td>College degree</td>
<td>41</td>
<td>30</td>
</tr>
<tr>
<td>Medical diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>CAHD, stroke</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34</td>
<td>34</td>
</tr>
</tbody>
</table>

(P Pinsky, Am J Epi, 2007)
### Standardized Mortality Ratio in PLCO Participants

<table>
<thead>
<tr>
<th>Cause</th>
<th>Standardized Mortality Ratio (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>All non-PLCO causes</td>
<td>43</td>
<td>42-44</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>37</td>
<td>35-38</td>
</tr>
<tr>
<td>Digestive</td>
<td>34</td>
<td>30-38</td>
</tr>
<tr>
<td>Respiratory</td>
<td>34</td>
<td>31-36</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28</td>
<td>24-31</td>
</tr>
<tr>
<td>Injuries and poisoning</td>
<td>64</td>
<td>58-70</td>
</tr>
<tr>
<td>All non-prostate, lung, colorectal or ovarian cancers</td>
<td>56</td>
<td>54-59</td>
</tr>
</tbody>
</table>

(P Pinsky, Am J Epi, 2007)
Length Biased Sampling

Test

Rapidly progressive

→ Dx → Dx → Dx → Dx

Slowly progressive

→ Dx → Dx → Dx → Dx → Dx → Dx → Dx
Overdiagnosis

- Cancer
  - Screened and “cured”
  - Death unrelated to cancer
- Never screened
Requirements for Overdiagnosis

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)

From G. Welch and W. Black, JNCI 2010
The Heterogeneity of Cancer Progression

- Size at which cancer causes symptoms
- Size at which cancer causes death
- Abnormal cell

Time

Death from other causes

This is over-Dx.

(Courtesy of H. Gilbert Welch, Dartmouth)
Evidence of Melanoma Overdiagnosis in the Medicare Population

G. Welch, BMJ, 2005
The Prostate Cancer Pseudo-Epidemic in the U.S

New Prostate Cancer Cases and Deaths (per 100,000 men)


TURP era

PSA era

Over 1 million men who would not have been diagnosed in 1973

(G. Welch, “Should I Be Tested for Cancer?”, 2004)
U.S. Prostate Cancer Incidence vs. Mortality Over-Diagnosis

New Prostate Cancer Cases and Deaths (per 100,000 men)

- New Cases
- Deaths

From: Welch, "Should I Be Tested for Cancer?", 2004
Use of Screening Mammography and Incidence of Stage-Specific Breast Cancer in the U.S., 1976–2008

Incidence and Mortality of Five Cancers:
(Surveillance, Epidemiology, and End Results: SEER)

- Thyroid Cancer
- Prostate Cancer
- Melanoma
- Breast Cancer
- Kidney Cancer

Source:
HG Welch,
JNCI 2010
Current Challenge with Cancer Screening

Predicting whether lesions that are detected by sensitive screening tests are indolent (hence, not requiring immediate treatment) or progressive and potentially life-threatening
Strategies to Investigate Overdiagnosis

Annotate collected specimens with method of diagnosis

- Molecular patterns of screen-detected cases are enriched with overdiagnosed cases
- Molecular patterns of true interval cases are enriched with aggressive cases that we need to prevent (and target pathways for prevention)

Collect normal organ as well as the tumor

- Study cancer as a tissue-level, not simply a cell-based, disease
- Examples: prostate, breast, esophageal, melanoma
Analytic Framework for Cancer Screening

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Intermediate Outcomes
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Health Outcomes
- Cancer Mortality
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Adverse Effects of Screening

Adverse Effects of Treatment
Consequences of Screening: The Good

1. Reduced risk of death from the target cancer (compared to no screening)
   • Nearly always need a randomized controlled trial to determine this

2. Reassurance (assuming healthy people need reassurance)
Consequences of Screening: The Bad

1. False reassurance when you have cancer
2. False alarms (false positive tests)
   • Harms of an unnecessary work-up
3. Harms of the test: bleeding, sepsis after biopsy, etc.
4. Detection of a lethal cancer without changing the outcome
   • Spend more of your life as a cancer patient
5. Detection of non-lethal cancers (over-diagnosis)
   • Unnecessary treatment
   • Treatment-related deaths of other causes (e.g., heart disease, secondary cancers)
How can we communicate the complexities of cancer screening to the public?
### Study Findings: Low-dose CT versus Chest X-ray screening

53,454 current and former smokers were randomly assigned to be screened once a year for 3 years with low-dose CT or chest X-ray. Here's what happened after an average of 6.5 years:

<table>
<thead>
<tr>
<th>Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?</th>
<th>Low-dose CT 26,722 people</th>
<th>Chest X-ray 26,732 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 in 1,000 fewer died from lung cancer</td>
<td>13 in 1,000</td>
<td>versus</td>
</tr>
<tr>
<td>5 in 1,000 fewer died from all causes</td>
<td>70 in 1,000</td>
<td>versus</td>
</tr>
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<table>
<thead>
<tr>
<th>Harm: What problems did CT scans cause compared to chest X-ray?</th>
<th>Low-dose CT 26,722 people</th>
<th>Chest X-ray 26,732 people</th>
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<tr>
<td>223 in 1,000 more had at least one false alarm</td>
<td>365 in 1,000</td>
<td>versus</td>
</tr>
<tr>
<td>18 in 1,000 more had a false alarm leading to an invasive procedure, such as bronchoscopy, biopsy, or surgery</td>
<td>25 in 1,000</td>
<td>versus</td>
</tr>
<tr>
<td>2 in 1,000 more had a major complication from Invasive procedures</td>
<td>3 in 1,000</td>
<td>versus</td>
</tr>
</tbody>
</table>
Benefit-Harm Trade Off for a Decade of Annual Mammography Beginning at Age 50

For every 1,000 women aged 50

**Benefit**

- 0.3-3.2 Women will avoid dying from breast cancer

**Harms**

- 490-670 Women will have at least 1 “false alarm”
- 70-100 Women with a “false alarm” will undergo a biopsy
- 3-14 Women will be overdiagnosed and treated needlessly with surgery, radiation, and/or chemotherapy

Welch, *JAMA Internal Medicine*, Dec 2013
Are there lessons for the research and health professional community?
OK, Stranger...
What's the circumference of the Earth? Who wrote "The Odyssey" and "The Iliad"? What's the average rainfall of the Amazon Basin?

Bart, you fool! You can't shoot first and ask questions later!
Benefit-Harm Trade Off for a Decade of Annual Mammography Beginning at Age 40

For every 1,000 women aged 40

**Benefit**

0.1-1.6 Women will avoid dying from breast cancer

**Harms**

510-690 Women will have at least 1 “false alarm”

60-80 Women with a “false alarm” will undergo a biopsy

7-11 Women will be overdiagnosed and treated needlessly with surgery, radiation, and/or chemotherapy

Welch, *JAMA Internal Medicine*, Dec 2013
Benefit-Harm Trade Off for a Decade of Annual Mammography Beginning at Age 60

For every 1,000 women aged 60

**Benefit**

- 0.5-4.9 Women will avoid dying from breast cancer

**Harms**

- 390-540 Women will have at least 1 “false alarm”
- 50-70 Women with a “false alarm” will undergo a biopsy
- 6-20 Women will be overdiagnosed and treated needlessly with surgery, radiation, and/or chemotherapy

*Welch, JAMA Internal Medicine, Dec 2013*