An Overview of Mammography: Benefits and Limitations

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Key Words

Adult, breast neoplasms/radiography, carcinoma/radiography, carcinoma, intraductal, noninfiltrating/radiography, female, logistic models, mammography/methods/standards, middle age, quality control, retrospective studies, sensitivity and specificity

Abstract

Although broad consensus exists that mammography is beneficial, there has been persistent and evolving debate over the extent of the benefit, as well as concerns about cost-effectiveness. Ongoing evaluation of the world's randomized clinical trials as well as new evaluations of population service screening (ie, organized, community-based screening) clearly show that mammography is beneficial and that the benefit of modern mammography among women who attend screening exceeds what has conventionally been estimated from the trials. Limitations of mammography include human and financial costs associated with missed cancers and false-positive results. However, it is important to distinguish those limitations of mammography that are inherent limitations of the technology from those that can be reduced through greater attention to quality assurance. (*JNCCN* 2003;1:264-271)

Although mammography is widely accepted as a key element in the control of breast cancer, there always has been an undercurrent of dissension about breast cancer screening. Broad consensus exists that mammography is beneficial, but there is persistent and evolving debate over the extent of the benefit overall and in different age groups. Other debated issues include cost-effectiveness, benefit versus risk, and informed choice related to benefit versus harm. Exactly how healthcare professionals should think about early breast cancer detection, the con-

tribution of mammography versus physical examination, and the performance of screening in different age groups of women is still contested.

Discussion about screening for cancer customarily includes the benchmarks established in Wilson and Junger's¹ important report to the World Health Organization on principles and practices on screening for disease. Wilson and Junger focused on fundamental criteria that must be met to justify inviting a nominally healthy population to be screened for the presence of occult disease. These criteria are well known today, and put simply state that: 1) disease burden must be significant; 2) earlier intervention must offer greater benefits compared with diagnosis of symptomatic disease; 3) the test must have acceptable performance characteristics; 4) there must be a clear indication that benefits exceed harms; and 5) screening must be affordable and cost-effective. Although each of these criteria is straightforward, there are no established benchmarks for satisfying any of them, either alone or in combination. Thus, against this general backdrop of criteria that should be met to regard screening favorably, opinions can differ about the degree to which mammography satisfies these criteria.

In this overview of the benefits and limitations of mammography, the criteria of Wilson and Junger provide a useful framework for how the role of mammography in breast cancer control should be considered and the degree to which the current evidence supports the value of mammography, both in practice and potential.

Disease Burden

In 2000, the International Agency for Research on Cancer (IARC) estimated that breast cancer accounted for 1 million new diagnoses of cancer among women, or 22% of all incident malignancies.² Breast cancer is the leading cause of cancer among women in the world, and a leading cause of death from cancer. In the United States, breast cancer

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is the most common cancer affecting women, and the second leading cause of death from cancer. In 2003, the American Cancer Society estimates that 211,300 women will be diagnosed with invasive breast cancer, 55,700 women will be diagnosed with ductal carcinoma in situ (DCIS), and 39,800 women are expected to die from breast cancer.³ What is especially sobering is that deaths from breast cancer accounted for an estimated 763,000 years of premature mortality in 1999, or an average of 18.5 years of potential life lost per woman dying of breast cancer.⁴

Although few dispute the seriousness of breast cancer as a public health problem, there has been considerable controversy about the age to begin screening, in particular whether to begin screening at age 40 or 50, and the age to stop screening.⁵⁻⁷ Here only disease burden is covered, because questions of age-specific efficacy will be taken up in the next section. Although the incidence of breast cancer is lower in women in their forties, 1 in 67 women will be diagnosed with breast cancer in that decade.⁴ These patients eventually account for approximately 16% of all breast cancer deaths.⁸ Furthermore, Shapiro et al⁹ chose to include women in their forties in the Health Insurance Plan of Greater New York Study of Breast Cancer Screening (HIP) because deaths from breast cancer diagnosed in that period of life accounted for about a third of the total annual premature mortality from breast cancer. They rightfully focused on the age at which the intervention would need to take place to avert death that could occur many years later.

