CLINICAL PRACTICE

Breast-Cancer Screening

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A healthy, 42-year-old white woman wants to discuss breast-cancer screening. She has no breast symptoms, had menarche at the age of 14 years, gave birth to her first child at the age of 26 years, is moderately overweight, drinks two glasses of wine most evenings, and has no family history of breast or ovarian cancer. She has never undergone mammography. She notes that a friend who maintained the "healthiest lifestyle possible" is now being treated for metastatic breast cancer, and she wants to avoid the same fate. What would you advise?

THE CLINICAL PROBLEM

Worldwide, breast cancer is now the most common cancer diagnosed in women and is the leading cause of deaths from cancer among women, with approximately 1.3 million new cases and an estimated 458,000 deaths reported in 2008.[1] A woman born in the United States today has a 1 in 8 chance of having invasive breast cancer during her lifetime.[2] The risk of breast cancer increases with age (Fig. 1) and with other risk factors (Table 1).

Tumor stage remains the most important determinant of the outcome for women with breast cancer. Among women with nonmetastatic breast cancer, the risk of distant recurrence is most closely correlated with the number of axillary nodes involved, followed by tumor size.[4] Moreover, there is a strong correlation between tumor size and the extent of axillary spread.[5] This means that the ideal screening regimen for breast cancer would be one that could detect a tumor before it was large enough to be palpable.

Since 1990, mortality from breast cancer in the United States and other industrialized countries has been decreasing at the rate of approximately 2.2% per year.[1] In the United States, this decline has been attributed both to advances in adjuvant therapy and to increasing use of screening mammography, in approximately equal measure.[6] Nevertheless, in contrast to its 2002 guidelines,[7] the more recent recommendations of the U.S. Preventive Services Task Force (USPSTF), published in November 2009, support a reduction in the use of screening mammography.[8] This revision resulted in considerable confusion and controversy. The two most disputed changes were the reclassification of screening for women between the ages of 40 and 49 years from a B recommendation (based on moderately strong evidence) to a C recommendation ("the decision . . . should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms"), and the recommendation that the frequency of screening be reduced from every 1 to 2 years to every 2 years.[8]

This article focuses on the updated evidence and recommendations for screening women who are at average risk for breast cancer that have been published since

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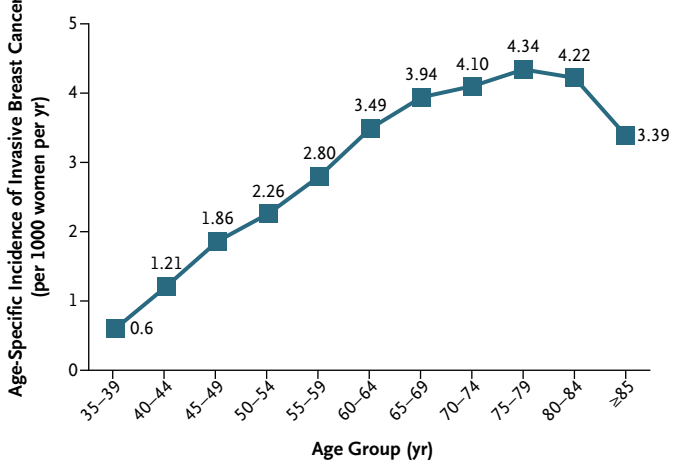

Figure 1. Age-Specific Incidence of Invasive Breast Cancer per 1000 Women per Year in the United States.

Data are from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, 2010.[2]

this topic was last reviewed in the *Journal*, in 2003. It does not address breast-cancer screening for women at high risk — that is, women with a lifetime risk of breast cancer that is greater than 20 to 25% on the basis of genetic testing, a strong family history (e.g., multiple cases of early-onset breast cancer, ovarian cancer, or both), or early therapeutic chest irradiation — which has been reviewed previously.[9]

