Breast cancer screening
From Data to Insight

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Importance of breast cancer and screening

- Second-leading cause of cancer death in US women
  - First is lung cancer
- Widespread use of screening and advances in treatments credited with significant reduction in mortality
Detection

- Film mammography recommended in 2002 by the USPSTF because of its adequate sensitivity (77% to 95%) and specificity (94% to 97%).

- **Sensitivity** measures the proportion of actual positives which are correctly identified as such.
  - 77% - 95% of women with breast cancer have positive mammography screening.
  - **False negatives**: 5% - 23% of women with breast cancer have negative mammography screening.

- **Specificity** measures the proportion of negatives which are correctly identified
  - 94% - 97% of women who don’t have breast cancer have negative mammography screening.
  - **False positives**: 3% - 6% of women who don’t have breast cancer have positive mammography screening.

From: [http://www.ahrq.gov/clinic/uspstf09/breastcancer/brcanup.htm](http://www.ahrq.gov/clinic/uspstf09/breastcancer/brcanup.htm)
Benefits of early detection & intervention

- Greatest benefit in women 60-69.

- Greater absolute reduction in mortality for women 50 - 75 than 40 - 49.

- For women 75 and older, evidence of benefits is lacking.

- Evidence of additional benefits of CBE and digital mammography and MRI as a replacement to film mammography is lacking.
Harms of early detection & intervention

- Psychological harms, unnecessary imaging tests and biopsies.
- Inconvenience due to false positive screening results (more common for women 40 - 49).
- **Overdiagnosis:** Treatment of cancer that would not become clinically apparent during lifetime (more common for women in older age groups).
- Unnecessary treatment of cancer that would have become clinically apparent but not have shortened life.
- Radiation exposure (minor concern).
2002 USPSTF Recommendations

- For women aged 40 and older: screening mammography, with or without CBE, every 1-2 years (grade B recommendation)

- Insufficient evidence to recommend for or against
  - routine CBE alone to screen for breast cancer (grade I statement)
  - teaching or performing BSE (grade I statement)

From: http://www.ahrq.gov/clinic/pocketgd09/gcp09s2.htm#BreastScreening
What do the USPSTF letter grades mean?

- The USPSTF's recommendations are based on its assessment of net benefit = identified benefits - identified harms.

- **A grade:** Interventions that are deemed to have substantial net benefit

- **B grade:** Interventions with moderate to substantial net benefit

- **C grade:** Interventions with small net benefit

- **D grade:** Interventions that have no net benefit (have harms that exceed the benefits)

- **I statement:** If the evidence does not meet USPSTF standards, an "I statement" is issued.
Early media coverage of proposed changes
<table>
<thead>
<tr>
<th>Film mammography</th>
<th>ACS Recommends</th>
<th>2009 USPSTF Recommendation</th>
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<tbody>
<tr>
<td>Ages 40-49</td>
<td>Yearly</td>
<td>No routine screening</td>
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<tr>
<td>Ages 50-74</td>
<td>Yearly</td>
<td>Biennial</td>
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<tr>
<td>Ages 75 and older</td>
<td>Yearly</td>
<td>Insufficient evidence to assess benefits</td>
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<tr>
<td>BSE</td>
<td></td>
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<tr>
<td>Starting in 20s</td>
<td>Recommends teaching</td>
<td>Recommends against teaching</td>
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<tr>
<td>CBE</td>
<td></td>
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<tr>
<td>20s &amp; 30s</td>
<td>Every 3 years</td>
<td>Insufficient evidence to assess benefits</td>
</tr>
<tr>
<td>40s</td>
<td>Every year</td>
<td>Insufficient evidence to assess benefits &amp; harms</td>
</tr>
<tr>
<td>DM &amp; MRI</td>
<td>N/A</td>
<td>Insufficient evidence to assess benefits &amp; harms</td>
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Based on what evidence did the USPSTF update their recommendations in November 2009?

