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Estimates of the Sizes at Which Breast Cancers Become Detectable on Mammographic and Clinical Grounds

James Michaelson, PhD,* Sameer Satija, AB,† Richard Moore, AB,‡ Griffin Weber, BS,§ Elkan Halpern,‖ Andrew Garland,¶ Daniel B. Kopans, MD,# and Kevin Hughes, MD**

Several new methods are proposed for measuring the ability to detect breast cancer, especially the sizes at which these cancers become operationally detectable by screening mammography, the sizes at which they become operationally detectable in the absence of screening, and how these aspects of breast cancer operational detectability vary from woman to woman. The term "operational detectability" is used herein to describe the combined effects of physical and human factor limits to cancer detection. With use of the new methods outlined here, together with data on the tumors seen over the last decade at the Massachusetts General Hospital Breast Imaging Division, the median size at which breast cancers become operationally detectable in the absence of screening was found to be approximately 15 mm, whereas the median size at which breast cancers become operationally detectable by screening mammography was found to be approximately 7.5 mm. The distribution of tumor sizes detected in the absence of screening was found to be roughly symmetric around its median value of 15 mm, whereas the distribution of tumor sizes operationally detectable by mammography appears to be asymmetric around its median value of 7.5 mm. The mammographic operational detectability of breast cancer was found to be affected by the breast's radiographic tissue density and possibly mildly affected by patient age. [Key words: breast cancer, mammographic detection, clinical detection, tumor size] Journal of Women's Imaging 2003;5;3–10

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.[1] 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.[2] 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.[3] 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.[4] 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-

*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.
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sions was assessed at the time of pathologic analysis, and the largest of these three measurements was entered into the MGH database as the tumor size. For the 491 cancers that arose in women who had had previous negative mammogram results (179 intervening cancers and 312 subsequent-screen–detected cancers), we were able to determine the length of time from the previous negative examination results until the time when the cancer was diagnosed. Tumor size data were also available for 182 invasive breast cancers seen at the Lahey clinic from 1997 to 2000.[5,6]

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 perceived by the woman, to be brought to the attention of the medical system, and to be acted on by the medical system, thereby leading to a diagnosis of breast cancer. Likewise, the phrase "mammographic operational detectability" 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. In our data set, most cases of nonmammographic detection occur when a palpable mass is found and, less frequently, when breast thickening, breast pain, nipple discharge, or nipple inversion are found. General clinical experience indicates that, most of the time, women make these findings themselves, although this information was not entered into our database.

The size at which an individual invasive breast cancer becomes operationally detectable by mammography shall be defined as "S_m" and the size at which an individual invasive breast cancer becomes operationally detectable in the absence of mammography shall be defined as "S_p" the subscript "p" reflecting the fact that most of these cancers are detected by palpation. By convention, "S_m" and "S_p" are usually referred to by the tumor diameter. "N_m" and "N_p" are defined as the number of cells in tumors of sizes S_m and S_p. Of course, not all tumors will be operationally detectable at the same size, and therefore, within populations of women, S_m and S_p are present as distributions of values, centered around some median values for S_m and S_p.

"Screening yield" is defined as the ratio of the number of cancers found at mammography to the total number of screening mammograms performed.

The categories for assessing radiographic density at MGH were created before the introduction of American College of Radiology (ACR) codes. The MGH system used seven tissue patterns.[1] Although they differ from Breast Imaging Reporting and Data System (BIRADS) classification, they are easily "collapsed" into that four-point tissue pattern scale.[1] MGH pattern 1 is equivalent to ACR code 1 and MGH pattern 3 is equivalent to ACR code 2. MGH pattern 2 does not precisely correspond to any ACR code and is very rarely found. Therefore, MGH patterns 1, 2, and 3, as a group, were considered low-density, corresponding roughly but not precisely to ACR codes 1 and 2, whereas MGH pattern 4 was considered intermediate-density (approximately equivalent to ACR code 3), and patterns 5, 6, and 7 were considered high-density (approximately equivalent to ACR code 4).

