7. Screening for Breast Cancer

RECOMMENDATION

Routine screening for breast cancer every 1–2 years, with mammography alone or mammography and annual clinical breast examination (CBE), is recommended for women aged 50–69. There is insufficient evidence to recommend for or against routine mammography or CBE for women aged 40–49 or aged 70 and older, although recommendations for high-risk women aged 40–49 and healthy women aged 70 may be made on other grounds (see *Clinical Intervention*). There is insufficient evidence to recommend for or against the use of screening CBE alone or the teaching of breast self-examination.

Burden of Suffering

In the U.S. in 1995, there were an estimated 182,000 new cases of breast cancer diagnosed and 46,000 deaths from this disease in women.[1] Approximately 32% of all newly diagnosed cancers in women are cancers of the breast, the most common cancer diagnosed in women.[1] The annual incidence of breast cancer increased 55% between 1950 and 1991.[2] The incidence in women during the period 1987–1991 was 110/100,000.[2] In 1992, the annual age-adjusted mortality from breast cancer was 22/100,000 women.[3] The age-adjusted mortality rate from breast cancer has been relatively stable over the period from 1930 to the present.[1,2] For women, the estimated lifetime risk of dying from breast cancer is 3.6%.[2] Breast cancer resulted in 2.2 years of potential life lost before age 65 per 1,000 women under age 65 in the U.S. during 1986–1988.[4] This rate was surpassed only by deaths resulting from motor vehicle injury and infections. Breast cancer is the leading contributor to cancer mortality in women aged 15–54,[1] although 48% of new breast cancer cases and 56% of breast cancer deaths occur in women age 65 and over.[2] As the large number of women in the "baby boom" generation age, the number of breast cancer cases and deaths will increase substantially unless age-specific incidence and mortality rates decline.

Important risk factors for breast cancer include female gender, residence in North America or northern Europe, and older age.[5] In American women, the annual incidence of breast cancer increases with age: 127

cases/100,000 for women aged 40–44; 229/100,000 for women aged 50–54; 348/100,000 for women aged 60–64; and 450/100,000 for women aged 70–74.[2] The risk for a woman with a family history of breast cancer in a first-degree relative is increased about 2–3-fold, and for women under 50 it is highest when the relative had premenopausally diagnosed breast cancer.[6–9] Women with previous breast cancer or carcinoma in situ and women with atypical hyperplasia on breast biopsy are also at significantly increased risk.[6,7,10–12] Other factors associated with increased breast cancer risk include a history of proliferative breast lesions without atypia on breast biopsy, late age at first pregnancy, nulliparity, high socioeconomic status, and a history of exposure to high-dose radiation.[6,7,10–12] Associations between breast cancer and oral contraceptives, long-term estrogen replacement therapy, obesity, and a diet high in fat have been suggested, but causal relationships have not been established.[6,7,13,14]

Accuracy of Screening Tests

The three screening tests usually considered for early detection of breast cancer are clinical breast examination (CBE), x-ray mammography, and breast self-examination (BSE). Estimates of the sensitivity and specificity of these maneuvers depend on a number of factors, including the size of the lesion, the characteristics of the breast being examined, the age of the patient, the extent of follow-up to identify false negatives, the skill and experience of the examiner or radiographic interpreter, and (in the case of mammography) the quality of the mammogram. Because multiple clinical trials have demonstrated the effectiveness of screening, measures of screening test performance (such as sensitivity and specificity) are primarily helpful in comparing trials, screening programs, and community practice. Uniform definitions, however, are necessary for such comparisons. For example, different studies may use similar definitions of sensitivity, such as the number of screen-detected cancers compared to the total of screen-detected cancers plus interval cancers, but one may use a fixed interval (e.g., 12 months)[15] and another a variable interval (e.g., time to next screen),[16] making direct comparisons difficult. The ability to detect interval cancers may also vary and will affect such estimates.