The age at which screening can be discontinued also has been debated. Some experts propose that a significant proportion of women could stop screening after age 69 on the basis of lack of efficacy data from randomized clinical trials (RCTs), the diminishing cost-effectiveness of screening in this age group due to rising prevalence of comorbidity and limited life expectancy, and personal preference for small gains in life expectancy.¹⁰ Disease burden is high in this age group. Although RCTs generally did not include or sufficiently follow up women over age 70, most organizations conclude that no evidence suggests that mammography is not effective in this group.^{11,12} In fact, due to involution and fat replacing glandular tissue, breast imaging is less challenging and more sensitive in this age group compared with in younger women.¹³

Although it is true that women aged 70 and older are more likely to have competing comorbidity and

limited longevity, Walter and Covinsky¹⁴ showed clear, substantial variability in the likelihood of benefit based on overall health and expected longevity. Thus, the challenge to the referring physician is to distinguish those patients who could benefit from preventive care from those who probably would not benefit. When women age 70 and older are painted with a broad brush, not screening women in the age group potentially leads to withholding beneficial preventive care from women who would be expected to benefit, but screening all women provides services to women who not only would probably not benefit, but also might experience significant degradation of quality of life due to additional testing and interventions.

Benefit of Early Breast Cancer Detection

Breast cancer is best understood as a progressive disease that becomes systemic as the size of the tumor increases. As Tabar et al¹⁵ have shown, tumor size, nodal involvement, and histologic grade are each associated with prognosis, and tumor size represents the best proxy indicator for nodal involvement and advanced histologic grade. The larger the tumor at diagnosis, the greater the likelihood that cancer will have spread to the axillary lymph nodes and that histologic grade will be less favorable.

The primary evidence supporting the recommendation for periodic mammographic screening for breast cancer derives from eight RCTs. Of these, two trials took place in North America, five were in Sweden, and one in Scotland.¹⁶⁻²³ As shown in Figure 1, the most recent data show a 24% reduction in breast

Figure 1

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cancer mortality associated with an invitation to screening. Similar meta-analyses also have shown statistically significant mortality reductions of 18% for women ages 40 to 49 and 27% for women ages 50 to 74 associated with an invitation to screening.^{24,25} More recent meta-analyses continue to confirm the association between an invitation to screening and breast cancer mortality reductions.^{26,27} These data have served as the basis for recommending regular breast cancer screening with mammography since 1977, when the first breast cancer screening guidelines were produced by the National Cancer Institute, and subsequently by the American Cancer Society.²⁸

Ongoing debates about mammography include considerable selectivity with regard to which individual trials and meta-analyses are highlighted as a basis for conclusions about the magnitude of benefit from mammography.^{29,30} While some researchers focus on clinical and methodologic shortcomings to argue that mammography is more effective than is evident from trial end results,³¹ others argue that flawed trial methodology actually has led to an overestimate of benefit.³²

One far-reaching example of this sort of selective methodology is a recent review of the RCTs by investigators at the Nordic Cochrane Center.^{33,34} Olsen and Gøtzsche^{33,34} evaluated seven randomized trials of breast cancer screening and concluded that the methodology of five trials was so flawed that they did not provide reliable scientific evidence. The authors also argued that breast cancer mortality was an unreliable endpoint in a trial, and that only comparison of all-cause mortality between the experimental and control groups could serve as an unbiased endpoint. Based on a new meta-analysis that included only the Malmö and Canadian trials,¹⁷⁻¹⁹ the authors concluded that there was no evidence of a reduced mortality associated with an invitation to mammography (RR = 1.0). They also argued that mammography was associated with a net harm, because it led to excess radical treatment and excess mortality caused by cardiovascular damage associated with radiation therapy.

Several guidelines groups, national boards of health, and numerous individual authors have reviewed and critiqued the Cochrane report.^{26,27,35-40} The reviews of the Cochrane report methodology and conclusions uniformly judged the report's methodology to be flawed and inconsistently applied. The reviews noted that it did not invalidate the conclusion that

screening for breast cancer with mammography reduces breast cancer mortality.

The publication of the recent Cochrane report in the Cochrane library and the *Lancet*^{33,34,41,42} as well as a recent update of the Canadian National Breast Screening Study-1 (NBSS-1) and several commentaries in the *Annals of Internal Medicine*^{26,29,30,43} highlight the degree to which continually revisiting the results of the RCTs is increasingly unproductive and polarizing.³⁵ The RCTs were conducted over a 40-year period and trial endpoints vary considerably. The differences in end results and performance were probably influenced by a number of factors, including the imaging technology used at the time, whether or not clinical breast examination was included in the screening regimen, the screening interval, number of views, experience of the personnel, quality control, diagnostic thresholds, randomization, and duration of follow-up.⁴⁴ Although few data exist to shed light on the extent to which these factors and combinations of factors influenced trial end results, each is known to be influential.^{45,46}

What is more important, however, and also clearly evident in each individual trial, is that the relative risk of being diagnosed with a node-positive tumor in the group invited to screening closely parallels the relative risk of dying from breast cancer. Therefore, in each of the RCTs, the relative risk of dying from breast cancer in the group invited to breast cancer screening is strongly associated with the relative risk of being diagnosed with an advanced breast cancer.^{8,38,47} Setting aside the various differences in methodology, the trials that were most effective in reducing the incidence rate of node-positive breast cancers also showed the greatest mortality reductions.

