LUNG CANCER WORKSHOP

prevent cancer FOUNDATION

Workshop X: Application of Quantitative CT Imaging to Early Lung Cancer Management: Accelerating Progress

May 2 - 3, 2013 • Bethesda, Maryland • USA

The Future of Lung Cancer Screening Guidelines: Is there a better way to move forward?

Robert A. Smith, PhD
Senior Director, Cancer Screening
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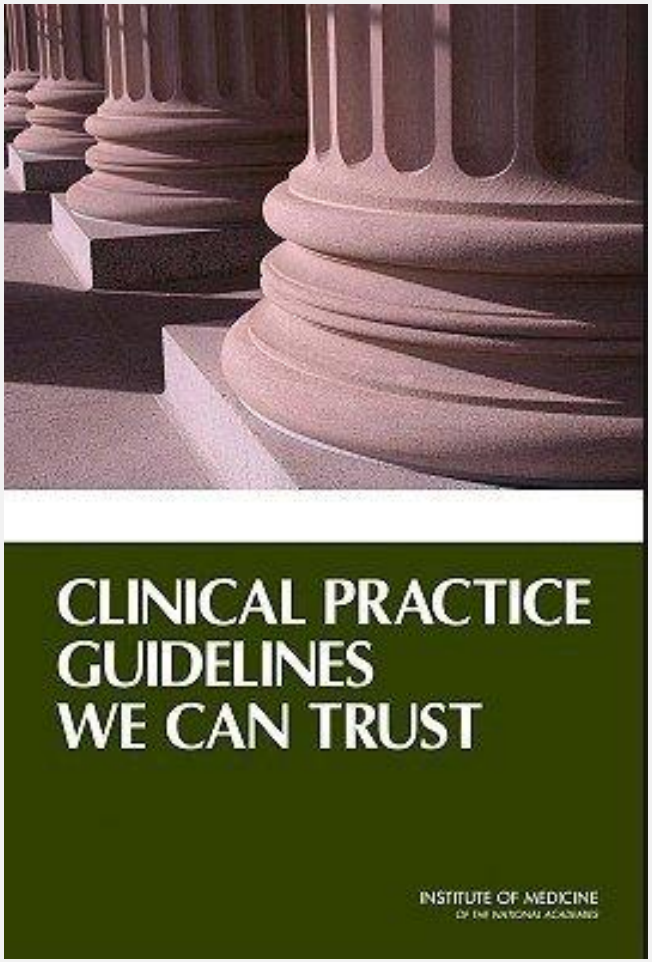
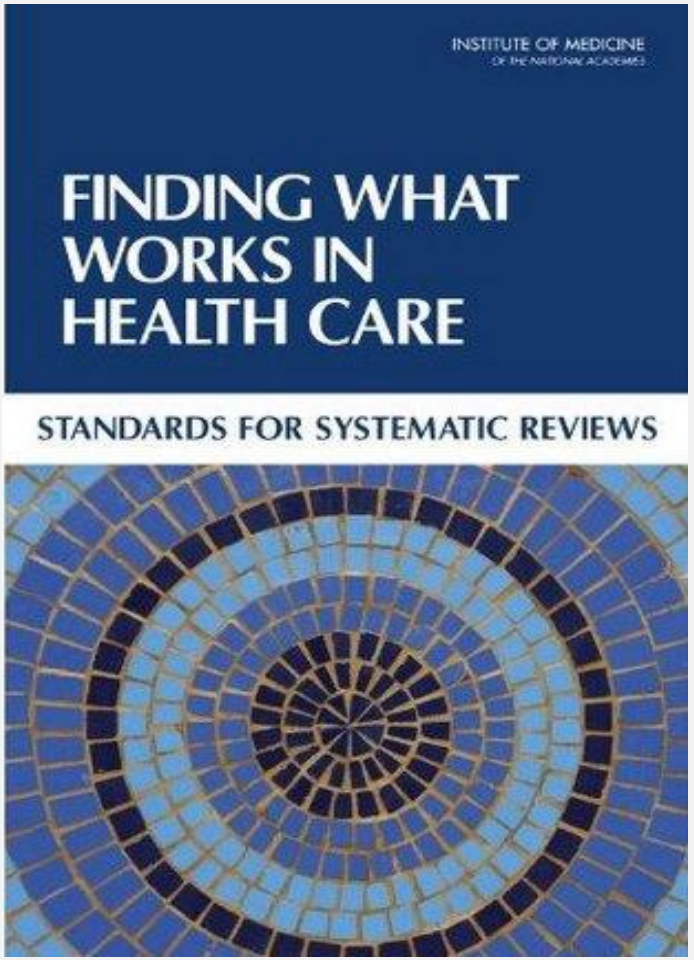
Guidelines for the Development of Guidelines

Two IOM reports were published in 2011 outlining best practices

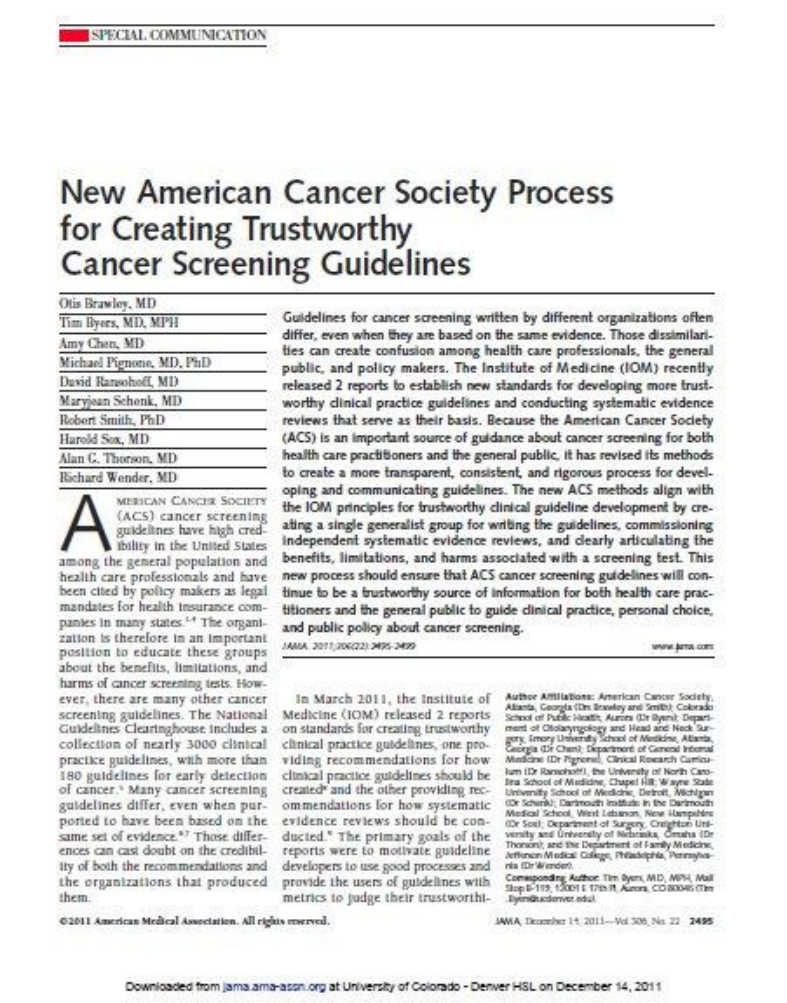




American Cancer Society
"New" Guideline Development Principles
[Based on IOM Standards & Recommendations]

1. Transparency
2. Conflicts of Interest
3. Group Composition
4. Systematic Review of Evidence
5. Grading Strength of Recommendations
6. Articulation of Recommendations
7. External Review
8. Updating

New Strategy for ACS Guidelines



SPECIAL COMMUNICATION

New American Cancer Society Process for Creating Trustworthy Cancer Screening Guidelines

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Guidelines for cancer screening written by different organizations often differ, even when they are based on the same evidence. Those dissimilarities can create confusion among health care professionals, the general public, and policy makers. The Institute of Medicine (IOM) recently released 2 reports to establish new standards for developing more trustworthy clinical practice guidelines and conducting systematic evidence reviews that serve as their basis. Because the American Cancer Society (ACS) is an important source of guidance about cancer screening for both health care practitioners and the general public, it has revised its methods to create a more transparent, consistent, and rigorous process for developing and communicating guidelines. The new ACS methods align with the IOM principles for trustworthy clinical guideline development by creating a single generalist group for writing the guidelines, commissioning independent systematic evidence reviews, and clearly articulating the benefits, limitations, and harms associated with a screening test. This new process should ensure that ACS cancer screening guidelines will continue to be a trustworthy source of information for both health care practitioners and the general public to guide clinical practice, personal choice, and public policy about cancer screening.

JAMA. 2011;306(22):2495-2499 www.jama.com

American Cancer Society (ACS) cancer screening guidelines have high credibility in the United States among the general population and health care professionals and have been cited by policy makers as legal mandates for health insurance companies in many states.[1-4] The organization is therefore in an important position to educate these groups about the benefits, limitations, and harms of cancer screening tests. However, there are many other cancer screening guidelines. The National Guidelines Clearinghouse includes a collection of nearly 3000 clinical practice guidelines, with more than 180 guidelines for early detection of cancer.[5] Many cancer screening guidelines differ, even when purported to have been based on the same set of evidence.[6,7] Those differences can cast doubt on the credibility of both the recommendations and the organizations that produced them.

In March 2011, the Institute of Medicine (IOM) released 2 reports on standards for creating trustworthy clinical practice guidelines, one providing recommendations for how clinical practice guidelines should be created[8] and the other providing recommendations for how systematic evidence reviews should be conducted.[9] The primary goals of the reports were to motivate guideline developers to use good processes and provide the users of guidelines with metrics to judge their trustworthi-

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Corresponding Author: Tim Byers, MD, MPH, Mail Stop E-119, 13001 E 17th Pl, Aurora, CO 80045 (Tim.Byers@ucdenver.edu).

