Draft Recommendation Statement

Breast Cancer: Screening

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For more information about the draft recommendation on screening for breast cancer, click **here**.

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Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Women ages 50 to 74 years	The USPSTF recommends biennial screening mammography for women ages 50 to 74 years.	B
Women ages 40 to 49 years	The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years. • For women at average risk for breast cancer, most of the benefit of mammography will result from biennial screening during ages 50 to 74 years. Of all age groups, women ages 60 to 69 years are most likely to avoid a breast cancer death through mammography screening. Screening mammography in women ages 40 to 49 years may reduce the risk of dying of breast cancer, but the number of deaths averted is much smaller than in older women and the number of false-positive tests and unnecessary biopsies are larger. • All women undergoing regular screening mammography are at risk for the diagnosis and treatment of noninvasive and invasive breast cancer that would otherwise not have become a threat to her health, or even apparent, during her lifetime (known as “overdiagnosis”). This risk is predicted to be increased when beginning regular mammography before age 50 years. • Women with a parent, sibling, or child with breast cancer may benefit more than average-risk women from beginning screening between the ages of 40 and 49 years. Go to the Clinical Considerations section for information on implementation of the C recommendation.	C
Women age 75 years and older	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women age 75 years and older.	I

All women	The USPSTF concludes that the current evidence is insufficient to assess the benefits and harms of tomosynthesis (3-D mammography) as a screening modality for breast cancer.	I
Women with dense breasts	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasound, magnetic resonance imaging (MRI), tomosynthesis, or other modalities in women identified to have dense breasts on an otherwise negative screening mammogram.	I

This recommendation applies to asymptomatic women age 40 years and older who do not have pre-existing breast cancer or a previously diagnosed high-risk breast lesion and who are not at high risk for breast cancer because of a known underlying genetic mutation (such as a BRCA mutation or other familial breast cancer syndrome) or a history of chest radiation at a young age.

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Draft: Preface

The USPSTF makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service, and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decisionmaking to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

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Draft: Rationale

Importance

Breast cancer is the second-leading cause of cancer death among women in the United States. In 2014, an estimated 233,000 women were diagnosed with the disease and 40,000 women died from it. It is most frequently diagnosed among women ages 55 to 64 years, and the median age of death from breast cancer is 68 years.[1]

Benefit and Harms of Screening and Early Treatment

The USPSTF found adequate evidence that mammography screening reduces breast cancer mortality in women ages 40 to 74 years. The number of breast cancer deaths averted increases with age; women ages 40 to 49 years benefit the least and women ages 60 to 69 years benefit the most. Age is the most important risk factor for breast cancer, and the increased benefit observed with age is at least partly due to the increase in risk. Women ages 40 to 49 years with a first-degree relative with breast cancer have a risk of breast cancer similar to those ages 50 to 59 years without a family history. Among women age 75 years and older, direct evidence about the benefits of screening mammography is lacking.

The USPSTF found adequate evidence that screening for breast cancer with mammography results in harms for women ages 40 to 74 years. The most important harm is the diagnosis and treatment of noninvasive and invasive breast cancer that would otherwise not have become a threat to a woman's health, or even apparent, during her lifetime (i.e., overdiagnosis and overtreatment). False-positive tests are common and result in unnecessary and sometimes invasive followup testing, with the potential for psychological harms (such as anxiety). False-negative tests (i.e., missed cancer) also occur and may provide false reassurance. Radiation-induced breast cancer and resulting death can also occur, although the number is predicted to be low.

The USPSTF found inadequate evidence on the benefits and harms of tomosynthesis (3-D mammography) as a primary screening modality for breast cancer. Similarly, the USPSTF found inadequate evidence on the benefits and harms of adjunctive screening for breast cancer using breast ultrasound, MRI, tomosynthesis, or other modalities in women identified to have dense breasts on an otherwise negative screening mammogram. In both cases, while there is some information about the accuracy of these modalities, there is no information on the effects of their use on health outcomes, such as breast cancer incidence, mortality, or overdiagnosis rates.

USPSTF Assessment

The USPSTF concludes with moderate certainty that the net benefit of screening mammography in women ages 50 to 74 years is moderate.

The USPSTF concludes with moderate certainty that the net benefit of screening mammography in the general population of women ages 40 to 49 years is small.

The USPSTF concludes that the evidence on mammography screening in women age 75 years and older is insufficient, and the balance of benefits and harms cannot be determined.

The USPSTF concludes that the evidence on tomosynthesis (3-D mammography) as a screening modality for breast cancer is insufficient, and the balance of benefits and harms cannot be determined.

The USPSTF concludes that the evidence on adjunctive screening for breast cancer using breast ultrasound, MRI, tomosynthesis, or other modalities in women identified to have dense breasts on an otherwise negative screening mammogram is insufficient, and the balance of benefits and harms cannot be determined.

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Draft: Clinical Considerations

Women Ages 50 to 74 Years

Benefit of Screening

The results of the USPSTF's commissioned systematic evidence review's meta-analysis of clinical trials are summarized in Table 1. Over a 10-year period, screening 10,000 women ages 50 to 59 years will result in 8 (95% confidence interval [CI], 2 to 17) fewer breast cancer deaths, and screening 10,000 women ages 60 to 69 years will result in 21 (95% CI, 11 to 32) fewer deaths.[2] Most of these trials are more than 30 years old, and these estimates may not reflect the current likelihood of avoiding a breast cancer death through screening mammography. Mammography imaging has since improved, which may result in more tumors being detected at a curable stage today than at the time of these trials. However, breast cancer treatments have also improved, and as treatment improves, the advantage of earlier detection decreases, so that some of the women who died of breast cancer in the nonscreened groups in these trials would survive today.

