Gauging the Impact of Breast Carcinoma Screening in Terms of Tumor Size and Death Rate

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BACKGROUND. While the question of whether the trials of breast cancer screening have resulted in a reduction in breast cancer death has been the subject of much scrutiny, there has been less attention to the reduction in tumor size achieved by screening.

METHODS. Size data for invasive breast tumors were assembled from a variety of sources. The health consequences that can be expected from finding tumors of various sizes were determined using a recently developed mathematical method for relating tumor size to death rate.

RESULTS. First, in both the Swedish two-country trial and at the MGH Breast Imaging Division, the sizes of the invasive breast cancers in the screening population (those masses seen at screening together with those found as palpable masses after screening examinations) were sufficiently smaller than the cancers found among women who had not used screening to have lead to considerable reductions in death. Second, the lack of reduction in death rates detected in both Canadian National Breast Screening Studies could be ascribed to the small reductions in tumor size achieved in these studies. Third, radiographic density had a small effect, whereas age had a negligible effect, on the capacity of mammographic screening to find breast carcinomas at smaller, and thus less lethal, sizes.

CONCLUSIONS. Prompt attendance at annual mammographic screening offers the potential to reduce tumor size and, presumably, breast carcinoma death, in women of all ages and density groups. ***Cancer* 2003;98:2114–24.**
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KEYWORDS: breast carcinoma, survival, tumor size, mammography, screening.

Breast carcinoma screening has been the subject of much uncertainty and controversy.[1–12] There has been uncertainty as to the best age for initial screening and the optimal interval between screens. There has also been controversy as to whether the trials of screening have demonstrated a reduction in breast carcinoma death.[13–17] For example, the Swedish Two-County trial reported a reduction in the number of deaths from breast carcinoma.[18–20] However, no reductions in death rate were reported in the Canadian National Breast Screening Study-1 trial of screening mammography versus a single clinical examination and the 'usual' care for women ages 40–49 years,[21] nor in the Canadian National Breast Screening Study-2 trial of clinical breast examination versus clinical breast examination plus mammography for women ages 50–59 years.[22] Although much scrutiny has been focused on whether trials of screening have resulted in reductions in breast carcinoma death,[1–12] there has been less attention paid to the reduction in tumor size achieved by screening. In the current study, we assemble size data to assess the impact of screening on the reduction in the sizes at which invasive tumors are detected. Furthermore, by using a recently developed

mathematical expression that can correlate tumor size to the death rate among women with invasive breast carcinoma,[23] we are able to gauge the impact that finding these tumors at these sizes can be expected to have on the survival of patients. These size data, and the estimates of expected survival based on them, provide insight into a number of highly contentious and previously ambiguous aspects of the screening debate and point to ways that screening might be used to its maximal life-sparing effect.

MATERIALS AND METHODS

Tumor size and patient survival data were available for 1352 women with invasive breast carcinoma. (Ductal carcinoma in situ [DCIS] has been excluded from analysis.) These women were treated at the Van Nuys Breast Center (Van Nuys, CA; now part of University of Southern California) between 1966 and December 31, 1990. Ninety percent of the invasive tumors were detected after 1980.[23] The macroscopic tumor size for the invasive carcinomas was measured on the pathologic specimen as the largest diameter of the tumor. Analysis of survival was determined by the Kaplan–Meier method using Winstat software (A-Prompt, Whitehall, PA). As in our previous study,[23] women were censored at the time of last follow-up (for those alive at the time of last follow-up) and at the time of death (for those who died of causes other than breast carcinoma). Tumor size and patient survival data also were available for 220 patients with invasive breast carcinomas who were treated at Massachusetts General Hospital (MGH, Boston, MA) between 1980 and 1985. The MGH and Van Nuys death rates reflect the Kaplan–Meier breast carcinoma death rates at 15 years (Table 1). The death rates at 160 months (13.33 years) for invasive breast carcinoma were obtained from the studies of Tabar et al.[18–20] The death rates obtained from the studies of Tubiana and colleagues[24–27] are 25-year Kaplan–Meier values for the appearance of distant metastatic disease (Table 1). The decision to evaluate the 15-year survival rate of patients with breast carcinoma in the Van Nuys dataset who were diagnosed before 1991 was made to make these values comparable to survival estimates made by Tabar et al.[18–20] and by Tubiana and colleagues.[24–27] However, similar survival calculations including all malignancies in the Van Nuys dataset (up to year 2000; not shown) yielded essentially the same results as those derived from the malignancies diagnosed before 1991. The survival values of Tabar et al. at 160 months (13.33 years) for invasive breast carcinoma were determined from 1977 to 1985 and analyzed in December 1990. The values of Tubiana and colleagues represent breast carcinomas diagnosed between 1954 and 1972. The precise time of these calculations was not given, but this work was submitted in December 1983. Therefore, we assume the calculations were made in the previous year. The values of Tubiana and colleagues reflect 25-year Kaplan–Meier values obtained for the appearance of distant metastatic disease, which we assume closely reflects ultimate mortality. In their 1999 study of 1547 patients with breast carcinoma who underwent surgery between 1945 and 1987, Karrison et al.[28] reported that most breast carcinoma deaths occurred within 10 years of surgery. Only 12% of deaths occurred after 13 years, at which time the hazard rate had declined approximately sevenfold. Thus, it is not unreasonable to compare the 15-year survival rates of the women in the Van Nuys population with the 13.33-year survival rates of Tabar et al. and the 25-year recurrence rates of Tubiana and colleagues.

