Breast Cancer Screening for Average-Risk Women: Recommendations From the ACR Commission on Breast Imaging

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Abstract

Breast cancer is the most common non-skin cancer and the second leading cause of cancer death for women in the United States. Before the introduction of widespread mammographic screening in the mid-1980s, the death rate from breast cancer in the US had remained unchanged for more than 4 decades. Since 1990, the death rate has declined by at least 38%. Much of this change is attributed to early detection with mammography. ACR breast cancer screening experts have reviewed data from RCTs, observational studies, US screening data, and other peer-reviewed literature to update our recommendations. Mammography screening has consistently been shown to significantly reduce breast cancer mortality over a variety of study designs. The ACR recommends annual mammography screening starting at age 40 for women of average risk of developing breast cancer. Our recommendation is based on maximizing proven benefits, which include a substantial reduction in breast cancer mortality afforded by regular screening and improved treatment options for those diagnosed with breast cancer. The risks associated with mammography screening are also considered to assist women in making an informed choice.

Key Words: Breast cancer screening, mammography screening, breast cancer, mammography, early detection

INTRODUCTION

Breast cancer is the most common non-skin cancer and the second leading cause of cancer death for women in the United States. One in eight women can expect to develop breast cancer over her lifetime. For 2017, we expect approximately 255,180 new invasive breast cancer cases, 63,410 in situ cancers, and 40,610 breast cancer deaths in women nationwide [1].

Before the introduction of widespread mammographic screening in the mid-1980s, the death rate from breast cancer in the United States had remained unchanged for more than 4 decades. Since 1990, the death rate has steadily declined by at least 38% through 2014 [2,3]. Although therapies have improved, screening has had a greater impact on mortality reduction [4-7]. Since our last update [8], advances in mammography have occurred nationally. Digital mammography has virtually replaced film-screen, and digital breast tomosynthesis (DBT) is becoming widely available. Although no new randomized controlled trials (RCT) have been...
reported, there is robust new evidence from observational studies. ACR breast cancer screening experts have reviewed data from RCTs, observational studies, US screening data, and other peer-reviewed literature. Our analysis includes consideration of the ACR Appropriateness Criteria (AC), which use robust strength-of-evidence methodology to create breast cancer screening appropriateness criteria, as accepted by the National Guidelines Clearinghouse [9]. This document involves recommendations for women of average risk for breast cancer. High-risk populations will be considered in a separate report.

MAMMOGRAPHIC SCREENING

For average-risk women, mammography is the main modality for the early detection of breast cancer. The ACR recommends annual mammographic screening starting at age 40. Our recommendation is based on maximizing proven benefits, which include a substantial reduction in breast cancer mortality afforded by regular screening. The risks associated with mammographic screening also are considered to assist women in making an informed choice.

Benefits of Mammographic Screening

Mammographic screening has consistently been shown to reduce breast cancer mortality across a variety of study designs. RCTs, which evaluate the invitation to mammographic screening, provide fundamental proof that early detection significantly reduces deaths from breast cancer for women ages 40 to 74 [10-21]. The RCTs have also shown a reduction in advanced cancers in women invited to screening, which is directly correlated with mortality reduction [22]. Considering all RCTs to date, the relative risk (RR) for breast cancer death is found to be approximately 0.78, or a 22% reduction in breast cancer mortality [22]; however, combining trials obscures the fact that some trials had much better outcomes than others. Trials that reduced advanced disease by at least 20% showed a 28% reduction in mortality with invitation to screening [22]. Although RCTs have proved mortality reduction, they do not give an appropriate estimate of its magnitude [23]. In RCTs, a sizable percentage of invited women decline mammography (noncompliance) yet are counted in the screening cohort, and a sizable percentage of noninvited women undergo screening outside the RCTs (contamination) yet are counted in the control cohort, both of which decrease the magnitude of benefit. RCTs underestimate mortality reduction for several other reasons, including that they began between 26 and 52 years ago, using imaging techniques now considered obsolete [23]. The Edinburgh trial [24] has been dropped from some analyses because of socioeconomic factors. The Canadian National Breast Screening Studies 1 and 2 are outliers as the only studies that failed to show mortality reduction; they are limited by poor-quality mammography [25-27] and randomization problems [28-30] that resulted in a significant excess of advanced cancers allocated to the screening cohort [28,31]. The RCTs were not individually powered for subset analysis, so they should not be used to evaluate efficacy by age groups, and they were not powered to assess the effect of screening on all-cause mortality. However, mammographic screening has been shown to reduce all-cause mortality among women diagnosed with breast cancer [32]. The most recent RCT, the UK Age Trial, proved benefit for women in their 40s [20], disproving the theory of “age creep” and reaffirming that age 50 should not be used as a threshold for initiating screening [33-35].