STRATEGIES AND EVIDENCE FOR SCREENING

The decision to screen either a particular population or a specific patient for a disease involves weighing benefits against costs. In the case of breast-cancer screening, the most important benefits are a reduction in the risk of death and the number of life-years gained. Costs include the financial costs and other costs of the screening regimen itself (radiation risk, pain, inconvenience, and anxiety), the ensuing diagnostic workup in the case of false positive results, and overdiagnosis (the detection of cancer that would never have become clinically evident). The ratio of benefit to cost varies significantly with the patient's age.[8]

WOMEN 50 TO 69 YEARS OF AGE

Screening mammography for women 50 to 69 years of age is universally recommended. All but one of the trials in the meta-analysis that included women in their 60s showed a significant reduction in mortality in the screened group, although this was not true for the subgroup of women in their 50s. Still, a meta-analysis[8] revealed significant reductions in the number of deaths due to breast cancer in both these age groups — 14% for women in their 50s and 32% for those in their 60s (Table 2). The greater reduction among the older group of women reflects the increasing sensitivity of mammographic testing with age, which is associated with a decrease in breast density and slower tumor growth. The fact that the number needed to screen to prevent one death from breast cancer is lower for women in their 60s reflects this higher sensitivity, as well as the higher incidence of breast cancer in this age group.

WOMEN 70 YEARS OF AGE OR OLDER

Data are limited regarding the effects of screening mammography in women who are 70 years of age or older. The only randomized trial that included such women showed no benefit in this age group (Table 2). In a national screening program in northern Sweden, the relative risk of death from breast cancer for women 70 to 74 years of age who were invited to undergo screening, as compared with those not yet invited, was 1.08 (95% confidence interval [CI], 0.58 to 2.03).[18] Using six independent statistical models based on clinical screening data and cancer outcomes in the United States, the Cancer Intervention and Surveillance Modeling Network (CISNET) of the National Cancer Institute estimated that two additional deaths from breast cancer would be prevented per 1000 women screened from the age of 70 to 74 years, with little additional benefit to be gained from extending screening beyond 74 years.[19] There is agreement that screening is not indicated in women who have serious coexisting illnesses and a life expectancy of less than 5 to 10 years.

WOMEN 40 TO 49 YEARS OF AGE

Although no single randomized trial has clearly shown a reduction in mortality from mammographic screening among women 40 to 49 years of age, several meta-analyses that included this age group have shown that mortality from breast cancer is significantly reduced (by 15 to 20%).[20,21] On the basis of these results, as well as those of its own meta-analysis, which showed that mammography was associated with a relative risk of

0.85 (95% CI, 0.79 to 0.99) for death from breast cancer,[17] the USPSTF previously recommended routine screening mammography for women in this age group.[7]

Since it had been argued that the benefit of screening women in their 40s could largely be attributed to the detection of cancers after the age of 50 years in women who had enrolled in the trials in their late 40s, the Age trial (ISRCTN24647151)[14] assessed the effects of screening among approximately 161,000 women 39 to 41 years of age. Those randomly assigned to annual mammography until the age of 48 years had a nonsignificant reduction in the risk of death from breast cancer (relative risk, 0.83; 95% CI, 0.66 to 1.04), and the relative risk for death from any cause was 0.97 (95% CI, 0.89 to 1.04) at a mean follow-up of 10.7 years (number needed to screen to prevent one death from breast cancer, 2512). However, this study had several limitations that might have decreased the observed benefit, including the mammographic technique used (single view), the failure to achieve the intended sample size and number of screenings, and the 70% compliance rate.

An updated USPSTF meta-analysis, which included results from the Age trial and longer-term results from the Gothenberg Breast Screening Trial,[13] yielded results similar to those of the earlier meta-analysis (relative risk for death from breast cancer, 0.85; 95% CI, 0.75 to 0.96); the number needed to invite for screening was 1904. A sensitivity analysis that excluded a trial in which an outdated mammographic technique was used[10] and a trial with serious methodologic limitations[11] did not substantially change the results.[8] The decision to change the USPSTF recommendation was heavily influenced by the nonsignificant findings of the Age trial — the only trial that specifically focused on women in their 40s. The lower breast-cancer risk, lower mammographic sensitivity, and higher rate of false positive results among younger women as compared with older women were considered to account for a benefit-to-risk ratio that was inadequate to allow a recommendation of routine screening of women under 50 years of age. However, this change in recommendation remains highly controversial,[22,23] especially because of the greater number of years of life expectancy gained from preventing death from breast cancer in younger women. According to statistical modeling,[19] screening initiated at the age of 40 years rather than 50 years would avert one additional death from breast cancer per 1000 women screened, resulting in 33 life-years gained.

