American Cancer Society guidelines for breast cancer screening: update 2003

Robert A. Smith
Debbie Saslow
Kimberly Andrews Sawyer

See next page for additional authors

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American Cancer Society guidelines for breast cancer screening: update 2003

Authors
Robert A. Smith, Debbie Saslow, Kimberly Andrews Sawyer, Wylie Burke, Mary E. Costanza, W. Phil Evans 3rd, Roger S. Foster Jr., Edward Hendrick, Harmon J. Eyre, and Steven Sener

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American Cancer Society Guidelines for Breast Cancer Screening: Update 2003

Robert A. Smith, PhD; Debbie Saslow, PhD; Kimberly Andrews Sawyer, Wylie Burke, MD, PhD (for the High-Risk Work Group); Mary E. Costanza, MD (for the Screening Older Women Work Group); W. Phil Evans III, MD (for the Mammography Work Group); Roger S. Foster, Jr., MD (for the Physical Examination Work Group); Edward Hendrick, PhD (for the New Technologies Work Group); Harmon J. Eyre, MD; Steven Sener, MD (for the Breast Cancer Advisory Group)

ABSTRACT In 2003, the American Cancer Society updated its guidelines for early detection of breast cancer based on recommendations from a formal review of evidence and a recent workshop. The new screening recommendations address screening mammography, physical examination, screening older women and women with comorbid conditions, screening women at high risk, and new screening technologies. (CA Cancer J Clin 2003;54:141-169.) © American Cancer Society, 2003.

INTRODUCTION

The underlying premise for breast cancer screening is that it allows for the detection of breast cancers before they become palpable. Breast cancer is a progressive disease, and small tumors are more likely to be early stage disease, have a better prognosis, and are more successfully treated.1 In this document, we use the term screening to refer to the testing of asymptomatic individuals for the detection of occult disease. Early detection means the application of a technique or strategy that results in earlier diagnosis of nonpalpable, as well as palpable, breast cancers than otherwise would have occurred.

The efficacy of breast cancer screening has been demonstrated in randomized controlled trials (RCTs) and observational studies; thus, most organizations that issue recommendations endorse regular mammography as an important part of preventive care. However, while it is true that screen-detected breast cancers are associated with reduced morbidity and mortality, the majority of women who participate in screening will not develop breast cancer in their lifetime. Screening also will not benefit all women who are diagnosed with breast cancer, and it leads to harms in women who undergo biopsy for abnormalities that are not breast cancer, as well as those who are overtreated for ductal carcinoma in situ (DCIS) that might have been nonprogressive. Thus, in addition to benefits, limitations of screening and harms associated with screening are addressed in this guideline update.

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Dr. Smith is Director, Cancer Screening, American Cancer Society, Atlanta, GA.

Dr. Saslow is Director, Breast and Gynecologic Cancer, American Cancer Society, Atlanta, GA.

Ms. Andrews Sawyer is Cancer Control Researcher, American Cancer Society, Atlanta, GA.

Dr. Burke is Chair and Professor of Medical History and Ethics, University of Washington, Seattle, WA.

Dr. Costanza is Professor of Medicine, University of Massachusetts Medical School, Worcester, MA.

Dr. Evans is Director of Breast Imaging, University of Texas Southwestern Center for Breast Care, Dallas, TX.

Dr. Foster is Wadley R. Glenn Professor of Surgery, Retired, Emory University School of Medicine, Atlanta, GA.

Dr. Hendrick is Research Professor and Director, Breast Imaging Research, Department of Radiology, Lynn Sage Comprehensive Breast Center and the Northwestern Memorial Hospital, Chicago, IL.

Dr. Eyre is Chief Medical Officer and Executive Vice President, Research and Cancer Control, American Cancer Society, Atlanta, GA, and Editor in Chief of CA.

Dr. Sener is Vice Chairman, Department of Surgery, Evanston Northwestern Healthcare, Evanston, IL.

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In 1997, the American Cancer Society (ACS) updated its guidelines for breast cancer screening. The most notable change in the 1997 guideline update was the recommendation that women should begin annual screening at age 40; the previous guideline had recommended mammography every one to two years for women beginning at age 40, and annual mammography for women beginning at age 50. The 1997 update also noted that there was no chronological age at which screening should stop, emphasizing that as long as a woman was in good health she likely would benefit from breast cancer screening. Recommendations for clinical breast examination (CBE) were modified by adding the advice that women 40 and older schedule annual CBE close to the time of, and before, their annual mammograms.

Guideline Development

In 2002, the ACS convened an expert panel to review the existing early detection guidelines based on evidence that has accumulated since the last revision. The panel was divided into work groups to review recent evidence and develop recommendations regarding: (1) mammography; (2) physical examination; (3) screening of older women and women with comorbid conditions; (4) screening high-risk women; and (5) screening with new technologies.

During the current guideline review, literature related to breast cancer screening published between January 1997 and September 2002, including new screening tests, was identified using MEDLINE (National Library of Medicine), bibliographies of identified articles, personal files of panel members, and unpublished manuscripts. Expert panel members reviewed articles using specified criteria and discussed them during a series of conference calls. Each work group developed recommendations, rationale, and evidence summaries, and reviewed the summaries developed by the other work groups prior to a September 2002 workshop. When evidence was insufficient or lacking, the final recommendations incorporated the expert opinions of the panel members. During the conference calls and workshop, consensus was reached on the key issues within the guideline recommendations. Following the workshop, ACS Breast Cancer Advisory Group members deliberated over the guideline modifications. Each work group member and workshop attendee was given the opportunity to review the draft of this manuscript. Numerous professional, advocacy, and governmental organizations also were invited to review the draft guidelines.

RECOMMENDATIONS, RATIONALE, AND EVIDENCE

Summary of Guidelines

A summary of the update of the ACS guidelines for early breast cancer detection is shown in Table 1.

SCREENING WITH MAMMOGRAPHY

Recommendation

Women at average risk should begin annual mammography at age 40. Women should have an opportunity to become informed about the benefits, limitations, and potential harms associated with regular screening.

Rationale and Evidence

Since 1997, there have been updates in the evidence from RCTs of breast cancer screenings. Several other reports have challenged the value of screening for breast cancer with mammography, leading to a surge of new literature reexamining the underlying evidence related to breast cancer screening.
updated clinical trial results from individual studies and meta-analyses continue to show a significant mortality reduction from mammography screening, and this finding is further supported by evidence from organized screening programs.

**Evidence From Randomized Trials of Breast Cancer Screening**

The primary evidence supporting the recommendation for periodic screening for breast cancer with mammography derives from seven RCTs. Two of the trials took place in North America, one in Scotland, and four in Sweden. One additional trial is underway in the United Kingdom evaluating the benefit of beginning screening in a woman’s early 40s.8 At the time of the previous guideline update in 1997, individual trials and meta-analyses of all trials combined showed statistically significant mortality reductions for women aged 40 to 69 associated with an invitation to screening.9-14 Since the last guideline review, updated results from several of the RCTs have been published.15-20

Long-term follow-up data from the UK Trial of Early Detection of Breast Cancer (TEDBC) and from the Edinburgh trial of breast cancer screening were published in the Lancet in 1999.15,16 The TEDBC is a nonrandomized study comparing observed versus expected breast cancer mortality in women aged 45 to 64 in eight centers, consisting of two mammography centers, two breast self-examination (BSE) centers, and four comparison centers. After adjusting for pre-trial mortality rates, breast cancer mortality was 27% lower in women aged 45 to 69 in the two centers in which women underwent mammography compared with the comparison centers. A 35% breast cancer mortality reduction was observed in cohorts aged 45 to 46 at entry into the study. Since the effect began to emerge after three to four years, it cannot be attributed to diagnosis after age 50 among women enrolled into the study in their

<table>
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<th>TABLE 1</th>
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<th>American Cancer Society Guidelines for Early Breast Cancer Detection, 2003</th>
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**Women at Average Risk**
- Begin mammography at age 40.
- 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.
- Beginning in their 20s, women should be told about the benefits and limitations of breast self-examination (BSE). The importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination. It is acceptable for women to choose not to do BSE or to do BSE irregularly.
- Women should have an opportunity to become informed about the benefits, limitations, and potential harms associated with regular screening.

**Older Women**
- Screening decisions in older women should be individualized by considering the potential benefits and risks of mammography in the context of current health status and estimated life expectancy. 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.

