Screening for breast cancer: Evidence for effectiveness and harms

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INTRODUCTION

There is more evidence related to screening for breast cancer, the most common non-skin cancer and second deadliest cancer in women, than for any other cancer.

Decisions about screening require evidence related to effectiveness and harms of screening, and risk of the condition, considered in the context of the patient's values. The evidence addressing the effectiveness (decreasing breast cancer mortality) of several modalities for screening for breast cancer in women and harms that occur from breast cancer screening are discussed here. Multiple aspects related to breast cancer screening are discussed in separate topics, as follows:

- Strategies and recommendations for breast cancer screening (see "Screening for breast cancer: Strategies and recommendations")
- Breast cancer risk and risk prediction models (see "Factors that modify breast cancer risk in women" and "Screening for breast cancer: Strategies and recommendations", section on 'Breast cancer risk determination')
- Performance characteristics of mammography (see "Breast imaging for cancer screening: Mammography and ultrasonography" and "Breast density and screening for breast cancer")
- Management options for women with a genetic predisposition to breast cancer (see "Cancer risks and management of BRCA1/2 carriers without cancer" and "Overview of

hereditary breast and ovarian cancer syndromes")

- Surveillance in women with a personal history of breast cancer (see "Approach to the patient following treatment for breast cancer", section on 'Breast imaging')

In this topic, we will use the term “woman/en” to describe genetic females. However, we recognize that not all people with breasts identify as female, and we encourage the reader to consider transgender and gender nonbinary individuals as part of this larger group.

EFFECTIVENESS OF IMAGING STUDIES IN BREAST CANCER SCREENING

A variety of imaging modalities have been developed for identifying lesions that are suspicious for breast cancer. Mammography remains the mainstay of screening for breast cancer. Digital breast tomosynthesis, which demonstrates potential improved performance over digital mammography, has been widely adopted as a primary screening tool [1,2]. Ultrasonography is commonly used for diagnostic follow-up of an abnormality seen on screening mammography to clarify features of a potential lesion. While ultrasound may also be used to supplement mammographic screening in women with dense breasts (eg, to identify cancers not seen on mammography), data supporting benefit for the addition of ultrasound for screening are inadequate. The role of magnetic resonance imaging (MRI) in combination with mammography for breast cancer screening is also expanding, but only in high-risk patients [3-5]. (See "MRI of the breast and emerging technologies", section on 'Screening high-risk women' and "Breast density and screening for breast cancer", section on 'Magnetic resonance imaging'.)

Mammography — Features of mammography, including test performance characteristics and interpretation of mammography reports, are discussed in greater detail separately (see "Breast imaging for cancer screening: Mammography and ultrasonography"). Of note, mammography is the only screening imaging modality that is recommended for asymptomatic screening of women at average risk by all major expert groups, including the US Preventive Services Task Force [6].

Prior to the 2000s, all breast cancer screening was performed using film mammography. By 2010, digital mammography had become the dominant screening mammographic modality. Beginning in 2011, digital breast tomosynthesis, or three-dimensional (3D) mammography, gained approval from the US Food and Drug Administration (FDA) and is now available at the majority of imaging facilities that offer breast cancer screening.

The clinically important question is whether screening with mammography decreases breast cancer mortality. Nine randomized controlled trials, including more than 650,000 women, have been conducted and reported mortality data. All used film mammography with or

without clinical breast examination (CBE). Results of systematic reviews of the trials comparing mammographic screening with no screening show a benefit among women ages 40 to 69. A 2014 long-term follow-up study raised questions of overdiagnosis and a possible decreased impact of mammography as treatment for breast cancer becomes more effective [7].

- A 2012 meta-analysis of randomized trials found a 20 percent relative risk reduction for breast cancer mortality in women invited to screening compared with controls (figure 1) [8]. It should be noted that most of these trials were performed decades earlier, at a time when treatment for breast cancer was less effective than with current protocols.

- A 2009 systematic review of screening mammography including eight studies of fair or better quality concluded that, with at least 11 years of follow-up, the pooled relative risk for breast cancer mortality was 0.85 (95% CI 0.75-0.96) for women 39 to 49 years of age, 0.86 (0.75-0.99) for women 50 to 59 years of age, and 0.68 (0.54-0.87) for women 60 to 69 years of age [9].

The strongest evidence for an effective screening test is identified when randomized trials demonstrate a decrease in all-cause, as well as disease-specific, mortality. All-cause mortality is rarely documented because the required sample size for such a study is so large. In an analysis of four randomized trials in Sweden, breast cancer screening was associated with a slightly reduced all-cause mortality, although the association was of borderline statistical significance. The four trials followed 247,010 women for a median of 15.8 years; age-adjusted relative risk for total mortality was 0.98 (95% CI 0.96-1.00) [10].

There are several caveats to the findings from these trials:

- Available data from most randomized trials of screening predate currently accepted treatment protocols for breast cancer, such as the use of tamoxifen or aromatase inhibitors for adjuvant treatment. Thus, it is uncertain how much of the 30 percent reduction in breast cancer mortality since 1990 is due to screening and how much to treatment advances. The randomized trials of screening also predate advances in breast imaging in that most were done using screen-film techniques.

- It is unclear whether the results of careful randomized controlled trials can be replicated in the community setting [11].

- One review raised concern that breast cancer mortality outcomes in trials that did not blind assessment of the cause of death may have produced biased results in favor of screening [12].

In the absence of more recent randomized trials, these questions have been evaluated by modeling and observational studies, including the following:

- Using seven different statistical models, estimates of the proportion of total reduction in overall United States breast cancer mortality attributable to mammographic screening ranged from 28 to 65 percent (median 46 percent), with adjuvant treatment accounting for the rest [13]. These results, based on studies when breast cancer mortality had dropped 20 percent, suggest that breast cancer mortality in the United States has dropped about 10 percent because of screening, a more modest reduction than that found in randomized trials.

