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Screening for Breast Cancer: Systematic Evidence Review Update for the U. S. Preventive Services Task Force

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Structured Abstract

Background: This systematic review is an update of new evidence since the 2002 U.S. Preventive Services Task Force recommendation on breast cancer screening.

Purpose: To determine the effectiveness of mammography screening in decreasing breast cancer mortality among average-risk women age 40-49 years and 70 years and older; the effectiveness of clinical breast examination (CBE) and breast self examination (BSE) in decreasing breast cancer mortality among women of any age; and harms of screening with mammography, CBE, and BSE.

Data Sources: The Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the fourth quarter of 2008), MEDLINE® searches (January 2001 to December 2008), reference lists, and Web of Science® searches for published studies and Breast Cancer Surveillance Consortium for screening mammography data.

Study Selection: Randomized, controlled trials with breast cancer mortality outcomes for screening effectiveness, and studies of various designs and multiple data sources for harms.

Data Extraction: Relevant data were abstracted, and study quality was rated by using established criteria.

Data Synthesis: Mammography screening reduces breast cancer mortality by 15% for women age 39-49 (relative risk [RR] 0.85; 95% credible interval [CrI], 0.75-0.96; 8 trials). Results are similar to those for women age 50-59 years (RR 0.86; 95% CrI, 0.75-0.99; 6 trials), but effects are less than for women age 60-69 years (RR 0.68; 95% CrI, 0.54-0.87; 2 trials). Data are lacking for women age 70 years and older. Radiation exposure from mammography is low. Patient adverse experiences are common and transient and do not affect screening practices. Estimates of overdiagnosis vary from 1-10%. Younger women have more false-positive mammography results and additional imaging but fewer biopsies than older women. Trials of CBE are ongoing; trials of BSE showed no reductions in mortality but increases in benign biopsy results.

Limitations: Studies of older women, digital mammography, and magnetic resonance imaging are lacking.

Conclusions: Mammography screening reduces breast cancer mortality for women age 39-69 years; data are insufficient for women age 70 years and older. False-positive mammography results and additional imaging are common. No benefit has been shown for CBE or BSE.

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CHAPTER 1. INTRODUCTION

Purpose of Review and Prior USPSTF Recommendation

This systematic evidence review is prepared for the U.S. Preventive Services Task Force (USPSTF) to update its previous recommendation on breast cancer screening for average-risk women.[1] In 2002, based on results of a systematic evidence review,[2, 3] the USPSTF recommended screening mammography, with or without clinical breast examination (CBE), every 1-2 years for women age 40 years and older. The USPSTF concluded that the evidence was insufficient to recommend for or against routine CBE alone to screen for breast cancer. The USPSTF also concluded that the evidence was insufficient to recommend for or against teaching or performing routine breast self examination (BSE). (See **Appendix A1** for abbreviations.)

The USPSTF made additional conclusions about the state of the evidence in 2002 including:

- The relative risk of breast cancer death for women randomized to mammography screening versus no mammography screening based on a meta-analysis of 8 trials was 0.84 (95% credible interval [CrI], 0.77-0.91).
- Older women have a higher risk of developing and dying from breast cancer, but they also have a higher chance of dying from other causes.
- Reductions in breast cancer mortality in studies using mammography alone versus studies using mammography and CBE are comparable. There is no direct evidence that CBE or BSE decreases mortality.
- Mammography sensitivity and specificity are higher than CBE sensitivity and specificity (77-95% and 94-97% versus 40-69% and 88-99%, respectively).
- The positive predictive value of mammography increases with age and with a family history of breast cancer.
- The benefit of regular mammography increases with age, while harms from mammography decrease with age. However, the age at which the benefits outweigh the harms is subjective. Biennial mammography is as effective as annual mammography for women age 50 years or older. Breast cancer progresses more rapidly in women younger than 50, and sensitivity of mammography is lower in this group. A clear advantage of annual mammography screening for women in this age group was not found.
- The majority of abnormal mammography examinations or CBEs are false-positives. Screening may increase the number of women undergoing treatment for lesions that might not pose a threat to their health.

Several evidence gaps were identified including:

- Definitive estimates of the proportion of benefits due to screening before age 50 years cannot be made. The cost-effectiveness of screening women younger than age 50 years is unknown.
- The age at which it is appropriate to cease breast cancer screening is unknown, as are the benefits of screening women older than 69 years.

- No screening trial has examined the benefits of CBE alone compared to no screening. The benefits of CBE as well as possible benefits of BSE are unknown.
- The magnitude of the harms associated with all methods and ages is unclear.
- None of the trials conducted to date has directly addressed the issue of the appropriate screening interval among any age group.

This update focuses on critical evidence gaps that were unresolved at the time of the 2002 recommendation, including the effectiveness of mammography in decreasing breast cancer mortality among average-risk women age 40-49 years and 70 years and older; the effectiveness of CBE and BSE in decreasing breast cancer mortality among women of any age; and harms of screening with mammography, CBE, and BSE. Studies of the cost-effectiveness of screening are described in the Appendix. Performance characteristics of screening methods (e.g., sensitivity and specificity) were previously reviewed and are not included in this update.

Condition Definition

Breast cancer is a proliferation of malignant cells that arises in the breast tissue, specifically in the terminal ductal-lobular unit. The term "breast cancer" represents a continuum of disease, ranging from noninvasive to invasive carcinoma.[4] Screening techniques may detect any of these disease entities as well as noncancerous lesions such as benign breast cysts.

Noninvasive carcinoma consists of epithelial proliferation confined to either the mammary duct, as with ductal carcinoma in situ (DCIS), or to the lobule, as with lobular carcinoma in situ (LCIS). Because noninvasive or in situ lesions do not invade the surrounding stroma, they cannot metastasize. LCIS is generally not considered a precursor lesion for invasive lobular carcinoma, but believed to be a marker for increased risk of invasive ductal or lobular breast cancer development in either breast.[5] However, DCIS is thought to be a precursor lesion to invasive ductal carcinoma. DCIS consists of a heterogeneous group of lesions with varying clinical behavior and pathologic characteristics. Common subtypes of DCIS include cribriform, comedo, micropapillary, papillary, and solid.[6]

Unlike noninvasive lesions, invasive breast cancers invade the basement membrane into the adjacent stroma, and therefore, have metastatic potential. The most common sites of metastasis include adjacent lymph nodes, lung, brain, and bone.[4] Approximately 70-80% of invasive breast cancers are invasive or infiltrating ductal carcinoma and approximately 10% are invasive lobular cancers.[4] Some other less common histologic subtypes of invasive breast cancer include apocrine, medullary, metaplastic, mucinous, papillary, and tubular.[4]

Prevalence and Burden of Disease

Breast cancer is the most frequently diagnosed non-cutaneous cancer and the second leading cause of cancer deaths after lung cancer among women in the United States.[7] 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.[8]

The incidence of breast cancer increases with age. Based on Surveillance Epidemiology and End Results (SEER) data from 2002-2004, the National Cancer Institute (NCI) estimates that 14.7% of women born in the United States today will develop breast cancer in their lifetimes, 12.3% with invasive disease.[9] The probability of a woman developing breast cancer in her forties is 1 in 69, in her fifties 1 in 38, and in her sixties 1 in 27.[10] Although the incidence rate of breast cancer has increased since the 1970s and 1980s, recent data suggest that it may have stabilized between 2001-2003. Overall, the incidence rate declined by 6.7% between 2002-2003 from 137.3 to 124.2 per 100,000 women.[11] Age-adjusted incidence rates for breast cancer also declined each year during 1999-2003.[12] This trend may be attributed to discontinuation of menopausal hormone therapy,[11, 13] and a plateau or decline in use of screening mammography.[14]

Breast cancer mortality has decreased since 1990 at a rate of 2.3% per year overall.[15, 16] Women age 40-50 years had a decline in breast cancer mortality of 3.3% per year. An evaluation of mortality trends from 1990 through 2000 from 7 studies attributed 28-65% of the decline to mammography screening, while the remainder of the decline was due to improved adjuvant treatments.[17]

Etiology and Natural History

The etiology of breast cancer is still largely unknown, although it is believed that breast cancer development is due to aberrations in cell cycle regulation. Current research focuses on clarifying the role of both inherited and acquired mutations in oncogenes and tumor suppressor genes and the consequences these mutations may have on the cell cycle, as well as investigating various prognostic biological markers. The contribution external influences, such as environmental exposures, may have on regulatory genes is unclear. Currently, no single environmental or dietary exposure has been found to cause a specific genetic mutation that causes breast cancer. Lifetime exposure to both endogenous and exogenous hormones has been hypothesized to play a role in tumorigenesis and growth. Other potential causes of breast cancer include inflammation and virally mediated carcinogenesis.[18]

The significance of DCIS as a precursor lesion is unclear. With the widespread use of screening mammography in the United States, nearly 90% of DCIS cases are now diagnosed only on imaging studies, most commonly by the presence of microcalcifications. These represent approximately 23% of all breast cancer cases (not including LCIS).[7] Although it is the most common type of noninvasive breast cancer, its natural history is poorly understood.

Whether DCIS in an obligate precursor to invasive ductal cancer, or if both entities derive from a common progenitor cell line is unclear. While some evidence suggests that DCIS and invasive ductal cancer may diverge from common progenitor cells,[19] indirect evidence supports the theory of linear progression through stages, from atypical hyperplasia to DCIS to invasive cancer.[19] Further evidence supports a hybrid of these two theories. Through an accumulation of genetic changes, atypical hyperplasia progresses to low grade DCIS, followed by high grade DCIS, and

from any point in this progression, the step to invasive cancer occurs.[20] Consistent with all three theories is evidence from studies in which DCIS coexists with adjacent invasive cancer in pathology specimens, as well as studies showing that at least 50% of local recurrences after treatment for DCIS are invasive cancers.[21] In both cases, DCIS and invasive ductal cancer breast tissues frequently share morphological and molecular characteristics, including grade and estrogen receptor status and HER2/neu oncogene expression.[21-23]

Several recent reviews include older studies of untreated DCIS cases that were diagnosed on retrospective review of previously reported benign biopsy specimens.[21, 24, 25] In these studies, untreated DCIS progressed to invasive cancer in 14-53% of cases over mean periods of 8-22 years. In a case series of 775 women diagnosed with DCIS who underwent breast conserving therapy, 66 eventually developed invasive cancer, and 71 developed recurrent DCIS at a mean follow-up of 5.4 years.[26]

Risk Factors

Although several risk factors have been associated with breast cancer, most cases occur in women with no specific risk factors other than sex and age. Family history of breast and ovarian cancer are strong risk determinants however, with the number of relatives, closeness of the degree of relationships, and ages of diagnosis of affected family members contributing. For example, two or more relatives with breast or ovarian cancer, a relative with both breast and ovarian cancer, and a relative diagnosed younger than age 50 years all substantially increase risk.[27] Hereditary mutations in tumor suppressor genes *BRCA1* and *BRCA2* increase individual risks for breast cancer 60-85% and may be identified in 5-10% of all breast cancer cases.[28]

Personal history of noninvasive breast cancer or previous abnormal breast biopsy containing LCIS or atypical ductal or lobular hyperplasia increase risk for invasive breast cancer. Extensive mammographic breast density is also associated with increased risk of breast cancer.[29] Endogenous estrogen exposure is associated with increased risk; thus early menarche, late menopause, nulliparity, and obesity are implicated as risk factors. Use of combination postmenopausal hormone therapy (estrogen and progestin) was associated with an increased relative risk for breast cancer compared to placebo in the Women's Health Initiative (WHI) randomized controlled trial.[30]

Environmental exposures are believed to increase risk. A history of chest radiation therapy, such as treatment for Hodgkin lymphoma, increases the risk for developing breast cancer.[31] However, current approaches may not pose this same magnitude of risk.[31] Use of alcohol at levels more than 1-2 drinks per day is also associated with increased breast cancer.[30]

Empiric models have been developed in attempts to predict risk of developing cancer for individual women (e.g., BRCAPRO, Gail, Claus, and Tyrer-Cuzick).[27] All of these models incorporate age and number of first-degree relatives with breast cancer into their calculations, but vary in their complexity. However, these models have been shown to perform better in predicting population risk than in predicting an individual's risk and it is unclear how to apply these models to screening.[27]

Current Clinical Practice

Screening

Breast cancer has a known asymptomatic phase that can be identified with mammography. Mammography screening is sensitive (77-95%), specific (94-97%), and acceptable to most women.[2] Breast cancer can be more effectively treated in an earlier stage than when clinical signs and symptoms present, justifying early detection efforts. Randomized trials of screening mammography demonstrate reduced mortality with screening.[2]

Screening mammography practices in the United States differ from those in the United Kingdom or Europe. A comparison between outcomes in the United States, using data from the Breast Cancer Surveillance Consortium (BCSC) and the National Breast and Cervical Cancer Early Detection Program, and the United Kingdom, using data from the National Health Service Breast Screening Program, indicated that recall and open surgical biopsy rates were twice as high in the United States while cancer detection rates were similar.[32] These outcomes may result from differences in health care delivery systems, organization of screening programs, training and practices of radiologists, quality assurance standards, and malpractice climates.

Mammography is performed using either plain film or digital technologies, although the shift to digital is ongoing. A large comparison study of film and digital mammography was conducted in a screening population of women in the United States and Canada. Results indicated that the overall diagnostic accuracy of digital and film mammography was similar, although digital was more accurate in women under age 50 years, women with radiographically dense breasts, and premenopausal women.[33]

In the past, contrast enhanced magnetic resonance imaging (MRI) was used to evaluate women already diagnosed with breast cancer. In studies of MRI and mammography in high-risk women without cancer, sensitivities of MRI ranged between 71-100%, and specificities between 81-97%.[34-38] The American Cancer Society (ACS) now recommends screening MRI for certain high-risk groups, including women with *BRCA1* or *BRCA2* mutations, women with greater than 20% lifetime risk of developing breast cancer as defined by risk prediction models based on family history of breast or ovarian cancer, and women who have been treated for Hodgkin lymphoma.[39] Use of MRI for screening women at average risk for developing breast cancer is not recommended.[39] Currently, there are no studies investigating MRI use in average-risk women and none showing decreased mortality with MRI screening.

The effectiveness of CBE in decreasing breast cancer mortality has been controversial. This procedure is relatively easy and inexpensive, and therefore, an attractive form of screening. However, few studies of effectiveness compare CBE to no intervention, and no studies compare its use in combination with mammography to mammography alone. Sensitivity of CBE ranges from 40-69%, specificity from 88-99%, and positive predictive value from 4-50%, using mammography and interval cancer as the criterion standard.[2]

The usefulness of BSE in decreasing breast cancer mortality has been recently questioned. Sensitivity of BSE ranges from 12-41% when compared with CBE and mammography and is age dependent. Specificity of BSE remains uncertain. Preliminary results from trials in Russia and China, as well as final results from a non-randomized trial in the United Kingdom indicated no mortality benefit to BSE.[2]

Strategies for high-risk women differ from those for average-risk women and may include genetic counseling and testing,[27, 40] earlier and more frequent mammography, and use of additional modalities such as MRI and ultrasound. These have been evaluated in a separate report for the USPSTF.[27]

Diagnosis

If a woman has an abnormal mammographic finding on screening, or a concerning finding on CBE or BSE, additional imaging and biopsy may be recommended. Additional imaging may consist of diagnostic mammography or mammography done with additional or special views (e.g., magnification, spot compression, and additional angles), a targeted breast ultrasound, or breast MRI.[41, 42] These additional imaging studies may help classify the lesion identified on screening as a benign or suspicious finding in order to determine the need for tissue sampling.