- Systematic review of published evidence of the efficacy of five screening methods:
  1. film mammography
  2. clinical breast examination (CBE)
  3. breast self-examination (BSE)
  4. digital mammography
  5. magnetic resonance imaging (MRI)

- Two studies commissioned by the task force:
  6. a decision analysis that used population modeling techniques to compare the expected health outcomes and resource requirements of starting and ending mammography screening at different ages and using annual vs. biennial screening intervals
  7. a targeted systematic evidence review of six selected questions relating to the benefits and harms of screening
Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms

Jeanne S. Mandelblatt, MD, MPH; Kathleen A. Cronin, PhD; Stephanie Bailey, PhD; Donald A. Berry, PhD; Harry J. de Koning, MD, PhD; Gerrit Draisma, PhD; Hui Huang, MS; Sandra J. Lee, DSc; Mark Munsell, MS; Sylvia K. Plevritis, PhD; Peter Ravdin, MD, PhD; Clyde B. Schechter, MD, MA; Bronislava Sigal, PhD; Michael A. Stoto, PhD; Natasha K. Stout, PhD; Peter Ravdin, MD, PhD; Nicolien T. van Ravesteyn, MSc; John Venier, MS; Marvin Zelen, PhD; and Eric J. Feuer, PhD; for the Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network (CISNET)*

- Relative contributions of screening and treatment to observed decreases in deaths from breast cancer were evaluated under 6 different models.

- Models differ in assumptions about development of cancer, tumor growth, effect of treatment on hazard for death from breast cancer, etc.

- Evaluated 20 different screening strategies in terms of start and end age and frequency (annual / biennial), including no screening.

- Models assume 100% adherence to screening and indicated treatment.

- Cohort of women born in 1960 followed throughout entire lifetime starting at age 25.

- Benefits considered: % of reduction in BC mortality and life years gained

- Harms: False-positive mammography, unnecessary biopsies and overdiagnosis
<table>
<thead>
<tr>
<th>Metric</th>
<th>Formula</th>
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<tbody>
<tr>
<td>False-positive rate</td>
<td># of mammograms read as abnormal or needing further follow-up in women without cancer / # of positive screening mammograms</td>
</tr>
<tr>
<td>Unnecessary biopsies</td>
<td># of women with false positive screening mammograms who receive a biopsy / # of women who receive a biopsy</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td># of cases that would not have clinically surfaced in a woman’s lifetime / # of all cases arising from age 40 onwards</td>
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**Results**

In an unscreened population, the models predict a cumulative probability of breast cancer developing over a woman’s lifetime starting at age 40 years ranging from 12% to 15%. Without screening, the median probability of dying of breast cancer after age 40 years is 3.0% across the 6 models. Thus, if a particular screening strategy leads to a 10% reduction in breast cancer mortality, then the probability of breast cancer mortality would be reduced from 3.0% to 2.7%, or 3 deaths averted per 1000 women screened.

10% of 3% is 0.3%; therefore, 10% reduction in breast cancer mortality reduces the probability of dying from breast cancer from 3% to 2.7%. 

(3% - 0.3% = 2.7%)
Results from 6 models studied

The panels show an efficiency frontier graph for each model. The graph plots the average number of mammographies performed per 1000 women against the percentage of mortality reduction for each screening strategy (vs. no screening). Strategies are denoted as annual (every 2 years) or with starting and stopping ages. We plot efficient strategies (that is, those in which increases in use of mammography resources result in greater mortality reduction than the next efficient strategy) and screening strategy.

No additional gains from annual screening

Additional gains from annual screening
Conclusion

- If the goal of a national screening program is to reduce mortality in the most efficient manner, then programs that screen biennially from age 50 years to age 69, 74, or 79 years are among the most efficient on the basis of the ratio of benefits to the number of screening examinations.

- If the goal of a screening program is to efficiently maximize the number of life-years gained, then the preferred strategy would be to screen biennially starting at age 40 years.

- Decisions about the best starting and stopping ages also depend on tolerance for false-positive results and rates of overdiagnosis.

- Substantial increases in false-positive results and unnecessary biopsies associated with annual intervals, and these harms are reduced by almost 50% with biennial intervals.
In 2008, an estimated 182,460 cases of invasive and 67,770 cases of noninvasive breast cancer were diagnosed, and 40,480 women died of breast cancer.

Incidence increases with age, and the probability of a woman developing breast cancer is 1 in 69 in her 40s, 1 in 38 in her 50s, and 1 in 27 in her 60s.

Incidence has stabilized in recent years and mortality has decreased since 1990 because of many factors, including screening.

In 2005 in the US, 68% of women aged 40 to 65 years had screening mammography within the previous 2 years.
Data & Methodology

‣ Systematic review of published studies.
  ‣ Randomized controlled trials, updates to previously published trials of screening with mammography (film and digital), MRI, CBE, or BSE with breast cancer mortality outcomes published since 2001.
  ‣ Meta-analyses that included studies with breast cancer mortality data, including controlled trials and systematic reviews.

‣ Meta-analysis:
  ‣ The statistical analysis of a large collection of analysis results for the purpose of integrating the findings.
  ‣ The basic purpose of meta-analysis is to provide the same methodological rigor to a literature review that we require from experimental research.