- A cohort study from Norway reviewed a 20-year span (1995 to 2005) of adjusted mortality data for women who were or were not invited for screening, as breast cancer screening programs were gradually introduced [14]. Fewer breast cancer deaths occurred in women invited for screening, and it was estimated that 27 deaths from breast cancer were avoided for every 10,000 women who were screened every other year for 10 screening rounds.

- A case-control study of women in the Netherlands found that women aged 49 to 75 years who died of breast cancer were less likely to have had a mammogram compared with controls matched for age and invitation for mammography (odds ratio [OR] 0.51, 95% CI 0.40-0.66) [15]. An earlier case control study in six community health plans in the United States did not show a statistical difference in screening rates (CBE and mammography) for women who died of breast cancer compared with control patients matched for age and breast cancer risk, although there was a trend towards screening benefit among higher-risk women [16]. However, study limitations make it difficult to draw firm conclusions from this report.

- In 2014, the International Agency for Research on Cancer (IARC), with representatives from 16 countries, evaluated evidence from 20 cohort and 20 case-control studies regarding breast cancer screening [17]. For women 50 to 69 years of age who were invited to screen with mammography, on average there was a 23 percent reduction on the risk of breast cancer death. Data were more limited for women 40 to 49 years, and the reduction in breast cancer death for these women was less pronounced. The IARC concluded a net benefit for invitation to organized mammographic screening programs for women 50 to 69 years of age, but that the evidence of efficacy for women in other age groups was inadequate.

In sum, systematic reviews of randomized controlled trials of film mammography screening in women ages 40 to 69 years found a long-term 15 to 20 percent decrease in breast cancer mortality. Because most of these studies were begun before 1990, however, there is increasing concern that the trials do not reflect modern therapy or modern imaging. More

recent modeling and community studies suggest that breast cancer screening may be less effective than in the past because of increasingly effective therapy, but most of these studies do not account for advances in imaging.

Digital mammography — Full-field digital mammography is similar to traditional film-screen mammography except that the image is captured by an electronic detector and stored on a computer [18]. As of 2015, 99.9 percent of all mammography units accredited by the FDA are digital units [19]. Several studies have found little difference in cancer detection rates between digital and film mammography [20-25]. The largest study, the Digital Mammographic Imaging Screening Trial (DMIST), found that while the overall diagnostic accuracy of film and digital mammography was similar, digital mammography was more accurate for women less than 50 years of age, for premenopausal and perimenopausal women, and for women with dense breasts [26]. Digital mammography may detect more breast cancers than film mammography in women younger than 50 years old but is also associated with an increased rate of false-positive findings in this population [27]. (See "Breast imaging for cancer screening: Mammography and ultrasonography".)

Tomosynthesis — Digital breast tomosynthesis provides 3D images and is a modification of digital mammography using a moving x-ray source and digital detector. Breast tomosynthesis has been approved in the United States for breast cancer screening [28].

Compared with digital mammography, multiple retrospective cohort and prospective clinical trials suggest that tomosynthesis modestly increases rates of cancer detection and decreases recall rates for false-positive mammography readings [29-31]. Tomosynthesis can be used in combination with digital mammography or can be acquired alone with a synthetic two-dimensional (2D) mammogram artificially generated from the 3D image acquisition. In a 2018 meta-analysis, the incremental cancer detection rate was higher with tomosynthesis than with digital mammography screening alone, with an increase of 1.6 cancers detected per 1000 screens (95% CI 1.1-2.0) [32]. The recall rate for tomosynthesis was lower than for digital mammography alone (pooled absolute reduction -2.2, 95% CI -3.0 to -1.4). No studies have assessed the effects of tomosynthesis on breast cancer mortality.

Two important clinical trials comparing screening digital mammography with tomosynthesis are ongoing: the Tomosynthesis Mammographic Imaging Screening Trial (TMIST) in North America [33] and the Digital Breast Tomosynthesis plus Synthesized Images versus Standard Full-Field Digital Mammography in Population-Based Screening (TOSYMA) trial in Germany [34].

Magnetic resonance imaging — There are no data from randomized trials that show a benefit of screening by MRI in women at average risk for breast cancer.

MRI for detecting breast cancer requires injection of intravenous contrast material and costs substantially more than mammography in the United States [35]. The technique of breast MRI and indications for MRI in the evaluation of known breast abnormalities are discussed separately. (See "MRI of the breast and emerging technologies" and "Diagnostic evaluation of suspected breast cancer", section on 'Breast MRI'.)

Screening breast MRI has been found to be more sensitive but less specific than mammography for the detection of invasive cancers in high-risk women in both retrospective [36-39] and prospective [40-45] studies. A systematic review included 11 studies comparing test performance of screening MRI with mammography in high-risk women [46]. The mean or median age of women in the studies ranged from 40 to 47 years. The women were at very high risk of breast cancer, with a prevalence of 2 percent (about 13 times the overall prevalence of approximately 0.15 percent in the general population of women of similar age). The following results were found:

- Sensitivity of MRI was higher than mammography: 0.77 (95% CI 0.70-0.84) versus 0.39 (95% CI 0.37-0.41).
- Specificity of MRI was lower than mammography: 0.86 (95% CI 0.81-0.92) versus 0.95 (95% CI 0.93-0.97).
- Sensitivity of MRI and mammography together was 0.94 (95% CI 0.90-0.97) and specificity was 0.77 (95% CI 0.75-0.80).

Results of two prospective studies include information about breast cancer mortality [41,47,48] and support MRI screening for women at highest risk for breast cancer, although the numbers are small and the conclusions are subject to multiple biases (patient selection, lead time bias, treatment differences) affecting observational studies. A prospective randomized trial to evaluate whether MRI screening improves survival in women with *BRCA* mutations is unlikely to be feasible because of the large numbers of women it would require and the possibility that women at high risk would not consent to be assigned to a non-screening arm.

