Breast cancer screening is believed to reduce breast cancer death by finding cancers at smaller sizes than would have been seen in the absence of screening. However, to our knowledge, there have been no previous estimates, in quantitative terms, of the sizes at which breast cancers become operationally detectable by screening mammography and in the absence of screening. By “operational detectability” we mean the combined effects of physical and human factor limits to cancer detection. An understanding of these features of breast cancer detection would allow a number of insights into the best ways to use breast cancer screening. Indeed, with use of rough estimates of these values, it has been possible to construct a computer simulation model of breast cancer growth and detection, which could estimate such things as the relationship between the breast cancer screening interval and the expected reduction in breast cancer death. Herein we describe and use several new methods for extracting estimates of the operational detectability of breast cancers, especially the sizes at which breast cancers become operationally detectable by mammography, the sizes at which these tumors become operationally detectable in the absence of mammography, and how these aspects of detectability vary from woman to woman.

### MATERIALS AND METHODS

#### Dataset and Basic Definitions

We reviewed features of the 810 invasive breast cancers seen at the Massachusetts General Hospital (MGH) Breast Imaging Division database between 1990 and 1999. Carcinomas in situ were not included in among these tumors. Invasive breast cancers were divided into categories: first-screen–detected cancer (invasive breast cancer identified by mammography in an asymptomatic woman at her first screening at MGH), subsequent-screen–detected cancer (invasive breast cancer identified by mammography in an asymptomatic woman who had at least one previous negative screening mammogram result at MGH), intervening cancer (invasive breast cancer identified by means other than a screening mammogram in a woman who had at least one previous negative screening mammogram result at MGH), and never-screened cancer (invasive breast cancer identified by means other than a screening mammogram in a woman who has no history of mammography at MGH).

Note that we have adopted the term “intervening cancer” to distinguish it from the term “interval cancer,” which is usually used to describe a tumor arising after negative examination results but within a specified period of time. For the cancers that arose in women who had had previous negative mammogram results (intervening and subsequent-screen–detected cancers), it was possible to determine the length of time from the previous negative examination results until when the cancer was diagnosed. Gross tumor size measured in three dimen-

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*Assistant Professor of Pathology, Division of Surgical Oncology, Massachusetts General Hospital, Boston, MA; †Medical Student, Emory Medical School, Atlanta, GA; ‡Director of Breast Imaging Research, Department of Radiology, Massachusetts General Hospital, Boston, MA; §Medical Student, Harvard Medical School, Boston, MA; ¶Statistician and Department of Radiology, Massachusetts General Hospital, Boston, MA; Consultant, Lexington, MA; #Professor of Radiology, Department of Radiology, Massachusetts General Hospital, Boston, MA; **Assistant Professor of Surgery, Division of Surgical Oncology, Massachusetts General Hospital, Boston, MA. The authors have disclosed that they have no significant relationships with or financial interest in any commercial companies pertaining to this educational activity.

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Breast cancer operational detectability is defined as the ratio of the number of cancers of a specific size that are capable of being found by a specific criterion of detection to the number of cancers of that size that are present in the population at the time when these cancers are detected. By “mammographic operational detectability” we shall mean a measure of the operational detectability of cancers by screening mammography, whereas, by “nonmammographic operational-detectability” we shall mean a measure of the operational detectability of cancers by means other than screening mammography. Therefore, the phrase “nonmammographic operational detectability of breast cancer” describes the combined potential of a tumor to be revealed by the mammographic technique together with the mammographer’s ability to identify these signs, leading to a diagnosis of invasive breast cancer. Likewise, the phrase “mammographic operational detectability” describes the combined potential of a tumor to be revealed by mammography, and we have developed two methods to estimate the distribution of values of \( S_m \) and \( S_p \). The method of absolute efficiency of mammographic detection relies on the fact that, with information on the tumor growth rate, it is possible to back-calculate (equation 18, see Appendix) the size that each intervening and subsequent-screen-detected cancer would have been at the time of the previous screening.

