



Breast Cancer Screening for Women at Average Risk

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Abstract

Purpose of Review The purpose of this review is to examine the most recent data and guidelines regarding screening for breast cancer in average risk women.

Recent Findings The differing recommendations for screening reflect differences in value judgements between the benefits (decreased cancer-related death and morbidity) and the harms (potential for overdiagnosis, false positives, false negatives, anxiety, and cost of care) of breast cancer screening.

Summary There are multiple organizations with recommendations for breast cancer screening in women at average risk. All organizations recommend mammography to screen for breast cancer but differ in the age at which to initiate mammograms, screening interval, and the age at which to stop screening. The final decision regarding breast cancer screening should be individualized based on the patient's needs and values and include shared decision-making.

Keywords Breast cancer · Screening mammogram · Average risk · Screening guidelines

Introduction

Second only to non-melanoma skin cancer, breast cancer is the most commonly diagnosed malignancy in women and the second most common cause of cancer mortality in women after lung cancer. Based on data published in Cancer Statistics 2019, an estimated 268,600 new cases of breast cancer will be diagnosed in 2019, and an estimated 41,760 deaths will occur in 2019 from breast cancer. These numbers reflect 15.2% of all new cancer cases and represent 6.9% of all cancer deaths. Because of improvements in screening and treatment, the five-year overall survival rate for breast cancer based on SEER data from 2009 to 2015 is 89.9%, improved from the five-year survival rate of 75.3% in 1975. Survival is dependent on stage at the time of diagnosis: patients diagnosed with localized disease having five-year survival rates of 98.8%; patients with regional disease,

as defined by having involvement of regional lymph nodes, having five-year survival rates of 85.5% [1].

Breast cancer is most commonly diagnosed in women between the ages of 55 and 74 (50.4% of all women) with a median age of 62 at the time of diagnosis. Additionally, patients diagnosed at advanced age may be more likely to die from breast cancer than younger women, with 22.9% of breast cancer deaths occurring in women aged 65 to 74 and 36.7% of deaths in women over the age of 75 [2].

The average risk of developing breast cancer is 12.8% [1]. Because the majority of women diagnosed with breast cancer are considered to be at average risk and because of the excellent prognosis of women with localized disease at the time of diagnosis, much focus has been on screening for breast cancer and identifying the optimal screening modality and interval. Screening mammography remains the imaging modality of choice for detecting breast cancer and there are several organizations which outline recommendations for age at which to start screening and time interval at which routine screening should occur (Table 1). Due to differing screening recommendations, patients and providers may be uncertain of the optimal screening schedule, especially for average risk women. We seek to review the evidence regarding screening and outline screening recommendations for women at average risk of developing breast cancer.

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Table 1 Summary of US Society and Expert Recommendations for screening mammography in women at average risk of breast cancer

Group (date)	Screening interval	Initiate at age 40–49	Initiate at age 50	Screen after age 70
American Academy of Family Physicians (2016) [3•]	Biennial	Decision should be based on shared decision-making	Yes	Yes, to age 74
American Cancer Society (2015)[4•]	Annual ages 45–54 Annual or biennial age over 55	Decision should be based on shared decision-making ages 40–44 Yes, age 45 and over	Yes	Yes, if patient is in good health and life expectancy is greater than 10 years
American College of Obstetricians and Gynecologists (2017) [5•]	Annual or biennial, based on shared decision-making	Decision should be based on shared decision-making	Yes	Yes to age 75 and based on shared decision making, general health status and life expectancy
American College of Physicians (2019) [6•, 7•]	Biennial	Decision should be based on shared decision-making	Yes	Yes, to age 74
American College of Radiology (2013) [8•]	Annual	Yes	Yes	Yes, if in good health and would be a candidate for treatment
National Comprehensive Cancer Network (2018) [9•]	Annual	Yes	Yes	Yes
US Preventative Services Task Force (2016) [10]	Biennial	Decision should be based on shared decision-making	Yes	Yes, to age 74

Screening: Benefits and Harms

Screening mammography improves breast cancer mortality [4•, 10–13]. For this reason, organizations that publish screening guidelines recommend routine screening mammography (Table 1). Although some organizations differ with respect to recommendations for the age at which to initiate screening mammography, the interval at which mammograms should be performed, and the age to discontinue screening, each organization recognizes the importance of this life-saving examination. For women at average risk of breast cancer, the debate has centered on whether to start screening mammography at 40, 45, or 50, at what age to stop performing mammograms, and whether to perform screening annually or biennially. All recommendations take into consideration the potential benefits of screening mammography at different ages weighed against the potential harms of this examination.

