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Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update from the American Cancer Society

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Abstract

Importance—Breast cancer is a leading cause of premature mortality among U.S. women. Early detection has been shown to be associated with reduced breast cancer morbidity and mortality. This report updates 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—Mammography screening in women aged 40–69 years is associated with a reduction in breast cancer deaths across a range of study designs, and inferential evidence supports breast cancer screening in women who are age 70 years and older and are in good health. Estimates of the cumulative lifetime risk of false positive exams are greater if screening begins at younger ages due to 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 average risk women.

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 who are ages 45 to 54 years should be screened annually *(qualified recommendation)*. Women who are age 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 more *(qualified recommendation)*. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age *(qualified recommendation).*

Breast cancer is the most common cancer in women worldwide.[1] In the United States, an estimated 231,840 women will be diagnosed with breast cancer in 2015.[2] Breast cancer continues to rank second, following 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.[3] Even though mortality from breast cancer has declined steadily since 1990, largely due to improvements in early detection and treatment,[4] an estimated 40,290 women in the U.S. will die of breast cancer in 2015.[2]

Since the last ACS breast cancer screening update for average-risk women was published in 2003,[5] new evidence has accumulated from long-term follow-up of the randomized clinical trials (RCTs) and observational studies of organized, population-based 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 (IOM) [6,7] into its guidelines development protocol to ensure a more trustworthy, transparent, and consistent process for developing and communicating guidelines.[8]

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), economists (n=1), and patient representatives (n=2). The GDG developed five key questions using the general approach of specifying populations, interventions, comparisons, outcomes, timing of outcomes, and settings (PICOTS) for each question.[9] 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.[10,11]

The ACS GDG selected the Duke University Evidence Synthesis Group to conduct an independent systematic evidence review of the breast cancer screening literature, following a response to a request for proposals. This effort is referred to as the 'evidence review.' Additionally, 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.[3]

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.[12,13] The GDG chose to assess recommendations as *'strong'* or *'qualified'*, in accordance with GRADE guidance.[13] 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).

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**).

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 eMethods.

All participants in the guideline development process were required to disclose all financial and non-financial (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 acknowledgment section, non-financial disclosures of the authors are reported in eMethods.

Questions Guiding the Evidence Review

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 (KQ) Guiding the Evidence Review[a]

KQ 1: What are the relative benefits, limitations, and harms associated with mammography screening compared to no screening in average-risk women ages 40 and older, and how do they vary by age, screening interval, and prior screening history?

KQ 2: In 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 40 years and older compared to no CBE, and how do they vary by age, interval, and participation rates in mammography screening?

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

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

KQ 5a: Among women with an increased risk of breast cancer due to factors known PRIOR to the onset of screening (e.g., 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 (e.g., 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?

[a]Only questions KQ1, KQ2, and KQ3 are considered in this guideline

1. What are the relative benefits, limitations, and harms associated with mammography screening compared to no screening in average-risk women ages 40 and older, and how do they vary by age, screening interval, and prior screening history?
2. In 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 to 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, i.e., women without a personal history of breast cancer, a confirmed or suspected genetic mutation known to increase risk of breast cancer (e.g., 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 of age and older, approximately 4% of the total population;[14] a 2005 prevalence estimate of those having received a diagnosis of in-situ breast cancer was 570,403, expected to increase to over 1 million by 2016;[15] 0.2 to 0.3 percent of the general population and 2 percent of Ashkenazi Jewish women are estimated to be carriers of the *BRCA1* or *BRCA2* mutation,[16] and overall 5.8% of mammography screening age women may be either known or suspected mutation carriers based on having approximately a 20% or greater lifetime risk of breast cancer based on assessment of family history with specialty software;[17] and in 2010 it was estimated that there were 50,000 to 55,000 women in the U.S. who had been treated with moderate to high-dose chest radiation for pediatric and young adult cancers.[18] 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,[19] women with a prior diagnosis of benign proliferative breast disease,[20] and women with significant mammographic breast density.[21]. At this time there are no reliable estimates of the number of women who have one 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, ACS provided recommendations for breast 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 between ages 10–30, or an estimated lifetime risk of approximately 20–25% or greater, as defined by risk assessment models largely dependent on family history.[22] 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 in women with less than a 15% lifetime risk.[22] Two additional key questions that focused on screening outcomes in

women at high risk of breast cancer were considered in our evidence review.[23] 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 Systematic Evidence Review

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.[24] 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 inclusion criteria of:

- Controlled studies, including randomized clinical trials (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 with an $n \geq 1000$ for average-risk women.
- Modeling/simulation studies, because these studies may be the only way to generate estimates of long-term outcomes associated with of 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 tests, 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.