Beyond the Randomized Clinical Trials: New Directions in Evaluating Breast Cancer Screening

A number of new investigations are moving beyond the RCTs to measure the impact of modern mammography in the community. This interest is stimulated by the sense that the benefit of modern mammography should be greater than the benefit shown in the trials because of the clinical and technologic gains along a 40-year learning curve. Investigators are interested in knowing how well service screening is performing and also in quantifying the benefit that accrues to women who

actually undergo screening. This latter focus is because estimates of benefit from the RCTs are based on an intention to treat comparison between invited and uninvited groups rather than screened and nonscreened groups. The recent trend toward evaluating the impact of large, population-based screening programs has the potential to provide us with a clearer measurement of the benefit of modern mammography.

Using data from seven Swedish counties representing more than one third of the Swedish female population, Duffy et al⁴⁰ evaluated long-term trends in breast cancer mortality among women aged 40 to 69 based on age at diagnosis and exposure to screening at both the population and individual level. In all counties together, breast cancer mortality was 44% lower in the postscreening period compared with the prescreening period among women who had actually undergone screening (RR = 0.56; 95% CI = 0.50–0.62). After adjusting for selection bias, when all incident tumors were examined (ie, cancers detected in women attending screening and not attending screening), the policy of offering screening to the population was associated with a 39% breast cancer mortality reduction (RR = 0.61; 95% CI 0.55–0.68).⁴⁰

Similar mortality reductions have been observed with the Florence, Italy Screening program, which also compared breast cancer mortality among attenders and nonattenders to screening and in the population as a whole before and after the introduction of screening.⁴⁸ After the breast cancer cases diagnosed at the first screening examination (the prevalent screening round) were excluded, the rate of stage II+ breast cancer cases was 42% lower in screened women compared with women diagnosed with breast cancer who had not been invited to screening (RR = 0.58; 95% CI = 0.45–0.74).

These findings reinforce observations from the trials that the primary contribution of a well-organized breast cancer screening program is to improve the prognosis of incident breast cancers by diagnosing them before they become advanced. These population-based data also corroborate the collective RCT evidence, and further show that screening with mammography not only can achieve the mortality reductions observed in the trials but also exceed them.

Limitations of Mammography

Although mammography is an effective technology for detecting occult breast cancer in women ages 40 and

older, it is also an imperfect technology. These imperfections are commonly highlighted as inherent and immutable, but to a large extent they reflect shortcomings in meeting quality assurance standards across the many elements that contribute to effective screening.

False-Negative Results

Sensitivity is the proportion of cases with a positive screening test among all individuals with preclinical disease,⁴⁹ or

$$\frac{\text{true positives}}{\text{true positives} + \text{false negatives}}$$

In a recent review of the RCTs, Humphrey et al²⁶ estimated sensitivity for mammography for a one-year screening interval to be between 71% and 96%, with lower sensitivity observed in younger compared with older women. Factors known to affect mammographic sensitivity include breast density, use of hormone replacement therapy, poor image quality, number of views, and the experience and skill of the interpreting physician.^{13,50–55} Although some of these factors represent inherent limitations in mammography technology, such as the influence of breast density, other factors are clearly modifiable with continued improvements in quality assurance and service delivery. In particular, greater experience in interpreting mammograms,⁵⁵ independent double reading,^{50,56,57} and computer-aided detection^{58,59} all have been shown to improve sensitivity.

False-Positive Results

Specificity is the proportion of all women with a normal screening test among all individuals without the disease, or

$$\frac{\text{true negatives}}{\text{true negatives} + \text{false positives}}$$

In general, most screening tests have relatively high specificity, but even small differences in these high percentages can result in very large additional program costs. Specificity in the RCTs was between 94% and 97%.²⁶ Most women with a false-positive result on screening usually undergo additional mammograms, ultrasound, or physical examinations, and the majority of these women subsequently are determined not to have breast cancer and returned to the normal screening pool. Similarly, specificity is influenced by many of the same factors that influence sensitivity, and also improves with increasing age. Sickles⁶⁰ has shown that improvements in specificity can be

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achieved with careful attention to imaging protocols and management.