**Women at Increased Risk**
- Women at increased risk of breast cancer might benefit from additional screening strategies beyond those offered to women of average risk, such as earlier initiation of screening, shorter screening intervals, or the addition of screening modalities other than mammography and physical examination, such as ultrasound or magnetic resonance imaging. However, the evidence currently available is insufficient to justify recommendations for any of these screening approaches.
In the Edinburgh trial follow-up, the investigators applied an improved method of adjusting for socioeconomic status and censored breast cancer diagnoses more than three years after the conclusion of the study, since cases diagnosed after three years were unlikely to have been prior false negatives; 29% fewer breast cancer deaths were observed in the group invited to screening compared with an initial estimate of 13 percent. The investigators also reported that there was no significant difference in the observed benefit based on age at randomization.

Updated results from the Canadian National Breast Cancer Screening Trial (NBSS-1 and NBSS-2) have been reported since 1997. In 2000, Miller et al. reported 13-year follow-up results from the NBSS-2, which compared annual two-view mammography and CBE with annual CBE only in women aged 50 to 59 at randomization. The authors reported no difference in the breast cancer mortality rate in the group randomized to receive an invitation to annual mammography and CBE compared with the group invited to receive CBE only (RR = 1.02), and concluded that mammography provided no additional advantage compared with carefully conducted CBE. In 2002, the Canadian investigators reported updated results from the NBSS-1, which compared annual mammography and CBE with usual care in women aged 40 to 49. After 11 to 16 years of follow-up there was no difference in the breast cancer mortality rate in the group invited to mammography screening compared with CBE with usual care (RR = 0.97).

In 2000, Tabár and colleagues reported 20-year follow-up of the Swedish Two-County Trial of breast cancer screening. With follow-up through 1998, there was a statistically significant 32% reduction in mortality in women aged 40 to 69 (RR = 0.68, 95% confidence interval (CI) 0.59 to 0.80) associated with an invitation to screening. A larger, consistent effect was observed in each of the two counties for women aged 50 to 69. Results for women aged 40 to 49 differed between the two counties, with a substantial reduction in breast cancer mortality in the W-county (RR = 0.76, 95% CI 0.42 to 1.40), but not in the E-county (RR = 1.06, 95% CI 0.65 to 1.76). Tabár et al. have reported previously that this inconsistency is explained by the observed higher fatality rates in nonattenders to screening in the invited group in the E-county.

Swedish investigators recently updated the overview analysis of the Swedish trials of mammography screening based on follow-up to 1996. With a median follow-up time from randomization to the end of follow-up of 15.8 years, the investigators observed an overall 21% statistically significant reduction in breast cancer mortality among women aged 40 to 74 at randomization associated with an invitation to mammography (RR = 0.79).

As part of the evidence review of the US Preventive Services Task Force (USPSTF), a new meta-analysis of the RCTs was conducted by Humphrey, et al. and published simultaneously with the updated USPSTF guidelines. The meta-analysis of trial results (excluding the Edinburgh trial) from all age groups showed a statistically significant 16% mortality reduction associated with an
Most Recently Published Results of the Breast Cancer Screening Trials on Breast Cancer Mortality Reduction With Invitation to Screening

<table>
<thead>
<tr>
<th>Study Age</th>
<th>Range</th>
<th>Percentage Mortality Reduction (95% CI†)</th>
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<tbody>
<tr>
<td>HIP</td>
<td>40 - 64</td>
<td>24 (7, 38)</td>
</tr>
<tr>
<td>Malmö</td>
<td>45 - 69</td>
<td>19 (-8, 39)</td>
</tr>
<tr>
<td>Two-County Trial, Sweden</td>
<td>40 - 74</td>
<td>32 (20, 41)</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>45 - 64</td>
<td>21 (-2, 40)</td>
</tr>
<tr>
<td>Stockholm</td>
<td>40 - 64</td>
<td>13 (-46, 12)</td>
</tr>
<tr>
<td>Canada NBSS-1</td>
<td>40 - 49</td>
<td>3 (-26, 27)</td>
</tr>
<tr>
<td>Canada NBSS-2</td>
<td>50 - 59</td>
<td>-2 (-33, 22)</td>
</tr>
<tr>
<td>Gothenburg</td>
<td>39 - 59*</td>
<td>16 (-39, 49)</td>
</tr>
<tr>
<td><strong>All Trials Combined</strong></td>
<td><strong>39 - 74</strong></td>
<td><strong>24 (18, 30)</strong></td>
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*There are more recent publications from the Gothenburg trial but they refer only to the under-50 age group.
†CI = Confidence interval.

invitation to screening (RR = 0.84). Similar meta-analyses were conducted for women aged 40 to 49 at randomization, with results leading the authors to conclude that the risk reduction from mammography screening does not differ substantially by age, although absolute benefits are lower in women under age 50 compared with women aged 50 and over. The authors of the updated reports from Edinburgh and the TEDBC reached similar conclusions about age-specific benefits.15,16

The most recent results from the randomized clinical trials are shown in Table 2.24 While there is variation in the observed mortality reductions, a meta-analysis of the most recent results showed a 24% mortality reduction associated with an invitation to screening. Further, although the trials vary somewhat in their design, their results are uniformly consistent with respect to the relationships between the observed shift in stage at diagnosis and reduction in mortality, i.e., those trials that achieved the greatest reduction in the relative risk of being diagnosed with a node-positive breast cancer also have shown the greatest mortality reductions.25,26

In October 2001, the Lancet published a research letter by Ole Olsen and Peter Gotzsche from the Nordic Cochrane Centre in Copenhagen. The authors evaluated the randomized trials of breast cancer screening through meta-analysis, concluding that five of the seven trials were flawed and should not be regarded as providing reliable scientific evidence. Olsen and Gotzsche further suggested that breast cancer mortality was an unreliable endpoint, and that only comparison of all-cause mortality between the experimental and control groups could serve as an unbiased endpoint. Based on their meta-analysis, which was restricted to the Malmö and Canadian trials, the authors found no evidence of a reduced mortality associated with an invitation to mammography (RR = 1.0),

American Cancer Society, Atlanta, GA; Robert A. Smith, PhD, Director, Cancer Screening, American Cancer Society, Atlanta, GA.

Physical Examination Work Group:
Roger S. Foster Jr., MD, (Chair), Wadley R. Glenn Professor of Surgery, Retired, Emory University School of Medicine, Atlanta, GA; Cornelia Baines, MD, Professor, Department of Public Health Sciences, University of Toronto, Toronto, Canada; Lynn Erdman, RN, MS, Vice President, Women’s and Cancer Services, NorthEast Medical Center, Concord, NC; Margaret R. A. Ayres, PT, PhD, Associate Professor, Department of Physical Therapy, Thomas Jefferson University, Philadelphia, PA; Ruby Senior, PhD, Professor of Epidemiology and Sociomedical Science, Mailman School of Public Health, Columbia University, New York, NY; David J. Winchester, MD, Assistant Professor of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL; William C. Wood, MD, Professor and Chairman, Department of Surgery, Emory University School of Medicine, Atlanta, GA; Debbie Saslow, PhD, Director, Breast and Gynecologic Cancer, American Cancer Society, Atlanta, GA; Robert A. Smith, PhD, Director, Cancer Screening, American Cancer Society, Atlanta, GA.

Mammography Work Group:
W. Phil Evans III, MD, (Chair), Director of Breast Imaging, University of Texas Southwestern Medical Center at Dallas, TX; Linda Warren Burrenne, MD, Clinical Professor, Diagnostic Radiology and Breast Imaging, University of British Columbia, Vancouver, BC; Carl J. D’Ora, MD, Professor of Radiology and Hematology/Oncology and Director, Division of Breast Imaging, The Emory Clinic, Atlanta, GA; Stephen A. Feig, MD, Director of Breast Imaging, Department of Radiology, Mount Sinai Hospital, and Professor of Radiology, Mount Sinai School of Medicine, New York, NY; Amy S. Langer, MBA, Executive Director, National Alliance of Breast Cancer Organizations (NABCO), New York, NY; A. Marilyn Leitch, MD, Professor, Department of Surgical Oncology, and Medical Director, UT Southwestern Center for Breast Care, University of Texas Southwestern Medical Center at Dallas, TX; Stephen Sener, MD, Vice Chairman, Department of Surgery, Evanston Northwestern Healthcare, Evanston, IL; Steven H. Woolf, MD, MPH, Professor, Department of Family Practice, Virginia Commonwealth University, Fairfax, VA; Bonnie C. Yankaskas, PhD, Professor, Department of Radiology, University of North Carolina, Chapel Hill,
and concluded that there was no reliable evidence that screening reduced breast cancer mortality. Several guideline groups, national boards of health, and numerous individual authors have provided formal critiques of the methodology and conclusions of Olsen and Gotzsche.20,22,24,26-30 The reviews uniformly concluded that the evidence provided by the Cochrane Review did not support the claim that methodological shortcomings in the conduct of the trials were of such significance to invalidate the conclusion that screening for breast cancer with mammography reduces breast cancer mortality.