Harms of Screening

The most important harm of screening is the detection and treatment of invasive and noninvasive cancer that would never have been detected in the absence of screening (overdiagnosis and overtreatment). It is not possible to know with certainty what proportion of cancers diagnosed are overdiagnosed, and estimates vary dramatically based on the underlying assumptions and methodology used to calculate the rate of overdiagnosis. Improvements in the sensitivity of mammography with technological advances may have led and continue to lead to increased rates of overdiagnosis. Across all study designs, overdiagnosis estimates range from as low as 0% to as high as 54%.[2] Randomized, controlled trials (RCTs) of mammography in which there was no screening of the control groups at the end of the study suggest an overdiagnosis rate of 19%, although they likely underestimate the magnitude of overdiagnosis associated with modern screening mammography programs.[2] About one out of every five women diagnosed by screening mammography and treated for breast cancer is being treated for cancer that would never have been discovered or caused her health problems in the absence of screening.

The other principal harms of screening are false-positive tests, which require further imaging and often biopsy, and false-negative tests. Table 2 summarizes the rates of these harms per screening round using registry data for digital mammography from the Breast Cancer Surveillance Consortium (BCSC), a collaborative network of five mammography registries and two affiliated sites with linkages to tumor registries across the United States.[2] Note that Table 2 describes a different time horizon than Table 1 (per screening round rather than per decade).

How Often to Screen

No clinical trials compared annual mammography with a longer interval in women of any age. In the randomized trials that demonstrated the effectiveness of mammography in reducing breast cancer deaths in women ages 40 to 74 years, screening intervals ranged from 12 to 33 months.[2] There was no clear trend for greater benefit in trials of annual mammography, but other differences between the trials preclude certainty that no difference in benefit exists. Available observational evidence specifically evaluating the effects of varying mammography intervals found no difference in breast cancer deaths between women age 50 years and older screened biennially versus annually.[2]

Modeling studies were conducted by the Cancer Intervention and Surveillance Modeling Network (CISNET) to predict the lifetime benefits and harms of screening digital mammography with different starting ages and screening intervals. The models varied in their assumptions about the natural history of invasive and noninvasive breast cancer and the impact of detection by digital mammography on survival. Each model predicted the lifetime benefits and harms of contemporary mammography technology using different screening intervals and ages to start and discontinue screening. The models assume the ideal circumstances of perfect adherence to screening and current best practices for therapy across the life span. Regardless of the starting age for screening, the models were consistent in predicting a small incremental increase in the number of breast cancer deaths averted when moving from biennial to annual mammography, but a large increase in the number of harms.[3]

When to Consider Stopping Screening

Clinical trial data for women ages 70 to 74 years are inconclusive. In its 2009 recommendation,[4] the USPSTF extended the recommendation for screening mammography to age 74 years based on the assumption that much of the benefit seen in women ages 60 to 69 years should continue in this age range, and modeling done at the time supported this assumption. Current CISNET decision models suggest that women ages 70 to 74 years with moderate to severe comorbid conditions that negatively affect their life expectancy are unlikely to benefit from mammography.[3, 5] Moderate comorbid conditions include cardiovascular disease, paralysis, and diabetes. Severe comorbid conditions include (but are not limited to) AIDS, chronic obstructive pulmonary disease, liver disease, chronic renal failure, dementia, congestive heart failure, and combinations of moderate comorbid conditions, as well as myocardial infarction, ulcer, and rheumatologic disease.[5]

Women Ages 40 to 49 Years

Implementation of the C Recommendation

The "C" recommendation for screening mammography in women ages 40 to 49 years means that the USPSTF concluded that the benefit of screening mammography outweighs the harms in this age range, but only by a small amount. It is an acknowledgement that the balance of benefits and harms for any individual woman in this age group is a delicate one. Women ages 40 to 49 years must weigh a very important but infrequent benefit (small reduction in breast cancer deaths) against a group of meaningful and much more common harms (overdiagnosis and overtreatment; unnecessary and sometimes invasive followup testing and psychological harms associated with false-positive tests; and false reassurance from false-negative tests). Women who value the possible benefit of screening mammography more than they value avoiding its harms can make an informed decision to begin screening.

Neither clinical trials nor models can precisely predict the potential benefits and harms an individual woman can expect from beginning screening at age 40 rather than 50 years, but models may be the easiest way for women to visualize the relative tradeoffs. Table 3 compares the median and range for predicted lifetime benefits and harms of screening biennially from ages 50 to 74 years with screening biennially from ages 40 to 74 years. Note that Table 3 differs from Tables 1 and 2 in terms of population metrics (per 1,000 vs. 10,000 women) and time horizon considered (lifetime vs. 10-year or single event).

Go to the "How Often to Screen" section for a discussion of screening intervals.

Risk Factors That May Influence When to Start Screening

Advancing age is the most important risk factor for breast cancer in most women, but epidemiological data from the BCSC suggest that having a first-degree relative with breast cancer is associated with an approximately two-fold increased risk of developing breast cancer in women ages 40 to 49 years.[2] Further, CISNET decision modeling suggests that for women with about a two-fold increased risk of developing breast cancer, starting annual digital screening at age 40 years results in a similar harm to benefit ratio (based on false-positives or overdiagnosed cases per 1,000 breast cancer deaths avoided) as beginning biennial digital screening in average-risk women at age 50 years.[3] This approach has not been formally tested in a clinical trial; therefore, there is no direct evidence that it would result in net benefit similar to that of women ages 50 to 59 years. However, given the increased burden of disease and potential likelihood of benefit, women ages 40 to 49 years who have a known first-degree relative (parent, child, or sibling) with breast cancer may consider initiating screening earlier than age 50 years. Many other risk factors have been associated with breast cancer in epidemiological studies, but most of these relationships are weak or inconsistent, and would not likely influence how women value the tradeoffs of potential benefits and harms of screening. Risk calculators, such as the National Cancer Institute's Breast Cancer Risk Assessment Tool (available at www.cancer.gov/BCRISKTOOL), have good calibration between predicted and actual outcomes in groups of women but are not accurate at predicting an individual woman's risk of breast cancer.[6]

Women Age 75 Years and Older: Insufficient Evidence

No randomized trials of screening included women in this age group, and as noted above, trial data are inconclusive for women ages 70 to 74 years.[2] Although the CISNET models suggest that biennial mammography screening may potentially continue to offer a net benefit after age 74 years,[3] the USPSTF believes these models alone are not sufficient to determine moderate certainty of the benefits and harms.

