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

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Abstract

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

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

Data Sources—Cochrane Controlled Trials Registry and Database of Systematic Reviews (4th Quarter 2008), MEDLINE® (January 2001 to December 2008), reference lists, and Web of Science® for published studies; Breast Cancer Surveillance Consortium for screening mammography data.

Study Selection—Randomized controlled trials with breast cancer mortality outcomes for screening effectiveness; multiple study designs and data sources for harms.

Data Extraction—Investigators abstracted relevant data and rated study quality using established criteria.

Data Synthesis—Mammography screening reduces breast cancer mortality by 15% for women age 39 to 49 (relative risk 0.85; 95% CrI 0.75 to 0.96; 8 trials); data are lacking for age ≥70. Radiation exposure from mammography is low. Patient adverse experiences are common, transient, and do not impact screening practices. Estimates of overdiagnosis vary from 1% to 10%. Younger women have more false positive mammograms and additional imaging, but fewer biopsies than older women.

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Trials of CBE are ongoing; for BSE, trials showed no reductions in mortality but increased benign biopsies.

Limitations—Studies of older women, digital mammography, and MRI are lacking.

Conclusions—Mammography screening reduces breast cancer mortality for women age 39 to 69; data are insufficient for older women. False positive mammograms and additional imaging are common. No benefit has been shown for CBE or BSE.

Introduction

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

Breast cancer is the most frequently diagnosed non-cutaneous cancer and the second leading cause of cancer deaths among women in the United States (4). 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 (4). Incidence increases with age, and 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 (5). Data suggest that incidence has stabilized in recent years (6-8), and mortality has decreased since 1990 (9,10) due to multiple factors including screening (11). In 2005, 68% of women age 40 to 65 had a screening mammogram within the prior 2 years in the United States (4).

Breast cancer has a known asymptomatic phase that can be detected with mammography. Mammography screening is sensitive (77% to 95%), specific (94% to 97%), and acceptable to most women (2). It is performed using either plain film or digital technologies, although the shift to digital is ongoing. Contrast enhanced magnetic resonance imaging (MRI) has traditionally been used to evaluate women already diagnosed with breast cancer. Recommendations for its use in screening pertain to certain high-risk groups only (12). If a woman has an abnormal mammographic finding on screening, or a concerning finding on physical examination, additional imaging and biopsy may be recommended. Additional imaging may consist of a diagnostic mammogram or a mammogram done with additional or special views, a targeted breast ultrasound, or breast MRI (13,14). Additional imaging may help classify the lesion as a benign or suspicious finding in order to determine the need for biopsy. Biopsy techniques vary in the level of invasiveness and amount of tissue acquired, impacting their yield and patient experience.

This review focuses on new studies and evidence gaps that were unresolved at the time of the 2002 USPSTF recommendation. These include the effectiveness of mammography screening in decreasing breast cancer mortality among average-risk women age 40 to 49 and 70 and older; the effectiveness of CBE and BSE in decreasing breast cancer mortality among women of any age; and the magnitude of harms of screening with mammography, CBE, and BSE.

Methods

Key questions guiding this update were developed by the USPSTF and Agency for Healthcare Research and Quality (AHRQ). Investigators created an analytic framework incorporating the key questions and outlining the patient population, interventions, outcomes, and harms of the

screening process (Appendix Figure 1). The target population includes women without pre-existing breast cancer and not considered 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. 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 diagnosing women with invasive or noninvasive breast cancer who had abnormal lesions that were unlikely to become clinically evident during their lifetimes in the absence of screening (15). Overdiagnosis may have more impact on women with shorter life expectancies because of age or comorbidities.

Data Sources and Searches

We searched the Cochrane Controlled Trials Registry and Cochrane Database of Systematic Reviews (through 4th Quarter 2008) and MEDLINE® database (January 1, 2001 to December 1, 2008) for relevant studies and meta-analyses (16). We also conducted secondary referencing by manually reviewing reference lists of key papers and searching citations using Web of Science® (17). Search results are indicated in Appendix Figure 2.

Study Selection

We selected studies based on inclusion and exclusion criteria developed for each key question (16). To determine the effectiveness of screening, we included randomized controlled trials and updates to previously published trials of screening with mammography (film, digital), MRI, CBE, or BSE with breast cancer mortality outcomes published since 2001. One trial was translated to English from Russian for this update (18). Meta-analyses that included studies with mortality data were also reviewed. Studies other than controlled trials and systematic reviews or without breast cancer mortality as an outcome were excluded.

We determined harms of screening using evidence from multiple study designs and data sources. For mammography, we focused our searches on recently published systematic reviews and meta-analyses of the harms listed above. 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 Breast Cancer Surveillance Consortium (BCSC), a collaborative network of 5 mammography registries and 2 affiliated sites with linkages to pathology and/or tumor registries across the United States, sponsored by the National Cancer Institute (19,20). These data draw from community populations representing a national demographic sample, and may be more applicable to current practice in the United States than other published sources. Data include a mix of film and digital mammograms. 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.

Data Abstraction and Quality Assessment

We abstracted details about the patient population, study design, analysis, follow-up, and results. Using predefined criteria developed by the USPSTF (21), two investigators rated the quality of each study as “Good,” “Fair,” or “Poor,” resolving 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.

Data Synthesis and Analysis

Meta-analysis of Mammography Trials—We updated the 2002 meta-analysis to include new findings from published trials of mammography screening compared to controls for women age 40 to 49 that reported relative risk reduction in breast cancer mortality. We conducted similar updates for other age groups for context. Breast cancer mortality results from

trials were used to estimate the pooled relative risk. Estimates were calculated from a random effects model under the Bayesian data analytic framework using the RBugs package in R (22,23); the same model as the previous report (2). Additional details are provided in the Appendix. We used funnel plots to assess publication bias and L'Abbé plots to assess heterogeneity.