Table 1. Risk Factors for Breast Cancer.*

Risk Factor	Relative Risk
BRCA1 or *BRCA2* mutation	10.0–32.0
Family history of cancer (no known mutation)†	
1 first-degree relative	1.5–2.0
2 first-degree relatives	3.0
3 or more first-degree relatives	4.0
1 second-degree relative	1.2–1.5
Therapeutic radiation to chest at <30 yr of age‡	7.0–17.0
Hormonal factors	
Late (age >30 yr) parity or nulliparity	1.2–1.7
Early (age <12 yr) menarche or late menopause (age >55 yr)	1.2–1.3
Combined hormone-replacement therapy (e.g., for 10 or more yr)	1.5
Postmenopausal obesity	1.2–1.9
Alcohol consumption (2 drinks/day vs. none)	1.2
Smoking before first live birth	1.2
Sedentary lifestyle	1.1–1.8
White race	1.1–1.5
Breast density (very dense vs. mainly fatty)	5.0
Atypical ductal or lobular hyperplasia or lobular carcinoma in situ on previous breast biopsy	4.0

* Data are in part from Tice and Kerlikowske, 2009.[3]
† Family history refers to breast or ovarian cancer. The risk varies with the age of the patient and that of the affected relative (or relatives). Women at very high risk may require earlier or additional screening.
‡ Women under 30 years of age who have undergone therapeutic radiation to the chest require earlier and additional screening.

FREQUENCY OF SCREENING

A controversial change from the 2002 USPSTF guidelines to the 2009 guidelines was a switch from recommending screening every 1 to 2 years to screening every 2 years.[7,8] Supporting this change was the observation that reductions in mortality from breast cancer were similar in the randomized trials that involved annual screening and those that involved screening every 18 to 33 months.[24] Moreover, there was little difference in the likelihood of detecting advanced breast cancer with annual versus biennial screening programs.[25,26] In statistical models,[19] screening of women 50 to 69 years of age every 2 years maintained 81% of the benefit associated with annual screening; as compared with screening every 2 years, annual

Table 2. Relative Risk of Death from Breast Cancer, Number Needed to Invite to Screening, and Rates of False Positive and False Negative Results, According to Age.*

Age	No. of Trials	Relative Risk of Death (95% CI)	Number Needed to Invite to Screening (95% CI)†	Rate per 1000 Women Screened				
				True Positive Rate		False Negative Rate	False Positive Rate	False Positive Rate on Biopsy
				Invasive	*DCIS*			
39–49 yr	8‡	0.85 (0.75–0.96)	1904 (929–6378)	1.8	0.8	1.0	97.8	6.7
50–59 yr	6§	0.86 (0.75–0.99)	1339 (322–7455)	3.4	1.3	1.1	86.6	6.1
60–69 yr	2¶	0.68 (0.54–0.87)	377 (230–1050)	5.0	1.5	1.4	79.0	5.1
70–79 yr	1‖	1.12 (0.73–1.72)	Not available	6.5	1.4	1.5	68.8	4.3

* Data are from a meta-analysis of randomized breast-cancer screening trials, performed by the U.S. Preventive Services Task Force,[8] and from the Breast Cancer Surveillance Consortium (for data in the five columns at the right) and are based on a single round of screening. CI denotes confidence interval, and DCIS ductal carcinoma in situ.

† Since the rate of compliance with screening was only 75 to 85% in most studies, the number needed to screen to prevent one death from breast cancer would be 15 to 25% lower but was not calculated.