- Follow new IOM Standards
- Panel of 12
  - 11 non-specialist experts
  - 1 patient advocate
- Advice from Expert Panel (non voting)
- Outsource systematic reviews

Has the additional rigor improved cancer screening guidelines? *Yes and No*

- Strategies to improve trustworthiness are a favorable new development, but generally involve tradeoffs…..
  - Guidance on avoiding **conflicts of interest** and bias, including the *appearance of bias,* are a step in the right direction
  - **Composition of guidelines groups** is a work in progress…experts can be biased, but generalists often don't understand the data, and **non-specialization is no assurance of lack of bias**
  - Standards for **systematic evidence reviews** and grading evidence/recommendations can insure that recommendations are based on sound science…..on the other hand, *sometimes the bar is set unreasonably high.*

Has the additional rigor improved cancer screening guidelines? *Yes and No*

The Elephant in the Room

- Guidelines are typically developed in isolation
- Different methodologies, evidence, and endpoints lead to different measures of **benefit**
- There is no clear metric for measuring and weighing the range and frequency of **harms**
- Evidence from **modeling** commonly is proprietary, and has not been available to other guideline development groups
- Recommendations are presented as if they were ***the only logical conclusion*** from an evidence-based comparison of benefits and harms (***the role of judgment is downplayed***)
- Intellectual bias is difficult to measure or critique
- Thus, there is ample opportunity for error

Has the additional rigor improved cancer screening guidelines? *Yes and No*

- **Guidelines development and updates take too long**
  - **Process is lengthy and expensive**
  - **Ability to update guidelines quickly is limited by time, resources, and other guideline updates in the pipeline**
  - **Comment periods add to delays**
- **Affordable Care Act requires *A* or *B* rating** from the USPSTF to determine coverage for preventive care

- **Opportunity to contest USPSTF decisions is limited, since decisions were based on an *evidence-based* process.**
- **The guideline group would need to be persuaded that the systematic review report was flawed.**

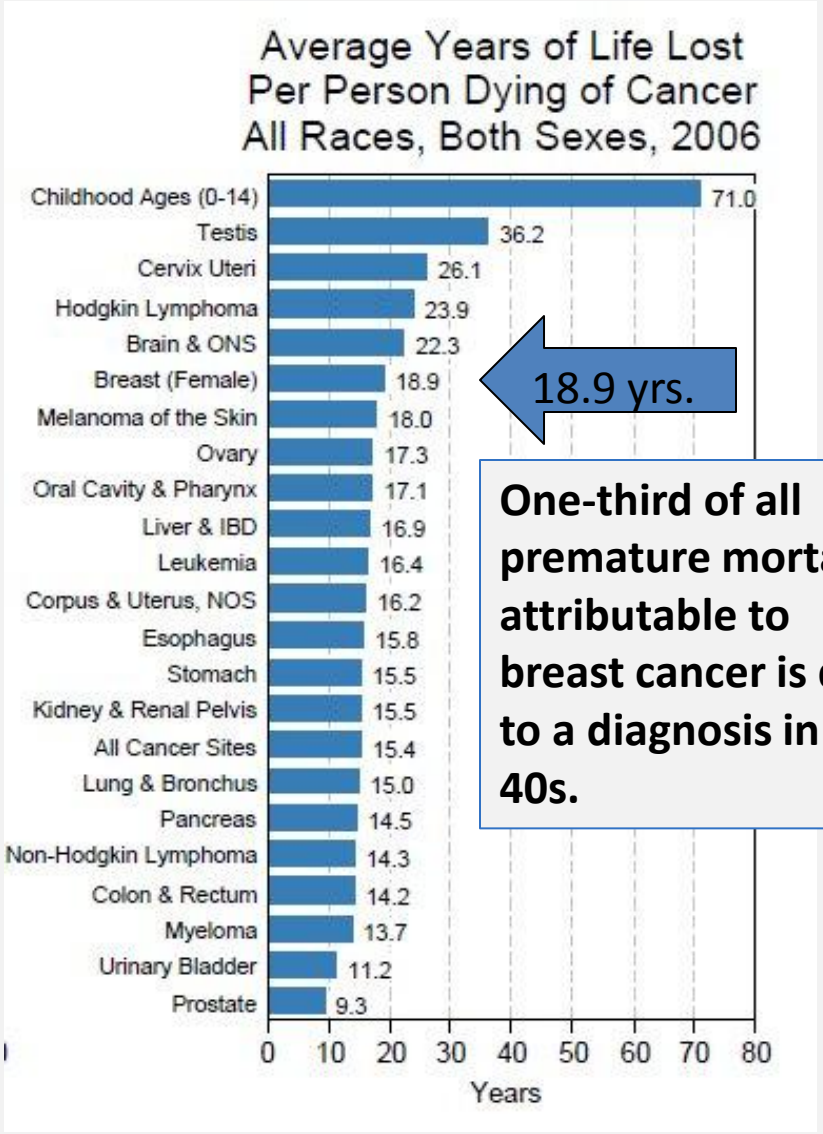
An example of screening recommendations as “contested terrain”

- Presently, there are fundamental differences in breast cancer screening guidelines
  - ACS, ACOG recommend annual screening beginning at age 40. AMA says women should have the option.
  - USPSTF, ACFP recommend biennial screening beginning at age 50
  - Stopping ages differ (poor health vs. fixed age)

The argument against screening women in their 40s

- Risk of developing and dying from breast cancer during the decade of the 40s is low
- While the reduced risk of dying from breast cancer associated with screening in women ages 40-49 is similar to women ages 50-59, *the absolute benefit is lower*
- The risk of harms (false positives, etc.) is high
- Thus, the balance of benefits and harms indicates a recommendation against routine screening (C rating)

Premature mortality and incidence based mortality from breast cancer, U.S Women

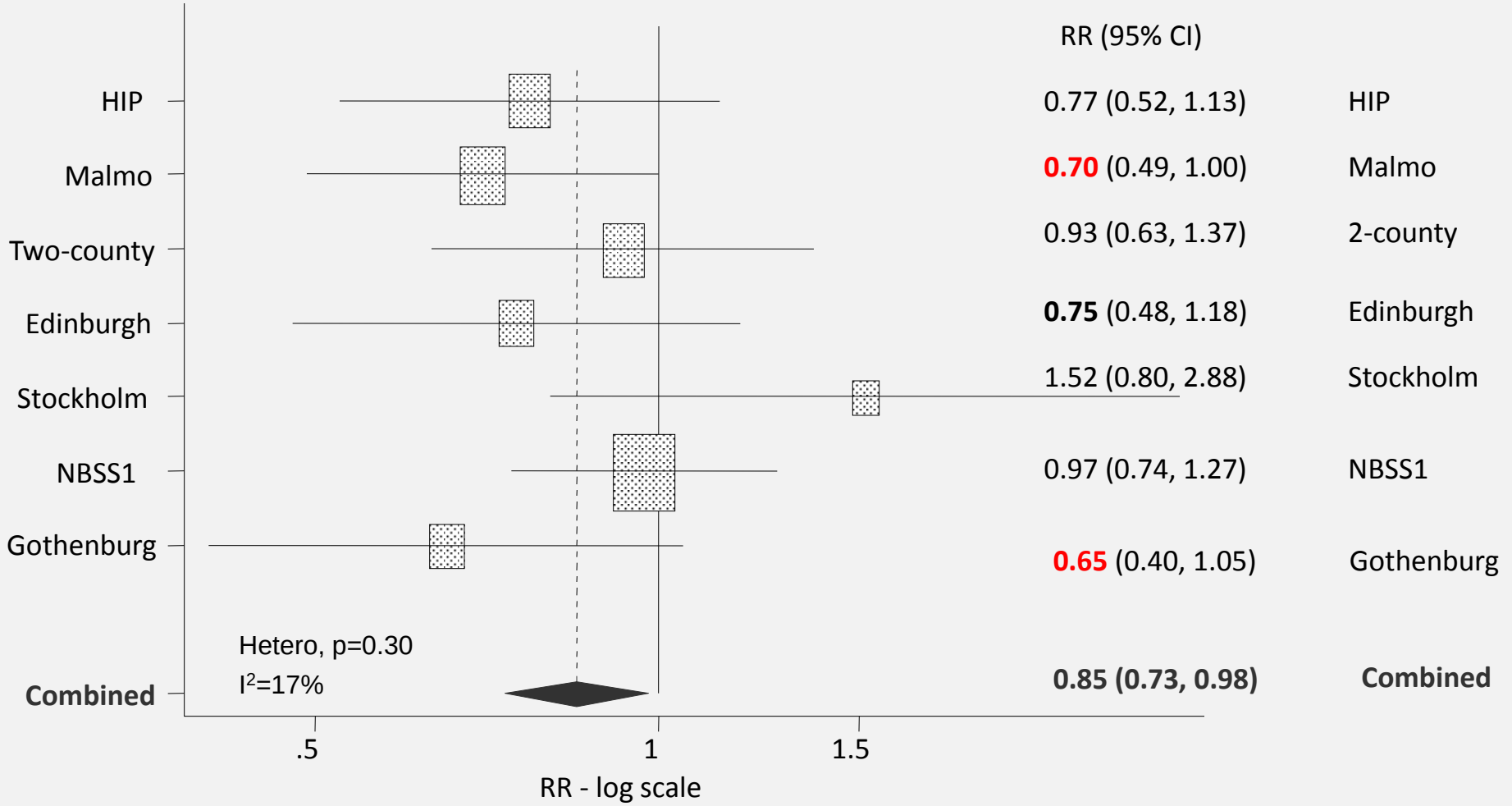


One-third of all premature mortality attributable to breast cancer is due to a diagnosis in the 40s.

- Percent of deaths from breast cancer by age at diagnosis, U.S., 2005-2006
  - < 40 7.7%
  - **40-49 17.8%**
  - 50-59 22.3%
  - 60-69 19.0%
  - 70-79 18.8%
  - 80+ 14.5%

Source: SEER Cancer Statistics Review,1975-2006.