Tumor size data were available for 810 women with invasive breast carcinomas (DCIS cases were not included) who were treated at the MGH Breast Imaging Division from January 1, 1990 to March 1, 1999,[29,30] 291 women with invasive breast carcinoma who were treated at the MGH Division of Surgical Oncology from 1990 to 1999 (which comprised women who received invasive carcinoma surgeries at the MGH, including women who were referred without a diagnostic mammogram at the MGH), and 182 women with invasive breast carcinomas who were treated at the Lahey Clinic (Burlington, MA) from 1997 to 2000. A previous study reported the general features of the invasive breast carcinomas treated at the MGH Breast Imaging Division,[31] which were divided into four categories based on the method of detection: first screen–detected carcinomas, subsequent screen–detected carcinomas, intervening carcinomas, and never-screened carcinomas. In that study,[31] 115 malignancies were detected at the first screening mammogram at the MGH (first screen–detected cancers), 312 were detected at a subsequent screening, after at least 1 negative screening mammogram (subsequent screen–detected cancers), 179 were clinically detected after a negative screening mammogram (intervening cancers), and 204 were clinically detected in women who had no record of a previous mammogram at the MGH and who received a diagnostic mammogram after the time of detection (never-screened cancers). We have adopted the term *intervening cancer* to distinguish it from the term *interval cancer*, which usually is used to describe an invasive malignancy arising after a negative examination, but within a specified period of time. The macroscopic tumor size for the invasive carcinomas was measured on the pathologic specimen as the largest diameter of the tumor. Patient age was recorded for the time of the relevant mammogram.