‡ The results are from the Health Insurance Plan (HIP) of Greater New York,[10] Canadian National Breast Screening Study 1 (CNBSS-1),[11] Stockholm,[12] Malmö Mammographic Screening Program,[12] the Swedish Two-County trials (two),[12] the Gothenburg Breast Screening Trial,[13] and the Age trial.[14]

§ The results are from the CNBSS-2,[15] the Stockholm, Malmö, and Swedish Two-County trials (two),[12] and the Gothenburg trial.[13] The New York HIP[10] and Edinburgh[16] trials were excluded because of outdated technology and inadequate randomization, respectively.[17] Excluding the Canadian trial, which has been heavily criticized for enrolling prescreened volunteers rather than unselected samples of participants, the relative risk was 0.81 (95% CI, 0.68 to 0.95).

¶ The results are from the Malmö trial[12] and one of the Swedish Two-County trials (Östergötland).[12]

‖ The results are from one of the Swedish Two-County trials (Östergötland), which included only women 70 to 74 years of age.[12]

screening prevented about two additional deaths from breast cancer per 1000 women screened.

In analyses based on data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute,[27] a 2-year screening interval was not associated with an increased risk of late-stage disease in women 50 years of age or older, as compared with a 1-year screening interval, but it was associated with an increased risk in women 40 to 49 years of age (odds ratio, 1.35; 95% CI, 1.01 to 1.81) — an observation attributed to the faster growth rate of breast tumors in younger women. Although this observation would seem to support annual screening for women in their 40s, a recent study showed that faster tumor growth was only a minor contributor to the lower sensitivity of mammography in younger women and that the major explanatory factor was poorer tumor detectability, predominantly owing to greater breast density.[28]

DIGITAL MAMMOGRAPHY

The contrast between breast tumors and surrounding normal parenchyma is greater with digital mammography than with film mammography, particularly when the breast tissue is dense. In the Digital Mammographic Imaging Screening Trial (DMIST [ClinicalTrials.gov number, NCT00008346])[29] in which almost 50,000 asymptomatic women 40 years of age or older underwent both digital and film mammography, the two techniques were equivalent overall in sensitivity (70% and 66%, respectively) and specificity (92% for both). However, in women under the age of 50 years, digital mammography was significantly more sensitive than film (78% vs. 51%). Digital mammography offered a similar advantage for premenopausal women and for women with dense breasts.

RISKS AND COSTS OF SCREENING

Aside from the discomfort many women experience from the breast compression necessary for a technically optimal mammogram, mammography poses several risks, including rates of false positive and false negative results, overdiagnosis, and radiation-induced cancers (Table 3). Overdiagnosis, with consequent overtreatment, is a particular concern. The diagnosis of ductal carcinoma in situ (DCIS) was rare before the introduction of screening mammography and now accounts for approximately 25% of all cases of breast cancer, with more than 90% of DCIS cases detected only

by imaging.[2] The natural history of DCIS is not clear, and many tumors, particularly those of low grade, may not grow or become invasive,[40] yet patients with DCIS are routinely treated with lumpectomy and radiation therapy and often undergo mastectomy. On the basis of simulation models, the incremental cost of screening every 2 years per quality-adjusted life-year from 40 to 80 years of age has been estimated to be between $35,000 and $47,000.[41,42]

AREAS OF UNCERTAINTY

RISK STRATIFICATION

Since the probability that a woman will benefit from screening varies with her risk of breast cancer, accurate risk stratification of individual patients is highly desirable. It is important to identify the small group of women who are at high risk (i.e., their lifetime risk of breast cancer exceeds 20 to 25%) and thus require earlier, more sensitive, and more frequent screening than do women at lower risk. It is also important to identify the larger group of women who are at moderately increased risk for breast cancer, as compared with the women at average risk, particularly for women in their 40s for whom the risks and benefits of screening may seem to be evenly balanced. This latter group may include women with a lifetime risk of 15 to 20% or a 5-year risk above 1.66% (e.g., those with a first-degree relative who had breast cancer before the age of 65 years or those with a previous breast-biopsy specimen showing atypical hyperplasia or lobular carcinoma in situ). Since the risk of breast cancer for a 40-year-old woman in one of these categories is at least as high as that for a 50-year-old woman at average risk, screening mammography should be advised.[43] Whether more frequent screening or additional screening techniques would be beneficial is unknown (as discussed below).

