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Breast Cancer: Computer Simulation Method for Estimating Optimal Intervals for Screening[1]

PURPOSE: To develop and evaluate a mathematic method that can be used to determine the optimal screening interval for detection of breast cancer prior to distant metastatic spread.

MATERIALS AND METHODS: A computer simulation was developed with the use of biologically based data from the literature on the rates of tumor growth and spread, which can be used to calculate the course of breast cancer growth and metastasis.

RESULTS: On the basis of the data available at this time, the results of the simulations suggested that a screening interval of 2 years would result in a 22% reduction in the rate of distant metastatic disease, an interval of 1 year would result in a 51% reduction, and an interval of 6 months would result in an 80% reduction.

CONCLUSION: These findings suggest that more frequent screening could dramatically reduce the death rate from breast cancer.

Author contributions:
Guarantor of integrity of entire study, J.S.M.; study concepts, J.S.M., E.H., D.B.K.; study design, J.S.M.; definition of intellectual content, J.S.M., E.H., D.B.K.; literature research, J.S.M., E.H., D.B.K.; statistical analysis, J.S.M., E.H.; manuscript preparation, editing, and review, J.S.M., E.H., D.B.K.

Invasive breast cancer is diagnosed in more than 180,000 women each year, and over 40,000 die of this disease annually. If these tumors can be identified while confined to the breast, then breast cancer usually can be cured by means of local treatment. It is distant metastatic disease, and the destruction of other organ systems, that causes death in women with breast cancer (1–14). Indeed, the results of randomized controlled trials of screening (9,10,13,14) have demonstrated that if breast cancer can be detected and treated before becoming metastatic, death due to breast cancer can be avoided.

Although the results of these trials have demonstrated that mammography can save lives, many aspects of screening remain undefined, including the optimal interval between screening sessions (15,16). The American College of Radiology and the American Cancer Society recommend that women aged 40 years and older undergo screening every year, whereas the National Cancer Institute recommends screening every 1–2 years (11,12). A 1-year interval has been chosen by several organizations, particularly for younger women, because the available data suggest that cancers grow faster in these women, and if the tumor is to be stopped prior to metastatic spread, a shorter time between screenings is needed (11,12).

Moskowitz (17) was one of the first to point out the importance of the screening interval. Subsequently, Tabar et al (18) demonstrated the same phenomenon by using interval cancer rates in which women aged 40–49 years underwent screening every 2 years, and women aged 50 years and older underwent screening every 3 years. More recently, Sickles (19) showed that the sensitivity of mammography was the same for women aged 40–49 years who underwent screening every year as it was for women aged 50 years and older who underwent screening every 2 years. Unfortunately, however, we are aware of no studies in which the issues of different screening intervals and how these intervals may influence mortality have directly and prospectively been addressed.

Although there has been a general appreciation that the rates of tumor growth and spread are fundamental to both the biology and the control of breast cancer, to our knowledge there has not been a mathematic model that could be used to determine such estimates in a quantitative fashion. In this article, we describe just such a computer simulation method, which is reliant on biologically based data on the rates of breast cancer

growth and spread. The purpose of this study was to develop and evaluate a mathematic method that can be used to determine the optimal screening interval for detection of breast cancer prior to distant metastatic spread. This simulation method has allowed us to examine a variety of aspects of breast cancer screening, including the effect of various screening intervals on the reduction in the breast cancer death rate. The results of our simulations are generally in agreement with the results of randomized controlled trials of breast cancer screening and confirm the widely held belief in the benefit of yearly mammographic screening. In addition, our results raise the surprising possibility that considerable reductions in the breast cancer death rate might be achieved if breast cancer screening was performed more frequently.

MATERIALS AND METHODS

Data for Estimates of Breast Cancer Growth Rate

By using data from a variety of sources, it is possible to estimate the growth rate of breast cancer. Some of the most telling data are from studies (20–27) of serial mammograms; these studies are reliant on the fact that, in a small number of patients, the signs of the tumor can be found at a review of an earlier mammogram. von Fournier et al (20) studied mammograms in 147 such patients whose tumors could be seen on two or more serial mammograms and found these tumors to have a doubling time of 88–383 days. Heuser et al (26) used the same approach and observed 16 patients whose tumors had a doubling time of 109–270 days, eight patients whose tumors had a doubling time of more than 1 year (393–944 days), and nine patients whose tumors had an essentially infinite doubling time (ie, the tumors showed no growth). Lundgren (27) examined the growth rates of 15 tumors and found a doubling time of 42–406 days. In one of the largest such studies, Spratt et al (24) estimated tumor growth rates in 448 patients and found a mean doubling time of approximately 250 days and a range of 10–7,051 days.

The difficulty with estimates of cancer growth that are based on sequential mammographic data is that slow-growing tumors are more likely to be seen on two consecutive mammograms than are fast-growing tumors. This means that estimates derived from sequential mammographic data are likely to yield artificially low breast cancer growth rates. In part to generate estimates less susceptible to this bias, Peer et al (23) used data on breast cancers arising during a screening program. The growth of tumors that did not appear on two consecutive mammograms could be estimated by assuming that at the time of the previous mammogram, the tumor was just below the limit of detectability. Of course, these tumors could have been far smaller than this minimum size, so this approach is not entirely free of the tendency to underestimate growth rate, but bias with this method is of a smaller magnitude than bias with estimates determined on the basis of serial mammograms alone. Indeed, the estimates by Peer et al did result in a downward revision of the estimated growth rates of breast cancer. Peer et al also sorted the data by age and found that in patients younger than 50 years of age, tumors have a median doubling time of 80 days (with 95% of doubling times between 44 and 147 days), whereas the tumors in patients aged 50–70 years have a median doubling time of 157 days (with 95% of doubling times between 121 and 204 days), and tumors in patients older than 70 years have a median doubling time of 188 days (with 95% of doubling times between 120 and 295 days).

