

New Guidelines for Breast Cancer Screening in US Women

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Despite the substantial interest and investment in research on breast cancer screening, there is uncertainty about the magnitude of mammography's benefits and harms and



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how to select patients and screening strategies to optimize the balance between benefits and harms. In the face of such uncertainty, thoughtful, evidence-based guidelines can play a powerful role in shaping policy and practice, supporting decision making by clinicians and patients, and identifying key research priorities. In this issue of *JAMA*, Oeffinger et al¹ present updated breast cancer screening recommendations from the American Cancer Society (ACS), an influential voice in cancer policy and clinical care in the United States for more than 100 years.²

Since last issuing breast cancer screening recommendations in 2003, the **ACS revised its guideline development procedures to ensure a more transparent, consistent, and rigorous process.**³ This effort was an important step forward in guideline development. In 2003, the ACS recommended annual mammography screening for all women starting at age 40 years and continuing as long as a woman remains in good health and clinical breast examination (CBE) periodically for women in their 20s and 30s and annually for women 40 years and older. **The new guideline, which addresses screening among average-risk women, recommends annual mammography for women aged 45 to 54 years and biennial mammography for women 55 years and older, as long as they are healthy and have a life expectancy of at least 10 years.** The guideline recommends against routine CBE for any woman. The authors give the starting age of 45 years a strong recommendation, while their guidance on screening intervals, screening in older women, and CBE earns qualified recommendations.

Several aspects of this new guideline will be particularly striking to patients, clinicians, and others involved in health care: (1) **the more conservative starting age** for mammography (45 vs 40 years), which brings the ACS recommendations closer to the US Preventive Services Task Force (USPSTF) guidelines (both the 2009⁴ guideline and the April 2015 draft recommendation statement⁵), which endorse biennial screening for women aged 50 to 74 years; (2) **the proposal for more frequent—annual—screening intervals among women aged 45 to 54 years;** (3) **the recommendation against routine screening CBE,** a marked deviation from prior ACS guidelines and a stronger statement than that of the USPSTF, which in 2009 concluded that the evidence was insufficient to recommend for or against CBE; and (4) **the recommendation to stop screening among women with a life expectancy of less than 10 years**

(the USPSTF concluded that evidence is insufficient to assess benefits and harms in women aged ≥ 75 years).

Oeffinger and colleagues,¹ the authors of the guideline, and Myers and colleagues,⁶ the group conducting the accompanying thorough evidence review, made several methodological decisions that led to these novel recommendations. First, the review extensively featured recent observational studies in assessing the benefits of mammography. This provided a wider range of estimates for breast cancer mortality relative risk reductions associated with screening mammography, which tend to be larger for observational studies than for randomized trials. In fact, the guideline provides estimates of number needed to screen for women in their 40s based on an estimated mortality reduction ranging from 20% to 40%,¹ much greater than the 15% estimated from randomized trials.⁷ The authors acknowledge the limitations of observational studies,¹ which include potentially noncomparable control groups, lead-time and length-time bias, and challenges differentiating effects of screening from changes in diagnosis and treatments over time. However, the authors also cite the limitations of the existing randomized trials, which were heterogeneous with regard to mammography exposure and whose findings are increasingly outdated.¹

Second, challenging the conventional strategy of estimating mammography's benefits and harms using 10-year age groups, the authors of the guideline describe the burden of breast cancer using Surveillance, Epidemiology, and End Results data categorized in 5-year age groups, noting that both the absolute risk and distribution of breast cancer deaths are more similar among women aged 45-49 years and 50-54 years than among women aged 45-59 years and 40-44 years. Thus, even though false-positive mammograms are more frequent among younger women, the authors conclude that the ratio of benefits to harms associated with screening 45- to 49-year-old women could be regarded as closer to the ratio among 50- to 54-year-old women.