A review[17] of the current clinical trial data, published and unpublished, summarized screening test performance for mammography using uniform definitions. Sensitivity of mammography did not dramatically differ across the trials. Estimates from three Swedish trials using mammography alone averaged about 75%, while estimates for mammography combined with CBE ranged from 75% in the Health Insurance Plan of Greater New York (HIP) to 88% in the Edinburgh trial and the Canadian National Breast Cancer Screening Study in women aged 50–59 (NBSS 2). Specificity estimates

ranged from 98.5% in the HIP trial to 83% in the Canadian NBSS 2. Sensitivity estimates for mammography alone and for combined screening with CBE have generally been 10–15% lower for women aged 40–49 compared with women greater than age 50.[15,17–19] Preliminary results from two North American demonstration projects suggest improved sensitivity of mammography, especially for women in their forties, with current mammographic techniques.[20] Significant variations in interpreter performance have also been observed.[21–23] In the Canadian trials, agreement was about 50% beyond that attributable to chance between radiologists at five screening centers and a single reference radiologist.[21]

The effectiveness of CBE alone has not been evaluated directly, but comparisons of the sensitivity and specificity of this maneuver to that of mammography can be considered. The Canadian NBSS 2 was designed to assess the incremental value of mammography above a careful, thorough (5–10 minutes) CBE.[24,25] Preliminary results showing no incremental benefit highlighted the fact that higher sensitivity (88% for mammography plus CBE vs. 63% for CBE alone)[17] may not guarantee improved effectiveness. Specificity was comparable or slightly better for CBE alone. Sensitivity of CBE for women aged 40–49 (Canadian NBSS 1) was about 10% lower at initial screen compared to the estimate for women aged 50–59 (Canadian NBSS 2).[26] Specificity estimates were similarly lower for younger women.

Data regarding the accuracy of BSE are extremely limited. One report calculated an upper limit of sensitivity ranging from 12 to 25% by assuming all interval cases in the clinical trials were detected by BSE.[17] Using a similar approach, the overall sensitivity of BSE alone was estimated to be 26% in women also screened by mammography and CBE in the Breast Cancer Detection Demonstration Project (BCDDP).[27] Estimated BSE sensitivity decreased with age, from 41% for women aged 35–39 to 21% for women aged 60–74.[27] Thus, as currently practiced, BSE appears to be a less sensitive form of screening than is CBE or mammography, and its specificity remains uncertain. The sensitivity of BSE can be improved by training, as measured by the proportion of benign lumps[28] detected on human models and artificial lumps[29] on silicone breast models, although whether this improved detection on models translates into improved personal BSE performance is unknown.

Adverse effects of screening tests are an important consideration. False-positive tests, resulting from the effort to maximize disease detection, may have negative consequences including unnecessary diagnostic tests. In the Canadian trials there were 7–10% false positives from combined screening with mammography and CBE among women aged 40–49 and 4.5–8% among those aged 50–59.[24,30] In a study of the yield of a first mammographic screening among women, half as many cancers per 1,000 first

screening mammograms were diagnosed in women aged 40–49 (3/1,00) compared to women aged 50–59 (6/1,000).[31] Yet, women aged 40–49 underwent twice as many diagnostic tests per cancer detected compared to women aged 50–59 (43.9 vs. 21.9). Women aged 60–69 had a higher yield from screening, with 13 breast cancers diagnosed per 1,000 first screening mammograms and 10.2 diagnostic tests performed per cancer detected.

Mammographic screening may also adversely affect psychological well-being. Increased anxiety about breast cancer after a false-positive mammogram has been reported both at short- and long-term follow-up in studies surveying groups of screened women.[32,33] No impact on compliance in obtaining future screening examinations was observed, however. Women who underwent a surgical biopsy as a result of a false-positive screening mammogram were more likely to report their workup as a stressful experience than were those who did not have a biopsy.[32]

Excess breast cancers in populations that received doses of ionizing radiation significantly greater than currently delivered by mammography, such as survivors from atomic bombing in Japan[34] and patients with benign breast disease,[35] have raised concerns about the potential radiation risk from screening mammograms. There is no direct evidence of an increased risk of breast cancer from mammographic screening, however. Assuming a mean breast dose of 0.1 rad from a mammogram and extrapolating from higher doses of radiation, modeling suggests that in a group of 100,000 women receiving annual screening from ages 50 to 75, 12.9 years would be lost due to radiogenic cancers but 12,623 years would be gained through a 20% reduction in breast cancer mortality as a result of that screening.[34]