Analysis of Breast Cancer Surveillance Consortium Data—Data from 600,830 women age 40 years and older undergoing routine mammography screening during 2000 to 2005 at the BCSC sites were obtained from the BCSC Statistical Coordinating Center and stratified by age in decades. Routine screening was defined as having at least one prior mammogram within the previous 2 years, consistent with current USPSTF recommendations. For women with multiple mammograms during the study period, one mammogram was randomly selected to include in the calculations. These data constitute a selected subset of 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 mammograms and, of these, the numbers of true negative and false negative results based on follow-up data within one year of mammography screening. A positive mammogram 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 (24). These include 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) (25). For women with positive screening mammograms, additional data include the number undergoing additional imaging, number undergoing biopsy, and diagnoses including invasive cancer, ductal carcinoma *in situ* (DCIS), and negative results. Additional imaging procedures and biopsies performed within 60 days of the screening mammogram were considered related to screening. From these data, we calculated age-specific rates (numbers per 1000 per round) of invasive breast cancer, DCIS, false positive and false negative mammograms, additional imaging, and biopsies. True positive and negative mammograms were based on invasive and noninvasive cancer diagnosis. Rates of additional imaging and rates of biopsies may be underestimated due to incomplete capture of these exams by the BCSC. A sensitivity analysis of missing values is presented in the full evidence review (16), although this does not include records that were unavailable to the BCSC.

Role of the Funding Source

The AHRQ funded this work, provided project oversight, developed key questions in conjunction with USPSTF members, and assisted with internal and external review of the draft, but had no additional role in the design, conduct, or reporting of the review. The draft was reviewed by 15 external experts not affiliated with the USPSTF.

Results

Breast Cancer Mortality Reduction with Mammography Screening For Women Age 40 to 49 and Over 70 (Key Question 1a)

The 2002 evidence review for the USPSTF included a meta-analysis (2) of 7 randomized trials of mammography screening rated fair quality (26-28). Since then, a randomized trial from the United Kingdom evaluating the effect of mammography screening specifically in women age 40 to 49 years has been published (29), as well as updated data from a previously reported Swedish trial (30). No trials of screening average-risk women specifically evaluating the effectiveness of digital mammography or MRI have been published.

The Age trial included 160,921 women ages 39 to 41 years who were randomly assigned between 1991 to 1997 to screening with annual mammography until age 48 years, or a control group receiving usual care in the United Kingdom (Table 1) (29). After 10.7 years of follow-up, the relative risk for all cause mortality was 0.97 (95% confidence interval [CI] 0.89 to 1.04) and for breast cancer mortality 0.83 (95% CI 0.66 to 1.04) among women in the screened group. Based on the absolute reduction in breast cancer mortality among women invited for 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 to 13,544). The Age trial met USPSTF criteria for fair rather than good quality because descriptions of contamination of groups were absent and 70% or fewer women attended screening across the trial.

A new publication provides additional data from the Gothenburg trial (Table 1) (30). In this paper, breast cancer mortality rates and risk ratios were calculated using three methods, including a more comprehensive method that considers breast cancer mortality from cancers diagnosed during the follow-up phase of the trial. Using this method for women ages 39 to 49 at trial entry, the relative risk for breast cancer mortality was 0.69 (95% CI 0.45 to 1.05) after 13 years of follow-up, among women in the screened group. (30).

Meta-analysis of Trials by Age—For women age 39 to 49 years, 8 trials provided data for the meta-analysis including 6 from the 2002 meta-analysis (Health Insurance Plan [HIP] of Greater New York (27), Canadian National Breast Screening Study-1 [CNBSS-1] (28), Stockholm (26), Malmo (26), Swedish Two-County [2 trials] (26)), an update of the Gothenburg trial (30), and the new Age trial (29). Combining results, the pooled relative risk for breast cancer mortality for women invited to mammography screening was 0.85 (95% Credible Interval [CrI] 0.75 to 0.96), indicating a 15% reduction in breast cancer mortality in favor of screening (Figure). This corresponds to a number needed to invite for screening to prevent one breast cancer death of 1,904 (95% C rI 929 to 6,378) over multiple screening rounds that varied by trial (2 to 9 rounds), and 11 to 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 (16). Results are consistent with the 2002 meta-analysis (relative risk 0.85; 95% CrI 0.73 to 0.99; 7 trials) (2,3).

Sensitivity analysis that 1) excluded the HIP trial because it was conducted over 30 years ago using outdated technology; 2) excluded the Canadian trial because it enrolled prescreened volunteers rather than unselected populations; and 3) excluded both the HIP and Canadian trials; did not significantly influence the results (16).

Results for women age 70 and older were confined to data from the Swedish Two-County trial (Ostergotland) of women age 70 to 74, precluding meta-analysis. These results indicate a relative risk for breast cancer mortality of 1.12 (95% CI 0.73 to 1.72) (26) based on a more conservative determination of cause of death than prior reports (31,32). The absolute numbers of deaths were not reported, the number of enrolled women was low (approximately 5,000 in each arm), and the number needed to screen was not estimable.

Meta-analyses of trials for women age 50 to 59 years and 60 to 69 years were performed to compare with results for women age 40 to 49 and over 70 (Table 2). Results are not directly comparable to the 2002 meta-analysis that provided a combined estimate for women age 50 to 74 years (relative risk 0.78; 95% CrI, 0.70 to 0.87; 7 trials) (2).