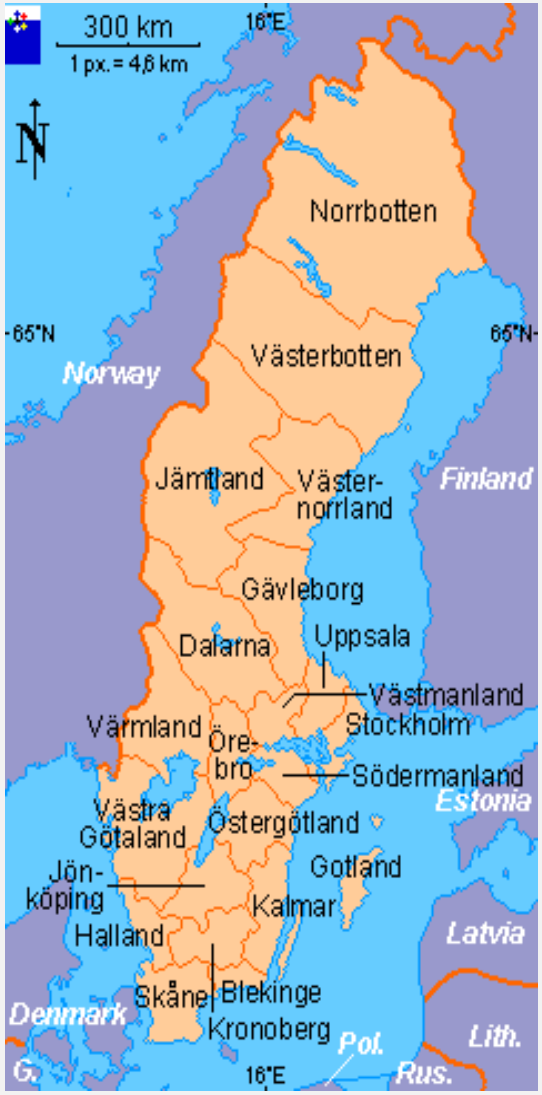
Meta-analysis of the RCTs, Women age 39-49



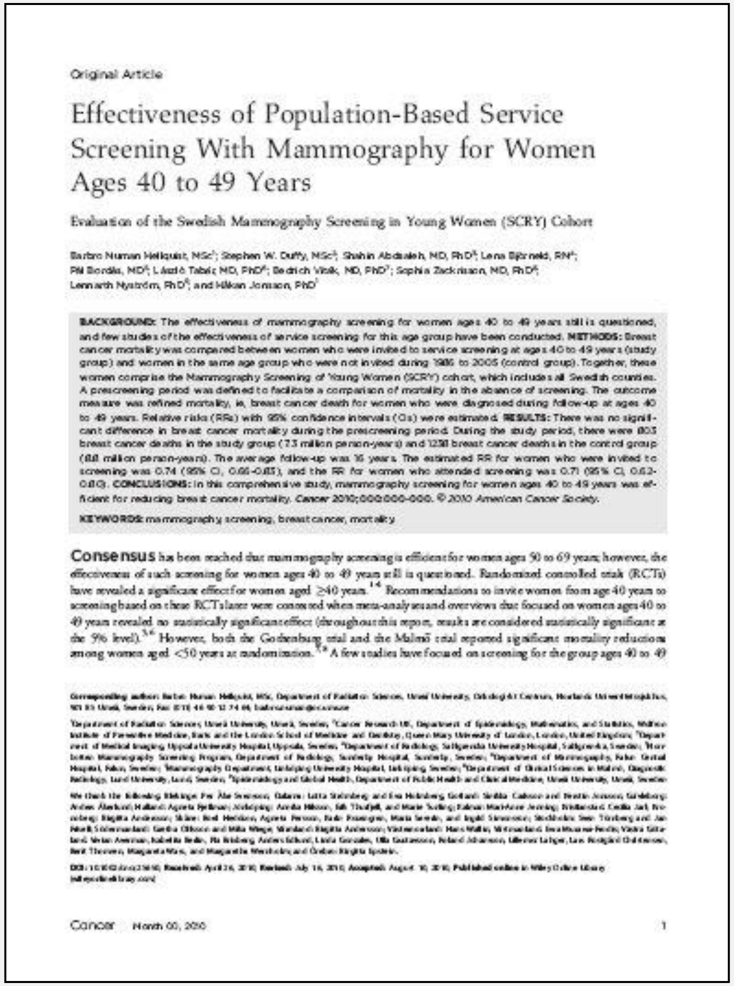
15% reduction in breast cancer mortality

20% reduction without NBSS-1

Evaluation of Service Screening in Sweden



Effectiveness of Population-Based Service Screening With Mammography for Women Ages 40 to 49 Years



Original Article

Effectiveness of Population-Based Service Screening With Mammography for Women Ages 40 to 49 Years

Evaluation of the Swedish Mammography Screening in Young Women (SCRY) Cohort

Barbro Numan Hellquist, MSc; Stephen W. Duffy, MSc; Shahin Abdsaleh, MD, PhD; Lena Björneld, RN; Pál Bordás, MD; László Tabár, MD, PhD; Bedrich Vitak, MD, PhD; Sophia Zackrisson, MD, PhD; Lennarth Nyström, PhD; and Håkan Jonsson, PhD

BACKGROUND: The effectiveness of mammography screening for women ages 40 to 49 years still is questioned, and few studies of the effectiveness of service screening for this age group have been conducted. **METHODS:** Breast cancer mortality was compared between women who were invited to service screening at ages 40 to 49 years (study group) and women in the same age group who were not invited during 1986 to 2005 (control group). Together, these women comprise the Mammography Screening of Young Women (SCRY) cohort, which includes all Swedish counties. A prescreening period was defined to facilitate a comparison of mortality in the absence of screening. The outcome measure was refined mortality, ie, breast cancer death for women who were diagnosed during follow-up at ages 40 to 49 years. Relative risks (RRs) with 95% confidence intervals (CIs) were estimated. **RESULTS:** There was no significant difference in breast cancer mortality during the prescreening period. During the study period, there were 803 breast cancer deaths in the study group (7.3 million person-years) and 1238 breast cancer deaths in the control group (8.8 million person-years). The average follow-up was 16 years. The estimated RR for women who were invited to screening was 0.74 (95% CI, 0.66-0.83), and the RR for women who attended screening was 0.71 (95% CI, 0.62-0.80). **CONCLUSIONS:** In this comprehensive study, mammography screening for women ages 40 to 49 years was efficient for reducing breast cancer mortality. *Cancer* 2010;000:000-000. © 2010 American Cancer Society.

KEYWORDS: mammography screening, breast cancer, mortality

Consensus has been reached that mammography screening is efficient for women ages 50 to 69 years; however, the effectiveness of such screening for women ages 40 to 49 years still is questioned. Randomized controlled trials (RCTs) have revealed a significant effect for women aged ≥40 years.[1-4] Recommendations to invite women from age 40 years to screening based on these RCTs later were contested when meta-analyses and overviews that focused on women ages 40 to 49 years revealed no statistically significant effect (throughout this report, results are considered statistically significant at the 5% level).[5,6] However, both the Gothenburg trial and the Malmö trial reported significant mortality reductions among women aged <50 years at randomization.[7,8] A few studies have focused on screening for the group ages 40 to 49

- Contemporaneous comparison of breast cancer mortality in Swedish counties offering mammography vs. those not offering mammography
- 1986-2005
- Average follow-up = 16 years

Cancer 2010; published online: 29 SEP 2010

Effectiveness of Population-Based Service Screening With Mammography for Women Ages 40 to 49 Years

- No difference in breast cancer mortality in the counties prior to the introduction of screening
- During the study period
  - 803 breast cancer deaths in the study group (**7.3 million person-years)**
  - 1238 breast cancer deaths in the control group **(8.8 million person-years).**

Cancer 2010; published online: 29 SEP 2010

Map of Study and Control Group Areas, and Crude Cumulative Breast Cancer Mortality per 100,000 Person Years

Figure 1. This is a simplified map of the areas that were included in the study group and the control group.

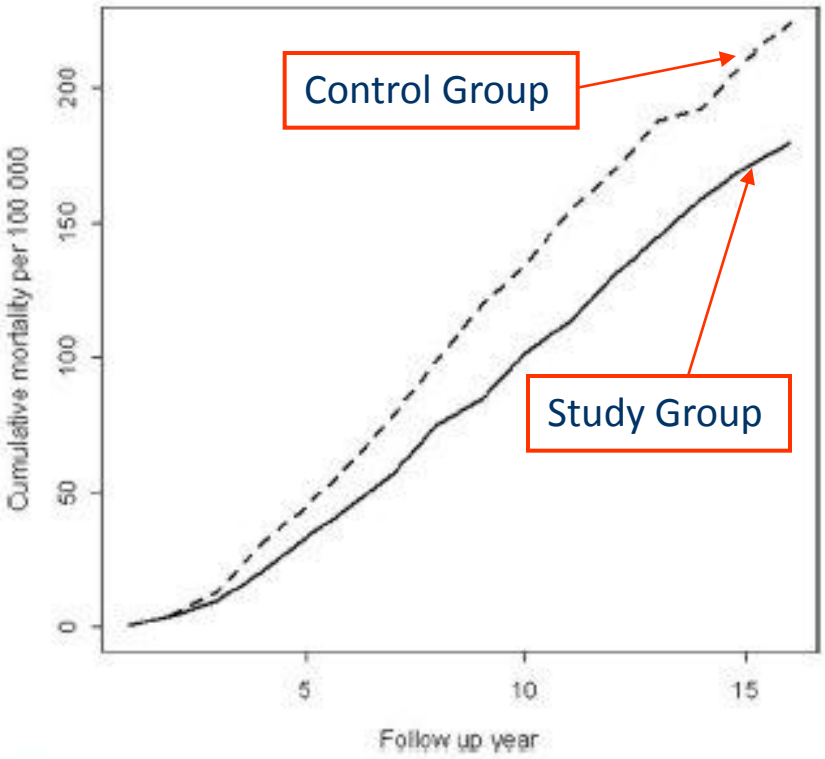
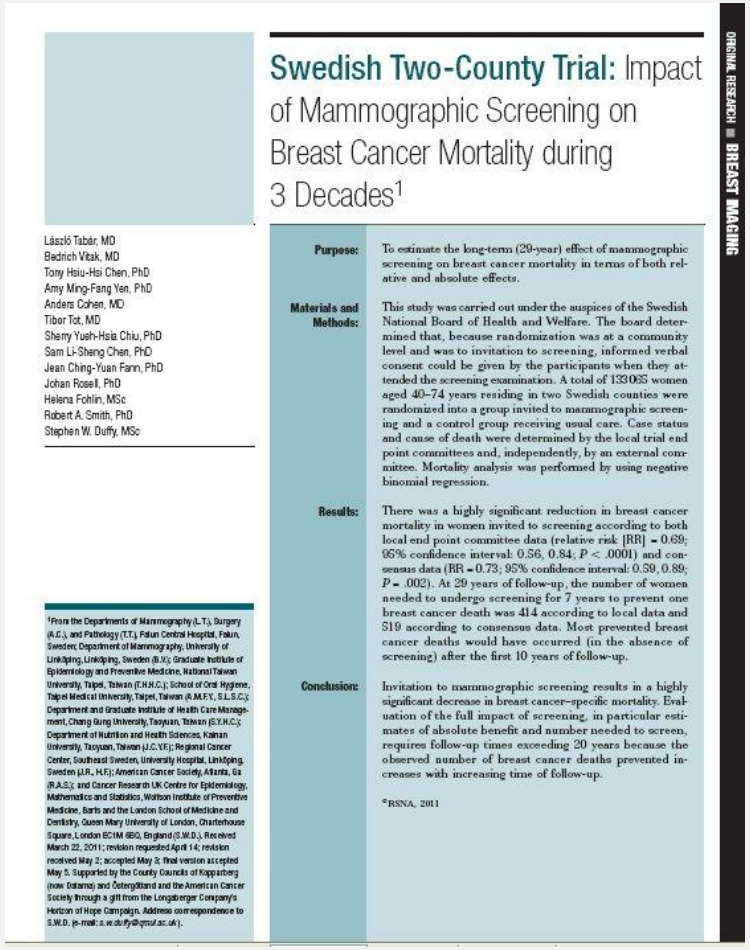