If tissue sampling is recommended, a biopsy is performed. The type of biopsy is based on the characteristics of the lesion (e.g., palpable versus nonpalpable; solid mass versus microcalcifications), as well as patient and physician preferences. Current biopsy techniques include fine-needle aspiration (FNA), stereotactic core biopsy (for nonpalpable, mammographic lesions), ultrasound-guided or MRI-guided core biopsy, non-image-guided core biopsy (for palpable lesions), incisional biopsy, or excisional biopsy. These techniques vary in the level of invasiveness and amount of tissue acquired, impacting their yield and patient experience. Although more invasive, core biopsies, as well as incisional and excisional biopsies, offer the pathologist a sample with intact cellular architecture, and thereby allow additional pathologic examination of the breast cancer. Testing includes examination of cellular receptors (e.g., estrogen/progesterone receptor, HER2/neu receptor), as well as identification of tumor type and grade.[43, 44] This additional information contributes to appropriate treatment planning for a patient who is newly diagnosed with breast cancer, and allows for definitive surgery to be completed with a single-stage procedure.[45]

Treatment

Currently, treatment for breast cancer in the United States is often multimodal, requiring a combination of therapies including surgery, chemotherapy, hormonal therapy, and radiation. The contemporary view of breast cancer as a systemic disease has lead to a shift to less radical surgery over time. Large randomized controlled trials conducted in the 1980s found no difference in overall survival between breast conservation therapy (lumpectomy followed by radiation) and mastectomy. These findings supported the use of breast conservation as an

acceptable surgical treatment for breast cancer.[46] As more knowledge is gained regarding genetic and molecular profiles of individual breast cancers, greater emphasis is being placed on targeted therapy. The goal is to tailor therapy to each particular patient in order to maximize benefits and minimize toxicity.[47] Because there are now often multiple options for treatment, patient preferences play a large role in determining the treatment course.

Screening Recommendations of Other Groups

Mammography

Most organizations in the United States support the use of mammography for average-risk women age 40 years and older; however, differences include the recommended starting age for screening and the screening interval (**Table 1**).

Clinical Breast Examination

The ACS recommends that women age 20-39 years undergo CBE every 3 years, and annually after age 40.[48] The NCI states that fair evidence shows that CBE reduces breast cancer mortality.[49] The American College of Obstetricians and Gynecologists (ACOG) recommends that all women have CBE annually as part of the physical examination.[50] The Canadian Task Force on Preventative Health Care (CTFPHC) recommends CBE for women age 50-69 years and makes no recommendation for or against CBE for women age 40-49 years.[51] The World Health Organization (WHO) does not recommend screening by CBE, but states CBE should be offered to women who present to a primary health care center for other medical reasons.[52]

Breast Self Examination

Since 2001, several organizations have changed their recommendations about BSE as a routine screening modality. The ACS changed its recommendation to make BSE optional as a screening method.[48] The NCI states that teaching BSE does not reduce breast cancer mortality.[49] The CTFPHC now recommends against its use, stating there is fair evidence of no benefit and good evidence of harm.[53, 54] The WHO advises that national cancer control programs should not recommend screening by BSE.[52] ACOG advises that despite a lack of definitive evidence for or against BSE, it can still be recommended.[50]

CHAPTER 2. METHODS

Key Questions and Analytic Framework

The USPSTF and Agency for Healthcare Research and Quality (AHRQ) developed the key questions that guided the update. Investigators created an analytic framework incorporating the key questions and outlining the patient population, interventions, outcomes, and harms of the screening process (**Figure 1**). The target population includes women without preexisting breast cancer and not considered at high risk for breast cancer based on extensive family history of breast or ovarian cancer or other personal risk factors, such as abnormal breast pathology or deleterious genetic mutations. Key questions include:

1a. Does screening with mammography (film and digital) or MRI decrease breast cancer mortality among women age 40-49 years and ≥70 years?
1b. Does CBE screening decrease breast cancer mortality? Alone or with mammography?
1c. Does BSE practice decrease breast cancer mortality?
2a. What are the harms associated with screening with mammography (film and digital) and MRI?
2b. What are the harms associated with CBE?
2c. What are the harms associated with BSE?

Harms include radiation exposure, pain during procedures, patient anxiety and other psychological responses, consequences of false-positive and false-negative tests, and overdiagnosis. Overdiagnosis refers to women receiving a diagnosis of invasive or noninvasive breast cancer who had abnormal lesions that were unlikely to become clinically evident during their lifetimes in the absence of screening.[55] Overdiagnosis may have more effect on women with shorter life expectancies because of age or comorbid conditions.

An additional contextual question on the cost effectiveness of screening is also included. Contextual questions are addressed as a narrative, not systematic, review of relevant studies. The purpose of the cost effectiveness question is to provide background information.

Search Strategies

We searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the 4th Quarter 2008) and the MEDLINE database (January 1, 2001 to December 1, 2008) for relevant studies and meta-analyses (**Appendix B1**). We also conducted secondary referencing by manually reviewing reference lists of key articles and searching citations by using Web of Science,[56] particularly searching for follow-up data from screening trials cited in the previous evidence review.[2, 3] **Appendix B2** shows our search results.

Study Selection

We selected studies on the basis of inclusion and exclusion criteria developed for each key question. Studies identified from our searches that did not meet inclusion criteria are listed in **Appendix B3**. To determine the effectiveness of screening, we included randomized controlled trials and updates to previously published trials of screening with mammography (film and digital), MRI, CBE, or BSE with breast cancer mortality outcomes published since 2001. One trial was translated into English from Russian for this update.[57] We also reviewed meta-analyses that included studies with mortality data. We excluded studies other than controlled trials and systematic reviews or those without breast cancer mortality as an outcome.

We determined harms of screening by using evidence from several study designs and data sources. For mammography, we focused our searches on recently published systematic reviews and meta-analyses of radiation exposure, pain during procedures, patient anxiety and other psychological responses, consequences of false-positive and false-negative tests, and overdiagnosis. We also conducted specific searches for primary studies published more recently than the included systematic reviews and meta-analyses. In addition, we evaluated data from the BCSC, which is a collaborative network of 5 mammography registries and 2 affiliated sites with linkages to pathology and/or tumor registries across the United States, that is sponsored by the National Cancer Institute.[58, 59] These data draw from community samples that are representative of the larger, national population and may be more applicable to current practice in the United States than other published sources. Data include a mix of film and digital mammography. For harms of CBE and BSE, we reviewed screening trials of these procedures that reported potential adverse effects, utilized recently published systematic reviews, and conducted focused searches.

We included studies of the cost effectiveness of screening that were relevant to the key questions and target population (**Appendix C1**). We excluded studies evaluating the cost of improving screening rates (e.g., post-card reminder versus telephone reminder), dual review of screening mammography, screening education programs, or studies of patients with a history of breast cancer or who were at high risk for developing breast cancer. We highlighted studies that expressed outcomes in quality-adjusted life-years (QALY). The QALY incorporates changes in length and quality of life, expressed as the extra dollars (cost per QALY ratio) required to achieve 1 extra QALY.[60] A year in perfect health is considered equal to 1.0 QALY.

Data Abstraction and Quality Rating

We abstracted details about the patient population, study design, analysis, follow-up, and results. By using predefined criteria developed by the USPSTF,[61] two investigators rated the quality of each study as good, fair, or poor (described in **Appendix B4 and B5**) and resolved discrepancies by consensus. We included only systematic reviews rated good quality in the report and randomized controlled trials rated fair or good quality in the meta-analysis.

Meta-analysis of Mammography Trials

We updated the 2002 meta-analysis to include new findings from published trials of mammography screening compared with control participants for women age 40-49 years that reported relative risk (RR) reduction in breast cancer mortality. We conducted similar updates for other age groups for context. We used breast cancer mortality results from trials to estimate the pooled RR. We calculated estimates from a random-effects model under the Bayesian data analytic framework by using the RBugs package in R,[62, 63] the same model as that used in the previous report.[2] **Appendix B6** provides additional details. We used funnel plots to assess publication bias and L'Abbé plots to assess heterogeneity.

Analysis of Breast Cancer Surveillance Consortium Data

Background information and additional details about methods of the BCSC are described in **Appendix B7**. We obtained data from 600,830 women age 40 years or older undergoing routine mammography screening from 2000-2005 at the BCSC sites from the BCSC Statistical Coordinating Center and stratified it by age in decades. Routine screening was having at least one mammography examination within the previous 2 years, which is consistent with current USPSTF recommendations. For women with several mammography examinations during the study, one result was randomly selected to be included in the calculations. These data constitute selected BCSC data intended to represent the experience of a cohort of regularly screened women without preexisting breast cancer or abnormal physical findings.

Variables include the numbers of positive and negative mammography results and, of these, the numbers of true-negative and false-negative results based on follow-up data within 1 year of mammography screening. A positive mammography result was defined according to standardized terminology and assessments of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) manual used by the BCSC.[64] These include four categories: needs additional evaluation (category 0), probably benign with a recommendation for immediate follow-up (category 3), suspicious (category 4), or highly suggestive of malignancy (category 5).[65] For women who had a positive screening mammography result, we evaluated data on the number of women undergoing additional imaging and biopsy, and diagnoses including invasive cancer, DCIS, and negative results. We considered additional imaging procedures and biopsies done within 60 days of the screening mammography to be related to screening. From these data, we calculated age-specific rates (numbers per 1000 women per round) of invasive breast cancer, DCIS, false-positive and false-negative mammography results, additional imaging, and biopsies. We based true-positive and true-negative mammography results on invasive and noninvasive cancer diagnosis. Rates of additional imaging and rates of biopsies may be underestimated because of incomplete capture of these examinations by the BCSC. We conducted a sensitivity analysis of missing values, although this does not include records that were unavailable to the BCSC.

External review

We distributed a draft of the systematic review for review by external experts not affiliated with the USPSTF (listed in **Appendix B8**).

CHAPTER 3. RESULTS

Key Question 1a. Does screening with mammography (film and digital) or MRI decrease breast cancer mortality among women age 40-49 years and 70 years and older?

Summary

No trials of screening average-risk women specifically evaluating the effectiveness of digital mammography or MRI have been published.

Since the 2002 review and meta-analysis of mammography screening trials,[2] 2 trials have been published that provide data for women age 40-49 years. The Age trial[66] was designed specifically to determine the effectiveness of screening women age 40-49 years in the United Kingdom. Results indicate a relative risk for breast cancer mortality of 0.83 (95% confidence interval [CI], 0.66-1.04) for women randomly assigned to screening, and a number needed to invite for screening to prevent one breast cancer death over 10 years of 2,512 (95% CI, 1,149-13,544). For women age 40-49 years, data from the Age trial[66] and updated results from the Gothenburg trial[67] from Sweden (age 39-49 years) were combined in a meta-analysis with 6 trials included in the previous review. Results indicate a relative risk for breast cancer mortality of 0.85 (95% CrI, 0.75-0.96) for women randomly assigned to screening, and a number needed to invite for screening to prevent one breast cancer death of 1,904 (95 % CrI, 929-6,378) over multiple screening rounds that vary by trial.

For women age 70 years and older, the only data from screening trials comes from the Swedish Two-County trial. Results indicate a relative risk for breast cancer mortality of 1.12 (95% CI, 0.73-1.72)[68] for women randomly assigned to screening. However, results are based on a small number of women (number needed to invite for screening not estimable from these data).

Detailed Findings

The 2002 evidence review for the USPSTF included a meta-analysis of 7 randomized trials of mammography screening that were rated fair quality (**Table 2**).[2] For women age 40-49 years, results of the 2002 meta-analysis indicated a relative risk for breast cancer mortality of 0.85 (95% CrI, 0.73-0.99) for women randomly assigned to screening over 14 years of follow-up, with a number needed to invite to screening of 1,792 (95% CrI, 764-10,540).[2, 3]

Since then, a randomized trial from the United Kingdom evaluating the effect of mammography screening specifically in women age 40-49 years has been published,[66] as well as updated data from a previously reported Swedish trial[67] which was included in the 2002 meta-analysis. Both of these trials meet USPSTF criteria for fair quality.

The Age trial included 160,921 women age 39-41 years who were randomly assigned between 1991-1997 to screening with annual mammography until age 48 years or a control group who received usual care.[66] The prevalent screen was with 2-view mammography and subsequent screens were 1-view. Follow-up was conducted through the National Health Service central register, and the analysis included deaths from breast cancer during the trial and during follow-up using intention-to-screen analysis. Overall, 81% of women attended at least one screen, and the mean number of screens in the trial was 4.5. After 10.7 years of follow-up, the relative risk was 0.97 (95% CI, 0.89-1.04) for all-cause mortality, and 0.83 (95% CI, 0.66-1.04) for breast cancer mortality among women randomly assigned to screening. On the basis of the absolute reduction in breast cancer mortality among women randomly assigned to screening, the number needed to invite for screening to prevent one death from breast cancer over 10 years was 2,512 (95% CI, 1,149-13,544). The Age trial met USPSTF criteria for fair rather than good quality because contamination of groups was not described and 70% or fewer women attended screening across the trial.

A new publication provides additional follow-up data from the Gothenburg trial,[67] rated fair quality in the 2002 report.[2] The trial began in 1982 to evaluate mammography screening among the entire female population of Gothenburg, Sweden born between 1923-1944 (age 39-59 years).[67, 69] The trial enrolled 21,904 women, and those randomly assigned to screening had mammography approximately every 18 months. The screening intervention included initial 2-view mammography followed by 1-view incident mammography unless 2-views were more appropriate based on the prevalence screen. The control group received usual care. Women with breast cancer diagnosed before randomization were excluded from the study. After the trial was closed, women in both groups were invited to regular screening.

Breast cancers among all women were ascertained through treatment centers, pathology laboratories, and the national cancer registration system, and follow-up was conducted until December 1996. Mortality from breast cancer was determined by local follow-up and the Swedish Cause of Death Register. Breast cancer mortality rates and risk ratios were calculated using 3 methods with 2 independent endpoint committees determining the cause of death for all women using blinded patient records. Attendance at the first screening round for the study group was above 80% and varied by age. Analysis was conducted using intention-to-screen analysis. Among women ages 39-49 at trial entry, the relative risk of breast cancer mortality using the

follow-up method was 0.69 (95% CI, 0.45-1.05) among women randomized to screening after 13 years of follow-up.[67]

Meta-analysis for women age 39-49 years

Eight trials provided data for the meta-analysis, including 6 from the 2002 meta-analysis (Health Insurance Plan [HIP] of Greater New York,[70] Canadian National Breast Screening Study-1 [CNBSS-1],[71] Stockholm,[68] Malmo,[68] Swedish Two-County [2 trials][68, 72]), and the 2 new trial reports (Age,[66] Gothenburg[67]). All trials met criteria for fair quality.[2] Combining results, the pooled relative risk for breast cancer mortality for women randomly assigned to mammography screening was 0.85 (95% CrI, 0.75-0.96), which indicates a 15% reduction in breast cancer mortality in favor of screening (**Figure 2**). This corresponds to a number needed to invite for screening to prevent one breast cancer death of 1,904 (95% CrI, 929-6,378) over multiple screening rounds that varied by trial (2-9 rounds), and 11-20 years of follow-up. A funnel plot did not indicate the presence of publication bias, and an L'Abbé plot did not reveal serious heterogeneity between the studies (**Appendix C2**). Results are consistent with the 2002 meta-analysis.

Sensitivity analysis excluded the HIP trial[70] because it was conducted more than 30 years ago and used outdated technology and the CNBSS-1 trial[71] because it enrolled prescreened volunteers rather than unselected samples. Exclusion of these trials did not significantly influence the results (**Table 3**).

