COMMENTARY

The Life-Sparing Potential of Mammographic Screening

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The article by Tabar et al.[1] in this issue of ***Cancer*** represents a milestone in evaluating the effects of population screening by mammography. The earlier two-county trial in Sweden,[2] which compared a group of women invited to screening with a control group of women not invited, provided data indicating that there was a significant reduction in mortality during the 10-year period of the scientific study. The controlled trial was followed by a 9-year period, when all women between the ages of 40–69 years in the same geographic area were offered mammographic screening. This 9-year period had an 85% attendance rate at the offered screenings. Control group contamination (women who obtained mammograms anyway) and experimental group compliance problems (women who were invited but did not get mammograms) of the trial were obviated in the most recent period by offering the entire age-defined population an invitation to screening. Data from these successive periods were compared with the 10 years prior to the beginning of the trial, when no screening was performed, and the results of the comparative analysis of the 3 periods are presented in their report. Tabar and his colleagues[1] examined data on the death rate in women who actually used screening versus those who did not, data regarding patients not screened, and data on population characteristics from the defined geographic area for all women, screened and not screened. They examined records from almost 7000 women who developed breast carcinoma and almost 2000 women who died of breast carcinoma discovered over the 29-year period in the 2 counties in Sweden. To avoid lead time bias from data that included longer patient follow-up and bias from patients who had cancers diagnosed in one decade but who died in a subsequent decade, Tabar et al. analyzed only the incident cancers that occurred and the deaths that resulted within the actual periods described for their study. Thus, only cancers and deaths within the 3 time periods (1968–1977, 1978–1987, and 1988–1996) were analyzed, resulting in a finding of 944 deaths out of a total of 1863 cancer deaths. There were 13 deaths per 100,000 woman-years among those screened, but there were 36 deaths per 100,000 woman-years for those not screened. Correcting for the possible selection bias that might have occurred (because healthier women attend screening, whereas women who are ill may not) only slightly reduces the esti-

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mate of the magnitude of the benefit (from 63% to 50% mortality reduction). Thus, the overall conclusion is that screening substantially reduces breast carcinoma mortality, at least by 50% and probably more. These results are of special interest coming so soon after a question that has been raised as to whether the randomization in these studies might have had hidden biases to account for the reduction in death.[3] Tabar's[1] current study suggests that such a possibility is extremely unlikely when examining the entire population.

Several principles of screening generally need to be met to confirm its usefulness in a particular disease. Effective treatment in the preclinical phase of the research must be available and effective, the study population must have access to the screening, low diagnostic morbidity must be present, and the screening must be affordable. Further, sensitivity and specificity should be reasonable. Finally, lead-time, length-time, and over-diagnosis biases must be overcome by demonstrating a decreased mortality rate in an entire population, not just an increased survival rate for detected cases.[4] This final, critical test has been passed in this report by Tabar, et al.[1] on the effect of screening mammography in breast carcinoma in women.

Two general theories of the natural history of breast carcinoma have shaped current thinking about the most effective way to reduce breast carcinoma deaths. The *systemic from origin* theory, promulgated by Fisher,[5] holds that the future survival or death of patients is already determined by the time the disease has become clinically evident; screening to discover cancers earlier would provide no benefit. The *progressive* theory holds that the chance of breast carcinoma metastasizing beyond the local site, thus rendering the disease incurable by local treatment, increases as tumors grow. In this biologic model, screening to discover smaller cancers would be important to improve results. Of course, both theories could be true in different proportions of patients if breast carcinoma is a heterogeneous disease, in which some cancers are fated to be either lethal (systemic from origin) or harmless (no metastatic potential regardless of size) from the outset, whereas most cancers become progressively more likely to cause death through their increasing virulence and capacity to metastasize as they grow, a viewpoint put forward by Hellman as the *spectrum* model.[6] The *systemic from origin* theory is biologically plausible, and has lead to great interest in providing systemic treatment of breast carcinoma, but clearly applies to only a small minority of mammographically discovered cancers, perhaps 10–15%. The *progressive* theory finds powerful support in many studies, most notably those of Tubiana and Koscielny and colleagues,[7] which have shown that the larger the primary tumor, the greater the chance of distant metastatic disease that leads to death. The practical application of the *progressive* theory has been seen in the randomized controlled trials of breast carcinoma screening,[8] which have shown that screening both finds cancers at smaller sizes, and lower grade and reduces the likelihood of breast carcinoma death. The largest proportion ($\pm$ 75%) of breast carcinomas probably conform to this model.