■ RESULTS

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,[7] 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

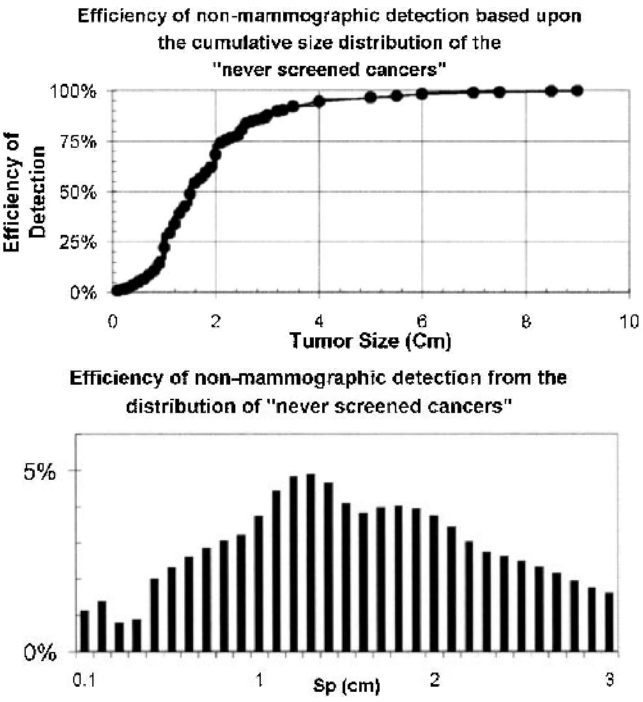

Figure 1. Efficiency of nonmammographic detection as seen from the cumulative distribution of the sizes of the never-screened breast cancers (top), together with the distribution of the sizes of never-screened breast cancers (bottom).

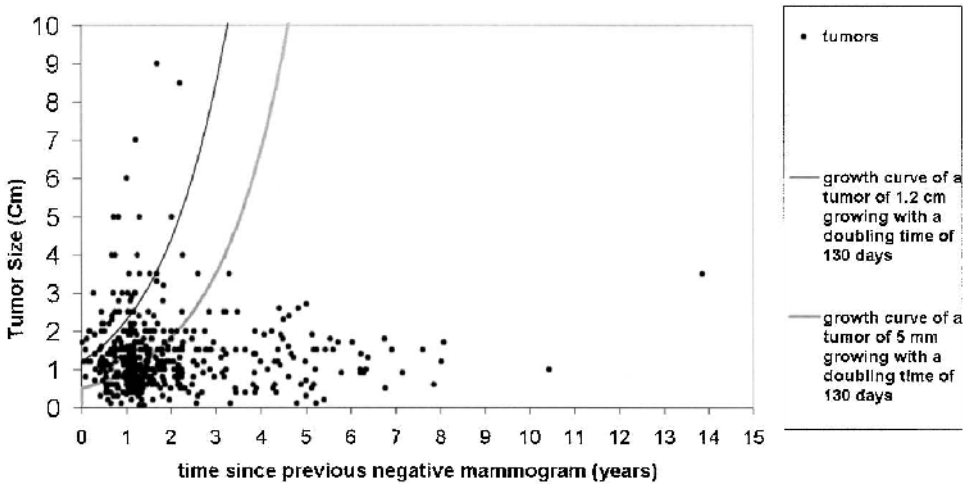

Figure 2. Scatter-plot showing tumor size versus time since the previous negative mammogram result for tumors found in women with a history of screening. Also shown are two expected growth curves, one of which is for a tumor that would have been 5 mm at the time of the negative mammogram result and the other of which would have been 12 mm at the time of the negative mammogram result, based on a tumor doubling time of 130 days. Tumors above the light curve would have been 12 mm or larger, based on a tumor doubling time of 130 days, when they were missed at the time of the previous negative mammogram result, whereas tumors above the wide gray curve would have been 5 mm or larger.