Results for women age 70-74 years

The 2002 evidence review did not report results specifically for women age 70-74 years, but included them in a larger age category of women age 65-74 years.[2] Results for women age 70 or older were confined to data from the Swedish Two-County trial[68] (Ostergotland) of women age 70-74 years, precluding meta-analysis. These results indicate a relative risk for breast cancer mortality of 1.12 (95% CI, 0.73-1.72),[68] based on a more conservative determination of cause of death than previous reports.[73] The absolute numbers of deaths were not reported, the number of enrolled women was low (approximately 5,000 in each group), and an estimate of number needed to screen was not estimable. Results are summarized in **Table 4**.

Comparisons with meta-analyses for women age 50-59 years and 60-69 years

Meta-analyses of trials for women age 50-59 years and 60-69 years included results of screening trials from the previous evidence review,[2] and new data utilizing the follow-up method from the Gothenburg trial for women age 50-59 years.[67] Not all of the published trials reported results by age and these could not be included in the meta-analysis.

For women age 50-59 years, 6 trials (CNBSS-1,[71] Stockholm,[68] Malmo,[68] Swedish Two-County [2 trials],[68] Gothenburg[67]) provided a pooled relative risk of 0.86 (95% CrI, 0.75-0.99) for breast

cancer mortality for women randomly assigned to mammography screening. The number needed to invite for screening to prevent one breast cancer death was 1,339 (95% CrI, 322-7,455). Sensitivity analysis that excluded the CNBSS-1 resulted in a lower relative risk (0.81; 95% CrI, 0.68-0.95).

For women age 60-69 years, 2 trials (Malmo[68] and Swedish Two-County [Ostergotland][68]) provided a pooled relative risk of 0.68 (95% CI, 0.54-0.87) for breast cancer mortality for women randomly assigned to mammography screening. The number needed to invite for screening to prevent one breast cancer death was 377 (95% CrI, 230-1,050). **Table 5** summarizes the meta-analysis results by age group.

Key Question 1b. Does CBE screening decrease breast cancer mortality? Alone or with mammography?

Summary

Few trials have evaluated the effectiveness of CBE in decreasing breast cancer mortality. In countries with widely practiced mammography screening, the use of CBE rests on its additional contribution to mortality reduction. The CNBSS-2 trial, which compares mammography with CBE versus CBE alone, showed no difference in mortality between the these two approaches.[74]

Three trials were designed to determine mortality outcomes by using CBE as the primary screening approach in countries with limited health care resources and without mammography screening programs (**Table 6**). The applicability of these trials to the United States is limited. A randomized trial comparing CBE with no screening was conducted in the Philipines.[75] However, it was discontinued after one screening round because of poor community acceptance and is inconclusive. Two randomized trials comparing CBE with no screening are ongoing in India[76] and Egypt.[77]

Detailed Findings

The CNBSS-2 was designed to evaluate the benefit of adding mammography to breast cancer screening using CBE and BSE before mammography screening programs were instituted in Canada in 1988.[74] From 1980 to 1985, 39,405 women, age 50-59 years, were randomly assigned to receive five annual screening visits consisting of mammography with CBE and BSE instruction versus CBE and BSE instruction without mammography. CBE was performed by a trained nurse or physician, and included visual inspection followed by a thorough 10-minute examination. With an average of 13 years follow-up through 1996, for cancers detected during the screening phase of the trial, the cumulative mortality rate ratio between study and control

groups was 1.09 (95% CI, 0.78–1.51). For cancers detected through the follow-up period, the cumulative mortality rate ratio was 1.02 (95% CI, 0.78–1.33).

A trial conducted in Manila, Philippines was designed to assess the feasibility of mass screening by CBE in an urban population where mammography screening is not available and determine effects on breast cancer mortality.[75] Women were assigned to receive either 5 annual CBEs conducted by trained nurses and midwives versus no active intervention on the basis of cluster randomization procedures determined by regional health center. CBE training used the MammaCare technique. The intervention was discontinued after the first round because of poor compliance with diagnostic follow-up evaluations. Only 35% of women with abnormal CBEs received further evaluations, primarily due to patient reticence. In the one round of screening conducted in 1996-1997, 151,168 women were offered CBE, 8% refused, 3,479 had abnormal CBEs, 1,293 had further testing, and 1,220 completed diagnostic workups. Of those completing diagnostic workups, 34 had breast cancer. This translates to sensitivity of 25.6% (34/133) and positive predictive value of 1.0% (34/3479). These values are considerably lower than reported in other studies and are influenced by high loss to follow-up. Mortality data were not reported.

A large population based trial has been ongoing at Tata Memorial Hospital in Mumbai, India since 1998.[76] This randomized controlled trial was designed to evaluate low-technology methods for detecting common cancers in women. The study compares the efficacy of CBE, BSE, and health education conducted every 24 months versus health education alone for women living in the slums of Mumbai. A total of 152,239 participants ranging in age from 35-64 years have been randomly assigned according to 20 geographic residential areas. Examinations and education are performed by trained female health workers who underwent 5 months of training prior to the study; specifics of the training have not yet been described. In addition, women in the intervention group also receive visual cervical inspection for cervical cancer. Women in the intervention group will receive 4 rounds of screening and thereafter 8 years of surveillance for cancer incidence and mortality. As of 2004, the third intervention round was underway.

The Cairo Breast Screening Trial is currently underway at the Italian Hospital in Cairo, Egypt.[77] A pilot study conducted in Cairo from May 2000 to June 2002, involving 5,000 women ages 35-64, was extended into this randomized trial of 10,000 women. The objective of the trial is to evaluate CBE and BSE in reducing mortality and morbidity in a defined geographical area of Cairo. As with the pilot study, trained social workers recruit women to the study by visiting their homes. Study participants are then invited to attend a primary health clinic for CBE as well as BSE instruction. Breast examinations are performed by female physicians who have been specially trained for 2 months prior to the study; the training technique was not specified in the report. To date, 10,000 women have been randomly assigned by cluster, however, results are not expected for several more years. In the pilot study, 4,116 women were invited to the health center for CBE, 2,481 attended, and of these 20 (8/1,000) were diagnosed with breast cancer. No mortality data were collected.

Key Question 1c. Does BSE practice decrease breast cancer mortality?

Summary

Although monthly BSE has been widely recommended to women for over 70 years, there have been few randomized controlled trials studying the effect of BSE on mortality. Preliminary results from trials in Russia and Shanghai were reviewed for the 2002 USPSTF report,[2] and final results have since been published (**Table 6**). The Russian trial indicated that despite a significant increase in the number of cases of breast cancer detected when BSE instruction was provided, there was no reduction in all-cause mortality.[57] The Shanghai trial showed no significant difference in breast cancer mortality as a result of BSE instruction.[78] Three new meta-analyses of published trials and nonrandomized studies of BSE, which all include the Russian and Shanghai trials, also indicate no significant differences in breast cancer mortality between BSE and control groups.

Detailed Findings

The effect of BSE on all-cause mortality in St. Petersburg, Russia, a community without routine mammography screening, was evaluated in a trial that met criteria for fair quality. In this trial, 123,748 women were assigned to receive either BSE training or no training on the basis of cluster randomization procedures determined by outpatient clinic.[57] Women between the ages of 40-64 years were enrolled from 1985-1989. Breast cancer diagnoses were tracked until 1994 and mortality data were recorded through 2001. BSE instruction was provided by physicians and nurses who took a 3-hour training course prior to instructing groups of 5-20 women. In addition, a CBE was performed and the BSE method reviewed with each woman in the intervention group at annual clinic visits. Compliance with monthly BSE dropped considerably in the intervention group. Within 4 years of study onset only 18% of women reported performing monthly BSE, thus a BSE refresher session was incorporated every 3 years. Despite this, only 58% of women continued to practice monthly BSE. The relative risk for all-cause mortality for women randomly assigned to BSE was 1.07 (95% CI, 0.88-1.29). Breast cancer mortality for the 2 groups was not reported.

Various publications of this trial report different numbers. In the most recent publication, the total number of women enrolled in the study was reported as 123,748 (58,985 intervention and 64,763 control), whereas previous reports indicated 120,310 (60,221 intervention and 60,089 control), and 122,471 (57,712 intervention and 64,759 control).[57, 79, 80] There is no explanation for these differing numbers. In addition, the number of women with benign biopsies and the number of women diagnosed with breast cancer do not add up to the number listed as having diagnostic biopsies in one of the key figures of the publication.[57]

A trial in Shanghai, China began in 1988 to evaluate whether instruction in BSE reduces breast cancer mortality.[78] This trial met criteria for good quality. It included women factory employees

in Shanghai between the ages of 31-64 years at the time of enrollment. Participants were assigned to receive either BSE instruction with periodic reinforcement versus no information on breast cancer screening (this group received instruction on low back injury prevention) on the basis of cluster randomization procedures determined by factory. BSE instruction was provided by trained former factory medical workers. It consisted of information on breast anatomy and cancer and teaching a 3-step BSE technique. At 1 and 3 years after initial instruction, reinforcement instruction sessions were provided. These included watching a video of BSE technique and practicing BSE under supervision by the trained medical workers. Additionally, women practiced supervised BSE at 1, 3, 6, and 9 months after initial instruction for the first year and every 6 months for the remaining 4 years. Only 10% of women attended fewer than 8 sessions. Actual practice of BSE by participants was not monitored.

In 11 years of follow-up, the rate of breast cancer was 6.5/1,000 women in the intervention group and 6.7/1,000 in the control group. The number of women considered to have died from breast cancer was equal in both groups (135/132,979 and 131/133,085, respectively; RR 1.03; 95% CI 0.81-1.31). Women who died of breast cancer were identified from a registry kept by the factory bureau, from records of other ongoing studies that used this trial cohort, and by active follow-up of all women known to have breast cancer. A physician reviewed records to ascertain the cause of death.

Three meta-analyses reviewed trials and observational studies of BSE.[54, 81, 82] All 3 included the Russian and Shanghai trials, while 2 of the 3 also included a non-randomized trial from the United Kingdom and cohort and case-control trials. Results indicate no significant differences in breast cancer mortality between BSE and control groups.

Key Question 2a. What are the harms associated with screening with mammography (film and digital) and MRI?

MRI and digital mammography

No studies specifically evaluated the adverse effects of MRI or digital mammography when used for breast cancer screening in average-risk women.

Radiation exposure

No studies directly measured the association between radiation exposure from mammography screening and breast cancer. The prevailing assumption has been that higher doses of high energy radiation induce cancers. Most x-rays are considered low-dose, low-energy radiation, with the mean glandular dose of bilateral, 2-view mammography averaging 7 mGy.[83] For women age 40-49 years, yearly mammography screening for one decade with potential

additional imaging would expose an individual to approximately 60 mGy, although these levels vary.[25] For comparison, the typical breast dose of radiation to treat Hodgkin lymphoma is 21-25 Gy. However, there is concern that high cumulative doses of low energy radiation may induce more cancers in younger women or those with deleterious mutations such as *BRCA1* and *BRCA2*.[84, 85]

A recently published systematic review included various types of studies of radiation exposure, such as radiation therapy, diagnostic radiation, and atomic bomb radiation, as the basis for predicting risk for inducing breast cancer.[25] In studies of low-dose exposures, associations were inconsistent, whereas those of high-dose exposures indicated increased risk for breast cancer.[25] The relative risks in studies of high-dose exposures ranged from 1.33-11.39 for exposures of 0.3-43.4 Gy, and were worse with higher doses of exposure, younger age at exposure, and longer follow-up.[25] A case-control study, published since the systematic review, found that women exposed to diagnostic radiographs for screening or monitoring tuberculosis or pneumonia, or to therapeutic radiation for previous cancer, had increased risks for breast cancer.[86]

An analysis estimating the net benefits and harms of radiation exposure used data from the National Health Service Breast Screening Programme (NHSBSP) in the United Kingdom.[87] In this analysis, assuming a linear dose-response relationship, the ratio of the number of lives saved to fatal breast cancers induced by radiation in women age 50-69 years was estimated at between 58-182.[87]

A recent simulation study designed to estimate the radiation doses received by organs of the body during standard two-view mammography of each breast found that the eye lens and lungs received the highest doses, although they were extremely low (4.4 μGy and 4.8 μGy, respectively).[88]

Pain during procedures

Breast compression is used during mammography to create uniform density, reduce breast thickness, and flatten overlying skin and tissues, which contributes to sharper images and reduces the radiation dose. However, compression may add to the discomfort of mammography for some women. A recent systematic review of 22 studies of pain and discomfort associated with mammography indicated that many women experience pain during the procedure (range, 1-77%), but few would consider this a deterrent from future screening.[25] In these studies, pain was associated with the stage of the menstrual cycle, anxiety, and the anticipation of pain.[25] A recent review of trials of various interventions to reduce pain experienced during screening mammography included 7 studies. One study found that women experienced little pain in both the control and intervention groups, whereas in the other 6 studies the control groups experienced varying levels of pain.[89]

Anxiety, distress, and other psychological responses

Studies have shown conflicting results about anxiety, distress, and other psychological responses that result from mammography screening. A systematic review of 54 studies evaluated the adverse psychological effects of mammography screening programs.[90] Most were cohort studies, and 24 used validated psychological measurement scales to assess the effects of screening. Studies indicated that women who received clear communication of their negative mammography results had minimal anxiety.[90] Results were mixed in studies of women who were recalled for further testing as a result of screening. In several studies, women had persistent anxiety, despite eventual negative results, whereas some showed only transient anxiety.[90] Some studies showed no differences between anxiety levels of women who had initial negative screening mammography results and those who had false-positive results.[90]

A recent systematic review of 23 studies specifically examined the effects of false-positive screening mammography results on women age 40 years or older.[91] Twenty-six studies were included: 9 on psychological distress, 11 on anxiety, and 6 on worry. False-positive mammography results had no consistent effect on most woman's general anxiety and depression but increased breast cancer-specific distress, anxiety, apprehension, and perceived breast cancer risk for some.[91]

False-positive and false-negative mammography results, additional imaging, and biopsies

Published data on false-positive and false-negative mammography results, additional imaging, and biopsies that reflect current practice in the United States are limited. False-positive mammography results subject women without cancer to additional imaging and biopsies. The probability of a false-positive screening mammography result was estimated at 0.9-6.5% in a meta-analysis of studies of sensitivity and specificity of mammography published 10 years ago.[92] The cumulative risk for false-positive mammography results has been reported as 21-49% after 10 mammography examinations for women in general,[93-95] and up to 56% for women age 40-49 years.[95]

Some women may have negative screening mammography results and be diagnosed with breast cancer shortly thereafter. For these women, screening failed to detect their cancer. Studies vary in how they determine false-negative rates,[95] and rapidly progressing interval cancers may sometimes be incorrectly counted as false-negative mammography results depending on the time frame used. Few studies evaluate the effect of negative mammography results. Women stated that they would not delay evaluation of a new abnormal physical finding despite a previous negative mammography result in one survey.[96] However, in another study of women with breast cancer, those with screen-detected cancer sought care earlier than women with prior negative mammography results.[97]

Unpublished data from the BCSC provide additional information on screening outcomes. Data for regularly screened women that are based on results from a single screening round indicate that rates of invasive breast cancer are lowest among women age 40-49 years (2.7 per 1,000

women per screening round) and increase with age (**Table 7**). Rates of DCIS are also lowest among women age 40-49 years (0.9 per 1,000 women per screening round), increase for women age 50-59 years (1.4 per 1,000 women per screening round), and remain at approximately this level for older women.

