

Northwestern University Feinberg School of Medicine



BREAST CANCER SCREENING: Ongoing Debate

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BREAST CANCER

American Cancer Society Statistics:

Chance of developing invasive breast cancer at some time in a woman's life 1 in 8 (12%)

United States estimates for 2011:

230,480 new cases of invasive cancer

57,650 new cases carcinoma in situ

39,970 breast cancer deaths--↓ since 1990

2,140 new cases -- men

BREAST CANCER SCREENING

There is (almost) universal agreement that the randomized controlled trials of screening have demonstrated that the death rate from breast cancer can be reduced by periodic screening using mammography.

Mammography

- Benefits of x-ray exams of the breasts studied since the 1960's
- Screening trials: 7 randomized controlled trials between 1963 and 1990, including HIP and Swedish Two-County trials, show benefit; Canadian study the outlier
- Mortality decrease is measure of success
Range of ↓mortality: 20-60%
≥60% mortality reduction (Tabar L, Cancer, 2001).
- Recurrent controversy about efficacy

Achievements of Screening Mammography

1983-96:

- incidence of DCIS ↑ by 280%
- incidence of Stage I ↑ by 117%
- incidence of Stages II-IV ↓ 36%

Feig SA. RCNA 2000;38:653

2002

USPSTF Recommendation

- The USPSTF recommends mammography every 1-2 years in women age 40-69 years.

To Screen or Not to Screen?

Benefits

- 1) ↓ mortality
 - 2) ↓ morbidity
- Vary with:
- Test (sensitivity, screening interval)
 - Population (disease prevalence, age)
 - Disease biology (sojourn time, effect of early detection on outcome)



Costs

- 1) Test cost & morbidity
 - 2) FP cost & morbidity
 - 3) Overdiagnosis
- Vary with:
- Test (cost, specificity, screening interval)
 - Population (size, age)

Why should all women age 40-49 have screening mammography?

- Breast cancer is commonest cause of death from any cause in this age group (~ 8000 annually in U.S.)
- Meta-analysis of 8 RCTs shows mortality ↓ of 15% (CI 4% to 25%)

Why shouldn't all women age 40-49 have screening mammography?

- Less benefit than older women
 - Lower sensitivity (breast density)
 - Lower disease incidence
 - Faster tumour doubling time
- Lower specificity

Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement

U.S. Preventive Services Task Force*

Description: Update of the 2002 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for breast cancer in the general population.

Methods: The USPSTF 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, and magnetic resonance imaging in order to update the 2002 recommendation. To accomplish this update, the USPSTF commissioned 2 studies: 1) a targeted systematic evidence review of 6 selected questions relating to benefits and harms of screening, and 2) 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 versus biennial screening intervals.

Recommendations: The USPSTF recommends against routine screening mammography in women aged 40 to 49 years. The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms. (Grade C recommendation)

The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years. (Grade B recommendation)

The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination beyond screening mammography in women 40 years or older. (I statement)

The USPSTF recommends against clinicians teaching women how to perform breast self-examination. (Grade D recommendation)

The USPSTF concludes that the current evidence is insufficient to assess additional benefits and harms of either digital mammography or magnetic resonance imaging instead of film mammography as screening modalities for breast cancer. (I statement)

Ann Intern Med. 2009;151:716-726.

www.annals.org

For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the **Appendix** (available at www.annals.org).

Nov. 10, 2009

2009 USPSTF RECOMMENDATIONS

- Against routine screening mammography in women 40-49 y.o.
- Biennial screening mammography for women 50-74 y.o.
- Insufficient evidence to assess benefits / harms of screening mammography in women > 75 y.o.
- Against teaching BSE
- Insufficient evidence to assess benefits / harms of CBE
- Insufficient evidence to assess benefits / harms of digital mammography or MRI as screening modalities for breast cancer

USPSTF RECOMMENDATIONS

- Used **computer models** to analyze data rather than using the source data themselves
- Acknowledge that many of the trials show mortality **benefit** for all women (including 40-49 y.o.) but then inexplicably conclude that the “**harms**” (pain, anxiety, radiation dose, false positives, unnecessary biopsies) outweigh the benefits without showing any scientific analysis of the “harms”.
- None of the members of the task force have any **experience** with mammographic screening or any aspect of imaging.

