To Seek, to Find, but Not to Yield:
The New Mammography Guidelines

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Objectives

- Review the USPSTF guidelines on routine screening mammography

- Determine when we should follow the guidelines...and how to explain them to patients

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Death (to mammograms) Panel?

- U.S. Preventive Services Task Force
- Independent panel of experts in prevention and primary care
- Appointed by the Department of Health and Human Services
- Systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services

USPSTF

- Bases its recommendations on:
  - systematic review of the evidence of the benefits and harms
  - assessment of the net benefit of the service
- Recommendation made if high or moderate certainty about net benefits
- Does NOT take costs into consideration

U.S.P.S.T.F.

- Recommendations are for *screening* programs
- Do not apply to high-risk patients
- Do not apply when disease is suspected

Current Review

- Examined the evidence on the efficacy of 5 screening modalities in reducing mortality from breast cancer
  - film mammography
  - clinical breast examination
  - breast self-examination
  - digital mammography
  - magnetic resonance imaging
- Goal: to update the 2002 recommendation
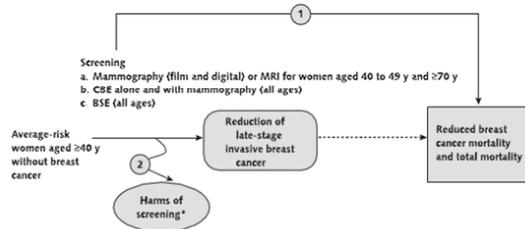
USPSTF 2009

Current Review

USPSTF commissioned 2 studies
- Targeted systematic evidence review
  - 6 selected questions
  - benefits and harms of screening (Nelson)
- Decision analysis
  - population modeling techniques
  - compare the expected health outcomes and resource requirements of starting and ending mammography screening at different ages
  - using annual versus biennial screening intervals (Mandelblatt)

USPSTF 2009

Analytic framework

Screening
a. Mammography (film and digital) or MRI for women aged 40 to 49 y and ≥70 y
b. CBE alone and with mammography (all ages)
c. BSE (all ages)

Average-risk women aged ≥40 y without breast cancer → Reduction of late-stage invasive breast cancer → Reduced breast cancer mortality and total mortality

Harms of screening*

Key Questions

- Does screening with mammography or MRI decrease BRCA mortality among women aged 40-49 and 70+?
- Does CBE screening decrease mortality?
- Does BSE practice decrease mortality?
- What are the harms associated with mammography and MRI?
- What are the harms with CBE and BSE?

What are the harms?

- Additional medical visits and imaging
- Radiation exposure
- Unnecessary biopsies
- Pain during procedures
- Psychological harms

What are the harms?

- Over-diagnosis
  - Harms from treatment of cancer that would not become clinically apparent during a woman's lifetime
- Over-treatment
  - Harms from unnecessary earlier treatment of breast cancer that would have become clinically apparent but would not have shortened a woman's life

Grading of Evidence

- "A" - great evidence favoring
- "B" - good evidence favoring
- "C" - a toss-up; either very limited benefits or too close to call
- "D" - good evidence against
- "I" - not enough data to make a recommendation

Nelson 2009

- Review of randomized trials
- Meta-analysis for mammography data
- The 2002 evidence review for the USPSTF included a meta-analysis of 7 randomized trials of mammography
- What's new:
  - Randomized trial from the United Kingdom that evaluated the effect of mammography screening, specifically in women aged 40 to 49 years
  - Data from a previously reported Swedish trial have been updated
- No trials of screening average-risk women that specifically evaluated the effectiveness of digital mammography or MRI have been published

Effectiveness of screening

- Included:
  - Randomized controlled trials (RCTs)
  - Updates to previously published trials with breast cancer mortality outcomes published since 2001
  - Reviewed meta-analyses that included studies with mortality data
- Excluded:
  - Studies other than controlled trials and systematic reviews
  - Studies without breast cancer mortality as an outcome

Harms of screening

- Mammography:
  - recently published systematic reviews and meta-analyses
  - specific searches for primary studies published more recently
  - data from the Breast Cancer Surveillance Consortium (BCSC)
    - network of 5 mammography registries & 2 affiliated sites
    - linkages to pathology and tumor registries across the United States
    - sponsored by the National Cancer Institute
  - data include a mix of film and digital mammography

- CBE and BSE:
  - screening trials of these procedures that reported potential adverse effects
 - recently published systematic reviews

Nelson 2009

Table 1. Pooled RRs for Breast Cancer Mortality From Mammography Screening Trials for All Ages