Fewer data are available regarding adverse effects associated with CBE and BSE. A dramatic increase in false-positives was observed after instruction in BSE in a non-randomized controlled trial evaluating performance on human models,[28] although no increase was found in a randomized controlled trial evaluating performance on silicone breast models.[29] The latter study also assessed the impact of training on variables other than detection performance on models. Adverse effects, such as unnecessary physician visits, heightened anxiety levels, or increased radiographic and surgical procedures, were not observed.[29]

Effectiveness of Early Detection

Seven randomized controlled trials[16,30,36–40] have evaluated the effectiveness of screening for breast cancer in women by either mammography alone or combined with CBE compared to no periodic screening. The age of participants at date of first invitation ranged from 40 to 74. The six trials[16,36–40] that included women aged 50 showed a reduction in breast cancer mortality of 20–30% in the intervention group. The reduction was

statistically significant in the Health Insurance Plan of Greater New York (HIP),[37] the Swedish two-county trials,[16] an overview of the Swedish trials,[40] and two meta-analyses of the trials.[41,42]

The results of these six trials including women aged 50 have convincingly demonstrated the effectiveness of mammographic screening (with or without CBE) for breast cancer in women aged 50–69. The HIP trial screened women aged 40–64 with annual CBE and two-view mammography.[37] For women who were over age 50 at the time of entry into the study, mortality from breast cancer in the intervention group was more than 50% lower than in the control group at 5 years, decreasing to a 21% difference after 18 years of follow-up. The Edinburgh trial[36] screened women aged 45–64 from 84 general medicine practices with two-view mammography and CBE on the initial screen followed by annual CBE and biennial single-view mammography. Preliminary results at seven years found a relative risk of 0.80 (95% confidence interval [CI], 0.54 to 1.17) for women aged 50 and older at entry. The results from 10-year follow-up showed little change.[17] An overview pooled the data through 1989 from the four Swedish randomized controlled trials of breast cancer screening with mammography alone.[40] All women diagnosed with breast cancer before randomization were excluded and endpoints were independently reviewed. Breast cancer mortality was reduced by about 30% for women aged 50–69 at entry using an endpoint of breast cancer as the underlying cause of death. A meta-analysis that included the most recently published results of these trials reported a 23% reduction in breast cancer mortality for women aged 50 and older.[42] A meta-analysis of European case-control studies done within screening mammography programs also reported significantly reduced breast cancer mortality among women aged 50 and older.[42]

There are few data regarding the optimal periodicity of screening in this age group. Although an annual interval has been recommended by many groups, an analysis of data from the Swedish two-county study found little evidence that an annual interval would confer greater benefit than screening every 2 years for women over the age of 50.[19] This trial used mammography alone, but the reduction in breast cancer mortality was similar to that seen in the trials combining CBE with mammography.[36,37] The similar mortality reductions found in screening trials using periodicities ranging from 12 to 33 months in women aged 50 suggests that biennial screening intervals are as effective as annual intervals. In a meta-analysis of the trials evaluating screening mammography,[42] the estimated reduction in breast cancer mortality was the same (23%) for screening intervals of 12 months and 18–33 months in women aged 50–74.

There is limited and conflicting evidence regarding the benefit of screening women aged 70–74. The Swedish two-county trial and BCDDP time series included women up to age 74 at entry, and each found a re-

duction of breast cancer mortality for the intervention group as a whole.[16,44] The Swedish overview, however, reported a relative risk of 0.98 (95% CI, 0.63 to 1.53) at 12-year follow-up for the age subgroup 70–74.[40] The wide confidence interval, due to small numbers in this subgroup analysis, does not preclude the possibility of a substantial benefit from screening in this age group. No clinical trials have evaluated screening in women over 74 years of age at enrollment.