Criticisms of New Guidelines

- 1) Evidence hasn't substantially changed!

2002 USPSTF Guidelines: Evidence for women Age 40- 49

- 7 RCTs
- 6 fair, 1 poor (Edinburgh trial)
- Only 1 trial specifically for women in their 40s (~ 50,000)
 - rest underpowered (~25,000)
- Median f/u ~ 13 years

RCT's Women Ages 40-49

| | Yr. | Screening Interval | Views | Rounds | CBE | RR breast cancer death (95% CI) |
|------------|-----|--------------------|--------|--------|-----|---------------------------------|
| HIP | '63 | 12 | 2 | 4 | yes | 0.78 (0.56-1.08) |
| CNBSS-1 | '80 | 12 | 2 | 4-5 | yes | 0.97 (0.74–1.27) |
| Gothenburg | '82 | 18 | 1 or 2 | 5 | no | 0.58 (0.35-0.96) |
| Stockholm | '81 | 24-28 | 1 | 2 | no | 1.52 (0.8- 2.88) |
| Malmo | '76 | 18-24 | 1 or 2 | 9 | no | 0.73 (0.51-1.04) |
| 2-County | '77 | 24-33 | 1 | 3 | no | 0.87 (0.54-1.41) |

Meta-analysis of RCTs 40-49

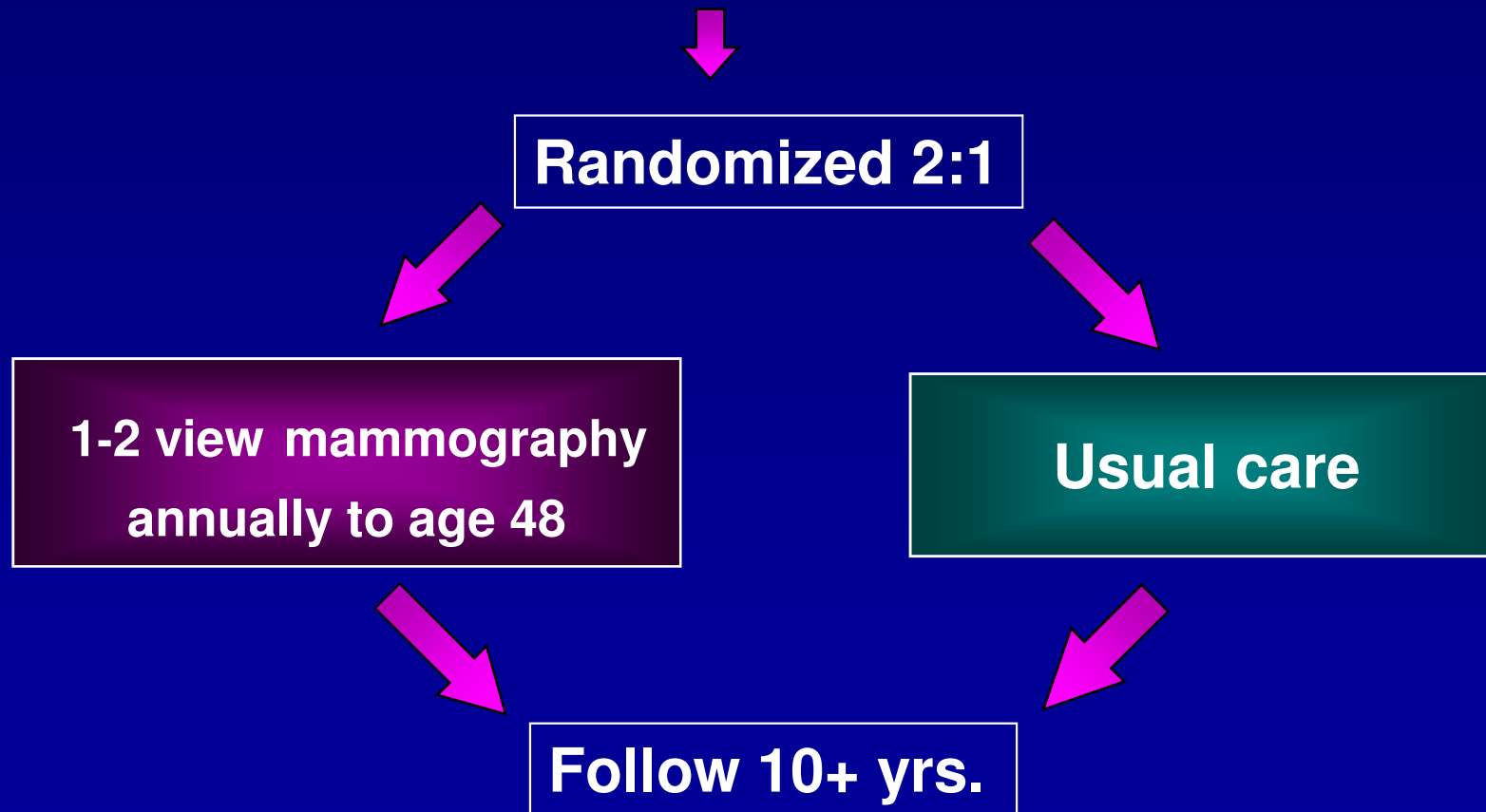
| Study | Assessed Quality? | Included Trials | Relative Risk Breast Cancer Death (95% CI) |
|-------------------------|-------------------|-----------------|--|
| Larsson 1997 | no | 4 Swedish | 0.77 (0.59-1.01) |
| Cox 1997 | no | All 7 | 0.93 (0.77-1.11) |
| Glasziou and Irwig 1997 | yes | All 7 | 0.85 (0.71-1.01) |
| Glasziou 1992 | no | All 7 | 0.82 (0.71-0.95) |
| Kerlikowske 1995 | no | All 7 | 0.84 (0.71-0.99) |
| Berry 1998 | no | All 7 | 0.82 (0.49-1.17) |
| Olsen and Gotzche 2001 | yes | 2 | 1.03 (0.77-1.38) |
| USPSTF 2002 | yes | 6 | 0.85 (0.73-0.99) |