For women age 50 to 59 years, 6 trials (CNBSS-2 (52), Stockholm (26), Malmo (26), Swedish Two-County [2 trials] (26), Gothenburg (30)) provided a pooled relative risk for breast cancer mortality for women invited to mammography screening of 0.86 (95% CrI 0.75 to 0.99); number needed to invite 1,339 (95% CrI 322 to 7,455). Sensitivity analysis that excluded the

Canadian trial resulted in a lower relative risk (0.81; 95% CrI 0.68 to 0.95). For women age 60 to 69 years, 2 trials (Malmo (26) and Swedish Two-County [Ostergotland] (26)) provided a pooled relative risk for breast cancer mortality for women invited to mammography screening of 0.68 (95% CrI 0.54 to 0.87); number needed to invite 377 (95% CrI 230 to 1,050).

Harms Associated with Mammography Screening (Key Question 2a)

Radiation Exposure—No studies directly measure the association between radiation exposure from mammography screening and breast cancer. Most x-rays are considered low dose, low energy radiation with the mean glandular dose of a bilateral 2-view mammogram averaging 7 mGy (33). For women age 40 to 49, yearly mammography screening for one decade with potential additional imaging would expose an individual to approximately 60 mGy, although these levels vary (34). A recent 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 cancers (34). In studies of low dose exposures, associations were inconsistent, while those of high dose exposures indicated increased risk for breast cancer (34). The relative risks in studies of high dose exposures ranged from 1.33 to 11.39 for exposures of 0.3 to 43.4 Gy, and were worse with higher doses of exposure, younger age at exposure, and longer follow-up (34). A more recent case-control study found that women exposed to diagnostic x-rays for screening or monitoring tuberculosis or pneumonia, or therapeutic radiation for a prior cancer, had increased risks for breast cancer (35).

Pain during Procedures—Breast compression is used during mammography to create uniform density, reduce breast thickness, and flatten overlying skin and tissues, contributing to sharper images and reducing radiation dose. This may contribute to discomfort 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 (ranging from 1% to 77%), but few women would consider this a deterrent from future screening (34). In these studies, pain was associated with the stage of the menstrual cycle, anxiety, and the anticipation of pain (34).

Anxiety, Distress, and Other Psychological Responses—Studies have shown conflicting results about anxiety, distress, and other psychological responses incurred as a result of mammography screening. A systematic review of 54 studies assessed the adverse psychological effects of mammography screening programs (36). 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 mammogram results had minimal anxiety (36). 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, while some showed only transient anxiety (36). Some studies showed no differences between anxiety levels of women who had initial negative screening mammograms and those who had false positives (36).

A recent systematic review of 23 studies specifically examined the effects of false positive screening mammograms on women over age 40 (37). Included were 9 studies on psychological distress, 11 studies on anxiety, and 6 studies on worry. In these studies, false positive mammograms had no consistent effect on most women's general anxiety and depression, but increased breast cancer specific distress, anxiety, apprehension, and perceived breast cancer risk for some (37).

False Positive and Negative Mammograms, Additional Imaging, and Biopsies—Published data on false positive and negative mammograms, additional imaging, and biopsies

reflecting current practices in the United States are limited. The probability of a false positive screening mammogram was estimated at 0.9% to 6.5% in a meta-analysis of studies of sensitivity and specificity of mammography published 10 years ago (38). The cumulative risk for false positive mammograms has been reported as 21% to 49% after 10 mammograms for women in general (39-41), and up to 56% for women age 40 to 49 years (41). Additional data about mammography test performance indicate that sensitivity, recall rates, and cancer detection rates increase as the months since prior mammography increase, while specificity decreases (42). Few studies evaluate the impact of negative mammogram results. Women stated that they would not delay evaluation of a new abnormal physical finding despite a prior negative mammogram in one survey (43).

Data from the BCSC for regularly screened women based on results from a single screening round indicate that false positive mammograms are common in all age groups, but are most common among women age 40 to 49 (97.8/1000 per screening round) (Table 3). False negative mammograms occur least among women 40 to 49 (1.0/1000 per screening round). Rates of additional imaging are highest among women age 40 to 49 (84.3/1000 per screening round) and decrease with age, while biopsy rates are lowest among women age 40 to 49 (9.3/1000 per screening round) and increase with age. The BCSC results indicate that for every case of invasive breast cancer detected by mammography screening in women age 40 to 49 years, 556 women undergo mammography, 47 additional imaging, and 5 biopsies.

Overdiagnosis—A review of randomized controlled trials of mammography screening compared the cumulative incidence of breast cancer in intervention and control arms to determine the extent of overdiagnosis (44). In the 5 trials in which the control group was not offered screening, the absolute excess cumulative incidence of invasive and *in situ* breast cancer attributed to overdiagnosis among women undergoing screening mammography ranged from 0.07 to 0.73 per 1,000 women years.

Eight other studies report estimates of overdiagnosis utilizing different methods (16). Estimates are derived from data from screening programs in Italy (45), Denmark (46), and Norway and Sweden (47); a microsimulation model (48); analysis of incidence data from screening trials (Swedish Two-County and Gothenburg trials (46,49) and the Malmo Trial (50)); and a Markov model with data from the Swedish Two-County trial and several screening programs (51). None of these studies provide estimates specific to United States populations. Rates of overdiagnosis vary from <1% (45,46,49) to 30% (47), with most between 1% to 10%. Estimates differ by outcome (invasive versus *in situ* breast cancer), by whether cases are incident or prevalent, and by age. Studies are too heterogeneous to combine statistically.

Clinical Breast Examination Screening (Key Questions 1b and 2b)

Few trials evaluate the effectiveness or harms of CBE in decreasing breast cancer mortality. In countries with widely practiced mammography screening, the utility of CBE rests on its additional contribution to mortality reduction. The Canadian National Breast Screening Study-2 (CNBSS-2) trial, comparing mammography with CBE versus CBE alone, showed no difference in mortality between these two approaches (52).