Given the limitations of RCT data, we place more weight on current and much larger scale observational study data. The EUROSCEEN Group assessed the impact of population-based screening on breast cancer mortality in Europe [36]. They analyzed 20 incidence-based mortality studies in women aged 50 to 69 and reported a 25% mortality reduction (RR, 0.75) among invited women and a 38% mortality reduction (RR, 0.62) among those actually screened. Estimates from case-control studies were a 31% mortality reduction (odds ratio, 0.69) with invitation to screening and a 48% mortality reduction (odds ratio, 0.52) for screened women. These data show that “invitation to screen” is subject to noncompliance and contamination, which results in underestimation of the mortality reduction achieved with actual screening. Furthermore, a meta-analysis of Australian and European case-control studies (age range, 40-75 years) showed that deaths were reduced by 49% in women who underwent mammographic screening [37]. The Pan-Canadian Study of Mammography Screening (1990-2009) included 2.8 million women, more than 4 times the number included in all of the RCTs combined [38]. The mortality reduction among screened women was 40%, with a range across provinces of 27% to 59%. This mortality reduction was consistent across all age
groups, including those 40 to 49 years of age, leading to the conclusion that participation in mammographic screening programs in Canada was associated with substantially reduced breast cancer mortality for all 4 age decades, 40 to 79 years.

The United States lacks such organized screening programs, but there are data available from opportunistic screening. The Cancer Intervention and Surveillance Modeling Network (CISNET) has developed detailed models of breast cancer screening benefits and risks under various screening strategies [39-41]. In both 2009 and 2016, CISNET models from six institutions advised the US Preventive Services Task Force (USPSTF) recommendations on breast cancer screening [42,43].

Mean values across the six CISNET 2009 models showed that mean mortality reduction is greatest with the ACR recommendation of annual screening of women ages 40 to 84 (A40-84; 39.6%), compared with the hybrid American Cancer Society (ACS) recommendation of screening annually from ages 45 to 54, then biennially from ages 55 to 79 (30.8%), and the USPSTF recommendation of biennial screening from ages 50 to 74 (23.2%) (Table 1) [44-46]. A40-84 also yields more breast cancer deaths averted and life years gained (LYGs) per 1,000 women screened, whereas number needed to screen per death averted and per LYG are lower for A40-84 than for the hybrid ACS or USPSTF recommendation (Table 1).

CISNET 2009 estimates of the risks of a lifetime of screening, including benign recalls and benign biopsies, are listed in Table 2 [46]. A metric of benefit versus risk is also listed in Table 2, showing an acceptable ratio of one LYG per benign biopsy performed for ACR-recommended A40-84.

CISNET 2016 modeling ended all screening strategies at age 74 years, so ACR and ACS recommendations were not modeled. Despite absence of modeling ACR and ACS recommendations, CISNET 2016 models consistently demonstrate that the greatest mortality reduction and LYGs are achieved with annual screening of women starting at age 40.

Additional indirect data on mammographic screening in the United States are available. Before the widespread use of mammography in the mid-1980s, the death rate from invasive breast cancer had been unchanged for 50 years [47]. From 1990 to 2014, there was a 38% reduction in breast cancer mortality in the United States [3]. There has been a similar magnitude reduction in advanced cancers in the mammography era [48]. Screening also reduces the size of cancers at diagnosis, which is associated with reduced cancer deaths [22,49,50]. Tumor size and stage remain important determinants of cancer treatment success and long-term survival [5,51].

