JOURNAL OF WOMEN'S IMAGING Volume 3, Number 2, pp 54–57

CME ARTICLE

Editorial

Using Information on Breast Cancer Growth, Spread, and Detectability to Find the Most Effective Ways for Screening to Reduce Breast Cancer Death

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Screening is believed to reduce breast cancer death by finding tumors before they have spread beyond the breast, when they can still be cured by local treatment. Thus, the effectiveness of screening is directly affected by the rates of breast cancer growth and spread and the detectability of breast cancer by screening mammography. During the past few years, my colleagues and I have developed a computer simulation model of breast cancer growth and spread that can calculate such things as the relation between the screening interval and the fraction of women likely to die of breast cancer. A nonmathematical summary of the results of these studies is presented here, which indicates that great reductions in breast cancer death should be achievable by prompt compliance with the annual screening recommendation and that even greater numbers of lives might be saved by screening more frequently than once a year. [Key words: breast cancer, screening, mammography, computer simulation, screening interval, optimization] **Journal of Women's Imaging 2001;3:54–57**

Learning Objectives: After reading this article and completing the posttest, the physician should be able to:

- describe the major biologic mechanism behind mammography's ability to reduce breast cancer death;
- explain the general principals of breast cancer growth and spread, and detail how they underlie the optimal screening interval;
- compare the magnitude of the theoretical life-sparing potential of mammographic screening with the actual benefit now being achieved by screening.

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The author has disclosed that he has no significant relationships with or financial interest in any commercial companies pertaining to this educational activity.
Acknowledgment date: October 12, 2000.
Revision date: February 27, 2001.
Acceptance date: March 8, 2001.

Challenge of Breast Cancer Control

We know from the results of the randomized controlled trails that screening mammography saves lives.[1–6] How, then, can screening be used to achieve its maximal benefit? Overuse will result in additional biopsies without the possibility of benefit,[7,8] whereas underuse will result in women dying of breast cancer who might otherwise have been cured.[9] During the past few years, my colleagues and I have been collecting data on the rates of breast cancer growth and spread and on the limits of mammographic detectability, and then using this information in a computer simulation model of breast cancer growth and spread to calculate the relation between screening interval and breast cancer survival.[10] The initial results of these studies are promising,[10] since they suggest that great reductions in breast cancer death might be achievable by the simple expedient of more frequent screening. Here are conveyed some of the main feature of these findings, leaving aside the mathematical details, which can be found elsewhere.[10]

Current State of Recommendations for the Screening Interval

The current level of uncertainty as to the best breast cancer screening interval is reflected in the lack of uniformity in the recommendations for the screening interval. While the American Cancer Society (ACS), the American Medical Association, and other major organizations recommend annual screening beginning by the age of 40 years, the National Cancer Institute has recommended screening every 1 to 2 years. In Canada, Australia, and much of Europe, screening every other year is the norm, whereas in Sweden

screening is recommended every 18 months for women age 40 to 49 and every 24 months for women age 50 and older. In the United Kingdom, screening is done every 3 years. These diverse recommendations have arisen largely in isolation from any empirical guidance as to the effect of the screening interval on mammography's capacity to reduce breast cancer death.

■ Breast Cancer Growth

From a number of studies, particularly those that have compared the size of breast cancers on two consecutive mammograms, it has been found that these tumors probably have a doubling time of about 130 days.[11–15] Thus, a tumor that is 1 mm^3 in size today can be expected to be 2 mm^3 in 130 days and 4 mm^3 in 260 days. It is easy to simulate such growth by computer and to examine how long it should take for a tumor to grow from a mammographically detectable size to a size that is detectable by the woman herself (Figure 1). In our initial studies,[10] it was assumed that tumors would become detectable by mammography at about 3 mm and by self-palpation at about 12 mm. We are now in the process of extracting more precise estimates of these values. Initial results suggest that both values were slightly underestimated but not so much as to change the general conclusions of our initial analysis.[10] By combining all this information in a computer simulation of breast cancer growth, it can be seen that the time that it takes for a tumor to grow from the median size at which it can be detected by mammography until it can be detected by palpation is about 18 to 24 months (Figure 1).

■ Breast Cancer Spread

Of course, the objective of breast cancer screening is not to find tumors at smaller sizes but to reduce breast cancer death. Preventing breast cancer death is best accomplished by finding breast cancers before they have spread beyond the breast, when they can still be cured by local treatment. This too is calculable, by finding the probability (1/P) per cell in the primary tumor, of a cell moving from the breast to the periphery and forming a distant, lethal metastasis. The value of this probability could be estimated from data that were collected in two large studies that examined the survival of women with breast cancers of various sizes.[1–3,16–19] Indeed, it appeared that the value of the probability of spread per cell in the primary mass is approximately one distant metastasis per billion cells in the primary mass ($1/P = 10^{-9}$ metastases per cell).[10] With this information on the value of 1/P, it was possible to estimate the likely number of metastases that would be given off by tumors of various sizes simply by multiplying the number of cells in the tumor times 1/P, and from this, to calculate the overall chance of tumor spread.[10] When used in our computer simulation, this also makes it possible to make simultaneous estimates of breast cancer growth (see Figure 1, *top*) and spread (see Figure 1, *bottom*). From this, it can be seen that the chance of distant lethal spread for the median tumor detectable by palpation is about 30%, and the chance of spread for the median tumor detectable by mammography is about 10%. Thus, our analysis has already revealed a fundamental result, which tells us why mammographic screening works; the rate of breast cancer growth, the probability of breast cancer spread, and the mammographic detectability of breast cancers all have such fortuitous values that mammography is capable of finding tumors not just at smaller sizes but also at stages before they have spread beyond the breast, and thus when they can still be cured by local treatment.

