Breast Cancer Screening for Average-Risk Women

Clinical Recommendations

The Women's Preventive Services Initiative recommends that average-risk women initiate mammography screening no earlier than age 40 and no later than age 50. Screening mammography should occur at least biennially and as frequently as annually. Screening should continue through at least age 74 and age alone should not be the basis to discontinue screening.

These screening recommendations are for women at average risk of breast cancer. Women at increased risk should also undergo periodic mammography screening, however, recommendations for additional services are beyond the scope of this recommendation.

Implementation Considerations

The Women's Preventive Services Initiative recommends, as a preventive service, that women initiate mammography screening no earlier than age 40 and no later than age 50 and continue through at least age 74. Screening mammography should occur at least biennially and as frequently as annually. Decisions regarding when to initiate screening, how often to screen, and when to stop screening should be based on a periodic shared decision-making process involving the woman and her health care provider. The shared decision-making process assists women in making an informed decision and includes, but is not limited to, a discussion about the benefits and harms of screening, an assessment of the woman's values and preferences, and consideration of factors such as life expectancy, comorbidities, and health status.

EVIDENCE MAP

- Average-risk women should initiate mammography screening no earlier than age 40 and no later than age 50.
- Screening should continue through at least age 74 and age alone should not be the basis to discontinue screening.

Systematic Reviews	Additional Studies	USPSTF[1]
USPSTF 2016 review[2]: • Meta-analyses of screening RCTs indicate statistically significant breast cancer mortality reductions with screening for ages 50-59 and 60-69 years; but not 39-49 and 70-74 years. Estimates for age >70 are limited by small sample sizes. • Meta-analysis of screening RCTs indicate no reductions in advanced breast cancer with screening for age 39 to 49 years; but reduced risk with screening for age 50 years and older.	Observational studies of screening indicate reduced breast cancer mortality for ages 50-69; studies of younger and older women are lacking or inconsistent.	• Age 40-49: Biennial screening mammography should be based on individual factors including the patient's values regarding specific benefits and harms (Level C; 2016). • Age 50-74: Biennial screening mammography (Level B; 2016). • Age 75 and older: Evidence is insufficient to assess the additional benefits and harms of screening mammography (2016).

Screening mammography should occur at least biennially and as frequently as annually.

Systematic Reviews	Additional Studies	USPSTF[1]
USPSTF 2016 review[2]: Screening trials do not compare screening intervals; observational studies are inconsistent and biases limit interpretation.	CISNET modeling study[3]: Biennial screening intervals provide the most benefit while minimizing potential harms.	Age 50-74: Biennial screening mammography (Level B; 2016).

Decisions regarding when to initiate screening, how often to screen, and when to stop screening should be based on a periodic shared decision-making process involving the woman and her health care provider.

Systematic Reviews	Additional Studies	USPSTF[1]
None	None	Suggests informed decision making, however, no studies have evaluated the effectiveness of this approach (2016).

Abbreviations: CISNET=Cancer Intervention and Surveillance Modeling Network; RCTs=randomized controlled trials; USPSTF=U.S. Preventive Services Task Force

SUMMARY OF EVIDENCE

Introduction

Breast cancer commonly includes an asymptomatic phase that can be identified with mammography. The rationale for screening is to improve survival by identifying treatable cancer at localized stages, although screening may not reduce mortality for some aggressive cancer types,[4] and has less impact on slowly progressive types.[5,6] Screening for women at average risk for breast cancer (i.e., without risk factors indicating high risk) is conducted using periodic mammography. Digital mammography has generally replaced film in the United States, and newer technologies, such as digital tomosynthesis, are rapidly disseminating. Rates of screening mammography in the United States are generally high and have remained relatively stable for the past decade. Mammography screening between 2009 and 2011 was performed by 71% of eligible women covered by commercial plans, 69% for Medicare plans, and 51% for Medicaid plans.[7]

While there is general consensus that mammography screening is beneficial for many women, conflicting screening recommendations have led to practice variability. Issues lacking consensus include the optimal ages to begin and end routine screening; optimal screening intervals; defining and balancing the benefits of screening with potential harms; appropriate use of various imaging modalities including supplemental technologies; values and preferences of women regarding screening; and how all of these considerations vary depending on a woman's risk for breast cancer.

Current Recommendations and Coverage of Services

The previous Institute of Medicine panel did not address breast cancer screening coverage[8] because a specific clause in the Affordable Care Act indicated that annual mammography screening would be covered for women age 40 years and older without a co-pay or deductible.[9] This coverage applies to the annual screening mammogram only, and subsequent related services are not similarly covered.