An abbreviated protocol for MRI with a three-minute acquisition time was shown to have a high negative predictive value (99.8 percent) in an observational study of 443 women at mild to moderate increased breast cancer risk [49] and is an investigational technique for breast cancer screening. (See "MRI of the breast and emerging technologies", section on 'Abbreviated breast MRI protocols'.)

MRI is under investigation as a supplement to mammography in women with dense breasts, but the data are insufficient to recommend MRI solely based upon breast density. (See "Breast density and screening for breast cancer", section on 'Magnetic resonance imaging'.)

Ultrasonography — Ultrasound has not been evaluated in randomized trials of breast cancer screening for an effect on reducing breast cancer mortality. It is not an appropriate initial screening modality for breast cancer, but it is being evaluated as an adjunct to mammography for screening in women with increased breast density. The role of ultrasound in breast imaging is discussed separately. (See "Breast density and screening for breast cancer" and "Breast imaging for cancer screening: Mammography and ultrasonography".)

BREAST PALPATION

Clinical breast examination — Because several randomized trials included both mammography and clinical breast examination (CBE), the extent of independent contribution of these methods is not clear. In these studies, mammography detected approximately 90 percent of screen-detected cancers and CBE approximately 50 percent. There is some but not total overlap.

The Canadian National Breast Screening Study compared the effects of careful CBE alone with CBE plus mammography on subsequent breast cancer mortality in women in their 50s [50,51]. After 13 and 25 years of follow-up, breast cancer mortality was the same in both groups even though mammography found more breast cancers [7,51]. This is the only randomized trial comparing mammography with a systematized thorough CBE taking 5 to 10 minutes, far different from typical clinical practice [51].

A review of controlled trials and case-control studies in which CBE was at least part of the screening modality estimated CBE sensitivity to be 54 percent and specificity 94 percent [52]. A subsequent study found that CBE plus mammography (with CBE performed by trained nurses) had greater sensitivity than mammography alone but a higher false-positive rate (12.5 versus 7.4 percent) [53]. Among 10,000 women screened with CBE and mammography, there were 55 additional false-positive screens for each additional cancer detected by CBE. A 2009 literature review concluded that the effectiveness of CBE has not been proven by well-designed large trials [9].

A key factor is the quality of each examination: mammography is better standardized than CBE. The preferred technique for CBE includes: proper patient positioning (to flatten the breast tissue against the chest); examining in vertical strips beginning in the axilla and extending in a straight line down the midaxillary line to the bra line, with the fingers then moving medially and continuing up and down between the clavicle and the bra line; making circular motions with the pads of the middle three fingers and examining each breast area with three different pressures; examining each breast for at least three minutes [52].

CBE sensitivity in community practice appears to be substantially lower than that reported in randomized trials [54]. The National Breast and Cervical Cancer Early Detection Program,

which studied the value of CBE in the community setting where procedural guidelines for performing the examination were not dictated, found that CBE still detected about 5 percent of cancers that were not visible on mammography [55]. Despite good specificity in women without symptoms (96.2 percent), the sensitivity was low (36.1 percent). In another community-based study, the specificity of screening CBE in average-risk women was even higher (99.4 percent), suggesting a lower sensitivity; specificity was slightly lower in women at increased risk (97.1 percent) and for diagnostic, rather than screening, examinations [56].

These studies suggest that a high-quality CBE may modestly improve early detection of breast cancer, but at potential significant expense (in terms of clinician availability and time, as well as workup of false-positives) when performed as an adjunct to mammography.

Breast self-examination — There are few randomized trials of breast self-examination (BSE) [57]. One study performed in China randomly assigned 266,064 women to a BSE instruction group or a control group [58]. The instruction group received initial instruction in BSE, reinforcement sessions one and three years later, supervised self-examination every six months for five years, and ongoing reminders. Over 10 years, there was no difference between the two groups in breast cancer deaths. More benign breast lesions were diagnosed in the self-examination group.

A review of eight other studies also failed to show a benefit of regular BSE in rates of breast cancer diagnosis, breast cancer death, or tumor stage or size [59]. In addition, several studies found the rate of breast biopsy for benign disease was significantly higher among women taught BSE [60].

The results of two case-control studies suggest that technique is important in BSE:

- A nested case-control study comparing Canadian women who died of breast cancer or had metastatic disease with control women found increased risk for death or metastatic disease (odds ratio [OR] 2.20, 95% CI 1.30-3.71) in women who did not perform technically correct BSE [61].
- A case-control study showed no overall effect of BSE on detecting breast cancer at an earlier stage [62]. However, the small number of women reporting more thorough examinations had about a 35 percent decrease in advanced-stage breast cancer compared with women not performing BSE.

INVESTIGATIONAL SCREENING TECHNIQUES

Artificial intelligence and computer-aided detection — Artificial intelligence holds promise for improved breast screening outcomes [63]. Several products approved by the US Food and Drug Administration (FDA) are now available as adjunct screening tools for

radiologists in the interpretation of digital mammography and tomosynthesis screening examinations [64]. Thus far, however, these algorithms have undergone little independent evaluation and no prospective studies have been performed [65,66]. In addition, although commercial artificial intelligence algorithms may improve screening performance, the radiologist interface and their impact on radiologist interpretation has not been fully evaluated [67]. Traditional computer-aided detection software also demonstrated promise in early studies but was ultimately proven to adversely affect the interpretive decisions made by radiologists [68-70].

Serum biomarkers — Active investigations, using proteomic technologies, are ongoing to identify reliable serum biomarkers for breast cancer that might be used for screening as well as for disease treatment and surveillance [71]. Despite increasing evidence that epigenetic changes contribute to breast cancer pathogenesis, it may be many years before these scientific observations are translated into clinically reliable screening tests; none are available for clinical use.

