

Special Communication | October 20, 2015

# Breast Cancer Screening for Women at Average Risk

## 2015 Guideline Update From the American Cancer Society

FREE

Kevin C. Oeffinger, MD<sup>1</sup>; Elizabeth T. H. Fontham, MPH, DrPH<sup>2</sup>; Ruth Etzioni, PhD<sup>3</sup>; Abbe Herzig, PhD<sup>4</sup>; James S. Michaelson, PhD<sup>5</sup>; Ya-Chen Tina Shih, PhD<sup>6</sup>; Louise C. Walter, MD<sup>7</sup>; Timothy R. Church, PhD<sup>8</sup>; Christopher R. Flowers, MD, MS<sup>9</sup>; Samuel J. LaMonte, MD<sup>10</sup>; Andrew M. D. Wolf, MD<sup>11</sup>; Carol DeSantis, MPH<sup>12</sup>; Joannie Lortet-Tieulent, MSc<sup>12</sup>; Kimberly Andrews<sup>12</sup>; Deana Manassaram-Baptiste, PhD<sup>12</sup>; Debbie Saslow, PhD<sup>12</sup>; Robert A. Smith, PhD<sup>12</sup>; Otis W. Brawley, MD<sup>12</sup>; Richard Wender, MD<sup>12</sup>

<sup>1</sup>Memorial Sloan Kettering Cancer Center, New York, New York

<sup>2</sup>Louisiana State University School of Public Health, New Orleans

<sup>3</sup>University of Washington and the Fred Hutchinson Cancer Research Center, Seattle

<sup>4</sup>Patient advocate, Troy, New York

<sup>5</sup>Massachusetts General Hospital and Harvard Medical School, Boston

<sup>6</sup>University of Texas MD Anderson Cancer Center, Houston

<sup>7</sup>University of California, San Francisco, and San Francisco VA Medical Center

<sup>8</sup>Masonic Cancer Center and the University of Minnesota, Minneapolis

<sup>9</sup>Emory University School of Medicine and Winship Cancer Institute, Atlanta, Georgia

<sup>10</sup>Independent retired physician and patient advocate

<sup>11</sup>University of Virginia School of Medicine, Charlottesville

<sup>12</sup>American Cancer Society, Atlanta, Georgia

*JAMA*. 2015;314(15):1599-1614. doi:10.1001/jama.2015.12783.

## ABSTRACT

**Importance** Breast cancer is a leading cause of premature mortality among US women. Early detection has been shown to be associated with reduced breast cancer morbidity and mortality.

**Objective** To update the American Cancer Society (ACS) 2003 breast cancer screening guideline for women at average risk for breast cancer.

**Process** The ACS commissioned a systematic evidence review of the breast cancer screening literature to inform the update and a supplemental analysis of mammography registry data to address questions related to the screening interval. Formulation of recommendations was based on the quality of the evidence and judgment (incorporating values and preferences) about the balance of benefits and harms.

**Evidence Synthesis** Screening mammography in women aged 40 to 69 years is associated with a reduction in breast cancer deaths across a range of study designs, and inferential evidence supports breast cancer screening for women 70 years and older who are in good health. Estimates of the cumulative lifetime risk of false-positive examination results are greater if screening begins at younger ages because of the greater number of mammograms, as well as the higher recall rate in younger women. The quality of the evidence for overdiagnosis is not sufficient to estimate a lifetime risk with confidence. Analysis examining the screening interval demonstrates more favorable tumor characteristics when premenopausal women are screened annually vs biennially. Evidence does not support routine clinical breast examination as a screening method for women at average risk.

**Recommendations** The ACS recommends that women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years (strong recommendation). Women aged 45 to 54 years should be screened annually (qualified recommendation). Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually (qualified recommendation). Women should have the opportunity to begin annual screening between the ages of 40 and 44 years (qualified recommendation). Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer (qualified recommendation). The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age (qualified recommendation).

**Conclusions and Relevance** These updated ACS guidelines provide evidence-based recommendations for breast cancer screening for women at average risk of breast cancer. These recommendations should be considered by physicians and women in discussions about breast cancer screening.

## INTRODUCTION

Breast cancer is the most common cancer in women worldwide.<sup>1</sup> In the United States, an estimated 231 840 women will be diagnosed with breast cancer in 2015.<sup>2</sup> Breast cancer continues to rank second, after lung cancer, as a cause of cancer death in women in the United States, and it is a leading cause of premature mortality for women. In 2012, deaths from breast cancer accounted for 783 000 years of potential life lost and an average of 19 years of life lost per death.<sup>3</sup> Even though mortality from breast cancer has declined steadily since 1990, largely due to improvements in early detection and treatment,<sup>4</sup> an estimated 40 290 women in the United States will die of breast cancer in 2015.<sup>2</sup>

Since the last ACS breast cancer screening update for average-risk women was published in 2003,<sup>5</sup> new evidence has accumulated from long-term follow-up of the randomized controlled trials (RCTs) and observational studies of organized, population-based screening (service screening) programs. In addition, there is now greater emphasis on estimating harms associated with screening; assessing the balance of benefits and harms; and supporting the interplay among values, preferences, informed decision making, and recommendations. In 2011, the ACS incorporated standards recommended by the Institute of Medicine<sup>6,7</sup> into its guidelines development protocol to ensure a more trustworthy, transparent, and consistent process for developing and communicating guidelines.<sup>8</sup>

## THE PROCESS

In accordance with the new guideline development process, the ACS organized an interdisciplinary guideline development group (GDG) consisting of clinicians (n = 4), biostatisticians (n = 2), epidemiologists (n = 2), an

economist (n = 1), and patient representatives (n = 2). The GDG developed 5 key questions using the general approach of specifying populations, interventions, comparisons, outcomes, timing of outcomes, and settings (PICOTS) for each question.<sup>9</sup> After evaluating available methods to grade the evidence and the strength of recommendations, the GDG selected the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. GRADE is an accepted approach with a defined analytic framework, an explicit consideration of values and preferences in addressing patient-centered outcomes, the capacity for flexibility in evaluating results from observational studies, and separation between quality of evidence and strength of recommendation.<sup>10,11</sup>

The ACS GDG selected the Duke University Evidence Synthesis Group to conduct an independent systematic evidence review of the breast cancer screening literature, after a response to a request for proposals. This effort is referred to as the evidence review. In addition, the ACS commissioned the Breast Cancer Surveillance Consortium (BCSC) to update previously published analyses related to the screening interval and outcomes. The ACS Surveillance and Health Services Research Program provided supplementary data on disease burden using data from the Surveillance, Epidemiology, and End Results (SEER) Program.<sup>3</sup>

The GDG deliberations on the evidence and framing of the recommendations were guided by the GRADE domains: the balance between desirable and undesirable outcomes, the diversity in women's values and preferences, and confidence in the magnitude of the effects on outcomes.<sup>12,13</sup> The GDG chose to assess recommendations as "strong" or "qualified," in accordance with GRADE guidance.<sup>13</sup> A strong recommendation conveys the consensus that the benefits of adherence to the intervention outweigh the undesirable effects. Qualified recommendations indicate there is clear evidence of benefit but less certainty about either the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions (Table 1).

**Table 1.** Interpretation of Strong and Qualified Recommendations by Users of the Guideline<sup>a</sup>

[View Large](#) | [Save Table](#) | [Download Slide \(.ppt\)](#) | [View in Article Context](#)

The GDG members voted on agreement or disagreement with each recommendation and on the strength of recommendation. A record of the vote with respect to each question was made without attribution. The panel attempted to achieve 100% agreement whenever possible, but a three-quarters majority was considered acceptable (see eMethods in the Supplement).

Prior to submitting the final guideline for publication, 26 relevant outside organizations and 22 expert advisors were invited to participate in an external review of the guideline. Responses were documented and reviewed by the GDG to determine if modifications in the narrative or recommendations were warranted. Details of the guideline development process are provided in the eMethods in the Supplement.

All participants in the guideline development process were required to disclose all financial and nonfinancial (personal, intellectual, practice-related) relationships and activities that might be perceived as posing a conflict of interest in development of the breast cancer screening guidelines. The chairpersons of the ACS GDG had the responsibility to ensure balanced perspectives were considered in deliberations and decision making. In addition to the disclosures listed in the Article Information section, nonfinancial disclosures of the authors are reported in the eMethods in the Supplement.

This evidence-based breast cancer screening guideline for women at average risk focuses on 3 key questions of the 5 original key questions (Box 1).

### **Box 1. Key Questions (KQs) Guiding the Evidence Review**

#### **Key Questions Addressed in This Guideline Update**

**KQ 1:** What are the relative benefits, limitations, and harms associated with mammography screening compared with no screening among

average-risk women 40 years and older, and how do they vary by age, screening interval, and prior screening history?

**KQ 2:** Among average-risk women who are screened with mammography, what are the relative benefits, limitations, and harms associated with annual, biennial, triennial, or other screening interval, and how do they vary by age?

**KQ 3:** What are the benefits, limitations, and harms associated with clinical breast examination (CBE) among average-risk women 20 years and older compared with no CBE, and how do they vary by age, interval, and participation rates in mammography screening?

### Other Key Questions

**KQ 4a:** Among women with an increased risk of breast cancer due to factors known prior to the onset of screening (eg, family history, *BRCA* mutation carrier, history of chest irradiation), what are the relative benefits, limitations, and harms associated with different screening modalities compared with no screening (ie, what ages to start and stop screening) and compared with each other?

**KQ 4b:** Among women with an increased risk of breast cancer due to factors identified as the result of screening or diagnosis (eg, prior diagnosis of proliferative lesions), what are the benefits, limitations, and harms associated with different screening modalities compared with no screening and compared with each other?

**KQ 5a:** Among women with an increased risk of breast cancer due to factors known prior to the onset of screening (eg, family history, *BRCA* mutation carrier, history of chest irradiation), what are the relative benefits, limitations, and harms associated with different screening modalities at different intervals, and how do these vary by age?

**KQ 5b:** Among women with an increased risk of breast cancer due to factors identified as the result of screening or diagnosis (eg, prior diagnosis of proliferative lesions), what are the benefits, limitations,

and harms associated with different screening modalities at different intervals, and how do these vary by age?

1. What are the relative benefits, limitations, and harms associated with mammography screening compared with no screening in average-risk women 40 years and older, and how do they vary by age, screening interval, and prior screening history?
2. Among average-risk women who are screened with mammography, what are the relative benefits, limitations, and harms associated with annual, biennial, triennial, or other screening interval, and how do they vary by age?
3. What are the benefits, limitations, and harms associated with clinical breast examination (CBE) among average-risk women 20 years and older compared with no CBE, and how do they vary by age, interval, and participation rates in mammography screening?