Results

- Breast cancer mortality is reduced for women of all age groups from 39 to 69 years with mammography screening.

- False-positive results are common in all age groups and lead to additional imaging and biopsies.

- Women aged 40 to 49 years experience the highest rate of additional imaging, whereas their biopsy rate is lower than that for older women.

Mammography screening at any age is a tradeoff of a continuum of benefits and harms. The ages at which this tradeoff becomes acceptable to individuals and society are not clearly resolved by the available evidence.
Based on the results of these studies, do you think the recommendations made by the USPSTF were reasonable?

*but before you answer,*

*here is a breast cancer survivor’s response...*
Once again, based on the results of these studies, do you think the recommendations made by the USPSTF were reasonable?

and what do you think about the news piece we just watched?
Understanding the USPSTF

- Independent, apolitical body established in 1984
- Issued recommendations on numerous topics from depression to exercise counseling
- Recommendations derived by weighing the benefits and harms to patients; costs and coverage issues are ignored
- Receives administrative support from the government but carries no official status
- Does not advise insurers
- Does not involve topic experts in order to keep the analysis objective

From: Woolf (2010)
Why the strong reaction to new recommendations?

- Woolf (2010) claims that the new recommendations were misunderstood due to poor wording:
  - The USPSTF recommends against *routine* screening mammography in women aged 40 to 49 years. The decision to start should be an individual one and take patient context into account, including the patient’s values regarding specific benefits and harms.
  - Panel did not oppose mammography but recommended against *automatic* routine screening.
  - In 2002 panel had recommended routine screening started at age 40 but urged clinicians to inform patients about the reduced net benefit at younger ages; this was largely ignored in practice.
So the real question is...

- Should hundreds of women endure the consequences of inaccurate mammograms to save one woman’s life?

- USPSTF did not answer this subjective question and left the decision to patients and their physicians.

- Should the government get involved and make recommendations?
But the statement also said mammography can “miss cancers that need treatment, and in some cases finds disease that does not need treatment.”

More research is needed to figure out which kind of tumor a patient has.

- Note that biopsies can tell if a tumor is benign or not, but they can’t predict the growth rate of the tumor.

Women should try to get a sense of their own risk.

- Women who have a strong family history of breast cancer or a mutation in a gene called BRCA, which greatly increases the risk, may benefit from early screening or even medication to lower the risk.

- Other risk factors: dense tissue, hormone therapy, biopsies, no pregnancies before age 30, mother or sister with BC and aging.
Researchers disagree

- Dr. Susan Love: “Boy, everybody was afraid to go there, like it was the third rail,” she said, adding: “I really don’t think we should be routinely screening women under 50. There’s no data showing it works.”

- Dr. Larry Norton: “Say someone fires a gun at you, and you know that there is a 30 percent chance that the bullet is a blank. Do you not still duck?”

Is it as simple as that?
Let’s revisit the data and the studies behind the USPSTF recommendations…
Behind Cancer Guidelines, Quest for Data

By GINA KOLATA

- One way of looking at cancer is as three different diseases:

  1. Grows so fast that early diagnosis is futile.

  2. Grows so slowly it does not need to be found early to be cured - as many as a quarter of those slowing-growing cancers would not be noticed in a woman’s lifetime.

  3. Can be cured if they are caught early - makes up only 15 percent of the deadly cancers.

- Overdiagnosis rate: 6% to 50% - interval too large to be accurate

- Screening rate:
  - Study indicated there is almost no benefit to screening women in their 40s and that women can be screened every two years instead of annually.
  - Author of study thought the task force would not dare to embrace the new findings.

Why is it considered “daring” to make objective recommendations based on scientifically solid studies?
What did the government officials actually say?
Congressional hearing
Lessons learned

On December 4, 2009, the USPSTF unanimously voted to update the language of their recommendation regarding women under 50 years of age to clarify their original and continued intent.

"So, what does this mean if you are a woman in your 40s? You should talk to your doctor and make an informed decision about whether mammography is right for you based on your family history, general health, and personal values."

Diana Petti, MD, MPH
Vice Chair, U.S. Preventive Services Task Force
November 19, 2009

From: http://www.ahrq.gov/clinic/uspstf/uspsbrca.htm
Benefits and harms

- Benefits are easily agreed upon:
  - “Take the test not the chance.”
  - 87% of 500 US adults surveyed said they think screening is a good idea and that they would overrule a physician's recommendation against it.