Of course, not all tumors grow at the same rate. However, there are excellent data on the distribution of growth rates. For example, the distribution of these doubling times has been characterized by Spratt et al (24), who found that roughly 50% of tumors have a doubling time close to the mean, whereas 25% of tumors have a doubling time of about twice the mean rate, and most of the remaining 25% have a doubling time of about half the mean rate.

There also are abundant data (28–38) that suggest that when breast cancers are much smaller than the size at which they become clinically evident, their growth is much more rapid than that during their clinical appearance. There also are data that indicate that breast cancers, if left untreated, will undergo a further decline in growth rate. Fortunately, however, as we shall report in this article, we have found that this so-called density-dependent change in growth rate, sometimes also called gompertzian growth (29), will not affect the general conclusions of our estimates on the outcome of breast cancer screening.

Tumor Size and Incidence of Metastasis

The probability that a breast cancer cell will leave the primary tumor and form a distant metastasis can be calculated from data on the relationship between tumor size and the incidence of distant metastatic disease. Many factors, including age and genotype, may play a role in the rate of metastasis. We can begin to gain some insight into this process from data collected by Tabar et al (9–11) and Tubiana and colleagues (6–8) on the relationship between the size of the primary breast cancer at the time of surgical removal and the subsequent incidence of distant metastatic disease (Table 1). By distant metastatic disease, we mean the spread and establishment of potentially lethal cancer to the periphery, beyond the breast and the regional lymph nodes. We emphasize that with this definition there are no assumptions about whether such spread occurs directly from the primary tumor or is mediated by an intervening step in the local lymph nodes.

A few simple mathematic tools are needed to extract an initial estimate of the probability of metastasis from the data collected by Tabar et al (9–11) and Tubiana et al (6–8). The number of cells n in a tumor can be roughly estimated from the tumor diameter by using the expression $n \approx B[4/3\pi(d/2)^3]$, where d is the tumor diameter, and B is the number of cells per cubic centimeter. Because most tumors cells are roughly 20 μm in diameter (39–41), a B value of approximately 10^8 cells per cubic centimeter is a reasonable approximation, although, as will become apparent later, our model does not require a precise estimate of B. The probability that a cell will leave the primary tumor and form a distant metastasis is defined as $1/P$, which is expressed in units of $cell^{-1} \cdot day^{-1}$. Thus, P may be thought of as the number cells for the number of days it takes until there will be, on average, one metastasis per tumor. P, therefore, is expressed with the unit "cell days." By definition, C is the number of cell days that a tumor with n cells has accumulated. If P should prove to be a constant, then it follows that the average number of metastases per tumor is equal to $C \times 1/P$.

To calculate the relationship between tumor size n and the number of cell days C that a tumor has accumulated requires consideration of the rate of tumor growth, as was discussed earlier. Such growth information can be incorporated into a simple computer simulation, and the relationship between n and C can be estimated. (The source code for these and other simulations described in this article is available at *http://webm9120.ntx.net/Breast CancerMath.html.* Accessed June 10, 1999.)

TABLE 1
Estimated Probability of Formation of Distant Metastasis from a Primary Breast Cancer Cell

Tumor Size (mm)	Fraction of Patients with Metastases	Constant Doubling Time			Density-dependent Growth with Terminal Doubling Time			Stochastic Process ($\times 10^{-12}$)*
		20 Days ($\times 10^{-12}$)	80 Days ($\times 10^{-12}$)	400 Days ($\times 10^{-12}$)	20 Days ($\times 10^{-12}$)	80 Days ($\times 10^{-12}$)	400 Days ($\times 10^{-12}$)	
12 (10–14)†	0.13	51.0	6.50	2.67	116.0	31.90	26.50	1,150
17 (15–19)†	0.20	29.0	7.50	1.50	57.6	15.40	3.12	865
17 (10–25)‡	0.27	41.0	10.60	2.10	80.0	22.00	4.40	1,225
25 (20–29)†	0.45	24.0	6.30	1.30	37.9	10.20	2.08	719
30 (26–35)‡	0.42	12.0	3.30	0.67	16.5	3.30	0.88	378
39 (30–49)†	0.55	8.4	2.20	0.44	9.5	2.40	0.48	251
40 (36–45)‡	0.56	8.3	2.10	0.43	9.1	2.10	0.50	245
50 (46–55)‡	0.66	5.6	1.40	0.29	5.9	1.40	0.31	167
60 (56–65)‡	0.78	3.9	0.99	0.20	4.0	0.99	0.21	114
70 (66–75)‡	0.83	3.4	0.87	0.18	3.4	0.87	0.18	99
80 (76–85)‡	0.81	2.1	0.53	0.11	2.1	0.53	0.11	62
90 (86–95)‡	0.92	2.2	0.57	0.12	2.2	0.57	0.12	64

Note.—Data are estimates of probability (1/P) expressed as number of metastases per cell day times 10^{-12}.
* Estimate determined on the basis of a stochastic process occurring once during each mitotic cycle.
† Data are from references 9–11. Numbers in parentheses are the range.
‡ Data are from references 6–8. Numbers in parentheses are the range.

TABLE 2
Estimated Reduction in Incidence of Distant Metastasis as a Function of Screening Frequency

Screening Frequency	Detection Method for Tumors with More than 10^8 Cells (%)*	Detection Method for Tumors with More than 10^7 Cells (%)†	Detection Method for Tumors with More than 10^6 Cells (%)‡
Every 3rd year	7	14	16
Every 2nd year	14	22	27
Every year	33	51	56
Every 6 months	62	78	84
Every 4 months	77	90	93
Every 3 months	86	96	98
Every 2 months	87	97	98

Note.—Reduction is relative to that in women who do not undergo screening.
* Corresponds to tumor diameter of approximately 12 mm.
† Corresponds to tumor diameter of approximately 3 mm.
‡ Corresponds to tumor diameter of approximately 1.2 mm.