In 2016, the U.S. Preventive Services Task Force (USPSTF) updated its recommendation for breast cancer screening for asymptomatic, average-risk women.[1,7,10] The new recommendation is similar to the previous recommendation issued in 2009.[11] The USPSTF recommends biennial screening mammography for women ages 50 to 74 years, and determined that the decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms.

The USPSTF concluded that evidence was insufficient to assess the additional benefits and harms of screening mammography in women age 75 years or older. In addition, they determined that evidence was insufficient to support digital breast tomosynthesis (DBT) as a primary screening method, and adjunctive screening for breast cancer using breast ultrasonography, magnetic resonance imaging (MRI), DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram.

Background

Breast cancer is the second most common cancer in women in the United States after non-melanoma skin cancer, and is the second leading cause of cancer death after lung cancer.[12] In 2016, an estimated 246,660 women in the United States will be diagnosed with breast cancer and 40,450 will die, representing 14.6% of all new cancer cases and 6.8% of all cancer deaths.[12] The overall 5-year relative survival rate for breast cancer from 2006 to 2012 was 89.7%, and approximately 3 million women were living with breast cancer in the United States in 2013.[12]

Although many risk factors have been associated with breast cancer in epidemiologic studies, most relationships are weak or inconsistent.[13] Most women who develop breast cancer have no identifiable risk factors beyond sex and age. However, a small number of clinically significant risk factors are associated with high risks for breast cancer and can be used to identify women who may be eligible for screening outside routine screening recommendations. These include women with deleterious BRCA mutations and their untested first-degree relatives; other hereditary genetic syndromes; previously diagnosed high-risk breast lesions;[14] and history of high-dose radiation therapy to the chest between the ages of 10 to 30 years, such as for treatment of Hodgkin lymphoma.

Family history of breast cancer, particularly among first-degree relatives, is also an important risk factor. Approximately 5 to 10% of women with breast cancer have a mother or sister with breast cancer, and up to 20% have either a first-degree or a second-degree relative with breast cancer.[15] The degree of risk associated with family history varies according to familial patterns of disease. Estimates of lifetime risk of breast cancer determined by kindred analysis of over 15 or 20% are considered high.

Breast density is a radiographic measure of breast tissue that is associated with increased risk for breast cancer and reduced mammography sensitivity. Breast density is currently described by four categories: almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense.[16] Approximately 37% of women had dense breasts in a recent U.S. study; however, there was a wide variation in density assessment across radiologists.[17] Increased breast density is more common among younger women.[18] Compared with women with scattered fibroglandular densities, hazard ratios for breast cancer are 1.6 for premenopausal women with heterogeneously dense breasts and 2.0 for those with extremely dense breasts.[19]

Models that incorporate several of these risk factors have been developed to predict breast cancer risk for individual women. All of the models include age and number of first-degree relatives with breast cancer into their calculations, but vary in their complexity. Studies of their diagnostic accuracy indicate that the models are poor predictors of an individual's risk[20] and their effectiveness in selecting candidates for breast cancer screening remains unproven.

Current practice guidelines vary across professional organizations (**Table 1**).

Table 1. Recommendations of Professional Organizations

American College of Obstetricians and Gynecologists (ACOG)[21]	Mammography screening should be offered annually to women beginning at age 40.
American Academy of Family Physicians (AAFP)[22]	The decision to conduct screening mammography prior to age 50 should be individualized and take into consideration the patient's context and risk factors. For women between ages 50 and 74, the AAFP recommends biennial screening.
American Cancer Society[23]	Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years; women aged 45 to 54 years should be screened annually; women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years and should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer.
American College of Radiology (ACR)[24]	Annual screening mammography for asymptomatic women 40 years of age and older. The decision as to when to stop routine mammography screening should be made on an individual basis by each woman and her physician based on a woman's overall health.
National Comprehensive Cancer Network (NCCN)[25]	Annual screening mammography, clinical breast exam, and breast awareness for asymptomatic, average risk women age 40 years and older.

UPDATE OF EVIDENCE

The WPSI update focuses on three issues: optimal ages to begin and discontinue regular screening mammography, and optimal screening intervals for women screened at any age. Several comprehensive evidence reviews on breast cancer screening were recently conducted, including reviews from the Pacific Northwest Evidence-based Practice Center for the USPSTF published in February 2016.[2,26] Results relevant to the three issues covered in this update are summarized below. Literature searches used for the USPSTF reviews were repeated in August 2016 to identify new evidence, however, no new studies relevant to the update met inclusion criteria.