Parenchymal density from the mammograms

TABLE 1
Tumor Sizes (Invasive Breast Carcinomas) by Method of Detection

Study population	*n*	Median tumor size (mm)	Expected breast carcinoma death rate according to Eq. 1[a] (%)	Observed breast carcinoma death rate (%)
MGH Breast Imaging Division (1990–1999)[b]				
All cancers	810	12	19.6	—
All screen-detected cancers	427	10	15.8	—
First screen–detected cancers[c]	115	12	17.9	—
Subsequent screen–detected cancers[c]	312	10	15.0	—
Intervening cancers[c]	179	15	22.2	—
Intervening cancers found within 1 yr of the previous negative mammogram	68	14	20.7	—
Intervening cancers found more than 1 yr after the previous negative mammogram	111	15	23.1	—
Never-screened cancers[c]	204	15	25.0	—
Cancers from the screening population (first screen–detected cancers, subsequent screen–detected cancers, and intervening cancers)	606	12	17.7	—
Cancers from the screening population of women age < 50 yrs (first screen–detected cancers, subsequent screen–detected cancers, and intervening cancers)	127	12	18.5	—
Cancers from the 1 yr screening population (first screen–detected cancers, subsequent screen–detected cancers, and intervening cancers found with 1 yr of a negative exam)	495	11	16.5	—
Cancers from the 6 mo screening population (first screen–detected cancers, subsequent screen–detected cancers, and intervening cancers found within 6 mos of a negative mammogram)	448	11	16.1	—
MGH Division of Surgical Oncology (1990–1999)[d]				
All cancers	291	19	30.0	—
MGH Division of Surgical Oncology (1980–1985)				
All cancers	220	20	35	42
Lahey Clinic (1997–2000)				
All cancers	182	12	19.1	—
Nonpalpable cancers	91	10	14.0	—
Palpable cancers	91	15	24.3	—
Van Nuys Breast Center (≈1980–1990)				
All cancers	1352	20	32.9	32
Nonpalpable cancers	216	11	16.9	12
Palpable cancers	1132	20	35.9	35
Van Nuys Breast Center (1991–1999)				
All cancers	881	17	29.9	—
Nonpalpable cancers	283	10	17.7	—
Palpable cancers	598	20	35.7	—
Tabar et al. (1977–1985)[18–20]				
All cancers	1800	17	29	32
First screen	382	12	22	15
Later screens	424	12	20	12
Intervals	267	18	33	36
Controls	727	20	36	37
Cancers from the screening population (screen-detected and interval cancers)	1073	12.5	24	19[e]
Canadian Study 2 (patients ages 50–59 yrs; 1980–1988)[22]				
Mammogram and physical examination arm	442	14	27.4	—
Physical examination arm	395	17	31.5	—
Canadian Study 1 (patients ages 40–49 yrs; 1980–1985)[21]				
Intervention arm	290	17	31.1	—
Usual care arm	237	18	33.0	—
Tubiana and colleagues (1954–1979)[24–27]				
All cancers	2648	40	60	60

MGH: Massachusetts General Hospital.

[a] Average of all individual Equation 1 calculations for a given group.

[b] Invasive malignancies seen at Massachusetts General Hospital on a screening or diagnostic mammogram, or a previous history of screening at Massachusetts General Hospital.

[c] See Materials and Methods for definition.

[d] Invasive cancer surgeries at Massachusetts General Hospital, including referred cases without a diagnostic mammogram at Massachusetts General Hospital.

[e] Not provided by Tabar et al.[18–20] Value listed is the average, weighted by the number of women in each group, of the values for the first screen, later screen, and interval cancer.

evaluated at MGH was assessed and recorded at the time of screening for each of the 196,891 mammograms performed during the time period described above. Parenchymal density was classified into one of the following seven categories at the time of the mammographic study[30]: MGH density code 1, *almost entirely radiolucent* (American College of Radiology Breast Imaging Reporting and Data System [ACR BIRADS] code equivalent, 1); MGH density code 2, *predominantly radiolucent with thick septations* (ACR BIRADS code equivalent, 1); MGH density code 3, *predominantly radiolucent with some fibronodular densities* (ACR BIRADS code equivalent, 2); MGH density code 4, *diffuse fibronodular densities* (ACR BIRADS code equivalent, 3); MGH density code 5, *heterogeneously dense* (ACR BIRADS code equivalent, 4); MGH density code 6, *dense tissue superimposed on fibronodular densities* (ACR BIRADS code equivalent, 4); MGH density code 7, *uniformly dense* (ACR BIRADS code equivalent, 4).

We lack information on the percentage of women in the MGH screening population who had mammograms performed elsewhere or who had subsequent breast carcinomas that were treated elsewhere and thus did not appear in our database. However, estimates of the overall impact of screening were determined by assessing the tumor sizes in the MGH screening population as a whole (first screen–detected, subsequent screen–detected, and intervening cancers), because doing so led to the inclusion of both the invasive malignancies observed at screening and the invasive malignancies not observed at screening. Michaelson et al.[31] recently reported that slightly more than 75% of women who have had 1 mammogram at the MGH Breast Imaging Division returned for a second mammogram. After 2 additional years of data since that report, the return rate has increased to 82% and among women who had previously returned promptly for a previous screening mammogram, 93% subsequently returned (unpublished data). Furthermore, many of the remaining 10-20% of the population that constitutes the nonreturnees remain within the population with respect to the palpable masses that appear. A significant percentage (approximately 20%) of the invasive tumors in the screening population are found as palpable masses among women who have gone more than a year since their previous negative mammogram.[31] Ten percent of nonmammographically detected malignancies were found more than 1.5 years after a previous negative mammogram, 7% were identified more than 2 years after, and 3% were detected more than 5 years, and up to 13.8 years, after the last negative mammogram.[31] Therefore, despite the finding that the MGH population is not geographically based, the combination of the first screen–detected, subsequent screen–detected, and intervening cancers can be expected to represent most (80+%) of the invasive cancers in the screening population, whether they are detected at screening or appear later as palpable masses. Nonetheless, it must be borne in mind that the MGH population is not a closed population, in contrast to the populations in the Swedish and Canadian trials.