Evidence From Service Screening

The inherent limitations of the breast cancer screening RCTs to estimate the benefits associated with exposure to modern mammography have led to increased interest in evaluating the impact of screening in the community setting, also referred to as service screening. Service screening evaluation can estimate breast cancer mortality for women who actually attend community screening programs and for the population as a whole. Service screening evaluation can also be used to attribute differences in mortality over time to screening, improvements in therapy, and increased awareness.31 However, establishing the relative value between screening and nonscreening factors is complex and can be only indirectly estimated.

Blanks, et al. reported on the impact of the UK National Health Service breast cancer screening program in women aged 55 to 69 years between 1990 and 1998,21 estimating a 21.3% reduction in breast cancer mortality, with a smaller direct effect of mammography (6.4%) compared with increased awareness and improvements in therapy (14.9%). Jonsson and colleagues have reported on service screening in Sweden for women aged 40 to 49,33 and 50 to 69,34 and the investigators concluded that the estimated mortality reductions were consistent with the estimates from the RCTs.

Two additional investigations from Sweden were able to classify breast cancer cases before and after the introduction to screening on the basis of exposure to screening.31,33 In the most recent report,35 which expanded an earlier analysis to seven counties in the Uppsala region, Duffy and colleagues compared breast cancer mortality in the prescreening and postscreening periods among women aged 40 to 69 in six counties and 50 to 69 in a seventh county. Overall, they observed a 44% mortality reduction in women who underwent screening and a 39% reduction in overall breast cancer mortality after adjustment for selection bias associated with the policy of offering screening to the population.35 Because the authors were able to distinguish between screened and unscreened cohorts, they estimated that about two-thirds of the observed mortality reductions were attributable to screening, with the remainder due to improvements in therapy and increased awareness. While Blanks, et al. estimate a smaller benefit of mammography, they acknowledge they were unable to identify which among the breast cancer deaths in the postscreening period were from cases diagnosed before screening was health policy.31,35 These data demonstrated that organized screening with high rates of attendance in a setting that achieves a high degree of programmatic quality assurance did achieve breast cancer mortality reductions equal to or greater than those observed in the randomized trials.
Breast cancer mortality reductions associated with screening have been reported from the Florence, Italy Screening program, also comparing breast cancer mortality among attenders and nonattenders to screening, and in the population before and after the introduction of screening between 1990 and 1996. The incidence-based mortality ratio (i.e., the rate of fatal incident breast cancer cases) comparing 1990 to 1996 with 1985 to 1986 shows a 50% reduction in the rate of breast cancer deaths (RR = 0.50, 95% CI 0.38 to 0.66). After excluding the breast cancer cases diagnosed at the first screening examination (i.e., the prevalent screening round), the rate of Stage II or higher breast cancer cases was 42% lower in screened women compared with the women diagnosed with breast cancer that had not been invited to screening (RR = 0.58, 95% CI 0.45 to 0.74). The investigators concluded that breast cancer mortality reductions were attributable to improvements in therapy and the introduction of a breast cancer screening program.

These data demonstrate that modern, organized screening programs with high rates of attendance can achieve breast cancer mortality reductions equal to or greater than those observed in the RCTs. Insofar as additional RCTs of breast cancer screening are unlikely, the evaluation of service screening represents an important new development for several reasons, specifically by measuring the value of modern mammography in the community and measuring the benefit from mammography screening to women who actually get screened.

Screening Intervals

Mortality reductions for women aged 40 to 69 have been observed in trials that screened at intervals of 12 and 24 (and over) months, and thus, some guidelines recommend screening at an interval of one-two years. However, data from two trials and inferential evidence used to estimate the duration of the detectable pre-clinical phase, i.e., sojourn time, have provided persuasive evidence that younger women likely will benefit more from annual screening compared with screening at two-year intervals, a conclusion also reached in the recent USPSTF evidence review. Further, data from both RCTs and from service screening programs have shown that the proportional incidence of interval cancers in the period after a normal screening examination is higher in younger women compared with older women, suggesting faster growth rates in younger women.

Tabár and colleagues have estimated that tumor sojourn times lengthen with increasing age, and using Two-County trial data have estimated the mean sojourn time for women by age as follows: 40 to 49 = 2.4 years, 50 to 59 = 3.7 years, 60 to 69 = 4.2 years, and 70 to 79 = 4 years.

Modeling data also have suggested that progressively shorter screening intervals result in both the detection of tumors at smaller sizes and in decreased mortality rates. Estimating tumor characteristics associated with screening intervals of 24, 12, and 6 months, Michaelson, et al. showed that shorter screening intervals were associated with greater reductions in the proportion of cases diagnosed with distant metastases. Also, in a subsequent modeling analysis of 1,352 women from the Van Nuys Breast Cancer Center between 1966 and 1990, Michaelson, et al. showed that smaller...
tumor size was highly correlated with longer survival time independent of method of cancer detection.41

While sojourn times lengthen with increasing age, these data provide only a limited basis for establishing screening intervals, and in particular, they provide only a rough approximation for an interval that should not be exceeded, since the recommended screening interval should always be shorter than the estimated mean sojourn time. Since the goal of screening is the reduction in the incidence rate of advanced disease, the screening interval should be set for a period of time in which adherence to routine screening is likely to result in the detection of the majority of cancers while still occult and localized. While annual screening likely is more beneficial for all women,1,40,42 the importance of annual screening clearly is greater in premenopausal women (< 55) compared with postmenopausal women. However, given the prognostic value of smaller tumors, and the finding that annual screening results in more favorable tumor characteristics in both pre- and postmenopausal women, annual screening may offer advantages over biennial screening well into the postmenopausal period.43

Limitations of Mammography and Harms Associated With Screening

As is the case with any screening examination, the goal of breast cancer screening is to detect occult breast cancer in a population of women in which the great majority will not have breast cancer on the occasion of a regular examination, and the large majority will not develop breast cancer in their lifetime. Although the efficacy of mammography has been demonstrated, it does not achieve perfect sensitivity or specificity in women undergoing screening, and as such, the issue of adverse consequences for women who do and who do not have breast cancer has been a source of growing attention, and has become one of the core issues in recent debates about mammography. False negatives can be attributed to inherent technological limitations of mammography, quality assurance failures, and human error; false positives also can be attributed to these factors as well as to heightened medical-legal concerns over the consequence of missed cancers. Further, in some instances, a patient’s desire for definitive findings in the presence of a low-suspicion lesion also contributes to false positives. The consequences of these errors include missed cancers, with potentially worse prognosis, as well as anxiety and harms associated with interventions for benign or nonobligate precursor lesions.

This issue of limitations and harms is both important and complex, since mammography’s shortcomings are due to the interplay between host characteristics (age, risk, breast density, and tumor growth rates) and provider factors (technical limitations and quality assurance failures). Thus, theoretically, there is at least some level of limitations and harms that is inherent to breast cancer screening and unavoidable. Beyond this level are potential improvements in screening and reductions in harms that could be achieved through various technical and system-related interventions. This relationship between risk, benefit, limitations, and harms is complicated by the fact that not only is it multifactorial, but also that individual women likely will weigh the benefits, limitations, and harms of screening differently depending on their age, values, and their understanding of the issues. Still, there is concern that the rate of false-positive mammography and benign biopsy is excessive and could be reduced with improvements in screening quality, although other factors such as medical-legal pressures and individual anxiety about uncertainty may partly be outside the influence of additional improvements in quality.44 There also is agreement that steps should be taken to reduce anxiety associated with screening,45 i.e., the waiting time to
diagnosis, and that there should be conscientious efforts applied toward informing women about the likelihood of both false-negative and false-positive findings.

A number of investigations have attempted to measure the extent of psychological and physical harms associated with false-positive mammography and, in particular, have attempted to identify whether or not harms are lasting and have consequences for psychological well-being and subsequent screening. In general, the evidence suggests that some women experience anxiety related to screening, and a greater percentage experience anxiety related to false-positive results, but for most women psychological distress is short-lived and does not have lasting consequences on either stress levels or likelihood of subsequent screening. A recent study by Schwartz and colleagues revealed that women are aware that false-positive results occur, accept false-positive results as a part of screening, and do not regard false positives as an important harm in the context of the underlying goal of early breast cancer detection. However, women’s awareness of the chance of a false-positive finding and acceptance of false positives as a cost of screening should not detract from organized efforts to provide information about the range of screening outcomes, to achieve an acceptable rate of false-positive results in screening programs, and to mitigate the spectrum of harms. Further, health professionals must become more sensitive to both short-term and long-term effects of false-positive results.