The BCSC data indicate that false-positive mammography results are common in all age groups. The rate is highest among women age 40-49 years (97.8 per 1,000 women per screening round) and declines with each subsequent age decade (**Table 7**). The rate of false-negative mammography results is lowest among women age 40-49 years (1.0 per 1,000 women per screening round) and increases slightly with subsequent age decades. Additional data about mammography test performance and its relationship with age and screening intervals has been analyzed by the BCSC. These data indicate that sensitivity, recall rates, and cancer detection rates increase as the months since previous mammography increase, whereas specificity decreases.[98]

In current practice, most women with an initial positive mammography result have additional imaging as a second step in the screening process. Rates of additional imaging and rates of biopsies may be underestimated by the BCSC data because of incomplete capture of these examinations. Rates of additional imaging are highest among women age 40-49 years (84.3 per 1,000 women per screening round) and decrease with age (**Table 7**). Biopsy rates are lowest among women age 40-49 years (9.3 per 1,000 women per screening round) and increase with age.

To consider the impact of screening, estimates of the numbers of women having mammography, additional imaging, and biopsies in order to diagnose one case of invasive breast cancer were calculated in 2 ways to account for missing values (assuming all women with missing values did not undergo procedures and assuming all did). This analysis does not include records that were unavailable to the BCSC. For every case of invasive breast cancer detected by mammography screening in women age 40-49 years, 556 women have mammography, 46-48 additional imaging, and 5-8 biopsies (**Table 7**, **Figures 3, 4**). Numbers decline with age for mammography and additional imaging, and only slightly for biopsies.

Overdiagnosis

Overdiagnosis refers to women receiving a diagnosis of invasive or noninvasive breast cancer who had abnormal findings on screening mammography that were unlikely to become clinically evident during their lifetimes in the absence of screening.[55] Although it has been generally acknowledged that overdiagnosis is an adverse outcome of mammography screening, it is difficult to quantify. Studies of overdiagnosis are primarily based on data from screening trials and programs or on modeled data (**Table 8**).

A review of 8 randomized controlled trials of mammography screening compared the cumulative incidence of breast cancer in screening and control groups to determine the extent of overdiagnosis.[99] In the 5 trials in which the control group was not offered screening, the absolute excess cumulative incidence of invasive and noninvasive breast cancer attributed to

overdiagnosis among women randomly assigned to screening mammography ranged from 0.07-0.73 per 1,000 women-years. One trial was still in progress when these rates were reported.[99]

Eight studies report estimates of overdiagnosis using different methods. An analysis of data from women age 50-74 years with breast cancer compared outcomes before and after implementation of a screening program in Italy.[100] Estimates of overdiagnosis were based on a model that assumed the mean sojourn time (time from onset of cancer to presence of symptoms) follows an exponential distribution and approximates lead time (time from screening to presence of symptoms) for screen-detected breast cancer. Using a mean sojourn time of 3.7 years, the rate of overdiagnosis for invasive and noninvasive breast cancer cases was calculated to be 4.6% (95% CI, 2-7%).[100] When considered separately, overdiagnosis of invasive cancer cases was 3.2% (95% CI, 1%-6%). In another analysis using this model and data from a screening program in Italy in which roughly 60,000 women between 50-69 were invited for screening, overdiagnosis was estimated to be 5% of the cases diagnosed (2% for invasive cancer separately).[101]

A microsimulation model was used to estimate breast cancer incidence rates both in the absence of screening and as a consequence of a Dutch screening program.[102] This model assumed 80% of women age 50-74 years would be screened every 2 years. It also assumed that 10% of invasive cancers are preceded by screen-detectable DCIS, and that the chance of DCIS progressing to clinically apparent disease is 90%. Estimates for overdiagnosis were 3% of the total breast cancer incidence and 8% of screen-detected cancers.[102]

An analysis of incidence data from the Swedish Two-County and Gothenburg screening trials used a model to estimate overdiagnosis.[103] Both trials randomly assigned women to screening or no screening and control groups were eventually invited to screening at the end of the trials. Data from screen-detected and interval cancers were used to estimate parameters for the model, including annual incidence of preclinical screen-detectable cancers, sojourn time, and screening sensitivity. Overdiagnosis was 3% in the first screening round for the Swedish Two-County trial and 4.2% for the Gothenburg trial, and less than 0.5% for both trials in subsequent rounds.[104] Estimates for the upper limit of DCIS overdiagnosis was 15-18% of all DCIS cases.[104] In another analysis using a similar model and data from two rounds of a screening program in Denmark, rates of overdiagnosis were 7.8% in the first round and 0.5% in the second round.[103]

A Markov model was used to estimate the incidence of non-progressive or overdiagnosed DCIS with data from the Swedish Two-County trial and several screening programs.[105] Pooling results from the various sources, the annual incidence rate of overdiagnosed DCIS was 1.11 per 100,000. On average, 37% of DCIS cases at prevalence and 4% at incidence screens were determined to be nonprogressive DCIS in this model.[105]

A comparison of breast cancer incidence rates between women age 55-69 years randomly assigned to screening and controls used data from the Malmo trial. Overdiagnosis was 4.5% (115/2525) of total breast cancer cases, with a 10% higher incidence in the screened group (7% for invasive cancer) 15 years after discontinuing screening.[106]

An estimate of overdiagnosis based on screening programs in Norway and Sweden was 30% of invasive cancer cases for women age 50-69 years, a much higher level than those described previously.[107] This estimate was based on changes in age-specific incidence rates of invasive breast cancer associated with the introduction of screening programs. The difference between increased incidence among women age 50-69 years and decreased incidence among women age 70-74 years was used as the definition of overdiagnosis in this analysis.

Key Question 2b. What are the harms associated with CBE?

Harms associated with CBE include false-positive results and subsequent diagnostic imaging or procedures, as well as psychological consequences such as anxiety, worry, and depression. The risk of a false-negative CBE and possible delay in breast cancer diagnosis also exists.

In the pilot study for the Cairo Breast Screening Trial of 2,481 women,[77] 291 women were referred for further testing due to an abnormal CBE. Of these, 80 had diagnostic imaging; 50 underwent diagnostic procedures, including FNA, nipple aspirate, or excisional biopsy; and 55 did not attend a follow-up visit.[77] Twenty women were diagnosed with breast cancer (0.8%), and 30 had procedures with benign results (1.2%).

The Philippines CBE study ended prematurely due to poor participant attendance for diagnostic work-ups although false-positive and false-negative results were reported for women who completed them.[75] Of the 138,392 women examined, 3,479 had abnormal CBEs and 1,220 completed diagnostic workups. Of these women, 34 (3%) had cancer, 563 (46%) had no detectable abnormalities, and 623 (51%) had biopsy results that were benign.

A community based case-control study of 485 women who received CBE within one year prior to breast cancer diagnosis and within 15 years of breast cancer death revealed that CBE failed to detect breast cancer in 4 out of 5 women.[108] These cases may have represented false-negative CBEs or aggressive breast cancers arising between routine examinations.

Key Question 2c. What are the harms associated with BSE?

Harms resulting from BSE are similar to those with CBE.

In the Russian[57] and Shanghai[78] trials, more women randomly assigned to BSE had benign biopsy results than women in the control groups (RR 2.05 [95% CI, 1.80-2.33] for women in the Russian trial and 1.57 [95% CI, 1.48-1.68] for women in the Shanghai trial).

A retrospective cohort study of 27,421 women age 40 year or older in the United States indicated that those performing more frequent or longer durations BSEs were more likely than women with less frequent and shorter BSEs to have diagnostic mammography or ultrasonography.[109]

Contrary to the Russian and Shanghai trials, there was no significant association between BSE and biopsy rates in this study.

CHAPTER 4. DISCUSSION

Summary

Table 9 summarizes the evidence for this review. Breast cancer mortality benefits from randomized controlled trials of screening are based on estimates of women who were randomly assigned to screening, whereas harms are based on data from women actually screened.

Trials of mammography screening for women age 39-49 years indicate a 15% reduction in breast cancer mortality for women randomly assigned to screening versus those assigned to controls. This translates to a number needed to invite for screening to prevent one breast cancer death of 1,904 (95% CrI, 929-6,378) over multiple screening rounds that varied by trial. These results are similar to those for women age 50-59 years, but indicate less effect than for women age 60-69 years. For women age 70 years or older, results from the Swedish Two-County trial[68] of women age 70-74 years indicate no mortality reduction. However, these results are limited by including only a few women from one sample. Interpreting trial results stratified by age requires caution because except for the Age trial,[66] age-specific results are subanalyses of trials designed for different purposes.

Although the addition of the Age trial[66] did not markedly change the results of the meta-analysis, its contribution to the evidence base is important. The Age trial is the only trial of mammography that specifically evaluates the effectiveness of screening women in their 40s. It is the largest trial and draws from a community population. It is the most recent trial that reflects current screening, diagnostic, and treatment practices better than its predecessors, particularly those from the pretamoxifen era. As such, it is the most relevant trial. However, its results, although consistent with the meta-analysis in the direction of benefit, are not statistically significant. Also, its applicability to women in the United States is not clear, in light of important differences between mammography screening practices in the United States and United Kingdom.[32]

Harms of mammography screening have been identified, but their magnitude and effect are difficult to measure. The absolute level of radiation exposure and corresponding radiation risk from mammography is very low. Special considerations may be needed, however, for women exposed to additional radiation for other purposes or women particularly susceptible to breast cancer such as *BRCA* mutation carriers. Patient adverse experiences, such as pain during procedures and anxiety and other psychosocial responses, are common but seem to be transient and do not discourage future screening practices. This may differ for individual women.

Estimates of the magnitude of overdiagnosis vary depending on the analytic approach used. These estimates are difficult to apply because, for individual women, it is not known which types of cancer will progress, how quickly cancer will advance, and expected lifetimes.

Harms also include downstream consequences of false-positive mammography results, such as additional imaging and biopsy. Younger women have higher rates of additional imaging and lower rates of biopsy than older women. Additional imaging may be particularly useful in selecting biopsy candidates among premenopausal women who have denser breast tissue and more fibrocystic changes than postmenopausal women.

The effectiveness of CBE has not been proven in large, well-designed trials. Current ongoing trials are limited to countries that do not provide routine mammography screening, which restricts their applicability to the United States. Work-ups for false-positive findings subject women to additional imaging and procedures countering the potential benefits of this low-technology approach. For BSE, the Russian[57] and Shanghai[78] trials simultaneously showed no reductions in mortality and increased numbers of benign biopsy results done as a result of BSE instruction.

Limitations

Although more information is available to determine the benefits and harms of routine breast cancer screening in average-risk women, questions remain unanswered. The least amount of data is available for women age 70 years and older, which is a rapidly growing population in the United States. Recent observational studies indicate that regular screening mammography among older women is associated with earlier-stage disease[110, 111] and lower breast cancer mortality.[111] For the many older women who might live 20-30 years longer, breast cancer detection and early treatment could reduce morbidity as well as mortality, thereby optimizing independence, function, quality-of-life, and costs of care in the final years.

Breast cancer is a continuum of entities, not just one disease that needs to be taken into account when considering screening and treatment options and when balancing benefits and harms. None of the screening trials consider breast cancer in this manner. As diagnostic and treatment experiences become more individualized[47] and include patient preferences, it becomes even more difficult to characterize benefits and harms in a general way. Many patients would consider quality-of-life an important outcome, although it is a more difficult outcome to measure and report in trials.

New technologies, such as digital mammography and MRI, have become widely used in the United States without definitive studies of their effect on screening. Consumer expectations that new technology is better than old may obscure potential adverse effects, such as higher false-positive results and expense. No screening trials incorporating newer technology have been published, and estimates of benefits and harms in this report are based predominantly on studies of film mammography. No definitive studies of the appropriate interval for mammography screening exist, although trial data reflect screening intervals from 12-33 months.

Future Research

Additional research on benefits and harms of mammography screening with quality-of-life outcomes, as well as morbidity and mortality outcomes, would provide further understanding of the implications of routine screening. Data for specific groups of women, based on racial and ethnic background, access to screening, or existence of co-morbidities, for example, could inform screening practice. Studies of older women are essential in order to determine appropriate screening regimens for them including when to discontinue screening. Studies on the role of MRI in screening are required in order to incorporate this technology appropriately in the screening process. More information on DCIS is needed, including its implications and outcomes.

Conclusions

Our meta-analysis of mammography screening trials indicates breast cancer mortality benefit for all age groups from 39-69 years, with insufficient data for older women. False-positive results are common in all age groups and lead to additional imaging and biopsies. Women age 40-49 years experience the highest rate of additional imaging whereas their biopsy rate is lower than 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 to society are not clearly resolved by available evidence.

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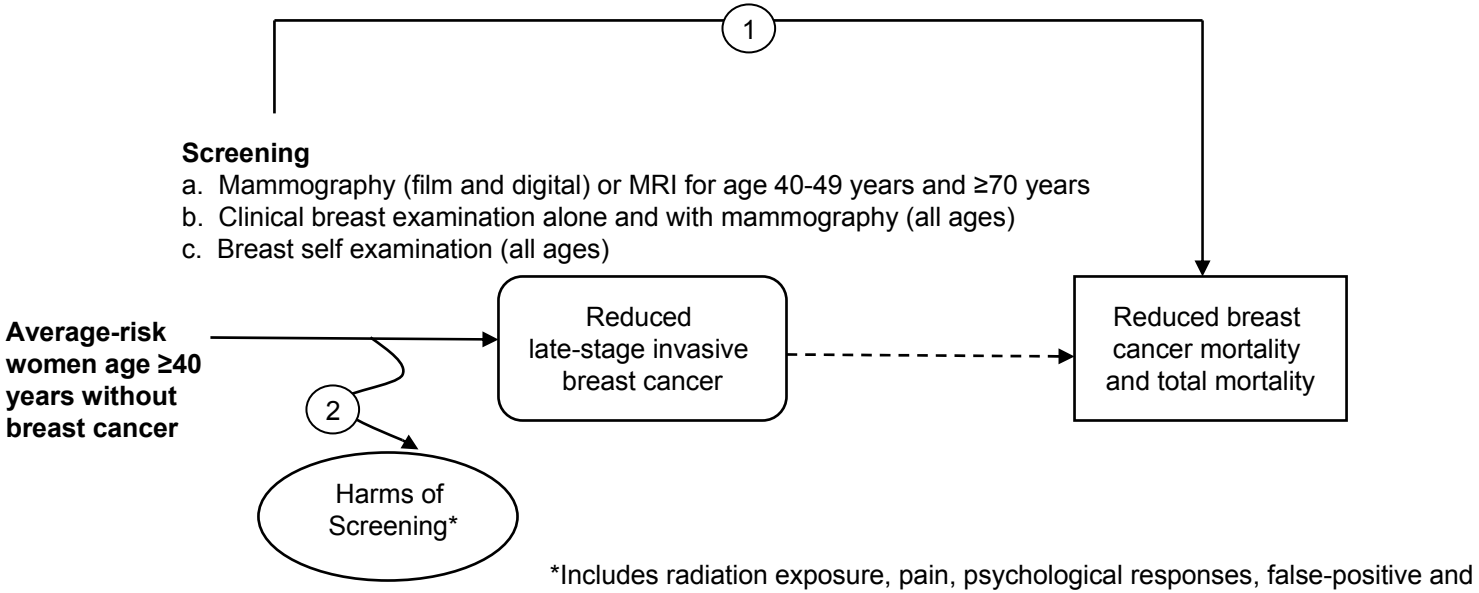
Figure 1. Analytic Framework and Key Questions



*Includes radiation exposure, pain, psychological responses, false-positive and false-negative test results, and overdiagnosis.

