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CME ARTICLE

Observations on Invasive Breast Cancer Diagnosed in a Service Screening and Diagnostic Breast Imaging Program

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

Six-hundred six cancers were found among 59,899 woman who had been screened in the Breast Imaging Division at the Massachusetts General Hospital (MGH) from 1990 to 1999 (427 invasive breast cancers detected by screening mammography and 179 invasive breast cancers detected by nonmammographic criteria in women who had previous negative mammograms), and 204 invasive breast cancers were identified during this period solely by nonmammographic criteria in women who had never been screened at MGH but who received a diagnostic mammogram after the time of cancer detection. The screen-detected invasive breast cancers in the MGH data set tended to be smaller, with a median size of 10 mm, than tumors detected by nonmammographic criteria, which had a median size of 15 mm ($P < 0.001$). The mammographically detected invasive breast cancers found in the past decade tended to be slightly smaller than the mammographically detected invasive breast cancers reported by others in previous decades, and the nonmammographically detected invasive breast cancers in the MGH data set were markedly smaller than the nonmammographically detected invasive breast cancers reported in the past. [Key words: breast cancer, mammography, screening] **Journal of Women's Imaging 2001; 3:99–104**

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

- distinguish between the median size that can be expected for screen-detected invasive breast cancers and that for invasive breast cancers found in the absence of screening;
- describe how the sizes at which the breast cancers that have been found in the absence of screening have change over the past four decades;
- estimate the fraction of breast cancers that are not detectable by mammography.

There is ample evidence that breast cancer death can be reduced by finding the tumors at smaller sizes.[1–15] In randomized, controlled clinical trials, the earlier detection of breast cancer has been shown to result in a decrease in breast cancer–related mortality.[6–8,13,15] The available data are primarily from studies undertaken before 1990. Many were from population-based trials in which thresholds for intervention were influenced by costs and required high cancer yields in proportion to biopsies performed (positive predictive value). This may have permitted some small cancers to slip through the screen. We performed a retrospective analysis of the tumors found in women who were screened in the early detection program at the Massachusetts General Hospital (MGH) and of tumors that were found at the same center in women who had not undergone screening. Although this is not a population-based study, and there is the potential for the introduction of unpredictable biases (*e.g.,* selection), we believe that the observations are of considerable value since most screening in the United States is performed as a "service" and is not population based.

Materials and Methods

The MGH Breast Imaging Division is an urban center where screening is available and aggressively encouraged. Patient ages reported here reflect the time when the tumor was first detected.

Our studies have relied on two related data bases, the first of which contained information on 59,899 women who underwent 196,891 mammograms at the MGH Breast Imaging Division from January 1, 1990, to March 1, 1999. The second data base contained entries on the biopsies of 10,885 patients with breast disease who were evaluated in the Department of Pathology at MGH during this period. The mammograms that lead to entry into the MGH Breast Imaging Division data base were screening mammograms, diagnostic mammograms, or needle localizations. Gross tumor size, measured in three di-

*Assistant Professor, Division of Surgical Oncology, ‡Director of Research and #Director, Breast Imaging Division, and ¶Statistician, Department of Radiology, Massachusetts General Hospital; *Assistant Professor of Pathology, #Professor of Radiology, and †student, Emory Medical School; §student, Harvard Medical School; and ‖independent researcher.
Drs Michaelson and Kopans and Mr Moore, Weber, and Garland have disclosed that they have no significant relationships with or financial interest in any commercial companies pertaining to this educational activity.
Mr Satija and Dr Halpern have declined to disclose to Lippincott Williams & Wilkins whether they have significant relationships with or financial interests in any commercial companies that pertain to this educational activity.
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Table 1. Definition of Tumor Categories, as Used in This Study