Tomosynthesis (3-D Digital Mammography) as a Primary Breast Cancer Screening Strategy: Insufficient Evidence

Background

Evidence on tomosynthesis is limited; no studies met the inclusion criteria for the commissioned systematic review on the test characteristics of tomosynthesis as a primary breast cancer screening strategy.[7]

Potential Benefits

From the limited data available, tomosynthesis appears to reduce recall rates for false-positive tests compared with 2-D digital mammography alone. Available data also suggest that tomosynthesis increases the cancer detection rate compared with 2-D digital mammography alone.[7] However, current study designs do not answer the question of whether all of the additional cancers detected would have become clinically significant (i.e., the degree of overdiagnosis), or whether there is an incremental clinical benefit to detecting these cancers earlier than with "standard" 2-D digital mammography. In addition, no studies of tomosynthesis looked at clinical outcomes, such as breast cancer morbidity or mortality or quality of life.[7]

Potential Harms

As currently practiced in most settings, tomosynthesis exposes women to approximately twice the radiation of 2-D digital mammography.[7] In 2013, the U.S. Food and Drug Administration approved a method to generate synthetic reconstruction of 2-D images from 3-D views, which reduces the total radiation dose associated with tomosynthesis. Although the extent to which this new software technology has been implemented in mammography screening centers is not precisely known, at the present time, it is thought to be low. Tomosynthesis may also increase the rate of breast biopsy in women with abnormal findings compared with 2-D digital mammography.[7]

Breast Density

Epidemiology

In the United States, the most commonly used classification system for breast density is the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) four-category scale (a=the breasts are almost entirely fatty; b=there are scattered areas of fibroglandular density; c=the breasts are heterogeneously dense, which may obscure small masses; or d=the breasts are extremely dense, which lowers the sensitivity of mammography). Data from the BCSC indicate that about 25 million women (about 43%) ages 40 to 74 years are classified as having heterogeneously or extremely dense breasts. The proportion of women with dense breasts is highest among those ages 40 to 49 years and decreases with age.[8]

Higher breast density is a risk factor for developing breast cancer. Data from the BCSC indicate that, compared with women with average breast density, women ages 40 to 49 years with heterogeneously or extremely dense breasts have a relative risk (RR) of 1.23 for developing invasive breast cancer. For women ages 50 to 64 years with heterogeneously or extremely dense breasts, the RR is 1.29, and for women ages 65 to 74 years, it is 1.30.[3] However, women with dense breasts who develop breast cancer do not have an increased risk of dying from the disease, after adjusting for stage, treatment, mode of detection, and other risk factors, according to data from the BCSC.[9]

Primary Screening Test Performance Characteristics

Increased breast density reduces the sensitivity and specificity of mammography for detecting cancer; a BCSC study of more than 300,000 women found that sensitivity decreased from 87% in the lowest density category to 63% in the highest, and specificity decreased from 96% to 90% as breast density increased.[10]

A woman's BI-RADS breast density category can be inconstant over time. Good-quality studies of U.S. radiologists demonstrate that major recategorization of sequential screening examinations (i.e., from "dense" [c/d] to "non-dense" [a/b] categories or vice versa) occurs in approximately 13% to 19% of women.[11] These studies excluded women taking hormone medications or those with other medical conditions that may have resulted in physiological changes that would explain the difference in breast density classification observed between examinations. Reclassification of breast density status from year to year complicates women's understanding of their underlying breast cancer risk, as well as informed screening and care decisions.

Primary Screening Frequency

In one BCSC study, biennial screening mammography was associated with greater risk of advanced-stage cancer (stage IIB+) (odds ratio, 2.39 [95% CI, 1.06 to 3.39]) or a breast tumor larger than 20 mm (odds ratio, 2.39 [95% CI, 1.37 to 3.18]) in women ages 40 to 49 years with extremely dense breasts (BI-RADS category d) compared with annual screening; this risk was not seen in women ages 50 to

74 years. No statistically significant differences for lymph node involvement were observed in either age group. No information about morbidity or mortality endpoints is available, so it is not known whether these women ultimately fared any differently in their clinical outcomes.[12]

All women ages 40 to 74 years with increased breast density are at increased risk of a false-positive test, an unnecessary breast biopsy, or a false-negative test compared with women without dense breasts. Screening more frequently (i.e., annually vs. biennially) further increases the probability that a woman will experience one of these screening-related harms. BCSC data indicate that the cumulative probability that a woman ages 40 to 49 years with extremely dense breasts screened annually for a decade will receive a false-positive test is about 69% compared with about 21% for biennial screening. Similarly, unnecessary breast biopsy rates are 12% versus 3%, respectively.[12]

Adjunctive Screening

Potential Benefits

Current evidence on adjunctive screening is very limited but suggests that for women identified to have dense breasts on an otherwise negative mammogram, ultrasound or MRI will detect additional breast cancers but will also result in a higher number of false-positive results. Data on tomosynthesis in women with dense breasts is limited, but in the short term, it appears to detect additional breast cancers as well. Most of the additional cancers detected by these modalities appear to be invasive tumors rather than ductal carcinoma in situ (DCIS).[11] A short-term increase in the number of cancers detected does not allow for the conclusion that adjunctive screening improves women's quality of life or reduces treatment-related morbidity or breast cancer mortality. Although adjunctive screening may detect more breast cancers, these cancers may fall into one of three categories: a) those for which earlier detection leads to improved outcomes, b) those that would have had the same outcome when detected later, or c) those that are overdiagnosed. Existing data do not allow for estimation of the proportion of cancers that fall into each category; therefore, the benefits on health cannot be estimated.