Although all six trials found a benefit of screening among the total group of enrolled women who were 40–74 years at entry,[16,36–40] there is uncertainty about the effectiveness of screening women between the ages of 40 and 49. The Canadian NBSS 1 was specifically designed to address this uncertainty.[30] This trial compared combined annual mammography and CBE to an initial CBE among women aged 40–49 at entry. At 7-year follow-up, no benefit of annual screening was observed (RR = 1.36; 95% CI, 0.84 to 2.21). This Canadian trial has been the subject of much criticism.[45–47] Possible irregularities with randomization have been refuted by its investigators.[48] An independent review is planned by the National Cancer Institute of Canada to determine whether the randomization was compromised. Although mammography quality issues have also been a concern, there is little evidence to suggest that the practices were inconsistent with the standards of the other clinical trials or community practice at the time of the study.[48] In addition, improvement in mammographic quality over the course of the study period was noted by both inside and outside observers.[48] The proportion of controls receiving mammography, 26%, can be compared to available estimates of 13% in the two-county trial, 24% in the Malmo trial (35% for women 45–49), and 24% in the Stockholm trial.[38,39,49] This contamination may nevertheless have reduced the trial's ability to detect a benefit from the screening intervention. An excess of node-positive cancers detected in the intervention group raised concerns about subject randomization.[30] While this may have been the result of chance, other contributing factors suggested by the investigators include under-ascertainment secondary to lower surgical dissection rates in the control group and incomplete breast cancer ascertainment at preliminary follow-up (although these possibilities are unlikely to account for all of the observed excess).[48] Although the effect of these factors should diminish with long-term follow-up, the results are unlikely to achieve statistical significance because sample size calculations were based on an estimated 40% reduction in breast cancer mortality, which is greater than the typical reduction in mortality observed in the other six trials that included women in this age group.[30]

Subgroup analyses of the other trials that included women under 50 have yielded conflicting evidence regarding the benefit of screening women aged 40–49. No benefit was observed in the Stockholm trial or in

one arm of the two-county trial, while the remaining trials reported non-significant benefits of about 22% or more.[17,50] One meta-analysis, which pooled the results from 7-year follow-up of six published clinical trials without adjustment for variation in screening method or interval, found no reduction in breast cancer mortality for women in their forties (RR = 1.08; 95% CI, 0.85 to 1.39).[41] When the Canadian trial was excluded from the analysis, the estimate changed little (RR= 0.99; 95% CI, 0.74 to 1.32). The overview of the Swedish trials found a nonsignificant 13% reduction (RR= 0.87; 95% CI, 0.63 to 1.20) only after 8–12 years of follow-up in this age group.[40] More recent meta-analyses of published mammography trial data reported nonsignificant 8–10% reductions in breast cancer mortality in women aged 40–49.[42,43] One meta-analysis reported a significant benefit for women in this age group when unpublished data were included and the Canadian trial was excluded.[43] Longer duration of follow-up was associated with a greater reduction in mortality, although this finding may have been due to chance.[42] Thus, there is conflicting evidence from clinical trials and meta-analyses, primarily based on subgroup analyses, regarding the benefit of screening women aged 40–49. An ongoing British trial is evaluating the effectiveness of annual mammography screening in women enrolled at age 40 or 41.

A recent analysis of data by tumor size, nodal status, and stage from the BCDDP, a U.S. screening project using annual two-view mammography and CBE, suggests comparable 14-year survival rates for women 40–49 and women 50–59.[51] A similar analysis of breast cancers detected in the Swedish two-county trial confirms this finding.[52] Based on these data, time series comparisons of survival, frequency of interval cancers in the two-county trial, and subgroup analysis of available clinical trial data, some experts have suggested that annual screening intervals may be necessary to achieve a reduction in breast cancer mortality from screening for women aged 40–49.[19,20,52] In a meta-analysis of published trial results, however, the estimated mortality reduction from screening women in this age group was similar for 12- and 18–33-month screening intervals (1% and 12%, respectively).[42]