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_m) 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

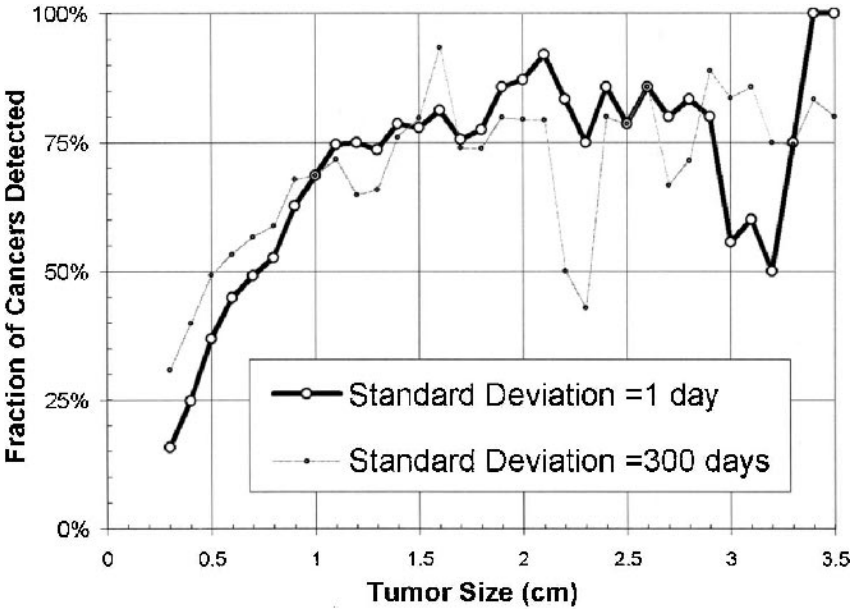

Figure 3. Efficiency of mammographic detection, by tumor size, determined by estimating the numbers of tumors found at screening, assuming a mean tumor doubling time of 130 days with various standard deviations. These calculations rely on the measurement of a median tumor doubling time of 130 days, as described elsewhere in this issue.[7] Of course, there is a distribution of doubling times reflecting the tumor-to-tumor variability in growth rate. To determine the effect the growth rate distribution has on the calculations of operational detectability, we repeated these calculations for hypothetical distributions with standard deviations ranging from 1 day to 300 days. Reassuringly, even high degrees of tumor-to-tumor variation in growth rate were found to have little effect on the measurements of the efficiency of mammographic detection made by this method.

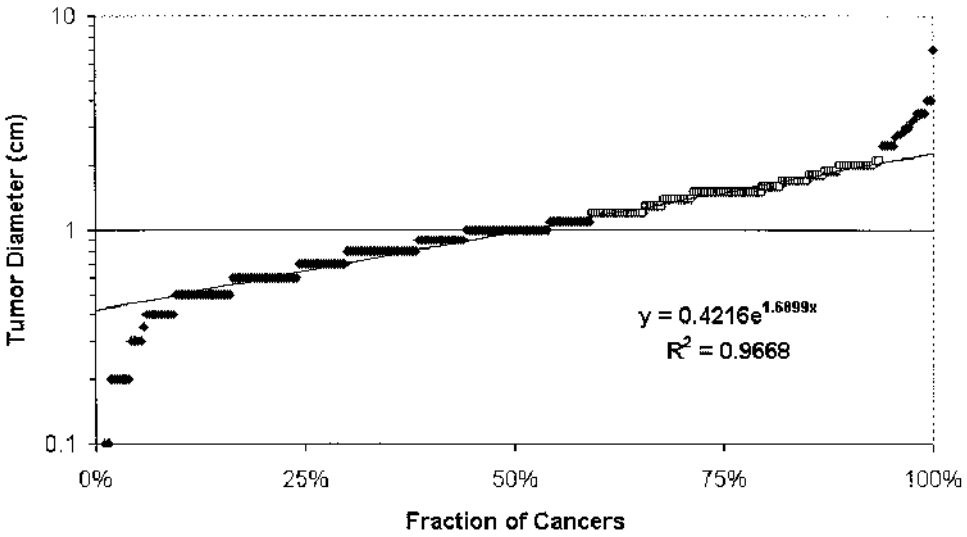

Figure 4. Cumulative size distribution of subsequent-screen–detected cancers, displayed by the Log of tumor size. Linear regression of data points for tumors 12–22 mm are shown. Tumors 12–22 mm are shown in open circles, all others are shown in closed circles.