Figure 2. This chart illustrates the crude cumulative breast cancer mortality per 100,000 person-years. Solid line indicates the study group; dashed line, control group.

RR = 0.74; 95% CI 0.66 – 0.83)

Cancer 2010; published online: 29 SEP 2010

29 Year Follow-up of the Swedish Two County Trial



ORIGINAL RESEARCH ■ BREAST IMAGING

Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades[1]

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Purpose: To estimate the long-term (29-year) effect of mammographic screening on breast cancer mortality in terms of both relative and absolute effects.

Materials and Methods: This study was carried out under the auspices of the Swedish National Board of Health and Welfare. The board determined that, because randomization was at a community level and was to invitation to screening, informed verbal consent could be given by the participants when they attended the screening examination. A total of 133 065 women aged 40–74 years residing in two Swedish counties were randomized into a group invited to mammographic screening and a control group receiving usual care. Case status and cause of death were determined by the local trial end point committees and, independently, by an external committee. Mortality analysis was performed by using negative binomial regression.

Results: There was a highly significant reduction in breast cancer mortality in women invited to screening according to both local end point committee data (relative risk [RR] = 0.69; 95% confidence interval: 0.56, 0.84; $P < .0001$) and consensus data (RR = 0.73; 95% confidence interval: 0.59, 0.89; $P = .002$). At 29 years of follow-up, the number of women needed to undergo screening for 7 years to prevent one breast cancer death was 414 according to local data and 519 according to consensus data. Most prevented breast cancer deaths would have occurred (in the absence of screening) after the first 10 years of follow-up.

Conclusion: Invitation to mammographic screening results in a highly significant decrease in breast cancer–specific mortality. Evaluation of the full impact of screening, in particular estimates of absolute benefit and number needed to screen, requires follow-up times exceeding 20 years because the observed number of breast cancer deaths prevented increases with increasing time of follow-up.

[1]From the Departments of Mammography (L.T.), Surgery (A.C.), and Pathology (T.T.), Falun Central Hospital, Falun, Sweden; Department of Mammography, University of Linköping, Linköping, Sweden (B.V.); Graduate Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan (T.H.H.C.); School of Oral Hygiene, Taipei Medical University, Taipei, Taiwan (A.M.F.Y., S.L.S.C.); Department and Graduate Institute of Health Care Management, Chang Gung University, Taoyuan, Taiwan (S.Y.H.C.); Department of Nutrition and Health Sciences, Kainan University, Taoyuan, Taiwan (J.C.Y.F.); Regional Cancer Center, Southeast Sweden, University Hospital, Linköping, Sweden (J.R., H.F.); American Cancer Society, Atlanta, Ga (R.A.S.); and Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, England (S.W.D.). Received March 22, 2011; revision requested April 14; revision received May 2; accepted May 3; final version accepted May 5. Supported by the County Councils of Kopparberg (now Dalarna) and Östergötland and the American Cancer Society through a gift from the Longaberger Company's Horizon of Hope Campaign. Address correspondence to S.W.D. (e-mail: s.w.duffy@qmul.ac.uk).

- 133,065 women ages 40-47 randomized to screening or usual care
- Screening phase = 7 years
- Screening interval
  - 40-49 = 24 months
  - 50-74 = 33 months
- Protocol
  - One view mammography
  - Single reader
  - No physical exam
- 1st mortality results published in 1985

- **Two important points:**
  - Long term follow-up is necessary to measure the full benefit of breast cancer screening
  - With long follow-up, the number-needed-to-screen to save one life steadily improves

Table 3

Local End Point Committee Data: Breast Cancer Deaths Avoided and Number of Women Needed to Screen for 7 Years to Prevent One Death according to Follow-up Time

Time between Randomization and Follow-up (y)	RR*	Deaths from Breast Cancer in ASP Group	Expected Deaths in ASP Group†	Deaths Prevented in ASP Group	No. of Women Needed to Screen*
10	0.74 (0.57, 0.98)	206	277	71	922 (515, 4410)
15	0.70 (0.56, 0.87)	284	408	124	526 (351, 1055)
20	0.70 (0.57, 0.85)	324	465	141	464 (316, 871)
25	0.70 (0.57, 0.85)	347	497	150	436 (297, 815)
29		351	509	158	414 (286, 748)

31% fewer deaths
After 29 years

* Numbers in parentheses a

† Expected deaths if the ASP had the same mortality rate as the PSP, calculated by dividing the observed deaths by the RR (eg, at 10 years, 206/0.7435 = 277 expected deaths).

Radiology June 28, 2011 110469

Number Needed to Screen (NNS) vs. Number Needed to Invite (NNI) to Avoid One Breast Cancer Death

Age Group	Swedish data (NNS)[1]	USPSTF (NNI)[2]
Overall	**464**	**1224**
40-49	726	1,904
50-59	260	1,339
60-69	198	377

[1] Number Needed to Screen (NNS) Every 2 Years (40-49—18 mos.) for a Period of Ten Years, with 20 Years of Follow-up, to Save One Life.

[2] Number Needed to Invite (NNI), estimated from randomized trial data with variable screening intervals, variable screening rounds, different rates of adherence and non-compliance, and variable periods of follow-up (14 yrs.)

Adverse Effects and Harms

- False positive findings
- Anxiety
- Overdiagnosis

Performance Measures for 3.6 Million Screening Mammography Examinations, 1996-2006, NCI-BCSC

	Sensitivity[2]	Specificity[3]	PPV[4]	Recall[5]
Total	80.2%	91.4%	4.3%	8.9%
Age 40-49	70.8%	89.8%	1.5%	10.3%
Age 45-49	74.3%	89.8%	2.3%	10.3%
Age 50-54	78.4%	90.9%	3.3%	9.2%
Age 55-59	81.6%	91.5%	4.6%	8.8%
Age 60-64	80.0%	91.9%	5.4%	8.4%
Age 65-69	82.5%	92.4%	6.3%	8.0%
Age 70-74	82.9%	93.1%	7.9%	7.3%
Age 75-89	84.5%	93.6%	9.8%	6.9%

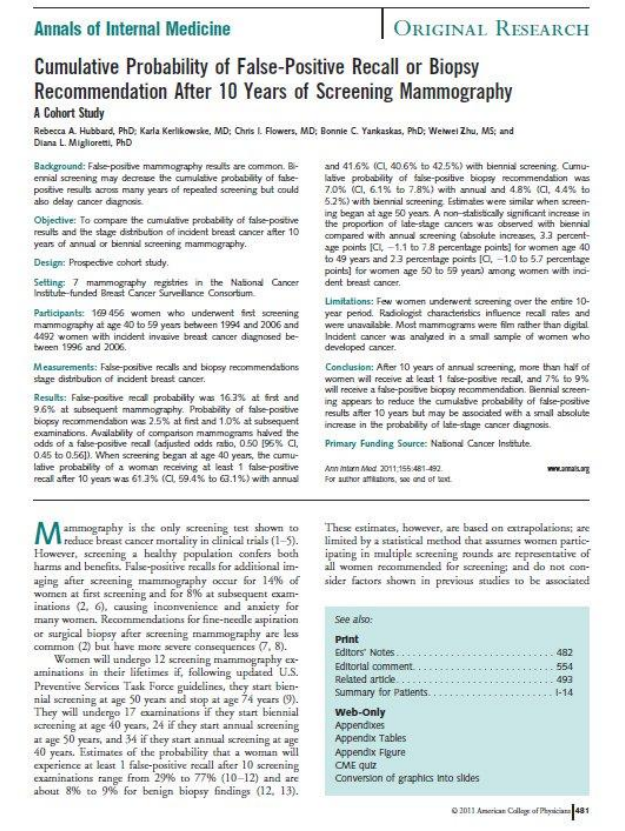
Two Key Points

1) There is *no* dramatic improvement in performance at age 50

2) Sensitivity, Specificity, and PPV improve steadily with increasing age

Source: National Cancer Institute Breast Cancer Surveillance Consortium

10 Year Probability of a False Positive Exam Based on Age at First Mammogram



Annals of Internal Medicine | ORIGINAL RESEARCH

Cumulative Probability of False-Positive Recall or Biopsy Recommendation After 10 Years of Screening Mammography

A Cohort Study

Rebecca A. Hubbard, PhD; Karla Kerlikowske, MD; Chris I. Flowers, MD; Bonnie C. Yankaskas, PhD; Weiwei Zhu, MS; and Diana L. Miglioretti, PhD

Background: False-positive mammography results are common. Biennial screening may decrease the cumulative probability of false-positive results across many years of repeated screening but could also delay cancer diagnosis.