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.[25]

Supplementary Analyses and Evidence

In addition to the evidence review, the ACS commissioned the BCSC to update previously published analyses[26] 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.[26]

An initial consideration in the decision to offer screening to the population is the burden of disease overall, and in age-specific subgroups.[27] 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).[3,28] Figure 1A shows the estimated distribution (%) of invasive female breast cancer cases among U.S. women for the period 2007–2011. Figure 2A shows the estimated distribution (%) of deaths from breast cancer by age at diagnosis among U.S. women for the period 2007–2011. Figure 3A shows the estimated distribution (%) of person years-of-life-lost due to breast cancer (followed for 20 years) by age at diagnosis among U.S. women for the period 2007–2011.

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 average-risk women. Recognizing that women's 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 (e.g., 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.

Recommendations:[a]

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

- **1a** Women who are ages 45 to 54 years should be screened annually. (*Qualified Recommendation*)
- **1b** Women who are 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 more. (*Qualified Recommendation*)

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

[a] 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.[12,13]

Recommendation 1

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

Recommendation 1a: Women who are ages 45 to 54 years should be screened annually. (Q*ualified Recommendation)*

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

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

Various key topics were considered by the GDG in making this 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 tradeoff for each age group. In addition, when developing the recommendation(s) for interval of screening, the GDG evaluated the findings of the BCSC analysis in addition to the results of the evidence review.

Outcomes of Screening Mammography—The evidence review considered five critical outcomes of screening mammography: breast cancer mortality, life expectancy, false positives, overdiagnosis, and quality-adjusted life expectancy.

Breast cancer mortality: 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 and case-control studies), with most studies demonstrating a significant benefit (Table 3).[4,29,30] The strength of the evidence that invitation or exposure to mammography screening compared to 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.

Pooled estimates for relative breast cancer mortality reductions after approximately 13 years of follow-up were similar for two meta-analyses of RCTs using random-effects models (UK Independent Panel,[31] Odds Ratio [OR], 0.80; 95% confidence interval [CI], 0.73–0.89; and

Canadian Task Force,[32] OR, 0.82; 95% CI, 0.74–0.94), and for the Cochrane analysis,[30] which used a fixed-effects model (OR, 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%.[29] 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.[29] The corresponding pooled estimates from case-control studies were 31% (RR, 0.69; 95% CI, 0.57–0.83), and 48% (RR, 0.52; 95% CI, 0.42–0.65) after adjustment for self-selection.[29]

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 the 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, the 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.[33] 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 2,000 women would need to be invited to screening and followed for mortality over a 10 year period to prevent 1 breast cancer death.[30] The U.K. Independent Review estimated that 180 women needed to be screened over a 20 year period beginning at age 50, with follow-up to age 79, to prevent 1 breast cancer death.[31] The main distinction between the Cochrane Systematic Review[30] and U.K. Independent Review[31] 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 screening and follow-up period that are contemporaneous.

As shown by Duffy et al, 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),[31] to estimate the NNS, a nearly 20-fold difference (from 111 to 2000) found in four well-known estimates[29–31,34] of the number needed to screen/invite to prevent 1 breast cancer death was reduced to a range of 96 – 257 women screened to prevent 1 breast cancer death.[35] 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 ages 40–74 needed to be screened 2–3 times over a 7 year period to prevent 1 breast cancer death at 10 years of follow-up, which decreased to 464 at 20 years of follow-up, and to 414 at 29 years of follow-up.[36]

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 one breast cancer death based on different relative mortality reductions. For women ages 40–49, the NNS ranged from 753 with a 40% mortality reduction to 1770 with a 20% mortality reduction. For women ages 50–59, the NNS ranged from 462 with a 40% mortality reduction to 1087 with a 20% mortality reduction. For women ages 60–69, the NNS ranged from 355 with a 40% mortality reduction to 835 with a 20% mortality reduction.[25] 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 here also would be more favorable if follow-up were projected to 25 years or longer.