Thermography — The use of thermography to detect occult breast cancer was based on the observation that patients have elevated breast skin temperatures over their breast cancers [72]. It was first investigated for screening in the Breast Cancer Detection Demonstration Project in the 1970s and was found to have poor test characteristics, with a false-positive rate of 25 percent and a false-negative rate of more than 60 percent [73].

In 2004, a breast thermography device received approval from the FDA on the basis of prior approval for infrared imaging technology because of demonstrated safety but not necessarily efficacy [72]. The specificity of thermography remains very low, even with modern equipment [72].

No major organization making screening recommendations recommends thermography. Of those commenting on it, the American Cancer Society states, "No study has ever shown that it is an effective screening tool for finding breast cancer early" [74], and the American College of Radiology specifically states it does not endorse thermography for detecting clinically occult breast cancer [75]. The FDA issued a safety communication in June 2011 notifying consumers that thermography is not a replacement for screening mammography and that thermography on its own is not an effective screening tool [76].

HARMS FROM SCREENING

Apart from any discomfort or risks of the screening procedure itself, screening for breast cancer can cause harm when false-positive or false-negative results occur.

Additionally, women may suffer harm if breast cancer is overdiagnosed. Overdiagnosis refers to the diagnosis of conditions that would not have become clinically significant if not detected by screening. Overdiagnosis leads to unnecessary testing and treatment, and psychological and other consequences of being diagnosed with and treated for cancer.

Women should understand the possibility of both benefits and harms from screening. (See "Screening for breast cancer: Strategies and recommendations", section on 'Benefits and harms of screening'.)

False-positive tests — Although both sensitivity and specificity of tests are important, patients and clinicians are often most concerned by false-positive readings. While the definition of "false-positive" varies, for this discussion a false-positive reading is considered to be a mammogram that prompted a recommendation for additional workup (including further imaging or tissue sampling) in a woman who had no finding of breast cancer within one year after the mammogram [77]. The clinical consequence is the recommendation for additional tests and procedures in a woman who does not have cancer. In the United States, for example, approximately 10 percent of screening mammograms require additional evaluation; the lesion turns out to be benign in more than 90 percent of cases [78,79]. Women undergoing routine screening may not be aware of the relatively high likelihood for false-positive results [80]. Despite their frequent occurrence, women in the United States largely view false-positive test results as an acceptable consequence of screening [81].

False-positive readings are more common in younger women, both because the tests are less specific and because breast cancer is less common [79,82,83]. As a result, more follow-up procedures will be done in younger women even though fewer cancers will be found. In one report, although fewer biopsies were done for abnormal mammograms in younger, compared with older, women (9.3, 10.8, and 11.6 per thousand mammograms for women ages 40 to 49, 50 to 59, and 60 to 69, respectively), more of the biopsies were benign in younger women (6.7, 6.1, and 5.2 per 1000 mammograms for women in their 40s, 50s, and 60s, respectively) [9]. Furthermore, because breast cancer screening occurs repeatedly, the risk of a false-positive study rises with repeated screening and will rise more quickly with annual, compared with biennial, screening (table 1) [84,85].

These points were illustrated in a 10-year retrospective cohort study of 2400 women who were 40 to 69 years of age at study entry [77]. The estimated cumulative risk of a false-positive result was 49.1 percent after 10 mammograms and 22.3 percent after 10 clinical breast examinations (CBEs). In another study, for women undergoing annual mammography starting at age 40, it was estimated that 61.3 percent would have at least one mammogram requiring recall over 10 years and 7.0 percent would undergo biopsy for a false-positive reading; for women undergoing biennial (every other year) mammography, the estimated rate of recall was 41.6 percent and biopsy 4.8 percent over 10 years [85].

The cumulative risk of a false-positive mammogram varied substantially according to both patient and radiology-related factors [86]. The risk of a false-positive study at the first, and by the ninth, screening mammogram was 98 and 100 percent in those women with the highest risk variables (young age, prior breast biopsies, a family history of breast cancer, current estrogen use, three years between screenings, no comparison to prior mammograms, and the tendency of the radiologist to call mammograms abnormal [radiologist's random effect]). By contrast, those with the lowest risk variables had estimated risks of 0.7 and 4.6 percent for the first and ninth mammogram, respectively. The authors postulated that if women understood their relative risk of a false-positive study based on these factors, their anxiety might be less when an abnormal mammogram was reported.

In addition to age and family or personal history of breast cancer, the frequency of mammography and the degree of breast density also affected the percentage of women who will experience a false-positive mammogram over a 10-year period [85,87].

Similar concerns about false-positive mammograms apply to older women. In a study of 23,000 women over the age of 65 undergoing one-time screening mammography, 8 percent had an abnormal result that required additional evaluation [88]. However, even in this group of women who were at high risk for breast cancer because of age, the majority with abnormal results (92 percent of abnormal mammograms in women ages 65 to 69 and 86 percent of abnormal mammograms in women age 70 or older) did not have cancer.

Practice variation may contribute to the rate of false-positive mammograms [89]. As an example, a study that compared results from large screening programs in the United States and the United Kingdom found that the rate of recommendations for further evaluation after a mammogram was twice as high in the United States as in the United Kingdom, but cancer detection rates were similar [90]. These data suggest that it may be possible to reduce the rate of false-positive mammography results in the United States without significantly increasing the rate of false-negative results. Newer technologies, such as digital breast tomosynthesis, have been shown to decrease false-positive rates without increasing false-negative rates for some populations of women [91-93].