Objective: To compare the cumulative probability of false-positive results and the stage distribution of incident breast cancer after 10 years of annual or biennial screening mammography.

Design: Prospective cohort study.

Setting: 7 mammography registries in the National Cancer Institute–funded Breast Cancer Surveillance Consortium.

Participants: 169 456 women who underwent first screening mammography at age 40 to 59 years between 1994 and 2006 and 4492 women with incident invasive breast cancer diagnosed between 1996 and 2006.

Measurements: False-positive recalls and biopsy recommendations stage distribution of incident breast cancer.

Results: False-positive recall probability was 16.3% at first and 9.6% at subsequent mammography. Probability of false-positive biopsy recommendation was 2.5% at first and 1.0% at subsequent examinations. Availability of comparison mammograms halved the odds of a false-positive recall (adjusted odds ratio, 0.50 [95% CI, 0.45 to 0.56]). When screening began at age 40 years, the cumulative probability of a woman receiving at least 1 false-positive recall after 10 years was 61.3% (CI, 59.4% to 63.1%) with annual and 41.6% (CI, 40.6% to 42.5%) with biennial screening. Cumulative probability of false-positive biopsy recommendation was 7.0% (CI, 6.1% to 7.8%) with annual and 4.8% (CI, 4.4% to 5.2%) with biennial screening. Estimates were similar when screening began at age 50 years. A non–statistically significant increase in the proportion of late-stage cancers was observed with biennial compared with annual screening (absolute increases, 2.3 percentage points [CI, −1.1 to 7.8 percentage points] for women age 40 to 49 years and 2.3 percentage points [CI, −1.0 to 5.7 percentage points] for women age 50 to 59 years) among women with incident breast cancer.

Limitations: Few women underwent screening over the entire 10-year period. Radiologist characteristics influence recall rates and were unavailable. Most mammograms were film rather than digital. Incident cancer was analyzed in a small sample of women who developed cancer.

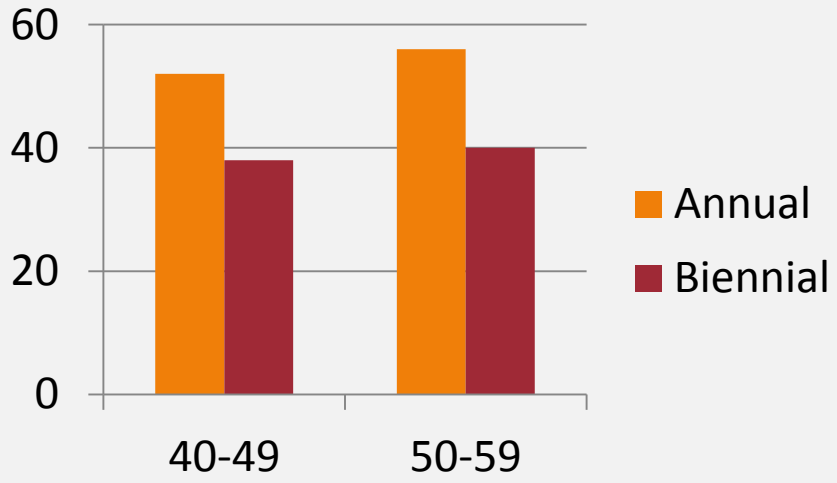
Conclusion: After 10 years of annual screening, more than half of women will receive at least 1 false-positive recall, and 7% to 9% will receive a false-positive biopsy recommendation. Biennial screening appears to reduce the cumulative probability of false-positive results after 10 years but may be associated with a small absolute increase in the probability of late-stage cancer diagnosis.

Primary Funding Source: National Cancer Institute.

Ann Intern Med. 2011;155:481-492. www.annals.org
For author affiliations, see end of text.

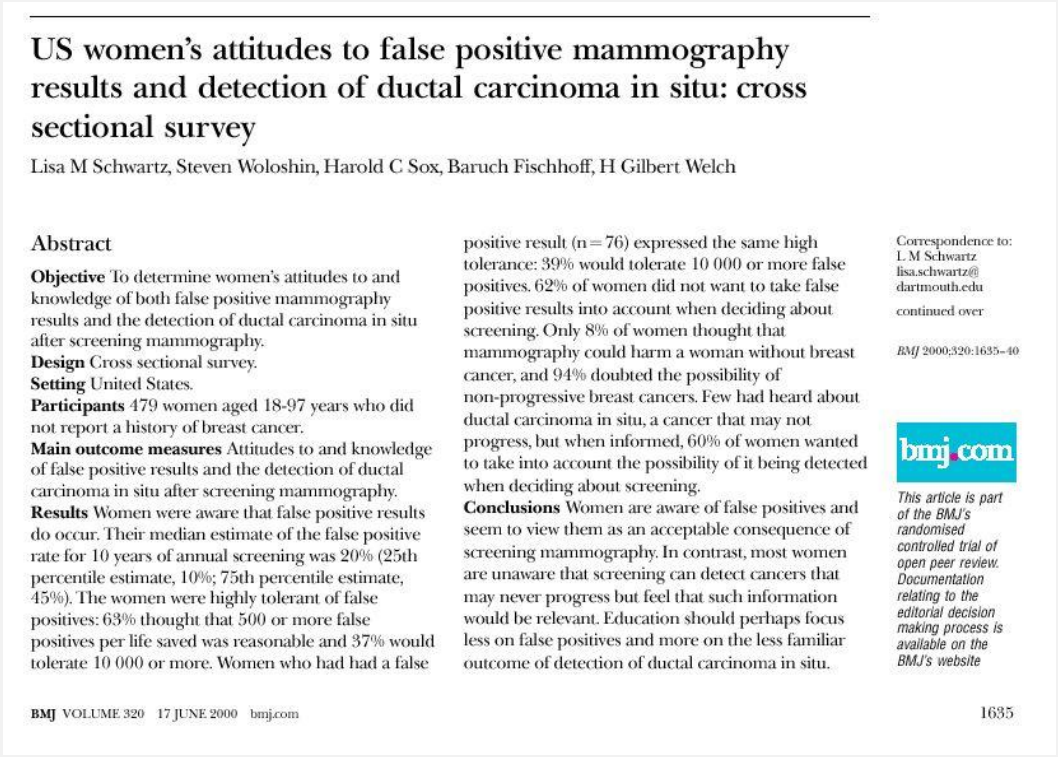
Mammography is the only screening test shown to reduce breast cancer mortality in clinical trials (1–5). However, screening a healthy population confers both harms and benefits. False-positive recalls for additional imaging after screening mammography occur for 14% of women at first screening and for 8% at subsequent examinations (2, 6), causing inconvenience and anxiety for many women. Recommendations for fine-needle aspiration or surgical biopsy after screening mammography are less common (2) but have more severe consequences (7, 8).

Women will undergo 12 screening mammography examinations in their lifetimes if, following updated U.S. Preventive Services Task Force guidelines, they start biennial screening at age 50 years and stop at age 74 years (9). They will undergo 17 examinations if they start biennial screening at age 40 years, 24 if they start annual screening at age 50 years, and 34 if they start annual screening at age 40 years. Estimates of the probability that a woman will experience at least 1 false-positive recall after 10 screening examinations range from 29% to 77% (10–12) and are about 8% to 9% for benign biopsy findings (12, 13). These estimates, however, are based on extrapolations; are limited by a statistical method that assumes women participating in multiple screening rounds are representative of all women recommended for screening; and do not consider factors shown in previous studies to be associated



Overall

- False-positive recall probability:
  - 16.3% at first mammogram
  - 9.6% at subsequent exams
- Probability of false-positive biopsy recommendation:
  - 2.5% at first mammogram
  - 1.0% at subsequent exams



US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey

Lisa M Schwartz, Steven Woloshin, Harold C Sox, Baruch Fischhoff, H Gilbert Welch

Abstract

Objective To determine women's attitudes to and knowledge of both false positive mammography results and the detection of ductal carcinoma in situ after screening mammography.
Design Cross sectional survey.
Setting United States.
Participants 479 women aged 18-97 years who did not report a history of breast cancer.
Main outcome measures Attitudes to and knowledge of false positive results and the detection of ductal carcinoma in situ after screening mammography.
Results Women were aware that false positive results do occur. Their median estimate of the false positive rate for 10 years of annual screening was 20% (25th percentile estimate, 10%; 75th percentile estimate, 45%). The women were highly tolerant of false positives: 63% thought that 500 or more false positives per life saved was reasonable and 37% would tolerate 10 000 or more. Women who had had a false positive result (n = 76) expressed the same high tolerance: 39% would tolerate 10 000 or more false positives. 62% of women did not want to take false positive results into account when deciding about screening. Only 8% of women thought that mammography could harm a woman without breast cancer, and 94% doubted the possibility of non-progressive breast cancers. Few had heard about ductal carcinoma in situ, a cancer that may not progress, but when informed, 60% of women wanted to take into account the possibility of it being detected when deciding about screening.
Conclusions Women are aware of false positives and seem to view them as an acceptable consequence of screening mammography. In contrast, most women are unaware that screening can detect cancers that may never progress but feel that such information would be relevant. Education should perhaps focus less on false positives and more on the less familiar outcome of detection of ductal carcinoma in situ.