For example, given a constant doubling time of 80 days, the simulation reveals that the various tumor sizes listed in the articles by Tabar et al (9–11) and Tubiana et al (6–8)—that is, 1.2, 1.7, 2, 2.5, 3, 3.9, 4, 5, 6, 7, 8, and 9 cm—correspond to C values of 0.1, 0.35, 0.48, 0.58, 1.6, 3.2, 3.8, 7.5, 13, 20, 31, and 44×10^{11} cell days, respectively. We also performed a similar calculation, taking into account the possibility that breast cancer may grow more rapidly when the tumor is small than when it is large (sometimes called gompertzian growth) (29,30); these estimates are shown in Table 2.

Now consider a group of patients whose tumors have grown to a size such that they have accumulated exactly P cell days ($C = P$). It would be expected in such a group of patients that, on average, there would be one metastasis per patient, since $C \times 1/P = P \times 1/P = 1$. Of course, this is an average. Although some of these patients would have one metastasis, others would have two metastases or four metastases, and some patients would have no metastases and would be free of metastatic disease. By using the Poisson distribution, it is possible to calculate that when the average number of metastases per patient is one, the fraction of patients with no metastases, that is, the fraction of metastatic disease–free patients is 1/e, or about 37% of patients. On the other hand, for a different group of patients whose tumors are of sufficient size to have accumulated, for example, $C = 3P$ cell days—that is, in whom the average number of metastases per patient is three—it then follows that the fraction of metastatic disease–free patients is 1/e^3. Thus, in general, if C equals the number of cell days a tumor has accumulated and P equals the number of cell days needed to cause one metastasis per patient, the fraction of metastatic disease–free patients fr is equal to 1/$e^{C/P}$ or ln(fr) = $-C/P$.

It follows from this latter equation that if 1/P is a constant, then a graph of the natural logarithm of fr versus C will form a straight, downward-pointing line that forms an intersection with the origin. In fact, the data of Tabar et al (9–11) and Tubiana et al (6–8) conform quite closely to the straight line predicted by ln(fr) = $-C/P$, with an r^2 value of 0.8976, which thus provides direct empiric evidence that the value of 1/P is fairly constant (Fig 1).

From a biologic standpoint, this relative constancy of 1/P is what would be expected for mechanisms of metastasis formation that are dependent on processes such as mutation or simple mechanical events such as detachment from the primary tumor, dissemination, survival, and reengraftment (42–45). What is especially powerful about the results of Tabar et al (9–11) and Tubiana et al (6–8), however, is that their data provide a way to measure the value of this probability. Thus, the graph shown in Figure 1 can be used to develop a rough estimate of the value of 1/P, which the equation ln(fr) = $-C/P$ indicates will correspond to the point on the x axis where fr is equal to 1/e, or about 37%, which yields an approximate value for 1/P from 10^{-11} to 10^{-13} metastases per cell day. Alterna-
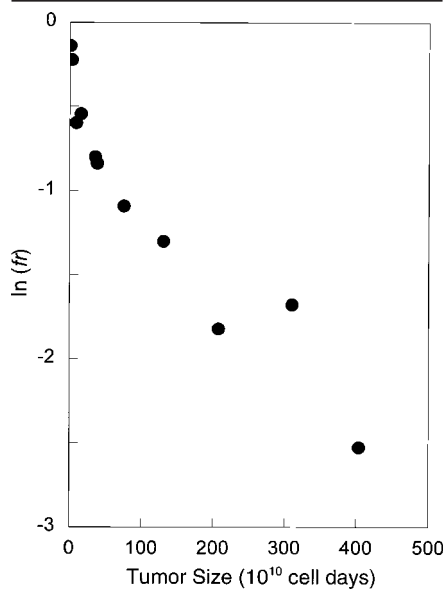
Figure 1. Graph shows the relationship between tumor size (in cell days) and the log of the incidence of metastatic disease (*fr*). The data are from studies by Tabar et al (9–11) and Tubiana et al (6–8). The number of cell days was calculated by using computer simulation in which a constant doubling time of 80 days was assumed. Tumor size (in number of cells *n*) was calculated on the basis of tumor diameter *d* by using the expression $n = B[4/3\pi(d/2)^3]$, with a *B* value of 10^8 cells per cubic centimeter. The r^2 value is 0.8976.

Figure 2. (a) Graph shows results of a computer simulation of breast cancer growth for a tumor with a doubling time of 80 days. This graph represents an idealized mean growth curve. The actual growth of tumors should be expected to display variation around this mean. (b) Graph shows computer simulation results for the development of distant metastatic disease. In this simulation, the probability that a cell will leave the primary tumor and form a distant metastasis (1/*P*) is $10^{-12} \, \mathrm{cell}^{-1} \cdot \mathrm{day}^{-1}$.

tively, the value of 1/*P* can be estimated directly with $\ln(fr) = -C/P$ for each tumor size and data point on the basis of metastatic disease incidence provided by Tabar et al (9–11) and Tubiana et al (6–8) (Table 1).