Potential Harms

Most positive adjunctive breast cancer screening tests are false-positives. Compared with mammography alone, adjunctive screening with ultrasound or MRI appears to increase recall and biopsy rates. Data on the effects of tomosynthesis on recall and biopsy rates in women with dense breasts is too limited to draw conclusions.[11] The effect on overdiagnosis rates is unknown.

Current Practice

At the present time, 22 States require patient notification of breast density status when mammography is performed; legislation in some States also includes language to be sent to women informing them that they should consider adjunctive screening.[11] No clinical practice guidelines explicitly recommend adjunctive screening in women identified to have dense breasts on an otherwise negative screening mammogram.[11]

Assessment

Increased breast density is very common. It is an independent risk factor for developing (but not dying of) breast cancer, and it reduces mammography's ability to find and accurately identify breast cancers. Many women will move between "dense" and "non-dense" breast categories with sequential screening mammograms, and these reclassifications are not primarily due to physiological causes. More evidence is needed to better understand how the frequency of screening might affect important health outcomes in women with dense breasts. Overall, many important questions remain about the potential role of breast density in individualizing screening approaches; the current evidence is insufficient to recommend a specific screening strategy for women with increased breast density.

Other Approaches to Prevention

The USPSTF has made recommendations about the use of medications to reduce women's risk of developing breast cancer, as well as risk assessment, genetic counseling, and genetic testing for BRCA-related cancer (including breast cancer). These recommendations are available on the USPSTF Web site (www.uspreventiveservicestaskforce.org).

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Draft: Other Considerations

Research Needs and Gaps

Trial data are too limited to directly inform the question of what the best screening strategy is for women, or how clinicians can best tailor that strategy to the individual woman.

Overdiagnosis and resulting overtreatment of breast cancer that would otherwise not have become a threat to a woman's health during her lifetime is the most important harm associated with breast cancer screening. Because it is impossible to determine for any individual patient whether a diagnosed cancer will progress or not, measurements of overdiagnosis are not straightforward but rather must be indirectly quantified. Current estimates of the magnitude of overdiagnosis associated with mammography screening vary widely. Researchers in the field must work together to critically evaluate and ultimately agree on uniform definitions and standards to optimally measure and monitor overdiagnosis and overtreatment in breast cancer screening programs.

In addition, research is critically needed to identify ways to reduce the occurrence of overdiagnosis and subsequent overtreatment associated with breast cancer screening. DCIS is one example of a breast lesion with the potential for high rates of overdiagnosis and overtreatment. Prior to the widespread use of screening mammography, about 6 cases of DCIS per 100,000 U.S. women per year were identified compared with about 37 cases of DCIS per 100,000 women per year after its introduction.[13] When classified as cancer, DCIS now accounts for about one fourth of all breast cancers diagnosed in a given year.[14] However, its nomenclature has recently been the subject of debate, since by definition, DCIS is confined to the mammary ductal-lobular system and incapable of metastasis (i.e., it is noninvasive, which is a classic characteristic of cancer).[15] DCIS might therefore be more appropriately classified as a risk factor for future development of cancer; the primary goal in its management is to reduce the incidence of new invasive carcinomas. The natural history of DCIS—particularly screen-detected DCIS—is poorly understood. Although a substantial proportion of these lesions will not progress to invasive cancer,[16] it cannot be predicted with high certainty which women will develop such cancer and which will not. As such, nearly all women diagnosed with DCIS receive treatment (generally either mastectomy or lumpectomy with or without radiation; a chemopreventive agent such as tamoxifen may also be offered).[17] The overall 10-year breast cancer mortality rate after treatment for DCIS is as low as 1% to 2%,[18] but whether this is due to the effectiveness of the interventions or the fact that the majority of DCIS cases being treated are essentially benign is unclear. Research is needed to develop better prognostic indicators to distinguish nonprogressive or slowly progressive lesions from tumors that are likely to affect quality or length of life. Research is also needed to compare the long-term benefits and harms of immediate treatment versus observation or surveillance with delayed intervention in women with screen-detected DCIS.

Most of the available screening trials and high-quality cohort studies were performed in Europe and predominately enrolled white women younger than age 70 years. Direct evidence about any differential effectiveness of breast cancer screening is lacking for important subgroups of women, such as African American women, who are at increased risk of dying from breast cancer, and older women, for whom balancing the potential benefits and harms of screening may become increasingly challenging with advancing age.

Newer technologies, such as tomosynthesis for primary screening or ultrasound and MRI for adjunctive screening in women with dense breasts, are being increasingly used in the United States without clear evidence to demonstrate their effectiveness in improving important health outcomes. Such studies are necessary prerequisites for the appropriate incorporation of these modalities into established screening programs.

Finally, a large proportion of women in the United States are classified as having dense breasts after a screening mammogram. Despite how common increased breast density is in the general population, critical questions remain about how best to manage these women. Research to help improve the validity and reproducibility of serial BI-RADS assessments would be useful if breast density is to be considered as a factor for personalized, risk-based approaches to breast cancer screening. In addition, long-term randomized trials or longitudinal cohort studies are needed that compare screening outcomes in women with dense breasts who are not otherwise at increased risk for breast cancer who receive adjunctive screening versus those who do not and report important outcomes, such as breast cancer stage at diagnosis, breast cancer recurrence rates, rates of overdiagnosis, and most importantly, breast cancer mortality.