- Harms are a little more complicated:
  - Screening reduces the chance of breast cancer from about 3.5 in 1000 to 3.
  - For most women with cancer, screening generally does not change the ultimate outcome; the cancer is usually just as treatable or deadly regardless of screening.
  - Overdiagnosis: Studies find that 2-10 women are overdiagnosed for every breast cancer death avoided,
Woolf, Woloshin and Schwartz agree ...

- Scientific panels on controversial topics should gauge public sensibilities and communicate clearly and outline harms and benefits in a manner that is easy for the public to understand.

- Society needs a forum for intelligent public debate, a challenge in today’s media environment.

- Independent panels should not be influenced by politics, and the public should safeguard the efforts of independent panels even if they disagree with the conclusions.
More on media coverage of the issue
Gov't Says No Mammograms Needed For Women Under 50

Celeb Survivors Protest Breast Cancer Screening Guidelines
Olivia Newton-John, Jaclyn Smith, and Sheryl Crow Express Concern

Former NIH chief: Ignore new mammogram guideline

Melissa Etheridge Addresses Mammogram Controversy

GOP Rep. on Mammograms: "This Is How Rationing Begins"
Some lawmakers on Capitol Hill are blasting new guidelines from a government task force that recommends against routine mammograms for women under 50, questioning whether they are tantamount to health care "rationing" in the fight against the No. 2 cancer killer in U.S. women.

"I absolutely believe this could be a form of rationing," said Rep. Phil Gingrey, R-Ga, a practicing obstetrician and gynecologist for 26 years. "It scares me."
Let’s turn to the *real* experts...
Back to the stats...
The answer, of course, is that they would cause more harm than good. Alas, it’s not easy to weigh the dangers of mammograms, the invasiveness of biopsies (some of them minor operations) and the aggressive and debilitating treatment of slow-growing tumors against the cumulative effects of radiation from dozens of relatively harmless tumors that would never prove fatal.

As we now know, the panel of scientists advised that routine screening for asymptomatic women in their 40s was not warranted and that more screening is always better leads us to note that if screening catches the breast cancers of some asymptomatic women in their 40s, then it would also catch those of some asymptomatic women in their 30s. But why stop there? Why not monthly mammograms beginning at age 15?

Much of our discomfort with the panel’s findings stems from a basic intuition: since earlier and more frequent screening increases the likelihood of detecting a possibly fatal cancer, it is always desirable. But is this really so? Consider the technique mathematicians call a little vignette with made-up numbers may shed some light. Assume there is a screening test for a small fraction of the population (say, 1% of asymptomatic women age 30–49), the test is highly accurate (95% of those with breast cancer are correctly identified as such, while only 5% of those without the disease are diagnosed as having it), and let’s also assume that if someone doesn’t have the cancer, the test will be certain cancer that is 95 percent accurate; that is, if someone has the cancer, the test will be positive 95 percent of the time. Let’s also assume that if someone doesn’t have the cancer, the test will yield a false positive 5 percent of the time.

Of the 100,000 women tested, 500 will have breast cancer, and the screening test will yield 475 true positives and 25 false positives. Of the 99,500 women who don’t have cancer, the test will render 1,470 false positives. Thus, if the test were 100% accurate, 475 of the 1,470 positive results would be positive for cancer, giving a positive predictive value of 475/1,470 = 32%, which is the desired rate of true positives.

By contrast, if the test did not work as well (false positives were 10% of asymptomatic women), the positive predictive value would be 75/147 = 51%, which is still a desirable rate. However, if the test were 50% reliable (false positives were 50% of asymptomatic women), the positive predictive value would be 20/147 = 13%, which is still a desirable rate. In fact, if the test worked exactly backwards (false positives were 95% of asymptomatic women), the positive predictive value would be 5/147 = 3%, which is still a desirable rate. This is a reminder that no screening test is perfect and that a positive result may not mean cancer is present.

John Allen Paulos is the author of several books, including "I Think Therefore I Funny." He is a professor of mathematics at Temple University in Philadelphia and a member of the American Mathematical Society and the Mathematical Association of America. His column appears twice monthly in The New York Times. The recent brouhaha over the guidelines put forth by the government task force on embryonic stem-cell lines has partly occurred, as evidenced by this month’s release of 13 new human embryonic stem-cell lines. The promise was to restore science to its “rightful place.” This promise was met by a response that was furious. Fortunately, both the panel’s concerns and the public’s reaction to its recommendations may be better understood by delving into the what they say is complex, counterintuitive or ambiguous.