Estimates in Probability of Distant Metastasis

It is possible to estimate the degree of variability in the value of 1/*P*. As already noted, if 1/*P* were perfectly constant, then it would follow from the expression $\ln(fr) = -C/P$ that a graph of the natural logarithm of *fr* versus *C* would form a straight, downward-pointing line that begins at the origin. Although close to this line, the data of Tabar et al (9–11) and Tubiana et al (6–8) display a slight curvature (Fig 1). There are a number of possible explanations for this rather subtle feature. For example, as tumors become larger, they may contain necrotic material, and this could cause overestimation of the number of cells in larger tumors and underestimation of the number of cells in smaller tumors, thus resulting in the curvature. Alternatively, cancer cells at the periphery of a tumor may have a

slightly better chance of detaching from the primary tumor and forming a metastatic colony than might cells located in the interior of the tumor. This would mean that the value of 1/*P* would decrease slightly as the tumor became larger. It also is possible that small tumors have a slower growth rate than large tumors; examination of Table 1 reveals that because the growth rate is necessary for the calculation of 1/*P*, this effect may account for the variability in 1/*P*. Finally, there may be a small amount of tumor-to-tumor variation in the value of 1/*P*. Indeed, the slight curvature seen in Figure 1 fits well with the type of curve we would expect if about 25% of tumors have a 1/*P* value of approximately 10^{-11}, another 50% of tumors have a value of approximately 10^{-12}, and the remaining 25% of tumors have a value of approximately 10^{-13}, as we have found by using a simulation that reconstructs a curve on the basis of a population of women with just this distribution of values (data not shown).
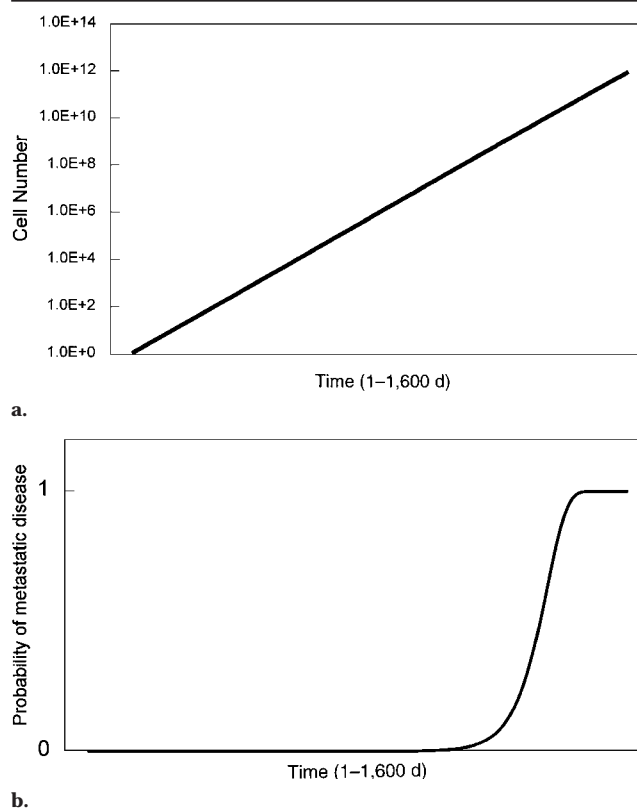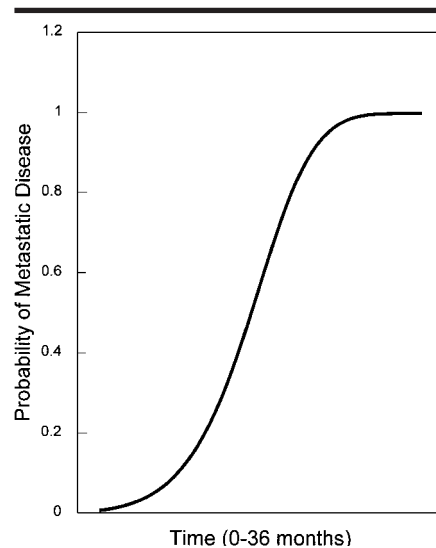

Figure 3. Graph shows computer simulation results for the probability of distant metastatic disease from the time when the primary tumor (doubling time, 80 days) is first detectable at mammography (tumor size, 10^7 cells). The 1/*P* value is approximately $10^{-12} \, \mathrm{cell}^{-1} \cdot \mathrm{day}^{-1}$.
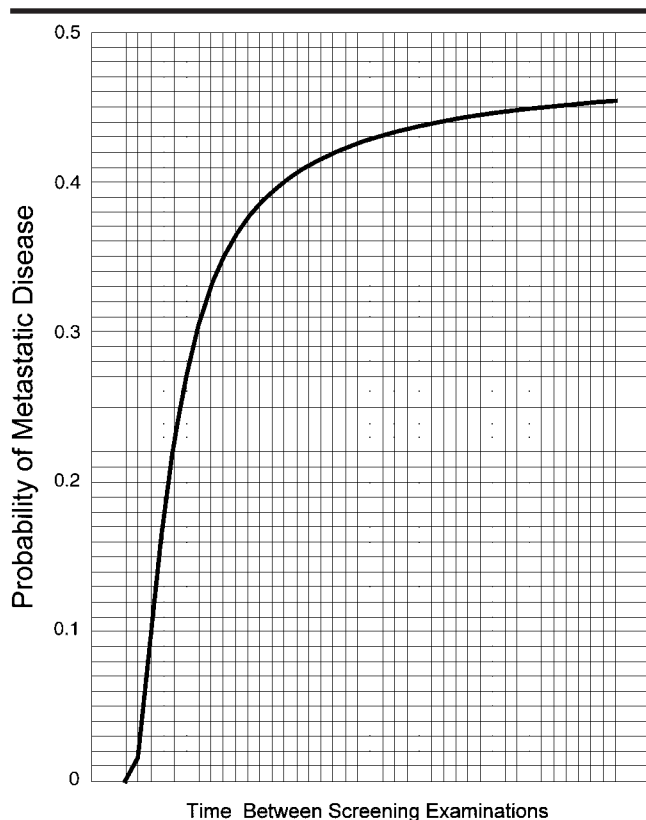
Figure 4. Graph shows the results of a computer simulation for the estimate of the effect of the interval, from 0 to 10 years in 3-month intervals, between screening examinations on the incidence of distant metastatic disease. For details about the simulation, see the text.