Potential Sources of New Evidence

- New RCT(s)
- Longer follow-up of old RCTs
- Reassessment of old RCT data

The Age Trial (1991)

161,000 women 39-41 in U.K.



Age Trial : Results

RR (95% CI)

Breast cancer mortality 0.83 (0.66-1.04)

All cause mortality 0.97 (0.89-1.04)

Number needed to screen (NNS) = 2512

RCT's Women Ages 40-49

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Gothenburg Trial Update

RR (95% CI)

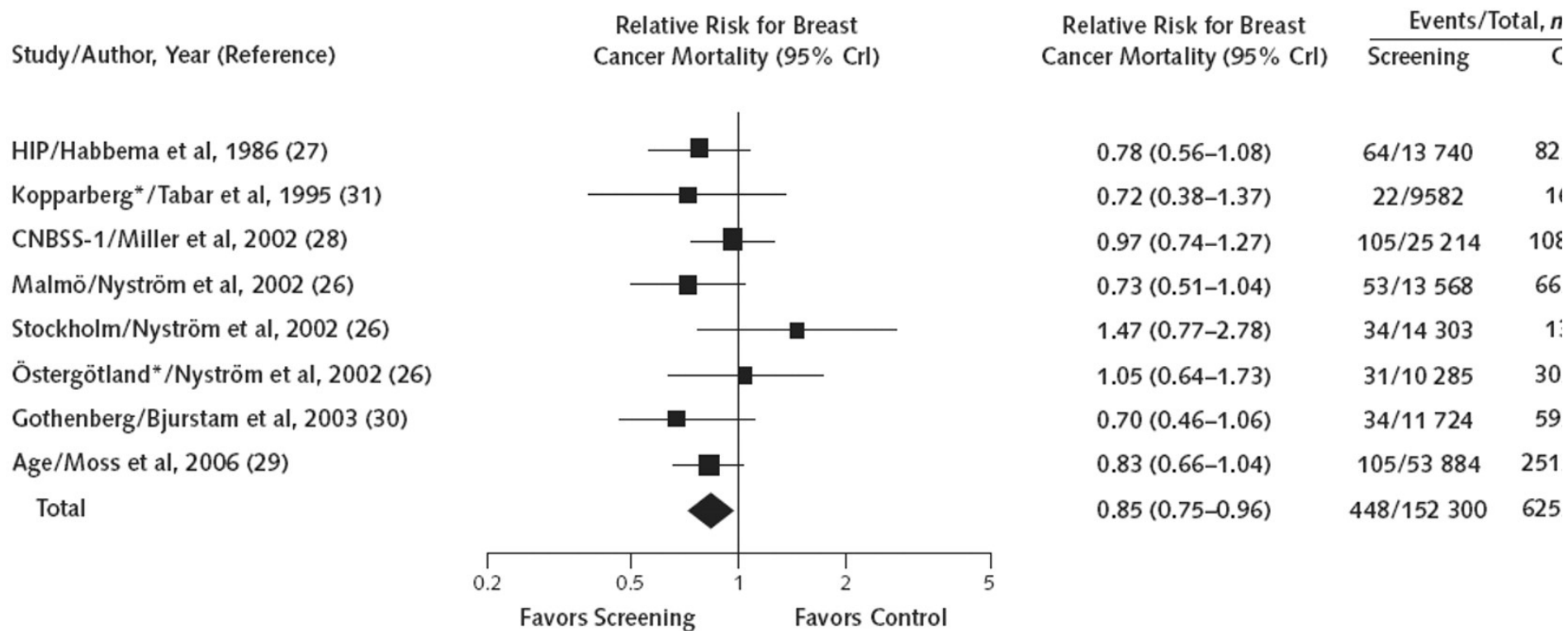
Previous report

0.58 (0.35 – 0.96)

Current report

0.69 (0.45-1.05)

Pooled relative risk for breast cancer mortality from mammography screening trials compared with control for women aged 39 to 49 years.



Nelson H D et al. Ann Intern Med 2009;151:727-737

Meta-analyses of RCTs 40-49

RR Breast Cancer Death
(95% CI)

USPSTF 2002

0.85 (0.73 – 0.99)

USPSTF 2009

0.85 (0.75 - 0.96)

2002

| <u>Ages</u> | <u>RR (95% CI)</u> | <u>NNS</u> |
|-------------|--------------------|------------|
| 40-49 | 0,85 (0.73-0.99) | 1792 |
| 40+ | 0.84 (0.77-0.91) | 1224 |

2009

| | | |
|-------|------------------|------|
| 40-49 | 0.85 (0.75-0.96) | 1904 |
| 50-59 | 0.86 (0.75-0.99) | 1339 |
| 60-69 | 0.68 (0.54-0.87) | 377 |

Screening Results from BCSC* by Age

| Outcome per 1000 screened | 40-49 | 50-59 | 60-69 |
|---------------------------------|-------|-------|-------|
| Screen-detected invasive cancer | 1.8 | 3.4 | 5.0 |
| False negative | 1.0 | 1.1 | 1.4 |
| False positive | 98 | 87 | 79 |
| Additional Imaging | 84 | 76 | 70 |
| Biopsy | 9 | 11 | 12 |