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Draft: Discussion

Scope of Review

A series of systematic evidence reviews were commissioned in support of this recommendation. The first addressed the effectiveness of breast cancer screening in reducing breast cancer–specific and all-cause mortality, as well as the incidence of advanced breast cancer and treatment-related morbidity. It also looked at the harms of breast cancer screening.[2] A second systematic review summarized the evidence about the test performance characteristics of tomosynthesis as a primary screening strategy.[7] A third systematic review evaluated the evidence on adjunctive screening in women with increased breast density, including the accuracy and reproducibility of dense breast classification systems and the diagnostic test performance characteristics, benefits, and harms of adjunctive screening in women identified to have dense breasts on an otherwise negative screening mammogram.[11]

In addition to the systematic reviews of the evidence, the USPSTF commissioned a report from the CISNET Breast Cancer Working Group to provide information from comparative decision models on optimal starting and stopping ages and intervals for screening mammography, as well as how breast density, breast cancer risk, and comorbidity level affect the balance of benefit and harms of screening mammography.[3] A second decision analysis estimated the number of radiation-induced breast cancer cases and deaths associated with different screening mammography strategies over the course of a woman's lifetime.[19]

Burden of Disease

There are approximately 125 new cases of breast cancer and about 22 deaths per 100,000 U.S. women each year. The median age at diagnosis is 61 years, and the median age at death is 68 years.[1]

Risk Factors: Additional Considerations

About 5% to 10% of women who develop breast cancer have a mother or sister who also has breast cancer.[2]

A small number of clinically significant factors are associated with high risk (RR, ≥4) for breast cancer (e.g., women with a *BRCA1* or *BRCA2* gene mutation or other hereditary genetic syndromes; women with a history of high-dose radiation therapy to the chest at a young age, such as for treatment of Hodgkin lymphoma).[2] Women with these risk factors are not within the scope of this recommendation statement.

Race/ethnicity is a factor that has prompted concern because of a growing disparity in breast cancer mortality rates. Although white women are more likely to be diagnosed with breast cancer than African American women (approximately 133 vs. 127 cases per 100,000 women per year), more African American women die each year as a result (approximately 31 vs. 22 breast cancer deaths per 100,000 women per year, respectively).[13] The reason for the difference in breast cancer mortality between white and African American women is not clear. It may be in part due to differences in biology—African American women are disproportionally affected with more aggressive and treatment-resistant forms of breast cancer (i.e., cancer with adverse histological features, such as poorly differentiated tumors and triple-negative phenotypes).[20, 21] Unfortunately, these types of cancer may be the least likely to be positively affected by screening programs, as they can grow so rapidly that they develop and spread entirely within the timespan between screening examinations. The difference in mortality rate may also be due to socioeconomic differences and health system failures. Multiple studies have shown an association between being an African American with cancer and increased risk of having health care services delayed, not receiving appropriate treatment, or even not receiving treatment at all.[22-24] African American women are also severely underrepresented in RCTs of mammography screening. As such, there is no high-quality evidence to conclude that screening African American women more often or earlier than already recommended for the overall population of women results in fewer breast cancer deaths or a greater net benefit.

Accuracy of Screening Tests

All available RCTs evaluating the effectiveness of breast cancer screening used film mammography. Despite a lack of direct evidence of effectiveness in reducing breast cancer deaths, digital mammography has essentially replaced film mammography as the primary modality for breast cancer screening in the United States. Digital screening mammography has been shown to have roughly the same diagnostic accuracy as film, although digital screening appears to have comparatively higher sensitivity in women younger than age 50 years.[25] Across all ages, screening mammography has a sensitivity of approximately 77% to 95% and a specificity of about 94% to 97%.[26]

Tomosynthesis is an emerging technology. No studies on the test characteristics of tomosynthesis as a primary breast cancer screening strategy met the minimum inclusion criteria (i.e., the study needed to be conducted in an asymptomatic screening population, use a comprehensive reference standard that applied to both negative and positive test results, and have a minimum of 1-year followup for negative results to ascertain interval breast cancers not identified by screening). As such, reliable estimates of its test performance are not available. However, the positive predictive value of tomosynthesis (when used in conjunction with 2-D digital mammography and calculated as the number of true positives [cancers] out of all positive examinations) ranges from 4.6% to 10.1% in studies conducted in the United States to date.[7]

Some information is available about the diagnostic test characteristics of adjunctive screening in women identified to have dense breasts on an otherwise negative screening mammogram. Handheld breast ultrasound has the most evidence available (five studies); its sensitivity to detect breast cancer ranges from 80% to 83%, and its specificity ranges from 86% to 94%, with a positive predictive value between 3% and 8%. Three small studies of MRI in high-risk women found that its sensitivity to detect breast cancer ranged from 75% to 100%, specificity ranged from 78% to 89%, and positive predictive value ranged from 3% to 33%, although the applicability of these studies to women in the general screening population is limited because of the source population.[11]

Effectiveness of Early Detection and Treatment

Primary Screening With 2-D Mammography

An updated meta-analysis by Nelson and colleagues of RCTs of screening mammography found similar RR reductions for breast cancer mortality by age group as the USPSTF's previous evidence review. For women ages 39 to 49 years, the combined RR was 0.88 (95% CI, 0.73 to 1.003); for women ages 50 to 59 years, the combined RR was 0.86 (95% CI, 0.68 to 0.97); for women ages 60 to 69 years, the combined RR was 0.67 (95% CI, 0.55 to 0.91); and for women ages 70 to 74 years, the combined RR was 0.80 (95% CI, 0.51 to 1.28).[2]

None of the trials nor the combined meta-analysis demonstrated a difference in all-cause mortality with screening mammography.[2]

Observational studies of screening mammography reported a wide range of breast cancer mortality reduction rates. Recent meta-analyses from the EUROSCREEN Working Group showed an approximate 25% to 31% relative reduction in breast cancer deaths in women ages 50 to 69 years who were invited to screening. By way of comparison, meta-analysis of RCTs that used an intention-to-treat analysis found a 19% to 22% breast cancer mortality reduction in women in the same age range.[2]