Tumor Type	Definition	n
First-screen–detected cancer	Invasive breast cancer identified by mammography in an asymptomatic woman at her first screen at MGH	115
Subsequent-screen–detected cancer	Invasive breast cancer identified by mammography in an asymptomatic woman with ≥1 previous negative screening mammogram at MGH	312
Intervening cancer	Invasive breast cancer identified by means other than a screening mammogram in a woman with ≥1 previous negative screening mammogram at MGH	179
Never-screened cancer	Invasive breast cancer identified by means other than a screening mammogram in a woman with no history of mammography at MGH	204

MGH = Massachusetts General Hospital.

mensions, was assessed at the time of pathologic analysis, and the largest of these three measurements was entered into the MGH data base. The invasive breast cancers studied here were divided into four categories (Table 1):

1. A *first-screen–detected* cancer was defined as an invasive breast cancer identified by first MGH mammogram in a woman with no symptoms.

2. A *subsequent-screen–detected* cancer was defined as an invasive breast cancer identified by mammography in a woman with no symptoms who had had a least one previous negative screening mammogram at MGH.

3. An *intervening* cancer was defined as an invasive breast cancer identified by means other than a screening mammogram in a woman who had a least one previous negative screening mammogram at MGH.

4. A *never-screened cancer* was defined as an invasive breast cancer identified by means other than screening mammography in a woman with no history of mammography at MGH before the discovery of the cancer.

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 a negative examination but within a specified period of time. The nonmammographic methods of detection listed in the MGH data base for the intervening and never-screened cancers involved examination for a palpable mass, thickening, breast pain, nipple discharge, or nipple inversion. Detection of a palpable mass was the most common criterion for discovery of these tumors, and general clinical experience indicates that this finding is most often made by the woman herself, although no direct data are available on this point in our data base. Tumors for which there was not enough information to be assigned to one these four tumor categories were not included in the analysis. Carcinomas *in situ* were not included in this analysis.

We also analyzed data on the cancers seen by Tabar and colleagues[6–8] and Tubaina and colleagues.[9–12] From these data and our data set, we assembled cumulative size distributions.

■ Results

A total of 1859 invasive breast cancers were identified among 59,899 women who underwent 196,891 mammograms at the MGH Breast Imaging Division from January 1, 1990, to March 1, 1999 (Table 2). Ductal carcinoma *in situ* was not included in this review. Of these 1859 patients with invasive breast cancer, 1337 cancers were identified in women who had undergone mammography at the MGH either before or at the time of the cancer's detection, whereas 522 women did not have an MGH mammogram at the time of diagnosis. Presumably, the initial cancer treatment for these 522 women would have been conducted either on the basis of mammography done at another institution and brought to MGH, or the treatment would have been carried out without a diagnostic mammogram, but these women would have undergone either screening or diagnostic mammography at MGH after their treatment, which is why they appeared in the mammography data base.

Of the 1337 invasive breast cancers identified in women with mammograms from MGH, 258 were identified in women who previously had breast cancer, and 1079 arose in women without such histories. Because it was not always possible to determine whether the cancers found in the 258 women were recurrences or new cancers, they were not studied further.

Of the 1079 cancers that arose in women without histories of breast cancer, 511 were in women who had no record of having had a screening mammogram before

Table 2. Tumors from the Massachusetts General Hospital (MGH) Data Base

Description	n
Women who underwent 196,891 mammograms at the MGH Breast Imaging Division 1/1/90 to 3/1/99	59,899
Invasive cancers from that pathology data base	1859
Cancers identified in women with MGH mammography either previous to or at time of cancer's detection	1337
Identified in women with previous breast cancer	258
Identified in women with no history of breast cancer	1079
Cancers identified in women with no record of screening mammography before tumor identification at MGH	511
Detected on screening (first-screen–detected cancers)	115
Identified by means other than mammography at MGH (never-screened cancers)	204
Unclassifiable	192
Cancers detected in women with at least one previous screening mammogram at MGH	568
Detected on screening (subsequent-screen–detected cancers)	312
Detected by means other than mammography at MGH (intervening cancers)	179
Unclassifiable	77

the identification of the tumor by the MGH Breast Imaging Division; 568 were detected in patients with previous screening MGH mammograms. Of the 511 cancers identified in women with no screening history at the MGH, 115 were detected by screening (first-screen–detected cancers), 204 were identified by means other than mammography at MGH (never-screened cancers), and 192 were unclassifiable with the data available (see Table 2).