\[ S_p \] has been defined as the size at which invasive breast cancers become operationally detectable in the absence of mammography, the distribution of which can be determined by assembling a cumulative distribution of the sizes of cancers appearing in women who had not undergone screening (never-screened cancers; Figure 1, top). This revealed a roughly symmetric distribution around a median \( S_p \) of 15 mm (Figure 1, bottom). Approximately one in 10 patients have an \( S_p \) less than 7 mm, whereas, at the other extreme, approximately 10% of patients have an \( S_p \) as great as 30 mm (Figure 1). These values were confirmed by assembling an equivalent cumulative distribution for the palpable cancers found in a separate institution, the Lahey Clinic.\(^5,6\)

\[ S_m \] has been defined as the size at which invasive breast cancers become operationally detectable by mammography, and we have developed two methods to estimate the distribution of values of \( S_m \) (see Appendix). The method of absolute efficiency of mammographic detection relies on the fact that, with information on the tumor growth rate, it is possible to back-calculate (equation 18, see Appendix) the size that each intervening and subsequent-screen-detected cancer (Figure 2) would have been at the time of the previous screening.
mammogram and then compare these with the actual number of tumors found at screening (first-screen-detected cancers and subsequent-screen-detected cancers). From such calculations, it could be seen that 5-mm tumors were found approximately 40% of the time, whereas 7-mm tumors were found approximately 50% of the time, 10-mm tumors were found approximately 70% of the time, and 15-mm tumors were found approximately 80% of the time (Figure 3). Therefore, the median size at which breast cancers become operationally detectable by screening mammography (median $S_{op}$) is approximately 7 mm, with variability among patients around this median value (Figure 3). This distribution is somewhat asymmetric (Figure 3), as can be seen in the finding that, whereas the operational detectability of breast cancer increases gradually from approximately 15% at 4 mm to approximately 75% detection at 11 mm, detection then reaches a plateau of approximately 80% detection for tumors of 12–22 mm. The presence of this plateau suggests that there may be a small subset of breast cancers (approximately 20%) that may be particularly difficult to detect. Tumors larger than 32 mm appear to be detected with an efficiency rate close to 100%: although there were 11 screen-detected cancers that were larger than 32 mm, by the method of back-calculation, there were no intervening cancers or subsequent-screen-detected cancers that would have been larger than 32 mm at the time of screening.

The second method for estimating mammographic operational detectability (the method of relative efficiency of mammographic detection; equation 16, see Appendix) was possible because the abundance of tumors of various sizes conforms to a uniform distribution.
by the Log of tumor size, a theoretical possibility (equation 3, see Appendix) that is confirmed empirically by the linearity of the cumulative distribution of the Log of tumor sizes of the cancers seen at screening (Figure 4). This uniform distribution by the Log of tumor size makes it possible to measure the efficiency with which mammography detects tumors of one size relative to the detection of tumors of another size. We used the group of tumors 12–22 mm in size as our reference group for these comparisons because, for reasons shown previously, it appears that these tumors are detected with an efficiency rate of approximately 80%. With equation 16, it appears that mammography detects tumors of 1, 2, and 3 mm with an efficiency rate of less than 5% (in comparison to the detection of the tumors of 12 mm to 22 mm), whereas 4-mm tumors are detected with a relative efficiency rate of approximately 20%, 7.5-mm tumors are detected with a relative efficiency rate of approximately 50%, and 10-mm tumors are detected with a relative efficiency rate of approximately 80% (Figure 5). Therefore, by the method of relative efficiency of mammographic detection, the median value for $S_m$ would appear to be approximately 7.5 mm (Figure 5), in close agreement with the 7-mm value estimated by the method of absolute efficiency described in the previous paragraph.

With use of the method of relative efficiency (equation 16), the mammographic operational detectability of breast cancer was found to be affected by the breast’s radiographic tissue density and mildly affected by the patient’s age. By visual inspection, it is clear that there are more small tumors in the population of women with breasts of intermediate density (ACR code 3) than in the population of women with breasts of high density (ACR code 4), and there are even more in women with breasts of the lowest density (ACR codes 1 and 2) (Figure 6). The statistical validity of this impression is confirmed by analysis of variance, indicating a $P$ value <0.05. With use of the method of equation 16 outlined earlier, we found that the median value of $S_m$ for women with the most transparent density was approximately 7 mm (ACR codes 1 and 2), whereas the median value of $S_m$ for women with intermediate density (ACR code 3) was approximately 10 mm and the median value of $S_m$ for women with the most opaque density (ACR code 4) was approximately 12 mm (Figures 6). Conversely, it appears that the relative abundance of small tumors may increase as women age, although the effect is much less pronounced than that seen in the comparison of women with different radiographic tissue densities (Figure 7). Indeed, none of the comparisons of cumulative size distributions of the tumors in women of various ages increased to the level of statistical significance. This is also reflected in the results from the use of equation 16 to estimate relative efficiencies of detection for women of various ages; for example, the value of $S_m$ was 9 mm for women in the bottom 15% of the screening population in terms of age (range, 33–49 years; median age, 46 years), whereas the value of $S_m$ was 7 mm for women in the top 65% of the screening population in terms of age (range, 60–92 years; median age, 70 years). Both these values are considerably lower than the median size of the tumors operationally detectable in the absence of mammography (median $S_p$ of approximately 15 mm), suggesting that all populations of women are likely to benefit from mammography, regardless of age.