Updated decision models performed by CISNET yielded somewhat higher estimates in lifetime relative breast cancer mortality reductions with biennial mammography screening in women ages 50 to 74 years compared with previous analyses (median reduction, 25.8% vs. 21.5%; ranges across models, 24.1% to 31.8% vs. 20.0% to 28.0%, respectively). Since its previous analysis, CISNET has revised the inputs of each of the six models (e.g., portraying distinct molecular subtypes and including digital mammography), which may account for some of the difference.[3] The updated estimate of mammography's mortality benefit is also higher than that obtained via meta-analysis of randomized trials for a similar age group (24.1% to 31.8% for women ages 50 to 74 years in the models vs. 19% to 22% for women ages 50 to 69 years in the RCTs).[3] One reason for the discrepancy is the difference in the time horizon evaluated; while the meta-analysis looked at the impact of screening across a single decade, the decision models evaluated the effect of screening across an entire lifespan. It is also important to recognize that the decision models assumed perfect (i.e., 100%) adherence to screening, followup for abnormal findings, and treatment of screen-detected breast cancer for every individual. In addition, the models also assumed that all women receive the most effective, stage-specific treatments available for their breast cancer once it is detected by mammography. As such, the decision models represent an ideal, or the absolute maximum benefit, that a screening mammography program could achieve given no barriers to the delivery of health care services. In reality, the magnitude of benefit would necessarily be lower, given the real-world constraints of implementing a preventive service to such a large proportion of women in the United States.

In addition to mortality, other outcomes—such as quality of life or reduction in advanced-stage disease and any associated treatment-related morbidity—are also important to consider when evaluating the potential benefits of a screening program. From randomized trial evidence, meta-analysis indicated a reduced risk for advanced cancer with the use of screening mammography in women age 50 years and older when "advanced disease" was defined by the most severe categories available from the trials (stage III + IV disease, tumor size ≥50 mm, or ≥4 positive lymph nodes) (RR, 0.62 [95% CI, 0.46 to 0.83]). A statistically significant reduction in advanced disease was not observed with the use of screening mammography in women ages 40 to 49 years.[2]

The effect of screening mammography on associated adverse effects of treatment or their intensity is not currently clear from the literature. A meta-analysis of five RCTs showed that women randomized to screening mammography were statistically significantly more likely to have a mastectomy (RR, 1.20 [95% CI, 1.11 to 1.30]) and surgical therapy (mastectomy and lumpectomy combined) (RR, 1.35 [95% CI, 1.26 to 1.44]) than women in the control groups.[27] However, critics have noted that these trials do not reflect modern treatment standards and may therefore not be representative of current practices. Four case-series included in the USPSTF systematic evidence review compared breast cancer treatments in women who had previous mammography screening with those who did not and reported statistically significantly more breast-conserving surgeries, fewer mastectomies, and less chemotherapy among women who had screening in the past.[2] However, all of these studies included women with DCIS in the denominator of screened women treated for cancer, leading to potential bias between the screened and nonscreened groups based on differences in how DCIS and invasive breast cancer are managed.

Primary Screening With Tomosynthesis

No studies evaluated the effect of screening for breast cancer with tomosynthesis on important health outcomes, such as mortality, treatment-related morbidity, or quality of life.[7]

Two case-series comparing 2-D digital mammography versus tomosynthesis plus 2-D digital mammography reported detection rates by cancer stage. One study (n=29,080) took place in the United States and one (n=12,631) was conducted in Norway. Neither found statistically significant differences between the study groups in breast cancer size or node status at the time of diagnosis.[28, 29]

Some evidence is available about the effect of tomosynthesis on recall rates for positive findings requiring additional evaluation. Seven studies compared findings from a single cohort of women undergoing two types of screening examinations or compared two screening cohorts of women (2-D digital mammography alone vs. 2-D digital mammography plus tomosynthesis). Overall, tomosynthesis was associated with a reduction in immediate recall rates (median reduction, 1.7%; range across studies, 0.1% to 3.6%).[7]

Adjunctive Screening in Women With Dense Breasts

No studies evaluated the effects of adjunctive screening with any modality in women with dense breasts on breast cancer recurrence rates, quality of life, or mortality.[11]

Harms of Early Detection and Treatment

Primary Screening With Mammography

Screening mammography can result in a number of potential harms. The most common is a false-positive test, which can result in psychological harms, as well as additional testing and invasive followup procedures. Studies show a fairly consistent association between receiving a false-positive screening mammogram and increased breast cancer–specific distress, anxiety, and apprehension, particularly in women who have an associated procedure, such as fine needle aspiration or breast biopsy. These effects improve over time for most women.[2] Table 4 summarizes BCSC data on the cumulative probability of a woman (with varying starting ages and intervals) receiving at least one false-positive mammogram or a recommendation for what turns out to be a false-positive biopsy over a 10-year period.[30]

The most serious harm of screening mammography is the diagnosis and treatment of breast cancer that would never have become a threat to a woman's health, or even apparent, during her lifetime (i.e., overdiagnosis and overtreatment). Overdiagnosis can result because the breast tumor does not progress or because the woman dies of a competing cause of death before the breast cancer advances to the point of causing symptoms. It is not possible to directly observe for any individual woman whether or not she has an overdiagnosed tumor; it is only possible to indirectly estimate the frequency of overdiagnosis that may occur across a screened population. Researchers have used multiple data sources to attempt to quantify overdiagnosis rates associated with mammography screening, including RCTs, pathology and imaging studies, ecological and cohort studies, and decision modeling. To additionally complicate matters, there is a lack of consensus concerning the optimal method for calculating the magnitude of overdiagnosis, and investigators differ in their approaches.[31, 32] This has resulted in a wide range of estimates in the available literature (0% to 54%).[2] The three RCTs of mammography in which there was no screening of the control groups at the end of the study (Malmö Mammographic Screening Trial I and the Canadian National Breast Screening Study [CNBSS] 1 and 2) provide the least biased estimates, as they have the advantage of having comparable groups at baseline, adequate followup beyond the screening period to distinguish between earlier diagnosis and overdiagnosis, and a clear distinction between which groups received screening and which did not (if screening was also provided to the control group, then overdiagnosis could also occur in this population).[31] These older trials likely underestimate the actual magnitude of overdiagnosis associated with modern screening mammography programs, given the increasing sensitivity of newer technologies (CNBSS 2, 16% [95% CI, 12.5% to 19.5%]; Malmö I, 18.7% [95% CI, 15.1% to 22.4%]; and CNBSS 1, 22.7% [95% CI, 18.4% to 27.0%]).[2]