Life expectancy: 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.[3]

False positive findings: 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 reported that among women in the BCSC who initiated screening at age 40 and had undergone either screen-film or digital mammography, the unadjusted cumulative probability of at least one false-positive recall after 10 years of screening was 61.3% with annual and 41.6% with biennial screening.[37] 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 two years rather than every year reduced the cumulative incidence of at least one false positive recall and false positive biopsy by about 32% and 31% respectively.[37,38] 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.[37,38]

Overdiagnosis: 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%[39–42] to more than 50%.[43,44] Estimates of overdiagnosis produced from modeling studies generally are lower than those from empirical studies.[41,45] 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.[42,46–50] 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.[42]

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.

Quality-adjusted life expectancy: 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.[51–58] Most of these studies showed that compared to 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[59] published in 1991 that was limited by a small sample size

and outdated mammography technology. While a recent study has collected more contemporary health utility information on false positives among women in the United States,[60] 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 versus 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.

Age to begin screening—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, and continues to increase until ages 75–79 (Table 3). Historically, the age to begin screening has been influenced by the majority of RCT designs, which included women ages 40–49 (based on the burden of disease),[61] 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,[29,62–64] and rates of recall and biopsy among women screened with screen-film and digital mammography were similar.[37,65] However, judgments about the absolute benefit of mammography in 10-year age groups, or for women in their 40s compared to women ages 50–74, have defined modern debates about when to begin screening. While the 5-year absolute risk of breast cancer has increased steadily during this period, the 5-year risk among women ages 45–49 (0.9%) and women ages 50–54 (1.1%) was similar, and greater than that for women ages 40–44 (0.6%) (Table 3). The proportion of all incident breast cancers in the population also was similar for ages 45–49 and 50–54 (10% and 12%, respectively), compared with women ages 40–44 (6%) (Figure 1A), as is the distribution of breast cancer deaths by age at diagnosis (10% and 11%, respectively), compared with women ages 40–44 (7%) (Figure 1B). Additionally, the age-specific incidence-based person years of life lost (PYLL) were similar for women ages 45–49 and 50–54 at the time of diagnosis (approximately 15% each), and together accounted for 30% of all PYLL 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 ages 50 years and older, obscures similarities in adjacent 5-year age groups.

The evidence review judged the quality of evidence for a relative mortality reduction associated with screening mammography among women younger than age 50 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 in women 40 years of age and older is associated with reduction in breast cancer mortality, with a larger magnitude of benefits observed in women 50–69 at randomization compared with women 40–49.[30,32,34] The synthesis for the 2009 USPSTF recommendations by Nelson et al compared women in 10 year age-groups and observed relative risks of 0.85, 0.86, and 0.68 for women ages 40–49, 50–59, and 60–69.[34]

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.[66,67] For the age group that tends to be most controversial (i.e., ages 40–49), Hellquist et al compared breast cancer mortality rates in 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.[68] After an average 16 years of follow-up, the investigators observed an overall 29% (RR, 0.71; 95% CI, 0.62–0.80) mortality reduction associated with exposure to screening, after adjustment for nonattendance. Among women ages 40–44, an 18% mortality reduction was observed, whereas among women ages 45–49, 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 one false positive finding (both those resulting in additional imaging examinations and those resulting in biopsies) were similar whether screening begins at age 40 or at age 50.[37] Although the false positive rates were similar when women begin screening at age 50 compared to age 40, estimates of the lifetime cumulative risk of at least one of either type of false positive outcome were consistently higher when screening begins 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 U.S., 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 upon all-digital, non-prevalent (first screening exam excluded) screening mammography, there was an inverse relationship between age and false-positive findings per 1000 screening exams among women ages 40–89, although the differences between 10 year age groups are modest.[65] For example, false positive findings per 1000 exams for women ages 40–49 (121.2) vs. 50–59 (93.2) differed by only 28 exams per 1000 women, and recommendations for biopsy per 1,000 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;[25] 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 wass increased by beginning screening earlier.