A third key decision of the guideline's authors was to commission an analysis by the Breast Cancer Surveillance Consortium (BCSC) assessing annual vs biennial screening.⁸ The study assessed the association of screening interval with tumor characteristics among 15 440 women aged 40 to 85 years diagnosed with breast cancer within 1 year of an annual screening mammogram or 2 years of a biennial screening mammogram from 1996 to 2012. The investigators found that the proportion of tumors that were stage IIB or higher and larger than 15 mm was greater for biennial screeners than annual screeners among premenopausal but not postmenopausal women. These findings influenced the guideline recommendation that among women aged 45 to 54 years, screening should occur annually.

Earlier work from the BCSC also suggested potential benefits of annual vs biennial screening in identifying smaller tu-

mors in younger women. One study found that among women aged 40 to 49 years with extremely dense breasts, biennial vs annual mammography was associated with increased likelihood of detection of advanced-stage breast cancer and large tumors.⁹ Nevertheless, other studies have not shown benefits of annual screening among young women; for example, a study in Finland that offered annual vs triennial screening for women aged 40 to 49 years based on birth year found no difference in breast cancer mortality at 13 years by screening interval.¹⁰

Although smaller tumors confer better prognosis than larger tumors,¹¹ the updated BCSC analysis does not provide definitive evidence that annual vs biennial mammography for premenopausal women decreases breast cancer mortality. Thus, despite some face validity in the idea that younger women, who often have more aggressive cancers, might benefit from shorter screening intervals, the actual clinical effects and importance remain uncertain, particularly given the relatively small absolute benefit of screening mammography among younger women, who are less likely than older women to develop or die from breast cancer. Furthermore, as Oeffinger et al¹ describe, annual mammography confers additional harms compared with biennial mammography, including more false-positive results and unnecessary biopsies.¹² Less clear is whether annual mammography increases risk of overdiagnosis. Particular uncertainty exists about the extent of overdiagnosis among younger women. Compared with older women, younger women likely have a lower risk of overdiagnosis related to competing mortality; however, the ratio of ductal carcinoma in situ (DCIS) to invasive cancer is much greater for younger vs older women.¹³ A recent cohort study of long-term mortality after DCIS diagnosis¹⁴ has brought renewed attention to the potential overtreatment of this common condition. Uncertainty about overdiagnosis seriously limits understanding of whether the potential benefits of annual mammography among younger women outweigh the risks.

In a final notable shift, the new ACS guideline recommends against screening CBE, a qualified recommendation based on the “very-low” quality of the evidence on which it is based.⁶ There are no trials comparing the effects of CBE vs no CBE on breast cancer mortality, although several of the mammography randomized trials included CBE in one or both study groups. The Health Insurance Plan¹⁵ and the Edinburgh trial¹⁶ found mortality benefits of mammography and CBE vs neither (although the Edinburgh findings were nonsignificant and its cluster randomized design has been criticized¹⁷). The Canadian National Breast Cancer Screening Study-2 found no benefit of CBE plus mammography vs CBE alone.¹⁸ Although not definitive, these findings together could be interpreted as indirect evidence for potential benefit of CBE. Nevertheless, without direct evidence of benefit and concerns about false positives, with a US-based cohort study estimating that the addition of CBE to mammography detects 0.4 additional invasive cancers per 1000 women, with an extra 20.7 false positives,¹⁹ limited enthusiasm for CBE is reasonable, particularly in settings with available mammography. (Trials of CBE in lower-income settings are ongoing.²⁰⁻²²) Moreover, because a high-quality CBE takes about 3 minutes per breast,²³ the opportunity cost is high, particularly if it comes at the expense of high-quality shared decision making about breast cancer screening or other evidence-based care.

Because some patients may nevertheless expect CBE, clinicians who elect not to perform CBE should share with patients the limited evidence and reasoning behind omitting it.