Of the 568 cancers found in patients who had had at least one previous negative screening mammogram at MGH, 312 were detected on screening (subsequent-screen–detected cancers), 179 were detected by means other than mammography at MGH (intervening cancers), and 77 were unclassifiable. The total number of screen-detected cancers was 427. The properties of these 810 invasive breast cancer (first-screen–detected cancers, never-screened cancers, subsequent-screen–detected cancers, and intervening cancers) were then analyzed, as described below.

The smallest invasive breast cancer in the data set was 1 mm, and the largest was 90 mm (Figure 1). As expected, the screen-detected cancers were generally smaller than the cancers detected by nonmammographic means (Table 3; see Figures 1 and 2). The median size of the screen detected cancers was 10 mm (12 mm for the first-screen–detected and 10 mm for the subsequent-screen–detected cancers), whereas the median size of the nonscreen-detected cancers was 15 mm (for both the intervening and never-screened cancers; see Table 3 and Figure 2). Estimates were made of the cumulative distribution of tumor sizes of the screen-detected cancers reported by Tabar and colleagues[6–8] in the period of 1977 to 1985 (median size, 12 mm) and were compared with the screen-detected cancers in the MGH data set seen during the past decade (median size, 10 mm; see Figure 2). Estimates were also made of the cumulative distribution of tumor sizes of the nonscreen-detected cancers reported by Tubiana and colleagues[9–12] between 1954 and 1979 (median size, ~40 mm) and by Tabar and colleagues[6–8] between 1977 and 1985 (median size, ~20 mm for the interval cancers in the screened population and ~18 mm for the cancers in the unscreened control group), and were compared with the nonscreen-detected cancers in the MGH data set from 1990 to 1999 (median size, ~15 mm for both the intervening cancers and the never-screened cancers; see Figure 2).

The youngest invasive breast cancer patient in the MGH data set was 25 years of age, and the oldest was 92 (see Table 3). The median age for the women with invasive breast cancer in the MGH data set was 65 years (Figure 3). Roughly equivalent numbers of patients were found in each decade of life from age 40 to 80 (Figure 4). About 5% of invasive breast cancers were found in women in their 30s, and about 25% of the cancers were found in women less than 50 years of age. The women with mammographically detected cancers tended to be older (median age for subsequent-screen–detected cancer, 66 years; median age for first-screened–detected cancer, 61.5 years) than the women with nonmammographically detected cancers (median age for intervening cancer, 57 years; median age for never-screened cancer, 60.5 years; $P < 0.001$; see Figures 1 and 2 and Tables 3 and 4). Among the women with screening histories, those with screen-detected cancers (subsequent-screen–detected cancers) also tended to be older (median age, 65 years) than those women with nonmammographically