Potential Benefits of Screening

The ultimate goal for screening mammography is to decrease morbidity and mortality from breast cancer. Numerous randomized controlled trials have investigated the effect of screening mammography on mortality from breast cancer, with the majority finding direct benefit [11–13].

Mammography has been shown to detect smaller breast cancers than clinical breast exam or patient detection, with the median size of masses seen on mammography being 1.0–1.5 cm compared with a median size of 2.0–2.5 cm in self- or physician-detected malignancies [14].

Additionally, there is significant benefit in terms of survival for stage I cancers (< 2 cm without nodal involvement) compared with stage II cancers (2.1–5 cm or 1–3 positive axillary lymph nodes) [1]. This suggests that earlier detection through mammography should have a significant survival benefit.

Several trials have sought to evaluate the effect of mammography on mortality, with wide variation in results. Some of these studies likely underestimate the benefits of screening due to protocol limitations. For example, the Canadian National Breast Screening Study (NBSS) suggested no benefit from screening mammography when compared with clinical breast exam alone [15, 16]. However, there were significant concerns regarding the study design, randomization, and quality of mammography with this study [17, 18]. Despite this, a large meta-analysis of several studies, including NBSS, focused specifically on patients aged 40–49 years old, found that screening mammography reduced deaths from breast cancer by approximately 15%. This reduction was even more dramatic if the NBSS data was excluded, with a mortality reduction of 24% [17, 19].

The United States Preventative Services Task Force (USPSTF) updated their recommendations for mammography in 2009 and again in 2016 taking into account the systematic reviews of eight large randomized clinical trials and data from the Cancer Intervention and Surveillance Modeling Network (CISNET) [10, 20•]. In the USPSTF 2009 recommendations, screening for women aged 40–49 was not recommended, and biennial screening was recommended for women ages 50–74 [20•]. The recommendations against screening women in their 40s was largely due to the number needed to be invited to

screen in order to prevent one breast cancer death being 1,904 women. Not every woman invited to screen actually underwent screening, making the numbers for reduction in rate of death look smaller proportionate to those invited, as opposed to those actually undergoing screening. However, when NBSS data is excluded, this number is much lower at 950 women invited to screen, so the excess of invited women who did not undergo screening is decreased [17, 21]. Consequently, in the 2016 Task Force update, the recommendation for screening women aged 40–49 years old was modified to encourage mutual decision-making [10]. Women who place higher value on the benefits of screening could consider screening mammography on an annual or biennial basis.

Along those same lines, the American College of Obstetrics and Gynecology (ACOG) updated their recommendations in 2017, recommending annual mammography beginning at age 40, following mutual decision making and discussion of risks vs benefits (5*). These recommendations are based upon the same studies but with a different interpretation. They note that although more women require screening to prevent a cancer death in the younger age group, tumors detected in this age group tend to grow faster and be more life threatening [22]. Additionally, when considering life years gained, as opposed to deaths prevented, women in the 40–49 age group benefit the most, with 38 needed to be screened per life year gained [21].

Potential Harms of Screening

The principal potential harms of breast cancer screening are overdiagnosis, false positives, and false negatives. These are often associated with anxiety for the patient and potential cost concerns due to additional testing.

Overdiagnosis is the concept of diagnosing a cancer that would not otherwise have clinical impact on a patient before they would die from other causes, or would be so slow growing that the patient would remain asymptomatic during their lifetime [23]. Overdiagnosis can lead to treatments, including surgery, radiation, chemotherapy, or hormonal therapy, that the patient would not otherwise have needed, which can lead to other secondary morbidities. This concept of overdiagnosis is reported for cancers that are detected at early stage (and thus triggering cancer treatment) unlike screening modalities that detect and prompt treatment of precursor lesions that would later become cancer. Breast cancer is a heterogeneous disease. Although some cancers are indolent, and therefore might not progress or cause symptoms during a patient's remaining lifespan, other cancers progress rapidly and lead to clinically significant disease. It is not possible today, to identify at diagnosis cancers that will progress from those that can be monitored. Because so few women with a newly diagnosed breast cancer choose to forego treatment, we are not able to accurately estimate the true rates of overdiagnosis. For indolent cancers

that would not otherwise spread, screening may have no health benefit and screening could result in harm if there are significant morbidities with the associated treatment [24, 25].