Effectiveness of Screening at Different Ages

Reducing breast cancer mortality

Meta-analyses of randomized controlled trials (RCTs) of breast cancer screening with updated data from the Canadian, Swedish Two-County Study, and Age trials indicated statistically significant breast cancer mortality reductions with screening for ages 50 to 59 years and 60 to 69 years, but not for age 39 to 49 years and 70 to 74 years (**Table 2**).[2] Estimates for women age 70 and older were limited by low numbers of events from trials that had smaller sample sizes of women in this age group.

Observational studies of the effectiveness of population-based mammography screening on breast cancer mortality reported a wide range of reductions in breast cancer death. Most studies were conducted in Europe or the United Kingdom and included women age 50 to 69 years. Meta-analyses from recent reviews from the EUROSCREEN Working Group indicated 25 to 31% mortality reduction for women invited to screening in the screening programs. This compares to 19 to 22% reduction for women age 50 to 69 years in the USPSTF meta-analysis of screening RCTs.[2]

Table 2. Age-specific Rates of Breast Cancer Mortality Reduction with Screening[2] Number of deaths prevented if 10,000 women were followed for 10 years

Age, yrs	Number of trials	Mortality rate in the control group per 100,000 person-years (95% CI)*	Breast cancer mortality reduction RR (95% CI)†	Deaths prevented with screening over 10 years (95% CI)
39-49	9	39-49	0.88 (0.73 to 1.003)	4.1 (-0.1 to 9.3)
50-59	7	50-59	0.86 (0.68 to 0.97)	7.7 (1.6 to 17.2)
60-69	5	60-69	0.67 (0.54 to 0.83)	21.3 (10.7 to 31.7)
70-74	3	70-74	0.80 (0.51 to 1.28)	12.5 (-17.2 to 32.1)

*Based on trials of screening included in the meta-analysis.
†From meta-analysis of screening trials using the longest follow-up time available.
CI=confidence interval; RR=relative risk.

The only U.S observational study of breast cancer mortality reduction is a record review that indicated no differences in breast cancer deaths between screened versus non-screened women older than age 80 years.[27] A large study of the Mammography Screening of Young Women Cohort in Sweden indicated reduced risk for breast cancer deaths for women age 40 to 49 years invited to screening compared with women not invited (RR 0.74; 95% CI, 0.66 to 0.83).[28] An observational study of Canadian women age 40 to 79 comparing screening program participants versus nonparticipants indicated 40% reduced breast cancer mortality among participants.[29] However, observational studies were susceptible to important methodologic biases limiting these conclusions, particularly regarding important fundamental differences between participants and nonparticipants of screening programs.

Reducing all-cause mortality

All-cause mortality did not differ between randomized groups in meta-analyses of the screening RCTs, regardless of whether trials were analyzed in combined or separate age groups

Reducing advanced breast cancer

The RCTs of mammography screening provided several measures of intermediate breast cancer outcomes. However, most comparisons between screening and control groups using these categories provided differences

between the two groups in relatively early stages of disease, rather than advanced stages. When thresholds were defined by the most severe disease categories available from the trials (Stage III + IV disease, size ≥50 mm, 4+ positive lymph nodes), meta-analysis indicated no reductions in advanced breast cancer with screening for age 39 to 49 years (RR 0.98; 95% CI 0.74 to 1.37); but reduced risk with screening for age 50 years and older (RR, 0.62; 95% CI 0.46 to 0.83). The majority of cases from screening were ductal carcinoma in situ (DCIS) and early stage, and screening resulted in more mastectomies (RR 1.20 [95% CI 1.11 to 1.30]; 5 trials) and radiation (RR 1.32 [95% CI 1.16 to 1.50]; 2 trials).

Several observational studies describe differences between screened and unscreened women, but report various definitions of advanced breast cancer.[2] Six observational studies compared advanced breast cancer outcomes between women in populations participating in screening versus nonparticipating. Of these, two studies indicated statistically significantly more Stage III and IV breast cancer among unscreened women; three reported more lymph node positive disease; and three reported more tumors greater than 20 mm in size. Four case series studies indicated less extensive surgery, such as fewer total mastectomies and more breast conservation therapies, and less chemotherapy among women who had previously had screening mammography compared with those who did not, but these studies included women with DCIS and early stage cancer as well as advanced cancer.