For purposes of the evidence review, the GDG considered average risk broadly: ie, women without a personal history of breast cancer, a confirmed or suspected genetic mutation known to increase risk of breast cancer (eg, *BRCA*), or a history of previous radiotherapy to the chest at a young age. Women in these risk categories constitute a small percentage of all women. In 2014, there were an estimated 3 088 180 female survivors of invasive breast cancer 40 years and older, approximately 4% of the total population<sup>14</sup>; a 2005 prevalence estimate of those having received a diagnosis of in situ breast cancer was 570 403, expected to increase to more than 1 million by 2016<sup>15</sup>; 0.2% to 0.3% of the general population and 2% of Ashkenazi Jewish women are estimated to be carriers of the *BRCA1* or *BRCA2* mutation,<sup>16</sup> and overall 5.8% of mammography screening–age women have a 20% or greater lifetime risk of breast cancer based on risk assessment with specialty software, largely dependent on family history.<sup>17</sup>; and in 2010, it was estimated that there were 50 000 to 55 000 women in the United States who had been treated with moderate- to high-dose chest radiation for pediatric

and young adult cancers.<sup>18</sup> There also are women outside of these risk categories who are still at higher than average risk of breast cancer and for whom mammography alone may be less effective, including women with significant family histories but who do not have a high probability of being carriers of identified mutations,<sup>19</sup> women with a prior diagnosis of benign proliferative breast disease,<sup>20</sup> and women with significant mammographic breast density.<sup>21</sup> At this time, there are no reliable estimates of the number of women who have 1 or more of these risk factors; nor are there widely accepted risk-based screening recommendations that differ for women in this intermediate-risk group compared with average-risk women.

In 2007, the ACS provided recommendations for breast magnetic resonance imaging (MRI) screening as an adjunct to mammography for women at high risk, based on a genetic mutation known to increase risk of breast cancer, a history of radiation to the chest at ages 10 to 30 years, or an estimated lifetime risk of approximately 20% to 25% or greater, as defined by risk assessment models largely dependent on family history.<sup>22</sup> At that time, the ACS concluded that the evidence was insufficient to recommend for or against MRI screening for women in other categories of increased risk but recommended against use of MRI screening among women with less than a 15% lifetime risk.<sup>22</sup> Two additional key questions that focused on screening outcomes in women at high risk of breast cancer were considered in our evidence review.<sup>23</sup> Following the publication of this update of recommendations for women in this broad category of average risk, the ACS plans to review this and additional evidence on factors associated with increased risk (including breast density) and screening outcomes and update its screening recommendations for women at increased and high risk.

The GDG, in consultation with a group of expert advisers (n = 22), worked with the evidence review group to develop the research plan. It was agreed that new meta-analyses of the RCTs would not be useful. Recent meta-analyses results could be used to estimate efficacy associated with screening but not to estimate effectiveness, due to variable rates of exposure to mammography within and across the individual studies, as well as other study differences that influenced outcomes. The GDG considered that it was



preferable to estimate benefits and harms of screening using contemporary data from which exposure to screening can be ascertained; observational studies, especially population-based studies of service screening derived from large national databases, were included. While concerns about the limitations of observational studies are well established, in the case of breast cancer screening, well-designed observational studies produce results that are qualitatively consistent with the majority of the RCTs.<sup>24</sup> Once the research plan was finalized, the evidence review group had full responsibility for the literature search strategy, interpretation, and grading of the evidence. Studies were included in the evidence synthesis if they met the following inclusion criteria:

- Controlled studies, including RCTs, pooled patient-level meta-analyses, systematic reviews, and study-level meta-analyses.
- Observational studies (prospective and retrospective cohort studies, incidence-based mortality studies, case-control studies, or cross-sectional studies) published since 2000 that included 1000 or more average-risk women.
- Modeling/simulation studies, because these studies may be the only way to generate estimates of long-term outcomes associated with screening that are not adequately addressed by the RCTs or using modern technology and protocols.

Critical and important outcomes considered in the review are provided in Table 2 and include the following: breast cancer mortality, quality of life, life expectancy, false-positive test results, overdiagnosis, and overtreatment. Other outcomes, such as morbidity related to treatment of breast cancer and radiation exposure from mammography, were considered but not included in the evidence review.

**Table 2.** Critical and Important Outcomes of Screening Mammography and Clinical Breast Examination (CBE) in the Systematic Evidence Review

**Table 2. Critical and Important Outcomes of Screening Mammography and Clinical Breast Examination (CBE) in the Systematic Evidence Review**

Definition	
<b>Critical Outcomes</b>	
Breast cancer mortality	Breast cancer deaths prevented by screening
Quality of life	Quality-adjusted life-years gained by screening
Life expectancy	Life-years gained by screening
False-positive findings	Recall for additional testing (imaging and/or biopsy) after abnormal CBE or mammography, in which further evaluation determines that the initial abnormal finding was not cancer
Overdiagnosis	Screen-detected cancers that would not have led to symptomatic breast cancer if undetected by screening
Overreatment	Cancer therapies (surgery, radiation, chemotherapy) performed for screen-detected cancers that would not have led to symptomatic breast cancer if undetected by screening
<b>Important but Not Critical Outcomes</b>	
Breast cancer stage	Tumor characteristics at diagnosis (including stage, tumor size, and nodal status)
Short- and long-term emotional effects	Anxiety, depression, quality of life associated with positive results (ie, true and false positives)

[View Large](#) | [Save Table](#) | [Download Slide \(.ppt\)](#) | [View in Article Context](#)

For each outcome considered for every key question, the strength of the overall body of evidence across all included study designs was rated, with consideration of risk of bias, consistency, directness, and precision, as well as strength of association (magnitude of effect). Results from meta-analyses were used when evaluating consistency, precision, and strength of association. The evidence summary and a detailed description of the evidence review methodology are published concurrently with this guideline.<sup>25</sup>

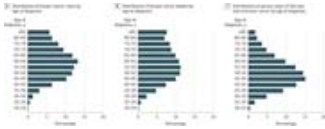
In addition to the evidence review, the ACS commissioned the BCSC to update previously published analyses<sup>26</sup> on the association between mammography screening intervals and tumor characteristics at diagnosis by age, menopausal status, and postmenopausal hormone use, to measure the outcomes related to screening intervals closer to 12 and 24 months instead of the wider intervals used as proxies for annual and biennial screening published in previous analyses.<sup>26</sup>

An initial consideration in the decision to offer screening to the population is the burden of disease overall and in age-specific subgroups.<sup>27</sup> To address the question of age to begin and to stop screening, the GDG examined a range of indicators, including age-specific incidence, mortality, age-specific incidence-based mortality, and years of potential life lost (Figure 1).<sup>3,28</sup>

## Figure 1.

### Breast Cancer Burden by Age at Diagnosis for the Period 2007-2011

A, Age distribution of invasive female breast cancer cases (n = 292 369). Source: Surveillance, Epidemiology, and End Results (SEER) 18 registries. B, Distribution of breast cancer deaths by age at diagnosis (n = 16 789), with patients followed up for 20 years after diagnosis. Source: SEER 9 registries. C, Distribution of person-years of life lost (PYLL) due to breast cancer by age at diagnosis (total = 326 560), with patients followed up for 20 years after diagnosis. Source: SEER 9 registries. The PYLL is based on the 2011 US Female Life Table.<sup>28</sup>



[View Large](#) | [Save Figure](#) | [Download Slide \(.ppt\)](#) | [View in Article Context](#)

## RESULTS (RECOMMENDATIONS)

These recommendations are based on the GDG's consensus judgment about when the benefits of mammography screening clearly or likely outweigh the harms in a population of women at average risk. Recognizing that individual values and preferences can lead to different decisions about the age to start and stop screening and screening intervals, some recommendations were graded as qualified to allow for informed decision making about options (Box 2).

### Box 2. American Cancer Society Guideline for Breast Cancer Screening, 2015

These recommendations represent guidance from the American Cancer Society (ACS) for women at average risk of breast cancer: women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (eg, *BRCA*), or a history of previous radiotherapy to the chest at a young age.

The ACS recommends that all women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.

#### Recommendationsa

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. (*Strong Recommendation*)

1a. Women aged 45 to 54 years should be screened annually. *(Qualified Recommendation)*

1b. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. *(Qualified Recommendation)*

1c. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. *(Qualified Recommendation)*

2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. *(Qualified Recommendation)*

3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. *(Qualified Recommendation)*

<sup>a</sup>A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions about screening.<sup>12,13</sup>

Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. *(Strong Recommendation)*

Recommendation 1a: Women aged 45 to 54 years should be screened annually. *(Qualified Recommendation)*

Recommendation 1b: Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. *(Qualified Recommendation)*

Recommendation 1c: Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. (*Qualified Recommendation*)

Various key topics were considered by the GDG in making these recommendations, beginning with the results of the evidence review regarding the benefits and harms associated with regular screening mammography. To determine the age to begin screening, the GDG reviewed the burden of disease across age groups while considering the harm-benefit trade-off for each age group. In addition, when developing the recommendations for interval of screening, the GDG evaluated the findings of the BCSC analysis in addition to the results of the evidence review.

The evidence review considered 5 critical outcomes of screening mammography: breast cancer mortality, life expectancy, false-positive findings, overdiagnosis, and quality-adjusted life expectancy.

Mammography screening has been shown to be associated with a reduction in breast cancer mortality across a range of study designs, including RCTs and observational studies (trend analyses, cohort studies, and case-control studies), with most studies demonstrating a significant benefit (Table 3).<sup>4,29,30</sup> The strength of the evidence that invitation or exposure to mammography screening compared with usual care or no screening was associated with reduced breast cancer mortality was judged to be high in the evidence review, although effect sizes differed depending on a range of factors, including the study design, protocol, population undergoing screening, and duration of follow-up.

**Table 3.** Estimated Relative Reduction in Breast Cancer Mortality Associated With Mammography Screening, by Study Design Among Pooled Studies

Study Design	Relative Risk Reduction	95% CI
Randomized Controlled Trial	10.0%	7.0% to 13.0%
Cohort Study	15.0%	10.0% to 20.0%
Case-Control Study	20.0%	15.0% to 25.0%
Trend Analysis	25.0%	20.0% to 30.0%
Overall Pooled	15.0%	10.0% to 20.0%

[View Large](#) | [Save Table](#) | [Download Slide \(.ppt\)](#) | [View in Article Context](#)

Pooled estimates for relative breast cancer mortality reductions after approximately 13 years of follow-up were similar for 2 meta-analyses of RCTs using random-effects models (UK Independent Panel,<sup>31</sup> relative risk [RR], 0.80; 95% CI, 0.73-0.89; and Canadian Task Force,<sup>32</sup> RR, 0.82; 95% CI, 0.74-0.94) and for the Cochrane analysis,<sup>30</sup> which used a fixed-effects model (RR, 0.81; 95% CI, 0.74-0.87).

Pooled effects from trend studies comparing mortality rates before and after the introduction of a screening program have reported a range of risk reductions of 28% to 36%.<sup>29</sup> In incidence-based mortality studies, the pooled mortality reduction was 25% (RR, 0.75; 95% CI, 0.69-0.81) among women invited to screening and 38% (RR, 0.62; 95% CI, 0.56-0.69) among those attending screening.<sup>29</sup> The corresponding pooled estimates from case-control studies were 31% (OR, 0.69; 95% CI, 0.57-0.83), and 48% (OR, 0.52; 95% CI, 0.42-0.65) after adjustment for self-selection.<sup>29</sup>

The magnitude of these estimates was influenced by a number of factors, including whether the estimate was based on invitation to screening or exposure to screening and the degree of heterogeneity of individual studies in meta-analyses or pooled observational study results. The analyses of RCTs follow the principle of intention-to-treat to reduce known and unknown biases. Observational studies may be evaluated by either invitation to screening or exposure to screening with appropriate adjustment for known biases. Although RCTs are the foundation of the supporting evidence for mammography screening, the GDG also concluded that contemporary, large well-designed observational studies provided valuable information on the effectiveness associated with modern mammography.