Will the new ACS guideline make it easier for clinicians and women to make decisions about screening mammography? In some ways, the messages from ACS and the USPSTF, 2 major guidelines, are now more consistent. Both guidelines agree that for average-risk women younger than 45 years, the harms of mammography screening likely outweigh the benefits. For women older than 55 years, biennial mammography is likely to provide the best balance of benefits to harms. The new ACS recommendation to stop screening older women with life expectancies of less than 10 years is practical and consistent with the increasing emphasis on functional vs chronologic age. The more challenging decisions are for women aged 45 to 54 years, for whom ACS recommends annual screening, but for whom the USPSTF recommends no routine screening (age 45-49 years) or biennial screening (age 50-54 years). In communicating with patients, clinicians will have to balance the ACS' recommendation for more frequent screening against the fact that younger women experience a lower absolute benefit from screening mammography. Women and clinicians following the ACS guideline may find it confusing to transition from no screening when younger than 45 years to annual screening from ages 45 to 54 years and then to biennial screening.

A key component of the ACS and USPSTF guidelines is the recommendation that screening decisions be individualized to reflect a woman's values and preferences, as well as her underlying risk of breast cancer (although the current ACS guideline does not address risk assessment in detail because that will be included in a future guideline on screening high-risk women). These recommendations to individualize decisions are stated primarily in the context of decisions to be screened more frequently or at younger ages; however, with increasing recognition of mammography's modest benefits even in women older than 50 years, informed decisions about mammography are important for women of all ages.^{24,25}

As clinicians embark on shared decision making about breast cancer screening with their patients, several key messages are worth highlighting. First, the vast majority of women who are diagnosed with breast cancer will do well regardless of whether their cancer was found by mammography.²⁴ For women in their 40s and 50s, randomized trial evidence suggests that screening mammography modestly decreases breast cancer mortality by approximately 15%.⁷ Although more recent observational studies may suggest a larger benefit, given the methodologic limitations of such studies, it seems that the randomized trial estimates, while imperfect, are likely to be most accurate. Thus, about 85% of women in their 40s and 50s who die of breast cancer would have died regardless of mammography screening. More sophisticated screening tests that confer a greater reduction in breast cancer mortality would likely decrease breast cancer mortality much more than expanding screening mammography for women in their 40s and 50s.

Moreover, because the risk of breast cancer is low for women in their 40s and to some extent women in their 50s, the modest relative benefit of 15% translates to a very small absolute benefit (approximately 5 of 10 000 women in their 40s and 10 of

10 000 women in their 50s are likely to have a breast cancer death prevented by regular mammography).²⁴ The absolute benefit will be higher for women with a higher absolute risk of breast cancer, underscoring the importance of identifying higher-risk women. Especially for average-risk women, decisions to undergo regular mammography screening must also consider the harms of mammography—most notably the possibility of overdiagnosis and resultant overtreatment (age-specific estimates of which are lacking) and also the risks of false positives and unnecessary biopsies (known to be greater in younger women and women screened more frequently).

Despite the vast literature on screening mammography, the evidence needed to help women make decisions remains incomplete. **Better evidence about the extent of overdiagnosis is especially crucial, as is more information about the preferences and decision processes of diverse populations.** In the meantime, it is important to remember and emphasize with average-risk women older than 40 years that there is no single

right answer to the question “Should I have a mammogram?” Instead, women should be supported in estimating and understanding their risk of developing breast cancer and articulating their values and preferences so that clinicians can help them make informed decisions. There is some evidence that decision aids can help women make more informed decisions about mammography,^{26,27} although much more work is needed to get such tools into the hands of patients and their clinicians. Ultimately, better screening tools are needed.

The future of breast cancer screening is likely to entail a more personalized understanding of breast cancer risk, one that incorporates both published risk assessment tools using combinations of known risk factors with newer techniques such as genomics. If women who are at higher risk of aggressive breast cancer could be more accurately identified, for example, it would be possible to more definitively identify those women who are most likely to benefit from earlier and more frequent breast cancer screening and less likely to experience the related harms.

ARTICLE INFORMATION

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