As use of mammography has increased, concerns have been raised about detection and overtreatment of DCIS. Although the detection of DCIS is an inevitable consequence of mammographic screening, the concern that not all DCIS is progressive has to be weighed against the estimate that a substantial portion is progressive. The actual fraction is not known, and historical estimates from case series may not be directly generalizable to cases identified through mammographic screening. However, in one series, invasive breast cancer developed in over half of women with low-grade DCIS lesions identified on biopsy but not treated. Further, incomplete excision of DCIS or failure to excise DCIS associated with an invasive cancer is a determinant for local failure. As with invasive breast cancer, the histologic subtype and grade of DCIS can be regarded as having prognostic value in relation to risk of recurrence of invasive cancer or DCIS. Thus, there is little question that some women benefit from detection and treatment of DCIS. However, since some DCIS is not progressive, diagnostic evaluation and treatment of DCIS lesions that would not progress to invasive disease is a harm associated with screening, although the extent of harm is uncertain, as is how it might be avoided. Overtreatment of a progressive DCIS lesion that could be cured with less aggressive treatment also represents a harm, although it should not be attributed to screening.

At this time, the majority of detected DCIS occurs as a result of identification of small lesions on a mammogram that are perceived to be important. It is not possible through image evaluation to either distinguish DCIS from invasive breast cancer or progressive DCIS from nonprogressive DCIS. Schwartz and colleagues have recommended that information provided to women undergoing mammography should include a discussion about detection of DCIS. Important questions remain about how to identify those noninvasive ductal cancers that are most likely to progress to become invasive cancers.

PHYSICAL EXAMINATION

Recommendations

Clinical Breast Examination

For average-risk asymptomatic women in their 20s and 30s, it is recommended that CBE be part of a periodic health examination, preferably at least every three years. The exam
should include BSE instruction for the purpose of gaining familiarity with breast composition. Information should be provided about the benefits and limitations of CBE and BSE, and it should be emphasized that breast cancer risk is very low for women in their 20s and gradually increases with age. The importance of prompt reporting of any new symptoms to a health professional also should be emphasized.

Asymptomatic women aged 40 and over should continue to receive CBE as part of a periodic health examination, preferably annually. Beginning at age 40, discussion during CBE should include information about screening mammography. There may be some benefit to performing the CBE shortly before the mammogram. At the time of CBE, the benefits and limitations of physical examination and mammography should be discussed with the patient.

**Breast Self-Examination**

Beginning in their 20s, women should be told about the benefits and limitations of BSE. The importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination. It is acceptable for women to choose not to do BSE or to do BSE irregularly.

**Rationale and Evidence**

The logic for the earlier detection of clinical findings in the breast is analogous to the logic for detecting breast cancer before a tumor is palpable. With increasing tumor size, even after breast cancers become palpable, the likelihood of regional and distant metastasis increases. Long-term survival measured either with registry data or with data from RCTs is poorer with each incremental 5 mm increase in tumor size. For average-risk women under age 40, earlier detection of palpable tumors with CBE or BSE can lead to earlier therapy. After age 40, CBE and BSE are regarded as adjunctive because mammography does not achieve perfect sensitivity. Although there are no direct clinical data linking an increased rate of breast preservation to CBE or BSE, it is plausible that earlier detection of symptomatic breast cancer results in a greater probability for a breast conserving approach.

The evidence supporting the value of CBE and BSE as methods of reducing breast cancer mortality is limited and mostly inferential, although there is no definitive prospective RCT evidence from which to draw conclusions about either exam. Thus, current recommendations rely on existing evidence, but also on expert opinion based on a recognition that population-based studies continue to show a relatively large proportion of self-detected cancers.

**Clinical Breast Examination**

Today, mammography and clinical breast examination are recommended to women 40 and older because: (1) there are RCT data showing the combination of mammography and CBE was associated with lower breast cancer mortality, and (2) evidence from these RCTs and demonstration projects showed that some cancers detected by CBE were not detected by mammography. The USPSTF recommends mammography with or without CBE, and it has concluded that there is insufficient evidence to recommend for or against breast cancer screening with CBE alone.

Evaluation of CBE as a detection modality has generally focused on the performance characteristics of the test, i.e., sensitivity, specificity, and positive predictive value. On all aspects, performance characteristics are poorer than those of mammography. Sensitivity of CBE in particular was estimated in a recent meta-analysis to be only 54 percent. While noting that two trials
demonstrated breast cancer mortality reductions associated with the combination of mammography and CBE, the USPSTF concluded there was insufficient evidence to quantify the incremental benefits of adding CBE to mammography. This particular question is more pertinent today, since much of the RCT data related to the value of CBE combined with mammography derives from a period that predates modern breast imaging. The proportion of breast cancers not visible with modern, high-quality mammography appears to be considerably lower today than in the past.

Based on findings from 752,081 CBEs, Bobo and colleagues reported that 6.9 percent of all CBEs were coded as abnormal, and that five cancers were detected per 1,000 examinations. However, only 5.1 percent of the malignancies (193/3,753), or 2.56 per 10,000 CBE exams, were detected in women with an abnormal CBE and benign findings on the mammogram. Since women with self-detected breast symptoms were 7.2 times as likely to have an abnormal exam, it is likely that some proportion of these CBE-positive cases were first detected by women themselves, leading to an even lower rate of breast cancer detection attributable to CBE alone. Newcomer, et al. recently reported on the mode of detection in 2,341 Wisconsin women greater than or equal to the age of 50 diagnosed with breast cancer from 1988 to 1991. Women were asked how their breast cancer was first discovered—48 percent were self-detected, 41 percent were detected by mammography, and 11 percent were detected by CBE. Oestreicher, et al. evaluated the sensitivity of CBE in 468 women diagnosed with breast cancer within a year of a screening CBE. Overall sensitivity was estimated to be 35 percent, but the majority of these cases (83.6 percent) also were detected by mammography. Among women with false-negative mammograms, 37 percent were detected by CBE, but overall only 5.7 percent (n = 27) of breast cancers were diagnosed by CBE only. Sensitivity ranged from 17.2 percent for tumors less than or equal to 0.5 cm to 58.3 percent for tumors greater than or equal to 2.1 cm, and was lower in younger women and women with higher body weight.

At this time, it is unclear what CBE contributes to detection of breast cancer, although it is likely that in presumably asymptomatic women the contribution is small. When done prior to mammography, CBE may identify an area of suspicion that will not be visible on mammography and/or provide information that guides subsequent imaging exams. As a growing proportion of women are receiving regular mammograms, the relative contribution of CBE to early breast cancer detection and its cost-effectiveness warrant renewed attention. At this time, in women screened with mammography, the cancer detection rate for CBE appears to be low, and the evidence for breast cancer mortality reduction associated with CBE is weak and indirect.

However, apart from some contribution to breast cancer detection, CBE may serve an additional, separate function: it can provide the occasion to raise awareness about breast cancer and to provide accurate education on the variety of breast cancer-related topics, including information about breast symptoms, genetics, risk factors, and newer cancer detection technologies. The consensus opinion of the ACS review panel was that until more informative scientific evidence is available, periodic CBE is recommended with the additional endorsement that the occasion of a CBE should be used to raise awareness about the early detection of breast cancer. In rendering this opinion, there were some panel members who believed that the evidence against the benefit of CBE was not strong enough to abandon the recommendation, while other panel members believed that the recommendation for CBE was not evidence-based and should be eliminated.
Breast Self-Examination and Self-Detection

The goal of periodic BSE, as with CBE, is to detect palpable tumors. An additional role of BSE is to increase awareness of normal breast composition, so that there is heightened awareness of changes that may be detected during BSE or at some other time. The value of heightened awareness, however it may be achieved, is commonly acknowledged based on the value of earlier treatment of both nonpalpable and palpable breast cancers. Stockton, et al. attributed a shift toward more favorable stage at diagnosis and declining breast cancer mortality in the 1980s in East Anglia to increasing awareness and prompt reporting of signs and symptoms of breast cancer that began before the beginning of a breast cancer screening program.

The first studies suggesting possible effectiveness of BSE were published in 1978. These two studies and many additional studies in the premammography era found that in general, women who reported that they had been BSE performers had their breast cancers detected at a smaller size and at earlier clinical and/or pathologic stage. Regular performance of BSE did not mean that the breast cancer was necessarily self-detected during a formal BSE procedure. Even regular BSE performers commonly detected their breast cancer incidentally, suggesting that there was a component of increased body awareness (or perhaps increased awareness of subtle symptoms) in addition to the self-performed physical examination.