In the simulations that follow, we have adopted this as the most likely and accurate estimate of $1/P$ that we can achieve at this time.

We might wonder what the limits are to such variation in the value of $1/P$. That is, might there be subpopulations of tumors with very high or very low values of $1/P$? For example, by performing a simulation of the type shown in Figures 2 and 3, we found that tumors for which $1/P$ is 10^{-16} or less would essentially never metastasize, even if the primary tumor were to grow to a kilogram in mass (approximately 125 mm in diameter). However, the data from Tubiana et al (6–8) show that 92% of patients with tumors 86–95 mm in diameter develop distant metastases, so we can expect that there are very few tumors with such favorable $1/P$ values.

At the other extreme, we might wonder whether there are certain tumors that have such a high $1/P$ value that they would already have metastasized at the time of detection. No degree of surveillance can help identify such tumors before metastasis has occurred, and such

tumors would thus be immune to the beneficial effects of screening. Simulation also revealed that tumors with a $1/P$ value of approximately 10^{-9} would have a 3% chance of metastasizing before they had reached a minimally detectable size of about 3 mm (approximately 10^7 cells), whereas tumors with larger $1/P$ values would have greater chances of metastasizing before detection. Fortunately, the data from Tabar et al (9–11) suggest that such tumors must be relatively rare. For example, in patients with tumors that are 1–9 mm in diameter, Tabar et al (9–11) found the frequency of distant metastatic disease to be about 7%. By using $\ln(fr) = -C/P$ and our simulation to calculate the number of cell days that are accumulated by a 9-mm tumor, it follows that the remaining 93% of these patients must have had tumors with $1/P$ values that were larger than 10^{-10} metastasis per cell day. The screening simulations described earlier demonstrated that frequent screening can substantially reduce the incidence of distant metastatic disease even in patients with tumors with this value of $1/P$. This does not mean that no tumors

will have such low $1/P$ values that there is no benefit to screening, but it does suggest that such tumors are likely to represent a small fraction of all breast cancers, which should not dampen the encouraging results that the simulations provide of the power of screening to reduce the death rate due to distant metastases.

Thus, these considerations suggest that for the majority of breast cancers, indeed for more than 93% of these tumors, $1/P$—the probability that each cancer cell will leave the primary tumor and form a distant metastasis—must have a value greater than 10^{-10} metastasis per cell day. As we shall show subsequently, this means that the overwhelming majority of patients with breast cancer will benefit from mammographic screening.

Estimates of Time Course of Cancer Growth

With the estimate of the probability of metastasis formation ($1/P \approx 10^{-12}$ metastases per cell day), it is possible to determine an initial rough estimate of the occurrence of metastases over time (Fig 2), because the average number of metastases formed each day is simply the probability that a single cell will form a metastasis (ie, $1/P$) times the number of cells in the tumor. By using such an approach, it is fairly straightforward to estimate the probability of distant metastatic disease from the time of occurrence of the first breast cancer cell (Fig 2b), as well as from the time when the tumor can first be detected (Fig 3).

The remarkable result of these simulations and the likely explanation as to why screening can reduce the death rate is that metastasis occurs late in the time course of breast cancer growth, generally after the minimal sizes usually detectable on mammograms (approximately 1–10 mm) have been reached (12). This suggests that breast cancer screening has the potential to help identify a large fraction of breast cancers before they metastasize, an impression that is borne out in the more detailed simulation described subsequently.

Practical Estimates of Relationship between Screening Interval and Incidence of Metastases

It is necessary to add several additional features to the simulation illustrated in Figures 2 and 3 before we can determine practical estimates of the influence of breast cancer screening on the reduction in distant metastatic disease.
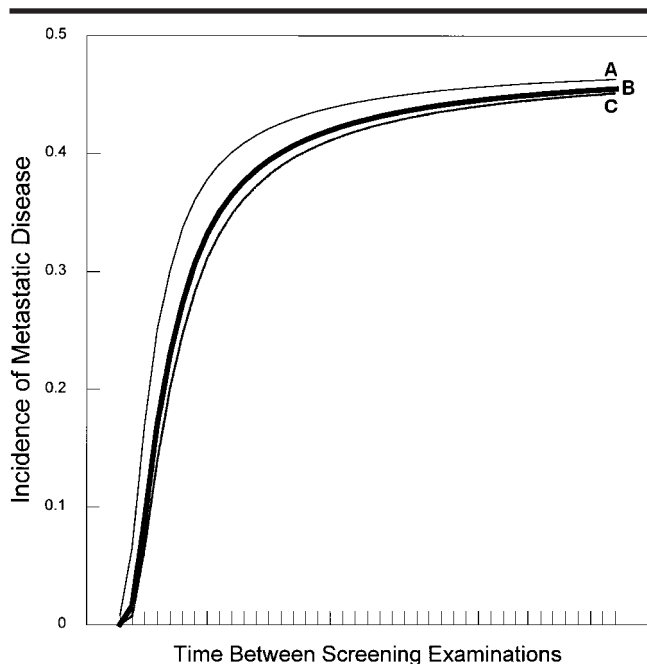
Figure 5. Graph shows the effect of physical sensitivity of the screening method on the incidence of distant metastatic disease. Details of this simulation were the same as those in Figure 4, except the three curves shown were calculated for detection sizes of 10^8 (*A*), 10^7 (*B*), and 10^6 (*C*) cells. The graph covers 0–10 years, and each hash mark represents 3 months.

a.

b.