False positive results of screening mammography can result in additional diagnostic imaging and potentially breast biopsies, for what is later found to be benign disease. Additional imaging and biopsies can be uncomfortable for patients. Further, the additional imaging and biopsies for false positive result in an increase in health care costs [26]. Breast biopsies are invasive procedures with a small but real risk of persistent pain, infection, and bleeding. High rates of anxiety are associated with both need for additional diagnostic imaging and breast biopsies [27]. A recent systematic review of studies examining perceived anxiety/distress and pain associated with false positive mammography revealed that many women do experience anxiety and pain with imaging but it is overall brief and has not been shown to be a deterrent for future screening [27].

There are multiple studies and reviews looking at the rates of false positives with screening mammography [13, 27, 28]. For every 1000 women screened, 80–100 are recalled for additional imaging, 15 (1.5%) will undergo biopsy, and 2 to 5 will have cancer [17, 29]. False positive rates are higher in women in their 40s compared with women screened after age 50. In women aged 40 to 49, per 1000 women screened, 124.9 will be recalled for additional imaging. This is compared with 98.5 women recalled for additional imaging for ages 50 to 59, 88.7 in women aged 60–69, and 79.0 in women aged 70–79 [28]. The probability of being given a recommendation for biopsy due to a false positive mammogram result after screening for 10 years has been reported at 7% versus 5% respectively, for annual versus biennial screening for women who initiate screening at 40, and 9% versus 6%, respectively, for annual versus biennial screening for women who initiate at age 50 [27]. Additionally, other risk factors increase the risk of false positive, including having a first-degree relative with breast cancer (women aged 40–49), having heterogeneously dense breast tissue (all age groups except 80–89), and having had a previous benign breast biopsy (women 40–79) [28]. Importantly, some false positives will lead to the diagnosis of high-risk breast lesions, such as atypical hyperplasia or lobular carcinoma in situ, and these lesions do have implications on screening and management.

False negative results occur when a patient undergoes a screening test and is given negative results when in fact a cancer is present. There are two main factors which are felt to contribute to false negative results with screening mammography: breast density and tumor biology. Studies show that increasing breast density is associated with higher rates of false negatives, with women having fat replaced and scattered density on mammogram showing lower rates of false negatives than those with heterogeneously dense or extremely dense tissue [27]. Tumor biology contributes to false negative

results as aggressive cancers may be detected between screening episodes. A small portion of breast cancers with aggressive biology are likely to cause symptoms and be diagnosed clinically within a year after a negative screening mammogram, resulting in the diagnosis of an “interval” cancer, detected between screening intervals.

Breast Cancer Screening and Supplemental Screening Options

Mammography is the standard of care for breast cancer screening. Although recommendations from various entities vary in terms of age of initiation and frequency of screening, traditional full-field 2D mammography remains the screening test of choice in current guidelines [3•, 4•, 5•, 6•, 7•, 8•, 9•, 10].

Screening mammography with tomosynthesis first received FDA approval in 2011. Mammography with tomosynthesis, otherwise known as 3D mammography, differs from traditional mammography in that it includes multiple images taken through the breast. These multiple images are then compiled using computer software to construct a composite image of the breast. Compared with traditional 2D mammography, tomosynthesis increases the yield of detected breast cancers by about 1.2–1.4 per 1000 women screened and decreases recall rate by 16 per 1000 women screened compared with traditional mammography [30]. The largest benefit of 3D tomosynthesis appears to be in women with heterogeneously dense breast tissue, while there was no clear increased benefit in extremely dense tissue [31].