Controlled randomized trials can show the statistical validity of screening as a tool for reducing breast carcinoma death, but they are a poor way to measure the magnitude of the benefit of screening. The inevitable occurrence in these trials of biases, such as experimental group compliance and control group contamination, dilutes the magnitude of screening's full capacity to reduce death. In addition, only 4–7 years separated the onset of screening in the experimental groups and the onset of screening initiated in the control groups at the conclusion of the trials, such that the comparison was only for a relatively short period of increased screening in the experimental group. Other aspects of the trials that are noteworthy are that one-view mammography frequently was the standard radiology technique, that screening intervals ranged up to every 3 years, and that women might not have attended repeated screenings in a timely fashion. All these factors have biased trials against the full display of the potential mortality reduction by screening and against complete estimations of mortality reduction. One could assume that the mortality reduction results of the scientific trials might have underestimated the potential by 50% or more, and the current report by Tabar et al.[1] amply confirms that conclusion, with a 63% reduction in breast carcinoma mortality in women actually screened, which, after adjustments, still displayed a mortality reduction of 50%. We believe these are minimum figures and, for the reasons stated above, mortality reduction in ideally screened patients may more closely conform to a mathematical model[9] suggesting that even greater mortality reduction (75% or more) occurs in the progressive disease model component of all breast carcinomas. Both the randomized controlled trials,[8] and the report in this issue by Tabar and colleagues,[1] attest to the benefit of screening, but many issues remain to be settled regarding the most effective screening. For example, in the recent report of the Canadian National Screening Study,[10] the researchers indicated that they did not see any difference in survival rates between women who were screened by physical examination versus women who were screened by physical examination plus mammography. However, it is controversial as to whether

the Canadian study had the statistical power to detect a difference in survival rates between these two interventions and whether mammography was utilized to its maximal effect. Whereas the tumors in the mammography or physical examination arm of the study were slightly smaller than the tumors in the only physical examination arm, the former were much larger than the tumors in the screening arm of the two-county trial, which used only mammography or reports of mammography detection. The real question is not whether clinical breast examination is better than mammography,[11] but it is whether both screening tools used together are better than either alone. Because almost all screening guidelines now recommend both a clinical breast examination and mammography, this question needs to be resolved. The optimal screening interval also remains to be determined. The recommended screening interval in the two-county trial period[2] was every 3 years and every 2 years in the service screening period.[1] In summarizing the overall effects of the mammographic screening interval on size, grade, metastatic rate, survival rate, and reduction in mortality, it is clear that the shorter the interval between screening mammograms, the greater the possible reduction in breast carcinoma mortality.[12] We have proposed[12] screening intervals that would be cost neutral and that are adjusted to the biologic behavior of the disease, which is greatly associated with age. Our suggested intervals are a semiannual screening interval for women age 40–49 years, an annual screening of women age 50–59 years, a biannual screening of women age 60–69 years, and an every third year screening of women age 70–79. Younger women have a shorter sojourn time with their tumors than older women; a greater proportion of younger patients have tumors that advance from lower grade to higher grade each year; and a higher proportion of their tumors have other poor prognostic features.[12] Another component of screening at more frequent intervals is the reduction in the proportion of "interval" cancers—those detected by physical examination between scheduled mammographic screenings. Interval cancers tend to be large, of course, because they are palpable, more aggressive in behavior, and have a poorer prognosis.[13,14] Analysis by computer simulation modeling[9] using empirically based estimates of the rates of breast carcinoma growth, metastatic potential, and detectability also suggest that annual screening should achieve greater reduction of deaths than screening every 2 years and that there also may be additional benefit by screening more frequently than once a year. Thus, the potential of reduced mortality from breast carcinoma by population screening at frequent regular intervals with mammography is inherently logical, substantiated by scientific trials, bolstered by a coherent biologic model, and now, to our knowledge, is demonstrated as never before on an entire geographically defined population.