Anxiety related to false-positive findings — Women may have heightened anxiety about breast cancer for weeks or months after a false-positive reading [94,95]. However, in the largest quality of life study completed as part of the Digital Mammography Imaging Screening Trial (DMIST), false-positive mammograms were associated with increased short-term anxiety, but there was no measurable health-related quality of life decrement after one year [96]. Specifically, although anxiety was higher for women with false-positive mammography at the initial survey compared with those with normal screening exams, there was no significant difference between groups at one year.

The impact of a false-positive mammogram on future screening behavior has been reported as variable. In a meta-analysis, women in the United States were more likely to have routine screening following a false-positive screen, while there was no effect on European women, and Canadian women were less likely to return for routine screening [95]. Having a false-positive mammogram result may lead to increased utilization of health care services [97], though further studies regarding the effects on trust and utilization are needed.

Anxiety associated with false-positive readings can be decreased by the immediate reading of screening mammograms, which allows for additional mammographic views or ultrasound to be performed during the same appointment [98].

False-negative tests — No medical tests, including screening tests, are perfect. There are some screening mammography examinations that are interpreted as negative, but the breast does harbor cancer at the time of the examination. These cancers are either missed by the radiologist or the lesions are not mammographically visible even on retrospective image review [99,100]. Nearly one in eight breast cancers are missed during screening mammography due to a combination of these reasons [101]. Therefore, women who have concerning signs or symptoms, such as a palpable breast lump or new nipple retraction, despite having had a recent negative screening imaging examination, should have follow-up evaluation, ideally with a breast surgeon or a breast cancer expert.

Overdiagnosis — Overdiagnosis is the detection of a disease that would not have caused morbidity or mortality if it had not been found. Some cancers are slow-growing, and some may even regress [102]. Overdiagnosis cannot be directly measured but can only be estimated using one of several approaches. Estimates for overdiagnosis in breast cancer range from 10 percent or less to over 50 percent of all women diagnosed with breast cancer, with variation in these estimates related to differences in definition (eg, whether ductal carcinoma in situ [DCIS] is included and what age women are studied) and approaches used for study design, measurement, and estimation [103-105]. (See "Evidence-based approach to prevention".)

An ideal screening test would distinguish between cancers that carry significant or minimal risk, allowing targeted treatment depending on the tumor biology [106]. Such testing is not available. As there is no reliable way to distinguish which cancer would never progress in an individual patient, some treatment is nearly always recommended. Overdiagnosis therefore leads to some patients receiving treatment for a cancer that, if undiscovered, would not cause harm, thus causing adverse effects (both medical and psychological) without decreasing mortality.

Evidence for overdiagnosis is suggested when the number of cancers detected in a screened group exceeds the number of cancers in an unscreened (but otherwise similar) population over long-term follow-up. If there was no overdiagnosis, then one would expect that over

time, the number of cancers in both the screened and the unscreened groups would equalize, although the cancers in the screened group would have been detected sooner and probably at an earlier stage.

The most rigorous way to ensure comparability between screened and unscreened groups is to follow women in a randomized trial where women in the control group are not offered screening, and to follow the women in both groups over an extended period (at least 5 to 10 years after the screening intervention).

- In follow-up of data from the Canadian National Breast Screening Study, in which women in the control group who were 50 to 59 years at the time of trial enrollment received careful annual CBE but not mammography, after 15 years of follow-up, there was an excess of 106 cancers observed in the mammography arm [7]. The study authors suggest that overdiagnosis was seen in 22 percent (106 of 484) of invasive breast cancers detected by screening in this trial.

- A meta-analysis analyzed three randomized trials including the Canadian study, evaluating them for evidence of overdiagnosis [8]. From the perspective of a woman who is diagnosed with breast cancer because of a screening mammogram, 19 percent (95% CI 15-22) of breast cancers detected by screening represented overdiagnosis. From a system perspective, 10.7 percent (95% CI 9.3-12.2) of all breast cancers detected over the entire follow-up period among women invited to participate in screening represented overdiagnosis.

- Another review of data from five randomized trials in which the control group was not screened found that there was an excess of breast cancers in the intervention group in every study [107]. In the screened groups, between 0.07 and 0.73 excessive cancers (either invasive or in situ) per 1000 women-years could be attributed to overdiagnosis. This would account for approximately 4 to 32 percent of all breast cancers found by screening.

Another method to study overdiagnosis is to observe the population incidence of breast cancer over time. The introduction of screening routinely raises incidence for a few years because at first screening detects new early cancers in addition to those that would soon come to clinical attention without screening. However, cancer incidence rates should fall back to baseline over time, with a shift in detection to earlier-stage cancers. When rates do not return to baseline, it is as if screening itself causes more cancer (overdiagnosis). A major problem with observational studies of overdiagnosis is the strong possibility that factors other than screening account for the changing cancer incidence over time. Representative observational studies include the following:

- In a Surveillance, Epidemiology, and End Results database study including United States women age 40 and older, data for women diagnosed with breast cancer in two time periods were considered: a baseline period before widespread mammography (1975 through 1979) and a later period after the advent of mammography where all women had at least 10 years of follow-up (2000 through 2002) [108]. After the introduction of widespread screening mammography, the incidence of large tumors (≥2 cm) decreased by 30 cases of cancer per 100,000 women (suggesting that screening mammography had the desired effect), and the incidence of small tumors increased by 162 cases of breast cancer per 100,000 women. Assuming that the underlying disease burden was stable between these two time periods, only 30 of the 162 additional small tumors that were diagnosed would have become large, which implied that the remaining 132 cases of cancer per 100,000 women (81 percent) were overdiagnosed (ie, would never have led to clinical symptoms). The authors also calculated that, among large tumors, the decline in size-specific mortality in the more recent time period of study was related to improved treatments rather than screening in at least two-thirds of cases. These estimates of overdiagnosis and the impact of treatment are not precise as the authors rely on data with extensive missing values and they make assumptions about underlying disease burden that cannot be verified.