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

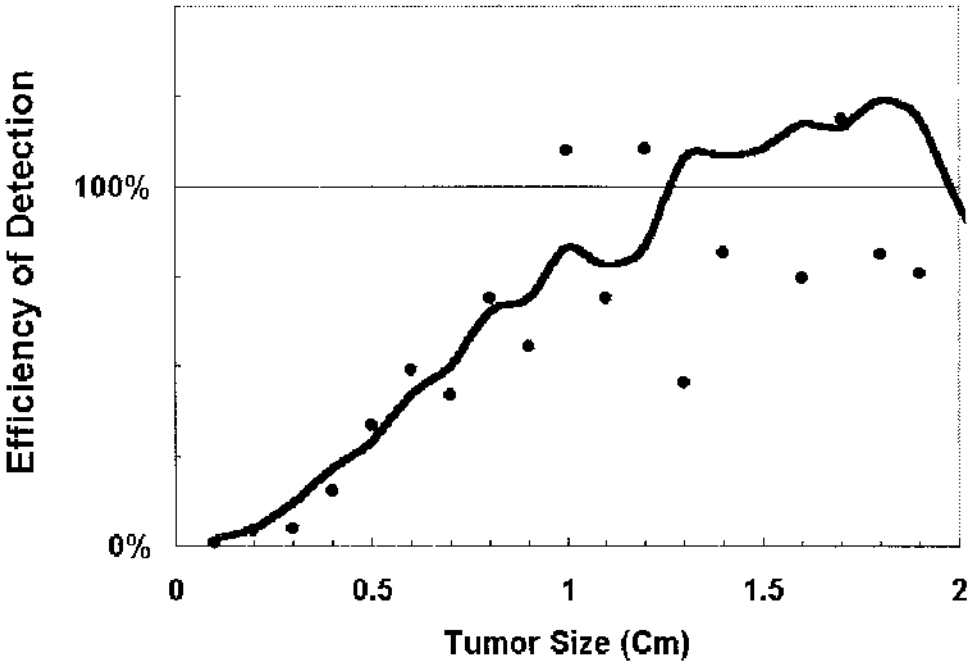

Figure 5. Efficiency of mammographic detection (relative to tumors of 1.2–2.2 cm) for women screened at MGH. Individual values for groups of tumors (1 mm to 20 mm in diameter, in 1-mm increments) are shown (black dots) and a smoothed running average (average of five adjacent values, black line) of these data is also shown. Note that the estimated efficiency for all tumors in the range of 12–22 mm is set at 100% by definition, but the natural scatter of the individual values in this region makes it appear as if some sizes are slightly over this 100% value and tumors of other sizes are slightly under this 100% value.