In addition to mortality reduction and LYGs, other benefits accrue to women who are regularly screened for

### Table 1. Benefits of three recommended screening strategies in terms of percentage mortality reduction, breast cancer deaths averted, LYGs, and NNS to avert one breast cancer death and to gain 1 life year based on mean 2009 Cancer Intervention and Surveillance Modeling Network

<table>
<thead>
<tr>
<th>Screening Strategy</th>
<th>Examinations per 1,000 Women</th>
<th>Percentage Mortality Reduction</th>
<th>BC Deaths Averted per 1,000 Women</th>
<th>LYGs per 1,000 Women Screened</th>
<th>NNS per Death Averted</th>
<th>NNS per LYG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual 40-84 y</td>
<td>36,550</td>
<td>39.6</td>
<td>11.9</td>
<td>189</td>
<td>84</td>
<td>5.3</td>
</tr>
<tr>
<td>Annual 45-54 y, biennial 55-79 y</td>
<td>19,846</td>
<td>30.8</td>
<td>9.25</td>
<td>149</td>
<td>108</td>
<td>6.7</td>
</tr>
<tr>
<td>Biennial 50-74 y</td>
<td>11,066</td>
<td>23.2</td>
<td>6.95</td>
<td>110</td>
<td>144</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Note: Adapted from Arleo et al [46]. BC = breast cancer; LYG = life year gained; NNS = number needed to screen.

### Table 2. Risks of three recommended screening strategies in terms of negative recalls and benign biopsies performed per 1,000 women screened based on mean 2009 Cancer Intervention and Surveillance Modeling Network

<table>
<thead>
<tr>
<th>Screening Strategy</th>
<th>Examinations per 1,000 Women</th>
<th>Negative Recalls per 1,000 Women</th>
<th>Benign Biopsies per 1,000 Women</th>
<th>LYGs per Benign Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual 40-84 y</td>
<td>36,550</td>
<td>2,780</td>
<td>195</td>
<td>1.0</td>
</tr>
<tr>
<td>Annual 45-54 y, biennial 55-79 y</td>
<td>19,846</td>
<td>1,680</td>
<td>116</td>
<td>1.3</td>
</tr>
<tr>
<td>Biennial 50-74 y</td>
<td>11,066</td>
<td>940</td>
<td>96</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Note: The last column shows the estimated ratio of life years gained (LYG) per benign biopsy performed. Adapted from Arleo et al [46].
breast cancer. Screened women diagnosed with breast cancer are more likely to be treated with breast-conserving surgery as opposed to mastectomy and are less likely to be treated with chemotherapy [52-57]. Screening-detected high-risk lesions, such as atypical ductal hyperplasia, allow women to discuss their options with their health care providers; some may benefit from risk-reducing medications or other interventions [58-61]. Similar strategies can be used to reduce cancer recurrence and second primary cancers in women diagnosed with breast cancer [62].

Risks of Mammographic Screening

The risks of screening involve both quantifiable events, such as recall for additional imaging and diagnostic biopsy, and events that cannot be easily quantified, such as anxiety and overdiagnosis.

The most common risk of mammographic screening is recall for additional imaging. The risk for recall for a woman of any age after a single screening mammographic examination ranges from 9.6% to 11.6% [63-66]. The highest estimate of recall, 11.6%, is associated with a cancer detection rate of 5.1 per 1,000, sensitivity of 87%, and specificity of 89% [65]. Low recall rates decrease benign workup and anxiety, but this may not be optimal for cancer detection. Indeed, recall rates of 10% to 14% have been associated with higher cancer detection than recall rates less than 10%, although rates higher than 14% produce diminishing returns [67]. Some organizations’ guidelines cite recall rates cumulatively by decade, giving the risk for at least one recall over 10 years as 61% for annual screening for a woman who begins screening at age 40. Cumulative data, however, also should be considered from the woman’s perspective, showing that on average, a woman undergoing annual screening between the ages of 40 and 49 years would experience a recall for additional imaging once every 12 years [44]. A recommendation for biopsy, the vast majority of which are performed with minimally invasive percutaneous needle biopsy, occurs for fewer than 2% of screened women [68]. For a woman who undergoes annual screening from ages 40 to 49, a benign biopsy will occur once every 149 years; that is, she has a 0.67% chance of undergoing a biopsy each year that she undergoes screening mammography [44]. Benign biopsy is even less frequent for older women. Long-term rates for false-positive events also are lower among women who are regularly screened compared with those who undergo intermittent screening [68].