**DISCUSSION**

Although mammography is widely used to find breast cancers at earlier stages, there has not been a clear understanding, in quantitative terms, of the sizes at which these tumors can be found by screening, nor of the sizes that will emerge if screening is not employed. To make such estimates of mammographic and nonmammographic operational detectability, we have had to develop new methods. With these new methods, we have found that the median value for $S_p$ (the size at which breast cancers become operationally detectable in the absence of screening) is approximately 15 mm, whereas
the median value for \( S_m \) (the size at which breast cancers become operationally detectable by screening mammography) is approximately 7 mm. Both of these median values are surrounded by distributions that appear to be roughly symmetric for clinical detection and asymmetric for mammographic detection. These size-specific estimates of the efficiency of breast cancer detection are, to our knowledge, the first such estimates to have been made.

The method of absolute mammographic operational detectability provided information not only on the efficiency of detection, but also on the numbers of cancers of various sizes that are not found at screening. These findings were very encouraging; they indicated that relatively few invasive breast cancers larger than 10 mm are missed at mammography. Therefore, it appears that, whereas 5-mm tumors are probably found only approximately 35% of the time and 7-mm tumors are...
found approximately 50% of the time, 10-mm tumors are found approximately 65% of the time and 15-mm tumors are found approximately 80% of the time. Tumors larger than 30 mm appear almost never to be missed. Indeed, tumors larger than 32 mm appear to be detected with efficiency rates close to 100%: there were 11 cancers larger than 32 mm detected by screening in our data set and, by the method of back-calculation, there were no tumors that would have been larger than 32 mm at the time of screening.

The new methods described herein allowed us to quantify the degree to which mammographic operational detectability differs between women with different characteristics. Therefore, mammography is capable of detecting invasive breast cancers at smaller sizes in women with radiolucent breasts than in women with radiodense breasts and may be capable of detecting invasive breast cancers at slightly smaller sizes in older women than in younger women. However, among women of all ages and all radiographic tissue densities, the mean and median tumor sizes that are operationally detectable by mammography are less than would be seen in the absence of screening (never-screened cancers). This suggests that all populations of women, regardless of age or radiographic tissue density, should benefit from mammographic screening, although the degree of benefit may vary.

■ APPENDIX

The following is the method for estimating the efficiency with which breast cancers are detected in the absence of screening mammography.

Because nonmammographically detected cancers are generally found by a process of continuous self-surveillance, the distribution of the sizes of the tumors found among women in the absence of screening directly reflects the nonmammographic operational detectability of breast cancer. The practical way to extract such an estimate of the nonmammographically operational detectability of breast cancer is to assemble a cumulative distribution of the tumors found in women who have never undergone a mammogram; i.e., the never-screened cancers. Such a cumulative distribution can be made by assembling these cancers from the smallest tumor to the largest and determining to which percentile each tumor belongs. The distribution of the never-screened cancers was found to be fairly constant when comparing women of different radiographic tissue densities and ages, except that there were fewer tumors larger than 25 mm in women 50–69 years of age. The latter point has only a minor effect on the overall cumulative distribution of these tumors (not shown).

The following is the method for estimating the relative efficiency with which mammography detects cancer, from data on the sizes of the tumors found at screening.

There is abundant evidence that, over the range of sizes for which most tumors are seen (approximately 1 mm to 2 cm), invasive breast cancer growth is roughly exponential, and therefore the relationship between the number of cells in a tumor (N) and time (t) can be expressed as:

\[ N = N_0 e^{rt} \]

where \( N \) = the number of cells in the tumor at time \( t \) and \( N_0 \) = the number of cells in the tumor at time \( t = 0 \).