In contrast to RRs, estimates of absolute benefit, measured by the number needed to invite (NNI) or the number needed to screen (NNS) to prevent 1 death are increasingly relied on as meaningful measures of benefit. The magnitude of the absolute benefit in the published literature is influenced by the RR, duration of follow-up, underlying mortality risk in the population from which the estimate is derived, and whether the estimate is the NNI or the NNS. Although NNI can be estimated from RCTs or observational studies, it is not a very useful indicator because this estimate will be inflated by deaths

among women invited to screening who never attended screening.<sup>33</sup> However, use of either NNI or NNS and other model inputs have resulted in quite disparate estimates of absolute benefit. For example, the Cochrane Systematic Review estimated that 2000 women would need to be invited to screening and followed up for mortality over a 10-year period to prevent 1 breast cancer death.<sup>30</sup> The UK Independent Review estimated that 180 women needed to be screened over a 20-year period beginning at age 50 years, with follow-up to age 79 years, to prevent 1 breast cancer death.<sup>31</sup> The main distinction between the Cochrane Systematic Review<sup>30</sup> and UK Independent Review<sup>31</sup> estimates is that the former was based on a less favorable mortality reduction (RR, 0.85 vs 0.80) over a shorter duration of the screening program (10 years vs 20 years), use of NNI, and a follow-up period that is contemporaneous with and limited to the period of the screening program.

As shown by Duffy et al,<sup>34</sup> when widely different estimates of absolute benefit are standardized to a common RR, number of screening rounds, and duration of follow-up, and then applied to a standard population and baseline risk (specifically, in this example, the UK Independent Review scenario described above),<sup>31</sup> to estimate the NNS, a nearly 20-fold difference (from 111 to 2000) found in 4 well-known estimates<sup>29-31,35</sup> of the NNS/NNI to prevent 1 breast cancer death was reduced to a range of 96 to 257 women screened to prevent 1 breast cancer death.<sup>34</sup> The importance of long-term follow-up in estimating the NNS is evident in the 29-year follow-up of the Swedish Two County Trial, in which the investigators observed that 922 women aged 40 to 74 years needed to be screened 2 to 3 times over a 7-year period to prevent 1 breast cancer death at 10 years of follow-up, which decreased to 464 women at 20 years of follow-up, and to 414 women at 29 years of follow-up.<sup>36</sup>

To assess the absolute benefits of screening over a 15-year time period, the evidence review group used the prevalence of screening every 2 years of 65% (derived from the National Health Interview Survey) and incidence-based mortality from SEER to estimate the NNS to prevent 1 breast cancer death based on different relative mortality reductions. For women aged 40 to

49 years, the NNS ranged from 753 with a 40% mortality reduction to 1770 with a 20% mortality reduction. For women aged 50 to 59 years, the NNS ranged from 462 with a 40% mortality reduction to 1087 with a 20% mortality reduction. For women aged 60 to 69 years, the NNS ranged from 355 with a 40% mortality reduction to 835 with a 20% mortality reduction.<sup>25</sup> As in other estimates of the NNI vs NNS, absolute benefit is more favorable when based on exposure to screening and is increasingly more favorable as disease prevalence increases. The estimates presented also would be more favorable if follow-up were projected to 25 years or longer.

The evidence review judged the quality of the evidence as high that reducing breast cancer mortality through mammographic screening should increase life expectancy. However, based on considerable uncertainty about several parameters important for estimating these gains (in particular, the magnitude of mortality reduction associated with screening at different ages and intervals), the quality of evidence for the magnitude of the strength of the association between screening and life expectancy was considered to be low. Estimates of life expectancy gains are by definition indirect and, when expressed across the entire population, have limited meaning when considered outside of the context of other interventions. In contrast, gains in life expectancy for individual women who avoid a premature death from breast cancer can be significant, given that the average and total years of life lost are greater for breast compared with other high-prevalence cancers affecting women.<sup>3</sup>

False-positive findings are common in breast cancer screening. The most common outcome of a false-positive finding is being recalled for additional imaging. A smaller percentage of women who are recalled go on to biopsy, and a majority of these women will have benign findings. In weighing harm, the GDG placed greater emphasis on false positives leading to a biopsy.

Hubbard et al<sup>37</sup> reported that among women in the BCSC who initiated screening at age 40 years and had undergone either screen-film or digital mammography, the unadjusted cumulative probability of at least 1 false-positive recall after 10 years of screening was 61.3% with annual and 41.6% with biennial screening. The 10-year cumulative probability of a false-positive



mammogram leading to a biopsy recommendation within the same cohort was 7.0% with annual and 4.8% with biennial screening. Thus, screening every 2 years rather than every year reduced the cumulative incidence of at least 1 false-positive recall and false-positive biopsy by about 32% and 31%, respectively.<sup>37,38</sup> A number of factors appear to be associated with an increased likelihood of false-positive results, including the first mammogram, greater mammographic breast density, use of postmenopausal hormone therapy, use of digital vs screen-film mammography, longer time intervals between screening, and lack of comparison mammography images (from previous examination), suggesting some clear opportunities to reduce the harms associated with false-positive findings.<sup>37,38</sup>

An overdiagnosed cancer is a screen-detected cancer that would not have led to symptomatic breast cancer if undetected by screening. Most published studies of overdiagnosis base their estimates on empirical comparisons of disease incidence under screening with observed or projected incidence in the absence of screening. However, estimates available from the literature vary widely, from less than 5%<sup>39-42</sup> to more than 50%.<sup>43,44</sup> Estimates of overdiagnosis produced from modeling studies generally are lower than those from empirical studies.<sup>41,45</sup> While modeling studies extrapolate beyond the empirical data to simulate disease natural history and derive estimates of overdiagnosis based on a comparison of the estimated risks of clinical diagnosis and other-cause death, these studies require their own assumptions pertaining to the times to key events. Regardless of the study design, practically all estimates require unverifiable assumptions or use methods that are biased by inadequate follow-up or failure to properly adjust for trends in incidence and lead time, leading to inflated estimates.<sup>42,46-50</sup> No published study directly provides reliable, policy-relevant measurements of overdiagnosis, although lower estimates of the fraction of cancers that were overdiagnosed tended to be based on studies that included adequate follow-up, had a control group or data on the incidence expected in the absence of screening, and properly adjusted for lead time as well as age and other potential confounders.<sup>42</sup>

The quality of evidence that overdiagnosis is a consequence of mammographic screening was judged to be high in the evidence review, but given the very wide range of estimates, the quality of the evidence for a quantitative estimate of the magnitude of overdiagnosis was judged to be low. While the GDG recognizes that overdiagnosis represents the greatest possible harm associated with screening because it would result in overtreatment, uncertainty about the magnitude of the risk of overdiagnosis poses a challenge to providing complete and accurate information to women about what to expect from breast cancer screening.

There are no clinical trials or observational studies that assess the effect of breast cancer screening on women's quality-adjusted life-years (QALYs) throughout the lifetime; all information available in the literature was based on modeling studies.<sup>51-58</sup> Most of these studies showed that compared with no screening, mammography screening was associated with a modest increase in QALY, although the magnitude of increase varied by screening intervals, the starting and stopping age of screening, and most importantly whether the model incorporated decrements in health utilities associated with mammography screening. The quality of evidence on QALY was subject to the limitations common to all modeling studies and to the quality of data used for modeling parameters related to health utilities, especially those capturing the negative effect of screening, which commonly rely on a single study<sup>59</sup> published in 1991 that was limited by a small sample size and outdated mammography technology. Although a recent study has collected more contemporary health utility information on false positives among women in the United States,<sup>60</sup> it did not explore the duration applicable to screening-related short-term reduction in health utilities, nor did it differentiate between women who underwent biopsy vs those who had repeat examinations. Thus, in the evidence review, the quality of evidence for the magnitude of the effect of different screening strategies on QALY was judged to be low.

To determine the age at which to recommend the initiation of screening, the burden of disease was examined by 5-year age categories, in addition to the evidence of benefits and harms within the age categories. The incidence of breast cancer noticeably begins to increase after age 25 years and continues

to increase until ages 75 to 79 years (Table 4). Historically, the age to begin screening has been influenced by the majority of RCT designs, which included women aged 40 to 49 years (based on the burden of disease)<sup>61</sup> and also by differing outcomes reported in RCTs. Evidence from the RCTs and observational data have shown similar relative benefits associated with invitation and exposure to screening among women in their 40s and 50s,<sup>29,62-64</sup> and rates of recall and biopsy among women screened with screen-film and digital mammography were similar.<sup>37,65</sup> However, judgments about the absolute benefit of mammography in 10-year age groups, or for women in their 40s compared with women aged 50 to 74 years, have defined modern debates about when to begin screening. While the 5-year absolute risk of breast cancer increases steadily over this age span, the 5-year risk among women aged 45 to 49 years (0.9%) and women aged 50 to 54 years (1.1%) is similar, and greater than that for women aged 40 to 44 years (0.6%) (Table 4). The proportion of all incident breast cancers in the population also is similar for ages 45 to 49 years and 50 to 54 years (10% and 12%, respectively), compared with women aged 40 to 44 years (6%) (Figure 1A), as is the distribution of breast cancer deaths by age at diagnosis (10% and 11%, respectively), compared with women aged 40 to 44 years (7%) (Figure 1B). In addition, the age-specific incidence-based person-years of life lost were similar for women aged 45 to 49 years and 50 to 54 years at the time of diagnosis (approximately 15% each) and together accounted for 30% of all person-years of life lost at 20 years of follow-up (Figure 1C). This examination of the burden of disease indicated that traditional comparisons of women in their 40s with women in their 50s, or with women 50 years and older, obscured similarities in adjacent 5-year age groups.

**Table 4.** Distribution of Female Population Size, 5-Year Absolute Breast Cancer Risk, and Age-Specific Breast Cancer Incidence Rates by Age

Age Group (years)	Population Size (millions)	5-Year Absolute Risk (%)	Age-Specific Incidence Rate (per 100,000)
40-44	10.0	0.6	6.0
45-49	10.0	0.9	9.0
50-54	10.0	1.1	11.0
55-59	10.0	1.4	14.0
60-64	10.0	1.8	18.0
65-69	10.0	2.3	23.0
70-74	10.0	3.0	30.0
75-79	10.0	4.0	40.0

[View Large](#) | [Save Table](#) | [Download Slide \(.ppt\)](#) | [View in Article Context](#)

The evidence review judged the quality of evidence for a relative mortality reduction associated with screening mammography among women younger

than 50 years to be high and the quality of the evidence of the magnitude of effect as moderate. Systematic reviews of RCTs have generally reported that invitation to screening for women 40 years and older is associated with reduction in breast cancer mortality, with a larger magnitude of benefits observed in women aged 50 to 69 years at randomization compared with women aged 40 to 49 years.<sup>30,32,35</sup> The evidence synthesis for the 2009 US Preventive Services Task Force (USPSTF) recommendations by Nelson et al<sup>35</sup> compared women in 10-year age groups and observed RRs of 0.85, 0.86, and 0.68 for women aged 40 to 49 years, 50 to 59 years, and 60 to 69 years.

In contrast, incidence-based mortality studies and case-control studies tended to show greater and more similar mortality reductions between age-specific groups based on age at diagnosis. Evaluation of screening by age at diagnosis more directly addresses the question of age-specific benefits and overcomes the issue of age migration in the evaluation of RCTs.<sup>66,67</sup> For the age group that tends to be most controversial (ie, 40-49 years), Hellquist et al<sup>68</sup> compared breast cancer mortality rates for Swedish women living in counties that invited women in their 40s to screening with breast cancer mortality rates among women living in counties that did not invite women in their 40s to screening. After an average 16 years of follow-up, the investigators observed an overall 29% mortality reduction (RR, 0.71; 95% CI, 0.62-0.80) associated with exposure to screening, after adjustment for nonattendance. Among women aged 40 to 44 years, an 18% mortality reduction was observed, whereas among women aged 45 to 49 years, a 32% mortality reduction was observed.