Information on invasive breast carcinomas in studies reported by others[18–27] usually consisted of grouped size data (Table 1). Therefore, inferences made from these data are, by necessity, less precise than inferences made from the MGH, Lahey, and Van Nuys data sets. However, the general trends from the data were clear. The median tumor size from the grouped data was determined by identifying the point where the cumulative distribution curve crossed the 50% point.

All studies had appropriate institutional review board approval for these retrospective analyses, in accordance with the National Institutes of Health human research study guidelines.

RESULTS

Tumor Size and Lethality

As we recently have demonstrated,[23] the relation between invasive breast tumor size and lethality is well captured by the expression

$$L = 1 - e^{-QD^Z} \quad (1)$$

where L is the percentage of women dying, D is the tumor diameter, e is the exponential constant, $Q = 0.0062$, and $Z = 1.3243$. Equation 1 has been shown to be biologically plausible,[23] because it is based on the most generally accepted mechanism of breast carcinoma death (i.e., the metastatic spread of cells from the primary site to the periphery, occurring with a definable probability per cell). Equation 1 also has been shown to be empirically sound.[23] Estimates of the expected death rate generated from size data agree closely with the actual death rate data from four separate populations of women, as well as from subpopulations of women whose tumors were clinically detected or detected by screening mammography (Table 1). The actual and estimated survival values agreed to within 5% of each other for 8 of the 11 populations in Table 1 for which actual survival data were available and to within 8% for all 11 populations, thus providing an empiric basis for using Equation 1 to calculate the reduction in death that should be expected for finding invasive breast tumors at various sizes.

Tumor Size in Screening Populations

The actual impact of screening on the sizes at which invasive tumors are detected could be seen from the tumors in screening populations, i.e., populations for