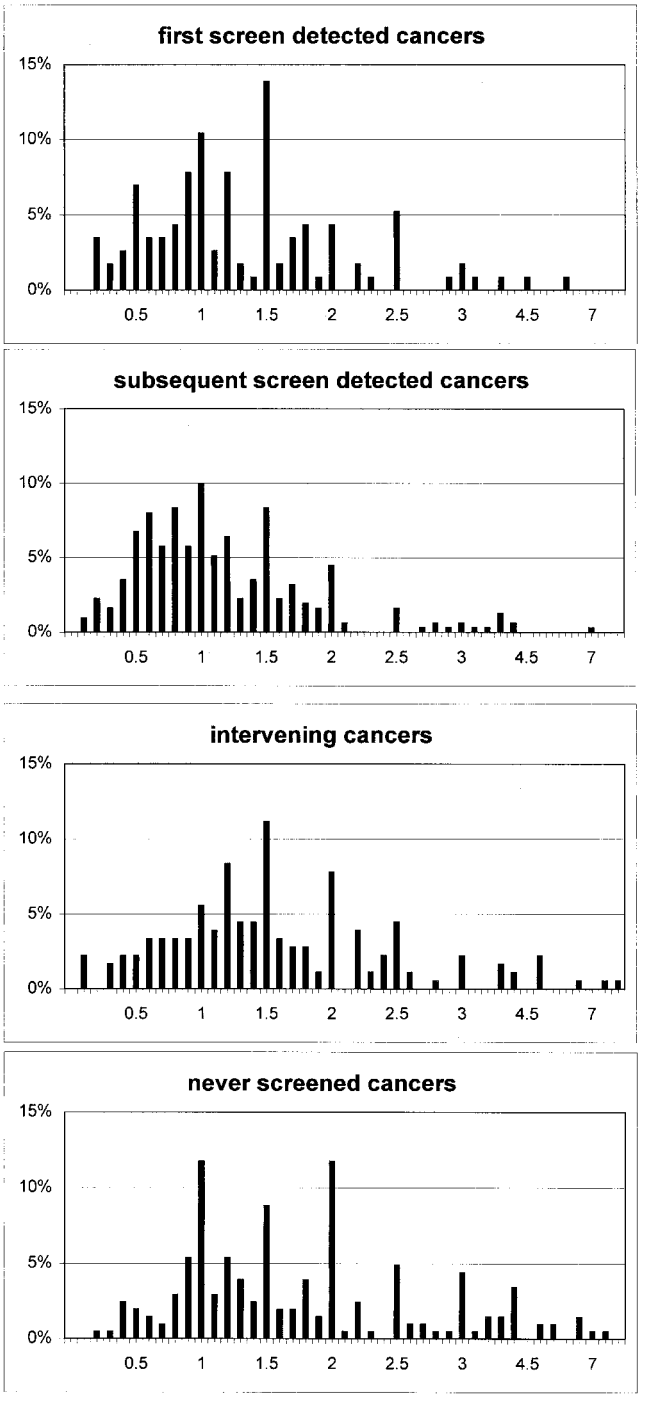

Figure 1. Size distributions (in centimeters) of the tumors in the Massachusetts General Hospital data set, by method of detection (see Table 1).

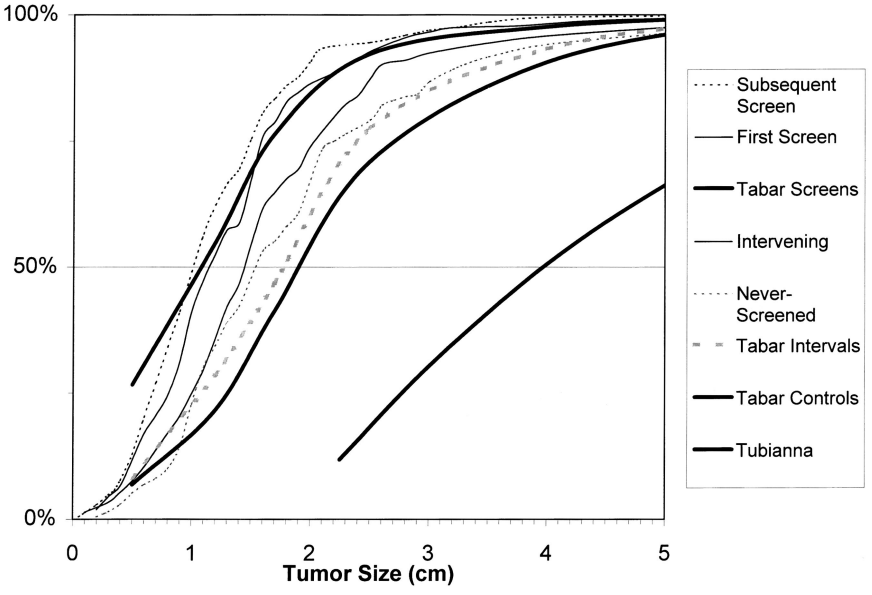

Figure 2. Cumulative size distributions of the tumors in the Massachusetts General Hospital data set in comparison to the estimated cumulative size distributions of tumors reported in earlier studies.

detected cancers (intervening cancers; median age, 57 year; $P < 0.0001$; see Figure 4 and Tables 3 and 4).