* Breast Cancer Surveillance Consortium

USPSTF Breast Screening Guidelines for Average Risk Women

| Age | 2002 | 2009 |
|-------|-------------------------------|---|
| 40-49 | Mammography q1-2 yrs. (B) | No routine screening (C) (Mammography q2yrs.) |
| 50-74 | Mammography q1-2 years (B) | Mammography q2yrs. (B) |
| 75+ | Mammography q1-2 years (B) | Insufficient evidence (I) |

Why Biennial Screening?

- RCTs shows same mortality ↓ with screening q18-33mos. vs. 12 mos.
- Screening programs report similar outcomes at 10 yrs. for 1 vs. 2 yr. screening interval
- In screening models 2yr. maintains 81% (67%-99%) of benefits of 1yr.
- Biological rationale: most breast cancers are slow-growing and fast-growing ones missed even by annual screening

Kerlikowske K. Ann Int Med 2009; 151: 750

Sojourn Time vs. Age

| <u>Age</u> | <u>Mean Sojourn Time</u> |
|------------|--------------------------|
| 40-49 | 1.7 years |
| 50-74 | 2.6 – 3.8 years |

Tabar et al. Cancer 1995; 75: 2507

Screening Interval vs. Age

- Study of 7 mammography screening registries
- 2 yr. interval (n=2440) vs. 1 yr. interval (n=5400)

Probability of late stage disease

| <u>Age</u> | <u>Odds Ratio (95% CI)</u> |
|------------|----------------------------|
| 40-49 | 1.35 (1.01 – 1.81) |
| 50-59 | 0.97 (0.75 - 1.25) |
| 60-69 | 0.99 (0.72 – 1.35) |

White et al. JNCI 2004; 96: 2004

Criticisms of New Guidelines

- ✓ 1) Evidence hasn't substantially changed
- 2) RCT's underestimate mammography benefits

Is Mammography Benefit Underestimated by RCTs?