Three trials were designed to determine mortality outcomes using CBE as the primary screening approach in countries with limited healthcare resources and without mammography screening programs (Table 4). A randomized trial comparing CBE to no screening was conducted in the Philippines, however, due to poor community acceptance it was discontinued after one screening round and is inconclusive (53). Two randomized trials comparing CBE to no screening are ongoing in Egypt (54) and India (55).

In the pilot study for the Cairo Breast Screening Trial, the risk of undergoing a benign procedure after one round of CBE was 1.2% (30/2481) (54). Of the 138,392 women examined in the Philippines study, 3,479 had abnormal CBEs and 1,220 completed diagnostic workups (53). Of these women, 34 (3%) had malignant cancers, 563 (46%) had no detectable abnormalities, and 623 (51%) underwent biopsies that were benign.

Breast Self Examination (Key Questions 1c and 2c)

Preliminary results from trials of BSE in Russia and Shanghai were reviewed for the 2002 report (2), and final results have since been published (Table 4) (18,56,57). The impact of BSE on all-cause mortality in St. Petersburg, Russia, a community without routine mammography screening, was evaluated in a trial meeting criteria for fair quality (18,56,57). Despite a significant increase in the number of breast cancers detected when BSE instruction was provided, there was no reduction in all-cause mortality (relative risk 1.07; 95% CI 0.88 to 1.29) (18). A good-quality randomized trial conducted in Shanghai, China indicated breast cancer rates of 6.5/1,000 for women instructed in BSE and 6.7/1,000 for controls after 11 years of follow-up (58). The numbers of women who died from breast cancer were equal in both groups (135/132,979 and 131/133,085, respectively; relative risk 1.03; 95% CI 0.81 to 1.31). Published meta-analyses of BSE randomized trials (59-61) and non-randomized studies (59-61) also indicate no significant differences in breast cancer mortality between BSE and control groups.

In the Russian (18) and Shanghai (58) trials, more women randomized to BSE had benign biopsies than women in control groups (Russian relative risk 2.05; 95% CI 1.80 to 2.33; Shanghai relative risk 1.57; 95% CI 1.48 to 1.68). A retrospective cohort study of 27,421 women over the age of 40 in the United States indicated that those performing more frequent or longer duration BSEs were more likely to have diagnostic mammograms or ultrasounds, compared to women with less frequent and shorter BSEs (62). Contrary to the Russian and Shanghai studies, there was no significant association between BSE and biopsy rates in this study.

Discussion

Table 5 summarizes the evidence for this review. Note that breast cancer mortality benefits from randomized controlled trials of screening are based on estimates of women invited to screening, whereas harms are based on data of women actually screened.

Trials of mammography screening for women age 39 to 49 indicate a statistically significant 15% reduction in breast cancer mortality for women randomized to screening versus those not. This translates to a number needed to invite for screening to prevent one breast cancer death of 1,904 (95% CrI 929 to 6,378). These results are similar to those for women age 50 to 59, but less than women age 60 to 69. For women age 70 and older, results from the Swedish Two-County trial of women age 70 to 74 indicate no mortality reduction. However, these results are limited by including only a small number of women from a single population. Interpreting trial results by age requires caution, because, except for the Age trial, age-specific results are sub-analyses of trials designed for different purposes.

Although the results of the meta-analysis have not changed markedly with the addition of the Age trial (29), 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 recently performed trial, reflecting current screening, diagnostic, and treatment practices better than its predecessors, particularly those from the pre-tamoxifen era. As such, it is the most relevant trial. However, its results, while 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 (63).

Harms of mammography screening have been identified, but their magnitude and impact 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 radiation and breast cancer such as *BRCA* mutation carriers. Patient adverse experiences, such as pain during procedures and anxiety and other psychological responses, are widely experienced, but appear to be transient and do not adversely influence future screening practices. This may vary 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 cancers will progress, how quickly cancers will advance, and expected lifetimes.

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, restricting 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 and Shanghai trials simultaneously showed no reductions in mortality and increased numbers of benign biopsies performed as a result of BSE instruction.

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 over age 70, 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 (64,65) and lower breast cancer mortality (65). For the many older women who might live another 20 to 30 years, breast cancer detection and early treatment could reduce morbidity as well as mortality, 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 this way. As diagnostic and treatment experiences become more individualized (66) and include patient preferences, it becomes even more difficult to characterize benefits and harms in a general way.

New technologies, such as digital mammography and MRI, are becoming widely used in the United States without definitive studies of their impact on screening. Consumer expectations that new technology is better than old may obscure potential adverse effects such as higher false positives 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. There are no definitive studies of the appropriate interval for mammography screening, although trial data reflect screening intervals from 12 to 33 months.

Our meta-analysis of mammography screening trials indicates breast cancer mortality benefit for all age groups between age 39 to 69, 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 to 49 experience the highest rate of additional imaging while 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. U.S. Preventive Services Task Force. Screening for breast cancer: recommendations and rationale. Ann Intern Med 2002;137(5 Part 1):344–6. [PubMed: 12204019]
2. Humphrey, L.; Chan, BKS.; Detlefsen, S.; Helfand, M. Screening for breast cancer: systematic evidence review, 2002. [June 2009]. Available at http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat3.chapter.27509
3. Humphrey LL, Helfand M, Chan BKS, Woolf SH. Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002;137(5):347–60. [PubMed: 12204020]
4. American Cancer Society. Statistics. 2008 [June 2009]. Available at: http://www.cancer.org/docroot/stt/stt_0.asp
5. Ries, LAG.; Harkins, D.; Krapcho, M.; Mariotto, A.; Miller, BA.; Feuer, EJ., et al. National Cancer Institute; Bethesda, MD: [June 2009]. SEER cancer statistics review, 1975-2003. Available at http://seer.cancer.gov/csr/1975_2003/
6. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ, et al. The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 2007;356(16):1670–4. [PubMed: 17442911]
7. Kerlikowske K, Miglioretti DL, Buist DS, Walker R, Carney PA, National Cancer Institute-Sponsored Breast Cancer Surveillance Consortium. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. J Natl Cancer Inst 2007;99(17):1335–9. [PubMed: 17698950]
8. Chagpar AB, McMaster KM. Trends in mammography and clinical breast examination: a population-based study. J Surg Res 2007;140(2):214–9. [PubMed: 17418862]
9. American Cancer Society. Breast Cancer Facts & Figures 2005-2006. [June 2009]. Available at http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf
10. Edwards BK, Brown ML, Wingo PA, Howe HL, Ward E, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. J Natl Cancer Inst 2005;97(19):1407–27. [PubMed: 16204691]