Among the women who did not undergo screening at MGH and who were found to have breast cancer (never-screened cancers), those aged 50 to 69 years had fewer very large tumors than did older or younger women (Figure 5). Indeed, just 3% (3 of 58) of the never-screened cancers in women aged 50 to 69 years were larger than 25 mm, whereas 25% (19 of 76) of these cancers in women younger than 50 and 20% (15 of 70) of those in women older than 60 were larger than 25 mm ($P < 0.01$).

Diagnostic mammography was performed for 104 of the 179 women with intervening cancers, of which 17 (16%) revealed no evidence of cancer.

■ Discussion

The data provide a picture of the breast cancers seen during the past decade at one large breast imaging center. One of the most surprising findings to emerge from this analysis was that the tumors seen among women who do not use screening have become much smaller than they were in the past.[6–12,16] Whereas the median size of the tumors in unscreened women seen at MGH during the past decade was 15 mm, the median size of the tumors found in unscreened women reported on by Tabar and colleagues[6–8] from 1977 to 1985 was about 20 mm, and the median size of the cancers found by Tubiana and colleagues[9–12] in the premammographic years of 1954 to 1979 was about 40 mm. Tumors with a diameter of 20 mm (Tabar, 1977–1985) contain almost three times as many cells as tumors of 15 mm (MGH, 1990–1999), and tumors with a diameter of 40 mm (Tubiana, 1954–1979) contain almost 20 times as many cells, assuming similar geometry and cell density. Since the probability of lethal spread from the primary tumor has been found to increase roughly with the number of cells in the tumor,[17] the reduction in the sizes of the nonmamographi-

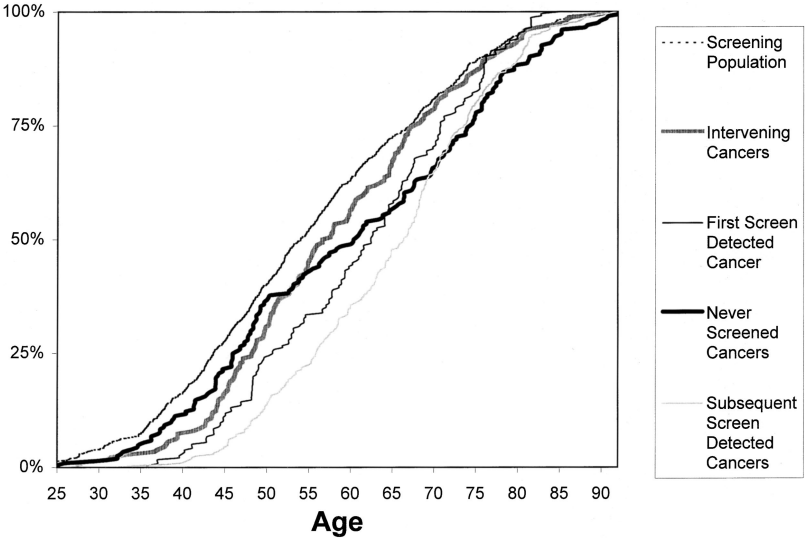

Figure 3. Cumulative age distribution for women with breast cancer, by detection category.