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

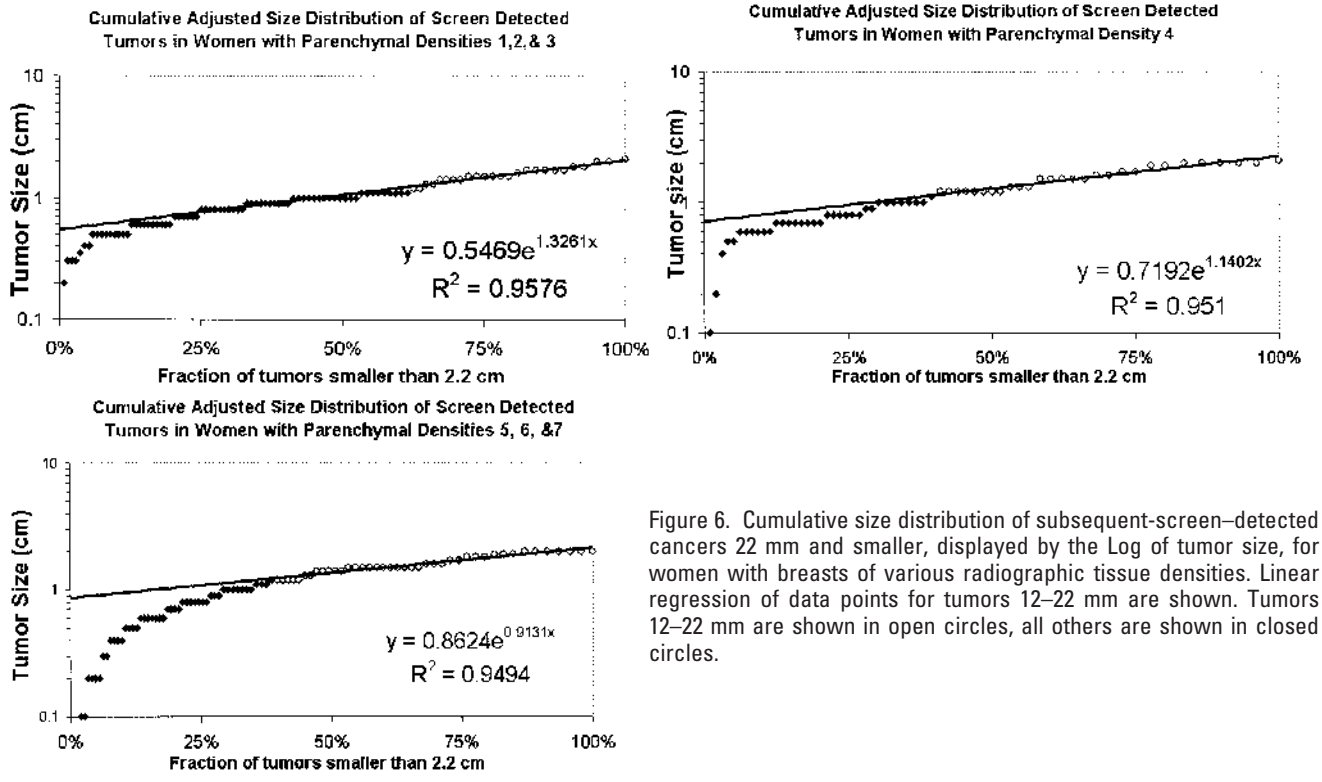

Figure 6. Cumulative size distribution of subsequent-screen–detected cancers 22 mm and smaller, displayed by the Log of tumor size, for women with breasts of various radiographic tissue densities. Linear regression of data points for tumors 12–22 mm are shown. Tumors 12–22 mm are shown in open circles, all others are shown in closed circles.