As noted earlier, based on published findings from the BCSC that mostly are based on outcomes of population screening with both screen-film and digital mammography, the cumulative 10-year rates for at least 1 false-positive finding (both those resulting in additional imaging examinations and those resulting in biopsies) were similar whether screening begins at age 40 years or at age 50 years.<sup>37</sup> Although the false-positive rates were similar when women began screening at age 50 years compared with age 40 years, estimates of the lifetime cumulative risk of at least 1 of either type of false-

positive outcome were consistently higher when screening began at younger ages because of an increased number of screening examinations over a lifetime. Because digital mammography has nearly entirely replaced screen-film mammography in the United States, evidence on the frequency of false-positive findings from the BCSC was sought by the Pacific Northwest Evidence-based Practice Center for their systematic review to update the USPSTF 2009 breast cancer screening recommendations. Based on all-digital, nonprevalent (first screening examination excluded) screening mammography, there was an inverse relationship between age and false-positive findings per 1000 screening examinations among women aged 40 to 89 years, although the differences between 10-year age groups were modest.<sup>65</sup> For example, false-positive findings per 1000 examinations for women aged 40 to 49 years (121.2) vs 50 to 59 years (93.2) differed by only 28 examinations per 1000 women, and recommendations for biopsy per 1000 women differed by less than 1 per 1000 (16.4 vs 15.9, respectively).

The evidence review noted that some overdiagnosis was associated with screening across all age groups<sup>25</sup>; however, the quality of evidence for estimating the magnitude of the risk of overdiagnosis by age was judged to be low. Thus, it is not possible to determine if the lifetime risk of overdiagnosis was increased by beginning screening earlier.

Of the 20 screening strategies considered in the 2009 report from the Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network (CISNET), only 2 strategies started at age 45 years: annual and biennial screening from ages 45 to 69 years.<sup>69</sup> The incremental differences in breast cancer deaths averted and the number of false-positive biopsies per 1000 women resulting from extending biennial screening from ages 50-69 years to ages 45-69 years were similar (0.8 additional deaths prevented and 19 additional biopsies per 1000 women screened) to those of extending screening from ages 55-69 years to ages 50-69 years (0.5 additional deaths averted and 15 additional biopsies).<sup>69</sup> Similarities also were evident when extending annual screening from ages 50-69 years to 45-69 years (with an estimated 0.7 additional deaths averted and 31 additional biopsies per 1000 women screened), compared with extending annual screening from ages 55-

69 years to ages 50-69 years (with an estimated 1.2 additional deaths averted and 28 additional biopsies per 1000 women screened).<sup>69</sup>

In the absence of direct evidence comparing breast cancer mortality by screening intervals, the GDG relied on indirect evidence, including meta-analyses, mathematical models, observational studies, and microsimulation models, to form recommendations regarding the interval for screening.

A meta-analysis of screening trials comparing broad age groups (<50 vs 50-69 years) and screening intervals (<24 vs  $\geq$ 24 months) found that the benefit of an invitation to screening was not related to screening intervals for women aged 50 to 69 years at randomization.<sup>32</sup> However, among women randomized before age 50 years, a significant reduction in mortality was observed only for invitation at intervals less than 24 months (RR, 0.82; 95% CI, 0.72-0.94), whereas for intervals of 24 or more months, no benefit was observed (RR, 1.04; 95% CI, 0.72-1.50). In the Swedish Two County Trial, women were screened at intervals of 24 months or longer, and investigators sought to identify the point at which breast cancers began to reemerge after a normal mammogram. Among women older than 50 years at entry to the study, few interval cancers were observed in the first 2 years, whereas among women aged 40 to 49 years at randomization, the rate of interval cancers was 40% of the control group incidence rate within the first 12 months after a normal screening mammogram.<sup>70</sup>

Mathematical models capture the benefit of screening by modeling its estimated ability to detect cancers at smaller sizes; several of these models suggested that annual screening intervals are associated with detection of fewer tumors at larger and more lethal sizes.<sup>71-73</sup> In the 2009 CISNET analysis of the effects of mammography screening under different screening schedules, results from an exemplar model (from model S, Stanford University, chosen by the investigators as an exemplar model to summarize the balance of benefits and harms) estimated more cancer deaths averted with annual compared with biennial screening for all age groups and a greater number of cancer deaths averted when screening began before age 50 years.<sup>69</sup> However, the additional benefit of annual screening and beginning screening earlier incurred higher rates of false-positive screening

examinations and biopsies. The CISNET study estimated that screening every other year maintained an average of 81% of the mortality benefit of annual screening with about half the number of false-positive results.<sup>69</sup> The exemplar model did not explore a hybrid strategy that varied the screening interval by age.

The ACS commissioned the BCSC to examine the association between annual vs biennial screening and outcomes using definitions of these intervals that more closely approximated 12 vs 24 months than were used in earlier BCSC publications. Miglioretti et al<sup>74</sup> examined the association between screening intervals and tumor characteristics (stage [IIB, III, IV], larger size [ $>15$  mm], positive nodes, and any 1 or more of these characteristics) as indicators for less favorable prognosis. Multivariable analyses suggested that somewhat more favorable characteristics were associated with a shorter interval among women aged 40 to 49 years, but not among older women ( $>50$  years), although the difference was not statistically significant. Additional analyses indicated that these results likely were influenced by menopausal status. Premenopausal women were more likely to have advanced stage (RR, 1.28; 95% CI, 1.01-1.63), larger tumor size (RR, 1.21; 95% CI, 1.07-1.37), and poor prognosis tumors at diagnosis (RR, 1.11; 95% CI, 1.00-1.22) associated with a screening interval of 23 to 26 months compared with a screening interval of 11 to 14 months. The degree to which this observation is due to age, premenopausal status, or reduced sensitivity of screening in young women (or a combination of these factors) is uncertain. The authors highlighted several potential limitations in their analysis, including whether women at higher risk may be motivated to seek more frequent screening (although the analysis adjusted for family history), and whether the decision to maximize sample sizes by inclusion of women exposed to screen-film and digital mammography affected the results. Although overall the sensitivity of digital and screen-film mammography is similar, digital mammography is more sensitive in younger women and women with mammographically dense breasts.<sup>75</sup>

When making decisions on screening intervals, it is important to consider the harm-benefit trade-off. While annual screening yielded a larger reduction in

breast cancer mortality than biennial screening,<sup>69</sup> a more frequent screening schedule also resulted in a higher rate of false-positive findings. Given that screening annually appears to provide additional benefit over biennial screening particularly in younger women, the GDG concludes that women aged 45 to 54 years should be screened annually (*Qualified Recommendation*), and women aged 40 to 44 years who choose to initiate screening also should be screened annually (*Qualified Recommendation*). Because relative benefits of annual vs biennial screening are less after menopause and as women get older,<sup>69</sup> and more frequent screening over a lifetime horizon carries with it an increased chance of additional false-positive results, women aged 55 years, the age at which the large majority of women are postmenopausal,<sup>76</sup> should transition to biennial screening or have the opportunity to continue screening annually (*Qualified Recommendation*).

Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. (*Qualified Recommendation*)

Breast cancer incidence continues to increase until ages 75 to 79 years, and 26% of breast cancer deaths each year are attributable to a diagnosis after age 74 years (Figure 1B).<sup>3</sup> Because the sensitivity and specificity of mammography improve with increasing age,<sup>77</sup> this suggests considerable opportunity to further reduce breast cancer deaths among older women. While none of the RCTs included women 75 years and older, observational<sup>78,79</sup> and modeling studies<sup>69</sup> have observed a reduction in breast cancer mortality associated with mammographic detection of breast cancer in women 75 years and older, although these findings must be interpreted with caution given the limitations of the study designs.

The reduced life expectancy associated with being older decreases the likelihood of screening benefit in some women. Observational studies have shown that older women in poor health, for example, those with Charlson Comorbidity Index scores of 2 or higher, do not experience a reduction in breast cancer mortality associated with screening mammography due to competing causes of mortality<sup>80</sup> and therefore may not be good candidates for screening. This is an issue of concern because recent studies suggest



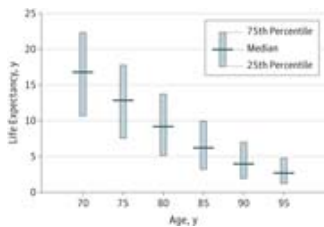
that many women who have serious or terminal health conditions are still receiving screening mammograms,<sup>81,82</sup> despite its low likelihood of increasing life expectancy or improving other outcomes. Women in poor health or with severe comorbid conditions and limited life expectancy may also be more vulnerable to harms of screening, including anxiety and discomfort associated with additional testing<sup>83-85</sup> and risk of overdiagnosis (due to increased risk of dying from non–breast cancer–related causes) as well as to harms from breast cancer treatment.<sup>86-88</sup> Thus, health and life expectancy, not simply age, must be considered in screening decisions.

A significant proportion of women 75 years and older are in good health and can be expected to live considerably longer than 10 more years.<sup>89</sup> Based on 2010 US Life Tables, approximately 50% of 80-year-old women and 25% of 85-year-old women will live at least 10 years (Figure 2).<sup>90</sup> Mortality indices that use age, comorbidities, and functional status to predict long-term mortality among community-dwelling older women can be useful for corroborating clinical judgment about the likelihood that an older woman's life expectancy exceeds 10 years (generally defined as having greater than a 50% probability of surviving 10 years).<sup>91,92</sup> For women who are healthy and have at least a 10-year life expectancy, individualized decisions about screening mammography should be considered.<sup>89</sup> Decision aids may help older women make decisions that are informed by an understanding of the potential benefits and harms of screening mammography.<sup>89</sup> Given the uncertainty surrounding the harm-benefit trade-off in older women and likely changes in health priorities over time, patient preferences should be weighed in the screening decision. The GDG recommends that women should continue screening as long as their overall health is good and they have a life expectancy of 10 years or longer.

## Figure 2.

### Upper, Middle, and Lower Quartiles of Life Expectancy for Women at Selected Ages Using 2010 US Female Life Tables

Adapted from: Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. *JAMA*. 2001;285(21):2750-2756.



[View Large](#) | [Save Figure](#) | [Download Slide \(.ppt\)](#) | [View in Article Context](#)

The ACS does not recommend clinical breast examination (CBE) for breast cancer screening among average-risk women at any age. (*Qualified Recommendation*)

Previous guideline recommendations for routine CBE have acknowledged the limitations in evidence. For Key Question 3, the evidence review found a lack of evidence showing any benefit of a CBE alone or in conjunction with screening mammography. There is moderate-quality evidence that adding CBE to mammography screening increased the false-positive rate. No studies were identified assessing other critical outcomes. A supplemental search identified studies on CBE performance characteristics, most of which show that the addition of CBE will detect a small number of additional breast cancers (ie, 2%-6%) compared with mammography alone.<sup>93-95</sup> There are no data on whether patient outcomes are improved with CBE. Given the lack of benefit concurrent with the increase in false-positive rates, CBE is not recommended for breast cancer screening among average-risk, asymptomatic women at any age. Recognizing the time constraints in a typical clinic visit, clinicians should use this time instead for ascertaining family history and counseling women regarding the importance of being alert to breast changes and the potential benefits, limitations, and harms of screening mammography.

