COMMENTARY

The Breast Carcinoma Screening Interval Is Important

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Three recent articles by Hunt et al.,[1] Tabar et al.,[2] and Michaelson et al.[3] have raised the long-standing question of the how frequently women should be screened for breast carcinoma. The current level of uncertainty regarding the best screening interval is reflected in the diversity of recommendations. In the U.S., the American Cancer Society, American Medical Association, and other major organizations recommend annual screening beginning by the age of 40 years. The National Cancer Institute recommends screening "every one to two years." Biennial screening is recommended in Canada, Australia, and much of Europe. In Sweden it is recommended every 18 months for women ages 40–49 years and every 24 months for women age $\geq$ 50 years, whereas in the United Kingdom screening is performed every 3 years. These diverse recommendations largely have arisen in isolation from any empiric guidance with regard to the effect of the screening interval on the ability of mammography to reduce deaths from breast carcinoma. The three recent articles[1-3] should help by framing the question concerning the proper screening interval in a form that is scientifically based, analyzable, and justifiable.

Hunt et al.[1] reported on the outcome of screening annually versus biennially in a screening program. Although women in their dataset were not assigned to annual versus biennial screening at the outset of the study, Hunt et al. were able extract estimates of the effect of various screening intervals by sorting women into those who returned to screening at either 10–14-month intervals ("annual") or those who returned at 22–24-month intervals ("biennial"). They combined these data with information from the cancer registry regarding women found to have interval tumors, defined as tumors not detected at screening that were noted within either 1 year ("annual") or 2 years ("biennial") of a negative screening examination. Two findings from this analysis were statistically significant and noteworthy. First, Hunt et al. found that the median and mean greatest dimensions of the tumors observed in the annual group were smaller than the median

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and mean greatest dimensions of the tumors observed in the biennial group. Because screening is presumed to work by identifying tumors at a smaller and thus more curable size, this finding provided direct evidence of the enhanced value of annual compared with biennial screening. Second, Hunt et al. found that the recall rate was lower in the annual group (2.6%) than in the biennial group (3.7%). There has been concern with regard to the cost and anxiety caused by false-positive mammograms.[4,5] The findings of Hunt et al.[1] are reassuring in this regard because they indicate that yearly screening, rather than screening every other year, should result in smaller tumors and thus presumably lower death rates, while lessening the burden of false-positive results.

The recent report by Tabar et al.[2] reviewed the latest analysis of the seminal randomized controlled trial of mammographic screening in Swedish women, and described many issues of importance in the reduction of breast carcinoma mortality. In this study, women ages 40–49 years were invited for screenings at 24-month intervals, whereas women age $\geq$ 50 years were invited for screening at 33-month intervals. Approximately 38% of the tumors in the age 40–49 years group emerged between screens as interval tumors, compared with 27% of the tumors in the age 50–59 years group, and 21% in women age $>$ 60 years. These and other findings have lead Tabar et al.[2] to deduce that the transition from the smallest mammographically detectable tumors to the clinically detectable tumors occurs more rapidly in younger women than in older women. From this, they concluded that more frequent screening may be necessary in younger women to achieve the same life-sparing benefit observed with less frequent screening in older women. Tabar et al.[6-8] developed a mathematic method, a Markov model, that could be used to calculate a number of features of breast carcinoma screening from their database.[6-8] These authors used their Markov model to estimate that for women age $<$ 50 years, screening twice yearly, yearly, every other year, or every third year might result in reductions in mortality of 45%, 36%, 18%, and 4%, respectively. For women ages 50–59 years, screening every year, every other year, or every third year might result in reductions in mortality of 46%, 39%, and 34%, respectively, whereas for women age $>$ 59 years the same screening intervals might result in reductions in mortality of 44%, 39%, and 34%, respectivley.[2]