It is often useful to describe growth in terms of doubling time \( (t_d) \), which can be derived from equation 1 as:

\[ t_d = \frac{\ln(2)}{r} \]

Note that \( r \) is inversely related to the doubling time:

\[ r = \frac{\ln(2)}{t_d} \]

By taking the natural logarithm of both sides of equation 1, we can see that this expression is equivalent to:
4. \[\ln(N) = rt + \ln(N_0)\]

It follows from equations 1 and 3 that the time that it takes for a tumor to grow from size \(N_0\) to size \(N\) is:

5. \[t = \frac{[\ln(N) - \ln(N_0)]}{r}\]

Now, let us consider a group of \(k\) cancers, present within a population of women at time \(t = 0\). Let us assign each of these cancers an index number \(c\), arranging them from smallest (\(N_1\) for \(c = 1\)) to largest (\(N_k\) for \(c = k\)). From equation 5, we can see that the time needed for tumor \(k\) to grow from size \(N_1\) to \(N_k\) is:

6. \[t_{1-k} = \frac{[\ln(N_1) - \ln(N_k)]}{r}\]

and

7. \[r = \frac{[\ln(N_1) - \ln(N_k)]}{t_{1-k}}\]

Whereas tumor \(k\) would have been size \(N_1\) at time \(t = -t_{1-k}\), all other tumors in our group would have been smaller than size \(N_1\) at time \(t = -t_{1-k}\). However, all these tumors would have reached size \(N_1\) sometime between time \(t = -t_{1-k}\) and time \(t = 0\). Because we may expect that these \(k\) tumors would have reached a regular rate, we may assume that they passed through size \(N_1\) one after another, separated by approximately \((1/k) \times t_{1-k}\) units of time. Therefore, it is a reasonable approximation to consider that tumor \(c = 1\) passed through size \(N_1\) at approximately time \(t = -(1/k) \times t_{1-k}\), that tumor \(c = 2\) passed through size \(N_1\) at approximately time \(t = -(2/k) \times t_{1-k}\), that tumor \(c = 3\) passed through size \(N_1\) at approximately time \(t = -(3/k) \times t_{1-k}\), and so on, until tumor \(c = k\) passed through size \(N_1\) at approximately time \(t = -(k/k) \times t_{1-k} = -t_{1-k}\). Therefore, it follows that the time \(t_{1-c}\) that it took each tumor \(c\) to grow from size \(N_1\) to size \(N_c\) was:

8. \[t_{1-c} = \frac{c}{k} \times t_{1-k}\]

Substituting equation 8 into equation 4 yields:

9. \[\ln(N_c) = r \left(\frac{c}{k} \times t_{1-k}\right) + \ln(N_1)\]

Substituting the value of \(r\) from equation 7 into equation 6 yields:

10. \[\ln(N_c) = \frac{([\ln(N_1) - \ln(N_k)] \times t_{1-k})}{c} \times \frac{(c/k)}{t_{1-k}} + \ln(N_1)\]

Canceling out redundant values yields:

11. \[\ln(N_c) = \frac{([\ln(N_1) - \ln(N_k)])}{(c/k)} + \ln(N_1)\]

And rearranging yields:

12. \[c = k \times \frac{\ln(N_c)}{N_1} / \ln(N_1) / N_k\]

Now, let us consider the number of tumors that we should expect between two sizes, \(N_{c1}\) and \(N_{c2}\). Let us call the number of invasive breast cancers between these two sizes \(B_{c1-c2}\). It follows that \(B_{c1-c2}\) should equal \(c_{1-c2}\). Therefore, building on equation 12:

13. \[B_{c1-c2} = \frac{[k \times \ln(N_{c1}) / N_1] / ([\ln(N_1) / N_k])}{- [k \times \ln(N_{c2}) / N_1] / ([\ln(N_1) / N_k])}\]

And rearranging yields:

14. \[B_{c1-c2} = \left[\frac{k}{[\ln(N_1) / N_k]} \times \ln(N_{c1}) / N_{c2}\right]\]

Therefore, we have arrived at a method to calculate \(B_{c1-c2}\), the number of cancers expected between any two sizes \((N_{c1} \text{ and } N_{c2})\) based on the abundance \((k)\) of tumors lying between any two other sizes \((N_1 \text{ and } N_k)\).

Until this point, we have considered the case in which all tumors in the population have the same growth constant, \(r\). However, it may be more realistic to consider the case in which there are a variety of growth rates among the tumors in the population. Note from equation 14 that the number of cancers \((B_{c1-c2})\) between any two sizes \((N_{c1} \text{ and } N_{c2})\) will be independent of the value of \(r\) and dependent only on the two sizes in question \((N_{c1} \text{ and } N_{c2})\), the sizes of the tumors in the reference group \((N_1 \text{ and } N_k)\), and the number of cancers in the reference group \((k)\). Therefore, equation 14 will yield the same number of cancers between any two sizes \((B_{c1-c2})\) regardless of whether the population has a single growth constant, \(r\), or a variety of growth rates.