Even though a substantial proportion of breast cancers are self-detected, the relative contributions of a systematic self-examination vs incidental discovery are unknown. Given the absence of evidence of improved outcomes associated with self-examination, the 2003 ACS guideline did not include a recommendation for routine performance of or instruction in breast self-examination. No new studies have been reported in recent years that warranted reconsideration of that conclusion.

## LIMITATIONS

There are invariably gaps between the available evidence and the evidence needed for the development of guidelines that precisely quantify and weigh the benefits vs the harms associated with breast cancer screening.<sup>96</sup> The GDG synthesized evidence from a variety of sources, including the RCTs, observational studies of modern service screening, and modeling studies. Still, even after broadening the evidence base, gaps remain. Empirical comparisons of screening programs that differ in terms of their ages to start and stop screening, and in their intervals between screening examinations, generally were lacking. Further, most breast screening studies did not provide estimates of benefits and harms over a lifetime horizon, which is important when considering policies that will span several decades or more of an individual's lifetime. The value and applicability of meta-analysis of mammography screening RCTs to guide current health policy also should be kept in perspective. While the RCT evidence demonstrated the efficacy of mammography screening, these studies were conducted from the 1960s through the 1990s with varying protocols, most using older screen-film systems and often using single-view mammography. The RCTs demonstrated a range of outcomes in terms of mortality reductions and, importantly, in terms of the degree to which an invitation to screening was associated with a reduced risk of being diagnosed with an advanced breast cancer, which is strongly associated with reduced breast cancer mortality.<sup>97</sup> Overall and age-specific mortality reduction estimates derived from meta-analysis of intention-to-treat results do not reveal these differences in the performance of the trials. In addition, RCT estimates based on intention-to-treat analyses are influenced by nonadherence to the protocol by both the invited and control group. In these respects, meta-analysis results are a sound basis for judging the efficacy of mammography screening, but a poor basis for estimating the effectiveness of modern, high-quality screening, especially when calculating absolute benefits and harms.

In evidence reviews, RCTs are favored over other study designs for their theoretical ability to provide the least biased estimates of efficacy.<sup>98</sup>

However, deriving estimates of absolute benefit from the RCTs means these

estimates are based on invitation to screening (NNI) rather than exposure to screening and therefore are contaminated by deaths from women in the study group who did not attend screening. Thus, it is preferable to regard the RCTs as providing the foundation on which mortality outcomes based on exposure to screening (NNS) from well-designed observational studies and evaluations of modern service screening can be viewed with greater confidence.

However, observational studies require methodological scrutiny, because they are subject to known and unknown bias and confounding. For example, comparison groups may be dissimilar in important ways that are not apparent, and there may be differential ascertainment of screening histories, quality of treatment, differences in selection bias, and other differences in the characteristics of exposed and unexposed persons that could influence results. With careful attention to possible threats to validity,<sup>29,99,100</sup> observational studies can provide evidence about the association between screening and outcomes among women who are exposed to screening. For this reason, the GDG considered observational studies of modern service screening (ie, organized, population-based screening) because these studies tend to demonstrate results that are consistent with the RCTs, while better reflecting contemporary screening protocols and providing evidence on both benefits and harms associated with exposure to screening.

Breast cancer treatment has improved over time, leading some to question whether or not advances in therapy have rendered screening less important.<sup>101</sup> There is little evidence from any study design to support this speculation. Berry et al<sup>4</sup> modeled the relative contributions of screening vs treatment and estimated that approximately half of the reduction in US breast cancer mortality was associated with screening and half was associated with improvements in adjuvant therapy. Higher fractions of the mortality reductions associated with screening have been estimated by other evaluations of screening programs.<sup>64,102,103</sup> While emphasis on the question of the relative contributions of therapy vs screening typically focuses on advances in treatment, it also is the case that substantial improvements in imaging technology and quality assurance have occurred over the past 30 to

40 years. Screen-film systems improved over time, and these mostly have been replaced by full-field digital mammography units, resulting in further improvements in imaging performance, particularly for younger women and women with mammographically dense breasts.<sup>75</sup> Accumulating data on digital breast tomosynthesis (DBT) appear to demonstrate further improvements in accuracy (both sensitivity and specificity),<sup>104</sup> and DBT is steadily increasing in prevalence in mammography facilities. At this time, both early detection and modern therapy have important roles in the control of breast cancer. The GDG did not attempt to disentangle the relative contribution of screening vs therapy in reducing breast cancer deaths.

The GDG did not formally compare the performance of screen-film mammography with full-field digital mammography, apart from noting that digital systems have been shown to have improved sensitivity in younger women and women with mammographically dense breasts<sup>75,105</sup> and new data showing slightly worse specificity in younger vs older women.<sup>65</sup> Because only a small fraction of mammography facilities are still using screen-film units, these comparisons would have had little practical purpose for policy or individual decision making. Although DBT units are steadily being introduced in mammography facilities, at the time the protocol for the evidence review was developed there were too few data on DBT to include comparisons of 2D vs 3D mammography.

The GDG recognizes that current knowledge suggests a continuum of risk; the categories of “average” and “high” or “higher” risk are not always distinct. Because an update of recommendations for women at high risk will follow this one, this guideline leaves unaddressed some important questions about mammography screening for women at increased risk for breast cancer or for diagnosis at a more advanced stage. At this time, women who are known or suspected carriers of deleterious mutations on breast cancer susceptibility genes and women treated with radiation at a young age are recommended to begin screening with mammography and breast MRI at a younger age.<sup>22,106,107</sup> There are other risk factors, such as family histories not linked to identified susceptibility genes, and history of invasive or in situ breast cancer or biopsy-confirmed proliferative lesions,<sup>20,108</sup> for which screening

recommendations and current practices may vary. The GDG also did not include in this review evidence on the effectiveness of supplemental breast imaging for women with mammographically dense breasts, which place some women at a higher risk of breast cancer and or a higher risk of having their breast cancer not detected by mammography.<sup>21,109,110</sup> The GDG will consider the evidence for screening effectiveness in women in these risk groups subsequent to the completion of the update of the guideline for average-risk women.

The issue of overdiagnosis is controversial, ranging from estimates of the overall rate, the relative fraction of overdiagnosis attributable to ductal carcinoma in situ (DCIS) vs invasive disease, and what women should be told about the possibility of overdiagnosis and overtreatment. There is an estimate in the literature to support almost any position on overdiagnosis and, likewise, almost any percentage of DCIS that is nonprogressive. The evidence review judged the evidence for the existence of overdiagnosis as high, but evidence for estimating the magnitude of overdiagnosis as low.<sup>23</sup> The UK Independent Panel also concluded that the uncertainties around the estimates reported result in a “spurious impression of accuracy.”<sup>111</sup>

The main goal of mammography screening programs is to reduce breast cancer mortality by reducing the incidence rate of advanced breast cancer. Thus, the aim of screening mammography is to detect breast cancer early in its natural history. A screening test that is successful in detecting small invasive cancers also will detect some precursor lesions. This likely does result in some overdiagnosis, but in other instances, it advances the time of diagnosis of a progressive lesion. Narod et al<sup>112</sup> recently reviewed outcomes of 108 196 women diagnosed with and treated for DCIS from 1998-2011 and concluded that both DCIS and invasive disease are heterogeneous with respect to prognostic features and outcomes and that DCIS and small invasive cancers share much in common. In the future, biological markers may be identified that will aid in treatment decision making and overcome the current inability to distinguish a nonprogressive tumor from one that is progressive and, among progressive tumors, less aggressive tumors from those that are more aggressive. New markers may also contribute to

progress in personalized medicine, providing opportunities for women to be counseled about treatment choices.<sup>113</sup>

Given the common agreement that women should know what to expect when undergoing breast cancer screening, there is a need for more research on communicating information about the benefits, limitations, and risks associated with screening. The current state of QALY literature related to mammography screening points to the need in future research for better utility assessment studies to address health states that accurately capture women's experience throughout the process of mammography screening and the associated health utilities, as well as time durations. Recognizing the high frequency of false-positive findings from screening mammography in the United States, more study is needed on understanding which women are at greater risk for near- and long-term psychological harm associated with false-positive results, and it also is a high priority to identify strategies that can reduce the stress associated with false-positive findings.<sup>60,114</sup>

## DISCUSSION

The 2015 updated recommendations from the ACS are intended to balance the goal of reducing the burden of breast cancer against the understanding that breast cancer screening is a preventive health intervention applied to the entire eligible population of women, most of whom will not develop breast cancer during their lifetime. In developing a guideline, some measure of judgment is required when weighing the balance of benefit and harm. The GDG carefully evaluated the burden of disease, the available evidence on the relative and absolute benefit of screening by age, the estimated frequency and relative importance of known and uncertain adverse events, and the importance of allowing for differences in women's values and preferences about the relative importance of potential benefits and harms in decisions about undergoing mammography screening.<sup>60,114-117</sup> There remain important differences of opinion about the trade-offs between benefits and harms of breast cancer screening in screening recommendations, and these differences were reflected in GDG deliberations. These new recommendations represent the collective judgment of the GDG and are

intended to provide guidance to women and health care professionals about breast cancer screening over a lifetime.

This updated guideline departs in some respects from the previous ACS recommendations for breast cancer screening (Table 5). Rather than view new evidence in the context of affirming existing guidelines, the GDG chose to more carefully examine the evidence on disease burden and the efficacy and effectiveness of screening in narrower age groups, with particular emphasis on the age range (40-55 years) for which disagreements about the age to begin screening and the screening interval have persisted over the past several decades. There also was greater scrutiny of the evidence on experiences collectively described as harms, but that more specifically differ quantitatively, from recall for additional imaging to biopsy to overtreatment, and differ qualitatively in terms of their effects. For some women, being recalled for additional imaging has little or no lasting adverse effects, while other women will experience greater and sometimes persistent adverse effects. The GDG also judged women's values and preferences as having a more important role in decisions where the balance of absolute benefits and harms is less certain. Historically, the ACS had recommended periodic CBE for women younger than 40 years and annual CBE for women 40 years and older. In this update, the absence of clear evidence that CBE contributed significantly to breast cancer detection prior to or after age 40 years led the GDG to conclude that it could no longer be recommended for average-risk women at any age. This new recommendation should not be interpreted to discount the potential value of CBE in low- and medium-resource settings where mammography screening may not be feasible. Clinical breast examination also may have a role in some groups of women at very high risk, but this question will be addressed in the update of recommendations for high-risk women. The GDG did not address breast self-examination, which the ACS did not recommend, and thus there is no change from the 2003 guidelines.

**Table 5.** Comparison of Current and Previous American Cancer Society (ACS) Guidelines for Breast Cancer Screening in Women at Average Risk<sup>a</sup>



[View Large](#) | [Save Table](#) | [Download Slide \(.ppt\)](#) | [View in Article Context](#)

The ACS endorses beginning annual screening mammography at age 45 years and transitioning to biennial screening at age 55 years, while retaining the option to continue annual screening, which some women may elect based on personal preference, clinical guidance, or both. After careful examination of the burden of disease among women aged 40 to 54 years, the GDG concluded that the lesser, but not insignificant, burden of disease for women aged 40 to 44 years and the higher cumulative risk of adverse outcomes no longer warranted a direct recommendation to begin screening at age 40 years. However, the GDG also concluded that women in this age group should have the choice to begin screening mammography at age 40 years or before age 45 years, based on their preferences and their consideration of the trade-offs. Some women will value the potential early detection benefit and will be willing to accept the risk of additional testing and will thus choose to begin screening earlier. Other women will choose to defer beginning screening, based on the relatively lower risk of breast cancer.