Age	Trials Included, *n*	RR for Breast Cancer Mortality (95% CrI)	NNI to Prevent 1 Breast Cancer Death (95% CrI)
39–49 y	8*	0.85 (0.75–0.96)	1904 (929–6378)
50–59 y	6†	0.86 (0.75–0.99)	1339 (322–7455)
60–69 y	2‡	0.68 (0.54–0.87)	377 (230–1050)
70–74 y	1§	1.12 (0.73–1.72)	Not available

CrI = credible interval; NNI = number needed to invite to screening; RR =

Women age 39 to 49

Figure. Pooled relative risk for breast cancer mortality from mammography screening trials compared with control for women aged 39 to 49 years.
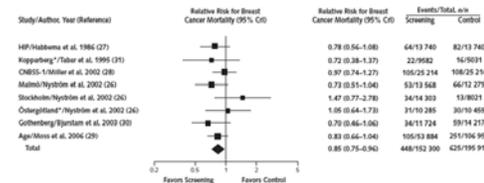
CNBSS-1 = Canadian National Breast Screening Study-1; CrI = credible interval; HIP = Health Insurance Plan of Greater New York.
* Swedish Two-County trial.

All age-specific results

Mandelblatt 2009

- Cancer Intervention and Surveillance Modeling Network (CISNET)
- Models to predict benefits and harms of different screening schedules
- Considered both "mortality" and "life-years gained" outcomes
- Since the age groups (40 - 49 years and 50 - 59 years) are adjacent, the Task Force elected to emphasize the mortality outcomes

Mandelblatt 2009

- 8 screening strategies found most efficient
- 6 start at age 50 rather than age 40
- Only small gains but larger numbers of mammograms required when screening is started at age 40 versus age 50
- Biennial screening produced 70% to 99% of the benefit of annual screening
  - significant reduction in the number of mammograms required
  - therefore a decreased risk for harms
  - 50% fewer false-positives

Mandelblatt 2009

- Screening between the ages of 50 and 69 years produced a projected 17% reduction in mortality (range, 15% to 23%) when compared with no screening
- Additional 3% reduction from starting at age 40 years
- Additional 7% from extending to age 79 years

Mandelblatt 2009

- "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."

USPSTF Conclusions

- Overall harms associated with mammography are moderate for every age group

- False-positive test results, over-diagnosis, and unnecessary earlier treatment are problems for all age groups
- False-positive results are more common for women aged 40 to 49 years
- Over-diagnosis is a greater concern for women in the older age groups

Recommendation for women age 40-49

- Against routine screening
- The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one
- Take patient context into account, including the patient's values regarding specific benefits and harms
- **C recommendation**

Recommendation for women age 50-74

- Biennial screening mammography
- **B recommendation**
- Screening every other year:
  - Preserves most of the benefits of annual screening
  - Cuts the harms in half

Recommendation for women age 75 and older

- Current evidence is insufficient
- **I statement**
- Benefits of screening occur only several years after the actual screening test, whereas the percentage of women who survive long enough to benefit decreases with age
- A higher percentage of the type of breast cancer is the more easily treated estrogen receptor–positive type
- Greater risk for dying of other conditions

Digital mammography

- Current evidence is insufficient to assess the additional benefits and harms
- **I statement**
- For younger women and women with dense breast tissue, overall detection is somewhat better with digital mammography
- ? More overdiagnosis
- More expensive

Magnetic resonance imaging (MRI)

- Current evidence is insufficient to assess the additional benefits and harms
- **I statement**
- Contrast-enhanced MRI has been shown to detect more cases of cancer in very high-risk populations
- Requires injection of contrast material
- MRI yields many more false-positive results and potentially more over-diagnosis
- Much more expensive

Breast exams

- Self-exams
  - against teaching breast self-examination (BSE)
  - **D recommendation**
- Clinical breast exams (CBE)
  - Current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 years or older
  - **I statement**

No change for:

- Women with BRCA mutations
- ~Women with family history of cancer suggestive of BRCA mutation
- Women with a history of chest radiation
- Women with clinical findings

Response from organizations

- Reevaluting the data themselves:
  - ACOG
  - National Cancer Institute (NCI)
- Staying with current guidelines:
  - American Cancer Society
  - American College of Radiology
- *Cheering* the new guidelines:
  - National Breast Cancer Coalition, Breast Cancer Action, and the National Women's Health Network