KEY QUESTIONS

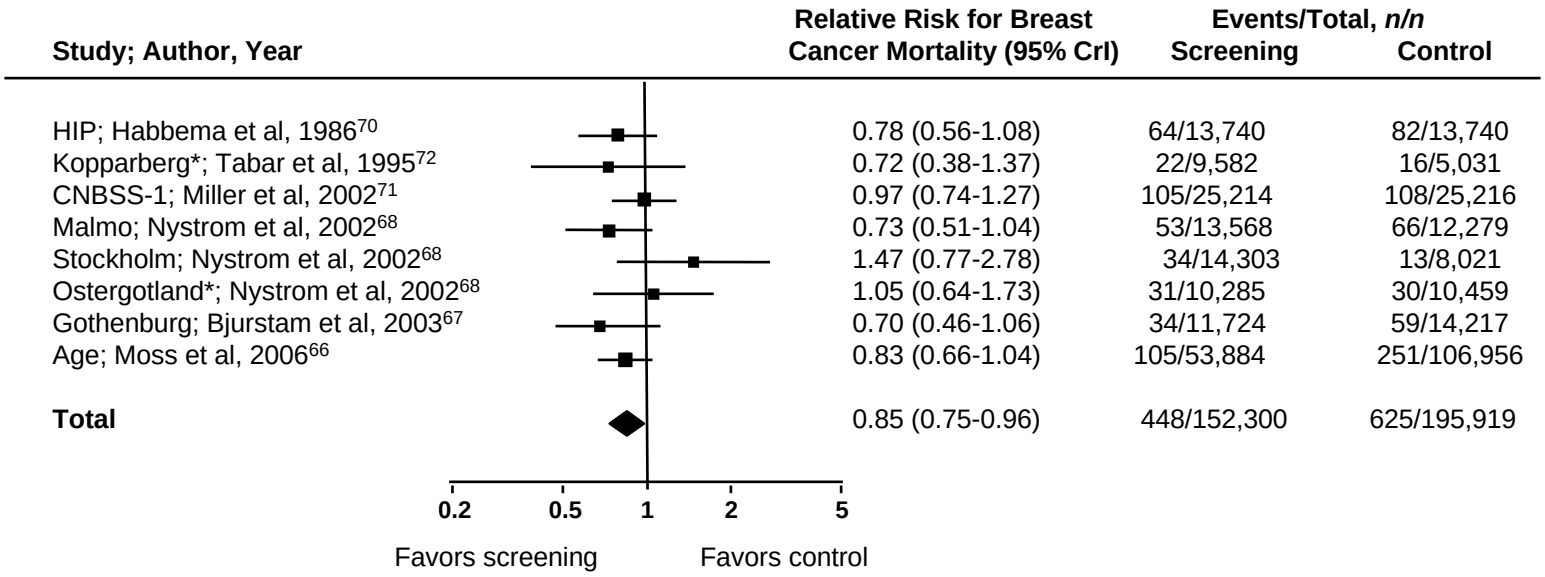
1a. Does screening with mammography (film and digital) or MRI decrease breast cancer mortality among women age 40-49 years and 70 years and older?
1b. Does clinical breast examination screening decrease breast cancer mortality? Alone or with mammography?
1c. Does breast self examination practice decrease breast cancer mortality?
2a. What are the harms associated with screening with mammography (film and digital) and MRI?
2b. What are the harms associated with clinical breast examination?
2c. What are the harms associated with breast self examination?

CONTEXTUAL QUESTION

1. What is the cost-effectiveness of screening?

Abbreviation: MRI=magnetic resonance imaging.

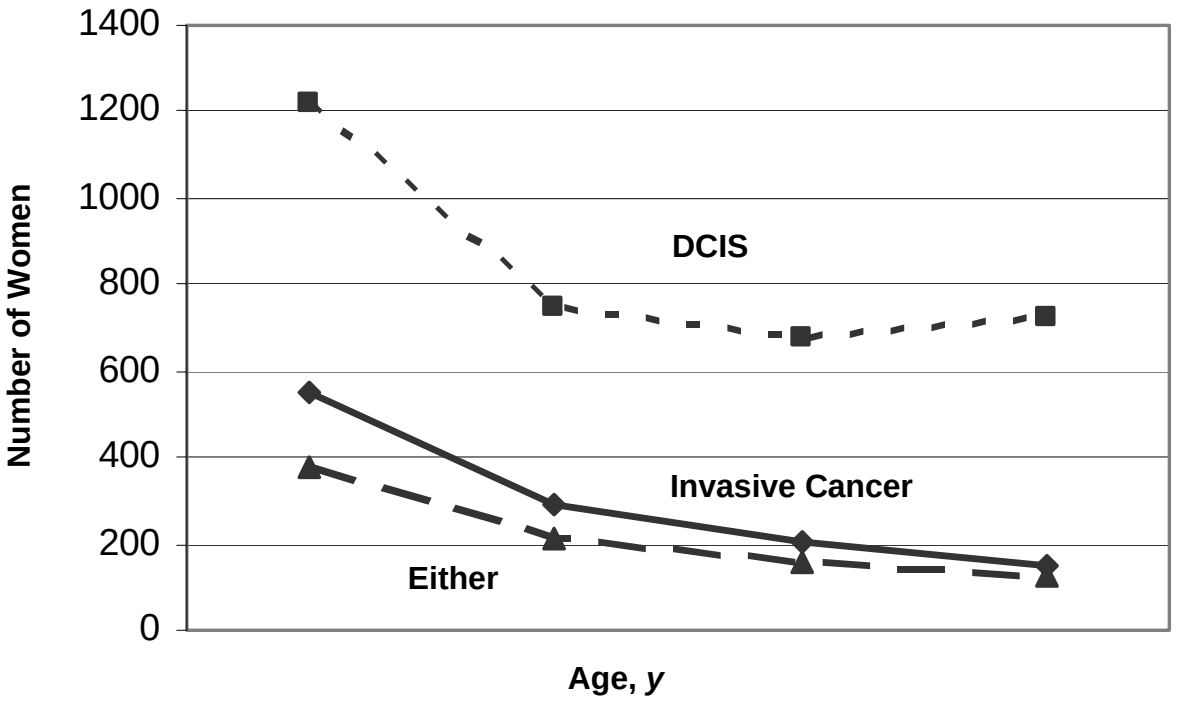
Figure 2. Pooled Relative Risk for Breast Cancer Mortality from Mammography Screening Trials for Women Age 39 to 49 Years



*Swedish Two-County Trial.

Abbreviations: CrI=confidence interval for individual trial results and credible interval for meta-analysis results; CNBSS-1=Canadian National Breast Screening Study-1; HIP=Health Insurance Plan of Greater New York.

Figure 3. Number of Women Undergoing Routine Mammography to Diagnose 1 Case of Invasive Cancer, DCIS, or Either from the Breast Cancer Surveillance Consortium

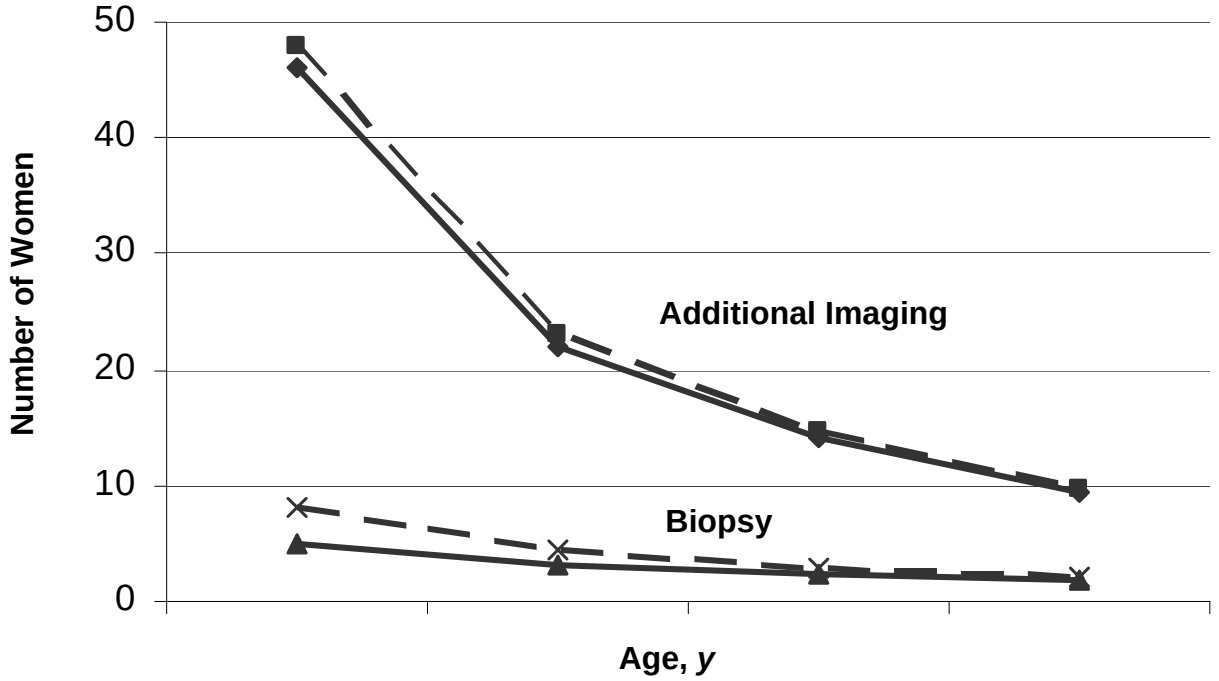


	40-49	50-59	60-69	70+
Invasive	556	294	200	148
DCIS	1,250	769	667	690
Either	385	213	154	122

Number undergoing mammography to diagnose 1 case of invasive cancer, DCIS or either = (# women screened/# cases detected among women by screening).

Abbreviation: DCIS=ductal carcinoma in situ.

Figure 4. Number of Women Undergoing Additional Imaging and Number Undergoing Biopsy to Diagnose 1 Case of Invasive Cancer from the Breast Cancer Surveillance Consortium



		40-49	50-59	60-69	70+
Additional imaging	Assumes missing values do not undergo procedure	47	22	14	9
	Assumes missing values undergo procedure	48	23	15	10
Biopsy	Assumes missing values do not undergo procedure	5	3	2	2
	Assumes missing values undergo procedure	8	4	3	2

Number undergoing additional imaging to diagnose 1 case of invasive cancer = (# women undergoing additional imaging/# cases of invasive cancer detected among women by screening).

Number undergoing biopsy to diagnose 1 case of invasive cancer = (# women undergoing biopsy/# cases of invasive cancer detected among women by screening).

Table 1. Breast Cancer Screening Recommendations for Average-Risk Women

	American Academy of Family Physicians (AAFP)	American Cancer Society (ACS)	American College of Obstetricians and Gynecologists (ACOG)	American College of Physicians (ACP)*	American College of Preventive Medicine (ACPM)	American College of Radiology (ACR)	American Medical Association (AMA)	Canadian Task Force on Preventive Health Care (CTFPHC)	National Cancer Institute (NCI)	National Compre-hensive Cancer Network (NCCN)	US Preventive Services Task Force (USPSTF)	World Health Organization (WHO)
Mammography												
Age 40+, annual		x				x	x			x		
Age 40+, every 1-2 years	x							x	x		x	
Age 40-49, every 1-2 years			x									
Age 50+, annual			x									
Age 50-69, annual or biennial					x							x
Age 70+					x							
MRI												
Not recommended for average risk women		x								x		
CBE												
Age 40+, annual		x	x							x		
Periodic evaluation (1-3 years), ages vary		x					x	x ages 50-69	x	x		
Insufficient evidence											x	
Not recommended												x
BSE												
Recommended			x				x			x		
Insufficient evidence	x	x							x		x	
Not recommended								x				x

*Suggests periodic, individualized screening for women age 40-49 years.

Abbreviations: BSE=breast self examination; CBE=clinical breast examination; MRI=magnetic resonance imaging.

Table 2. Mammography Screening Trials Included in Meta-analysis

Study; Author, Year	Baseline Study Year	Setting or Population (screening, *n*; control, *n*)	Enrollment Age, *y*	Randomization Method	Study Group	Screening Protocol				USPSTF Quality Rating
						Interval, *mo*	Round, *n*	View, *n*	Follow-up, *y*	
Health Insurance Plan (HIP) of Greater New York; Habbema et al,1986[70]	1963	New York health plan members (30,239; 30,256)	40-64	Pairs of women stratified by age and family size were individually randomly assigned by drawing from a list.	Mammography + CBE vs. usual care	12	4	2	18	Fair
Canadian National Breast Screening Study-1 (CNBSS-1); Miller et al, 2002[71]	1980	15 centers in Canada, self-selected participants (25,214; 25,216)	40-49	Blocks were stratified by center and 5-year age group after CBE.	Mammography + CBE vs. usual care (all women prescreened and instructed in BSE)	12	4-5	2	13	Fair
Gothenburg* Breast Screening trial; Bjurstam et al, 2003[67]	1982	All women born from 1923-1944, living in Gothenburg, Sweden (20,724; 28,809)	39-59	Cluster, based on day of birth (1923-1935 cohort [18%]), and individual (1936-1944 cohort [82%]).	Mammography vs. usual care; control participants offered screening after 5 years, completed screening at approximately 7 years.	18	5	1-2	12	Fair
Stockholm; Nystrom et al, 2002[68]	1981	Residents of southeast greater Stockholm, Sweden (40,318; 19,943)	40-64	Individual, by day of month; screening to control group ratio is 2:1.	Mammography vs. usual care	24-28	2	1	11.4	Fair

Table 2. Mammography Screening Trials Included in Meta-analysis

Study; Author, Year	Baseline Study Year	Setting or Population (screening, *n*; control, *n*)	Enrollment Age, *y*	Randomization Method	Study Group	Screening Protocol				USPSTF Quality Rating
						Interval, *mo*	Round, *n*	View, *n*	Follow-up, *y*	
Malmo; Nystrom et al, 2002[68]	1976-1978	All women born from 1927-1945 living in Malmo, Sweden (21,088; 21,195)	45-70	Individual, within birth year.	Mammography vs. usual care; control participants offered screening after 14 years.	18-24	9	1-2	11-13 15.5	Fair
Swedish Two-County trial (2 trials); Nystrom et al, 2002[68]; Tabar et al, 1995[72]	1977	From Ostergotland and Kopparberg counties in Sweden (77,080; 55,985)	40-74	Clusters, based on geographic units; blocks designed to be demographically homogeneous.	Mammography vs. usual care; control participants offered screening after 7 years.	24-33	3	1	20 15.5	Fair
Age trial;* Moss et al, 2006[66]	1991	23 National Health Service breast screening units in England, Scotland, and Wales (53,884; 106,956)	39-41	Individual, stratified by general practitioner group with random number generation (1991-1992); randomization through Health Authority computer system (1992-onward).	Mammography vs. usual care; all women offered screening at age 50-52.	12	4-6, varied by center	2	10.7	Fair

*New data since the previous recommendation.

Abbreviations: BSE=breast self examination; CBE=clinical breast examination; USPSTF=U.S. Preventive Services Task Force.

Table 3. Sensitivity Analysis: Meta-analysis of Screening Trials of Women Age 39 to 49 Years

Meta-analysis	Differences from Updated Meta-analysis*	Number of trials	RR for Breast Cancer Mortality (95% CrI)	NNI to Prevent 1 Breast Cancer Death (95% CrI)
2002 Review[2,3]	Does not include Age trial; includes older Gothenburg data	7	0.85 (0.73-0.99)	1,787 (715-10,737)
Update		8	0.85 (0.75-0.96)	1,904 (929-6,378)
Sensitivity analysis #1	Excludes HIP trial	7	0.87 (0.75-0.98)	2,253 (1,016-10,927)
Sensitivity analysis #2	Excludes CNBSS-1 trial	7	0.82 (0.72-0.94)	1,677 (881-4,915)
Sensitivity analysis #3	Excludes HIP and CNBSS-1 trials	6	0.83 (0.72-0.96)	1,877 (904-8,969)

*Trials and their acronyms are discussed in the text.