Table 3. Features of the Breast Cancers in This Study, by Means of Detection

	Subsequent-Screen–Detected Cancers* (n = 312)			First-Screen–Detected Cancers† (n = 115)		Intervening Cancers‡ (n = 179)			Never-Screened Cancers§ (n = 204)	
	Age (yr)	Years Since Previous Negative Mammogram	Size (mm)	Age (yr)	Size (mm)	Age (yr)	Years Since Previous Negative Mammogram	Size (mm)	Age (yr)	Size (mm)
Median	66.3	1.31	10	61.5	12	56.6	1.19	15	60.5	15
Mean	64.8	1.92	11.7	61.0	13.7	57.3	1.89	16.8	60.1	18.7
SD	11.8	1.49	7.6	12.0	8.9	15.5	1.85	12.2	16.3	12.3
Maximum	91.8	10.42	70	85.0	63	90.6	13.86	90	92.5	75
Minimum	33.5	—	0.5	35.7	2	27.5	—	1	25.0	2

* Invasive breast cancers identified by mammography in asymptomatic women who have had at least one previous negative screening mammogram at MGH.
† Invasive breast cancers identified by mammography in asymptomatic women at the first screen at MGH.
‡ Invasive breast cancers identified by means other than a screening mammogram in women who have had at least one previous negative screening mammogram at MGH.
§ Invasive breast cancers identified by means other than a screening mammogram in women who have no history of mammography at MGH.
MGH = Massachusetts General Hospital; SD = standard deviation.

cally detected tumors might be associated with as much as a several-fold reduction in breast cancer death. This reduction in the sizes of cancers seen in the absence of mammography could account for a part of the reduction in breast cancer death in recent years.[18] Although we can only guess as to the basis of this favorable trend, several explanations seem intuitively likely, including the generally greater awareness of breast cancer among women and their physicians. In part, this may be due to the widespread media coverage of breast cancer in recent years. The wider availability of diagnostic mammography and other tools for assessing women's self-reported breast cancers could also be playing a role.[13]

Another sign that nonmammographically detected cancers are coming to medical attention at smaller sizes can be seen in the relative absence of tumors larger than 25 mm in women aged 50 to 69, in comparison with younger and older women. Women of this age group are believed to have a higher level of awareness of breast cancer than younger and older women,[19] and this could contribute to an unwillingness to let masses grow to a very large size.

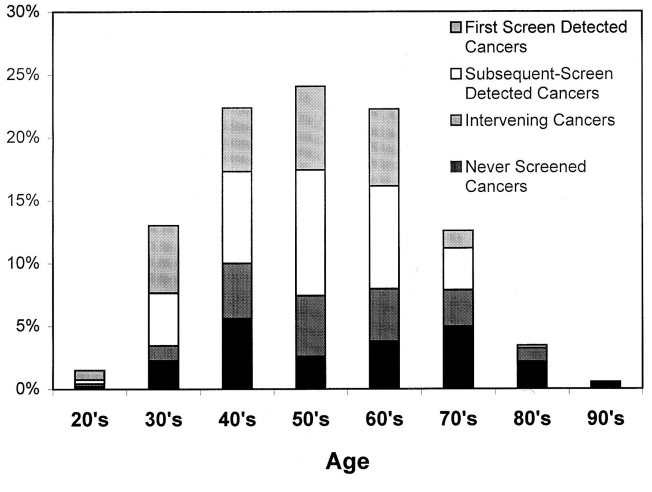

Figure 4. Age distribution of women with breast cancer at Massachusetts General Hospital, by decade.

Not only have the nonmammographically detected tumors become smaller over the past decade, but the cancers seen by mammography have become smaller as well. Thus, the mammographically detected cancers in the MGH data set (median size, 10 mm) were slightly smaller than the mammographically detected cancers found by Tabar and colleagues[6–8] between 1977 and 1985 (median size, 12 mm). We suspect that our lower size could reflect aggressive thresholds for intervention and improvements in mammographic technique that have occurred in the past few decades.