An analysis of data from the Breast Cancer Surveillance Consortium (BCSC) indicated a lower proportion of Stage III + IV disease among women age 40 to 49 years screened annually versus biennially, but not for women age 50 to 59 years. A second analysis of BCSC data indicated that women age 40 to 49 years with extremely dense breasts had increased risks for advanced stage cancer (IIB+) and large-size tumors (>20 mm) with biennial compared with annual screening. Differences were not significantly different for positive lymph nodes, other density categories, other age groups, or between biennial and triennial screening.

Effectiveness of Screening Using Different Intervals

There are no head-to-head trials of the effectiveness of different screening intervals, and existing trials do not provide enough information to determine the specific effects of screening intervals. Two observational studies of screening intervals indicated no breast cancer mortality differences between annual and biennial screening for women 50 years or older, or between annual and triennial screening among women age 40 to 49 years. No RCTs evaluated the incidence of advanced breast cancer outcomes and treatment on the basis of screening intervals.

Because of the lack of studies addressing the effectiveness of different screening intervals, the USPSTF commissioned a modeling study from the CISNET modeling group.[3] Results indicated that biennial screening intervals provided the most benefit while minimizing potential harms.

Harms of Screening

The USPSTF weighs the benefits of screening against potential harms, including false-positive results leading to additional imaging and biopsies, false-negative results, overdiagnosis, anxiety and distress with screening, pain, and radiation exposure.

False-Positive and False-Negative Mammography Results, Recommendations for Additional Imaging, and Recommendations for Biopsies

Data from the BCSC for regularly screened women using digital mammography based on results from a single screening round indicated that false-positive mammography rates were highest among women age 40 to 49 years (121.2 per 1,000 women; 95% CI 105.6 to 138.7) and declined with age; rates of false-negative results tended to increase with age, but were not statistically significantly different across age groups (**Table 3**).[30] Rates of recommendations for additional imaging were highest among women age 40 to 49 years (124.9 per 1,000 women; 95% CI 109.3 to 142.3) and decreased with age, while rates of recommendations for biopsy did not differ between age groups. For every case of invasive breast cancer detected by mammography screening in women age 40 to 49 years, 464 women had screening mammography, 58 were recommended for additional imaging, and 10 were recommended for biopsies. These estimates declined with age. These results did not differ by time since last mammography screening regardless of whether broad or narrow estimates of one versus two years were used.

When these outcomes were evaluated by breast cancer risk factors, family history of breast cancer, high breast density, and previous benign breast biopsy were associated with higher rates of false-positive and false-negative results and recommendations for additional imaging and biopsy across most age groups. Premenopausal status, use of menopausal hormone therapy, and lower BMI were associated with some of the outcomes for specific age groups only. Rates for all outcomes were lowest for women with almost entirely fat breasts, and highest for women with heterogeneously dense breasts or for those in the combined category of heterogeneous and extreme density.

Published data from the BCSC using film and digital mammography provided 10-year cumulative rates of false-positive results and biopsies.[31,32] Rates of false-positive mammography results were 61% for annual and 41% for biennial screening, while rates of false-positive biopsy were 7 to 9% for annual and 5 to 6% for biennial screening. Women older than age 50 years had higher false-positive biopsy rates. Rates of false-positive mammography results and biopsy were highest among women receiving annual mammography, those with heterogeneously dense or extremely dense breasts, and those either 40 to 49 years old or who used combination hormone therapy.

Overdiagnosis

Overdiagnosis refers to breast cancer cases that are detected by screening that would not become clinically important to the patient in the absence of screening. A meta-analysis of three RCTs, a systematic review of 13 observational studies, and 18 individual studies of overdiagnosis were identified for the USPSTF update.[33]

Studies of overdiagnosis were primarily based on screening trials, screening programs and registries, or modeled data. Studies differed by their characteristics, methods, and measures. These differences influenced their estimates of overdiagnosis, limited comparisons, and prohibited combined estimates.

Estimates from RCTs indicate overdiagnosis rates of 10.7 to 19.0%. Unadjusted estimates from 13 observational studies included in the EUROSCREEN review indicated overdiagnosis rates ranging from 0 to 54%. For six studies that adjusted overdiagnosis estimates for breast cancer risk and lead time, rates varied from 1 to 10%. Additional observational studies not included in the EUROSCREEN review reported overdiagnosis estimates of 3 to 50%, with most between 14 to 25%. Although several statistical models of overdiagnosis have been published, these studies have been less acceptable to guideline development groups because of the many assumptions that were used to construct them. Models indicated estimates ranging from 0.4 to 50%.