CISNET decision models also investigated the degree of overdiagnosis likely to result from a screening mammography program. The six decision models reported a wide range of estimates of the magnitude of overdiagnosis associated with screening mammography (1.4% to 24.9% of invasive cancer and 30.5% to 84.5% of DCIS, depending on the screening strategy).[3] Assumptions in several of the models may have increased the likelihood that these are underestimates of the true burden of overdiagnosis associated with screening mammography. Most importantly, four of the six models assumed that all diagnosed invasive cancers can progress to lethality; only one (Model W) allowed for the possibility of cancer with "limited malignant potential," whereby the tumor stops progressing at an early invasive stage. In addition, one of the models omitted DCIS.

Recurrent radiation exposure from a lifetime program of mammography screening may slightly increase the risk of developing breast cancer, although no empirical studies have directly measured this effect. Simulation models performed in support of this recommendation estimate that the mean lifetime attributable risk (LAR) of radiation-induced breast cancer from biennial screening mammography in women ages 50 to 74 years is 27 cases per 100,000 women screened. The mean LAR of breast cancer deaths is 5 deaths per 100,000 women screened. If biennial screening begins at age 40 instead of 50 years, the mean LAR of developing breast cancer increases to 41 cases per 100,000 women screened, and the number of breast cancer deaths increases to 8 deaths per 100,000 women screened. Of note, women with large breasts, who require extra views—and thus higher radiation doses—for complete mammography examination appear to be at increased risk for radiation-induced breast cancer or breast cancer death. For biennial screening in women ages 50 to 74 years, the mean LAR of developing breast cancer is an estimated 57 versus 24 cases per 100,000 screened women with and without large breasts, respectively; the mean LAR of breast cancer deaths is 10 versus 4 deaths per 100,000 screened women with and without large breasts, respectively.[19]

Primary Screening With Tomosynthesis

Currently, tomosynthesis is most frequently performed in combination with 2-D mammography; this practice essentially doubles the resulting radiation exposure to the patient. The U.S. Food and Drug Administration has approved a method to generate synthetic reconstructions of 2-D images from 3-D views, which reduces the total radiation dose emitted. However, study data on the performance of tomosynthesis in isolation (i.e., with synthetic reconstruction of 2-D views) is limited (one mammography reading study that compared sensitivity and specificity and one prospective clinical trial),[33] and the method is not yet thought to be in widespread clinical use at this time.

Limited evidence suggests that tomosynthesis may slightly increase the risk of breast biopsy compared with standard 2-D digital mammography. In four U.S. studies of tomosynthesis that reported breast biopsy rates, three noted higher rates in the combined tomosynthesis and digital mammography group compared with standard digital mammography alone (median difference, 0.2%; range, −0.1% to 0.4%).[7]

Adjunctive Screening in Women With Dense Breasts

Although evidence is limited, the use of adjunctive screening in women with increased breast density via alternative technologies, such as handheld ultrasound or MRI, generally appears to increase recall and breast biopsy rates compared with standard screening mammography alone.[11] A single good-quality U.S. study that evaluated the use of adjunctive handheld ultrasound and MRI found that the recall rate for handheld ultrasound after a negative mammogram was about 14% compared with 11% for primary screening mammography alone. In women who received adjunctive screening with MRI after a negative mammogram and negative ultrasound, the recall rate was 23%.[34]

Estimate of Magnitude of Net Benefit

For women not known to be at increased risk of breast cancer, the value of screening mammography increases with age, with the greatest benefit occurring in women ages 50 to 74 years. In particular, women ages 60 to 69 years are the most likely to avoid a breast cancer death. Screening women every 2 years provides the best balance of benefit and harms. For women ages 40 to 49 years, the potential of benefit is smaller, and the risk of harms is proportionally greater. However, the potential outcomes that need to be considered are not identical, and individual women may differ in how they prioritize them. The small probability that a woman may avoid a breast cancer death must be weighed against the more likely scenario that she may have a false-positive result and possible unnecessary followup testing, some of which may be invasive; a false-negative result, with false reassurance or delayed diagnosis; or most critically, diagnosis and treatment of cancer that would otherwise not have threatened her health or even come to her attention. Women who value the possible breast cancer mortality benefit more than they value avoiding the harms can make an informed decision to begin screening. For women age 75 years and older, the evidence is too limited to understand with certainty the true value of screening mammography. However, since the mortality benefits of screening mammography (as with almost any cancer screening test) generally take years to accrue but many of the harms can be experienced immediately, women with limited life expectancy or severe comorbid conditions are unlikely to benefit.