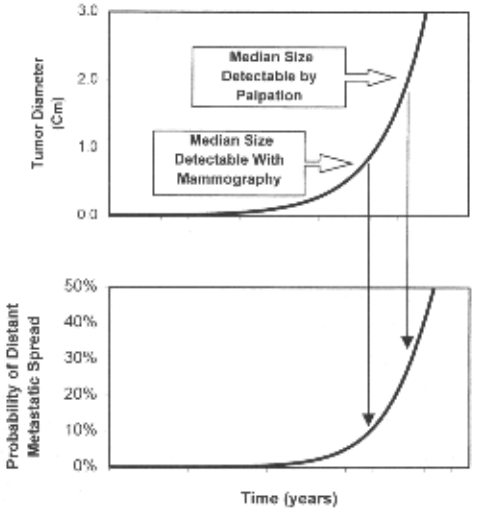

Figure 1. Simultaneous calculation of breast cancer growth, based on a doubling time of 130 days, and the probability of distant metastasis spread, based on 10^{-8} to 10^{-10} metastases per cell. Tumor sizes detectable by screening mammography and detectable in the absence of screening that are shown here are approximations for illustrative purposes. (For details, see Michaelson and colleagues.[10])

■ Making Quantitative Predictions of Screening's Capacity to Reduce Breast Cancer Deaths

Of course, not all tumors will be detectable by mammography at the same size, nor will all tumors have the same doubling time, but the simulation could take these considerations into account. There will also be a range of sizes at which breast cancers will become detectable on clinical grounds, but the distribution of these values is also estimable and has been incorporated into the simulation. These values have been incorporated into our simulation to keep it as accurate and realistic a simulation of breast cancer growth, spread, and detectability as possible.[10] When a tumor becomes detectable as a palpable mass by the woman herself between screening examinations and is brought to the attention of the medical system, these tumors appear as interval cancers, and the simulation also takes these into account. The simulation was then modified to provide estimates of the effect of various screening intervals on the fraction of women in the screening population who will die of breast cancer.[10] A typical result of these calculations is shown in Figure 2, which encouragingly suggests that screening mammography has the potential to lead to breast cancer survival rates of better than 90% (with a reduction in breast can-

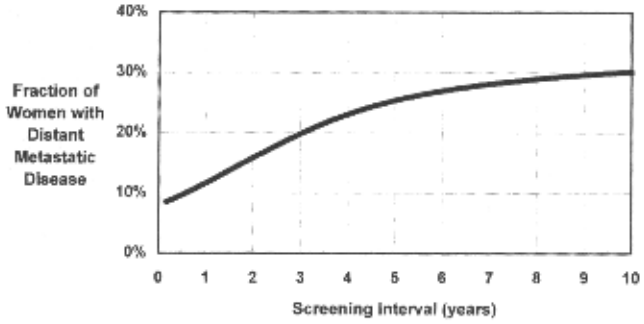

Figure 2. Expected relationship between the screening interval and the fraction of women with distant metastatic disease, for women age 65. For details, see reference 10.

cer death of 70% or more in comparison with women who are not screened) if screening is carried out with sufficient frequency.[10]

■ Finding the Most Efficient Ways to Use Screening to Save Lives

How can we use this information to find the best way to employ screening in the reduction of breast cancer death? By incorporating data on the age-associated incidence of cancer[20] and the number of years of life that are left for women of various ages,[21] the computer simulation could be made to produce estimates of the *average benefit* of screening, in terms of cancer-free years of life saved per year of screening for various screening intervals, and the *marginal benefit* of screening, the benefit of the last extra decrease in the screening interval (Table 1).[10] As we shall see, information on the average benefit is particularly useful for calculating the overall savings in life that can be achieved by screening, whereas information on the marginal benefit is helpful for making decisions about how often screening should be carried out.