Given that annual screening mammography appears to provide additional benefit over biennial screening, particularly among younger women, the GDG recommends that women aged 45 to 54 years should be screened annually, that women aged 40 to 44 years who choose to be screened should do so annually, and that women 55 years and older should transition to biennial screening but also have the opportunity to continue screening annually. The guideline recognizes the potential benefit of continuing screening mammography for women in good health who are older than 74 years, but also the importance of identifying those women with life-limiting comorbidity who are unlikely to benefit from screening.

The GDG remains concerned about the contentious nature of debates surrounding breast cancer screening. At the extreme, these debates challenge the value of screening altogether, whereas more generally the debate is characterized by disparate characterizations, in both the academic

literature and the media, of the balance of benefits and harms. Given the weight of the evidence that mammography screening is associated with a significant reduction in the risk of dying from breast cancer after age 40 years, a more productive discussion would be focused on how to improve the performance of mammography screening. The absence of organized screening in the United States contributes to many of the shortcomings commonly attributed to the screening test. For example, the lack of central registries for call/recall hampers the efficiency with which women are invited to screening, meaning adherence to recommended screening remains suboptimal. There is too much variability in the sensitivity and specificity of mammography, which could be improved with better training, stronger qualifying standards, continuing education, and regular feedback on performance.<sup>118,119</sup> Improved accuracy (both sensitivity and specificity) would contribute to increased benefits and reduced harms.

Improving access to high-quality breast imaging remains a priority. In the United States, barriers to access continue to exist among low-income or uninsured women, those without a usual source of care, or those residing in rural counties.<sup>120-122</sup> These and other barriers are a formidable challenge to the delivery of preventive services and likely will remain so for some time without further policy changes. While the intent of the Affordable Care Act (ACA) is to eliminate cost sharing for mammography screening, there is still a lack of clarity about coverage as it pertains to breast cancer screening at some ages and at some intervals that the ACS either recommends or endorses for informed and shared decision making. It is the ACS' very strong position that average-risk women should not face financial disincentives when making decisions about mammography screening, either when adhering to these recommendations or when weighing the pros and cons of a different starting age or screening interval when informed or shared decision making is recommended.

## CONCLUSIONS

This guideline is intended to provide guidance to the public and clinicians, and it is especially designed for use in the context of a clinical encounter.

Women should be encouraged to be aware of and to discuss their family history and medical history with a clinician, who should periodically ascertain whether a woman's risk factor profile has changed. If the woman has an average risk of developing breast cancer, the ACS encourages a discussion of screening around the age of 40 years. The ACS also recommends that women be provided with information about risk factors, risk reduction, and the benefits, limitations, and harms associated with mammography screening.

In conclusion, the ACS recommendations are made in the context of maximizing reductions in breast cancer mortality and reducing years of life lost while minimizing the associated harms among the population of women in the United States. The ACS recognizes that the balance of benefits and harms will be close in some instances and that the spectrum of women's values and preferences will lead to varying decisions. The intention of this new guideline is to provide both guidance and flexibility for women about when to start and stop screening mammography and how frequently to be screened for breast cancer.

## ARTICLE INFORMATION

**Corresponding Author:** Robert A. Smith, PhD, Cancer Control Department, American Cancer Society, 250 Williams St, Ste 600, Atlanta, GA 30303 (robert.smith@cancer.org).

**Author Contributions:** Drs Oeffinger and Fontham had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Oeffinger, Etzioni, Michaelson, Shih, Church, Flowers, LaMonte, Wolf, Andrews, Manassaram-Baptiste, Saslow, Smith, Brawley.

*Acquisition, analysis, or interpretation of data:* Oeffinger, Fontham, Herzig, Michaelson, Shih, Walter, Church, Flowers, Wolf, DeSantis, Lortet-Tieulent, Saslow, Smith, Wender.

*Drafting of the manuscript:* Oeffinger, Fontham, Etzioni, Herzig, Michaelson, Shih, Walter, Flowers, Saslow, Smith, Brawley.

*Critical revision of the manuscript for important intellectual content:* Oeffinger, Etzioni, Herzig, Michaelson, Shih, Walter, Church, Flowers, LaMonte, Wolf, DeSantis, Lortet-Tieulent, Andrews, Manassaram-Baptiste, Saslow, Smith, Brawley, Wender.

*Statistical analysis:* Etzioni, Michaelson, Church, DeSantis, Lortet-Tieulent, Smith.

*Administrative, technical, or material support:* Fontham, Church, LaMonte, Andrews, Manassaram-Baptiste, Smith, Brawley, Wender.

*Study supervision:* Oeffinger, Shih, Church, Flowers, Smith, Brawley.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Etzioni reported owning stock in Seno Medical Instruments. Dr Michaelson reported receiving compensation for consulting on lawsuits involving delay in the treatment of cancer from CRICO Medical Insurance Company, University of Missouri, PPIC Medical Insurance Company, NORCA Mutual Insurance Company, MCIC Vermont Insurance Company, the law office of Hart Warner, Ford, Parshall & Baker, Haut & Marsh, Newber Pepe & Monteith, Meredith, Wildberger & Brennan, and Offutt Nord Burchett, Barger & Wolen, and receiving grant funding from Nikon. Dr Flowers reported receiving compensation as a consultant to Spectrum, Celgene, Optum Rx, and Seattle Genetics; serving as an unpaid consultant to Genentech/Biogen-Idec/Roche, and Millennium/Takeda; receiving compensation for development of educational presentations from Clinical Care Options, Educational Concepts, PRIME Oncology, and Research to Practice; and his institution receiving research funding from AbbVie, Acerta, Celgene, Gilead Sciences, Infinity Pharmaceuticals, Janssen Pharmaceutical, Millennium/Takeda, Spectrum, Onyx Pharmaceuticals, and Pharmacocyclics. Dr Smith reported serving as an unpaid advisor on General Electric Health Care's Breast Medical Advisory Board in 2015, to provide advice on appropriate implementation of

technology in low- and middle-income countries. No other disclosures were reported.

**Funding/Support:** The American Cancer Society (ACS) supported the development of this guideline through the use of general funds. Dr Oeffinger was supported in part through a Cancer Center Support Grant from the National Institutes of Health/National Cancer Institute (P30 CA008748).

**Role of the Sponsor:** The ACS had an advisory role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; and decision to submit the manuscript for publication. The ACS Mission Outcomes Committee and Board of Directors reviewed and approved the guideline. Final decisions were the responsibility of the Guideline Development Group.

### **Members of the American Cancer Society Guideline Development**

**Group (GDG):** Timothy R. Church, Ruth Etzioni, Christopher R. Flowers, Elizabeth T. H. Fontham, Abbe Herzig, Samuel J. LaMonte, James S. Michaelson, Kevin C. Oeffinger, Ya-Chen Tina Shih, Louise C. Walter, Andrew M. D. Wolf. (The Breast Cancer Screening Subgroup included Kevin C. Oeffinger, Elizabeth T. H. Fontham, Ruth Etzioni, Abbe Herzig, James S. Michaelson, Ya-Chen Tina Shih, and Louise C. Walter.) The ACS established the GDG, and all members served as volunteers and received no compensation from the ACS.

**Additional Contributions:** We thank the individuals who served as expert advisors to the GDG and provided review of the protocol for the systematic evidence review, the draft evidence report, and the draft guideline (see the eMethods in the Supplement). We would also like to thank the representatives of stakeholder organizations (listed in the eMethods) who provided comments on the draft guideline as part of the external review process.

## **REFERENCES**

Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.

[PubMed](#) | [Link to Article](#)

2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin*. 2015;65(1):5-29.

[PubMed](#) | [Link to Article](#)

3 Howlander N, Noone A, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2012*. Bethesda, MD: National Cancer Institute; 2015.

4 Berry DA, Cronin KA, Plevritis SK, et al; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784-1792.

[PubMed](#) | [Link to Article](#)

5 Smith RA, Saslow D, Sawyer KA, et al; American Cancer Society High-Risk Work Group; American Cancer Society Screening Older Women Work Group; American Cancer Society Mammography Work Group; American Cancer Society Physical Examination Work Group; American Cancer Society New Technologies Work Group; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast cancer screening: update 2003. *CA Cancer J Clin*. 2003;53(3):141-169.

[PubMed](#) | [Link to Article](#)

6 Institute of Medicine. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011.

7 Institute of Medicine. *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: National Academies Press; 2011.

8 Brawley O, Byers T, Chen A, et al. New American Cancer Society process for creating trustworthy cancer screening guidelines. *JAMA*. 2011;306(22):2495-2499.

[PubMed](#) | [Link to Article](#)

9 Samson D, Schoelles KM. Developing the topic and structuring systematic reviews of medical tests: utility of PICOTS, analytic frameworks, decision trees, and other frameworks. *Methods Guide for Medical Test Reviews*. AHRQ publication 12-EHC017.

<http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>. Accessed September 24, 2015.

Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1, Introduction: GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.

[PubMed](#) | [Link to Article](#)

- 
- 11 Atkins D, Best D, Briss PA, et al; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490.

[PubMed](#) | [Link to Article](#)

- 
- 12 Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14, Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719-725.

[PubMed](#) | [Link to Article](#)

- 
- 13 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15, Going from evidence to recommendations: determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726-735.

[PubMed](#) | [Link to Article](#)

- 
- 14 DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin*. 2014;64(4):252-271.

[PubMed](#) | [Link to Article](#)

- 
- 15 Sprague BL, Trentham-Dietz A. Prevalence of breast carcinoma in situ in the United States. *JAMA*. 2009;302(8):846-848.

[PubMed](#) | [Link to Article](#)

- 
- 16 Nelson HD, Pappas M, Zakher B, et al. Risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer in women: a systematic review to update the US Preventive Services Task Force recommendation. *Ann Intern Med*. 2014;160(4):255-266.

[PubMed](#) | [Link to Article](#)

- 
- 17 Ozanne EM, Drohan B, Bosinoff P, et al. Which risk model to use? clinical implications of the ACS MRI screening guidelines. *Cancer Epidemiol Biomarkers Prev*. 2013;22(1):146-149.

[PubMed](#) | [Link to Article](#)

- 
- 18 Henderson TO, Amsterdam A, Bhatia S, et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med*. 2010;152(7):444-455, W144-454.

[PubMed](#) | [Link to Article](#)

---

- 19 Holm J, Humphreys K, Li J, et al. Risk factors and tumor characteristics of interval cancers by mammographic density. *J Clin Oncol*. 2015;33(9):1030-1037.  
[PubMed](#) | [Link to Article](#)

---

- 20 Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast: risk assessment and management options. *N Engl J Med*. 2015;372(1):78-89.  
[PubMed](#) | [Link to Article](#)

---

- 21 Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007;356(3):227-236.  
[PubMed](#) | [Link to Article](#)

---

- 22 Saslow D, Boetes C, Burke W, et al; American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin*. 2007;57(2):75-89.  
[PubMed](#) | [Link to Article](#)

---

- 23 Systematic review of cancer screening literature for updating American Cancer Society Breast Cancer Screening Guidelines. Duke Evidence Synthesis Group.  
<http://www.cancer.org/breastcancerevidencereport>. Accessed September 28, 2015.

---

- 24 Hackshaw A. The benefits and harms of mammographic screening for breast cancer: building the evidence base using service screening programmes. *J Med Screen*. 2012;19(suppl 1):1-2.  
[PubMed](#) | [Link to Article](#)

---

- 25 Myers ER, Moorman P, Gierisch JM, et al. Benefits and harms of breast cancer screening: a systematic review. *JAMA*. doi:10.1001/jama.2015.13183.