There is no direct evidence that assesses the effectiveness of CBE alone compared to no screening. Modeling studies of the HIP trial estimated that two thirds of the effectiveness of the combined screening may have been a result of CBE.[53–56] The Canadian NBSS 2 was designed to test the incremental value of annual mammography over a careful annual CBE among women aged 50–59 at study entry.[24] At 7-year follow-up, there was no difference in breast cancer mortality for the group receiving combined screening compared to CBE alone (RR = 0.97; 95% CI, 0.62 to 1.52). This result suggests that thorough CBE may be as effective as mammography for screening in this age group. The confidence interval is wide, however,

and substantial benefit or harm from screening is not excluded by the preliminary data. Concerns regarding the early quality of mammography of Canadian NBSS 1 also apply to this trial.[48] Long-term follow-up and additional studies are needed to confirm this apparent lack of an incremental benefit of mammography above a careful, thorough annual CBE. It is also unclear whether CBE adds benefit to screening with mammography. A meta-analysis of mammography trial results reported similar reductions in breast cancer mortality with and without the addition of CBE.[42]

Evidence for effectiveness of BSE alone is also limited. In the United Kingdom Trial of Early Detection of Breast Cancer, a nonrandomized community trial, 40–50% of women living in two districts participated in BSE instruction that included a short film and a lecture by a specially trained health provider.[57] At 7-year follow-up, there was no reduction in breast cancer mortality in the BSE communities compared with the control districts. Baseline comparability of intervention and control districts, treatment variation by community, and contamination by other screening modalities were not assessed, however. A World Health Organization (WHO) population-based randomized controlled trial in Leningrad comparing formal BSE instruction to no intervention in women aged 40–64 has reported increases in physician visits, referrals for further screening tests, and excisional biopsies in the intervention group at 5-year follow-up.[58] Breast cancer patients in the two groups did not differ in number, size, or nodal status of their tumors. Completeness of endpoint assessment is a concern in this study, given the lack of a national tumor registry. Follow-up through 1999 is planned for reporting mortality results. In a case-control study of women who had been diagnosed with advanced stage (TNM II or IV) breast cancer, there was no association between disease status and self-reported BSE.[59] Proficiency in practicing BSE, however, was reported as poor by both cases and controls. For the small group of women reporting thorough BSE compared to all others, the relative risk was 0.54 (95% CI, 0.30 to 0.98). A meta-analysis of pooled data from 12 descriptive studies found that women who practiced BSE before their illness were less likely to have a tumor of 2.0 cm or more in diameter or to have evidence of extension to lymph nodes.[60] The studies from which these data were obtained, however, suffer from important design limitations and provide little information on clinical outcome (i.e., breast cancer mortality). Retrospective studies of the effectiveness of BSE have produced mixed results.[27,61–63]

Recommendations of Other Groups

The American Cancer Society (ACS),[64] American College of Radiology,[65] American Medical Association,[66] American College of Obstetricians and Gynecologists (ACOG),[67] and a number of other organizations[65] recom-

mend screening with mammography every 1–2 years and annual CBE beginning at the age of 40, and annual mammography and CBE beginning at age 50.

The American Academy of Family Physicians (AAFP) recommends CBE every 1–3 years for women aged 30–39 and annually for those aged 40 and older, and mammography annually beginning at age 50;[68] these recommendations are currently under review. The American College of Physicians (ACP) recommends screening mammography every 2 years for women aged 50–74 and recommends against mammograms for women under 50 or over 75 years and baseline mammograms.[69] The ACP makes the same recommendations for high-risk women, unless the woman expresses great anxiety about breast cancer or insists on more intensive screening. The Canadian Task Force on the Periodic Health Examination recommends annual CBE and mammography for women aged 50–69 and recommends against mammograms in women under 50.[70] The National Cancer Institute states there is a general consensus among experts that routine mammography and CBE every 1–2 years in women aged 50 and over can reduce breast cancer mortality and that randomized clinical trials have not shown a statistically significant reduction in mortality for women under the age of 50.[71]

Organizations that presently recommend routine teaching of BSE include the AAFP,[68] ACOG,[67] and ACS.[64] The recommendations of the AAFP are currently under review.