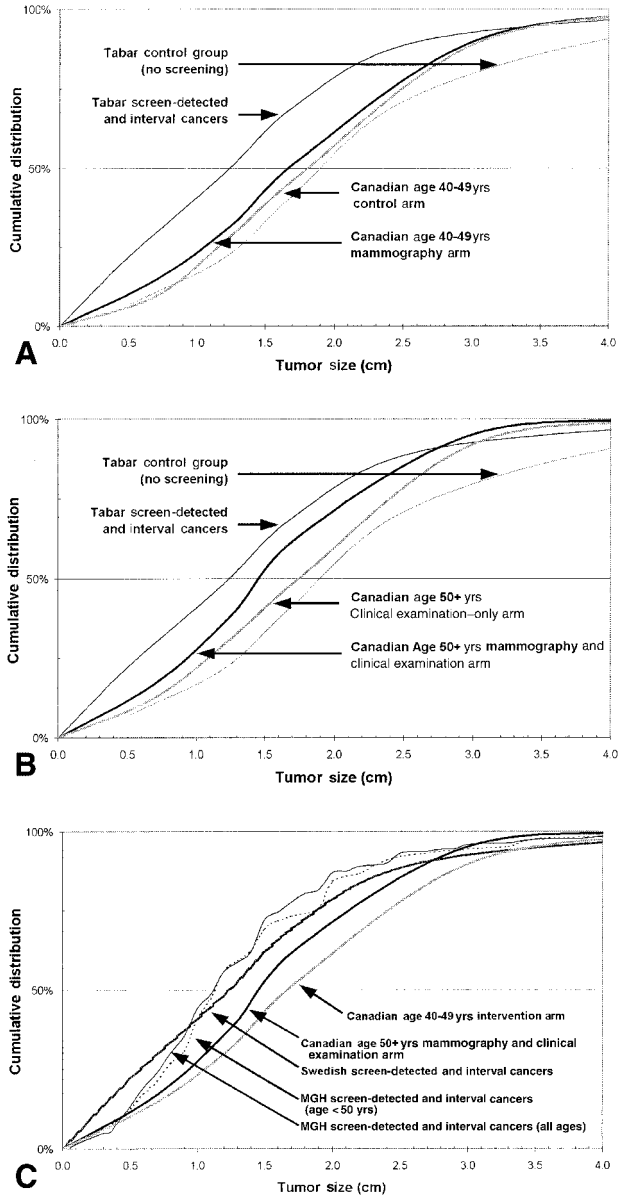

FIGURE 1. Cumulative distributions of invasive breast tumor size in various screening populations. (A) Invasive breast carcinomas in the intervention and control arms of the Swedish Two-County trial and the Canadian Study-2 trial (women ages 40–49 years). (B) Invasive breast carcinomas in the intervention and control arms of the Swedish Two-County trial and the Canadian Study-1 trial (women ages 50–59 years). (C) Invasive breast carcinomas in the screening population (i.e., both screen-detected and palpable tumors found in women with a previous mammogram) of the Massachusetts General Hospital (MGH) Breast Imaging Division; in women at MGH who were younger than age 50 years; in women in the Swedish Two-County trial; in women in the Canadian Study-1 trial; and in women in the Canadian Study-2 trial.

which information is available on both the invasive malignancies detected at screening and on the clinically detected malignancies found after screening examinations. Figure 1 shows the cumulative distributions of the sizes of the invasive breast tumors detected in the Swedish Two-County trial (invitation to screening vs. no intervention),[18–20] the Canadian National Breast Screening Study-1 trial (screening mammography vs. usual care for women ages 40–49 years),[21] and the Canadian National Breast Screening Study-2 trial (clinical breast examination plus mammography vs. clinical breast examination only for women ages 50–59 years).[22] For the Swedish Two-County trial, the difference between the median sizes of the invasive tumors detected in the control and intervention groups was 8 mm (12.5 mm vs. 20 mm). For both Canadian studies, the differences were much smaller—1 mm for the Canadian Study-1 trial (17 mm vs. 18 mm) and 3 mm for the Canadian Study-2 trial (14 mm vs. 17 mm; Fig. 1). Using Equation 1 with the full set of size distribution data yields an expected 33% reduction in the death rate in the Swedish Two-County trial (24% vs. 36%); this result agrees with the actual reductions in death rates reported by Tabar et al.[18–20] Equivalent calculations yield an estimated 5% reduction in the death rate for the Canadian Study-1 trial (31.1% vs. 33.0%) and an estimated 13% reduction for the Canadian Study-2 trial (27.4% vs. 31.5%; Table 1).[21,22] Because neither Canadian study contained enough women to detect such small survival differences,[32] this provides an obvious explanation for why actual reductions in the death rate were not detected.

Figure 1C shows the cumulative distributions of sizes of the invasive breast tumors detected in 5 screening populations: the MGH screening population (median tumor size, 12 mm); the subset of women at MGH who were younger than age 50 years (median tumor size, 12 mm); the Swedish Two-County trial population (median tumor size, 12.5 mm); the Canadian Study-1 trial population (median tumor size, 17 mm); and the Canadian Study-2 trial population (median tumor size, 14 mm). These findings reveal that considerable reductions in the sizes at which invasive cancers come to medical attention are possible by mammographic screening, but were not realized in either of the Canadian trials.

The expected death rate calculated with Equation 1 and tumor size data yielded an expected breast carcinoma death rate of 24% for the screening population of the Swedish Two-County trial (1977–1985) and 17.7% for the MGH screening population (Table 1). In contrast, the invasive breast carcinomas detected in the absence of screening were larger and more lethal, as observed in the control group in the Swedish Two-County trial[18–20] (median tumor size, 20 mm; actual death rate, 37%; death rate expected according to Equation 1, 36%) and in the studies performed by Tubiana and Koscielny,[24,27] which were largely conducted in the premammographic era (median tumor size, 40 mm; actual death rate, 60%; death

rate expected according to Equation 1, 60%). These findings provide a measure of the magnitude in the reduction in invasive tumor size and lethality that can be achieved by screening.