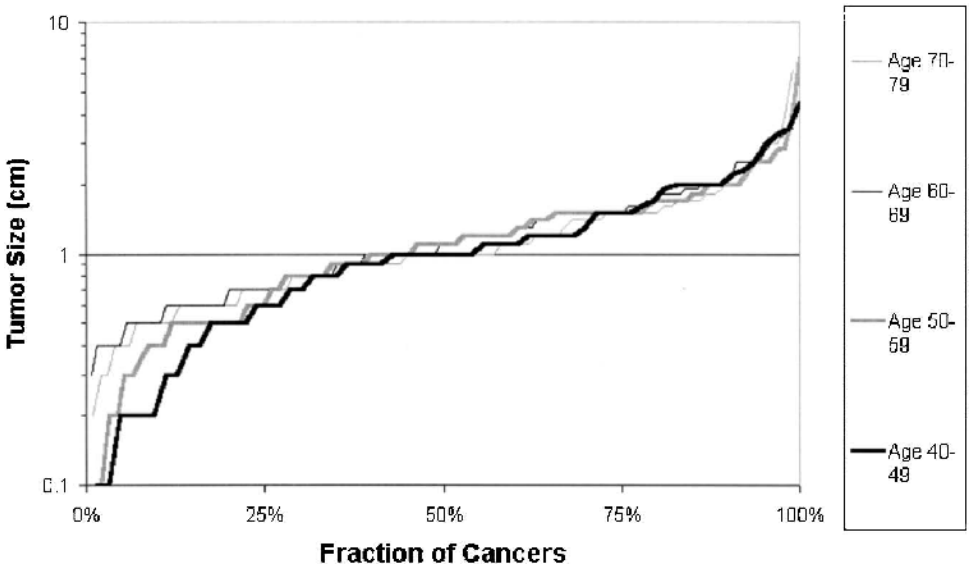

Figure 7. Cumulative size distribution of subsequent-screen–detected cancers, displayed by the Log of tumor size, for women of various ages.

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 in who have never underwent 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.[8] 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,[8–15] and therefore the relationship between the number of cells in a tumor (N) and time (t) can be expressed as:

$$1.\ N = N_O e(rt)$$

where N = the number of cells in the tumor at time t and N_O = 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:

$$2.\ t_D = \ln(2) / r$$

Note that r is inversely related to the doubling time:

$$3.\ r = \ln(2) / t_D$$

By taking the natural logarithm of both sides of equation 1, we can see that this expression is equivalent to:

4. $\ln(N) = rt + \ln(N_O)$

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

5. $t = [\ln(N / N_0)] / r$

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, or $t_{1\text{-}k}$, is:

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

and

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

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

8. $t_{1\text{-}c} = c / k(t_{1\text{-}k})$

Substituting equation 8 into equation 4 yields:

9. $\ln(N_c) = r\,(c / k(t_{1\text{-}k})) + \ln(N_1)$

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

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

Canceling out redundant values yields:

11. $\ln(N_c) = ([\ln(N_1 / N_k)])\,(c / k) + \ln(N_1)$

And rearranging yields:

12. $c = k \times \ln(N_c / N_1) / \ln(N_1 / N_k)$

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 $Bc_1 - c_2$. It follows that $Bc_1 - c_2$ should equal c1 – c2. Therefore, building on equation 12:

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

And rearranging yields:

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

Therefore, we have arrived at a method to calculate $Bc_1 - c_2$, the number of cancers expected between any two sizes (N_{c1} and N_{c2}) based on the abundance (k) of tumors lying between any two other sizes (N_1 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 ($Bc_1 - c_2$) between any two sizes (N_{c1} and N_{c2}) will be independent of the value of r and dependent only on the two sizes in question (N_{c1} and N_{c2}), the sizes of the tumors in the reference group ($N_1$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 ($B_{c1\text{-}c2}$) regardless of whether the population has a single growth constant, r, or a variety of growth rates.

Let us define E_m 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} and N_{c2} and to compare these expected numbers of cancers with the actual number of cancers of these sizes, which we shall call $Mc_1 - c_2$. In this way, we have arrived at a way to estimate the relative efficiency with which mammography detects cancer:

15. $E_m = M_{c1\text{-}c2} / B_{c1\text{-}c2} = M_{c1\text{-}c2} / ([k / (\ln(N_1 / N_k))] \times (\ln(N_{c1} / N_{c2})))$

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. $E_m = M_{c1\text{-}c2} / B_{c1\text{-}c2} = M_{c1\text{-}c2} / ([k / (\ln(S_1 / S_k))] \times (\ln(S_{c1} / S_{c2})))$

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 (Nc) 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. $D_S = [(D_D\text{^}3) / e\text{^}(\{(\ln(2) / t_{Dapprox}\} \times t_P)]\text{^}0.33$

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 are 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. $t_S = [\ln(Np / Nm)] / r$

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.

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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