Discussion

At this time, there is little doubt that breast cancer screening by mammography with or without CBE has the potential of reducing mortality from breast cancer for women aged 50 through about 70. The benefit derived from biennial screening appears to be quite similar to the benefit derived from annual screening. Given this similarity in effectiveness, biennial screening is likely to have the added benefit of increased cost-effectiveness. The incremental value of CBE above mammography or vice versa is uncertain, although the Canadian NBSS 2[24] suggests that careful CBE may be as effective as mammography.

Evidence does not establish a clear benefit from screening in women aged 40–49. Only the Canadian NBSS 1[30] was designed to test the effectiveness of screening in this age group, however, and none of the trials had adequate power for subgroup analysis. If screening is in fact ineffective in younger women, one possible explanation is a lower sensitivity of mammography in younger women (see *Accuracy of Screening Tests*). Other possibilities include suboptimal screening intervals, differential (less aggressive) treatment offered to women with mammographically detected cancer, and varying biologic characteristics of breast tumors.[52,72] The Swedish

overview,[40] HIP,[37] and Edinburgh[36] trials suggest some benefit in women aged 40–49 after 8–12 years of follow-up, but it is possible that the delayed benefit is due to screening women in their fifties who entered the trials in their middle to late forties.[72a] The final results of the Canadian NBSS 1 may provide important information. An ongoing British trial and a pro-

lines for breast cancer screening should be interpreted with this in mind.

No large study has quantitated the effectiveness of breast cancer screening by either CBE or mammography for women who are at higher risk of developing breast cancer than the general population. The increased incidence of disease in high-risk women increases the positive predictive value (PPV) of screening tests used in this group. For example, in a community screening program, the PPV of mammography was increased 2–3-fold for women with a family history of breast cancer.[31] This is an especially important consideration for women under 50, in whom the benefit of screening has not been established for the general population. There may be a benefit from screening younger women in high-risk groups, but studies confirming this effect are lacking. Nevertheless, given their increased burden of suffering, screening high-risk women under age 50 may be considered on an individual basis for women who express a strong preference for such screening.

Data regarding the effectiveness of BSE are extremely limited, and the accuracy of BSE as currently practiced appears to be considerably inferior to that of CBE and mammography. False-positive BSE, especially among younger women in whom breast cancer is uncommon, could lead to unnecessary anxiety and diagnostic evaluation, although a small randomized clinical trial[29] did not find such adverse effects. A point also worth consideration is that time devoted to teaching BSE may reduce time available for prevention efforts with proven effectiveness. Given the present state of knowledge and the potential adverse effects and opportunity cost, a recommendation for or against inclusion of teaching BSE during the periodic health examination cannot be made.

CLINICAL INTERVENTION

Screening for breast cancer every 1–2 years, with mammography alone or mammography and annual clinical breast examination (CBE), is recommended for women aged 50–69 ("A" recommendation). Clinicians should refer patients to mammographers who use low-dose equipment and adhere to high standards of quality control. Such standards have recently been established by the Mammography Quality Standards Act, a federal law mandating that all mammography sites in the U.S. be accredited through a process approved by the Department of Health and Human Services.[78] There is insufficient evidence to recommend annual CBE alone for women aged 50–69 ("C" recommendation). For women aged 40–49, there is conflicting evidence of fair to good quality regarding clinical benefit from mammography with or without CBE, and insufficient evidence regarding benefit from CBE alone; therefore, recommendations for or

against routine mammography or CBE cannot be made based on the current evidence ("C" recommendation). There is no evidence specifically evaluating mammography or CBE in high-risk women under age 50; recommendations for screening such women may be made on other grounds, including patient preference, high burden of suffering, and the higher PPV of screening, which would lead to fewer false positives than are likely to occur from screening women of average risk in this age group. There is limited and conflicting evidence regarding clinical benefit of mammography or CBE for women aged 70–74 and no evidence regarding benefit for women over age 75; however, recommendations for screening women aged 70 and over who have a reasonable life expectancy may be made based on other grounds, such as the high burden of suffering in this age group and the lack of evidence of differences in mammogram test characteristics in older women versus those aged 50–69 ("C" recommendation). There is insufficient evidence to recommend for or against teaching BSE in the periodic health examination ("C" recommendation).

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Marisa Moore, MD, MPH, and Carolyn DiGuiseppi, MD, MPH.

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