Of the twenty screening strategies considered in the 2009 report from the Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network (CISNET), only two strategies started at age 45: annual and biennial screening from age 45 to 69.[69] The incremental differences in breast cancer deaths averted and the number of false positive biopsies per 1000 women resulting from extending biennial screening from age 50–69 to age 45–69 were similar (0.8 additional deaths prevented and 19 additional biopsies per 1000 women screened) to those of extending screening from age 55–69 to age 50–69 (0.5 additional deaths averted and 15 additional biopsies).[69] Similarities also were evident when extending annual screening from ages 50–69 to 45–69 (with an estimated 0.7 additional deaths averted and 31 additional biopsies per 1000 women screened), compared with extending annual screening from ages 55–59 to ages 50–69 (with an estimated 1.2 additional deaths averted and 28 additional biopsies per 1000 women screened).[69]

Screening interval—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 (under 50 versus 50–69 years) and screening intervals (less than 24 versus 24 months or more) found that the benefit of an invitation to screening was not related to screening intervals for women ages 50–69 at randomization.[32] 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 greater, and investigators sought to identify the point at which breast cancers began to reemerge after a normal mammogram. Among women over 50 years of age at entry to the study, few interval cancers were observed in the first two years, whereas among women ages 40–49 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.[70]

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.[71–73] 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.[69] However, the additional benefit of annual screening and beginning screening earlier incurred higher rates of false positive screening exams 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.[69] 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 versus 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 examined the association between screening intervals and tumor characteristics (stage [IIb, III, IV], larger size [>15 millimeters], positive nodes, and any one or more of these characteristics) as indicators for less favorable prognosis.[74] Multivariable analyses suggested that somewhat more favorable characteristics were associated with a shorter interval among women ages 40–49, but not among older women (over age 50), 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.[75]

When making decisions on screening intervals, it is important to consider the harm-benefit tradeoff. While annual screening yielded a larger reduction in breast cancer mortality than biennial screening,[69] 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 who are ages 45–54 should be screened annually (*qualified recommendation*), and women ages 40–44 who choose to initiate screening also should be screened annually (*qualified recommendation*). Since relative benefits of annual versus biennial screening are less after menopause and as women get older,[69] and more frequent screening over a lifetime horizon carries with it an increased chance of additional false positive results, women who are age 55, the age at which the large majority of women are postmenopausal,[76] should transition to biennial screening or have the opportunity to continue screening annually (*qualified recommendation*).

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 more. (Q*ualified Recommendation)*

Breast cancer incidence continues to increase until ages 75–79, and 26% of breast cancer deaths each year are attributable to a diagnosis after age 74 (Figure 1B).[3] Since the sensitivity and specificity of mammography improve with increasing age,[77] this suggests considerable opportunity to further reduce breast cancer deaths in older women. While none of the RCTs included women 75 years of age and older, observational[78,79] and modeling studies[69] 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 scores of 2 or higher, do not experience a reduction in breast cancer mortality associated with screening mammography due to competing causes of mortality,[80] 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,[81,82] 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,[83–85] 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.[86–88] Thus, health and life expectancy, not simply age, must be considered in screening decisions.

A significant proportion of women age 75 and older are in good health and can be expected to live considerably longer than 10 more years.[89] Based on 2010 U.S. Life Tables, approximately 50% of 80-year-old women and 25% of 85-year-old women will live at least 10 years (Figure 3).[90] 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)[91]. For women who are healthy and have at least a 10-year life expectancy, individualized decisions about screening mammography should be considered.[89] Decision aids may help older women make decisions that are informed by an understanding of the potential benefits and harms of screening mammography.[89] Given the uncertainty surrounding the harm-benefit tradeoff 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 more.