11. Berry DA, Cronin KA, Plevritis SK, Fryback DG, Clarke L, Zelen M, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353(17):1784–92. [PubMed: 16251534]
12. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin 2007;57 (2):75–89. [PubMed: 17392385]
13. Flobbe K, Bosch AM, Kessels AG, Beets GL, Nelemans PJ, von Meyenfeldt MF, et al. The additional diagnostic value of ultrasonography in the diagnosis of breast cancer. Arch Intern Med 2003;163 (10):1194–9. [PubMed: 12767956]
14. Bedrosian I, Mick R, Orel SG, Schnall M, Reynolds C, Spitz FR, et al. Changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer 2003;98(3):468–73. [PubMed: 12879462]
15. Day NE. Overdiagnosis and breast cancer screening. Breast Cancer Res 2005;7(5):228–9. [PubMed: 16168144]
16. Nelson, HD.; Tyne, K.; Naik, A.; Humphrey, L.; Bougatsos, C.; Nygren, P., et al. Screening for breast cancer: systematic evidence review update for the US Preventive Services Task Force Evidence Review Update. (Prepared by the Oregon Evidence-based Practice Center under contract 290-02-0024 with the Agency for Healthcare Research and Quality). Rockville, MD: 2009. in press
17. Web of Science®. [June 2009]. Software by Thomson. Available at http://isiwebofknowledge.com/products_tools/multidisciplinary/webofscience/
18. Semiglazov VF, Manikhas AG, Moiseenko VM, Protsenko SA, Kharikova RS, Seleznev IK, et al. Rezul'taty prospektivnogo randomizirovannogo isledovaniia [Rossiia (Sankt-Peterburg)/VOZ] znacheniia samoobsledovaniia v rannem vyiavlenii raka molochnoi zhelezy. [Results of a prospective randomized investigation [Russia (St.Petersburg)/WHO] to evaluate the significance of self-examination for the early detection of breast cancer]. Vopr Onkol Voprosy onkologii Vol 2003;49:434–41.
19. Breast Cancer Surveillance Consortium. [June 2009]. Available at: http://breastscreening.cancer.gov/
20. Ballard-Barbash R, Taplin SH, Yankaskas BC, Ernster VL, Rosenberg RD, Carney PA, et al. Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. Am J Roentgenol 1997;169:1001–8. [PubMed: 9308451]
21. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med 2001;20(3 Suppl):21–35. [PubMed: 11306229]
22. R Foundation for Statistical Computing. Expert manual. 2006. R: A language and environment for statistical computing [Expert program].
23. Thomas A, O'Hara B, Ligges U, Sturtz S. Making BUGS open. R News 2006;6(1):12–7.
24. D'Orsi, CJ.; Bassett, LW.; Berg, WA. Breast imaging reporting and data system: ACR BIRADS. 4th. Reston, VA: American College of Radiology; 2003. Follow-up and outcome monitoring; p. 229-51.
25. Rosenberg RD, Yankaskas BC, Abraham LA, Sickles EA, Lehman CD, Geller BM, et al. Performance benchmarks for screening mammography. Radiology 2006;241(1):55–66. [PubMed: 16990671]
26. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. Lancet 2002;359 (9310):909–19. [PubMed: 11918907]
27. Habbema JD, van Oortmarssen GJ, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. J Natl Cancer Inst 1986;77(2):317–20. [PubMed: 3461193]
28. Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. Ann Intern Med 2002;137(5 Part 1):305–12. [PubMed: 12204013]
29. Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L, et al. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. Lancet 2006;368(9552):2053–60. [PubMed: 17161727]

30. Bjurstam N, Bjorneld L, Warwick J, Sala E, Duffy SW, Nystrom L, et al. The Gothenburg Breast Screening Trial. Cancer 2003;97(10):2387–96. [PubMed: 12733136]

31. Tabar L, Fagerberg G, Chen HH, Duffy SW, Smart CR, Gad A, et al. Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. Cancer 1995;75(10):2507–17. [PubMed: 7736395]

32. Tabar L, Vitak B, Chen HH, Duffy SW, Yen MF, Chiang CF, et al. The Swedish Two-County Trial twenty years later. Updated mortality results and new insights from long-term follow-up. Radiol Clin North Am 2000;38(4):625–51. [PubMed: 10943268]

33. Spelic, DC. U.S. Food and Drug Administration; 2003 [June 2009]. Dose and image quality in mammography: trends during the first decade of MQSA. Available at: http://www.fda.gov/CDRH/MAMMOGRAPHY/scorecard-articles.html

34. Armstrong K, Moye E, Williams S, Berlin JA, Reynolds EE. Screening mammography in women 40 to 49 years of age: a systematic review for the American College of Physicians. Ann Intern Med 2007;146(7):516–26. [PubMed: 17404354]