---

- 26 White E, Miglioretti DL, Yankaskas BC, et al. Biennial versus annual mammography and the risk of late-stage breast cancer. *J Natl Cancer Inst*. 2004;96(24):1832-1839.  
[PubMed](#) | [Link to Article](#)

---

- 27 Wilson J, Jungner G. *Principles and Practice of Screening for Disease*. Geneva, Switzerland: World Health Organization; 1968.

---

- 28 Centers for Disease Control and Prevention. *Deaths: Final Data for 2011*. Vol 63. Hyattsville, MD: National Center for Health Statistics; 2014.



- 
- 29 Broeders M, Moss S, Nyström L, et al; EUROSCREEN Working Group. The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies. *J Med Screen*. 2012;19(suppl 1):14-25.  
[PubMed](#) | [Link to Article](#)
- 
- 30 Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev*. 2013;6:CD001877.  
[PubMed](#)
- 
- 31 Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet*. 2012;380(9855):1778-1786.  
[PubMed](#) | [Link to Article](#)
- 
- 32 Tonelli M, Connor Gorber S, Joffres M, et al; Canadian Task Force on Preventive Health Care. Recommendations on screening for breast cancer in average-risk women aged 40-74 years. *CMAJ*. 2011;183(17):1991-2001.  
[PubMed](#) | [Link to Article](#)
- 
- 33 Tabar L, Vitak B, Yen MF, et al. Number needed to screen: lives saved over 20 years of follow-up in mammographic screening. *J Med Screen*. 2004;11(3):126-129.  
[PubMed](#) | [Link to Article](#)
- 
- 34 Duffy SW, Chen TH, Smith RA, et al. Real and artificial controversies in breast cancer screening: a perspective article. *Breast Cancer Manag*. 2013;2(6):519-528.  
[Link to Article](#)
- 
- 35 Nelson HD, Tyne K, Naik A, et al; US Preventive Services Task Force. Screening for breast cancer: an update for the US Preventive Services Task Force. *Ann Intern Med*. 2009;151(10):727-737.  
[PubMed](#) | [Link to Article](#)
- 
- 36 Tabár L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology*. 2011;260(3):658-663.  
[PubMed](#) | [Link to Article](#)
- 
- 37 Hubbard RA, Kerlikowske K, Flowers CI, et al. Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. *Ann Intern Med*. 2011;155(8):481-492.  
[PubMed](#) | [Link to Article](#)

- 
- 38 Kerlikowske K, Zhu W, Hubbard RA, et al; Breast Cancer Surveillance Consortium. Outcomes of screening mammography by frequency, breast density, and postmenopausal hormone therapy. *JAMA Intern Med.* 2013;173(9):807-816.  
[PubMed](#) | [Link to Article](#)
- 
- 39 Olsen AH, Agbaje OF, Myles JP, Lynge E, Duffy SW. Overdiagnosis, sojourn time, and sensitivity in the Copenhagen mammography screening program. *Breast J.* 2006;12(4):338-342.  
[PubMed](#) | [Link to Article](#)
- 
- 40 Paci E, Miccinesi G, Puliti D, et al. Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. *Breast Cancer Res.* 2006;8(6):R68.  
[PubMed](#) | [Link to Article](#)
- 
- 41 Duffy SW, Agbaje O, Tabar L, et al. Overdiagnosis and overtreatment of breast cancer: estimates of overdiagnosis from two trials of mammographic screening for breast cancer. *Breast Cancer Res.* 2005;7(6):258-265.  
[PubMed](#) | [Link to Article](#)
- 
- 42 Puliti D, Duffy SW, Miccinesi G, et al; EUROSCREEN Working Group. Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. *J Med Screen.* 2012;19(suppl 1):42-56.  
[PubMed](#) | [Link to Article](#)
- 
- 43 Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *BMJ.* 2009;339:b2587.  
[PubMed](#) | [Link to Article](#)
- 
- 44 Zahl PH, Strand BH, Maehlen J. Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. *BMJ.* 2004;328(7445):921-924.  
[PubMed](#) | [Link to Article](#)
- 
- 45 de Gelder R, Heijnsdijk EA, van Ravesteyn NT, et al. Interpreting overdiagnosis estimates in population-based mammography screening. *Epidemiol Rev.* 2011;33(1):111-121.  
[PubMed](#) | [Link to Article](#)
- 
- 46 Biesheuvel C, Barratt A, Howard K, et al. Effects of study methods and biases on estimates of invasive breast cancer overdiagnosis with mammography screening: a systematic review. *Lancet Oncol.* 2007;8

(12):1129-1138.

[PubMed](#) | [Link to Article](#)

---

47 Etzioni R, Gulati R, Mallinger L, Mandelblatt J. Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. *Ann Intern Med.* 2013;158(11):831-838.

[PubMed](#) | [Link to Article](#)

---

48 Duffy SW, Parmar D. Overdiagnosis in breast cancer screening: the importance of length of observation period and lead time. *Breast Cancer Res.* 2013;15(3):R41.

[PubMed](#) | [Link to Article](#)

---

49 Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med.* 2012;367(21):1998-2005.

[PubMed](#) | [Link to Article](#)

---

50 Helvie MA, Chang JT, Hendrick RE, Banerjee M. Reduction in late-stage breast cancer incidence in the mammography era: implications for overdiagnosis of invasive cancer. *Cancer.* 2014;120(17):2649-2656.

[PubMed](#) | [Link to Article](#)

---

51 Carles M, Vilapriyo E, Cots F, et al. Cost-effectiveness of early detection of breast cancer in Catalonia (Spain). *BMC Cancer.* 2011;11:192.

[PubMed](#) | [Link to Article](#)

---

52 Stout NK, Rosenberg MA, Trentham-Dietz A, et al. Retrospective cost-effectiveness analysis of screening mammography. *J Natl Cancer Inst.* 2006;98(11):774-782.

[PubMed](#) | [Link to Article](#)

---

53 Pataky R, Ismail Z, Coldman AJ, et al. Cost-effectiveness of annual versus biennial screening mammography for women with high mammographic breast density. *J Med Screen.* 2014;21(4):180-188.

[PubMed](#) | [Link to Article](#)

---

54 Souza FH, Polanczyk CA. Is age-targeted full-field digital mammography screening cost-effective in emerging countries? a micro simulation model. *Springerplus.* 2013;2:366.

[PubMed](#) | [Link to Article](#)

---

55 de Gelder R, Bulliard JL, de Wolf C, et al. Cost-effectiveness of opportunistic versus organised mammography screening in

Switzerland. *Eur J Cancer*. 2009;45(1):127-138.

[PubMed](#) | [Link to Article](#)

- 
- 56 Lee CI, Cevik M, Alagoz O, et al. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. *Radiology*. 2015;274(3):772-780.  
[PubMed](#) | [Link to Article](#)
- 
- 57 Stout NK, Lee SJ, Schechter CB, et al. Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. *J Natl Cancer Inst*. 2014;106(6):dju092.  
[PubMed](#) | [Link to Article](#)
- 
- 58 Raftery J, Chorozioglou M. Possible net harms of breast cancer screening: updated modelling of Forrest report. *BMJ*. 2011;343:d7627.  
[PubMed](#) | [Link to Article](#)
- 
- 59 de Haes JC, de Koning HJ, van Oortmarsen GJ, et al. The impact of a breast cancer screening programme on quality-adjusted life-years. *Int J Cancer*. 1991;49(4):538-544.  
[PubMed](#) | [Link to Article](#)
- 
- 60 Tosteson AN, Fryback DG, Hammond CS, et al. Consequences of false-positive screening mammograms. *JAMA Intern Med*. 2014;174(6):954-961.  
[PubMed](#) | [Link to Article](#)
- 
- 61 Shapiro S, Venet W, Strax P, Venet L. *Periodic Screening for Breast Cancer: The Health Insurance Plan Project and Its Sequelae*. Baltimore, MD: Johns Hopkins Press; 1988.
- 
- 62 Nelson HD, Fu R, Griffin JC, et al. Systematic review: comparative effectiveness of medications to reduce risk for primary breast cancer. *Ann Intern Med*. 2009;151(10):703-715, W-226-W-235.  
[PubMed](#) | [Link to Article](#)
- 
- 63 Coldman A, Phillips N, Wilson C, et al. Pan-Canadian study of mammography screening and mortality from breast cancer. *J Natl Cancer Inst*. 2014;106(11):dju261.  
[PubMed](#) | [Link to Article](#)
- 
- 64 Swedish Organised Service Screening Evaluation Group. Reduction in breast cancer mortality from organized service screening with mammography: 1, further confirmation with extended data. *Cancer Epidemiol Biomarkers Prev*. 2006;15(1):45-51.  
[PubMed](#) | [Link to Article](#)
-

- 65 Nelson HD, Cantor A, Humphrey L, et al. *Screening for Breast Cancer: A Systematic Review to Update the 2009 US Preventive Services Task Force Recommendation*. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
- 
- 66 de Koning HJ, Boer R, Warmerdam PG, et al. Quantitative interpretation of age-specific mortality reductions from the Swedish breast cancer-screening trials. *J Natl Cancer Inst*. 1995;87(16):1217-1223.  
[PubMed](#) | [Link to Article](#)
- 
- 67 Tabár L, Duffy SW, Chen HH. Re: Quantitative interpretation of age-specific mortality reductions from the Swedish Breast Cancer-Screening Trials. *J Natl Cancer Inst*. 1996;88(1):52-55.  
[PubMed](#) | [Link to Article](#)
- 
- 68 Hellquist BN, Duffy SW, Abdsaleh S, et al. Effectiveness of population-based service screening with mammography for women ages 40 to 49 years: evaluation of the Swedish Mammography Screening in Young Women (SCRY) cohort. *Cancer*. 2011;117(4):714-722.  
[PubMed](#) | [Link to Article](#)
- 
- 69 Mandelblatt JS, Cronin KA, Bailey S, et al; Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med*. 2009;151(10):738-747.  
[PubMed](#) | [Link to Article](#)
- 
- 70 Tabár L, Faberberg G, Day NE, Holmberg L. What is the optimum interval between mammographic screening examinations? an analysis based on the latest results of the Swedish two-county breast cancer screening trial. *Br J Cancer*. 1987;55(5):547-551.  
[PubMed](#) | [Link to Article](#)
- 
- 71 Michaelson J, Satija S, Moore R, et al. The pattern of breast cancer screening utilization and its consequences. *Cancer*. 2002;94(1):37-43.  
[PubMed](#) | [Link to Article](#)
- 
- 72 Michaelson JS, Satija S, Kopans D, et al. Gauging the impact of breast carcinoma screening in terms of tumor size and death rate. *Cancer*. 2003;98(10):2114-2124.  
[PubMed](#) | [Link to Article](#)
-

Blanchard K, Colbert JA, Puri D, et al. Mammographic screening: patterns of use and estimated impact on breast carcinoma survival. *Cancer*. 2004;101(3):495-507.