Michaelson et al.[3] described a computer simulation model of breast carcinoma growth and spread that could be used to predict the effect of various screening intervals on the reduction in breast carcinoma mortality. Their model was possible in part because there are data available in the literature that can be used to extract rough estimates of the rate of breast carcinoma growth and spread.[9-11] In particular, Michaelson et al. were able to rely on data collected regarding the relation between tumor size and distant metastatic disease[9-11] to determine that the probability of potential lethal spread beyond the primary tumor is fairly constant and measurable (approximately 10^{-13} metastases/cell/day).[3] Using these features of breast carcinoma growth and spread, and making rough estimates of the sizes of those tumors detectable by mammography and palpation, Michaelson et al. were able to estimate the effect that various screening intervals might have on the ability of mammography to reduce breast carcinoma mortality. These initial estimates indicated that screening twice yearly, yearly, ever other year, and every third year might result in reductions in mortality of 80%, 51%, 22%, and 14%, respectively, for all women ages 40–74 years. Although they emphasized that the precise values from their initial calculations are likely to be revised as the underlying estimates of the rate of breast carcinoma growth, spread, and detectability are improved, the conclusion that more frequent screening may lead to greater reductions in breast carcinoma mortality appears to be general.

Although conclusive proof of the value of more frequent screening can come only from prospective, randomized, controlled trials that might be expensive, difficult to implement, and that would not yield useful results for a number of years, some general conclusions can be drawn from these three articles. Based on the best available information, women should be advised to undergo annual mammography, and they should attend their screening appointments regularly. We believe that personal, institutional, and public health policy should reflect the many strong recommendations for annual screening, and that compliance should be emphasized. Remarkably, few women return on schedule for their annual examination. At the Massachusetts General Hospital, $>$ 50% of women wait longer than 16 months before returning for "annual" screening, and many women wait 2, 3, or more years between examinations (unpublished data). Women need to be educated to understand that a finding of breast carcinoma on a mammogram is not bad news but good news, because the curability of these tumors is extremely high. In the study by Tabar et al., which began in the 1970s, women whose tumors were detected on a mammography screen had a $>$ 85% or 90% chance of disease specific survival at 16 years[2]; with contemporary screening technology, the current rate of survival is likely to be higher. By allowing $>$ 1 year to pass between examinations, women

increase the possibility of breast tumors emerging as interval tumors, which long have been recognized to be both larger in size and of greater lethality than tumors detected by mammography. Even with the many logistical problems in mammographic screening, in the U.S., Surveillance, Epidemiology, and End Results data[12] and other studies[13-15] have shown a sharp decline in the mean and median greatest dimensions that is dramatic and continuing. If the decrease in tumor size continues as predicted (an objective that should be aided greatly by prompt compliance with the annual screening recommendation), we believe that the decrease in breast carcinoma mortality that has appeared in the U.S. in recent years[16] will continue.

We also believe that those involved in the science and practice of screening should begin to consider whether there might be additional lives saved by screening at intervals that are more frequent than now are common. The potential benefit of twice yearly screening that is suggested by the computed simulation model of Michaelson et al.,[3] and by Tabar et al.,[2] Duffy et al.,[6] and Chen et al.[7,8] suggest a trial of twice yearly screening. Tabar et al.[2] point out that twice yearly screening might degrade the overall level of screening compliance,[2] although whether such a difficulty would emerge in practice would be testable with a small preliminary study to determine the operational consequences of twice yearly screening. Tabar et al. have suggested the possibility of an 18-month screening interval for women ages 40–54 years, and a 2-year screening interval for older women.[2] One of the authors (B.C.) suggests that a rational mammographic screening program for American women might be 6-month mammographic screening in women in their 40s, yearly mammographic screening in women in their 50s, biennial mammographic screening in women in their 60s, and triennial screening for women in their 70s. Such a schedule would be cost neutral and, through excision of the ductal carcinomas in situ discovered, would prevent many later invasive breast carcinoma cases.[17] Such alternative ideas for a screening schedule should be given serious consideration because they raise the possibility of greater reductions in breast carcinoma mortality than have been achieved to date. What these three recent articles make clear is that through both the collection of screening data[1,2] and the development of mathematic methods to predict the consequences of various screening strategies,[3,6-8] it should be possible to arrive at the most effective screening intervals of mammography screening to prevent deaths from breast carcinoma.

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