Let us define \(Em\) as the relative efficiency with which mammography detects cancer. It is now possible to use equation 14 to estimate the predicted cancers between any two sizes \((N_{c1} \text{ and } N_{c2})\) and to compare these expected numbers of cancers with the actual number of cancers of these sizes, which we shall call \(M_{c1-c2}\). In this way, we have arrived at a way to estimate the relative efficiency with which mammography detects cancer:

15. \[Em = \frac{M_{c1-c2}}{B_{c1-c2}} = \frac{M_{c1-c2}}{\left[(k / [\ln(N_1) / N_k)] \times (\ln(N_{c1}) / N_{c2}))\right]\]

Finally, note that, because this expression used the natural logarithm of the ratio of the tumor sizes, equation 15 can be carried out with the number of cells in the tumors \((N_1 / N_k, N_{c1} / N_{c2})\) or with the tumor diameters \((S_1 / S_k, S_{c1} / S_{c2})\).

16. \[Em = \frac{M_{c1-c2}}{B_{c1-c2}} = \frac{M_{c1-c2}}{\left[(k / [\ln(S_1) / S_k)] \times (\ln(S_{c1}) / S_{c2}))\right]\]

The general validity of thinking that led to equation 16 can be confirmed empirically. To test this, equation 12 can be rearranged to see the relationship between the number of cancers, \(c\), and the tumors size, \(S_c\):

17. \[c = q \times \ln(S_c) - W\]

where \(q = k / (\ln(S_1) / S_k)\) and \(W = \ln(S_1) \times k / \ln(S_1 / S_k)\).

Note that equation 17 indicates that the relationship between the number of tumors found \((c)\) and the Log of tumor size \((N_c)\) should be linear, and this provides a way to test the general validity of this approach for estimating the efficiency of mammographic detection.

The following is the method for estimating the absolute efficiency with which mammography detects cancer, from data on the sizes of the tumors not found at screening.

In addition to the method described for estimating
the relative efficiency of mammographic detection with information on the cancers found at screening, it is also possible to measure the absolute efficiency of mammographic detection with information on the cancers not found at screening (subsequent-screen–detected and intervening cancers). This can be accomplished with information on tumor size at the time of detection ($D_D$) and time since the previous negative mammogram result for those tumors found in women with a history of screening ($t_P$) (Figure 4), together with information on the breast cancer doubling time ($t_D$), which we have found to be 130 days, as described elsewhere in this issue of the Journal of Women’s Imaging^7). The estimated tumor size at the time of the previous mammography procedure ($D_S$) can then be calculated with the expression:

$$18. \quad D_S = \left[ \frac{(D_D^3)}{e^{(\{ln(2) / t_D\text{approx}\} \times t_P)} \right]^{0.33}$$

To estimate the absolute efficiency of mammographic detection, the estimated size at the time of the previous negative mammogram result was determined with use of equation 18 for each subsequent-screen–detected and intervening cancer, and the number of missed cancers of each size was compared to the number of cancers of each size found at screening (subsequent-screen–detected and first-screen–detected cancers). Such estimates could be made for cases in which there is but a single tumor doubling time and for cases in which there is a variety of doubling times with a defined standard deviation.

The following is the method for estimating the distributions of values of $S_m$ and $S_p$ from data on the efficiency of mammographic and nonmammographic detection.

It is useful to describe tumor growth in terms of the sojourn time ($t_S$), the time it takes for tumors to grow from size $S_m$ (the size at which an individual invasive breast cancer will become operationally detectable by mammography) to size $S_p$ (the size at which an individual invasive breast cancer will become operationally detectable in the absence of mammography). By convention, $S_m$ and $S_p$ will be referred to by the tumor diameter. Let us call the number of cells in tumors of sizes $S_m$ and $S_p$, $N_{m}$, and $N_{p}$. Therefore, from equation 3, it follows that, for the simple case in which we approximate tumor detection with discrete values of $S_m$ and $S_p$:

$$19. \quad t_S = \left[ \frac{\ln(N_p / N_m)}{r} \right]$$

In addition, because, as we shall see, $S_m$ and $S_p$ are distributions of values, it is possible to estimate the distribution of the sojourn time by permuting the distributions of $S_m$ and $S_p$.

References


Address correspondence to:
James S. Michaelson, PhD
Division of Surgical Oncology
Cox Building, Room 626
Massachusetts General Hospital
100 Blossom Street
Boston, MA 02114
E-mail: michaelj@helix.mgh.harvard.edu