False-positive results are frequently highlighted as one of the risks associated with periodic screening. Elmore et al⁶¹ showed that the 10-year probability of a false-positive screening mammogram for a 60-year-old woman was 47%, and the probability of a false-positive mammogram result leading to a biopsy was 19%. Elmore et al's study has been widely cited as if it was an absolute measure of the decade risk of a false-positive result, and yet it is better understood as the likelihood of a false-positive result in a screening setting characterized by irregular attendance, screening at different sites, and interpretation by many different radiologists with a wide range of experience. Other factors that probably contributed to the high rate of false positives include the higher than average prevalence of women with a family history in the group studied and the unique presence in the United States of background concerns about medical-legal liability related to failure to diagnose breast cancer.⁶²

When sensitivity and specificity in a screening program are being evaluated, both overall and in terms of women in different age groups, it is important to recognize the influence of screening history.^{13,63} Overall, sensitivity tends to be better on initial screening, because there is a greater abundance of larger, length bias cancers. Conversely, specificity tends to be poorer, which is related to the need to reconcile areas of possible abnormality that are seen for the first time. On subsequent screenings, sensitivity declines, which is to be expected because the majority of new tumors will be relatively small, and specificity improves if a woman continues screening in the same setting.

Concerns about false-positive results have extended to include the detection of ductal carcinoma in situ (DCIS), for which rates have increased with greater use of mammography.⁶⁴ Clearly, not all DCIS is progressive, but a significant percentage is, and it is probably progressive at a variable rate. This means that some lesions might progress slowly over one or two decades. Studies of local recurrence after treatment of DCIS by excision alone have showed recurrence rates of 12% to 43%.^{65,66} Duffy et al⁶⁷ showed that detection of DCIS contributes to mortality reductions as a result of stage shifting, although the contribution is relatively small compared with the stage shifting from stage II+ to stage I among invasive cancers.

Yen et al⁶⁸ also showed that estimates of the proportion of nonprogressive DCIS are higher on a prevalent screen (44%) compared with subsequent incident screens (9%). This conclusion is consistent with the characteristics of a length-bias lesion. Thus, a woman undergoing an incidence screening has a 36-times higher probability of being diagnosed with progressive DCIS or invasive lesion than of having a nonprogressive DCIS diagnosed. Duffy et al⁶⁷ also advised against comparing the relative proportion of DCIS against invasive disease detected in a screening program, because a high proportion of DCIS may simply reflect a comparatively low detection rate of invasive lesions.

Concerns about detecting DCIS are largely misplaced, since the goal of breast cancer screening is not the detection of DCIS, but rather the detection of small lesions. Detection of DCIS occurs coincident to the process of screening for invasive cancer. The only way to avoid detection of DCIS, whether progressive or not, is to avoid screening for breast cancer. It is reasonable to be concerned about overly aggressive treatment of some DCIS lesions,⁶⁹ but addressing the problem of overtreatment rests with therapeutic decisions, not screening. This distinction perhaps takes on greater meaning for women over age 70. Breast cancer incidence declines after age 75, but never to a rate lower than the incidence rate for women 65 to 69, and mortality rates in these older age groups of women steadily increase with increasing age. Although most organizations recommend that screening should continue as long as a woman is in good health, treatment decisions for DCIS might reasonably include less aggressive options based on the characteristics of the tumor.

Anxiety

One persistent concern with respect to screening costs relates to the psychosocial effects of screening, specifically anxiety associated with false-positive examinations. Because breast cancer is a major concern for women around the world, efforts to understand anxiety associated with screening and reduce avoidable anxiety are important. As would be expected, some studies have shown anxiety associated with an abnormal mammographic examination, although some also have not shown an effect.⁷⁰ Of greatest importance is that the scientific literature reveals little evidence of any lasting consequence in terms of enduring anxiety or influence on subsequent screening behavior.⁷¹ Furthermore, data show that anxiety can be reduced if

there is an emphasis on rapidly resolving uncertainty by insuring prompt diagnostic evaluation.⁷²

A survey by Schwartz et al⁷³ found that most women (99%) were aware that false-positive results occur, and most also felt that false-positive results were an acceptable risk to save lives. Sixty-three percent felt that 500 or more false-positive results would be acceptable for each life saved, and 37% would tolerate 10,000 (the actual rate is between 30 and 200 for each life saved). These findings represent considerable tolerance for false-positive findings among the women surveyed, as well as the women's understanding of the limitations of mammography and a preference for the greater value of saving lives.

Conclusions

At this point in time, detecting breast cancer early is the single most important element in the overall strategy to reduce morbidity and mortality of breast cancer. Although these performance indicators show a favorable benefit to risk ratio, most limitations associated with mammography, or at least the magnitude of those limitations, should be regarded less as immutable and more in terms of a degree of failure to meet a state of the art in service delivery. Ongoing, systematic monitoring of the performance of a screening program is essential to measure effectiveness and identify areas for improvement.⁷⁴ Given the numerous factors influencing program performance, more favorable outcomes in a screening program can be achieved with greater adherence to best practices that have been shown to improve outcomes.

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