Anxiety related to mammography, although valid, is subjective and personal. Individual investigations and meta-analyses have failed to produce consensus regarding the extent and value of anxiety in weighted comparisons of risks and benefits. Most describe short-term anxiety without long-term effects [69-79]. Others indicate persistent anxiety [80-83]. Some fail to delineate between anxiety specific to screening mammography and anxiety related to breast cancer. A prospective, test-specific survey found that screening mammography recalls increase short-term general anxiety and intention to participate in future screening without long-term health utility decrements [84]. Screening programs reduce anxiety when they reduce the time between imaging and diagnosis [85,86]. When questioned directly, 86% of women are amenable to recall in exchange for opportunities to detect cancer at earlier presentation [87].

Overdiagnosis is the detection of a cancer at screening that would not have become clinically evident or diagnosed by usual care in a woman’s lifetime absent screening. The pejorative use of “over” in “overdiagnosis” implies excessive or unnecessary diagnosis and suggests that the level of diagnosis among nonscreened women is ideal. However, because screening reduces mortality, the optimal level of diagnosis seems to be at the screening level and not at that of symptomatic disease. Modern medicine deliberately diagnoses and treats many conditions, such as elevated cholesterol and hypertension, before the development of symptoms, with little concern for level of diagnosis [88].

All attempts to measure overdiagnosis are limited [89-91]. The wide range of estimates of frequency, from 0% to 54%, underscores these limitations [48,89-100]. The age of population, lead time, temporal trends in background incidence, risk level of population, and inclusion or exclusion of ductal carcinoma in situ (DCIS) dramatically alter estimates. To the extent that DCIS is an obligatory precursor lesion to invasive cancer, removal of DCIS prevents some invasive cancer [98].

A review of 16 publications by the EUROSCREEN group showed overdiagnosis to range from 0% to 10% (including DCIS) among adequately adjusted studies [89]. The Malmo trial of older women demonstrated a 10% overdiagnosis rate (7% for invasive cancer), whereas the UK Age Trial of younger women estimated a rate of 1% [92,93]. High estimates in the US population using Surveillance, Epidemiology, and End Results data (which are of limited value in estimating overdiagnosis because they are not linked to mammography use) have incorrectly assumed a 0% to
0.25% background incidence change over decades, whereas observed data show a 1% to 1.5% background incidence increase [95,96]. US studies properly adjusted for known background incidence trends show little or no overdiagnosis [48,97,99,100].

Screening is likely associated with the detection of some cancers that would not become apparent in a woman’s lifetime. However, usual care without screening is associated with excess mortality. Given the uncertainty of overdiagnosis estimates, most likely being <10%, the ACR considers proven screening benefits to greatly outweigh the risk for overdiagnosis.

**Age to Initiate Screening**

The ACR recommends starting screening at age 40. There is a sharp increase in breast cancer incidence beginning at age 40. Indeed, cancer incidence more than doubles for women ages 40 to 44 compared with women ages 35 to 39 [91]. The RCT data show benefits starting at age 40, and extensive observational study data confirm this. Hellquist et al [4] performed a contemporaneous comparison of breast cancer mortality in Swedish counties offering mammography versus those not offering mammography from 1986 to 2005 among women ages 40 to 49 years. With an average follow-up duration of 16 years, the estimated RR for women who were invited to screening was 0.74 (26% mortality reduction), and the RR for women who attended screening was 0.71 (29% mortality reduction). The investigators concluded that mammographic screening for women ages 40 to 49 years was efficient for reducing breast cancer mortality. The pan-Canadian study showed that screened women ages 40 to 49 had 44% fewer breast cancer deaths [38]. The US data–based CISNET models consistently show more mortality reduction starting at age 40 than waiting until age 45 or 50. Among all nine age quintiles from ages 40 to 84, the life years lost because of breast cancer diagnosed is third highest for ages 40 to 44 and highest for ages 45 to 49 [91].