ACOG Recommendations

- Screening mammography every 1-2 years for women aged 40-49 years
- Screening mammography every year for women aged 50 years or older
- BSE (has the potential to detect palpable breast cancer and can be recommended)
- CBE every year for women aged 19 or older

ACOG
THE AMERICAN CONGRESS of
OBSTETRICIANS AND GYNECOLOGISTS

Why aren't mammograms the best thing ever?
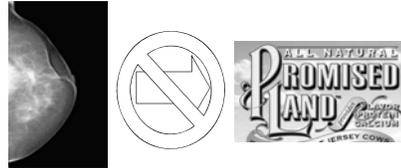
1. Accuracy of screening tests

- Mammography screening
  - Sensitivity 77% to 95%
  - Specificity 94% to 97%
  - Affected by multiple factors
- Only one large comparison study of film and digital mammography
- Showed similar diagnostic accuracy for the 2 methods

Accuracy of screening tests

- MRI
  - sensitivity of 71% to 100%
  - specificity of 81% to 97%
- Recommended by the American Cancer Society for women at high risk for breast cancer
- No studies have been done on using MRI to screen women at average risk

Accuracy of screening tests

- Clinical breast examination
  - sensitivity of 40% to 69%
  - specificity of 88% to 99%

- Breast self-exam
  - sensitivity ranges from 12% to 41%
  - age-dependent

Effectiveness of early detection

- Overall, screening mammography reduces mortality...

- ...but early detection by mammogram may not always = more survival

2. Cancer biology

- Screening tests, including mammography, tend to be better at detecting slow-growing good-prognosis cancers, which will thus have that good outcome
- Screening is worse at detecting the fast-growing bad-prognosis cancers that kill

Optimal screening programs

- Should be followed by:
  - ⇧ in the rate of detection of early disease
  - ⇩ in the rate of detection of regional disease
  - the rate of detection of cancer overall remains <u>constant</u>

- Cervical cancer
- Colon cancer
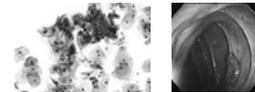
Optimal screening program?

- But **screening mammography has not reduced the incidence of invasive breast tumors**

- What has it increased the incidence of?
- Ductal carcinoma in-situ

DCIS

- Not always a precursor to invasive ductal cancer
  - Pathway isn't linear
- Untreated DCIS progresses to invasive disease in half or fewer of the cases
- Because DCIS is often found only by mammography, its incidence has increased steadily
  - 1983: 4900 cases of DCIS
  - 2008: ~ 67,770 cases
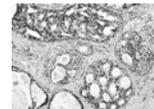
DCIS

- Because if/when DCIS will progress to invasive cancer is unknown for each patient, surgical removal—with or without adjuvant treatment—may represent over-diagnosis or over-treatment

Why has widespread screening had a limited impact on mortality from breast cancer?

Limitations of Screening

- Screening increases the detection of indolent tumors that may not lead to life-threatening disease
- Annual screening isn't frequent enough to detect aggressive, rapidly growing tumors at a curable stage
- We have limited ability to distinguish low-risk cancer from high-risk cancer

Costs of Screening

- **For every 1 death from breast cancer that is prevented by screening**—even in the age group, 50 to 70 years, in which screening is least controversial—**838 women must be screened for 6 years**
- Thousands of screens
- Hundreds of biopsies that carry their own costs and risk of morbidity
- Many cancers treated aggressively even though they are not destined to progress

Patient Care

- Importance of medical history
  - Age
  - Age at menarche
  - Age at first delivery
  - Biopsies, DCIS/LCIS
- Importance of family history
  - Which relatives
  - Which side of family
  - How old at diagnosis
  - Breast, ovarian, endometrial, colon

What to tell patients?

- Clinical breast exam
  - Probably doesn't hurt
- Self breast exam
  - Doesn't help (so don't do it)
- Mammograms
  - Definitely start at age 50
  - Not likely to save your life starting any sooner

For mammograms in your 40s

- For each woman who might avoid a breast cancer death due to screening, there will be at least 10 additional women who are diagnosed with and treated for a cancer that would have never affected their health
- Those women will spend the rest of their lives receiving what is actually unnecessary treatment (painful, expensive, complicated, etc) and extra surveillance for that cancer

With apologies to Alfred, Lord Tennyson...

- *To Seek*
  - Exams
  - Mammography
- *To Find*
  - Life-threatening cancer
  - Indolent cancer? DCIS?
- *But Not to Yield*
  - Best tool available
  - But far from perfect, and not for everyone