35. John EM, Phipps AI, Knight JA, Milne RL, Dite GS, Hopper JL, et al. Medical radiation exposure and breast cancer risk: findings from the Breast Cancer Family Registry. Int J Cancer 2007;121(2): 386–94. [PubMed: 17372900]

36. Brett J, Bankhead C, Henderson B, Watson E, Austoker J. The psychological impact of mammographic screening. A systematic review. Psychooncology 2005;14(11):917–38. [PubMed: 15786514]

37. Brewer NT, Salz T, Lillie SE. Systematic review: the long-term effects of false-positive mammograms. Ann Intern Med 2007;146(7):502–10. [PubMed: 17404352]

38. Mushlin AI, Kouides RW, Shapiro DE, Mushlin AI, Kouides RW, Shapiro DE. Estimating the accuracy of screening mammography: a meta-analysis. Am J Prev Med 1998;14(2):143–53. [PubMed: 9631167]

39. Olivotto IA, Kan L, Coldman AJ. False positive rate of screening mammography. N Engl J Med 1998;339:560. [PubMed: 9714619]

40. Hofvind S, Thoresen S, Tretli S. The cumulative risk of a false-positive recall in the Norwegian Breast Cancer Screening Program. Cancer 2004;101(7):1501–7. [PubMed: 15378474]

41. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 1998;338(16):1089–96. [PubMed: 9545356]

42. Yankaskas BC, Taplin SH, Ichikawa L, Geller BM, Rosenberg RD, Carney PA, et al. Association between mammography timing and measures of screening performance in the United States. Radiology 2005;234(2):363–73. [PubMed: 15670994]

43. Drossaert CHC, Boer H, Seydel ER. Does mammographic screening and a negative result affect attitudes towards future breast screening? J Med Screen 2001;8(4):204–12. [PubMed: 11743037]

44. Moss S. Overdiagnosis and overtreatment of breast cancer: overdiagnosis in randomised controlled trials of breast cancer screening. Breast Cancer Res 2005;7(5):230–4. [PubMed: 16168145]

45. Paci E, Miccinesi G, Puliti D, Baldazzi P, De Lisi V, Falcini F, et al. Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. Breast Cancer Res 2006;8(6):R68. [PubMed: 17147789]

46. Olsen AH, Agbaje OF, Myles JP, Lynge E, Duffy SW. Overdiagnosis, sojourn time, and sensitivity in the Copenhagen mammography screening program. Breast J 2006;12(4):338–42. [PubMed: 16848843]

47. Zahl PH, Strand BH, Maehlen J. Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: Prospective cohort study. BMJ 2004;328(7445):921–4. [PubMed: 15013948]

48. de Koning HJ, Draisma G, Fracheboud J, de Bruijn A. Overdiagnosis and overtreatment of breast cancer: microsimulation modeling estimates based on observed screen and clinical data. Breast Cancer Res 2006;8(1):202–6. [PubMed: 16524452]

49. Duffy SW, Agbaje O, Tabar L, Vitak B, Bjurstam N, Bjorneld L, et al. Overdiagnosis and overtreatment of breast cancer: estimates of overdiagnosis from two trials of mammographic screening for breast cancer. Breast Cancer Res 2005;7(6):258–65. [PubMed: 16457701]

50. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmo mammographic screening trial: follow-up study. BMJ 2006;332(7543): 689–92. [PubMed: 16517548]
51. Yen MF, Tabar L, Vitak B, Smith RA, Chen HH, Duffy SW. Quantifying the potential problem of overdiagnosis of ductal carcinoma in situ in breast cancer screening. Eur J Cancer 2003;39(12):1746–54. [PubMed: 12888370]
52. Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. J Natl Cancer Inst 2000;92(18):1490–9. [PubMed: 10995804]
53. Pisani P, Parkin DM, Ngelangel C, Esteban D, Gibson L, Munson M, et al. Outcome of screening by clinical examination of the breast in a trial in the Philippines. Int J Cancer 2006;118(1):149–54. [PubMed: 16049976]
54. Boulos S, Gadallah M, Neguib S, Essam E, Youssef A, Costa A, et al. Breast screening in the emerging world: High prevalence of breast cancer in Cairo. Breast 2005;14(5):340–6. [PubMed: 16131468]
55. National Cancer Institute. U.S. National Institutes of Health. Cancer control research. [June 2009]. Available at http://cancercontrol.cancer.gov/grants/abstract.asp?applid=6965060
56. Semiglazov VF, Moiseyenko VM, Manikhas AG, Protsenko SA, Kharikova RS, Popova RT, et al. Interim results of a prospective randomised study of self-examination for early detection of breast cancer. Vopr Onkol 1999;45:265–71. [PubMed: 10443229]
57. Semiglazov VF, Moiseyenko VM, Bavli JL, Migmanova N, Seleznyov NK, Popova RT, et al. The role of breast self-examination in early breast cancer detection (results of the 5-years USSR/WHO randomized study in Leningrad). Eur J Epidemiol 1992;8(4):498–502. [PubMed: 1397215]
58. Thomas DB, Gao DL, Ray RM, Wange WW, Allison CJ, Chen FL, et al. Randomized trial of breast self-examination in Shanghai: final results. J Natl Cancer Inst 2002;94(19):1445–57. [PubMed: 12359854]
59. Hackshaw AK, Paul EA. Breast examination and death from breast cancer: A meta-analysis. Br J Cancer 2003;88(7):1047–53. [PubMed: 12671703]
60. Baxter N, Canadian Task Force on Preventive Health Care. Preventive health care, 2001 update: should women be routinely taught breast self-examination to screen for breast cancer? CMAJ 2001;164(13):1837–46. [PubMed: 11450279]
61. Kosters JP, Gotzsche PC. Regular self-examination or clinical examination for early detection of breast cancer. Cochrane Database Syst Rev 2008;1
62. Tu SP, Reisch LM, Taplin SH, Kreuter W, Elmore JG. Breast self-examination: self-reported frequency, quality, and associated outcomes. J Cancer Educ 2006;21(3):175–81. [PubMed: 17371185]
63. Smith-Bindman R, Chu PW, Miglioretti DL, Sickles EA, Blanks R, Ballard-Barbash R, et al. Comparison of screening mammography in the United States and the United Kingdom. JAMA 2003;290(16):2129–37. [PubMed: 14570948]
64. Badgwell BD, Giordano SH, Duan ZZ, Fang S, Bedrosian I, Kuerer HM, et al. Mammography before diagnosis among women age 80 years and older with breast cancer. J Clin Oncol 2008;26(15):1–8.
65. Galit W, Green MS, Lital KB. Routine screening mammography in women older than 74 years: a review of the available data. Maturitas 2007;57(2):109–19. [PubMed: 17336004]
66. Tripathy D. Targeted therapies in breast cancer. Breast 2005;11(Suppl 1):S30–S5.
67. Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses—sometimes informative, usually misleading. BMJ 1999;318(7197):1548–51. [PubMed: 10356018]