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continued over

BMJ 2000;320:1635–40

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Findings

1. Women had a high degree of awareness about false positives

2. Women demonstrated a high tolerance of false positives, i.e. 63% felt 500 false positives per life saved was reasonable

– 63% did not regard false positives as an important factor in decisions about screening

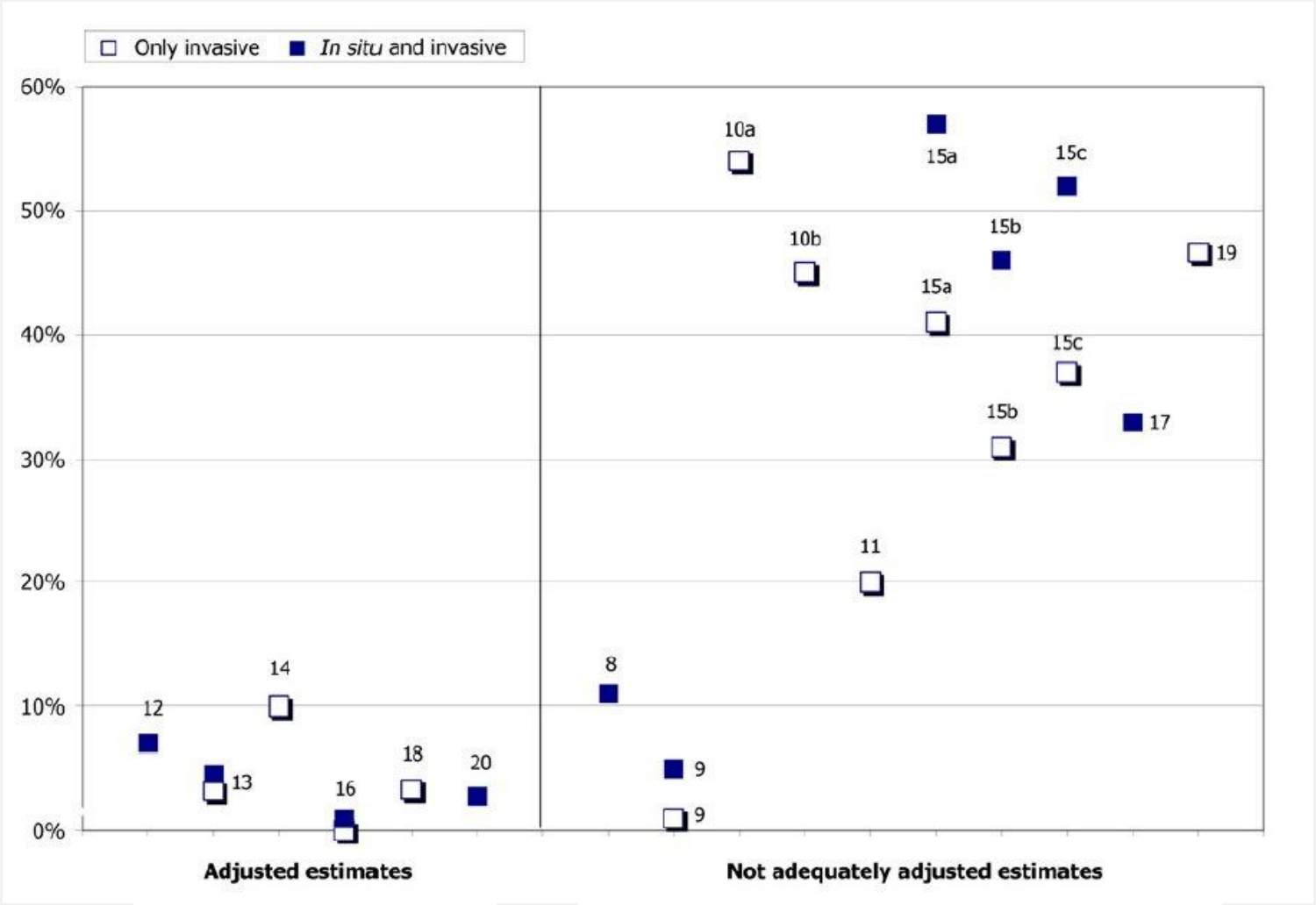
Overdiagnosis

- **Estimates of overdiagnosis of screen detected breast tumors range from 0 - > 50%, with some claiming that it is *the* major harm of screening**

- **Overdiagnosis**- is diagnosis by screening of cancer that never would have arisen symptomatically in the person's lifetime, and never would have been detected if screening had not taken place

- **Reality:** To estimate overdiagnosis, we must examine incidence rates over time, **and adjust for:**
  - Pre-existing trend of increasing incidence
  - Lead time

Overdiagnosis Estimates Based on Adjustment for Incidence Trends and Lead-time

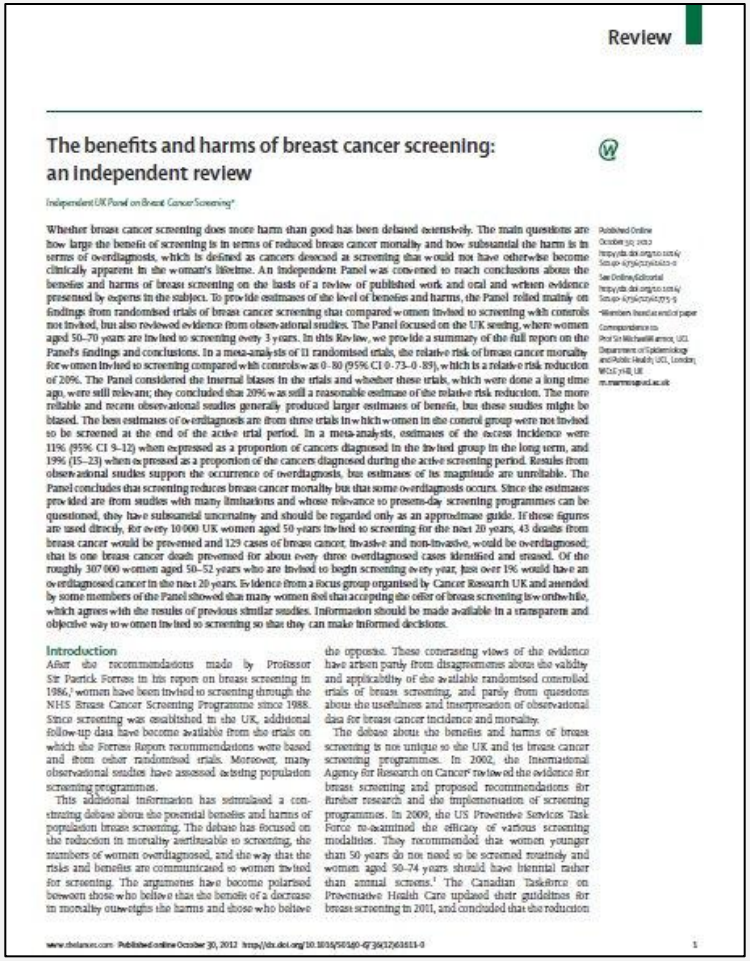


Adjusted Estimates

Not Adequately Adjusted Estimates

Puliti, et al. JMS 2012;19(1)

UK Independent Review of the Benefits and Harms of Breast Cancer Screening



Review

The benefits and harms of breast cancer screening: an independent review

Independent UK Panel on Breast Cancer Screening*

Whether breast cancer screening does more harm than good has been debated extensively. The main questions are how large the benefit of screening is in terms of reduced breast cancer mortality and how substantial the harm is in terms of overdiagnosis, which is defined as cancers detected at screening that would not have otherwise become clinically apparent in the woman's lifetime. An independent Panel was convened to reach conclusions about the benefits and harms of breast screening on the basis of a review of published work and oral and written evidence presented by experts in the subject. To provide estimates of the level of benefits and harms, the Panel relied mainly on findings from randomised trials of breast cancer screening that compared women invited to screening with controls not invited, but also reviewed evidence from observational studies. The Panel focused on the UK setting, where women aged 50–70 years are invited to screening every 3 years. In this Review, we provide a summary of the full report on the Panel's findings and conclusions. In a meta-analysis of 11 randomised trials, the relative risk of breast cancer mortality for women invited to screening compared with controls was 0·80 (95% CI 0·73–0·89), which is a relative risk reduction of 20%. The Panel considered the internal biases in the trials and whether these trials, which were done a long time ago, were still relevant; they concluded that 20% was still a reasonable estimate of the relative risk reduction. The more reliable and recent observational studies generally produced larger estimates of benefit, but these studies might be biased. The best estimates of overdiagnosis are from three trials in which women in the control group were not invited to be screened at the end of the active trial period. In a meta-analysis, estimates of the excess incidence were 11% (95% CI 9–12) when expressed as a proportion of cancers diagnosed in the invited group in the long term, and 19% (15–23) when expressed as a proportion of the cancers diagnosed during the active screening period. Results from observational studies support the occurrence of overdiagnosis, but estimates of its magnitude are unreliable. The Panel concludes that screening reduces breast cancer mortality but that some overdiagnosis occurs. Since the estimates provided are from studies with many limitations and whose relevance to present-day screening programmes can be questioned, they have substantial uncertainty and should be regarded only as an approximate guide. If these figures are used directly, for every 10 000 UK women aged 50 years invited to screening for the next 20 years, 43 deaths from breast cancer would be prevented and 129 cases of breast cancer, invasive and non-invasive, would be overdiagnosed; that is one breast cancer death prevented for about every three overdiagnosed cases identified and treated. Of the roughly 307 000 women aged 50–52 years who are invited to begin screening every year, just over 1% would have an overdiagnosed cancer in the next 20 years. Evidence from a focus group organised by Cancer Research UK and attended by some members of the Panel showed that many women feel that accepting the offer of breast screening is worthwhile, which agrees with the results of previous similar studies. Information should be made available in a transparent and objective way to women invited to screening so that they can make informed decisions.

Published Online October 30, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61611-0

See Online/Editorial http://dx.doi.org/10.1016/S0140-6736(12)61775-9

*Members listed at end of paper

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Introduction

After the recommendations made by Professor Sir Patrick Forrest in his report on breast screening in 1986,[1] women have been invited to screening through the NHS Breast Cancer Screening Programme since 1988. Since screening was established in the UK, additional follow-up data have become available from the trials on which the Forrest Report recommendations were based and from other randomised trials. Moreover, many observational studies have assessed existing population screening programmes.