Tomosynthesis is an emerging technology for breast cancer screening. Preliminary evidence suggests that it can reduce recall rates for false-positive tests and detect more cancers compared with 2-D digital mammography. However, it may increase breast biopsy rates, and as currently practiced in most settings, tomosynthesis exposes women to more radiation than standard 2-D mammography. It is not clear whether all of the extra cancers detected by tomosynthesis actually represent a benefit (i.e., cancer that is clinically significant rather than overdiagnosis, and of any additional benefit compared with detection by standard digital mammography at the next scheduled examination). Most importantly, no studies assessed the effect of tomosynthesis on important health outcomes for women, such as quality of life, morbidity, or mortality. Finally, the use of adjunctive screening in women with increased breast density is an important area for future research. Although it is clear that increased breast density is a common condition that imparts some increased risk of developing

breast cancer, as well as reduces the test performance characteristics of mammography, the current evidence on the use of other adjunctive screening modalities is not sufficient to recommend a specific screening strategy for women with dense breasts.

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Draft: Update of Previous USPSTF Recommendation

This recommendation updates the 2009 USPSTF recommendation by providing additional clarity on what is meant by the C recommendation for women ages 40 to 49 years. A C recommendation is not a recommendation against mammography screening in this age group; it denotes that there is moderate certainty of a small net benefit in the population. Rather, a C recommendation emphasizes that the decision to screen must be an individual one, made only after a woman weighs the potential benefit against the possible harms. This updated recommendation also notes that women ages 40 to 49 years with a first-degree relative (parent, sibling, or child) with breast cancer may potentially benefit more than average-risk women in this age group from beginning screening mammography before age 50 years.

The USPSTF did not update its recommendation on the additional benefits and harms of the use of digital mammography or MRI instead of film mammography for breast cancer screening in women not at increased risk (I statement); instead, the USPSTF chose to evaluate the effectiveness of an emerging technology—tomosynthesis—as a primary screening strategy. The USPSTF also evaluated the effectiveness of adjunctive screening using ultrasound, MRI, tomosynthesis, or other modalities in women identified to have dense breasts on an otherwise negative mammogram. In both cases, the USPSTF found insufficient evidence to recommend for or against these preventive services (I statements).

The USPSTF did not update its recommendation against clinicians teaching breast self-examination to patients (D recommendation); however, the USPSTF believes it is important for women to report lumps or other significant changes that they note in their breasts to their health care provider.

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Draft: Recommendations of Others

Many organizations have issued recommendations about mammography screening. All of the following recommendations apply to asymptomatic women not known to be at increased risk for breast cancer.

The American College of Physicians recommends that screening mammography decisions in women ages 40 to 49 years should be based on individualized assessment of risk for breast cancer; that clinicians should inform women in this age range about the potential benefits and harms of screening mammography; and that clinicians should base screening mammography decisions on the benefits and harms of screening, as well as on a woman's preferences and breast cancer risk profile.[35] The American Academy of Family Physicians is in the process of updating its guidelines.

The American Congress of Obstetricians and Gynecologists recommends that mammography screening be offered annually to women beginning at age 40 years.[36] The American Cancer Society recommends annual screening mammography beginning at age 40 years and continuing as long as the woman is in reasonably good health and a candidate for treatment.[37] The American College of Radiology and the Society for Breast Imaging jointly recommend that women begin annual mammography screening at age 40 years and continue until life expectancy is less than 5 to 7 years on the basis of age or comorbid conditions, or when abnormal results of screening would not be acted upon because of age or comorbid conditions.[38]

The Canadian Task Force on Preventive Health Care recommends not routinely screening women ages 40 to 49 years with mammography. It recommends routine screening mammography every 2 to 3 years in women ages 50 to 74 years.[39]

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Draft: Table 1. Breast Cancer Deaths Avoided per 10,000 Women Screened by Repeated Screening Mammography Over 10 Years: RCT Data

	Ages 40–49 Years	Ages 50–59 Years	Ages 60–69 Years	Ages 70–74 Years
Breast cancer deaths avoided	4 (95% CI, 0 to 9)	8 (95% CI, 2 to 17)	21 (95% CI, 11 to 32)	13 (95% CI, 0 to 32)

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Draft: Table 2. Harms of Mammography per 10,000 Women Screened Once: BCSC Registry Data

	Ages 40–49	Ages 50–59	Ages 60–69	Ages 70–74

	Years	Years	Years	Years
False-positive mammograms (false alarms)	1,212	932	808	696
Number of biopsies needed per case of invasive breast cancer diagnosed	100	60	30	30
False-negative mammograms (missed cancers)	10	11	12	13

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Draft: Table 3. Lifetime Benefits and Harms of Biennial Screening Mammography per 1,000 Women Screened: Model Results Compared With No Screening

	Ages 40–74 Years	Ages 50–74 Years
	Median (Range)	Median (Range)
Benefits		
Reduced breast cancer deaths	8 (5–10)	7 (4–9)
Life-years gained	152 (99–195)	122 (75–154)
Harms		
False-positive tests	1,529 (1,100–1,976)	953 (830–1,325)
Unnecessary breast biopsies	204 (140–264)	146 (120–205)
Overdiagnosed breast tumors	20 (2–38)	18 (2–34)

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Draft: Table 4. 10-Year Cumulative Probability of a False-Positive Mammogram or Biopsy Recommendation From Annual or Biennial Mammography Screening Beginning at Age 40 or 50 Years: BCSC Registry Data

	Beginning at Age 40 Years		Beginning at Age 50 Years	
	Annual	Biennial	Annual	Biennial
False-positive mammogram	61.3% (95% CI, 59.4 to 63.1)	41.6% (95% CI, 40.6 to 42.5)	61.3% (95% CI, 58.0 to 64.7)	42.0% (95% CI, 40.4 to 43.7)
False-positive biopsy recommendation	7.0% (95% CI, 6.1 to 7.8)	4.8% (95% CI, 4.4 to 5.2)	9.4% (95% CI, 7.4 to 11.5)	6.4% (95% CI, 5.6 to 7.2)

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Current as of: April 2015

Internet Citation: *Draft Recommendation Statement: Breast Cancer: Screening*. U.S. Preventive Services Task Force. May 2015. http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementDraft/breast-cancer-screening1