The literature on the effectiveness of BSE as a detection modality has shown mixed results, but recent evidence reviews have focused on the absence of direct evidence of benefit in two RCTs, and data indicating that the rate of benign biopsy is higher in women who regularly perform BSE compared with women who do not regularly perform BSE. The USPSTF concluded that the evidence is insufficient to recommend for or against teaching or performing routine BSE. The Canadian Task Force on Preventive Health Care went further and recommended against routine instruction in BSE in periodic health examinations on the basis of fair evidence of no benefit and good evidence of harm (false-positive results). The Canadian Task Force did recommend that women should be taught to promptly report any breast changes or concerns, and those women who choose to practice BSE should receive careful instruction as well as information about risks, benefits, and limitations. However, in an accompanying editorial, Neklyudov and Fletcher argued that the existing data do not provide a sound basis for dismissing the value of BSE based on both the limitations in the RCT data and observational studies, and on the basis of the principle that when evidence is lacking, it is best to err on the side of prudence.

There are a number of methodological challenges to the evaluation of BSE, not the least of which is the difficulty of measuring adherence and competence. While early and recent null results from the Shanghai trial are commonly cited as evidence that BSE is ineffective, the investigators have cautioned that the trial was a study of BSE instruction and not BSE per se, and that it should not be inferred that there would be no reduction in the risk of dying from breast cancer if women practiced BSE competently and frequently. However, the findings do suggest that in populations where heightened awareness and prompt reporting of breast symptoms is common, BSE may offer less potential for earlier interventions than in populations where awareness is low and presentation of large, advanced tumors is more common. The value of BSE may be even lower for women with heightened awareness who are having regular mammograms.

As with CBE, it is unclear what BSE instruction, irregular BSE, or adherent, highly competent BSE contributes to earlier detection of and reduced mortality from breast cancer.
However, given variable adherence to screening guidelines, imperfect sensitivity, and uneven access to mammography, incidental self-detection of breast cancer still accounts for a significant percentage of incident cases. For these and other reasons, women should be encouraged to be aware of how their breasts look and feel in order to be able to recognize any changes and promptly report them.

As with CBE, there were some panel members who believed that the evidence against a benefit of BSE is not strong enough to abandon the recommendation, while other panel members believed that there was insufficient evidence to continue to recommend BSE.

Need for Further Research

The evidence supporting the value of CBE and BSE is largely inferential. The most recent literature reviews revealed the limitations of the current data for drawing evidence-based conclusions about the value of physical exams. The ACS review panel recognized that there were fundamental questions about the value of physical examinations in average-risk asymptomatic women that should be addressed in a research agenda. The actual contributions of CBE and BSE to the detection of breast cancer, training and performance issues, the importance of heightened awareness of breast cancer signs and symptoms, as well as understanding how that awareness is achieved and maintained, represent important areas for research.

MAMMOGRAPHY SCREENING IN OLDER WOMEN

Recommendation

Screening decisions in older women should be individualized by considering the potential benefits and risks of mammography in the context of current health status and estimated life expectancy. 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. However, if an individual has an estimated life expectancy of less than three to five years, severe functional limitations, and/or multiple or severe comorbidities likely to limit life expectancy, it may be appropriate to consider cessation of screening. Chronological age alone should not be the reason for the cessation of regular screening.

Rationale and Evidence

The size of the older population is growing exponentially. Persons over age 65 years currently represent approximately one-eighth of the US population (35 million), and their numbers are expected to double in the next 20 years (accounting for one in five Americans). Increasing numbers of women and their health care providers are faced with questions about whether and when to end breast cancer screening. They will be required to make judgments on the balance between the potential benefits of screening—reduction of breast cancer morbidity and mortality resulting from early detection—and potential harms, which among women with comorbidity or limited longevity could cause suffering and diminished quality of life in remaining years without appreciable benefit. The balance of this equation shifts with chronological age, life expectancy, comorbidity, and functional limitation.

Disease Burden

Diagnosis of invasive breast cancer in women aged 65 and older accounts for approximately 45 percent of all new breast cancer cases, and diagnosis of breast cancer in women aged 65 and older accounts for about 45 percent of all breast cancer deaths. Breast cancer mortality increases with advancing age, ranging from 86 deaths per 100,000 women aged 65 to 69 years to 200 deaths per 100,000 women aged 85 years and older. Although incidence and...
mortality rates are higher in older women, the question of screening in this population must be considered in the context of competing risks of death from comorbid conditions, limited longevity, and a woman’s overall health status.

Characteristics of the Disease: Biology of Breast Cancer in Older Women

Theoretical considerations suggest that older women may have a higher prevalence of less aggressive tumors than younger women. In general, the growth rate of a tumor is related to its aggressiveness: if less aggressive tumors have longer sojourn times (i.e., a longer mammographically detectable preclinical phase), they are also more likely to become manifest later in life and to be more prevalent among older individuals. Clinical observations support this hypothesis. Nixon, et al. and Lyman, et al. have shown that the prevalence of poorly differentiated (Grade 3) tumors decreases, and the prevalence of hormone-receptor-rich tumors increases as the age of the patient population increases. Evidence also suggests that growth and metastatic spread of breast cancer is slower in older women compared with younger women. In a series of 819 Finnish women, Holmberg, et al. found that for tumors of similar size, the prevalence of axillary lymph node involvement decreased with the age of the patient after age 55. Tabár and colleagues reported that for any given tumor size, the presence of Grade 3 tumors and the likelihood of nodal involvement are lower in older women compared with younger women. These data indicate that the prevalence of less aggressive tumors increases with age.

While overall lower aggressiveness of breast cancers in older women offers greater potential for detection at a favorable stage and successful treatment, it is important to emphasize that breast cancer is a potentially lethal disease at any age. Regardless of patient age, larger tumor size is associated with higher nuclear grade, greater risk of nodal involvement, and a poorer outcome. Thus, the greater prevalence of less aggressive tumors should not result in less vigilant efforts focused on early detection and treatment of breast cancers in older women.

Effectiveness of Mammography in Older Women

There are limited data on the efficacy of screening mammography in women over the age of 69. Only one RCT included women older than 69. Published screening studies have concluded that the performance and effectiveness of mammography is at least as good if not better in women aged 70 and older compared with younger women. In the absence of more definitive data, groups that have issued screening guidelines have reached the same conclusion.

Rosenberg, et al. used a population-based database and statewide tumor registry in New Mexico to study the factors (including age) affecting mammography sensitivity and stage at diagnosis. Among women 65 and over (47,000 examinations), sensitivity was 81 percent; the sensitivity for women aged 50 to 64, 40 to 49, and less than 40 was 78 percent, 77 percent, and 54 percent, respectively. For women older than 65 who did not have dense breasts, Rosenberg’s study showed that the sensitivity for the detection of breast cancer was comparable regardless of whether the women used hormone replacement therapy (83 percent versus 86 percent). However, for women over age 65 with dense breasts, screening mammography sensitivity was lower among women on hormone replacement therapy compared with women not on hormone replacement (64 percent versus 84 percent). Because there are many complex issues, unanswered questions, and research needs related to hormone replacement therapy and mammographic density, there is insufficient evidence at this time to make a specific recommendation regarding differential screening for older women who take hormone replacement therapy and/or who have radio-
graphically dense breasts.

Faulk compared data for women in the age groups 50 to 64 and 65 and over. Abnormal mammogram interpretations and number of biopsies were comparable among the women in both groups, but positive predictive value, biopsy yield, and rate of cancers per thousand screens were higher in the older age group as would be expected on the basis of higher disease prevalence. In the same study, there also was a tendency toward lower stage at diagnosis in the group of older women.

Data from the screening mammography program of British Columbia showed comparable abnormal interpretation rates for women aged 70 and above compared with women 40 to 69 but higher cancer detection rates. Medical audit data from the University of California, San Francisco, on a small number of older women showed similar results. In other words, while the likelihood of an abnormal mammogram is similar across age groups, the cancer yield is greater with increasing age.

Smith-Bindman, et al. studied female California Medicare beneficiaries aged 66 to 79 years. In this series, the risk of detecting metastatic breast cancer was significantly reduced among women 60 to 79 years who underwent screening mammography, with a RR of 0.57 (CI 0.45 to 0.72). Although these data are indirect, these findings are consistent with evidence from the randomized trials demonstrating that sensitivity increases due to decreased density, and positive predictive value increases due to high prevalence, making yield higher in older versus younger women.