- Analysis issues:
 - Intent-to-treat (non-compliance & contamination)
 - Follow-up method
- Minority groups under-represented
- Mammography technique
 - Number of views
 - Old equipment
 - Film

Other Guidelines

| | Mammography | Interval |
|---------------------------------|--|------------------|
| ACS 2009 | Age 40+ | 1 year |
| NCCN 2010 | Age 40+ | 1 year |
| ACP 2007 | Age 50+ Individualize 40-49 | 1-2 years |
| Canadian Task Force 2001 | Age 50+ Individualize 40-49 | 1-2 years |
| NICE 2008 | Age 50+ | 3 years |
| WHO 2009 | Age 50+ | 1-2 years |

BREAST CANCER SCREENING RECOMMENDATIONS: U.S.A.

- Mammography: **annually from age 40**; based on randomized controlled trials
- USPSTF: biennially from age 50 for average risk population; based on statistical modelling
- HHS: Do not change guidelines at this point—retain 2002 recommendation for mammography annually from age 40
- **High risk**
 - **5 – 10 years younger than 1st degree premenopausal relative(s)**
 - **BR CA 1 & 2: mammography**
 - **Mantle radiation for Hodgkin' s**
- MRI: annually *in addition* to mammography; lifetime risk greater than 20%: alternate studies or do synchronously?
- No recommendation for ultrasound

ACR PRACTICE GUIDELINE FOR PERFORMANCE OF BREAST US, 2007

EVOLVING

“The efficacy of ultrasound as a screening study for masses in dense fibroglandular breasts of high risk women or women with newly diagnosed or suspected breast cancer is an area of research.”

PASSED by ACR Council in May, 2011:
Include screening as an indication for
ultrasound

ACRIN 6666: First-year Results

Berg WA, Blume JD, Cormack JB, Mendelson EB et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA; 299:18; 2151-2163.

- **Diagnostic accuracy of**
 - mammography + US = 91%**
 - mammography alone = 78%**
- **US only cancers: 12 (11 invasive; median size 1 cm; 8 of 9 neg. nodes)**
- **Diagnostic yields:**
 - **mammography alone--7.6/1000 women screened**
 - **mammography plus US--↑11.8/1000**

Breast MRI Sensitivity

- **Highest sensitivity** for detecting invasive breast cancer and recently reported high for DCIS
- Range between **89-100%**
- Unaffected by density of the fibroglandular tissue, mature scar tissue, radiation therapy, implants or breast reconstruction
- **Highest cost; requires IV gadolinium**

Breast MRI

Indications and Applications

- **Screening for highest-risk women**
 - BR CA genes and familial patterns suggesting genetic predisposition *with mammography*, 92 % overall sensitivity
- **Screening of contralateral breast in breast cancer patients**
 - single-site studies 4-5% synchronous occult cancers
 - C. Lehman, NEJM 2007 ACRIN study: 3.1 % had contralateral occult cancer, fatty or dense

Cost-Effectiveness of Screening Mammography

- Simulation model of 64 screening scenarios

| | <u>Cost</u> | <u>Cost/QALY</u> |
|------------------|---------------|------------------|
| age 40, annual | \$150 billion | \$58,000 |
| age 40, biennial | \$84 billion | \$47,000 |
| age 50, biennial | \$57 billion | \$34,000 |

Stout et al. JNCI 2006; 98: 774.

Déjà vu?

- 1997 NIH panel concluded against routine screening for women age 40-49
- Panel called before Senate for ‘condemning women to death’
- Senate voted 98 – 0 in support of mammography for women in their 40’ s.

**Thank-you for your
attention!**