Tumor Size at Screening

The sizes of the invasive tumors detected at screening alone do not indicate the benefit of screening because they do not include cancers missed at screening that appear later as palpable masses. However, understanding tumor size distributions can be of importance in terms of communicating to women the health consequences of screen-detected malignancies. The five groups listed in Table 1 provide information on the distribution of the sizes of tumors detected by mammography. These groups include 1) first screen–detected cancers in the Swedish Two-County trial[18,20] (median tumor size, 12 mm; death rate expected according to Equation 1, 22%; actual death rate, 15%); 2) later screen–detected cancers in the Swedish Two-County trial (median tumor size, 12 mm; death rate expected according to Equation 1, 20%; actual death rate, 12%); 3) nonpalpable breast carcinomas in the Van Nuys population[23] (median tumor size, 11 mm; death rate expected according to Equation 1, 17%; actual death rate, 12%); 4) nonpalpable breast carcinomas observed at the Lahey Clinic (median tumor size, 10 mm; death rate expected according to Equation 1, 14%); and 5) screen-detected breast carcinomas observed at MGH[29,31] (median tumor size, 10 mm; death rate expected according to Equation 1, 16%). These findings suggest that women with invasive breast carcinomas detected at screening can expect a very high chance (78–88%) of survival.

Tumor Size in the Population as a Whole

The invasive breast carcinomas detected in the population as a whole comprise tumors found at screening and at clinical examination, many of which occur in women who have never used screening. Four of the groups included in Table 1 reflect population-wide values: 1) all invasive breast carcinomas at the Van Nuys Breast Center (1980–1990)[23] (median tumor size, 20 mm; death rate expected according to Equation 1, 32.9%; actual death rate, 32%); 2) invasive breast carcinomas observed at the MGH Division of Surgical Oncology (1990–1999) (median tumor size, 19 mm; death rate expected according to Equation 1, 30%); 3) all invasive malignancies observed at the Van Nuys Breast Center (1991–1999)[23] (median tumor size, 17 mm; death rate expected according to Equation 1, 29.9%); and 4) all invasive malignancies observed at the Lahey Clinic (1997–2000;) (median tumor size, 12 mm; death rate expected according to Equation 1, 19.1%). The reduction in tumor size and expected death rate between the Van Nuys population in the 1980–1990 period (median tumor size, 20 mm; expected death rate, 32.9%) compared with the 1991–1999 period (median tumor size, 17 mm; expected death rate, 29.9%) can be ascribed to the increase in the percentage of mammographically detected nonpalpable tumors from 16% in the earlier period to 32% in the later period. Likewise, the even smaller tumor size (median, 12 mm) and expected death rate (19.1%) in the Lahey Clinic population can be explained by the even higher percentage (50%) of mammographically detected nonpalpable tumors in that population.

Effect of Age and Density on Tumor Size in a Screening Population

The impact of age and tissue density on the screening was gauged by evaluating size data from subgroups of the MGH screening population. The data revealed that regardless of age and tissue density, the invasive tumors in the screening population (i.e., screen-detected and palpable tumors in women with a previous negative mammogram) were smaller that the tumors found in women who did not use screening (Table 2, Fig. 2). Calculations involving these data and Equation 1 further suggested that women in the lowest density groups could expect a 38% reduction in death rate, whereas women with the highest tissue density could expect a 20% reduction in death rate, compared with women who did not undergo screening. The expected reductions in the death rate by age are 26% for women younger than age 50 years, 27% for women ages 50–59 years, 32% for women ages 60–69 years, and 30% for women age 70 years or older (Fig. 3; Table 2). Therefore, these data suggest that groups of women of all ages and density categories should benefit from screening, although the degree of benefit may vary.

Because the change in the efficiency of mammographic detection with age is believed to result from the change in breast density with age,[30,33–39] the impact of age on the effectiveness of screening also was estimated by combining the estimated death rates for the screened women in each density group (Table 2) with data on the abundance of each of these density groups by age (Fig. 3). The calculations suggest that the effectiveness of screening mammography should increase as women age, but only slightly, from an estimated 18% level of breast carcinoma lethality for women in their 30s to a 17% level for women in their late 70s.