Sojourn Time and Screening Interval

As noted earlier, the length of the sojourn time increases with increasing age, and is estimated to be approximately four years for women aged 70 to 79. Longer sojourn times in older women have raised the question of whether a subset of screen-detected incidence cases represent overdiagnosis, i.e., detection of cases that would not have been manifested clinically in the patient’s lifetime. One method of estimating overdiagnosis is the prevalence screen predictive index (PSPI), which is the proportion of tumors diagnosed at a prevalence screen that would have arisen clinically if screening had not taken place. From evaluation of Two-County Trial data, Tabár and colleagues estimated that the percentage of the PSPI tumors for women aged 70 to 79 is 87 percent, and for women aged 50 to 69 it is 100 percent. Thus, there is little or no evidence to suggest that there is significant overdiagnosis of breast cancers by mammographic screening of older women.

As noted above, Field, et al. showed that shorter screening intervals in women aged 65 and over also were associated with more favorable tumor characteristics. In this small study, the average tumor size in women who had undergone annual screening (N = 93) was 10.7 mm (median = 9.5 mm), and for women who had undergone biennial screening (N = 27), the average tumor size was 16.5 mm (median = 15 mm). Seventy-two percent of the women who had undergone annual screening had a tumor T1bN0 or less, whereas only 44 percent of the women who underwent biennial screening were of comparable stage.

The lengthening of the sojourn time with increasing age was among the important factors contributing to greater mortality reductions observed in older versus younger women in the R.CTs and is a basis for offering screening at wider intervals to older women in some service screening programs. However, inferential evidence suggests that annual screening still results in more favorable tumor characteristics at diagnosis compared with screening every two years, although the magnitude and importance of this difference is less for postmenopausal women compared with premenopausal women. Based on inferential evidence and expert opinion, the majority of panel members endorsed continuing to recommend annual screening for younger and older women.
Comorbidity and Breast Cancer

With advancing age, incidence of breast cancer remains high, breast cancer mortality rate increases, but overall life expectancy decreases. Because the survival benefit from screening mammography takes several years to emerge, consideration of the effectiveness of screening mammography in older women must address issues of comorbidity and life expectancy as well as questions of test performance.93,94

In the National Health Interview Survey (NHIS), the percentage of women who reported two or more comorbid conditions increased from 45 percent among those aged 60 to 69 years to 61 percent for those aged 70 to 79 to 70 percent for those aged 80 years and over.95 Results of one national study indicated that many older people with cancer are concurrently being treated for other conditions that include arthritis, hypertension, and heart disease.96 However, these data also revealed that there are significant numbers of older individuals who are in good health. A central issue is whether detecting early stage breast cancer confers an advantage among women with comorbidity as it does among women without comorbidity. Breast cancer patients with comorbidity have poorer chances of survival than patients without comorbidity after adjustment for other prognostic indicators, such as stage of disease at diagnosis, tumor grade, and histology.97-102 Diabetes, renal failure, stroke, liver disease, and a previous cancer were among the conditions that predicted early mortality among women with breast cancer.97,102 Satariano and Ragland found that the relative risk of breast cancer death declined, but the relative risk of deaths due to other causes increased as the number of comorbid conditions increased.97 A study by McPherson and colleagues based on breast cancer cases detected by screening mammography in women aged 65 to 101 from the Upper Midwest Oncology Registry System found a significantly lower relative risk of death for women without multiple comorbidities than for women with multiple comorbidities. However, women with multiple or severe comorbidities comprised only 13 percent of 5,186 women.98 It is important to remember that many women in older age groups will not have comorbidity severe enough to negate the benefits in survival and quality of life derived from screening.

Life Expectancy

At age 70, the average life expectancy for a woman in the United States is 15.4 years. Indeed, even women at very advanced ages may be expected to have considerable additional years of life, as is shown in Table 3.

Cancer screening decisions in older women are complicated by the heterogeneity in health status of this population. As noted above, there is great variation in number and severity of comorbidities, suggesting that screening guidelines based solely on chronological age are incomplete. Figure 1 shows the distribution of life expectancy for US women according to the upper, middle, and lower quartiles of life expectancy at each age. For example, approximately 25 percent of 75-year-old women will live more than 17 years, 50 percent will live at least 11.9 years, and 25 percent will live less than 6.8 years.99

In using Figure 1 to anchor life expectancy

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<th>Age</th>
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estimates, physicians can assess many clinical variables to determine whether a woman is typical of someone in the lower quartile of life expectancy for her age or is more likely to be in the middle or upper quartile. For example, conditions such as congestive heart failure (Class III or IV), end-stage renal disease on dialysis, oxygen-dependent chronic obstructive pulmonary disease, or moderate to severe dementia would result in a life expectancy in the lowest 25th percentile. Figure 1 shows that women 80 years old and older in the lowest quartile have life expectancies of less than five years, so the likelihood that they will benefit from screening mammography is comparatively lower than women in upper quartiles. Conversely, up until age 85, most women have a life expectancy exceeding five years, as do some very healthy 90-year-old women. These women potentially may benefit from screening mammography. These data reveal that estimating longevity requires consideration not only of chronological age but also the presence of chronic conditions.

Finally, some older women with physical or cognitive problems may be particularly vulnerable to the burdens, discomfort, and anxiety associated with screening. However, there is evidence that some physicians overestimate physical, cognitive, and even financial burdens of screening, and may fail to refer older women for mammography based

on the anticipation that the patient will refuse to be screened. These are challenging circumstances for the physician and the patient, and there will be individuals where foregoing screening is appropriate. Talking to patients and if appropriate, with an involved caregiver, about personal preferences and the balance of benefit to harm can lead to a shared decision that is appropriate.93

Though estimations of life expectancy that incorporate severity of comorbidity and functional impairments are imperfect predictors of longevity, they allow for a more complete consideration of the potential benefits and harms of screening mammography than simply focusing on chronological age.

**ACCEPTABILITY, QUALITY OF LIFE, AND HARMS ASSOCIATED WITH SCREENING**

Although the majority of women understand that false-positive test results are an inevitable part of screening,48 abnormal mammogram results can result in significant short-term psychological distress as well as increased health care utilization and costs.49,108,109

Previous work has identified a number of domains, particularly psychosocial, that are affected during the interval from notification of an abnormal mammogram to determination that cancer is absent. Though the overwhelming majority of these studies have been conducted in younger women, there is no reason to believe that the effects of a false-positive screening result will vary substantially by age. However, these effects, when noted, are generally transient,17,109-112 have no effect on endocrine and immunological function,113 and are inversely related to the time from abnormal notification to resolution with a result of benign pathology.17 The short-term experiences following false-positive mammogram results have not been consistently linked to future screening behaviors.114

One concern frequently raised about screening older women with a life expectancy of five to ten years is the detection and treatment, including overtreatment, of DCIS. As stated earlier, detection of DCIS is an inevitable consequence of mammography screening. The rate of screen-detected DCIS increases with age but is a lower proportion of screen-detected breast cancers in older women compared with younger women.113 It is important to note that the incidence rate of invasive disease dwarfs that of DCIS, and it is not currently possible to identify which in situ cancers will progress to become invasive. While it would be shortsighted to forgo screening older women because of the possibility of detecting DCIS, treatment decisions for older women with DCIS should include consideration of life expectancy and health status.

**EARLY DETECTION OF BREAST CANCER IN WOMEN AT INCREASED RISK**

**Recommendation**

Women at increased risk of breast cancer might benefit from additional screening strategies beyond those offered to women of average risk, such as earlier initiation of screening, shorter screening intervals, or the addition of screening modalities (such as ultrasound or magnetic resonance imaging [MRI]) other than mammography and physical examination. However, the evidence currently available is insufficient to justify recommendations for any of these screening approaches. In lieu of recommendations, points of discussion have been developed for women at increased risk and their health care providers when considering screening options. These points are based on the limited available evidence and expert opinion. Decisions about screening options for women at increased risk of breast cancer should be based on shared decision-making after a review of potential
benefits, limitations, and harms of different screening strategies and the degree of uncertainty about each. In order to pursue answers to unresolved questions, important elements of a research agenda are identified, and efforts to collect needed outcome data are encouraged.

Identification of Women at Significantly Increased Risk

Over the years, a number of risk factors have been identified for breast cancer. Overall, the most important risk factors are age and sex. Although approximately one percent of all cases are in males, the remainder is in females, and risk increases with age. After controlling for age, the greatest increase in risk has generally been associated with a family history of breast and/or ovarian cancer, with the number, type, and age at onset of affected relatives being important determinants of risk. Within the group of women with a family history of breast and/or ovarian cancer, a relatively small subset of women with inherited mutations deserves special mention. Over the past decade, two breast/ovarian cancer susceptibility genes have been identified, named BRCA1 and BRCA2. Women who are known carriers of mutations in either of these two genes have particularly high risks of breast and ovarian cancer. Although only laboratory testing can confirm that a woman carries a deleterious mutation in one of these genes, genetic and epidemiologic studies document several family history characteristics that suggest an increased risk of breast cancer. These reflect the autosomal dominant mode of inheritance and include:

- Two or more relatives with breast or ovarian cancer;
- Breast cancer occurring before age 50 in an affected relative;
- Relatives with both breast and ovarian cancer;
- One or more relatives with two cancers (breast and ovarian cancer or two independent breast cancers);
- Male relatives with breast cancer;
- A family history of breast or ovarian cancer and Ashkenazi Jewish heritage.