- One review looked at breast cancer incidence over three decades in the United States stratified according to breast cancer stage at diagnosis [109]. From 1976 (when mammography screening was uncommon) through 2008, the incidence of early-stage cancer increased 100 percent (from 112 to 234 cases per 100,000 women), while the rate of late-stage cancer dropped by 8 percent (from 102 to 94 cases per 100,000 women). The results suggest that only 8 of the 122 additional early breast cancers diagnosed were destined to progress to advanced disease. Assuming that the underlying incidence of breast cancer (regardless of screening) increased at an average rate of 0.25 percent per year (the rate of increase observed among women younger than 40 years of age), and accounting for the effect of hormone-replacement therapy from 1990 to 2006, the authors estimated that 26 percent of breast cancers were overdiagnosed.

- An ecological study across nearly 550 counties in the United States, involving 16 million women 40 years and older, compared rates over 10 years of breast cancer incidence, breast cancer mortality, and size of breast cancer among counties with differing rates of screening mammography [110]. Significant overdiagnosis was suggested by the following findings: a 10 percent increase in the screening rate was associated with a 16 percent increase in the incidence of breast cancer but no significant change in breast cancer death; a 10 percent increase in the screening rate was associated with a 25 percent increase in the incidence of small breast cancers, but no decline in large breast cancers.

- Additional cohort studies have also noted overdiagnosis of breast cancer in other countries including Norway, Sweden, Denmark, Finland, the United Kingdom, Australia, and Canada [103,105,111-115].

- Overdiagnosis is more likely to occur in older women. In a 2023 retrospective cohort study among 54,635 women 70 years and older who had recently been screened, the cumulative incidence of breast cancer was compared between those who continued screening and those who did not continue screening [116]. The estimated percent of breast cancer cases that were overdiagnosed was 31 percent among women aged 70 to 74 years, 47 percent among women aged 75 to 84 years, and 54 percent among women aged 85 and older, cumulative incidence 2.8 (95% CI 2.3 - 3.4) among screened women versus 1.3 (95% CI, 0.9 - 1.9) among those not screened. In a younger cohort of 35,986 women age 50 to 74 years undergoing biennial screening, 15.4 percent (95% CI 9.4- 26.5) of screen-detected cancer cases were estimated to be overdiagnosed [117].

Ductal carcinoma in situ — With an increase in breast cancer screening, the detection of DCIS rose dramatically from the 1970s to the early 2000s but has subsequently plateaued (figure 2) [118-121]. Approximately 16 percent of breast cancers diagnosed in the United States are DCIS [121]. In 2019, over 48,000 women in the United States were diagnosed with DCIS [121].

The natural history of DCIS is not clear, and about half of the DCIS cases may not proceed to invasive cancer [122]. Concerns have been raised that detection of DCIS by mammography may lead to overdiagnosis and overtreatment, as the diagnosis usually leads to surgical and systemic therapy as it remains unknown which cases of DCIS will progress to invasive disease. An additional concern is raised by suboptimal concordance (84 percent agreement) between pathologists in diagnosing DCIS in a breast biopsy sample, in which DCIS was both under-interpreted as benign with or without atypia and over-interpreted as invasive breast cancer by study pathologists [123]. (See "Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis" and "Ductal carcinoma in situ: Treatment and prognosis".)

Radiation — Ionizing radiation increases the risk for breast cancer, but most cohort studies of the phenomenon have included women exposed to much larger radiation doses than the mean glandular dose for a two-view per breast digital mammogram at American College of Radiology accredited facilities [124,125]. (See "Radiation-related risks of imaging".)

In a 2015 modeling study to support revision of the US Preventive Services Task Force breast cancer screening guidelines, the number of deaths due to radiation-induced cancer from annual screening over a lifetime with mammography was estimated to be 16 per 100,000 women [126]. Earlier models incorporating higher radiation doses per mammogram estimated higher rates of radiation-induced breast cancer [127], but even at this greater risk,

still estimated a net positive benefit for screening [127,128]. Women with large breasts may be at higher risk of radiation-induced breast cancer.

Tomosynthesis examinations acquire multiple x-ray image slices through the breast in each standard projection and has comparable or slightly higher radiation dose compared with digital mammography examinations [129]. When first adopted, two-dimensional (2D) digital mammographic projections were obtained along with the three-dimensional (3D) tomosynthesis acquisitions; these combined acquisitions effectively doubled the screening examination radiation dose. However, most facilities now opt to obtain the tomosynthesis images and then synthesize artificial 2D images in lieu of also obtaining the standard digital mammography images. The 2D projections are still helpful for evaluating calcifications on 3D tomosynthesis examinations, however. Thus, tomosynthesis with synthetic 2D projections now has a radiation dose comparable to the standard digital mammography examination and should not deter women from opting for tomosynthesis screening [129,130].

The risk of radiation in women with *BRCA1* or *BRCA2* mutations is discussed separately. (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Cancer surveillance'.)

Discomfort — Mammographic screening can be uncomfortable or painful, as the breast needs to be compressed to achieve adequate images. There are few high-quality studies examining methods to reduce discomfort [131]. One well-designed study found that patient-controlled breast compression reduced patient discomfort while achieving good image quality [132]. Another randomized trial in women with high expectation of pain from the procedure found that topical application of 4% lidocaine gel to the breast and chest wall reduced discomfort but premedication with acetaminophen or ibuprofen did not [133]. Reduced discomfort correlated with increased intent to return for another screening examination.

Other potential harms — There are additional potential harms associated with other screening modalities. For instance, with breast magnetic resonance imaging (MRI), women may not be able to tolerate intravenous gadolinium injection (eg, due to allergic reaction or kidney dysfunction) or may suffer from claustrophobia preventing MRI use [134]. In addition, the US Food and Drug Administration (FDA) has also issued a warning about intravenous gadolinium as it has been linked to gadolinium deposition disease, which is of unknown clinical significance [135]. (See "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Screening for breast cancer".)