Of course, screening not only has the potential for saving lives, but also has the potential for doing some harm. Mammography does lead to false-positive findings and, thus, biopsies in women who are then found not to have breast carcinoma, and it also leads to false-negative findings.[15] Whereas it is imperative to reduce the discomfort of mammography and to achieve better results by reducing false-positive and false-negative rates, it also is important to put mammography in the context of its major role in reducing mortality, thus saving literally thousands of lives. The answer to false alarms is not to get rid of the community fire department! What is needed is research to find ways to help mammographers identify those women at most risk for unnecessary biopsies and surgeries, without missing women who have cancer at it earliest stages. For example, the simple availability of an earlier mammogram for comparative review reduces the incidence of these unnecessary procedures by 50%.[16]

Screening has potential to change the appearance of the disease of breast carcinoma. The most dramatic effect of mammographic screening that explains how it achieves a reduction in mortality is the marked reduction in the size of invasive cancers, which is accompanied by an increase in the proportion of screened patients who have a lower grade histology and a marked reduction in the incidence of axillary lymph node metastases.[17] In recent years, more intensive histologic analysis by special stains of a few lymph nodes obtained by sentinel lymph node biopsy has yielded many micrometastases (of uncertain biologic importance)[18,19] such that the apparent rate of lymph node metastases increased artifactually. This result of a more sophisticated technical diagnostic procedure is a classic example of the "Will Roger's effect" of stage-shifting and does not alter the fact that, with screening, breast carcinoma presentation now is markedly earlier in the clinical evolution of disease. The usual, small, solitary, lower grade, screen-detected cancers without lymph node metastases have 20-year disease-specific survival rates of over 90%.[2] Further, small subsets of these screened patients may be examples of *systemic from origin cancer* and selected for systemic therapy because of poor prognostic features of their tumors,[20,21] whereas the residual majority have survival rates of $>$ 95% at prolonged follow-up.[20,21] Another result of mammographic screening is the sharply increased incidence of duct carcinoma in situ (DCIS), a precursor lesion or preinvasive cancer.[22]

When DCIS is removed, later invasive cancer is prevented in the proportion of cases with potential for progressive growth.[23] High grade DCIS, particularly with certain genetic alterations, progresses, in a very high proportion of cases, to invasive breast carcinoma in a few years.[24] Low grade, small DCISs that are biopsied but not completely excised lead to invasive carcinoma in 30%[25] to 60%[26] of patients after periods of up to 30 years. Therefore, with a lag period of 10, 20, or 30 years, the incidence of invasive breast carcinoma in a population will invariably decline by the extensive detection and removal of precursor DCIS that is seen so frequently with mammographic screening. This assumption in breast carcinoma is as valid as it is in uterine or colon carcinomas, where removal of in situ lesions or dysplasia reduces the incidence of invasive cancers and improves the stage and survival of the cancers that are discovered.