In general, the likelihood of inherited breast cancer risk is higher when the biologic relationship of the affected relative is closer, e.g., when cancer occurs in a first-degree relative (such as a mother or sister) rather than in a second-degree relative (such as a grandmother or aunt). However, risk can be inherited equally from maternal and paternal sides of the family, and when risk is inherited from the paternal side, there may be no apparent affected first-degree relatives.

Several statistical models exist that attempt to predict the risk of breast cancer for women with identifiable factors associated with the disease. Within the group of women with a family history of breast and/or ovarian cancer, a relatively small subset of women with inherited mutations deserves special mention. Over the past decade, two breast/ovarian cancer susceptibility genes have been identified, named BRCA1 and BRCA2. Women who are known carriers of mutations in either of these two genes have particularly high risks of breast and ovarian cancer. Although only laboratory testing can confirm that a woman carries a deleterious mutation in one of these genes, genetic and epidemiologic studies document several family history characteristics that suggest an increased risk of breast cancer. These reflect the autosomal dominant mode of inheritance and include:

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addition, it has been shown that while these models are accurate for groups of women with a particular risk factor, they are less successful in estimating risk for an individual woman.\textsuperscript{137,138} Thus, the risk estimates generated from these models should not be considered precise but rather a means to identify subsets of women at increased risk.

The threshold for defining a woman as having elevated risk of breast cancer is based on expert opinion. Any woman with a \textit{BRCA1} or \textit{BRCA2} mutation should be considered at high risk. If mutation testing is not available, or has been done and is noninformative, pedigree characteristics suggesting high risk (as noted above) are also considered to be an indicator of increased risk. Risk assessment is likely to offer the greatest potential benefit for women aged less than 40.

Additional factors that increase the risk of breast cancer and thus may warrant earlier or more frequent screening include previous treatment with chest irradiation (e.g., for Hodgkin disease), a personal history of breast cancer, or a family history of diseases known to be associated with hereditary breast cancer such as Li-Fraumeni or Cowdens Syndromes.

Screening Options for Women at Increased Risk

Four screening options may be considered for women at increased risk of breast cancer:

- Initiation of mammography screening at age 30 or, rarely, at younger ages;
- Shorter mammography screening intervals, e.g., every six months;
- Addition of MRI screening;
- Addition of ultrasound screening.

\textit{Initiation of Mammography Screening at Age 30}

The age at which screening should be initiated for women at high risk is not well established. The argument for early screening is based on the cumulative risk of breast cancer in women with \textit{BRCA1} mutations and a strong family history of early breast cancer, which is estimated to be three percent by age 30 and 19 percent by age 40.\textsuperscript{139} Population-based data also indicate that risk for early breast cancer is increased by a family history of early breast cancer.\textsuperscript{134,140} Based on these observations, some experts have suggested that breast cancer screening begin five to ten years prior to the earliest previous breast cancer in the family. In 1997, an expert panel suggested that screening be initiated at some time between the ages of 25 and 35 for women with a \textit{BRCA1} or \textit{BRCA2} mutation.\textsuperscript{141} Because these recommendations were based on limited observational data, the decision regarding when to initiate screening should be based on shared decision-making, taking into consideration individual circumstances and preferences.

\textit{Mammography}

There are no RCT data and few observational data to assess mammography screening in high-risk women younger than age 40. Although a number of observational studies have evaluated screening in young women at increased risk, most of the subjects in these studies have been between the ages of 40 and 50. However, the breast cancer incidence observed in these studies confirms that family history indicators and \textit{BRCA1/2} mutation status can identify women at increased risk of breast cancer, and that mammography has performance characteristics in high-risk young women similar to those in women from the general population at older ages.\textsuperscript{90,142} High-risk women under age 50 who have regular screening are more likely to be diagnosed at earlier stages and tend to have more favorable tumor characteristics than those who do not have regular screening. Thus, initiation of mammography screening under age 40 may permit the identification of early breast cancer in women at significantly elevated risk, in
particular, women with *BRCA1* and *BRCA2* mutations.\textsuperscript{143}

Sensitivity and specificity of mammography are not well established in women under age 40. In general, accuracy measured by both sensitivity and specificity is lower in younger women compared with older women but still is favorable, and both sensitivity and specificity improve incrementally as women get older.\textsuperscript{90} Several studies have provided evidence for an increased risk of breast cancer after therapeutic radiation exposure or multiple exposures to diagnostic radiation.\textsuperscript{144-146} Overall risk from single and cumulative diagnostic exposures is small, but risk increases with the amount of exposure and with younger age at exposure.\textsuperscript{146,147} Thus, it is theoretically possible that cumulative radiation exposure associated with screening mammography increases the risk of breast cancer.\textsuperscript{148} It has also been hypothesized that some women at increased inherited risk for breast cancer may also have increased radiation sensitivity, which could increase their risk for radiation-induced breast cancer. This hypothesis may be plausible because studies of *BRCA1* and *BRCA2* suggest that these genes code for functions related to repair of radiation damage to DNA.\textsuperscript{149-153} However, in a report from a multi-institutional study, there was no evidence of increased radiation sensitivity in 71 *BRCA1/2* carriers receiving radiotherapy after breast-conserving surgery, within the five-year follow-up of the study.\textsuperscript{154,155} In addition, in a second study, family history did not influence treatment outcome among women who received breast-conserving surgery and radiation therapy.\textsuperscript{156} Even if the highest estimates of increased risk of radiation-induced cancers from low mammographic doses beginning at a younger age are true, the risk-benefit equation still favors mammography screening for most or all women, particularly if radiation exposure from the screening process is kept as low as possible.\textsuperscript{148} However, given concerns and uncertainties about possible radiation risk, it is important not to screen young women for whom there is not a firm basis for assigning high risk, and to limit radiation exposure during the screening process to the lowest level that still ensures a favorable image. Further, as part of a decision-making process, women should be informed about the uncertain but still unlikely potential for radiation-induced cancers as a possible harm associated with regular screening at young ages (e.g., age 30 or, rarely, younger).

**Clinician Examination and Breast Self-Examination**

There are limited data on the effectiveness of CBE and BSE in high-risk women. A recent study from Memorial Sloan-Kettering Cancer Center suggested a value for BSE in that five breast cancers were detected by BSE less than a year after a previous screen among a cohort of high-risk women (as compared with one cancer detected by clinical exam and 11 cancers detected as a result of mammographic screening). However, it was not clear in this study whether the detection of interval cancers occurred through deliberate self-examination according to instruction or whether discovery occurred during the course of normal activities.\textsuperscript{157,158} There are no systematic studies in high-risk women that evaluate harms (including anxiety, false-positive work-ups, and complacency) associated with physical exam, and there has been no systematic comparison of different screening intervals.

**Mammography Screening Intervals of Less Than One Year**

There are no known studies that evaluate a semi-annual versus annual screening interval, although those comparing annual versus biennial favor annual screening. Recommendations for shorter intervals have generally been based on the incidence of interval cancers.
An important potential research question relates to what extent the incidence of interval cancer diagnoses should be used as a basis for recommending more frequent screening. It is not clear whether interval cancers in younger women at increased risk are attributable to faster tumor growth rates and shorter sojourn times or to greater difficulty in imaging dense parenchyma. Data from the Two-County trial showed that women with family histories of breast cancer had tumors with faster growth rates than those without family histories of breast cancer, but the difference was not large.

Alternative Screening Modalities for Women at Increased Risk

Several groups of investigators have evaluated the relative contributions of mammography, MRI, and ultrasound in women with either a family history of breast cancer or a documented BRCA1/2 mutation. In addition to the published studies, there are several ongoing MRI high-risk screening studies throughout the world, including the United States, Canada, England, Germany, the Netherlands, France, and Italy. These studies suggest that MRI or ultrasound may be beneficial if used as an adjunct to mammography for women with an increased risk of breast cancer, but not as stand-alone tests. The following discussion pertains only to women at increased risk; alternative screening modalities for women at average risk are covered in the next section on new technologies.

Studies of screening MRI in younger high-risk women have found that sensitivities and cancer yields were improved over those of mammography. Specificity of MRI varied according to follow-up management but was generally lower than that of screen-film mammography. In studies in which both prevalent (first) and incident (subsequent) screens were performed, the higher yield of cancers detected with MRI was true for both prevalent and incident screens.