Mathematical models have been developed that integrate multiple risk factors to create a risk score.[44] Currently, the most commonly used risk-prediction model in the United States is the National Cancer Institute's Breast Cancer Risk Assessment Tool (based on the Gail model).[45] Validation studies have shown that it accurately predicts risk within a population but is much less accurate in predicting risk for individual women[46] and should not be used to determine the need for screening with magnetic resonance imaging (MRI).[9] The Tyrer–Cuzick model[47] includes additional variables that are not considered in the Gail model (e.g., cancer in second-degree relatives), but its usefulness has not yet been validated.

Table 3. Risks Associated with Mammography.

Risk	Comments
False positive result leading to recall, with or without biopsy	Inversely related to age; for women 40 to 49 yr of age, cumulative risk at 10 years is approximately 49% in the United States[30]
	Higher risk is also associated with Prior breast biopsies Family history of breast cancer Current estrogen use No prior mammogram or a longer screening interval Individual radiologist[31]
	May cause short-term anxiety and psychological distress[32]
	May have small but significant long-term negative effects on health behaviors and psychological well-being[33]
False negative result leading to false reassurance	Little research has been conducted to determine the effect of this finding; in one survey, more than 99% of women stated that they would not delay evaluation of a new abnormal physical finding despite a recent negative mammogram[34]
Overdiagnosis (and overtreatment)	Increases with age; a review of five randomized trials showed an excess of breast cancers (both invasive and in situ) in all studies, accounting for 4 to 32% of cancers found by screening[35]
	Screening programs and simulation models report rates from 1 to 10%, depending on age, outcomes included (invasive vs. in situ disease), country, and whether cases are incident or prevalent[36,37]
Radiation-induced breast cancer	Estimated risk is 86 cancers and 11 deaths per 100,000 women screened annually from 40 to 55 years of age and biennially thereafter; ratio of benefit to risk is 4.5:1 for lives saved and 9.5:1 for life-years saved[38]
	Level of exposure to radiation with digital mammography is the same as or lower than that with film mammography[39]

RELEVANCE AND GENERALIZABILITY OF DATA FROM RANDOMIZED TRIALS

Data obtained from randomized trials of screening mammography that were performed decades ago may no longer be relevant. In light of subsequent improvements in technology, it is possible that these earlier results underestimate the current benefit of screening, or they may overestimate the current benefit because treatment options have

improved. Furthermore, since most of the participants in these earlier trials were white, the degree to which the results are generalizable to other racial and ethnic groups is unclear. Young black women have a higher incidence of breast cancer than white women,[2] which might increase the benefit from mammographic screening at the age of 40 years, but they also have a higher proportion of high-grade breast cancers that are negative for estrogen and progesterone receptors and for HER2 overexpression,[48] which grow faster than other breast cancers and thus may be less amenable to detection by screening. As compared with other racial and ethnic groups, Asian women have a lower incidence of breast cancer[2] and greater breast density,[49] which might attenuate the benefits of screening.

VALUE OF OTHER SCREENING METHODS

Since mammography is the only screening method to date that has been proved to reduce mortality from breast cancer, any other type of screening must be carried out as a supplement to mammography. Although clinical breast examination detects some cancers that are missed on mammography, no randomized trial has compared the combination of mammography plus clinical breast examination with mammography alone. Of three randomized trials designed to compare clinical breast examination with no screening in countries without screening-mammography programs, one had inconclusive results[50] and two are ongoing.[51,52] Meta-analyses of randomized and nonrandomized studies of breast self-examination have shown that it has no effect on mortality from breast cancer.[53]

Screening ultrasonography has been reported to result in up to a 30% absolute increase in the detection of invasive cancer in women with dense breasts, for whom the sensitivity of mammography is reduced and the risk of cancer is increased.[54,55] However, the rate of false positive results ranges from 2.4 to 12.9%, as compared with 0.7 to 6.0% for mammography. Studies assessing the effect of screening ultrasonography on mortality from breast cancer are under way in Japan and Sweden.