Abbreviations: CNBSS-1=Canadian National Breast Screening Study-1; CrI=credible interval; HIP=Health Insurance Plan of Greater New York; NNI=number needed to invite to screening; RR=relative risk.

Table 4. Summary of Screening Trials of Women Age 70 to 74 Years

Study; Author, Year	Trials Included*	Number of trials	RR for Breast Cancer Mortality (95% CrI)	NNI to Prevent 1 Breast Cancer Death (95% CrI)
2002 Review (age 65-74 y); Humphrey, et al, 2002[2,3]	Malmo and Swedish 2-County trials	2	0.78 (0.62-0.99)	Not available
Swedish 2-County trial (age 70-74 y); Nystrom et al, 2002[68]	Swedish 2-County trial least biased estimate using Ostergotland only	1 subgroup of 1 trial	1.12 (0.73-1.72)	Not available

*Trials and their acronyms are discussed in the text.

Abbreviations: CrI=confidence interval for individual trial results and credible interval for meta-analysis results; NNI=number needed to invite to screening; RR=relative risk.

Table 5. Pooled Relative Risk for Breast Cancer Mortality from Mammography Screening Trials for All Ages

Age, *y*	Trials Included, *n* *	RR for Breast Cancer Mortality (95% CrI)	NNI to Prevent 1 Breast Cancer Death (95% CrI)
39-49	8	0.85 (0.75-0.96)	1,904 (929-6,378)
50-59	6	0.86 (0.75-0.99)	1,339 (322-7,455)
60-69	2	0.68 (0.54-0.87)	377 (230-1,050)
70-74	1	1.12 (0.73-1.72)	Not available

*Trials and their acronyms are discussed in the text.

Abbreviations: CrI=confidence interval for individual trial results and credible interval for meta-analysis results; NNI=number needed to invite to screening; RR=relative risk.

Table 6. Trials of Clinical Breast Examination and Breast Self Examination

Author, Year	Technique	Years	Setting or Population (screening, *n*; control, *n*)	Enrollment Age, *y*	Study Design	Intervention
Pisani et al, 2006[75]	CBE	1996-1997	Manila, Philippines; women living in the 12 central areas (151,168; controls not indicated)	35-64	RCT; block randomization of 202 health centers	5 annual CBEs vs. usual care provided by nurses and midwives; CBE instruction using the MAMMACARE program
Boulos et al, 2005[77]	CBE/BSE	Pilot: 2000-2002 RCT: ongoing	Cairo, Egypt; women living in area around Italian Hospital (1,924; 1,927)	39-65	RCT; block randomization	CBE/BSE x2 (intervention) vs. CBE/BSE x1 (control) provided by female physicians; CBE training at Italian Hospital 2 months before study
National Cancer Institute[76]	CBE/BSE	1998 and ongoing	Mumbai, India; women living in area around Tata Memorial Hospital (150,000; controls not indicated)	35-64	RCT; cluster randomization	CBE + BSE + breast health education every 24 months for 4 rounds vs. education alone provided by trained female health workers; CBE training for 5 months before trial
Thomas et al, 2002[78]	BSE	1989-2000	Shanghai, China; women working at 1 of 519 factories (132,979; 133,085)	31-65	RCT; factories assigned to BSE or control group	BSE instruction with periodic reinforcement provided by trained former factory medical workers vs. no instruction; initial BSE instruction, follow-up sessions at 1 and 3 years, medically supervised BSE every 6 months
Semiglazov et al, 2003[57]	BSE	1985-2001	St. Petersburg, Russia; women attending 1 of 28 clinics (58,985; 64,763)	40-64	RCT; cluster randomization	BSE instruction with refresher every 3 years provided by trained nurses or physicians vs. no instruction; providers received 3-hour training; instruction given to groups of 5-20 women

Table 6. Trials of Clinical Breast Examination and Breast Self Examination

Author, Year	Primary Outcomes	Secondary Outcomes	USPSTF Quality Rating
Pisani et al, 2006[75]	Breast cancer mortality not reported	*False-negative result: 80 of 133 diagnosed breast cancer cases; *False-positive result: 1,182 of 1,220 (96.9%) who completed follow-up	Poor; low participation, discontinued after 1 round
Boulos et al, 2005[77]	Breast cancer incidence	Benign procedures: 1.2% after 1 round	Not rated (in progress)
National Cancer Institute[76]	Breast cancer mortality	Not available	Not rated (in progress)
Thomas et al, 2002[78]	Breast cancer mortality: RR 1.03 (95% CI, 0.81-1.31)	Benign biopsies: RR 1.57 (95% CI, 1.48-1.68)	Good
Semiglazov et al, 2003[57]	All cause mortality: RR 1.07 (95% CI, 0.88-1.29)	Benign biopsies: RR 2.05 (95% CI, 1.80-2.33)	Fair; low adherence, inconsistent data reported

*****Risks not calculated because diagnostic follow-up for a positive CBE was 35%.

Abbreviations: BSE=breast self examination; CBE=clinical breast examination; CI=confidence interval; RCT=randomized controlled trial; RR=relative risk.

Table 7. Age-specific Screening Results from the Breast Cancer Surveillance Consortium

Screening Result	Age, *y* 40-49	50-59	60-69	70-79	80-89
Outcomes per Screening Round (per 1,000 screened), *n**					
False-negative mammography	1.0	1.1	1.4	1.5	1.4
False-positive mammography	97.8	86.6	79.0	68.8	59.4
Additional imaging	84.3	75.9	70.2	64.0	56.3
Biopsy	9.3	10.8	11.6	12.2	10.5
Screen-detected invasive cancer	1.8	3.4	5.0	6.5	7.0
Screen-detected DCIS	0.8	1.3	1.5	1.4	1.5
Yield of Screening per Screening Round, *n*					
Patients undergoing mammography to diagnose 1 case of invasive breast cancer†	556	294	200	154	143
Patients undergoing additional imaging to diagnose 1 case of invasive breast cancer‡	47	22	14	10	8
Patients undergoing biopsy to diagnose 1 case of invasive breast cancer§	5	3	2	2	1.5

*Calculated from Breast Cancer Surveillance Consortium (BCSC) data of regularly screened women based on results from a single screening round. Rates of additional imaging and rates of biopsies may be underestimated due to incomplete capture of these exams by the BCSC.

†1 per rate of screen detected invasive cancer.

‡Rate of additional imaging per rate of screen-detected invasive cancer.

§Rate of biopsy per rate of screen-detected invasive cancer.

Abbreviation: DCIS=ductal carcinoma in situ.

Table 8. Studies of Breast Cancer Overdiagnosis

Author, Year	Age, *y*	Rates of Overdiagnosis: All Diagnoses	Rates of Overdiagnosis: Invasive Cancer	Rates of Overdiagnosis: Noninvasive Cancer	Method	Population
de Koning et al, 2006[102]	50-74	3% of incidence in screened population 8% screen-detected	NR	NR	Microsimulation model	Netherlands
Duffy et al, 2005[104]	40-74	1% of incidence in screened population	<1%	1% (upper limit)	Multistate	Swedish Two-county trial
	39-59	2% of incidence in screened population	1.66%	2% (upper limit)	Multistate	Gothenburg trial
Olsen et al, 2006[103]	50-71	7.8% of screen-detected, prevalence 0.5% of screen-detected, incidence 4.8% of incidence in screened population	7.3% prevalence 0.5% incidence	0.5% prevalence	Multistate	Copenhagen
Paci et al, 2004[101]	50-69	5% of incidence predicted without screening	2%	3%	Corrected for lead time vs. predicted	Florence
Paci et al, 2006[100]	50-74	4.6% of incidence predicted without screening	3.20%	1.40%	Corrected for lead time vs. predicted	Italy
	50-54	7.40%	NR	NR	Corrected for lead time vs. predicted	
	55-59	-0.60%	NR	NR	Corrected for lead time vs. predicted	
	60-64	0.70%	NR	NR	Corrected for lead time vs. predicted	
	65-69	5.70%	NR	NR	Corrected for lead time vs. predicted	
	70-74	9.70%	NR	NR	Corrected for lead time vs. predicted	
Svendsen et al, 2006[112]	50-69	If overdiagnosis occurred it was limited	NR	NR	Comparison of incidence in screened vs. unscreened	Denmark
Yen et al, 2003[105]	40-69	NR	NR	37% of DCIS prevalence, 4% incidence	Six state Markov model	Swedish Two-county trial, United Kingdom, Netherlands, Australia, New York
	40-49	NR	NR	19%, 3%	Six state Markov model	Swedish Two-county trial
	50-59	NR	NR	23%, 4%	Six state Markov model	Swedish Two-county trial
	60-69	NR	NR	46%, 6%	Six state Markov model	Swedish Two-county trial
Zackrisson et al, 2006[106]	55-69	10% of incidence in control (unscreened) group	7%	3%	Comparison of incidence in screened vs. unscreened	Malmo trial
Zahl et al, 2004[107]	50-69	NR	30% incidence in screened population	NR	Changes in age-specific incidence rates associated with the introduction of screening programs	Norway and Sweden

Abbreviations: DCIS=ductal carcinoma in situ; NR=not reported.

Table 9. Summary of Evidence

Number of Studies and Type	Design	Limitations	Consistency	Applicability	Overall Quality	Findings
KQ1a. Does screening with mammography (film and digital) and MRI decrease breast cancer mortality among women age 40-49 and over the age of 70?						
8 for women age 40-49 y; 1 for age 70-74 y; no screening trials of MRI or digital technologies	RCTs	Several trials were conducted before current mammography technology and treatment approaches; all trials met criteria for fair quality	Consistent	Fair: all but 1 trial were conducted outside of the U.S. but recruited large community-based populations	Fair	For women age 39-49 y, the combined relative risk for breast cancer mortality was 0.85 (95% CrI, 0.74-0.95; 8 trials) and the number needed to screen 1,894 (992-6,201). Evidence for women 70 y or older is insufficient
KQ1b. Does CBE screening decrease breast cancer mortality? Alone or with mammography?						
1 (2 in progress)	RCTs	The trial was discontinued after one round because of poor community acceptance	Not applicable	Poor	Poor	Inconclusive findings.
KQ1c. Does BSE practice decrease breast cancer mortality?						
2 trials + 3 systematic reviews	RCTs	Both trials were conducted in countries that do not have mass mammography screening	Consistent	Fair: Although trials were conducted in populations very different than the U.S., results could be useful for U.S. practice	Fair	Both trials indicated no reduction in mortality rates
KQ2a. What are the harms associated with screening with mammography (film and digital) and MRI?						
Several systematic reviews and primary studies; no studies of MRI for screening average-risk women	Several study designs and data sources including RCTs, observational studies, surveys, and data from the BCSC	Adverse effects have been studied in various ways, most studies are descriptive	Varies by type of harm	Poor to good: The applicability of some studies, such as those about radiation exposure, may be low because they provide indirect evidence for the association between radiation exposure from routine mammography and breast cancer; other studies, such as those of patient anxiety with false-positive mammography results, come from direct patient experiences	Poor to good	Evidence supports a relationship between radiation exposure and breast cancer with much higher doses of radiation than obtained through screening. Pain during procedures is common, brief, and not a barrier. Anxiety, distress, and other psychosocial effects of screening are usually transient and do not influence future screening practices. False-positive results are common. Younger women have more false-positive mammography results and more additional imaging than older women, but rates of biopsy are lower. Rates of overdiagnosis vary by study methodology and are 1-10%
KQ2b. What are the harms associated with CBE?						
3	1 RCT and 2 descriptive studies	Identified studies provide isolated descriptive data and are insufficient to address the question	Not applicable	Poor	Poor	Inconclusive findings
KQ2c. What are the harms associated with BSE?						
3	2 RCTs and 1 observational study	Both trials were conducted in countries that do not have mass mammography screening	Not applicable	Fair: Although trials were conducted in populations very different than the U.S., results could be useful for U.S. practice	Fair	2 trials indicated increased benign breast biopsies with breast self-examination; biopsies were not increased in the observational study

Abbreviations: BCSC=Breast Cancer Surveillance Consortium; BSE=breast self examination; CBE=clinical breast examination; CrI=credible interval; MRI=magnetic resonance imaging; RCTs= randomized controlled trials; U.S.=United States.

Appendix A1. Acronyms and Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ACS	American Cancer Society
AHRQ	Agency for Healthcare, Research, and Quality
BCSC	Breast Cancer Surveillance Consortium
BI-RADS	Breast Imaging Reporting and Data System
BSE	Breast Self Examination
CBE	Clinical Breast Examination
CI	Confidence Interval
CTFPHC	Canadian Task Force on Preventative Health Care
CrI	Credible Interval
DCIS	Ductal carcinoma in situ
EBCN	European Breast Cancer Network
EPC	Evidence-based Practice Center
EUREF	European Reference Organisation for Quality Assured Breast Screening and Diagnostic Services
EUSOMA	European Society of Mastology
FNA	Fine Needle Aspiration
LCIS	Lobular carcinoma in situ
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NHSBSP	UK National Health Service Breast Screening Programme
NNI	Number Needed to Invite to Screen
NNS	Number Needed to Screen
NR	Not reported
QALY	Quality-adjusted life-year
RR	Relative Risk
SEER	Surveillance Epidemiology and End Results
SES	Socioeconomic Status
USD	US Dollar
USPSTF	US Preventive Services Task Force
WHI	Women's Health Initiative
WHO	World Health Organization

Appendix B1. Literature Search Strategies

Screening

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 ((Breast$ or mammary) adj3 (Neoplas$ or tumor$ or cancer$ or carcinom$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp.
3 ((clinical$ or physical$) adj3 (exam$ or detect$ or diagnos$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 2 or 3
5 1 and 4

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
---
1 ((Breast$ or mammary) adj3 (Neoplas$ or tumor$ or cancer$ or carcinom$)).mp. [mp=title, abstract, full text, keywords, caption text]
2 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp.
3 ((clinical$ or physical$) adj3 (exam$ or detect$ or diagnos$)).mp. [mp=title, abstract, full text, keywords, caption text]
4 2 or 3
5 1 and 4
6 ((Breast$ or mammary) adj3 (Neoplas$ or tumor$ or cancer$ or carcinom$)).kw.
7 1 not 6
8 4 and 6

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp Breast Neoplasms/
2 exp neoplasms/di
3 exp breast/
4 2 and 3
5 1 or 4
6 exp mass screening/
7 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 6 or 7
9 5 and 8
10 exp Physical Examination/
11 exp Breast/
12 exp Breast Neoplasms/
13 11 or 12
14 10 and 13
15 exp Mammography/
16 9 and 14
17 9 and 15
18 exp Mortality/
19 mo.fs.
20 18 or 19
21 16 and 20
22 17 and 20
23 21 or 22
24 limit 23 to (humans and english language)

25 limit 24 to (guideline or meta analysis or randomized controlled trial)
26 (random$ or rct).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
27 24 and 26
28 (meta-analy$ or metaanaly$ or (systematic$ adj10 review$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
29 24 and 28
30 25 or 27 or 29
31 24 not 30

Digital Mammography

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 ((digital$ or computer$) adj7 mammogra$).mp.
2 from 1 keep 1-37

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
---
1 ((digital$ or computer$) adj7 mammogra$).mp.
2 from 1 keep 1