In agreement with a number of previous studies,[33–39] the percentage of palpable tumors detected within a year of a negative mammogram at the MGH was greater for women in the densest (ACR BIRADS 4: palpable tumors within 1 year = 28%) and youngest (ages 40–49 years: 22%) groups than for women in the

TABLE 2
Size of Invasive Breast Carcinomas[a] in the Massachusetts General Hospital Screening Population, by Density and Age, together with Survival Predictions (Eq. 1) Based on Tumor Size[b]

Density[c] or age group[d]	No. of women	Palpable tumors found within 1 yr[e] (%)	Median tumor size (mm)	Estimated breast carcinoma death rate according to Eq. 1 (%)	Estimated reduction in breast carcinoma death rate[f] (%)
All patients	606	14	12	17.7	29
MGH density code					
6	69	25	12	18.3	27
5	144	25	14	20.2	19
4	126	9	12	18.7	25
3	128	4	11	15.6	38
1 and 2	45	8	9	15.6	38
ACR BIRADS density code					
4	306	28	12	18.5	26
3	127	9	12	18.6	26
1 and 2[g]	173	5	11	15.6	38
Age (yrs)					
< 50	127	22	12	18.5	26
50–59	138	22	12	18.2	27
60–69	164	10	12	17.0	32
≥ 70	177	5	10	17.4	30

MGH: Massachusetts General Hospital; ACR BIRADS: American College of Radiology Breast Imaging Reporting and Data System.

[a] First screen–detected cancers, subsequent screen–detected cancers, and intervening cancers.

[b] The small difference in the numbers of cancers listed here and in TABLE 1 reflects the fact that age and/or density data were absent in the database for approximately 15% of the cancers.

[c] Estimates could not be made for Massachusetts General Hospital density code 7 due to an insufficient number of patients.

[d] Statistical comparisons: MGH 5 vs. MGH 6, not significant; MGH 4 vs. MGH 6, not significant; MGH 4 vs. MGH 5, not significant; MGH 3 vs. MGH 6, $P = 0.003$; MGH 3 vs. MGH 5, $P = 0.003$; MGH 3 vs. MGH 4, $P = 0.16$; MGH 1 and 2 vs. MGH 6, not significant; MGH 1 and 2 vs. MGH 5, not significant; MGH 1 and 2 vs. MGH 4, not significant; MGH 1 and 2 vs. MGH 3, not significant; ACR BIRADS 3 vs. ACR BIRADS 3, not significant; ACR BIRADS 1 and 2 vs. ACR BIRADS 4, $P = 0.03$; ACR BIRADS 1 and 2 vs. ACR BIRADS 3, $P = 0.03$. None of the age-associated differences in tumor size were statistically significant. $P < 0.0001$ for comparisons between the sizes of never-screened cancers for all density and age groups shown.

[e] Defined as the number of intervening cancers found within 1 year of a negative screening mammogram divided by the sum of the number of cancers found at screening and the number of intervening cancers found within 1 year.

[f] Compared with patients who did not undergo screening.

[g] Values for the ACR BIRADS 1 group alone are not presented, as the number of tumors in this category ($n = 45$ for the entire population and $n = 37$ for 1-year values) was insufficient for making reliable estimates.

least dense (ACR BIRADS 2: 5%) and oldest (age ≥ 70 years: 5%) groups. However, the impact of these missed tumors on the distribution of tumor size in the screening population as a whole was diluted somewhat by the finding that palpable tumors detected within a year of a negative mammogram were smaller than the palpable tumors found more than a year later (Fig. 2; Table 1). Macroscopic tumors that go undetected at screening tend not to be relatively large tumors, thus lessening their impact on the distribution of tumor sizes seen in the screening population as a whole (Fig. 2).

Effect of the Screening Interval on Tumor Size in a Screening Population

Insight into the effect of the screening interval on the effectiveness of screening was gained from the finding that there is a great range of return times among women who use screening. Consequently, many malignancies appear as palpable tumors long after negative screening examinations.[29,31] For example, as we recently reported,[29,31] although 30% of the invasive breast carcinomas in the MGH screening population were palpable tumors larger (median tumor size, 15 mm) than the screen-detected tumors (median tumor size, 10 mm), only 12% of these palpable tumors were found within a year of the previous negative examination and only 3% were found within 6 months. Similar findings have been reported by others.[33,34] By back-calculating the likely size of each palpable tumor at the time of the previous negative mammogram, it was determined that most of these tumors probably went undetected at the previous negative mammogram (because they were too small then to have been reasonable candidates for detection) rather than because too much time had elapsed since the previous mammogram. Thus, it is likely that most of these palpable tumors would have been detected at screening if return had occurred at the recommended annual interval. Figure 4 shows the average size of the tumors detected at screening (first screen–detected and subsequent-screen–detected cancers) plus palpable masses (intervening cancers) found during various periods of time after a previous negative mammogram.