This additional information has stimulated a continuing debate about the potential benefits and harms of population breast screening. The debate has focused on the reduction in mortality attributable to screening, the numbers of women overdiagnosed, and the way that the risks and benefits are communicated to women invited for screening. The arguments have become polarised between those who believe that the benefit of a decrease in mortality outweighs the harms and those who believe the opposite. These contrasting views of the evidence have arisen partly from disagreements about the validity and applicability of the available randomised controlled trials of breast screening, and partly from questions about the usefulness and interpretation of observational data for breast cancer incidence and mortality.

The debate about the benefits and harms of breast screening is not unique to the UK and its breast cancer screening programmes. In 2002, the International Agency for Research on Cancer[2] reviewed the evidence for breast screening and proposed recommendations for further research and the implementation of screening programmes. In 2009, the US Preventive Services Task Force[3] re-examined the efficacy of various screening modalities. They recommended that women younger than 50 years do not need to be screened routinely and women aged 50–74 years should have biennial rather than annual screens.[3] The Canadian Taskforce on Preventative Health Care[4] updated their guidelines for breast screening in 2011, and concluded that the reduction

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- *"The Panel concludes that the UK breast screening programmes confer significant benefit and should continue. The greater the proportion of women who accept the invitation to be screened, the greater is the benefit to the public health in terms of reduction in mortality from breast cancer."*

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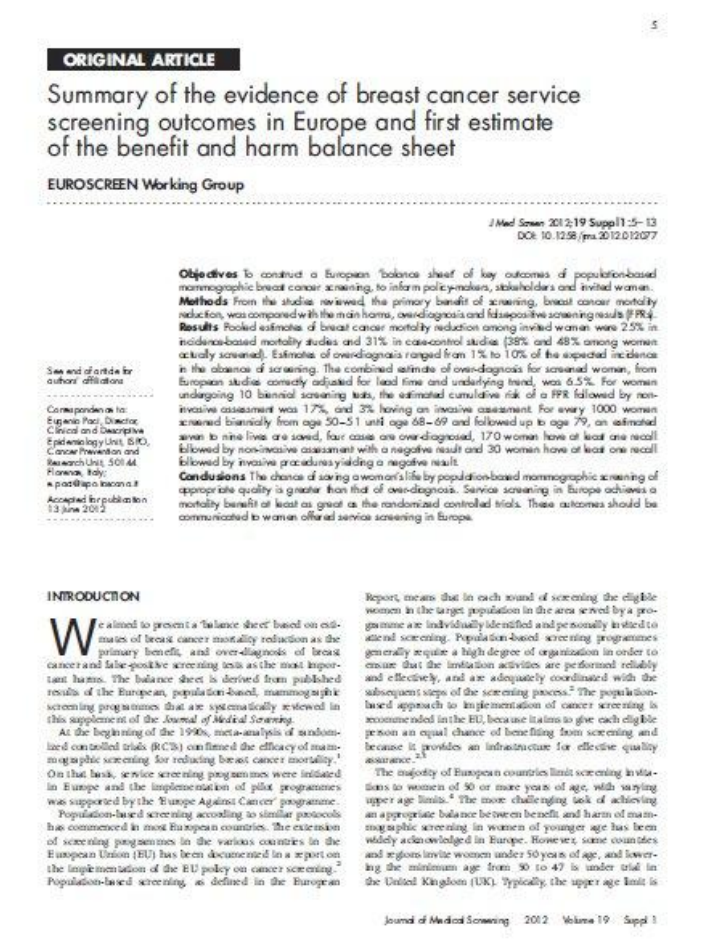
Absolute risk reduction, expressed as number of women who need to be invited or screened to prevent one breast cancer death, in the trials of breast cancer screening

	Description	Number of women
This review	Based on an RR reduction of 20% for women aged 55–79 years in the UK	235 women invited, 180 women screened
Cochrane review[5]	Absolute risk reduction based on the 13-year follow-up in the trials considered adequately randomised	2000 women invited
US Task Force[9]	Based on 7 years of screening and 13 years of follow-up	1339 women invited aged 50–59 years, and 377 invited aged 60–69 years
Canadian Task Force[4]	Women aged 50–69 years screened every 2–3 years for about 11 years	720 women screened
Duffy et al, 2010[12]	Based on 22-year follow-up of women aged 50–69 years in the Swedish Two-County trial, assuming that the absolute risk reduction for the 7 years of screening can be multiplied up to reflect 20 years in the UK screening programmes	113 women screened
Beral et al, 2011[13]	Women aged 50–70 years regularly screened for 10 years, based on summary of published evidence	400 women screened

RR=relative risk.

Which estimate of the number needed to screen commonly is quoted in the medical literature and the press about the limits of modern mammography? The estimate from the Cochrane Collaboration

“Balance Sheet” based on the European breast cancer service screening programs



ORIGINAL ARTICLE

Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet

EUROSCREEN Working Group

J Med Screen 2012;19 Suppl 1:5–13
DOI: 10.1258/jms.2012.012077

Objectives To construct a European 'balance sheet' of key outcomes of population-based mammographic breast cancer screening, to inform policy-makers, stakeholders and invited women.
Methods From the studies reviewed, the primary benefit of screening, breast cancer mortality reduction, was compared with the main harms, over-diagnosis and false-positive screening results (FPRs).
Results Pooled estimates of breast cancer mortality reduction among invited women were 2.5% in incidence-based mortality studies and 31% in case-control studies (38% and 48% among women actually screened). Estimates of over-diagnosis ranged from 1% to 10% of the expected incidence in the absence of screening. The combined estimate of over-diagnosis for screened women, from European studies correctly adjusted for lead time and underlying trend, was 6.5%. For women undergoing 10 biennial screening tests, the estimated cumulative risk of a FPR followed by non-invasive assessment was 17%, and 3% having an invasive assessment. For every 1000 women screened biennially from age 50–51 until age 68–69 and followed up to age 79, an estimated seven to nine lives are saved, four cases are over-diagnosed, 170 women have at least one recall followed by non-invasive assessment with a negative result and 30 women have at least one recall followed by invasive procedures yielding a negative result.
Conclusions The chance of saving a woman's life by population-based mammographic screening of appropriate quality is greater than that of over-diagnosis. Service screening in Europe achieves a mortality benefit at least as great as the randomized controlled trials. These outcomes should be communicated to women offered service screening in Europe.

See end of article for authors' affiliations

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INTRODUCTION

We aimed to present a 'balance sheet' based on estimates of breast cancer mortality reduction as the primary benefit, and over-diagnosis of breast cancer and false-positive screening tests as the most important harms. The balance sheet is derived from published results of the European, population-based, mammographic screening programmes that are systematically reviewed in this supplement of the *Journal of Medical Screening*.

At the beginning of the 1990s, meta-analysis of randomized controlled trials (RCTs) confirmed the efficacy of mammographic screening for reducing breast cancer mortality.[1] On that basis, service screening programmes were initiated in Europe and the implementation of pilot programmes was supported by the 'Europe Against Cancer' programme.

Population-based screening according to similar protocols has commenced in most European countries. The extension of screening programmes in the various countries in the European Union (EU) has been documented in a report on the implementation of the EU policy on cancer screening.[2] Population-based screening, as defined in the European Report, means that in each round of screening the eligible women in the target population in the area served by a programme are individually identified and personally invited to attend screening. Population-based screening programmes generally require a high degree of organization in order to ensure that the invitation activities are performed reliably and effectively, and are adequately coordinated with the subsequent steps of the screening process.[3] The population-based approach to implementation of cancer screening is recommended in the EU, because it aims to give each eligible person an equal chance of benefiting from screening and because it provides an infrastructure for effective quality assurance.[2,3]

The majority of European countries limit screening invitations to women of 50 or more years of age, with varying upper age limits.[4] The more challenging task of achieving an appropriate balance between benefit and harm of mammographic screening in women of younger age has been widely acknowledged in Europe. However, some countries and regions invite women under 50 years of age, and lowering the minimum age from 50 to 47 is under trial in the United Kingdom (UK). Typically, the upper age limit is

- **Assumption: Women ages 50-51 screened biennially until age 69 and followed until age 79**

- Cumulative risk of BC = 6.7%
- Cumulative risk of death = 3%
- Reduction in BC mortality = 38-48%
- Risk of overdiagnosis = 1 – 10%
- Cumulative risk of a FP with and without biopsy = 3% and 17%

Table 4 Balance sheet for 1000 women aged 50–51 years, screened biennially until 69 years (according to the EU policy on cancer screening[3]) and followed until 79 years

Outcome	For every 1000 women screened for 20 years:	The number of women that need to be screened:
Number of breast cancer cases diagnosed	71	14 women: to diagnose 1 case
BC mortality reduction	7–9 women's lives are saved (out of 30 BC deaths expected)*	111–143 women: to save 1 life
Over-diagnosis	4 cases are over-diagnosed (in addition to 67 BC expected)	250 women: to over-diagnose 1 case
False-positive test results among women without breast cancer	200 women recalled for further assessment procedures: 170 women with non-invasive assessment only 30 women with invasive assessment	6 women: to have 1 with at least one who has non-invasive assessment only 33 women: to have 1 with at least one invasive assessment

BC, breast cancer; EU, European Union

*19 out of the 30 expected BC death were diagnosed in ages 50–69

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 367;11 NEJM.ORG SEPTEMBER 13, 2012

There Is More to Life Than Death

Pamela Hartzband, M.D., and Jerome Groopman, M.D.

Physicians and patients alike crave certainty. We all want to know that we're making the best decisions about our health. But

Daniel Bernoulli, an 18th-century mathematician who devised a formula to determine the "best" choice.[1] When an outcome is un-

In clinical decision analysis, the outcome that is generally measured is death. This outcome fits neatly into the Bernoulli formula

- .. "when experts judge risk, their responses correlate highly with technical estimates of annual fatalities." However, most people's conceptualization of risk is much richer than that of the experts and reflects legitimate concerns that are typically omitted from expert risk assessments."

How should we be thinking about harms?