One suspects that the findings reported in this issue of ***Cancer*** by Tabar and colleagues[1] are just the first extractions of data on the benefits of population screening. The characteristics of the two-county area in Sweden, with its geographic definition, population stability, and detailed data accessibility, will no doubt make this area a rich source of further information on the benefits and possible drawbacks of screening. For instance, it would be of great interest to learn how age, parenchymal density, interval between screens, postmenopausal estrogen use, and family history effect the ability of mammography to reduce breast carcinoma deaths. As screen-detected and interval- or palpable-cancer survival data are dissected, the relative biologic behaviors and mortality rates of these types of tumors will emerge more clearly. One also would hope that data will emerge that will answer the main concerns of critics of mammographic screening, such as the incidence of false-positive and false- negative findings, the performance of unnecessary biopsies, and the patient discomfort caused by the mammography machine. Finally in Tabar's[1] seminal research, women were divided into users and nonusers of screening, but their actual compliance resulted in considerable variations of use. For example, several studies have found that 1 in 4 women who have 1 mammogram do not return for a second, and the usual interval of "annually" screened patients may actually be 16 months or more. Thus one suspects that the mortality reduction will be even greater than reported here for women who not only use screening but also use it consistently at a defined frequent interval. We expect that this data, which measures the full consequences of screening, will make an increasingly compelling argument for the benefits of screening for breast carcinoma by mammography.

Whereas it is clear, in retrospect, that there is no epidemic of breast carcinoma as was feared in the 1980s, and that steady gains have been made with increasingly sophisticated, but still highly toxic and morbid systemic and regional therapeutic programs, Tabar et al.[1] points out that avoidance of mortality from breast carcinoma can be achieved in great measure by universal mammographic screening, which carries little morbidity. Peto[27] recently proposed that the declines in breast carcinoma mortality observed in the United States and in the United Kingdom were largely due to the use of adjuvant tamoxifen and systemic treatments. Tabar's data[1] demonstrates that the largest proportion of declining mortality can be attributed to screening, particularly emphasized by the lack of progress in mortality reduction in young women not screened, who generally received adjuvant systemic therapy because their tumors so often demonstrated poor prognostic features. A comprehensive overall plan for the control of breast carcinoma should include both components of management, that is, screening and therapeutic advances. However, it is an open question whether, with limited resources, a country should focus on expensive and morbid treatments for advanced breast carcinoma and metastatic disease or instead, focus on screening, because finding disease at a much earlier stage means that extensive therapeutic efforts are less necessary, less radical, and less expensive.

The American Cancer Society has proposed goals for the year 2015 that challenge us to obtain a 50% reduction in cancer mortality and a 25% reduction in cancer incidence.[28] In breast carcinoma, these goals probably can be met if the subsidiary goal of annual screening of 90% of the women older than age 40 years is realized by the year 2008.[28] Tabar's report[1] gives concrete evidence that such an ambitious goal actually can be achieved by the appropriate mobilization of national resources. Tabar's landmark article emphasizes that a nearly two-thirds reduction in breast carcinoma deaths accrued to women who actually did attend screening in the Swedish Two-County Study area. Whereas corrections for apparent biases may reduce that advantage to about 50%, both figures can be improved still further by regular, yearly, screening intervals that use two-view mammography, and, perhaps, double reading also. Such a well defined national priority could be measured each year. Some states in the United States are close to achieving that goal in women who are 40–49 years of age and in higher social economic groups,[29] but an obligation to expand this usage to older women and to women in lower social economic categories who are underserved by the current screening policies[30] is an important

national health priority.[28] The political advocacy surrounding breast carcinoma management that has occurred in the United States over the past 20 years has raised awareness of this important issue to the health of women. Hopefully, it can be further mobilized to achieve fully the important public health goal of extensive population screening by mammography to reduce dramatically the mortality associated with carcinoma of the breast.

Tabar's[1] report from Sweden results from a nearly 30-year diligent and meticulous study of mammographic screening and sets the direction for our future efforts. The overall population impact is so impressive that technical concerns about false-positive and false-negative mammographic findings, while important and requiring improvement, can be put in prospective and should be secondary to this major public health achievement. This is especially important considering the difficulty, expense, and morbidity of our current focus on efforts to control poor prognosis and larger palpable breast carcinoma by systemic drugs and radical regional treatments.

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