**Screening Interval**

The ACR recommends annual mammographic screening. Annual screening affords the greatest mortality reduction for women undergoing regular mammography [44]. This is true up to at least age 84, the age limit for which we have results from CISNET models [39,44]. Compared with biennial screening, annual screening leads to 5,676 more breast cancer deaths averted and 96,252 more LYGs during the lifetime of the single-year cohort of 40-year-old US women born in 1960 and alive in 2000, on the basis of 2009 CISNET models [46]; numbers of similar magnitude are expected for single-year cohorts each year thereafter. The number of interval cancers (cancers that become symptomatic between screenings) increases markedly with biennial screening, with twice the number of interval cancers in the second year of the interval as in the first year [101], pertinent because interval cancers are closely associated with increased breast cancer mortality [102-106]. Cancers detected with biennial screening tend to be larger than with annual screening, which limits treatment options. Annual screening results in more frequent additional testing than biennial screening, but women who want to maximize their mortality benefit, LYGs, and other benefits of screening should choose an annual schedule.

**Age to Stop Screening**

The upper age at which routine screening is no longer indicated has not been established, as women older than 74 years were not included in the RCTs. Recent analysis of screening outcomes as a function of patient age confirms that cancer detection rates and positive predictive value for biopsy are highest and recall rates are lowest in the 70-plus age group, confirming screening efficacy in the elderly [66,107]. Additionally, elderly women who forgo screening are more likely to present with higher stage cancers [108-110] and show reduced survival [110-113]. Because this strongly suggests that the benefits proven for screening up to age 74 continue with advancing age, whereas the risks of screening decrease, the ACR does not recommend stopping screening on the basis of age. Rather, as mortality benefit may not be realized for many years [114] and decreases when associated comorbidities are present [109,112], screening recommendations should be tailored to individual circumstances such as life expectancy, comorbidities, and the intention to seek (and ability to tolerate) treatment if a cancer is detected. If performed, annual screening provides the greatest benefit.

**Other Considerations**

The ACR AC are evidence-based imaging guidelines that follow Protecting Access to Medicare Act development requirements and robust methodology that includes thorough literature search and strength-of-evidence
assessment, expert authorship, and multilevel committee review. The ACR AC for breast cancer screening [115] outline that for average-risk women, mammography and DBT receive the highest rating (“usually appropriate”) and recommend that screening commence at age 40 and proceed annually and that there is no specific upper limit age at which screening should stop. DBT addresses some of the limitations encountered with standard digital mammography. Multiple studies confirm that in the screening setting, cancer detection rates can be increased with use of DBT compared with 2-D mammography alone [116-131]. Additionally, the rate of recall for benign findings (false positives) can be decreased [117-120,123-128,130-134]. Some authors found these advantages to be especially pronounced in women younger than 50 years of age [123,135].

The ACR Practice Parameters are expert-authored policy statements regarding the safe and effective use of imaging. They are based on evidence, expert opinion, and open-forum commentary and undergo an extensive review and approval process across multiple levels of the ACR. The ACR Practice Parameter for the Performance of Screening and Diagnostic Mammography [136] recommends annual screening starting at age 40 for average-risk women and concludes that at this time, there is no specific upper limit age at which screening should stop.

There are insufficient data at this time to support the use of breast MRI as a screening tool for average-risk women. The further development of abbreviated examinations [115,137,138] as well as sensitive and specific noncontrast sequences (eg, diffusion-weighted imaging) may change this approach in the future.

Although supplemental detection of small, node-negative invasive cancers using whole-breast ultrasound screening has been confirmed in patients at elevated risk [139,140], there is insufficient evidence to recommend its use in average-risk patients at this time [115,141]. Investigation of whole-breast ultrasound screening in cohorts whose elevated risk is exclusively [142] or mainly [143,144] attributable to increased breast density do show supplemental cancer detection rates ranging from 1.9 to 7.7 per 1,000. However, this is accompanied by substantially more false-positive examinations and lower positive predictive values for biopsy compared with mammography [142-144].