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp Breast Neoplasms/
2 exp neoplasms/di
3 exp breast/
4 2 and 3
5 1 or 4
6 exp mass screening/
7 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 6 or 7
9 5 and 8
10 exp Physical Examination/
11 exp Breast/
12 exp Breast Neoplasms/
13 11 or 12
14 10 and 13
15 exp Mammography/
16 9 and 14
17 9 and 15
18 16 or 17
19 (digital$ adj7 mammogra$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
20 exp Image Processing, Computer-Assisted/
21 exp Mammography/
22 20 and 21
23 19 or 22
24 8 and 23
25 limit 24 to english language
26 from 25 keep 1-395

Appendix B1. Literature Search Strategies

MRI

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 ((Breast$ or mammary) adj3 (Neoplas$ or tumor$ or cancer$ or carcinom$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (mri or magnetic resonance imag$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 1 and 2
4 from 3 keep 1-29

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
---
1 ((Breast$ or mammary) adj3 (Neoplas$ or tumor$ or cancer$ or carcinom$)).mp. [mp=title, abstract, full text, keywords, caption text]
2 (mri or magnetic resonance imag$).mp. [mp=title, abstract, full text, keywords, caption text]
3 1 and 2
4 from 3 keep 1-9

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp Breast Neoplasms/
2 exp neoplasms/di
3 exp breast/
4 2 and 3
5 1 or 4
6 exp mass screening/
7 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 6 or 7
9 5 and 8
10 exp Physical Examination/
11 exp Breast/
12 exp Breast Neoplasms/
13 11 or 12
14 10 and 13
15 exp Mammography/
16 9 and 14
17 9 and 15
18 16 or 17
19 exp Magnetic Resonance Imaging/
20 5 and 19
21 8 and 20
22 from 21 keep 1-232

DCIS

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp Carcinoma, Intraductal, Noninfiltrating/
2 exp Breast Neoplasms/

3 1 and 2
4 overdiagno$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5 over-diagno$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6 (overtreat$ or over-treat$).mp.
7 exp Diagnostic Errors/
8 exp Mass Screening/
9 exp mammography/
10 8 or 9
11 3 and 7 and 10
12 4 or 5 or 6
13 3 and 12
14 from 13 keep 1-22

Adverse Effects

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 exp mammography/
2 mammogra$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3 exp physical examination/
4 ((physical$ or clinical$ or manual$) adj3 exam$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 exp mass screening/
6 screen$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
7 1 or 2 or 3 or 4 or 5 or 6
8 exp breast/
9 exp breast diseases/di, ep
10 (breast$ or mammar$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
11 8 or 9 or 10
12 7 and 11
13 ((advers$ adj3 effect$) or harm$ or contraindicat$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
14 ae.fs.
15 13 or 14
16 12 and 15
17 exp Mammography/ae, ct [Adverse Effects, Contraindications]
18 exp Physical Examination/ae, ct
19 exp Mass Screening/ae, ct [Adverse Effects, Contraindications]
20 17 or 18 or 19
21 11 and 20
22 exp Diagnostic Errors/
23 (overtest$ or overdiagnos$ or over-test$ or over-diagnos$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
24 (false$ adj2 (result$ or positiv$ or negativ$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
25 (observer$ adj3 bias$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
26 (diagnos$ adj3 (error$ or mistak$ or incorrect$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
27 22 or 23 or 24 or 25 or 26
28 12 and 27
29 exp "Wounds and Injuries"/ci, et [Chemically Induced, Etiology]
30 exp Stress, Psychological/
31 exp Prejudice/
32 exp Stereotyping/

33 (anxiet$ or anxious$ or fear$ or discriminat$ or unfair$ or prejudic$ or stigma$ or stereotyp$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
34 29 or 30 or 31 or 32 or 33
35 12 and 34
36 16 or 21 or 28 or 35
37 from 36 keep 1-240

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp mammography/
2 exp physical examination/
3 exp mass screening/
4 1 or 2 or 3
5 exp breast/
6 exp breast diseases/di, ep
7 5 or 6
8 4 and 7
9 exp Mammography/ae, ct [Adverse Effects, Contraindications]
10 exp Physical Examination/ae, ct
11 exp Mass Screening/ae, ct [Adverse Effects, Contraindications]
12 9 or 10 or 11
13 7 and 12
14 exp Diagnostic Errors/
15 (overtest$ or overdiagnos$ or over-test$ or over-diagnos$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16 14 or 15
17 8 and 16
18 exp "Wounds and Injuries"/ci, et [Chemically Induced, Etiology]
19 exp Stress, Psychological/
20 exp Prejudice/
21 exp Stereotyping/
22 18 or 19 or 20 or 21
23 8 and 22
24 13 or 17 or 23
25 limit 24 to english language
26 limit 25 to (meta analysis or randomized controlled trial)
27 exp Evaluation Studies/
28 Comparative Study.pt.
29 exp Epidemiologic Studies/
30 27 or 28 or 29
31 25 and 30
32 26 or 31
33 from 32 keep 1-319

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp mammography/
2 exp physical examination/
3 exp mass screening/
4 1 or 2 or 3
5 exp breast/
6 exp breast diseases/di, ep
7 5 or 6
8 4 and 7

9 exp Mammography/ae, ct [Adverse Effects, Contraindications]
10 exp Physical Examination/ae, ct
11 exp Mass Screening/ae, ct [Adverse Effects, Contraindications]
12 9 or 10 or 11
13 7 and 12
14 exp Diagnostic Errors/
15 (overtest$ or overdiagnos$ or over-test$ or over-diagnos$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
16 misdiagnos$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17 (false$ adj (positiv$ or negativ$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
18 ((incorrect$ or false$ or wrong$ or bias$ or mistake$ or error$ or erroneous$) adj3 (result$ or finding$ or test$ or diagnos$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
19 ((inappropriat$ or unnecess$ or unneed$) adj3 (treat$ or surg$ or therap$ or regimen$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
20 (observ$ adj3 bias$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
21 14 or 15 or 16 or 17 or 18 or 19 or 20
22 8 and 21
23 exp "Wounds and Injuries"/ci, et [Chemically Induced, Etiology]
24 exp Stress, Psychological/
25 exp Prejudice/
26 exp Stereotyping/
27 23 or 24 or 25 or 26
28 8 and 27
29 13 or 22 or 28
30 limit 29 to english language
31 limit 30 to (meta analysis or randomized controlled trial)
32 exp Evaluation Studies/
33 Comparative Study.pt.
34 exp Epidemiologic Studies/
35 32 or 33 or 34
36 30 and 35
37 31 or 36
38 limit 30 to yr="2000 - 2007"
39 from 38 keep 1-391

Cost

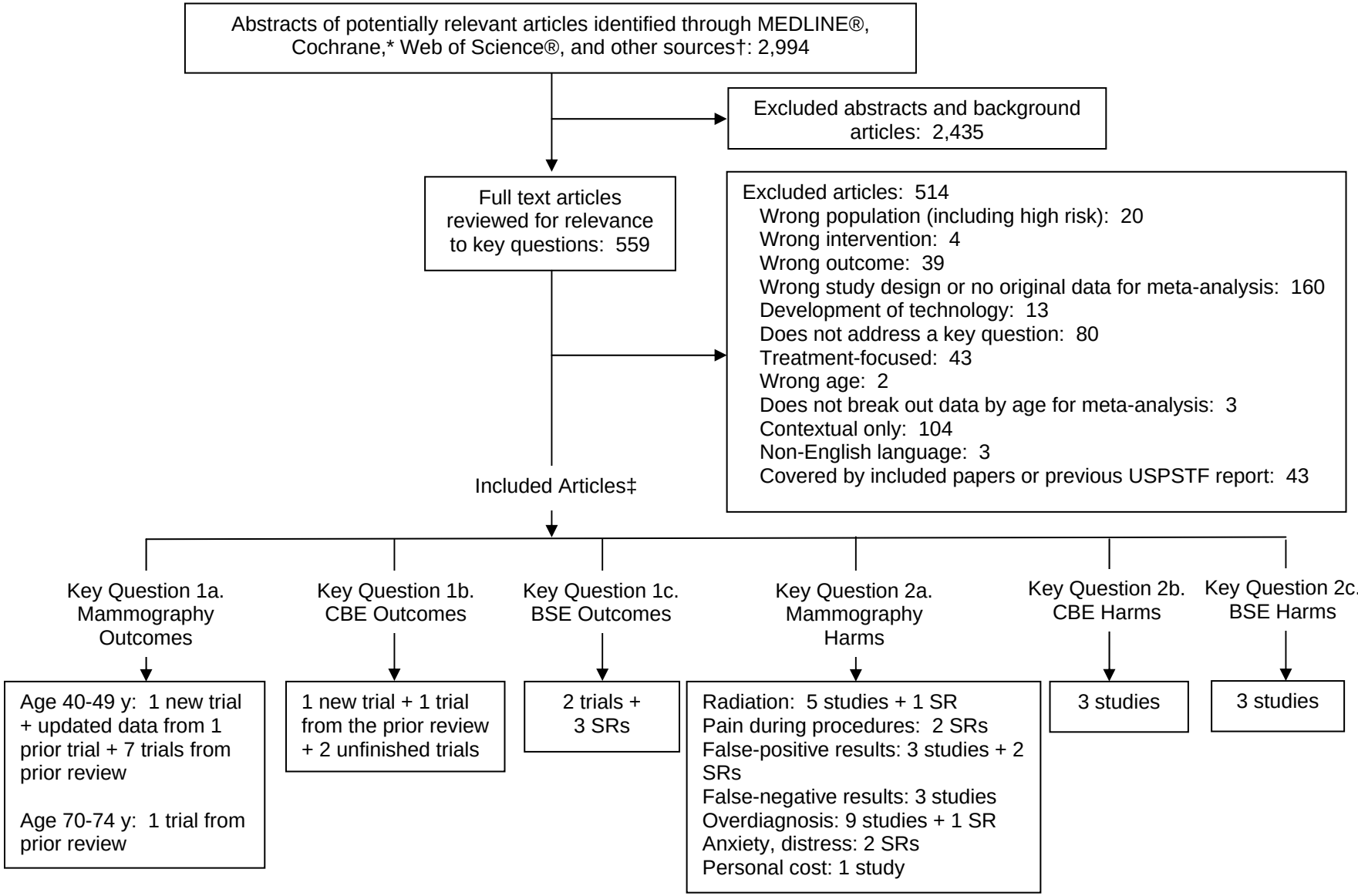
Database: EBM Reviews - Cochrane Central Register of Controlled Trials
Search Strategy:
---
1 ((Breast$ or mammary) adj3 (Neoplas$ or tumor$ or cancer$ or carcinom$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
2 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp.
3 ((clinical$ or physical$) adj3 (exam$ or detect$ or diagnos$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4 (cost or costs or costing or economic$ or financial$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
5 1 and (2 or 3) and 4
6 from 5 keep 1-86

Appendix B1. Literature Search Strategies

Database: EBM Reviews - Cochrane Database of Systematic Reviews
Search Strategy:
---
1 ((Breast$ or mammary) adj3 (Neoplas$ or tumor$ or cancer$ or carcinom$)).mp. [mp=title, abstract, full text, keywords, caption text]
2 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp.
3 ((clinical$ or physical$) adj3 (exam$ or detect$ or diagnos$)).mp. [mp=title, abstract, full text, keywords, caption text]
4 (cost or costs or costing or economic$ or financial$).mp. [mp=title, abstract, full text, keywords, caption text]
5 1 and (2 or 3) and 4
6 from 5 keep 1-97

Database: Ovid MEDLINE(R)
Search Strategy:
---
1 exp Breast Neoplasms/
2 exp neoplasms/di
3 exp breast/
4 2 and 3
5 1 or 4
6 exp mass screening/
7 (screen$ or (routine$ adj3 (test$ or check$ or diagnos$ or detect$))).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8 6 or 7
9 5 and 8
10 exp Physical Examination/
11 exp Breast/
12 exp Breast Neoplasms/
13 11 or 12
14 10 and 13
15 exp Mammography/
16 9 and 14
17 9 and 15
18 16 or 17
19 exp "Costs and Cost Analysis"/
20 18 and 19
21 limit 20 to english language
22 from 21 keep 1-376

Appendix B2. Search Results by Key Question



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Other sources include reference lists, studies suggested by experts, etc.
‡ Some articles are included for more than one key question.

Abbreviation: BSE= Breast self examination; CBE=Clinical breast examination; SR=systematic review.

Appendix B3. List of Excluded Studies

Wrong population, including high risk:

Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA.* 2008;299(18):2151-2163.

Boetes C. The evaluation of women with familial risk of breast cancer. *J Exp Clin Cancer Res*. 2002;21 (3 Suppl):97-101.

Bordas P, Jonsson H, Nystrom L, et al. Early breast cancer deaths in women aged 40-74 years diagnosed during the first 5 years of organised mammography service screening in north Sweden. *Breast*. 2004;13(4):276-283.

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Joensuu H, Lehtimaki T, Holli K, et al. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. *JAMA.* 2004;292(9):1064-1073.

Lalonde L, David J, Trop I. Magnetic resonance imaging of the breast: current indications. *Can Assoc Radiol J*. 2005;56(5):301-308.

Lash TL, Fox MP, Buist DSM, et al. Mammography surveillance and mortality in older breast cancer survivors. *J Clin Oncol.* 2007;25(21):30001-30006.

Leach MO, Boggis CRM, Dixon AK, et al. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: a prospective multicentre cohort study (MARIBS). *Lancet.* 2005;365(9473):1769-1778.

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MARIBS Study Group. Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: A prospective multicentre cohort study. *Lancet*. 2005;365(9473):1769-1778.

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Rijnsburger AJ, Essink-Bot ML, van Dooren S, et al. Impact of screening for breast cancer in high-risk women on health-related quality of life. *Br J Cancer*. 2004;91(1):69-76.

Sim LSJ, Hendriks JHCL, Fook-Chong SMC. Breast ultrasound in women with familial risk of breast cancer. *Ann Acad Med Singapore*. 2004;33(5):600-606.

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Warnberg F, Casalini P, Nordgren H, et al. Ductal carcinoma in situ of the breast: a new phenotype classification system and its relation to prognosis. *Breast Cancer Res Treat*. 2002;73(3):215-221.

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Wrong intervention:

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Appendix B4. U.S. Preventive Services Task Force Quality Rating Methodology for Randomized Controlled Trials and Observational Studies[1]

Randomized Controlled Trials (RCTs) and Cohort Studies

Criteria:

- Initial assembly of comparable groups**:** RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intension-to-treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Case Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variable

Appendix B4. U.S. Preventive Services Task Force Quality Rating Methodology for Randomized Controlled Trials and Observational Studies[1]

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

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Appendix B5. Quality Rating Methodology for Systematic Reviews[1-3]

1. Comprehensiveness of sources/search strategy used:
    a. Were search terms reported?
    b. Was the search comprehensive (Medline, search reference lists and/ or experts)?
    c. Were the search terms applicable?

2. Standard appraisal of included studies:
    a. Were inclusion/exclusion criteria reported?
    b. Are criteria valid?

3. Quality/validity assessment:
    a. Were criteria for validity/quality assessment explicit and applied to all studies?
    b. Were quality criteria appropriate (e.g. criteria appropriate for study design)?

4. Analysis/synthesis:
    a. Were methods used to combine studies reported?
    b. Were studies that were combined similar to one another (e.g. appropriate to combine, similar patient populations etc)?

5. Validity of conclusions:
    a. Were conclusions supported by the data?

6. Recency and relevance:
    a. Is the study recent and relevant to scope?

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Appendix B6. Details of the Meta-analysis

The meta-analysis is an update of the previous 2002 meta-analysis that includes results from published trials of mammography screening for women age 39-49 years reporting reduction in breast cancer mortality. With the addition of only 1 new data point, the meta-analysis for the update was less extensive than the 2002 meta-analysis. We did not update the model for relative risk and length of follow-up (the two-level hierarchical model). We conducted similar updates for other age groups for context.