We found that 5% of the breast cancers in our data set are detectable by palpation before they are detectable by mammography. This could be seen from the results of diagnostic mammograms that were carried out for 104 of the 179 women with intervening cancers, of which 17 (16%) revealed no mammographic evidence of cancer. Since these 179 intervening cancers constituted 36% of the 491 women who had had at least one previous negative screening mammogram and who were subsequently found to have invasive breast cancer, it would

Table 4. Statistical Comparisons of Tumor Size and Patient Age Data Shown in Table 3

	Subsequent Screen Detected Cancers	Intervening Cancers	First Screen Detected Cancers
Wilcoxon comparisons (size)*			
Intervening cancers	$P < 0.0001$		
First-screen–detected cancers	$P = 0.0206$	$P = 0.0102$	
Never-screened cancers	$P < 0.0001$	$P = 0.1086$	$P < 0.0001$
Least square means *t* test (age)			
Intervening cancers	$P = 0.0492$		
First-screen–detected cancers	$P < 0.0001$	$P = 0.0002$	
Never-screened cancers	$P = 0.0245$	$P = 0.5620$	$P = 0.0155$

* Kolmogorov-Smirnoff comparisons revealed equivalent outcomes.

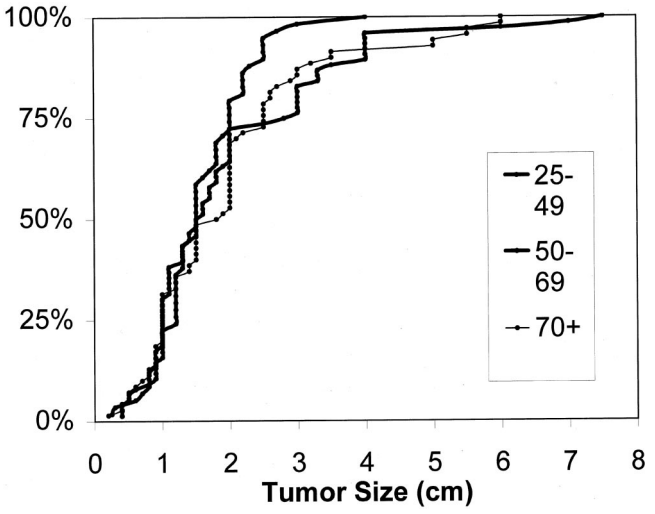

Figure 5. Cumulative size distribution of the never-screened cancers, by age. Note the relative absence of tumors larger than 2.5 cm in women aged 50 to 69 years.

appear that about 5% (*i.e.*, 36% of 16%) of all invasive breast cancers might be detectable as palpable masses, or by other nonmammographic criteria, before they are detectable by mammography. Women with these tumors will not benefit from mammography, but they might benefit from other forms of breast cancer screening, such as clinical breast examination.[20,21] Future work should be aimed at finding ways to identify such women and at determining the best screening procedures for them. However, the relatively small number of such women reinforces the belief in the population-wide effectiveness of mammographic screening.

We recognize that there are a number of limitations to our analysis. Because all patients are physician referred, there are likely unknown selection biases. Furthermore, some of the women who were categorized as having never undergone mammography at MGH before may have been screened elsewhere. Nevertheless, since their cancers were not found at imaging-guided biopsy, they were clearly evident clinically. Similarly, women whose cancers are counted as having been detected by their first MGH mammogram may have had mammography previously at another institution. We suspect that these limitations have a relatively small effect on the inferences made on the size of tumors seen at screening, and for this reason it would be of value if similar data were collected from geographically based populations and compared with the results described here.

Despite the reduction during the past few decades in the sizes of the tumors found without the benefit of screening, mammography is still the best way to find breast cancer at its smallest possible size. The median size of the screen-detected cancers in the MGH data set was about 10 mm, whereas the median size of the cancers detected by nonmammographic criteria (usually palpation) was around 15 mm. Assuming similar geometry and cell density, a tumor of 15 mm should contain more than three times as many cells as a tumor of 10 mm. This supports the view that screening mammography probably affords the most effective way to identify breast cancers at the smallest, and thus it is hoped most curable, sizes.

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Address correspondence to:

James 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