Figure 6. **(a)** Graph shows the effect of the value of the probability of metastasis formation ($1/P$) on the effectiveness of screening. Details of these simulations were the same as those in Figure 4, except mean values of $1/P$ were calculated for means of (from top to bottom) 10^{-9}, 10^{-10}, 10^{-11}, 10^{-12}, 10^{-13}, 10^{-14}, and 10^{-15}. The graph covers 0–10 years in 3-month intervals. **(b)** Graph shows the effect of tumor growth rate on the effectiveness of screening. Details of these simulations were the same as those in Figure 4, except that mean tumor doubling times were calculated for values (from steepest to shallowest curve) of 20, 30, 40, 60, 80, 200, 400, 800, and 2,000 days. The graph covers 0–10 years in 3-month intervals.

First, breast cancers that appear between screenings will be detected if they become palpable. This is the minimal size detectable with palpation, *Sp.* Bear in mind that *Sp* will likely represent a mean size and a distribution of sizes around that mean. Because the median size of breast cancers reported in studies by Tubiana and colleagues (9–11), which were conducted in the era before mammography, was approximately 10^{10} cells, the simulation assumes that tumors that had escaped detection at screening would be identified and removed when they reached this size ($Sp \approx 10^{10}$ cells).

Second, the simulation must take into account that breast cancers will eventually become detectable at mammography. The minimal size detectable at mammography, *Sd,* will also likely represent a mean size with a distribution of sizes around that mean, because not all tumors of the same size will be detectable.

Third, because, as already noted, tumors arise with a variety of growth rates and a variety of probabilities of metastasis, the simulation must incorporate a consideration of this feature of breast cancer biology.

Fourth, in a screening program, tumors detected with the aid of screening come to the attention of the physician at the time of the examination and not at the time when they reach minimum detectable size. Thus, the simulation was adapted to examine the case where a breast cancer might reach minimum detectable size on any day between mammographic examinations.

Figure 4 shows the results of our simulation for what we believe are the most likely features of breast cancer biology. Peer et al (23) selected 3 mm (approximately 10^7 cells) as a reasonable estimate of *Sd,* and the results of our simulation with this value of *Sd* are shown in Figure 4. Figure 5 displays the results of simulations in which *Sd* is 10^6 cells (approximately 1 mm) and 10^8 cells (approximately 12 mm). The simulation shown in Figure 4 illustrates the case where 25% of new breast cancers have a $1/P$ value of approximately 10^{-11}, 50% of tumors have a $1/P$ value of approximately 10^{-12}, and
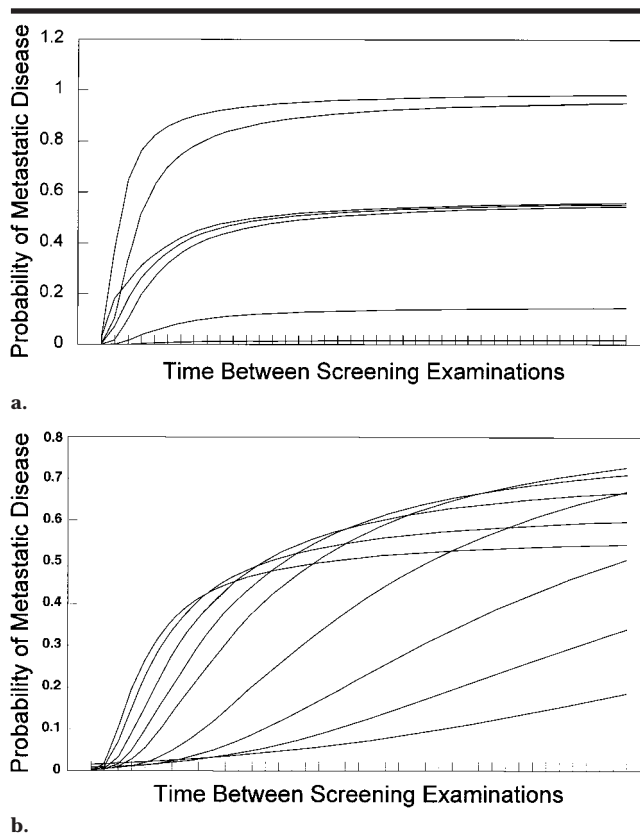
the remaining 25% of tumors have a $1/P$ value of approximately 10^{13}. The justification for the distribution of $1/P$ values was discussed earlier. Figure 6 shows the results of simulations with other mean values of $1/P$. The simulation in Figure 4 shows the case in which the mean tumor doubling time at the time of clinical detectability was 40 days, where 50% of tumors have a doubling time of this mean, 25% have a doubling time of twice the mean, and 25% have a doubling time of half the mean. These tumor doubling times and distributions were derived from the data of Peer et al (23) and Spratt et al (24), as already discussed. Figure 6 shows the results of simulations for other growth rates. The combination of these three metastasis probability groups and three tumor growth groups yields a total of nine groups, and the weighted contributions of each of these nine groups were summed.

Finally, a large number of observations (29–38) suggest that when breast cancers are small, they are likely to grow more rapidly than when they first become detectable at mammography. In the simulation shown in Figure 4, we incorporated such ''density-dependent'' growth, although equivalent simulations in which constant exponential growth was examined yielded essentially identical results (data not shown). (The precise schedule of such a density-dependent feature of breast cancer growth and the source code for these and other simulations described in this article are available at *http://webm9120.ntx.net/BreastCancerMath.html*. Accessed June 10, 1999.)

RESULTS

The results of the simulation designed to estimate the relationship between the screening interval and the incidence of distant metastases from breast cancer are shown in Figure 4 and Table 2. Results of this simulation suggest that in the absence of screening, the incidence of distant metastatic disease would be approximately 45%, which is in good agreement with the incidence actually seen in women with a diagnosis of breast cancer (1–8). Furthermore, the results of this simulation also predicted that for a screening method that can help detect tumors larger than 3 mm in diameter (approximately 10^7 cells), screening performed every 3 years would result in a 14% reduction in the incidence of distant metastatic disease (in comparison with that in women who do not undergo screening), screening performed every 2 years would be expected to result in a 22% reduction, and screening performed every year would be expected to result in a 51% reduction. This is also in general agreement with actual experience: In randomized mammographic screening trials (9–14), a reduction of approximately 30% in the breast cancer death rate has been achieved with screening intervals of 1–3 years.