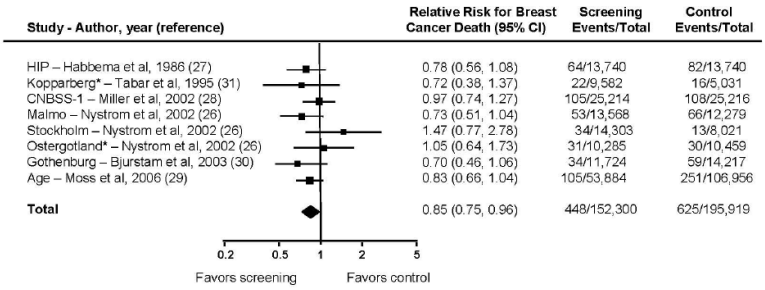

Figure. Pooled Relative Risk for Breast Cancer Mortality from Trials of Mammography Screening Compared to Control for Women Age 39 to 49 Years

*Swedish Two-County Trial.

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

Table 1

Mammography Screening Trials Included in Meta-analysis

Trial; Author, Year (reference)	Year Study Began	Setting/ Population (no. screening; no. control)	Ages at Enrollment (years)	Method of Randomization	Study Groups	Screening Protocol			Follow- up (years)	USPSTF Quality Rating
						Interval (mo.)	No. of Rounds	No. of Views		
Health Insurance Plan (HIP) of Greater New York; Habbema et al, 1986 (27)	1963	New York health plan members (30,239; 30,256)	40-64	Age and family size stratified pairs of women were individually randomized by drawing from a list.	M + CBE vs. usual care	12	4	2	18	Fair
Canadian National Breast Screening Study-1 (CNBSS-1); Miller et al, 2002 (28)	1980	15 centers in Canada, self-selected participants (25,214; 25,216)	40-49	Blocks stratified by center and 5- year age group after CBE.	M + CBE vs. usual care (all women prescreened and instructed in BSE)	12	4-5	2	13	Fair
Gothenburg *; Bjurstam et al, 2003 (30)	1982	All women born between 1923 to 1944, living in Gothenburg, Sweden (20,724; 28,809)	39-59	Cluster, based on day of birth for 1923 to 1935 cohort (18%), by individual for 1936 to 1944 cohort (82%).	M vs. usual care; controls offered screening after year 5, completed screening at approximately year 7	18	5	1-2	12	Fair
Stockholm; Nystrom et al, 2002 (26)	1981	Residents of southeast greater Stockholm, Sweden (40,318; 19,943)	40-64	Individual, by day of month; ratio of screening to control group 2:1.	M vs. usual care	24-28	2	1	11.4	Fair
Malmo; Nystrom et al, 2002 (26)	1976 to 1978	All women born between 1927 to 1945 living in Malmo, Sweden (21,088; 21,195)	45-70	Individual, within birth year.	M vs. usual care; controls offered screening after year 14.	18-24	9	1 to 2	11-13; 15.5	Fair

Trial; Author, Year (reference)	Year Study Began	Setting/ Population (no. screening; no. control)	Ages at Enrollment (years)	Method of Randomization	Study Groups	Screening Protocol			Follow- up (years)	USPSTF Quality Rating
						Interval (mo.)	No. of Rounds	No. of Views		
Swedish Two-County 2 Trials; Nystrom et al, 2002 (26); Tabar, et al 1995 (31)	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.	M vs. usual care; controls offered screening after year 7.	24-33	3	1	20; 15.5	Fair
Age, Moss et al, 2006 (29)	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 to 1992; 1992 onwards randomization via Health Authority computer system.	M vs. usual care; all women offered screening at ages 50 to 52.	12	4-6, varied by center	2	10.7	Fair

* New data since prior recommendation.

Abbreviations: BSE = breast self examination; CBE = clinical breast examination; M = mammography; Mo = month(s); No = number; NR = not reported; SES = socioeconomic status; USPSTF = U.S. Preventive Services Task Force.

Table 2

Summary of Meta-analyses of Risk Ratios for Breast Cancer Mortality from Mammography Screening Trials for All Ages

Age (years)	Number of Included Trials	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

*Health Insurance Plan of Greater New York (27), Canadian National Breast Screening Study-1 (28), Stockholm (26), Malmo (26), Swedish Two-County (2 trials) (26,31), Gothenburg (30), Age (29).

†Canadian National Breast Screening Study-2 (52), Stockholm (26), Malmo (26), Swedish Two-County (two trials) (26,31), Gothenburg (30).

‡Malmo (26) and Swedish Two-County (Ostergotland) (26).