In Table 1, the simulation estimates of the average and marginal benefits of screening are shown for women 65 years of age, but they are approximately representative for women aged 40 years and older. As the screening interval is reduced, the fraction of women surviving breast cancer goes up, as does the average benefit of screening in terms of cancer free hours of life saved, but the marginal benefit per mammogram gradually declines, a process familiarly knows as the law of diminishing returns. We can use this information to estimate at what point it no longer make sense to further decrease the screening interval. For example, the simulation results shown in Table 1 reveal that a woman who is screened every 12 months will be receiving a marginal benefit of 27 extra cancer-free hours of life per mammogram, and thus will be getting many more hours of life from screening than she is loosing every time she goes for a mammogram. If, conversely, she chose screening every 3 months, she would be receiving a marginal benefit of only about 1 hour of cancer-free hours of life, and will be spending more time *at* her last examination than she would be gaining in cancer-free hours of life *from* the examination! Clearly, the best choice would appear to lie somewhere in between. A reasonable compromise strategy would appear to be about twice a year, which returns a marginal benefit of a bit more than 6 extra cancer-free hours of life and an overall average return of a 166 cancer-free hours of life.

Table 1. Estimated Consequence of Various Screening Intervals, as Determined by Computer Simulation, for Women Aged 65 Years

Screening Interval (mo)	Reduction in Death (%)	Survival Rate (%)	Average Benefit*	Marginal Benefit†
48	34.8	77.0	80	287
36	44.0	80.2	101	215
30	49.5	82.1	113	161
24	55.2	84.2	127	108
18	61.2	86.3	140	62
12	67.1	88.4	154	26
9	69.9	89.4	160	14
6	72.6	90.3	166	6
3	75.1	91.2	172	1

* In cancer-free hours of life saved per women per year of screening.
† In cancer-free hours of life saved per mammogram for the last incremental reduction in the screening interval.

It is not too difficult to use this information to examine screening not only in terms of a reasonable return for the amount of time women are spending on screening but also in terms of a reasonable return for how much money they are spending on screening. Many insurance programs reimburse screening mammography in the $50 to $100 range. Again skipping the mathematical details but using the approach shown in Table 1, it follows that, for most women, twice-yearly screening can be accomplished for a marginal screening cost (the inverse of the marginal benefit times the cost per mammogram) of less than $100,000 per cancer-free year of life saved and an average screening cost (the inverse of the average benefit times the cost per mammogram divided by the number of mammograms per year) of less than $20,000 per cancer-free year of life saved.[10]

■ Potential Savings in Life That Might Be Achieved by Screening

The estimation method considered so far can be thought of as an elaborate calculator for taking everything we know about the rate of breast cancer growth, the probability of spread, and the limits of mammographic detectability to predict the outcome of various screening usages.[10] There are no "imagined" assumptions in the calculations. Thus, the results generated can be considered the likely consequences of what we now know about the rates of breast cancer growth, the probability of breast cancer spread, and the limits of the mammographic detectability of breast cancer. What do these results mean, in terms of the improvements in breast cancer survival? Perhaps the most important result of the simulations shown in Table 1 is that survival rates of 88% or more should be achievable simply by following the ACS recommendation of prompt annual

screening.[6] Reaching a survival level of 88% would be an enormous reduction in breast cancer death in comparison to the current breast cancer survival rate, which is believed to be about 55% to 65%.[22] Since more than 40,000 deaths are caused by breast cancers in the United states each year,[20] the results of the simulations translate into tens of thousands of lives that could potentially be saved by prompt compliance with the annual screening recommendation from age 40 onward. Unfortunately, few women are now following this recommendation. For example, for the women who use screening at the Massachusetts General Hospital, the median age for the first screen is 50 years, and the median return time is 18 months, and many women go 2, 3, or more years before returning.[9] Furthermore, it is not unreasonable to expect that screening utilization might be even lower elsewhere, since Massachusetts has been found to have the highest self-reported levels of mammographic screening in the United States.[23]

■ Future Possibilities

During the past several decades, there have been great improvements in breast cancer surgery, radiation therapy, and adjuvant chemotherapy,[24,25] but the results of the simulation studies described earlier suggest that the best hope for saving lives lies in screening. Thus, it is the mammographers who provide screening, and the women themselves who attend screening, who possess the greatest power to prevent breast cancer death. The results of the simulation studies have also shown that while annual screening should lead to an 88.3% survival rate, twice-yearly screening might yield breast cancer survival rates of 90.5% (see Table 1). Although at first glance that extra 2% may seem to be an unimpressive number, it translates into more than 3000 additional lives saved in the 180,000 US women found to have breast cancer each year.[20] As we have seen, twice-yearly screening is also justifiable as a rational return on the time and expense spent on screening. Conversely, more aggressive screening might also lead to extra false-positives, unnecessary medical procedures, additional anxiety, and higher medical costs.[7,8] Furthermore, there may be other ways of reaching greater reductions in breast cancer death, such as efficiently combining screening tools (*e.g.*, mammography plus clinical breast examination, magnetic resonance imaging, ultrasound) or individualizing optimal screening intervals based on parenchymal density and history. These considerations should be measurable and their consequences examinable by simulation analysis, but, at the least, the potential benefit of more aggressive screening raises the question of whether a trial of twice-yearly screening should be carried out.

ACKNOWLEDGMENTS

I thank my colleagues in this work, Sameer Satija, Richard Moore, Griffin Weber, Elkan Halpern, Andrew Garland, and Daniel B. Kopans.

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