As with the original 2002 meta-analysis, we estimated the model by using a Bayesian data analytic framework but this time using the BRugs package in R.[1,2] BRugs is an R interface to OpenBUGS, the successor to WinBUGS. The R code to create the dataset is below.

```
# R code to create dataset
study <- c('Age', 'CNBSS-1', 'HIP', 'Gothenburg', 'Stockholm', 'Malmo', 'Kopparberg', 'Ostergotland')
y.int  <- c(   105,   105,    64,    34,    34,    53,    22,    31)
n.int  <- c(  53884,  25214,  13740,  11724,  14303,  13568,   9582,  10285)
py.int  <- c( 578390, 282606, 192360,     NA, 203000, 184000, 124566, 172000)
y.cntl  <- c(   251,   108,    82,    59,    13,    66,    16,    30)
n.cntl  <- c( 106956,  25216,  13740,  14217,   8021,  12279,   5031,  10459)
py.cntl <- c(1149380, 282575, 192360,     NA, 117000, 160000,  65403, 176000)
n <- 10000
rate.int  <- n * y.int /n.int
rate.cntl <- n * y.cntl/n.cntl
rr <- rate.int/rate.cntl
rd <- rate.int-rate.cntl
nns <- 1 / ((y.cntl/n.cntl) - (y.int /n.int))
dataset <- data.frame(
  study,
  y.int , n.int , py.int , rate.int ,
  y.cntl, n.cntl, py.cntl, rate.cntl,
  rr, rd, nns
)
# Save dataset for BRugs to use
dataset.bugs <- cbind(y.int, n.int, y.cntl, n.cntl)
colnames(dataset.bugs) <- c("y.int", "n.int", "y.cntl", "n.cntl")
bugsData(data.frame(dataset.bugs), fileName="dataset.bugs", digits = 5)
constants <- cbind(nrow(dataset.bugs))
colnames(constants) <- c("n")
bugsData(data.frame(constants), fileName="constants.bugs", digits = 1)
```

The model assumes that the number of deaths from each study come from a binomial distribution with the probability parameter of α for the control group and $\alpha + \beta$ for the screening group. A random component, σz_i, is added to both probability parameters to allow for the random effect of the study $_i$. Noninformative prior probability distributions were used.

```
# BUGS model
# This model is saved in a text file named “model.bugs”
model;
{
  for( i in 1 : n ) {
    z[i] ~ dnorm(0, 1)
    logit(p.int[i] ) <- alpha + beta + sigma * z[i]
    logit(p.cntl[i]) <- alpha        + sigma * z[i]
```

```
    y.int[i]  ~ dbin(p.int[i] , n.int[i] )
    y.cntl[i] ~ dbin(p.cntl[i], n.cntl[i])
  }
  alpha ~ dnorm(-5.0, 1.0E-1)
  beta  ~ dnorm(0.0, 1.0E-1)
  sigma ~ dnorm(0.5, 1.0E-1) I(0, )
}
```

Four separate Markov chains with overdispersed initial values were used for estimation. A burn-in of 10,000 draws was used to initialize the chains and was checked for convergence.

```
# Check the model and load the dataset
modelCheck("model.bugs")
modelData("constants.bugs")
modelData("dataset.bugs")
# Compile the model with 4 MCMC chains
modelCompile(numChains=4)
# Generate overdispersed initial values
modelGenInits()
# Keep MCMC samples of parameters alpha, beta, and sigma
samplesSet("alpha")
samplesSet("beta")
samplesSet("sigma")
# Thin samples so only 1000 draws are left
samplesSetThin(10000/(1000/getNumChains()))
# Generate 10,000 burn-in draws
modelUpdate(10000)
samplesHistory("*", thin=samplesGetThin())
```

The convergence of the parameter estimation was assessed and deemed adequate from the 10,000 burn-in draws. Next, we generated 100,000 draws from the four chains. These draws were thinned to yield a sample of 1,000 uncorrelated estimates from the posterior distributions.

```
# Clear samples from the previous burn-in
samplesClear("*")
# Keep MCMC samples of parameters alpha, beta, and sigma
samplesSet("alpha")
samplesSet("beta")
samplesSet("sigma")
# Thin samples so only 1000 draws are left
samplesSetThin(100000/(1000/getNumChains()))
modelUpdate(100000)
samplesHistory("*", thin=samplesGetThin())
# Check correlation of the thinned samples
for (i in 1:getNumChains()) {
  samplesAutoC("*", i, thin=samplesGetThin())
}
# Check the probability distribution of the parameters
samplesDensity("*", thin=samplesGetThin())
# Output sample estimates to an R object
brugs.nodes <- samplesHistory("*", thin=samplesGetThin(), plot=FALSE)
```

After the model was estimated and the samples were thinned, sample rates per 10,000 women screened

with mammography and control participants were calculated from the estimates of alpha and beta. Sample relative risk, risk difference, and number needed to invite to screening were calculated from the sample rates.

```
# Assign parameter samples to separate R vectors
alpha <- as.vector(brugs.nodes$alpha)
beta  <- as.vector(brugs.nodes$beta )
sigma <- as.vector(brugs.nodes$sigma)
# Rate calculations
# Note: this produces 1000 samples for each rate, RR, RD, and NNS
n <- 10000
rate1 <- n * exp(alpha+beta) / (1+exp(alpha+beta))
rate2 <- n * exp(alpha     ) / (1+exp(alpha     ))
rr <- rate1 / rate2
rd <- rate1 - rate2
nns <- n / (rate2 - rate1)
```

From the 1,000 thinned posterior samples, point estimates (mean) and 95% credible intervals (2.5 and 97.5 percentiles) for relative risk, risk difference, and number needed to invite to screening were calculated.

```
# Define R function; it will be used a number of times
brugs.nodesummary <- function(x, name) {
  Samples <- length(x)
  Mean <- mean(x)
  SD <- sd(x)
  MCMC.error <- sd(x) / sqrt(length(x))
  Median <- median(x)
  P.025 <- quantile(x, prob=c(0.025))
  P.975 <- quantile(x, prob=c(0.975))
  nodesummary <- data.frame(cbind(Samples, Mean, Median, P.025, P.975, SD, MCMC.error))
  rownames(nodesummary) <- name
  colnames(nodesummary) <- c("Samples", "Mean", "Median", "P.025", "P.975", "SD", "MCMC.error")
  data.frame(nodesummary)
}
# Call defined function brugs.nodesummary
print(brugs.nodesummary(alpha , "alpha" ))
print(brugs.nodesummary(beta  , "beta"  ))
print(brugs.nodesummary(sigma , "sigma" ))
print(brugs.nodesummary(rate1 , "rate1" ))
print(brugs.nodesummary(rate2 , "rate2" ))
print(brugs.nodesummary(rr    , "rr"    ))
print(brugs.nodesummary(rd    , "rd"    ))
print(brugs.nodesummary(nns   , "nns"   ))
```

The pooled number needed to invite to screening could be misleading if the baseline risk of mortality is appreciably varied between studies.[3] One recommendation to accommodate this is to apply the pooled relative risk estimate to a range of control rates and then calculate number needed to invite to screening. The pooled rate of mortality among the control groups of our studies was estimated to be 35.5 deaths per 10,000 women (95% CrI, 25.1-48.3). The range of mortality rates among the control

groups was 16.2 to 59.7 per 10,000 women. Applying the pooled relative risk estimate of 0.85 to the high end of the mortality rate range (59.7) yields a number needed to invite to screening estimate of 1,116 per 10,000 women. Applying the pooled relative risk estimate of 0.85 to the low end of the mortality rate range (16.2) yields a number needed to invite to screening estimate of 4,115 per 10,000 women. This range 1,116 to 4,115 per 10,000 women is within the 95% CrI we report for number needed to invite to screening that we estimated from the posterior distributions of our mortality rate estimates. Alternatively, the bounds of our 95% CrI to number needed to invite to screening correspond to a range of control group mortality rates of 10.5 to 71.8 per 10,000 women, a range beyond that seen in the studies included in our analysis.

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Appendix B7. Breast Cancer Surveillance Consortium Methods

Breast Cancer Surveillance Consortium

In 1994 the National Cancer Institute (NCI) established the Breast Cancer Surveillance Consortium (BCSC) to study breast cancer screening practices in the United States, with the recognition that results from controlled clinical trials of mammography may differ from the results of community screening practices. Each of the Consortium's seven research sites collects population-based screening and diagnostic mammography data and links it to state cancer registries. Sites include the Carolina Mammography Registry (North Carolina), Group Health Cooperative (Seattle), New Hampshire Mammography Network, San Francisco Mammography Registry, Vermont Breast Cancer Surveillance System, Colorado Mammography Project, and New Mexico Mammography Project. In five of the states, mammography data is also linked to pathology registries, which include benign as well as malignant outcomes. A comparison of women represented in the BCSC against 2000 Census data shows that Consortium sites are located in counties that contain slightly more than 5% of the U.S. population, and represent the population in important sociodemographic respects.[1]

Currently, the Consortium's database contains information on 6,000,000 mammography examinations, 2,017,869 women, and 74,000 breast cancer cases.[2] Detailed information on the distribution of key variables, mammographic data, characteristics of cases, and screening performance, among others, are detailed on the BCSC website: http://breastscreening.cancer.gov/data/

BCSC data include screening as well as diagnostic mammography. Screening mammography examinations are those designated as such by the ordering provider or radiologist, and not performed within 9 months of a previous one. Diagnostic mammography examinations are those indicated as such when ordered, or by the radiologist, or those performed for a woman reporting breast symptoms. Mammography information includes breast density, BI-RADS score, and recommendations for further imaging or work-up. In addition, prior to each mammography examination, a woman fills out a questionnaire which includes demographic as well as previous mammography information. Each mammography examination is given an initial BI-RADs score which categorizes it as "positive" or "negative." In our analysis, an initial score of 0, 4, 5, or 3 with immediate work-up is considered positive, whereas a score of 1, 2 or 3 with short-term interval work-up (3-6 months) is negative. Additional imaging, such as such as magnification, ultrasound, compression or repeat views, or a diagnostic procedure is linked to screening mammography if done within 60 days of mammography.

In this report, we included BCSC data from 2000-2005 to examine the 1) frequency of additional imaging and biopsy procedures resulting from positive screening mammography, 3) potential adverse effects of mammography screening, and 4) relative incidence of DCIS and invasive cancers detected by mammography screening. Information for women under age 40 years or who have a history of breast augmentation or previous breast cancer diagnosis has been excluded.

Appendix B7. Breast Cancer Surveillance Consortium Methods

REFERENCES

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Appendix C1. Contextual Question: What is the cost-effectiveness of screening?

A total of 298 abstracts relevant to costs of breast cancer screening were identified by searches and 29 full text articles were retrieved for further review. Studies focused on costs and cost savings of screening, comparisons of screening strategies or programs, and costs for older women.

Data from 10,048 women screened at an integrated cancer center in the United States were used to estimate the financial impact of a screening mammography program, including costs for mammography, diagnostic procedures, and therapeutic procedures.[1] Overall results showed that screening mammography operated at a loss, and payer reimbursement was not sufficient to cover overhead costs. The screening mammography program was not financially viable without clear criteria to increase the yield of diagnostic and therapeutic procedures.

A retrospective cohort study of 566 Finnish women diagnosed with invasive cancer determined mortality rates and costs for screened and unscreened women.[2] Women were age 40-74 years at time of diagnosis. Twenty-five percent of unscreened women died of breast cancer versus 12% of screened ($p<0.001$). The non-discounted mean treatment costs were 2.8-fold for those dying of breast cancer compared to survivors (26,222 euros [$36,283 USD] versus 9,434 euros [$13,053.8 USD]; mean difference 16,788 euros; 95% confidence interval (CI), 14,915, 18,660; $p<0.001$). Approximately one third of costs for fatal breast cancer were avoided through mammography screening, accounting for 72-81% of the estimated total treatment cost savings achieved by screening. It was also estimated that approximately 31-35% of the screening costs for 1987-1993 were offset by savings in treatment costs.[2]

A recent retrospective cost-effectiveness analysis in the United States compared costs when using actual patterns of screening mammography for women age 40-80 years, no screening, and other screening strategies.[3] Usual screening practices in the model were informed by data from the National Health Interview Survey and the Breast Cancer Surveillance Consortium (BCSC) using a combination of frequent and infrequent screening patterns including no screening. Screening patterns from 1990-2000 accrued 947.5 million quality-adjust life years (QALYs) and cost $166 billion over the lifetimes of the screened women. This represents a gain of 1.7 million QALYs for an additional cost of $62.5 billion compared with no screening. The actual population screening scenario presumed that in the year 2000, 25% of the population had no screening, women being screened every 1 or 2 years increased to 50%, and overall screening participation rose to nearly 70%.[3] The incremental cost per QALY accrued was estimated at $37,000 for actual screening patterns compared to no screening, well within the accepted level of $50,000 per QALY for health services in general. The most expensive option was annual screening of all women age 40-80 years, consistent with current guidelines. Many alternative screening strategies generated more QALYs for less cost compared to current guidelines. However, results differed depending on the level of participation in the program and when considering adverse effects of screening.

An analysis of Japanese data compared the cost-effectiveness of 3 screening strategies in a hypothetical cohort of 100,000 women age 30-79 years. These included annual clinical breast exam (CBE), annual CBE combined with mammography, and biennial CBE combined with mammography.[4] The number of expected survival years was highest for annual CBE combined

with mammography, implying the most effective treatment. Biennial CBE combined with mammography had a higher cost-effectiveness ratio compared with annual CBE combined with mammography, followed by annual CBE in all age groups. Annual CBE did not confer any advantages in terms of effectiveness or cost-effectiveness.[4]

An evaluation of the cost-effectiveness of a quality controlled mammographic screening program compared to an opportunistic screening program used cancer registry and clinical data from Switzerland.[5] Results showed that the discounted incremental cost-effectiveness ratio comparing quality controlled mammographic screening programs verses established opportunistic screening programs ranged from $73,018 ($61,545.8 USD) at age 40 years to $118,193 ($99,623.2 USD) at age 70 years per life-year gained.

Many cost-effectiveness decision modeling studies focus on mammography screening for older women to consider the appropriate age to discontinue screening. A decision analysis model suggested that screening saves lives at all ages, even among older women.[6] For women age 65-69 years or age 85 years or older with screen-detected breast cancer, screening increased life expectancy by 311 and 126 days, respectively. An analysis utilizing measurement of bone mineral density to predict higher breast cancer risk among elderly women found that continuing biennial mammography from ages 65-79 years among women in the top 3 quartiles of bone density would avert 9.4 deaths per 10,000 women screened.[7] As treatment for chronic diseases improves and life expectancy increases, screening for breast cancer among older women may yield greater benefit.

Using a $50,000 (USD) per life-year saved acceptability threshold, a recent cost-effectiveness and computer modeling study suggested screening was equitable when starting at age 35 and ending at age 85.[8] Also, two reviews in this area focused on the costs, benefits, and harms of screening mammography in older women. One systematic review and cost-analysis showed that the estimated cost of extending biennial screening mammography to 75 or 80 years was $34,000-$88,000 (2002 USD) per life-year gained, compared with stopping screening at 65 years.[9] In a similar review done in Australia, cost-effectiveness estimates for extending the upper age limit for screening from 69 to 79 years ranged from $8,119 to $27,751 [6,746.88 to 23,061 USD] per QALY saved.[10]

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Appendix C1. Contextual Question: What is the cost-effectiveness of screening?

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Appendix Figure C2. Statistical Tests for Meta-analysis of Screening Trials of Women Age 39 to 49 Years