SUMMARY AND RECOMMENDATIONS

- **Breast cancer screening efficacy** – There is more evidence related to screening for breast cancer, the most common non-skin cancer and second deadliest cancer in women, than for any other cancer. Systematic reviews of randomized trials have mostly found a significant 15 to 20 percent reduction in breast cancer mortality with mammographic screening for women aged 40 to 69. However, since treatment for breast cancer has improved since many of these trials were performed, it is possible that the magnitude of the effect of screening has lessened. It is also unclear whether the results of randomized controlled trials are replicated in the community setting. (See 'Introduction' above and 'Mammography' above.)

- **Digital mammography** – Digital mammography currently remains the standard routine breast cancer screening tool. It has equivalent accuracy compared to film mammography, but has increased accuracy among younger, pre-menopausal women and women with dense breasts compared to film mammography. (See 'Digital mammography' above.)

- **Digital tomosynthesis** – Several prospective studies suggest modest improvements in recall rates and cancer detection rates with digital breast tomosynthesis versus digital mammography. Digital breast tomosynthesis may detect more breast cancers in younger women and women with extremely dense breasts and is associated with a decreased rate of false-positive findings. (See 'Tomosynthesis' above.)

- **Role of breast ultrasound** – Breast ultrasound is not a primary screening tool but can be considered as an adjunct tool for women with dense breasts and for those women at high lifetime risk and who have contraindications to MRI. (See 'Ultrasonography' above and "Breast density and screening for breast cancer" and "Breast imaging for cancer screening: Mammography and ultrasonography".)

- **Role of MRI** – Magnetic resonance imaging (MRI) is more sensitive but less specific than mammography for the detection of breast cancer and may be most effective as an adjunct to mammography for women at high lifetime risk for breast cancer (eg, women with *BRCA* mutations or those with >20 percent lifetime risk). However, the effect of MRI screening on survival in high-risk groups has not been demonstrated in a prospective randomized trial. (See 'Magnetic resonance imaging' above.)

- **Efficacy of breast palpation**
  - Clinical breast examination – The effectiveness of the clinical breast examination (CBE) in screening is difficult to determine because it is often done in conjunction with mammography, is very dependent on clinician skill, and has not been standardized. The sensitivity of CBE is likely to be low in the community setting. CBE modestly improves early detection of breast cancer as an adjunct to mammography in a program that is able to deliver high-quality CBE. (See 'Clinical breast examination' above.)
  - Breast self-examination – Multiple studies have failed to demonstrate a beneficial effect of regular breast self-examination (BSE) on rates of breast cancer diagnosis and breast cancer death. Additionally, BSE is associated with higher rates of breast biopsy for benign disease. (See 'Breast self-examination' above.)
- **Harms from screening** – The most important harms from mammography screening are false-positive results and overdiagnosis. (See 'Harms from screening' above.)
  - Over a 10-year period of annual mammography screening in the United States, about half of women will experience at least one false-positive mammogram. There are short-term negative psychological consequences of experiencing a false-positive mammogram that may last days to weeks, but there is no evidence of long-term, persistent adverse psychological consequences after a false-positive mammogram. (See 'False-positive tests' above and 'Anxiety related to false-positive findings' above.)
  - Overdiagnosis is the detection of a disease by screening that would not have caused morbidity or mortality if it had not been found. Estimates of the rate of overdiagnosis with mammographic screening vary from a few percent to over 50 percent, probably due to different definitions and methods. A systematic review and meta-analysis of randomized trials estimated that 19 percent of breast cancers detected by screening represented overdiagnosis. (See 'Overdiagnosis' above.)
  - Different considerations between the benefits and harms of routine screening have led to different guidelines regarding recommended starting ages and screening intervals. (See "Screening for breast cancer: Strategies and recommendations", section on 'Benefits and harms of screening'.)

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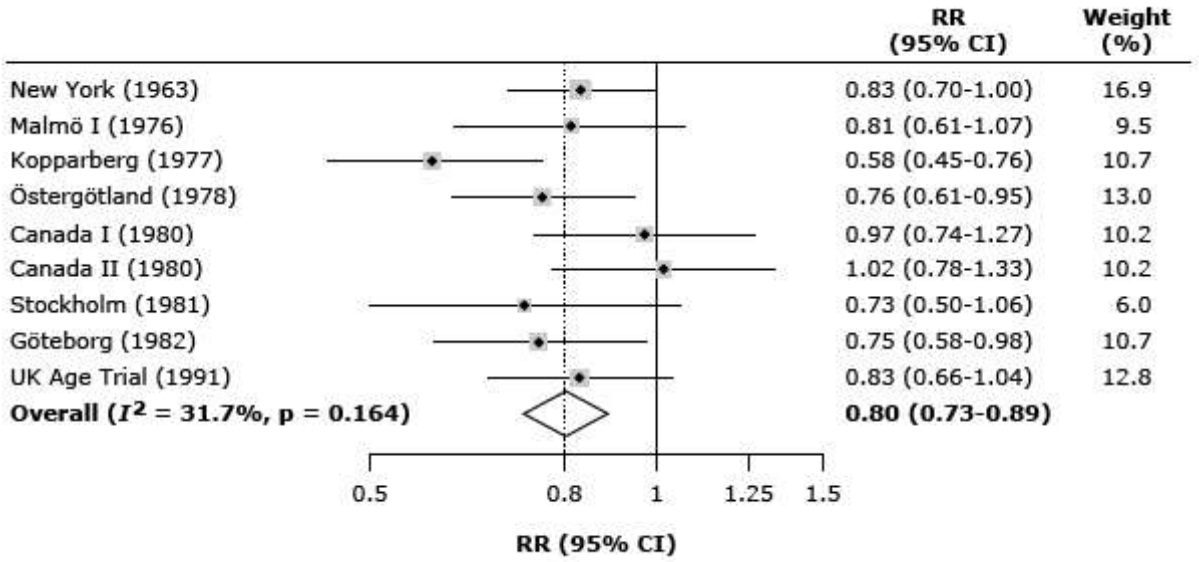
Topic 87311 Version 44.0

GRAPHICS

Meta-analysis of breast cancer mortality after 13 years of follow-up in breast cancer screening trials



Malmö II is excluded because follow-up of about 13 years was not available; the Swedish Two Count (Kopparberg and Östergötland) and Canada I and II trials are split into their component parts; the Edinburgh trial is excluded because of severe imbalances between randomised groups. Weights are from random-effects analysis.