Although the use of MRI more than doubles diagnostic sensitivity when it is used to screen women at high risk for breast cancer, it is not recommended for screening the general population because of the higher rate of false positive results and higher cost.[9]

Breast tomosynthesis, a three-dimensional version of digital mammography that generates images of thin sections of the breast, was recently approved for screening by the Food and Drug Administration. However, this technique has not been shown to improve diagnostic sensitivity, as compared with standard digital mammography.[56]

GUIDELINES

Although all medical professional organizations in industrialized countries recommend screening mammography for women between 50 and 69 years of age, recommendations differ substantially with respect to other age groups, screening intervals, and breast examinations in the clinic or by the patient herself (Table 4).

CONCLUSIONS AND RECOMMENDATIONS

How should one approach the question of screening mammography in a patient in her 40s, such as the woman described in the vignette? The decision should be individualized, with the recognition that the probability of a benefit is greater for women at higher risk. This patient has no major risk factors, such as a family history of breast cancer or a history of a premalignant lesion on biopsy, that would put her at even moderately increased risk. Her chance of having invasive breast cancer over the next 8 years is about 1 in 80, and her chance of dying from it is about 1 in 400. Mammographic screening every 2 years will detect two out of three cancers in women her age and will reduce her risk of death from breast cancer by 15%. However, there is about a 40% chance that she will be called back for further imaging tests and a 3% chance that she will undergo biopsy, with a benign finding. Lifestyle modifications (e.g., weight control and avoidance of excessive alcohol consumption) that might lower her risk should also be discussed.

Given the data from randomized trials, which consistently show a 14 to 32% reduction in mortality from breast cancer with annual or biennial mammography in women 50 to 69 years of age, screening mammography should be recommended for women in this age group provided that their life expectancy is 5 years or more. For women 70 years of age or older, data from randomized trials are lacking, and the decision about screening should therefore be individualized on the basis of life expectancy and the patient's preference.

Table 4. Guidelines for Breast-Cancer Screening.*

Organization	Year Guidelines Issued	Mammography	Clinical Breast Examination	Breast Self-Examination
USPSTF	2009	Age 50–74 yr, every 2 yr; age 40–49 yr and age ≥75 yr, individualize the decision (every 2 yr, if performed)	Insufficient evidence for recommendation	Not recommended
American Cancer Society	2010	Age ≥40 yr, annually†	Age 20–39 yr, every 3 yr Age ≥40 yr, annually	Optional, ≥20 yr of age
National Comprehensive Cancer Network	2011	Age ≥40 yr, annually†	Age 20–39 yr, every 1–3 yr Age ≥40 yr, annually	Optional, ≥20 yr of age
National Cancer Institute	2010	Age ≥40 yr, every 1–2 yr†	Age and frequency not stated	Optional
American College of Physicians	2007	Age 50–74 yr, every 1–2 yr‡; age 40–49 yr, individualize the decision (every 1–2 yr, if performed)	Not stated	Not stated
American College of Obstetricians and Gynecologists	2003	Age 40–49 yr, every 1–2 yr; age ≥50 yr, annually†	Age ≥20 yr, annually	Optional
American College of Radiology	2008	Age ≥40 yr, annually†	Not stated	Not stated
Canadian Task Force on Preventive Health Care	1998–2001	Age 50–69 yr, every 1–2 yr; age 40–49 yr, individualize the decision (every 1–2 yr, if performed)	Every 1–3 yr, with periodic health examinations, for ages <40 and >70 yr	Not recommended for women 40–69 yr of age Optional, ≥70 yr of age
National Health Service, United Kingdom	2011	Age 47–73 yr, every 3 yr	Not stated	Not stated

* USPSTF denotes U.S. Preventive Services Task Force.
† No upper age limit was specified.
‡ These recommendations have not been updated since 1989.

On the basis of the DMIST study results,[29] I would recommend digital mammography for screening women in their 40s, older premenopausal women, and women of any age whose breasts are heterogeneously dense or very dense.

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