Even as studies report high sensitivity with MRI, there are substantial concerns about costs and limited access for women with familial risk. In addition, MRI-guided biopsies are not widely available. Since false-positive results appear to be common, more data are needed on factors associated with lower specificity rates. Among higher risk women undergoing MRI, there are no data on anxiety and quality of life effects related to false-positive results.

There have not been any studies of ultrasound as a screening modality in high-risk women. (See discussion below regarding the use of ultrasound in average-risk women.)

Need for Further Research

In order to address unanswered clinical research questions, whenever feasible, women at increased risk should be enrolled in protocols assessing early screening, more intensive screening, and the use of new screening modalities. Screening MRI should take place in centers with extensive experience in diagnostic MRI and that have the capacity to perform MRI-guided biopsies. Many women at increased risk are currently being screened with MRI and ultrasound outside of clinical trials. Collection of observational data and development of a national MRI screening registry should be strongly encouraged. While some experts have expressed concerns about these tests being used outside of clinical trials before they are shown to be efficacious for screening, others are concerned about limiting these tests only to those women at increased risk who have access to these trials.
New technologies proposed for breast cancer screening must equal or, preferably, exceed the performance of SFM in order to find acceptance as screening tools. New technologies for breast cancer screening should aim at identifying more of the cancers that are missed by SFM, identifying a higher fraction of early stage cancers (Stages 0 and I), and identifying which early stage cancers require aggressive treatment or no treatment. In addition, any new technology should meet the goals of an ideal screening tool, i.e., it should be simple to perform, noninvasive, cost-effective, and widely available and acceptable to patients.

A list of potential new technologies for breast cancer screening is included in Table 4. Several of these modalities have been Food and Drug Administration (FDA) approved for clinical use, but in most cases, not explicitly for breast cancer screening. One recently approved technology that also has been approved for breast screening and diagnostic use is full-field digital mammography (FFDM). To obtain FDA approval, FFDM manufacturers had to demonstrate that their digital mammography systems were not inferior to screen-film mammography in terms of sensitivity, specificity, and receiver-operator characteristic (ROC) curve areas. Three FFDM manufacturers have received FDA approval. As of September 2002, there were approximately 300 FFDM systems in clinical use in the United States.

The only completed study comparing FFDM to SFM in a screening cohort was done on a single manufacturer’s prototype system at two sites.\textsuperscript{165,166} FFDM had a significantly lower recall rate (11.8\% versus 14.9\%, \(P > 0.001\)) and significantly lower biopsy rate than SFM (94 versus 143 out of 6,736 exams, \(P < 0.001\)). However, FFDM had insignificantly lower sensitivity.\textsuperscript{166}

**Computer-Aided Detection and Diagnosis**

Over the last two decades, computer-aided detection and diagnosis (CAD) has been developed to aid radiologists in detecting mammographic abnormalities suspicious for breast cancer.\textsuperscript{167,168} Three commercial systems designed to digitize screen-film mammograms and analyze them for suspicious lesions have received FDA approval for clinical use. There are approximately 500 CAD systems installed in the United States. Only one commercial CAD system has been approved by the FDA for use with digital mammography. Several clinical studies have been conducted to evaluate the effectiveness of commercial CAD systems in aiding radiologists in the performance and interpretation of screening mammography.\textsuperscript{169-171}

In the largest clinical series to date,\textsuperscript{170} radiologists reading with CAD increased their overall screening recall rate from 6.5\% percent to 7.7\% (an 18.5\% percent increase), while increasing the number of detected cancers from 41\% percent to 49\% percent (a 19.5\% percent increase) compared with interpretation without CAD. Use of CAD increased overall detection rate from 3.2 to 3.8 cancers per 1,000 women screened. These results suggest that CAD systems may aid the average radiologist by substantially improving detection of early stage malignancies with no more than a proportionate increase in recall rate.

With the potential use of ultrasound and breast MRI for screening (see below), development of CAD systems is underway to aid breast ultrasound and breast MRI interpretations. Most CAD methods for these two modalities have focused on characterization of identified breast lesions.\textsuperscript{172,173} Recently, however, new methods have been developed for the detection of lesions on ultrasound.\textsuperscript{174}

**Ultrasound**

Ultrasound has become a valuable diagnostic adjunct to mammography because it is widely available and relatively inexpensive to perform. Usually, however, breast ultrasound is used clinically as a targeted exam, limiting scanning to the focal area of concern.\textsuperscript{175} Recent improvements in breast ultrasound technology
and its application have demonstrated that ultrasound can help distinguish not only between cyst and solid masses but also between benign and malignant masses. Ultrasound may also be used to perform image-guided biopsy of a mass, which allows histologic and/or cytologic assessment for abnormalities detected through the screening process. Prevalence screening studies in women with radiographically dense breasts have reported
three to four breast cancers per 1,000 women that were detected by ultrasound only.\textsuperscript{175-180} Despite these findings, breast ultrasound has known limitations as a screening tool. Breast ultrasound requires a skilled operator, and the numbers of radiologists and technologists trained to perform the exam is limited. Other concerns include the lack of standardized exam techniques and interpretation criteria, the inability of breast ultrasound to detect microcalcifications, the variability of equipment, and preliminary data suggesting a substantially higher rate of false-positive exams than mammography.\textsuperscript{175,178,179} Like mammography, ultrasound has a lower specificity in younger women.\textsuperscript{181}

Studies of ultrasound imaging have shown an ability to find cancers not found on mammography but with sensitivity inferior to that of MRI. The value of ultrasound is greatest for women with significant breast density. Ultrasound is less sensitive than MRI, but has the advantage of being more widely available and considerably less expensive.

\textbf{Magnetic Resonance Imaging}

Over the past decade, MRI of the breast has become a useful diagnostic adjunct to mammography and breast ultrasound for evaluation of breast cancer. When used with intravenous injection of an FDA-approved MR contrast agent, gadolinium DTPA, breast MRI has been shown to be sensitive to 83 to 100 percent of breast cancers above a few millimeters in size.\textsuperscript{182} A summary analysis of breast MRI cases showed an overall sensitivity to breast cancer of 96 percent.\textsuperscript{182} The high sensitivity of breast MRI suggests that it might also be useful in screening for breast cancer. However, current concerns about the potential of MRI as a screening test include costs, the lack of standardized exam techniques and interpretation criteria, the inability of MRI to detect microcalcifications, the ultimate sensitivity of the test, variability of equipment, and preliminary data suggesting a higher rate of false-positive exams than mammography. Furthermore, as noted in the previous section, MRI-guided biopsies are not widely available, so it may not currently be feasible to follow up findings detected by MRI that cannot be visualized by other imaging technologies.

\textbf{Other Imaging Technologies}

Table 4 also includes potential new technologies that are being investigated primarily as diagnostic adjuncts to mammography. Some, such as scintimammography, positron emission tomography, and electrical impedance imaging, have received FDA approval as diagnostic adjuncts to mammography. None of these new technologies has successfully undergone clinical testing that would justify its use in screening for breast cancer. Other technologies on the list are still being investigated in the laboratory setting and are not yet ready to begin clinical evaluation.

\textbf{Nonimaging Tests: Ductal Lavage}

Ductal lavage is a procedure targeted to asymptomatic women who are assessed to be at significantly increased risk for breast cancer.\textsuperscript{183} It was developed in order to collect breast duct epithelial cells for cytologic analysis. There are currently insufficient data to recommend the use of ductal lavage either as an independent screening modality or in combination with screening mammography.

\textbf{CONCLUSION}

The guideline panel reaffirmed the value of breast cancer screening based on updated results from RCTs and new evidence published since the last ACS guideline review in 1997. However, each of the screening methods that was considered has limitations, and there are potential harms associated with false-positive findings. Thus, women should be informed both about the benefits and limitations of
screening and the possibility of harms associated with false-positive findings.

Areas for future research in breast cancer screening have been identified, including distinguishing aggressive from nonaggressive cancers, identifying better screening methods for high-risk women, understanding the impact of hormone replacement treatment on breast density and screening efficacy, clarifying the role of physical exam in cancer detection, and improving the efficacy of screening mammography.

During the last decade, breast cancer screening gained wide acceptance by women and physicians, data supporting the efficacy of screening mammography have undergone intensive re-examination, and the benefits of regular mammography have been affirmed. Now, breast cancer screening is at yet another critical juncture due to multiple factors that may be eroding access, including declining interest in performing the procedure by radiologists, low reimbursement, and high malpractice exposure. At a time when the size of the population at risk for breast cancer is increasing every year, we must not allow the ability to provide timely, high-quality breast imaging to decline.

REFERENCES


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