RR: relative risk.

Graphic 94373 Version 2.0

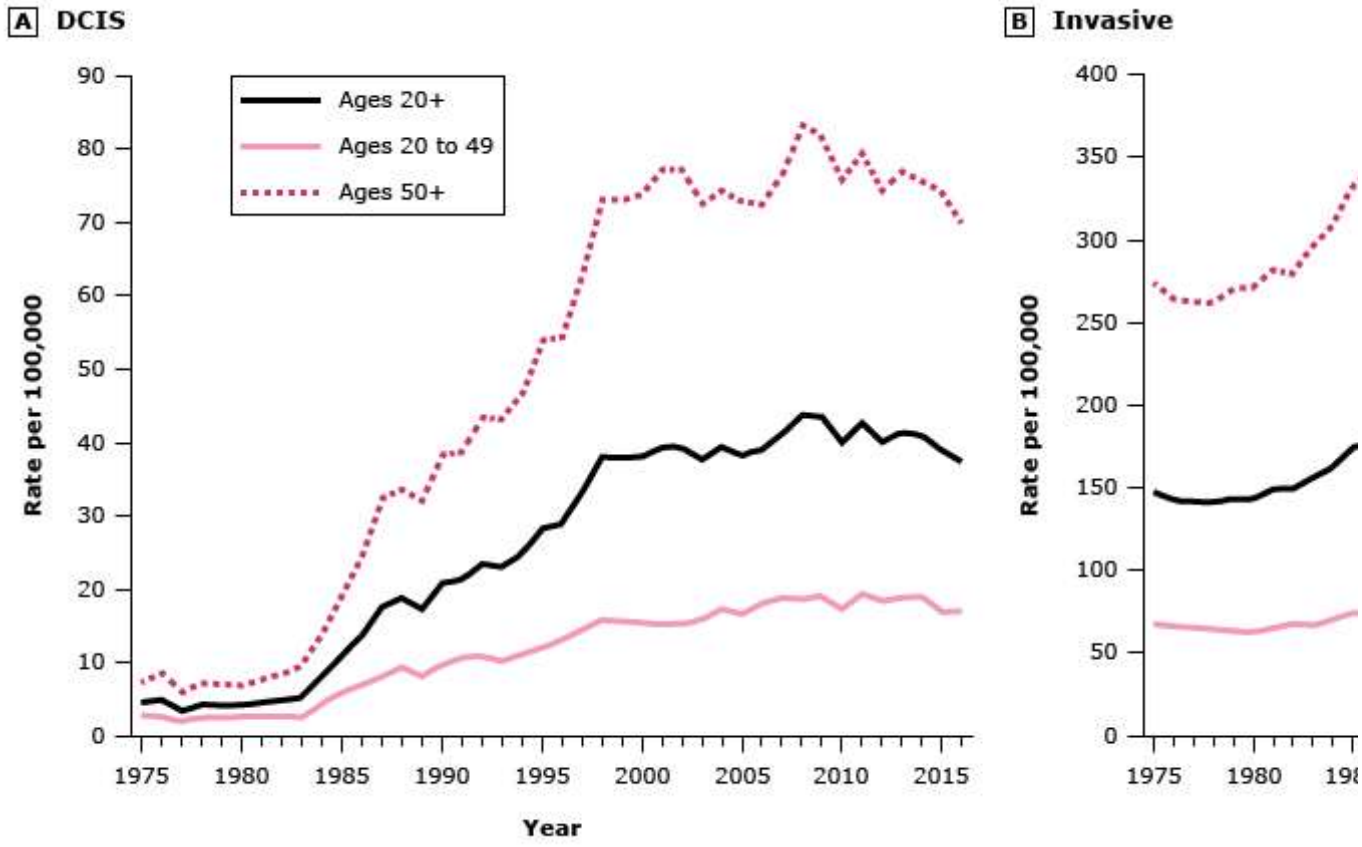
Chances of breast cancer-related outcomes among 1000 women screened annually or biennially, starting at age 40 or 50 and continuing through age 69 or 74

Screening program			Cumulative consequences of screening program			
Mammogram frequency	Starting age	Ending age	Lives saved (number)	Life-years gained (number)	False-positive mammograms (number)	Unnecessary biopsies (number)
Annual						
	40	69	8.3	164	2250	158
	50	69	7.3	132	1350	95
	40	74	10.5	188	2470	173
	50	74	9.5	156	1570	110
Biennial						
	40	69	6.1	120	1250	88
	50	69	5.4	99	780	55
	40	74	8.2	142	1410	99
	50	74	7.5	121	940	66

Adapted and calculated from: Mandelblatt JS, Cronin KA, Bailey S, et al. Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms. Ann Intern Med 2009; 151:738.

Graphic 69681 Version 5.0

Trends in incidence rates of DCIS and invasive female breast cancer by age, U



Rates are per 100,000 and age adjusted to the 2000 United States standard population.

DCIS: ductal carcinoma in situ.

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