Recommendation 3

The ACS does not recommend clinical breast examination 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 (i.e. 2%–6%) compared to mammography alone.[92–94] There are no data on whether CBE is associated with improved patient outcomes. 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 versus the harms associated with breast cancer screening.[95] 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 exams, 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 RCT's 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.[96] 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 non-adherence 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.

Methodological rigor favors RCTs for their theoretical ability to provide the least biased estimates of efficacy,[97] 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 still 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,[29,98,99] 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 (i.e., organized, community-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.[100] There is little evidence from any study design to support this speculation. Berry, et al. modeled the relative contributions of screening vs. treatment and estimated that approximately half of the reduction in U.S. breast cancer mortality was associated with screening, and half was associated with improvements in adjuvant therapy.[4] Higher fractions of the mortality reductions associated with screening have been estimated by others' evaluations of screening programs.[64,101,102] 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 30–40 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 in younger women and women with mammographically dense breasts.[75] Accumulating data on digital breast tomosynthesis (DBT) appears to demonstrate further improvements in accuracy (both sensitivity and specificity),[103] 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,[104] and new data showing slightly worse specificity in younger vs. older women.[65] 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 digital breast tomosynthesis 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 digital breast tomosynthesis 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.[22,105,106] 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,[20,107] 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.[21,108,109] 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 DCIS versus 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 non-progressive. The evidence review judged the evidence for the existence of overdiagnosis as high, but evidence for estimating the magnitude of overdiagnosis as low.[23] The U.K. Independent Panel also concluded that the uncertainties around the estimates reported result in a "spurious impression of accuracy."[110]

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. 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.[111] In the future, biological markers may be identified that will aid in treatment decision-making, and overcome the current inability to distinguish a non-progressive 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.[112] 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 mammography screening 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.[60,113]

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.[60,113–116] There remain important differences of opinion about the tradeoffs 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 4). Rather than viewing 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) 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 which 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, 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 under age 40, and annual CBE for women age 40 years and older. In this update, the absence of clear evidence that CBE contributes significantly to breast cancer detection prior to or after age 40 led the GDG to conclude that it could no longer be recommended for average risk women at any age. CBE 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.

The ACS endorses beginning annual mammography screening at age 45 and transitioning to biennial screening at age 55, while retaining the option to continue annual screening, which some women may elect based on personal preference and/or clinical guidance. After careful examination of the burden of disease among women ages 40–54, the GDG concluded that the lesser, but not insignificant, burden of disease for women ages 40–44 and the higher cumulative risk of adverse outcomes no longer warranted a direct recommendation to begin mammography screening at age 40. However, the GDG also concluded that women in this

age group should have the choice to begin screening at age 40 or before age 45, based on their preferences and their consideration of the tradeoffs. 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. Others will choose to defer beginning screening, based on the relatively lower risk of breast cancer.

Given that annual mammography screening appears to provide additional benefit over biennial screening, particularly among younger women, the GDG recommend that women who are ages 45 to 54 years should be screened annually, that women ages 40 to 44 who choose to be screened should do so annually, and that women who are age 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 mammography screening in women in good health who are over age 74, but also the importance of identifying those women with life-limiting comorbidity who are unlikely to benefit from screening.