- We should recognize that:
  - Harms range in frequency and experience from minor & inconsequential to quite serious
  - Recognize that most individuals do not experience harms in the same way
  - ***Harms occur—we can take steps to reduce them***
    - We need to do a better job of informing adults undergoing screening about what to expect
    - Stronger quality assurance programs are needed to reduce the rate of harms—the rate of harms is not fixed

Measuring benefits vs. harms

- Guideline developers should agree on standardized methods/metrics for measuring benefit and harms
  - *This affects the benefits vs. harms estimate*

- Is there a threshold of benefit vs. harm where screening *could* be recommended when it is not?
  - *If the observed balance of benefits and harms could be improved, shouldn't those targets be identified?*

ACS Lung Cancer Screening Guidelines, 2013

CA CANCER J CLIN 2013;000:000-000

American Cancer Society Lung Cancer Screening Guidelines

Richard Wender, MD[1]; Elizabeth T. H. Fontham, MPH, DrPH[2]; Emilio Barrera, Jr, MD[3]; Graham A. Colditz, MD, DrPH[4]; Timothy R. Church, PhD[5]; David S. Ettinger, MD[6]; Ruth Etzioni, PhD[7]; Christopher R. Flowers, MD[8]; C. Scott Gazelle, MD, MPH, PhD[9]; Douglas K. Kelsey, MD, PhD[10]; Samuel J. LaMonte, MD[11]; James S. Michaelson, PhD[12]; Kevin C. Oeffinger, MD[13]; Ya-Chen Tina Shih, PhD[14]; Daniel C. Sullivan, MD[15]; William Travis, MD[16]; Louise Walter, MD[17]; Andrew M. D. Wolf, MD[18]; Otis W. Brawley, MD[19]; Robert A. Smith, PhD[20]

Findings from the National Cancer Institute's National Lung Screening Trial established that lung cancer mortality in specific high-risk groups can be reduced by annual screening with low-dose computed tomography. These findings indicate that the adoption of lung cancer screening could save many lives. Based on the results of the National Lung Screening Trial, the American Cancer Society is issuing an initial guideline for lung cancer screening. This guideline recommends that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients aged 55 years to 74 years who have at least a 30–pack-year smoking history and who currently smoke or have quit within the past 15 years. A process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with low-dose computed tomography should occur before any decision is made to initiate lung cancer screening. Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. Screening should not be viewed as an alternative to smoking cessation. CA Cancer J Clin 2013;000:000-000. ©2013 American Cancer Society.

Keywords: humans, lung neoplasms, mortality, radiography, radiation dosage, randomized controlled trials as topic, risk, risk reduction behavior, x-ray, computed tomography, adverse effects, lung cancer screening

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We thank Timothy Byers, MD, MPH, for his contributions as an American Cancer Society Cancer Screening Guidelines Development Member.

DISCLOSURES: Dr. Flowers has received consulting fees from Celgene Corporation; Spectrum; Seattle Genetics, Inc; OptumRx Clinical Care Options; and Education Concepts Group. He has performed contracted research for Millennium Pharmaceuticals, Celgene Corporation, Spectrum, Gilead Pharmaceuticals, and Janssen Pharmaceuticals. Dr. Gazelle is a consultant to GE Healthcare. His work for GE Healthcare is not directly related to this article. Dr. Kelsey is employed by Eli Lilly and Company.

[1]2013 American Cancer Society, Inc. doi:10.3322/caac.21172. Available online at caancerjournal.com

- Clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients aged 55 years to 74 years who have at least a 30–pack-year smoking history and who currently smoke or have quit within the past 15 years.

- **A process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with low-dose computed tomography should occur before any decision is made to initiate lung cancer screening.**

- Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. ***Screening should not be viewed as an alternative to smoking cessation***.

Available at: http://onlinelibrary.wiley.com/doi/10.3322/caac.v63.2/issuetoc

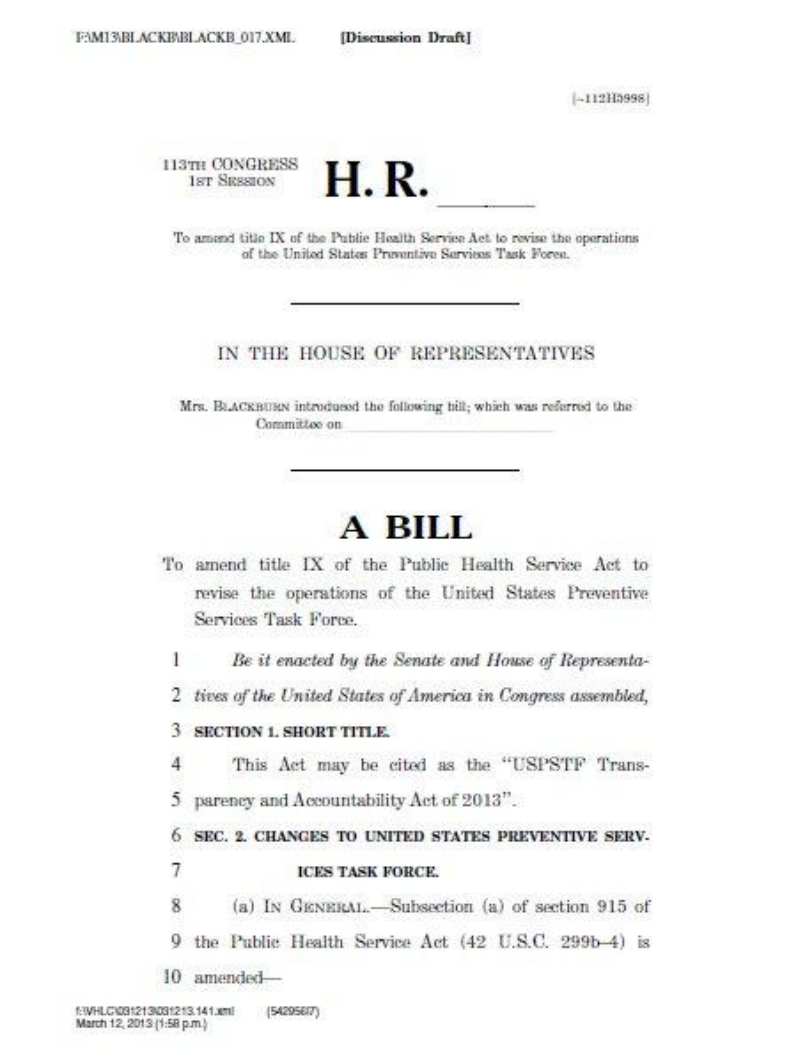
Current Lung Cancer Screening Guidelines

Published: 31 January, 2013
Journal of Carcinogenesis 2012, 11:2

Table 1: Recommendations of various organizations for lung cancer screening

Name of society	Year	Recommendation
National comprehensive cancer network (NCCN)	2012	Screen: Age 55-74, ≥30 pack years, smoking cessation within previous 15 year (category 1) Screen: Age ≥50-74, ≥20 pack years, and one additional risk factor other than second hand smoke (category 2B). Risk factors including exposure to radon and occupational contaminants, cancer history, family history, COPD, pulmonary fibrosis Do not screen moderate or low risk subjects
American association for thoracic surgery (AATS)	2012	Screen: Age 55-79, ≥30 pack years (tier 1) Screen: Age≥50, ≥20 pack years and ≥5% risk of developing lung cancer in 5 years (category 2). Risk factors including COPD with FEV1<70%, environmental/occupational exposures, prior cancer/thoracic radiation, genetic/family history Screen: Lung cancer survivors having completed 4 years of surveillance without recurrence as long as they can tolerate potential treatment for lung cancer. (tier 2)
American cancer society (ACS)-interim guidelines	**2013**	Follow NLST enrollment criteria Make shared informed decision with physician Participate in an institution with multidisciplinary team and expertize in LDCT interpretation Vigorous smoking cessation
American lung association (ALA)	2012	Follow NLST enrollment criteria Encourage smoking cessation No chest radiograph for screening Screening centers should develop ethical practices for advertising and promoting screening Screening should be linked to best access multi-disciplinary teams
American college of chest physicians (ACCP) and american society of clinical oncology (ASCO)	2012	Screen the subjects who meet NLST enrollment criteria Screening should be done only in the setting that can provide comprehensive care similar to what the NLST participants received (grade 2B) No screening if: Age <55 or >74, smoking cessations >15 years ago, co-morbidities that preclude curative treatment of lung cancer, limited life expectancy (grade 2C)
United States Preventive Services Task Force (USPSTF	**2013**	**Update in progress, Expected in 2013**

USPSTF Transparency and Accountability Act of 2013



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[~112H5998]

113TH CONGRESS
1ST SESSION

H. R. _____

To amend title IX of the Public Health Service Act to revise the operations of the United States Preventive Services Task Force.

IN THE HOUSE OF REPRESENTATIVES

Mrs. BLACKBURN introduced the following bill; which was referred to the Committee on _____

A BILL

To amend title IX of the Public Health Service Act to revise the operations of the United States Preventive Services Task Force.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "USPSTF Transparency and Accountability Act of 2013".

SEC. 2. CHANGES TO UNITED STATES PREVENTIVE SERVICES TASK FORCE.

(a) IN GENERAL.—Subsection (a) of section 915 of the Public Health Service Act (42 U.S.C. 299b–4) is amended—

f:\VHLC\031213\031213.141.xml (5429567)
March 12, 2013 (1:58 p.m.)

- "IN GENERAL.—The Task Force shall be composed of individuals that collectively have appropriate scientific expertise, including in fields of health sciences research, health economics, health promotion, disease prevention, and clinical care. The Task Force shall include balanced representation of practicing primary and specialty care providers, patient and health care consumers, and relevant stakeholders from the medical products manufacturing community."

Alternative Approaches Guidelines Development and Setting Policy

- For All Options: ***Annual review of current recommendations***
- **Option 1**: USPSTF decisions and critiques should be referred by an independent group with open discussion and complete transparency
- **Option 2**: Eliminate linking preventive health to USPSTF *A & B* recommendations. Decisions made by an independent HHS committee with broad scientific, specialty, and consumer representation

Thank you