Frequency of Screening

The results of the simulation shown in Figure 4 and Table 2 are of most interest where they show the consequences of screening at intervals not presently employed. Indeed, the simulation shown in Figure 4 suggests that more frequent screening could result in the identification of a much larger number of breast

cancers before the onset of distant metastatic disease and thus a great reduction in the breast cancer death rate. Thus, the curve shown in Figure 4 and the summary in Table 2 suggest that, for a screening method that could help detect tumors larger than 3 mm in diameter (approximately 10^7 cells), there would be a 66% reduction in the frequency of distant metastatic disease in women who undergo screening every 9 months, as compared with that in women who do not undergo screening. Moreover, there would be a 78% reduction in the frequency of metastases in women who undergo screening every 6 months and a 96% reduction in frequency in women who undergo screening every 3 months. These are potentially enormous improvements in the effectiveness of screening, which thus deserve careful consideration.

Large Range of Values for Tumor Growth and Metastasis

One concern of any computer simulation study is that the results may not reflect the general features of the system but rather the specific values employed in the simulation. We could rule out this possibility by using a large range of values in the simulation shown in Figure 4. Thus, we found that the benefit of more frequent screening seen in Figure 4 was almost independent of the value of the probability of metastasis formation, with reductions in the incidence of distant metastatic disease to about 5% in simulations that incorporated $1/P$ values that ranged from 10^{-9} to 10^{-16} (Fig 6). As outlined earlier, the actual values of $1/P$ from most tumors probably range from 10^{-11} to 10^{-13}, so it appears likely that the general results of the simulations are relevant for the majority of breast cancers. Likewise, the ability to reduce the breast cancer mortality rate to less than 5% with more frequent screening was found for simulations in which tumor doubling times of 20–2,000 days were examined (Fig 6). We also did not find a substantial difference in the general results of the simulations, whether they were formulated to estimate a constant tumor growth rate (Fig 2) or a growth rate that declines with increasing tumor size (Fig 4) (24, 25,29–37).

Another detail of the model concerns the definition of $1/P$ in terms of $cell^{-1} \cdot days^{-1}$. One might wonder whether $1/P$ should be calculated in terms of mitotic cycles rather than cell days, because mutation is more likely to occur when cells

divide. However, an estimate of the value of $1/P$ in terms of mitotic cycles revealed $1/P$ to be just as constant when calculated in terms of mitotic cycles as in terms of cell days (Table 1). Furthermore, a reformulation of the simulations in terms of mitotic cycles did not materially change the general results.

Finally, the outcome of the simulations also was found to be independent of the value of the density of cells per cubic centimeter (*B*). Identical curves resulted whether *B* was equal to 10^7, 10^8, or 10^9 cells per cubic centimeter.

Estimates of Physical Sensitivity of Screening

Both the detection method and the nature of the patient are likely to affect the minimal tumor size detectable at mammography. Some tumors may be detectable when very small, whereas others may not be detectable until they are much larger (12). The radiographic density of noncancerous breast tissues and possibly of the tumors themselves are likely to differ from woman to woman and to change with age (12). Presumably, *Sd,* the mean minimally detectable size, and the actual distribution of sizes around this mean must be reflections of the physics of depiction, the location and character of the tumor, and the nature of the surrounding tissue.

Our simulation allowed us to examine the effect of these limits of physical detectability on the capacity of mammography to help identify breast cancers before they spread distally. Figure 5 shows the results of simulations with cases where detection would occur for tumors larger than 10^6 cells (approximately 1.2 mm), 10^7 cells (approximately 3 mm), or 10^8 cells (approximately 12 mm); that is, *Sd* values of 10^6, 10^7, or 10^8 cells, respectively. Surprisingly, these three curves proved to be similar. This has two practical implications. First, the simulation results shown in Figure 5 revealed that although the capacity to identify smaller tumors results in greater ability to reduce the breast cancer death rate, such a reduction is more easily achieved by increasing the frequency of screening than by increasing the physical sensitivity of the screening method. Thus, the simple expedient of carrying out screening at more frequent intervals may be a more effective way to improve the outcome of screening than would be the development of improved screening technology. Consider the case where screening is performed every 2 years with a technology that can

be used to detect tumors no smaller than 10^8 cells ($Sd = 10^8$ cells, or approximately 12 mm). Figure 5 shows that a screening program that used this method but with which examinations were performed every 3 months would achieve a reduction of approximately 80% in the breast cancer death rate in comparison with that in which examinations were performed every 2 years. On the other hand, even a hundredfold increase in detection sensitivity ($Sd = 10^6$ cells, or approximately 1 mm) would yield only a 20% reduction in mortality rate if the program maintained the 2-year screening interval. Second, not all breast cancer tumors of the same size will be detectable. Figure 5 reveals that a more realistic assessment of screening, in which the detection limit represents a distribution of values centered around a mean of about 10^7 cells, would yield roughly the same outcome as that shown in Figure 4 for the simple case of a single discrete detection limit of 10^7 cells.