The ACS 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, a more productive discussion would be focused on how to improve the performance of mammography screening. The absence of organized screening in the U.S. 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 sub-optimal. 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.[117,118] 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 or those without a usual source of care, or those residing in rural counties.[119–121] 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 recommend 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 mammography screening and how frequently to be screened for breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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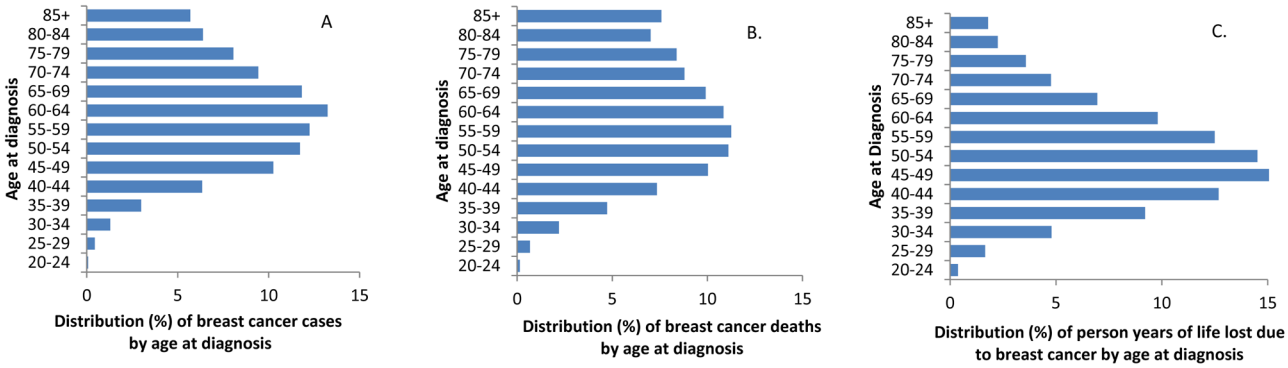

Figure 1. Breast cancer burden by age at diagnosis, 2007–2011

Panel A. Age distribution of invasive female breast cancer cases (n=292,369), 2007–2011. Source: SEER 18 registries.

Panel B. Distribution of breast cancer deaths by age at diagnosis (n=16,789), with patients followed for 20 years after diagnosis, 2007–2011.

Source: SEER 9 registries.

Panel C. Distribution of person years of life lost due to breast cancer by age at diagnosis (Total= 326,560), with patients followed for 20 years after diagnosis, 2007–2011.

Source: SEER 9 registries. The YPLL is based on the 2011 US female life table.[27]

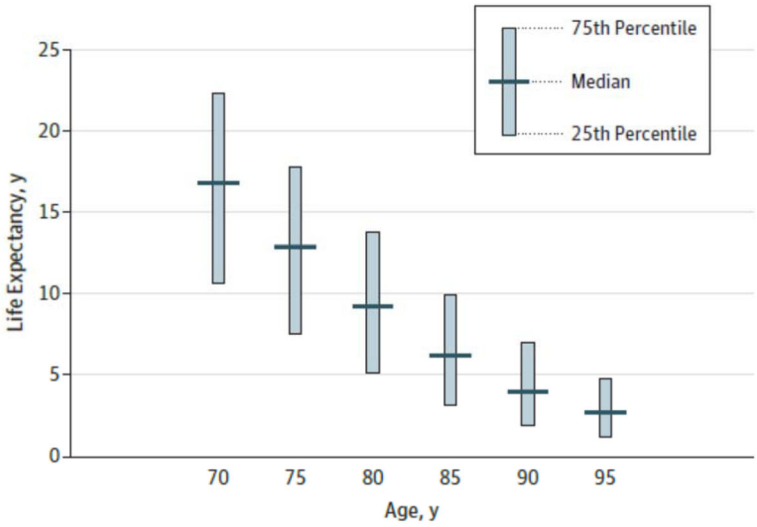

Figure 2. Upper, Middle, and Lower Quartiles of Life Expectancy for Women at Selected Ages
Adapted from from Walter LC, Covinsky KE. Cancer screening in elderly patients: a framework for individualized decision making. JAMA, 2001; 285:2750–2756; using 2010 United States Life Tables.

Table 1

Interpretation of Strong and Qualified Recommendations by Users of the Guideline

	Strong Recommendations	Qualified Recommendations
For Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Patient preferences and informed decision making are desirable for making decisions.
For Clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should acknowledge that different choices will be appropriate for different patients, and that clinicians must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

Source: *Adapted from the Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013.* http://www.guidelinedevelopment.org/handbook/#h.33qgws879zw

Table 2

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

Critical Outcome	**Definition**
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 tests	Recall for additional testing (imaging and/or biopsy) after abnormal CBE or mammography, in which further evaluation determines that the initial adnormal finding was not cancer.
Overdiagnosis	Screen detected cancers that would not have led to symptomatic breast cancer if undetected by screening
Overtreatment	Cancer therapies (surgery, radiation, chemotherapy) performed for screen-detected cancers that would not have led to symptomatic breast cancer if undetected by screening
Important but not critical outcomes	
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 (i.e. true and false positives)