§Swedish Two-County trial (Ostergotland) (26).

Abbreviations: CrI = credible interval; NNI = number needed to invite to screening; RR = relative risk.

Table 3

Age-specific False Positive and Negative Mammograms, Additional Imaging, and Biopsies from the Breast Cancer Surveillance Consortium

	Age (years)				
	40-49	**50-59**	**60-69**	**70-79**	**80-89**
Number per Screening Round (per 1000 screened)*					
False negative mammograms	1.0	1.1	1.4	1.5	1.4
False positive mammograms	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					
Number undergoing mammography to diagnose one case of invasive breast cancer†	556	294	200	154	143
Number undergoing additional imaging to diagnose one case of invasive breast cancer‡	47	22	14	10	8
Number undergoing biopsy to diagnose one 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.

†Number undergoing mammography to diagnose 1 case of invasive cancer = (1/rate of screen detected invasive cancer).

‡Number undergoing additional imaging to diagnose 1 case of invasive cancer = (rate of additional imaging/rate of screen detected invasive cancer).

§Number undergoing biopsy to diagnose 1 case of invasive cancer = (rate of biopsy/rate of screen detected invasive cancer).

Abbreviations: DCIS = ductal carcinoma *in situ*.

Table 4

Trials of Clinical Breast Examination and Breast Self Examination

Author, Year (reference)	Technique	Years	Setting/ Population (no. screening; no. control)	Ages at Enrollment (years)	Study Design	Intervention	Primary Outcomes	Secondary Outcomes	USPSTF Quality Rating
Pisani et al, 2006 (53)	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	Breast cancer mortality not reported	*False negative: 80/133 diagnosed breast cancers *False positive: 1182/1220 (96.9%) of those who completed follow-up	Poor: low participation; discontinued after one round
Boulos et al, 2005 (54)	CBE/BSE	Pilot: 2000-2002 RCT: ongoing	Cairo, Egypt; women living in area around Italian Hospital (screening phase 1= 4,116 with 1,924 at early follow-up; controls late follow-up 1,927)	Phase 1: 35-64 Phase 2 and 3: 39-65	Phase 1: cohort Phase 2: RCT; block randomization	CBE/BSE× (intervention) vs CBE/BSE× (control) provided by female physicians; CBE training at Italian Hospital 2 months prior to study	Breast cancer incidence	Benign procedures: 1.2% after one round	Not rated (in progress)
Trial in progress (55)	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 prior to trial	Breast cancer mortality	Not available	Not rated (in progress)
Thomas et al, 2002 (58)	BSE	1989-2000	Shanghai, China; women working at one of 519 factories	31-65	RCT; factories assigned to BSE or control group	BSE instruction with periodic reinforcement provided by trained former factory medical workers vs no	Breast cancer mortality: RR 1.03 (95% CI 0.81-1.31)	Benign biopsies: RR 1.57 (95% CI 1.48-1.68)	Good

Author, Year (reference)	Technique	Years	Setting/ Population (no. screening; no. control)	Ages at Enrollment (years)	Study Design	Intervention	Primary Outcomes	Secondary Outcomes	USPSTF Quality Rating
			(132,979; 133,085)			instruction; initial BSE instruction, follow-up sessions at 1 and 3 years, medical supervised BSE every 6 months			
Semiglazov et al, 2003 (18)	BSE	1985-2001	St. Petersburg, Russia; women attending one 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 to 20 women	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; RCT = randomized controlled trial; RR = relative risk; CI = confidence interval.

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Table 5

Summary of Evidence

Number of Studies	Design	Limitations	Consistency	Applicability	Overall Quality	Findings
Breast Cancer Mortality Reduction with Mammography Screening (Key Question 1a)						
8 for age 40-49 years; 1 for age 70-74 years; no screening trials of MRI or digital technologies.	RCTs	Several trials were conducted prior to current mammography technology and treatment approaches; all trials met criteria for fair quality.	Consistent	Fair: All but one trial were conducted outside the U.S. but recruited large community-based populations.	Fair	For women age 39-49 years, the combined relative risk for breast cancer mortality = 0.85 (95% CrI 0.74, 0.95; 8 trials); evidence for women 70 and older is insufficient.
Harms Associated with Mammography Screening (Key Question 2a)						
Several systematic reviews and primary studies; no studies of MRI for screening average-risk women.	Multiple study designs and data sources including RCTs, observation al studies, surveys, and data from the Breast Cancer Surveillance Consortium.	Adverse effects have been studied in various ways, most studies are descriptive.	Varies by type of harm	Poor-good: The applicability of some studies, such as those on 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 mammograms, come from direct patient experiences.	Poor-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 impacts of screening are usually transient and do not influence future screening practices. False positive results are common. Younger women have more false positive mammograms and more additional imaging than older women, but rates of biopsy are lower. Rates of overdiagnosis vary by study methodology and are 1-10%.
Clinical Breast Examination Screening Benefits (Key Question 1b)						
1 (2 in progress)	RCT	The trial was discontinued after one round because of poor community acceptance.	Not applicable	Poor	Poor	Inconclusive findings.
Clinical Breast Examination Screening Harms (Key Question 2b)						
2	1 RCT and 1 descriptive study	Identified studies provide isolated descriptive data and are insufficient to address the question.	Not applicable	Poor	Poor	Inconclusive findings.
Breast Self Examination Screening Benefits (Key Question 1c)						
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.
Breast Self Examination Screening Harms (Key Question 2c)						

Number of Studies	Design	Limitations	Consistency	Applicability	Overall Quality	Findings
3	2 RCTs; 1 observation al 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 instruction; biopsies were not increased in the observational study.

Abbreviations: RCT = randomized controlled trial, CrI = credible interval.