Molecular breast imaging (MBI) has high sensitivity (95%) and specificity (80%) for the detection of breast cancer, especially in tumors ≥1 cm in size [145]. Its accuracy is not adversely affected by breast density [146]. However, MBI administers radiation to the whole body by virtue of radionuclide biodistribution, mandating careful consideration of dose-related benefit-to-risk ratio, which is shown to be unfavorable for MBI compared with mammography for all age groups and intervals examined [147]. There is insufficient evidence to support the use of MBI for screening of average-risk women [115].

**DISCUSSION**

The ACR recommendation of annual mammographic screening beginning at age 40 is strongly supported by evidence from a variety of sources and seeks to maximize the benefits afforded by regular screening. The most current evidence suggests that a reduction in breast cancer mortality of approximately 40% can be achieved among women who undergo regular mammography [22,38]. The risks of screening are important and should be conveyed to women as they consider their options. The most common risk is recall for additional imaging, usually for additional mammography or ultrasound. In the United States, biopsy is recommended in fewer than 2% of screening examinations, almost all with minimally invasive technique. Women should be able to decide for themselves if these risks are worth the opportunity to reduce their chance of dying from breast cancer and to find those cancers as early as possible. Mammography is not perfect, as some cancers are not detected at screening. Image-based screening is, however, the only way to find tumors before they are detectable clinically.

ACR recommendations are similar to those of other national societies, notably the American Congress of Obstetricians and Gynecologists, the National Comprehensive Cancer Network, and the Society of Breast Imaging [148-150]. Although the ACR, ACS, and USPSTF agree that screening reduces breast cancer mortality beginning at age 40, both the ACS and USPSTF find the balance of benefits to risks to be low in younger women [43,91]. However, both the ACS and USPSTF guidelines consider only one benefit, mortality reduction, in their assessment and ignore the other benefits of screening. The incidence of breast cancer doubles for women ages 40 to 44 compared with women ages 35 to 39; among all nine age quintiles from ages 40 to 84, the life years lost because of breast cancer diagnosed at ages 40 to 44 is third highest [91]. The ACR considers unacceptable the years of life that would be lost by waiting to start screening until age 45 or 50.
The USPSTF suggests that starting screening at age 50 and screening biennially instead of annually will decrease overdiagnosis. Neither approach will decrease the frequency of overdiagnosis. All “overdiagnosed” cancers are assessed as suspicious at screening, just as are all lethal cancers. Screen-detected cancers do not disappear spontaneously without excision or treatment [151]. Those that are overdiagnosed will remain visible and suspicious if screening starts after age 40 or biennially, hence overdiagnosis is simply delayed, not reduced in frequency with later initiation or less frequent screening [151]. Overdiagnosis should not be a factor in deciding when to start screening or what screening interval to choose.

The ACR, like most other national organizations, does not pretend to understand how women would, or should, balance mortality reduction, LYGs, other benefits of screening (less aggressive surgery, less frequent and less toxic chemotherapy), and risks such as recall, biopsy, anxiety, and overdiagnosis. This balance reflects a value judgement rather than scientific calculation. Weighing benefits and risks should be done by women, not for women, after counseling about the benefits and risks. Women who prefer to maximize the benefits should choose annual screening starting at age 40.

TAKE-HOME POINTS

- Regular mammographic screening results in a substantial reduction in breast cancer mortality across multiple study designs.
- The ACR recommends annual mammographic screening beginning at age 40 for women at average risk for developing breast cancer.
- The age to stop screening should be based on each woman’s health status rather than an age-based determination.
- These ACR recommendations allow women to obtain the maximum life-extending benefits and provide improved treatment options for those diagnosed with breast cancer.
- Women should be helped to understand the risks of screening; weighing benefits and risks should be done by women, not for women.
- Overdiagnosis should not be factor in deciding when to start screening or what screening interval to choose.

ADDITIONAL RESOURCES

References can be found online at: http://dx.doi.org/10.1016/j.jacr.2017.06.001.