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Table 3

Estimated Relative Reduction (with 95% CI or Range) in Breast Cancer Mortality Associated with Mammography Screening, by Study Design among Pooled Studies

Source	Study design	Sample Size or Population	Age, range, y	Period (range) or Duration of follow-up, y	Exposure or Intervention	Relative Mortality Reduction With Screening (95% CI or Range)
Case-control studies						
Broeders, et al[28]	Meta-analysis of 7 studies; publication years, 2004–2012	18,842	40–>79	1987–2008	Screening mammography Screening mammography (corrected for self-selection), Invitation to screening mammography	OR 0.46, (0.4–0.54) OR 0.52, (0.42–0.65) OR 0.69, (0.57–0.83)
Incidence-based mortality studies						
Broeders, et al[28]	Meta-analysis of 7 studies; publication years, 1997–2010	>2 million	45–69	6–22y	Screening mammography Invitation to screening mammography	RR 0.62, (0.56–0.69 RR 0.75, (0.69–0.81)
Randomized clinical trials						
Gotzsche and Jorgenson,[29]	Meta-analysis of 8 trials; publication years 1963–1991	289,552-invited 309,538-not invited	39–74	7 and 13 y	Screening mammography	RR 0.81, (0.74–0.87)
Model-based estimates						
Berry, et al[4]	7 models		30–79	NA	Screening mammography	Median 15%, (range 7–23)

Table 4

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

Age	Population size (x 1,000)[a]	5-year absolute risk, 2009–2011[b]	Incidence rate, 2007–2011[c]
0–34	71,948	0.2%	5.3
35–39	9,719	0.3%	59.5
40–44	10,532	0.6%	122.5
45–49	11,000	0.9%	188.6
50–54	11,466	1.1%	224.0
55–59	10,592	1.3%	266.4
60–64	9,223	1.6%	346.7
65–69	7,139	2.0%	420.2
70–74	5,265	2.1%	433.8
75–79	4,209	2.0%	443.3
80–84	3,365	1.9%	420.6
85+	3,196	2.5%	354.4

[a]Source: U.S. Census Bureau, Current Population Survey, Annual Social and Economic Supplement, 2012. Internet release date: December, 2013

[b,c]Source: Absolute risk and age-specific incidence rates are from the Surveillance, Epidemiology, and End Results (SEER) Program, SEER 18 registries, National Cancer Institute. Rates are per 100,000 population. Percentages may not sum to 100 due to rounding.

Table 5

Comparison of Current and Previous ACS Guidelines for Breast Cancer Screening in Women at Average Risk[a]

	Recommendations for Breast Cancer Screening	
Population	**ACS, 2015**	**ACS, 2003[5]**
Women ages 40–44	Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. (*Qualified Recommendation[b]*)	Begin annual mammography screening at age 40.
Women ages 45–54	Women should undergo regular screening mammography beginning at age 45 years. *(Strong Recommendation[b])* Women who are ages 45 to 54 years should be screened annually. *(Qualified Recommendation[b])*	Women should have annual screening mammography.
Women ages 55 and older	Women who are 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. *(Qualified Recommendation[b])* Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or more. *(Qualified Recommendation[b])*	Women should have annual screening mammography. As long as a woman is in reasonably good health and would be a candidate for treatment, she should continue to be screened with mammography.
All women	Clinical breast examination is not recommended for breast cancer screening among average-risk women at any age. (*Qualified Recommendation[b]*) All women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.	For women in their 20s and 30s, it is recommended that clinical breast examination be part of a periodic health examination, preferably at least every three years. Asymptomatic women aged 40 and over should continue to receive a clinical breast examination as part of a periodic health examination, preferably annually. Women should have an opportunity to become informed about the benefits, limitations, and potential harms associated with regular screening

[a]Average-risk women are defined as those without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (e.g., BRCA), or a history of previous radiotherapy to the chest at a young age.

[b]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.[12,13]