Cost-Benefit Consequences of Different Screening Intervals

Because our simulations yielded data on the relationship between the frequency of mammographic screening and the reduction in the rate of distant metastatic disease and thus in the breast cancer death rate, it is fairly straightforward to use this information to calculate the cost per year of life saved for the various screening intervals. The results of these simulations, determined on the basis of an estimated cost per examination of $100 and the expected incidence of breast cancer in a 50-year-old woman, are shown in Table 3. These initial estimates indicate that, within limits, more frequent screening would appear to yield considerable reductions in the breast cancer death rate with only modest increases in cost per year of life saved. Thus, for example, a program in which 50-year-old women underwent screening every 3 years would reduce the incidence of distant metastatic disease by a modest 19% and would cost approximately $10,661 for every year of life saved, whereas screening twice a year would reduce the incidence of breast cancer by 81% and lead to only a small increase ($14,172) in cost per year of life saved. On the other hand, these estimates allow us to define screening intervals that are clearly too frequent for the marginal benefit derived. Indeed, the results shown in Table 3 indicate that screening more frequently than every 3 months is likely to be a waste of time and money.

TABLE 3
Cost-Benefit Estimates as a Function of Screening Frequency

Screening Frequency	Reduction in Incidence of Metastases*	Cost per Patient per Year ($)	Mean Cost per Year of Life Saved ($)	Marginal Cost per Year of Life Saved ($)
Every 3rd year	19.0	33	10,661	5,029
Every 2nd year	27.0	50	10,601	5,030
Every year	52.0	100	10,986	6,756
Every 6 months	81.0	200	14,172	16,973
Every 4 months	92.4	300	18,740	40,242
Every 3 months	97.0	400	23,927	118,312
Every 2 months	98.9	600	35,074	634,802
Every month	99.7	1,200	96,291	1,019,037

Note.—Estimates are based on data in Table 2. The estimated cost per mammogram is $100. The estimates are for the incidence of breast cancer and expected years of life in a 50-year-old woman. (Source code for these estimations is available at *http://webm9120.ntx.net/BreastCancerMath.html.* Accessed June 10, 1999.)
* Estimated reduction is for screening that can help detect a tumor larger than 10^7 cells (approximately 3 mm).

DISCUSSION

We developed a computer simulation model of breast cancer growth and spread, and the results of our model suggest that an increase in the frequency of breast cancer screening could lead to substantial reductions in the incidence of metastatic disease and, thus, in the breast cancer death rate. Of course, estimates for the optimal screening intervals that are shown in Figure 4 and Table 2 must be considered only as first approximations. Further work will be needed to improve the precision of the underlying data used in construction of these simulations and to test the results of these simulations against available clinical data. At a minimum, however, these results are in general agreement with the suggestions by many groups about the value of annual screening (12); the results also raise the question about whether more frequent screening might be of value.

The computer simulation approach described here can provide a method for quantitative evaluation of a number of aspects of screening both for breast cancer and for other tumors. One of the major areas of controversy and ambiguity in breast cancer screening concerns the question of when women should begin screening (9–14). Whereas some have argued that screening should begin at the age of 40 years, others have suggested that the age of 50 years is more appropriate (9–14,46). The simulation method we have outlined here should be helpful in assessing the effectiveness of screening in women with different genotypes and ages. For example, breast cancers in young

women have been found to have faster growth rates than breast cancers in older women (23). Our simulations have revealed that this variation should not have an important influence on the effectiveness of screening (Fig 6), and this will certainly be an area for further analysis.

Although our simulations were developed with mammographic screening in mind, the general lessons should be applicable to other screening tests that can be used to identify breast cancers before they become clinically apparent (47). Of course, the potential beneficial effects of mammography must be considered together with the radiation required by this test, which is potentially carcinogenic (48,49). There are several ways to estimate this effect, one of the best of which uses epidemiologic data derived from studies with Japanese survivors of atomic bomb blasts (48,49). Although no effect of radiation on breast cancer incidence has been seen in individuals exposed to less than 250 mGy of radiation, survivors exposed to higher levels of radiation displayed a modest increase in breast cancer incidence. The current radiation dose per two-view mammogram is approximately 2.8 mGy (48,49). From these data, Mettler et al (48) estimated that yearly mammographic examinations in women from the age of 35 years to the age of 75 years would result in an increased incidence of breast cancer at the age of 75 years of 0.62%. By extrapolating from these data, we estimate that if these women underwent mammography four times a year, there would be a 2.5% increase in the incidence of cancer. By using this value and the data in Figure 4 and Table 2, it may be estimated that for every addi-

tional lethal breast cancer induced by the radiation associated with mammography four times a year, 32,333 lives would be saved because of screening.

Our initial cost-benefit estimates (Table 3), calculated for 50-year-old women, suggest that cost may not be a barrier to the possible benefit of more frequent screening (50). Of course, it remains to be seen what the cost-benefit estimates will be for women of other ages after taking into account other additional costs—both in terms of savings achieved from the prevention of distant metastatic disease and the additional costs raised by the discovery of these tumors (50).

More accurate assessments will also require us to take into account age-associated changes in breast cancer incidence, lead-time bias, age-associated change in life expectancy, and age-associated changes in the biologic properties of breast cancer, particularly changes in tumor growth rate. It also will be necessary to take into account the effect on the system as a whole, such as increases in the number of facilities, mammographic equipment, and radiology specialists, to determine whether the implications of our model can be accommodated in practice. This clearly will be a major task for investigators of the simulation approach in future studies.

In conclusion, we developed a computer simulation that calculated the time course of breast cancer growth and metastasis. These simulations were possible because the data from Tabar et al (9–11) and Tubiana et al (6–8) show that the probability of each cell in a breast cancer tumor leaving the primary tumor and forming a distant metastasis is relatively constant and measurable. With this information, as well as information on tumor growth rate (20–38), it was possible to estimate the effect screening can have on the incidence of distant metastatic disease and concomitantly on the breast cancer death rate. The results of these simulations suggest that screening may have a much greater potential for reduction in the breast cancer death rate than is presently achieved. Indeed, the findings described in this article suggest that screening, if used frequently enough, has the potential to convert breast cancer from a disease that is frequently fatal to a disease that can usually be cured.

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