Molecular breast imaging (MBI) is a novel modality of supplemental breast screening [32]. It involves injection of a ^{99m}Tc-sestamibi radiopharmaceutical with images taken in CC and MLO views, similar to traditional mammography. Because of the requirement for specialized equipment and additional training in interpretation of the images, it is not yet widely available. In studies evaluating its efficacy, it does demonstrate a significantly increased cancer detection rate, detecting an additional 8.8 cancers per 1000 exams. The rate of false positive results is elevated, but overall positive predictive value is similar to that of mammography [32].

Whole-breast ultrasound is a widely utilized method for supplemental screening [33]. Screening ultrasound demonstrates an increased cancer detection of approximately 4.4 cancers per 1000 exams [34]. However, the false positive rate is prohibitively high, with a positive predictive value of only 11.2% versus 22.6% with mammogram alone [35]. While this is not desirable, in many centers, it may be the only supplemental screening tool available and given the reduced sensitivity of mammography in very dense breast tissue, whole-breast ultrasound can be considered a supplemental screen.

Breast MRI has the highest sensitivity of available breast screening modalities [34]. However, due to costs and increased potential for false positive test results, breast MRI is

only recommended in the high-risk population, including women with deleterious gene mutations increasing their risk of breast cancer, patients with an estimated lifetime breast cancer risk greater than 20% as calculated from family history–based risk models (i.e. Tyrer-Cuzick), or a personal history of chest radiation prior to the age of 30 [36•].

Emerging Screening Modalities

Contrast-Enhanced Mammography

This technique utilizes iodinated contrast-enhanced recombined images that assess for neovascularity [37]. Images included are those of traditional 2D mammography as well as post-contrast recombined images that show areas of contrast enhancement while ideally subtracting away normal background parenchymal enhancement. Early data suggests that contrast-enhanced mammography (CEM) approaches the sensitivity and specificity of breast MRI, but at approximately one-fourth the cost [37], making it a more viable option for women with dense breast tissue who do not have breast cancer risk greater than 20%, or in women who are at elevated risk but have other contraindications to breast MRI.

Abbreviated Breast MRI

Abbreviated breast MRI is a protocol that is being evaluated throughout Europe and the USA [38, 39]. It includes focused acquisition protocols tailored to evaluate for the presence or absence of breast cancer. With fewer images needed, acquisition time is greatly reduced, as is the radiologist reading time, making it more tolerable to patients and at a lower cost. A prospective proof-of-concept trial performed in Germany and published in 2014, comparing the abbreviated protocol with that of standard breast MRI, demonstrated that the abbreviated protocol produced similar cancer detection rate and diagnostic accuracy [38]. A multi-center trial performed in the USA showed that the sensitivity and specificity of the abbreviated versus full protocols were not significantly different [39]. Though very promising, it is unclear if this modality will be reserved for women with elevated breast cancer risk, or, due to significantly improved cost profile, may be indicated for average risk patient, particularly those with very dense breast tissue.

Shared Decision-Making

The differing recommendations for screening reflect differences in value judgements between the benefits (decreased cancer-related death and morbidity) and the harms (potential for overdiagnosis, false positives, false negatives, anxiety, and cost of care). Women who value the potential benefits for

screening mammography over the value of avoiding the harms may choose to begin screening at the age of 40 and do so annually. They may also choose to continue to screen beyond the age of 75 if their health is good. Women who value avoiding the potential harms more so than the potential benefits may forego screening until the age of 45 or 50 and have screening biennially. They may also choose to stop screening at the age of 75 [40]. As these are highly individualized decisions, we advocate for a shared decision-making process. This involves discussing screening mammography with the patient, including reviewing the potential benefits and harms, to come to a mutual decision based on the patient's goals, judgements, and preferences regarding when to initiate screening and the interval at which to screen.

Conclusion

The goal of any major screening program is early diagnosis which will decrease mortality and morbidity related to treatment without adding significant additional harms. There are multiple organizations with recommendations for breast cancer screening in women at average risk. All organizations recommend mammography to screen for breast cancer but differ in the age at which to initiate mammograms, screening interval and the age at which to stop screening. These differences are based on analyzing and weighing the potential benefits and harms of screening for each age group. The final decision regarding breast cancer screening should be individualized based on the patient's needs and values and include shared decision-making.

Compliance with Ethical Standards

Conflict of Interest Christina Dilaveri, Christine Klassen, Robert Fazio, and Karthik Ghosh declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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