Table 3. Age-Specific Rates of False-Positive and False-Negative Digital Mammography Results and Recommendations for Additional Imaging and Biopsies From a Single Screening Round in the BCSC[3]

	Age, y					Difference
	40–49	50–59	60–69	70–79	80–89	(P-value)*
Women screened, n	113,770	127,958	94,507	50,204	18,752	
Invasive breast cancer cases, n	349	574	651	427	154	
DCIS cases, n	191	246	208	120	43	
***Outcomes, n per 1,000 women screened* (95% CI)**						
False-positive mammography result	121.2 (105.6 to 138.7)	93.2 (82.8 to 104.7)	80.8 (72.9 to 89.4)	69.6 (62.6 to 77.3)	65.2 (58.8 to 72.2)	<0.001
False-negative mammography result	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.3)	1.2 (0.9 to 1.5)	1.5 (1.1 to 1.9)	1.3 (0.9 to 1.9)	0.32
Additional imaging recommended†	124.9 (109.3 to 142.3)	98.5 (88.0 to 110.1)	88.7 (80.6 to 97.4)	79.0 (71.9 to 86.9)	74.4 (67.4 to 82.2)	<0.001
Biopsy recommended†	16.4 (13.2 to 20.3)	15.9 (12.7 to 19.7)	16.5 (14.3 to 19.1)	17.5 (15.2 to 20.2)	15.6 (13.4 to 18.2)	0.12
Screen-detected invasive cancer	2.2 (1.8 to 2.6)	3.5 (3.1 to 4.0)	5.8 (5.3 to 6.4)	7.2 (6.4 to 8.1)	7.1 (5.9 to 8.5)	<0.001
Screen-detected DCIS	1.6 (1.3 to 1.9)	1.8 (1.5 to 2.2)	2.1 (1.7 to 2.5)	2.3 (1.7 to 3.0)	2.1 (1.5 to 3.0)	0.05

*2-sided P-values and 95% confidence intervals from a logistic regression model that accounts for clustering by radiology facility using generalized estimating equations.
†After positive mammography result.
Abbreviations: CI=confidence interval; DCIS=ductal carcinoma in situ.

Anxiety, Distress, and Other Psychological Responses

Systematic reviews including over 100 descriptive studies of anxiety, distress, and other psychological responses to mammography screening have been published, but provide mixed results.[33-37] In general, women with false-positive results had more anxiety, psychological distress, and breast cancer specific worry after screening compared with those with normal screening results in most studies. Anxiety improved over time for most women, but persisted for over 2 years for some. Two studies reported that women with false-positive results were less likely to return for their next mammogram; two other studies reported no differences; however, when women were given letters tailored to their last screening result they were more likely to re-attend.

Pain during Procedures

A review of 22 descriptive studies indicated that many women experience pain during mammography (1% to 77%), but the proportion of those experiencing pain who do not attend future screening varies (11% to 46%).[38]

Radiation Exposure

Published models calculate the number of deaths due to radiation induced cancer using estimates for digital mammography is between 2 per 100,000 in women age 50 to 59 years screened biennially, and up to 11 per 100,000 in women ages 40 to 59 years screened annually.[39] A new model for the USPSTF reported similar findings.[39]

CONCLUSIONS

Results of trials comparing mammography screening to no screening indicate reduced breast cancer deaths with screening for women ages 50 to 69 years, but not for women in their 40s or age 70 and older. Individual factors that increase risk for breast cancer, such as family history of breast cancer, previous biopsies, increased breast density, and others, have not been evaluated in screening trials. Models indicate that women with some of these factors may benefit from screening beginning in their 40s. Given the reduction in mortality and years of life extended by screening women starting at age 40, it is appropriate to begin offering screening starting at age 40 using shared decision-making involving a discussion of the anticipated benefits and adverse consequences. Given that the benefit-to-harm ratio improves with age, women who have not chosen to initiate mammography in their 40s should be recommended to do so at age 50.

Estimates for women age 70 and older are limited by the low numbers of older women in the trials. Deaths from all causes are not reduced with screening; while advanced breast cancer is reduced for women age 50 and older, but not younger women. False-positive results are common and are higher with annual screening, for younger women, and for women with dense breasts. Although overdiagnosis, anxiety, pain, and radiation exposure may cause harm, their effects on individual women are difficult to estimate and vary widely. No trials provide information regarding optimal screening intervals. Estimates based on models indicate that biennial screening intervals provide the most benefit while minimizing potential harms. No studies have evaluated the effectiveness of shared decision making in determining whether to undergo mammography screening.

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