[PubMed](#) | [Link to Article](#)

- 
- 74 Miglioretti D, Zhu W, Kerlikowske K, et al. Breast tumor prognostic characteristics and biennial vs annual mammography, age, and menopausal status. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.3084.
- 
- 75 Kerlikowske K, Hubbard RA, Miglioretti DL, et al; Breast Cancer Surveillance Consortium. Comparative effectiveness of digital versus film-screen mammography in community practice in the United States: a cohort study. *Ann Intern Med*. 2011;155(8):493-502.  
[PubMed](#) | [Link to Article](#)
- 
- 76 Gold EB, Crawford SL, Avis NE, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am J Epidemiol*. 2013;178(1):70-83.  
[PubMed](#) | [Link to Article](#)
- 
- 77 Performance measures for 1,838,372 screening mammography examinations from 2004 to 2008 by age: based on BCSC data through 2009. Breast Cancer Surveillance Consortium.  
<http://breastscreening.cancer.gov/statistics/performance/screening/200>  
Accessed July 15, 2015.
- 
- 78 Jonsson H, Bordás P, Wallin H, et al. Service screening with mammography in Northern Sweden: effects on breast cancer mortality: an update. *J Med Screen*. 2007;14(2):87-93.  
[PubMed](#) | [Link to Article](#)
- 
- 79 Roder D, Houssami N, Farshid G, et al. Population screening and intensity of screening are associated with reduced breast cancer mortality: evidence of efficacy of mammography screening in Australia. *Breast Cancer Res Treat*. 2008;108(3):409-416.  
[PubMed](#) | [Link to Article](#)
- 
- 80 Braithwaite D, Zhu W, Hubbard RA, et al; Breast Cancer Surveillance Consortium. Screening outcomes in older US women undergoing multiple mammograms in community practice: does interval, age, or comorbidity score affect tumor characteristics or false positive rates? *J Natl Cancer Inst*. 2013;105(5):334-341.  
[PubMed](#) | [Link to Article](#)
-

Sima CS, Panageas KS, Schrag D. Cancer screening among patients with advanced cancer. *JAMA*. 2010;304(14):1584-1591.

[PubMed](#) | [Link to Article](#)

---

82 Tan A, Kuo YF, Goodwin JS. Potential overuse of screening mammography and its association with access to primary care. *Med Care*. 2014;52(6):490-495.

[PubMed](#) | [Link to Article](#)

---

83 Walter LC, Eng C, Covinsky KE. Screening mammography for frail older women: what are the burdens? *J Gen Intern Med*. 2001;16(11):779-784.

[PubMed](#) | [Link to Article](#)

---

84 Sox HC. Screening for disease in older people. *J Gen Intern Med*. 1998;13(6):424-425.

[PubMed](#) | [Link to Article](#)

---

85 Raik BL, Miller FG, Fins JJ. Screening and cognitive impairment: ethics of forgoing mammography in older women. *J Am Geriatr Soc*. 2004;52(3):440-444.

[PubMed](#) | [Link to Article](#)

---

86 de Glas NA, Kiderlen M, Bastiaannet E, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. *Breast Cancer Res Treat*. 2013;138(2):561-569.

[PubMed](#) | [Link to Article](#)

---

87 Hurria A, Browner IS, Cohen HJ, et al. Senior adult oncology. *J Natl Compr Canc Netw*. 2012;10(2):162-209.

[PubMed](#)

---

88 Dijkstra JB, Houx PJ, Jolles J. Cognition after major surgery in the elderly: test performance and complaints. *Br J Anaesth*. 1999;82(6):867-874.

[PubMed](#) | [Link to Article](#)

---

89 Walter LC, Schonberg MA. Screening mammography in older women: a review. *JAMA*. 2014;311(13):1336-1347.

[PubMed](#) | [Link to Article](#)

---

90 Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. *JAMA*. 2001;285(21):2750-2756.

[PubMed](#) | [Link to Article](#)

---

91

Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK.  
Prognostic indices for older adults: a systematic  
review. *JAMA*.2012;307(2):182-192.

[PubMed](#) | [Link to Article](#)

---

92 Lee SJ, Smith AK, Widera EW, Yourman LC, Schonberg MA, Ahalt C. Eprognosis: Estimating prognosis for elders. <http://www.eprognosis.org>. Accessed September 29, 2015.

---

93 Bobo J, Lee N. Factors associated with accurate cancer detection during a clinical breast examination. *Ann Epidemiol*. 2000;10(7):463.  
[PubMed](#) | [Link to Article](#)

---

94 McDonald S, Saslow D, Alciati MH. Performance and reporting of clinical breast examination: a review of the literature. *CA Cancer J Clin*. 2004;54(6):345-361.  
[PubMed](#) | [Link to Article](#)

---

95 Bancej C, Decker K, Chiarelli A, et al. Contribution of clinical breast examination to mammography screening in the early detection of breast cancer. *J Med Screen*. 2003;10(1):16-21.  
[PubMed](#) | [Link to Article](#)

---

96 Habbema JD, Wilt TJ, Etzioni R, et al. Models in the development of clinical practice guidelines. *Ann Intern Med*. 2014;161(11):812-818.  
[PubMed](#) | [Link to Article](#)

---

97 Tabár L, Yen AM, Wu WY, et al. Insights from the breast cancer screening trials: how screening affects the natural history of breast cancer and implications for evaluating service screening programs. *Breast J*. 2015;21(1):13-20.  
[PubMed](#) | [Link to Article](#)

---

98 Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4, rating the quality of evidence: study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407-415.  
[PubMed](#) | [Link to Article](#)

---

99 Moss SM, Nyström L, Jonsson H, et al; Euroscreen Working Group. The impact of mammographic screening on breast cancer mortality in Europe: a review of trend studies. *J Med Screen*. 2012;19(suppl 1):26-32.  
[PubMed](#) | [Link to Article](#)

---

100 Verbeek AL, van Dijck JA, Broeders MJ. The effect of cancer screening on mortality: the case-control study as evaluation method



[in Dutch]. *Ned Tijdschr Geneeskd*. 2014;158(0):A7047.

[PubMed](#)

- 
- 101** Welch HG. Screening mammography: a long run for a short slide? *N Engl J Med*. 2010;363(13):1276-1278.  
[PubMed](#) | [Link to Article](#)
- 
- 102** Otto SJ, Fracheboud J, Looman CW, et al; National Evaluation Team for Breast Cancer Screening. Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet*. 2003;361(9367):1411-1417.  
[PubMed](#) | [Link to Article](#)
- 
- 103** Vervoort MM, Draisma G, Fracheboud J, van de Poll-Franse LV, de Koning HJ. Trends in the usage of adjuvant systemic therapy for breast cancer in the Netherlands and its effect on mortality. *Br J Cancer*. 2004;91(2):242-247.  
[PubMed](#)
- 
- 104** Friedewald SM, Rafferty EA, Rose SL, et al. Breast cancer screening using tomosynthesis in combination with digital mammography. *JAMA*. 2014;311(24):2499-2507.  
[PubMed](#) | [Link to Article](#)
- 
- 105** Pisano ED, Hendrick RE, Yaffe MJ, et al; DMIST Investigators Group. Diagnostic accuracy of digital versus film mammography: exploratory analysis of selected population subgroups in DMIST. *Radiology*. 2008;246(2):376-383.  
[PubMed](#) | [Link to Article](#)
- 
- 106** Mulder RL, Kremer LC, Hudson MM, et al; International Late Effects of Childhood Cancer Guideline Harmonization Group. Recommendations for breast cancer surveillance for female survivors of childhood, adolescent, and young adult cancer given chest radiation. *Lancet Oncol*. 2013;14(13):e621-e629.  
[PubMed](#) | [Link to Article](#)
- 
- 107** Breast Cancer Screening and Diagnosis (version 1.2015) [login required]. National Comprehensive Cancer Network.  
[http://www.nccn.org/professionals/physician\\_gls/PDF/breast-screening.pdf](http://www.nccn.org/professionals/physician_gls/PDF/breast-screening.pdf). Accessed September 28, 2015.
- 
- 108** Houssami N, Abraham LA, Kerlikowske K, et al. Risk factors for second screen-detected or interval breast cancers in women with a personal history of breast cancer participating in mammography

screening. *Cancer Epidemiol Biomarkers Prev.* 2013;22(5):946-961.

[PubMed](#) | [Link to Article](#)

---

- 109** Chiu SY, Duffy S, Yen AM, Tabár L, Smith RA, Chen HH. Effect of baseline breast density on breast cancer incidence, stage, mortality, and screening parameters: 25-year follow-up of a Swedish mammographic screening. *Cancer Epidemiol Biomarkers Prev.* 2010;19(5):1219-1228.

[PubMed](#) | [Link to Article](#)

---

- 110** Boyd NF, Huszti E, Melnichouk O, et al. Mammographic features associated with interval breast cancers in screening programs. *Breast Cancer Res.* 2014;16(4):417.

[PubMed](#) | [Link to Article](#)

---

- 111** Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer.* 2013;108(11):2205-2240.

[PubMed](#) | [Link to Article](#)

---

- 112** Narod SA, Iqbal J, Giannakeas V, Sopik V, Sun P. Breast cancer mortality after a diagnosis of ductal carcinoma in situ [published online August 20, 2015]. *JAMA Oncol.* doi:10.1001/jamaoncol.2015.2510.

[PubMed](#)

---

- 113** Esserman L, Yau C. Rethinking the standard for ductal carcinoma in situ treatment [published online August 20, 2015]. *JAMA Oncol.* doi:10.1001/jamaoncol.2015.2607.

[PubMed](#)

---

- 114** Schwartz LM, Woloshin S, Sox HC, Fischhoff B, Welch HG. US women's attitudes to false positive mammography results and detection of ductal carcinoma in situ: cross sectional survey. *BMJ.* 2000;320(7250):1635-1640.

[PubMed](#) | [Link to Article](#)

---

- 115** Schwartz LM, Woloshin S, Fowler FJ Jr, Welch HG. Enthusiasm for cancer screening in the United States. *JAMA.* 2004;291(1):71-78.

[PubMed](#) | [Link to Article](#)

---

- 116** Allen JD, Bluethmann SM, Sheets M, et al. Women's responses to changes in US Preventive Task Force's mammography screening guidelines: results of focus groups with ethnically diverse women. *BMC Public Health.* 2013;13:1169.

[PubMed](#) | [Link to Article](#)

---

117

Thomson MD, Siminoff LA. Perspectives on mammography after receipt of secondary screening owing to a false positive. *Womens Health Issues*. 2015;25(2):128-133.

[PubMed](#) | [Link to Article](#)

---

**118** Buist DS, Anderson ML, Smith RA, et al. Effect of radiologists' diagnostic work-up volume on interpretive performance. *Radiology*. 2014;273(2):351-364.

[PubMed](#) | [Link to Article](#)

---

**119** Assessing and improving imaging interpretation in breast cancer screening. Institute of Medicine. <http://iom.nationalacademies.org/Activities/Disease/NCPF/2015-MAY-12.aspx#sthash.BiDFaY5P.dpuf>. Accessed August 10, 2015.

---

**120** Anderson RT, Yang TC, Matthews SA, et al. Breast cancer screening, area deprivation, and later-stage breast cancer in Appalachia: does geography matter? *Health Serv Res*. 2014;49(2):546-567.

[PubMed](#) | [Link to Article](#)

---

**121** Brown ML, Klabunde CN, Cronin KA, et al. Challenges in meeting Healthy People 2020 objectives for cancer-related preventive services, National Health Interview Survey, 2008 and 2010. *Prev Chronic Dis*. 2014;11:E29.

[PubMed](#) | [Link to Article](#)

---

**122** Elkin EB, Paige Nobles J, Pinheiro LC, Atonia CL, Schrag D. Changes in access to screening mammography, 2008-2011. *Cancer Causes Control*. 2013;24(5):1057-1059.

[PubMed](#) | [Link to Article](#)

---

Copyright ©2015 American Medical Association