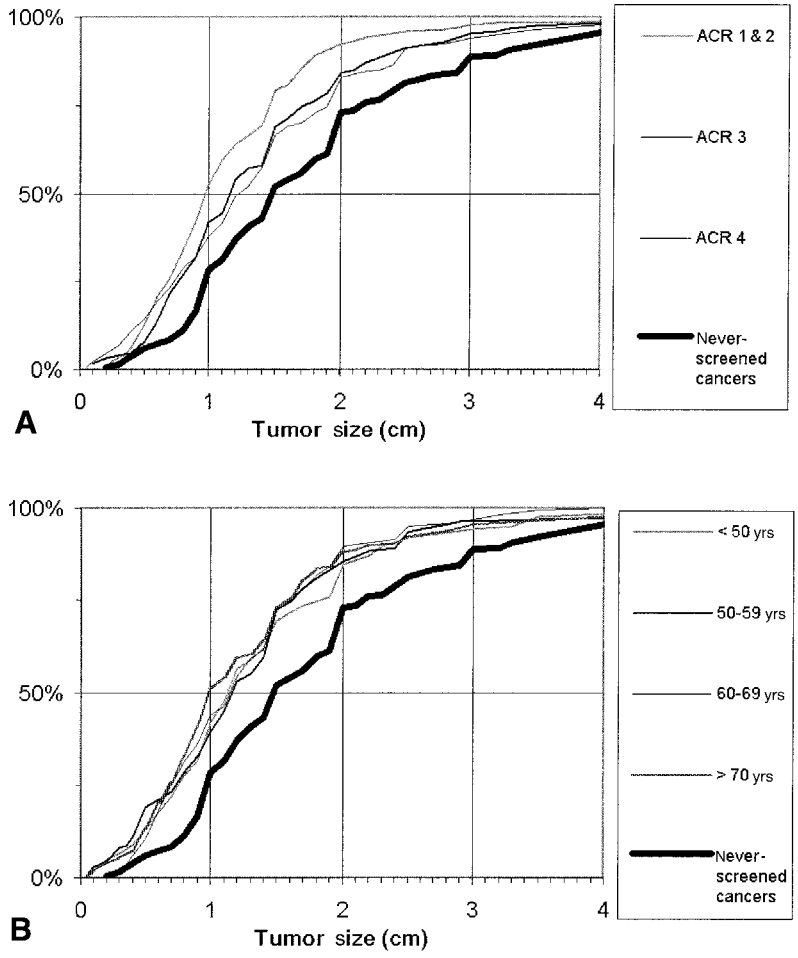

FIGURE 2. Cumulative distributions of invasive breast tumor size in the screening population (first screen–detected and subsequent screen–detected cancers and intervening cancers), (A) by density and (B) by age (bottom), compared with the cumulative distribution of tumor size in women with no record of previous screening at Massachusetts General Hospital (MGH; never-screened cancers). See Table 2 for mean and median values. The invasive tumors observed among women in the screening population who were in the low tissue density group were slightly but significantly smaller (American College of Radiology Breast Imaging Reporting and Data System [ACR BIRADS] 1 and 2; median tumor size, 10 mm) compared with invasive tumors in the high tissue density group (ACR BIRADS density code 4; median tumor size, 12 mm; $P = 0.03$). There was no evident difference in the size of invasive tumors in the screening population based on age. However, tumor size among women in all age and tissue density groups was significantly smaller than the invasive tumors in women who had not used screening, indicating that women in all age and tissue density groups benefit from screening ($P < 0.0001$). See Materials and Methods for definitions of the MGH density groups.

These values provide a rough approximation of what can be expected, in terms of both tumor size and breast carcinoma death, if screening is used with various screening intervals. Thus, the values shown in Figure 4 suggest that although women with breast carcinoma in the MGH population, who returned to screening at a great variety of intervals, can expect an 18% death rate, prompt return to annual screening should yield a somewhat lower (i.e., 16.5%) death rate (Fig. 4; Table 1). Indeed, the calculations shown in Figure 4 suggest that reducing the screening interval to once every 6 months should yield an even lower death rate (16.1%) but that there probably is little additional benefit to be gained by screening more frequently than that.

DISCUSSION

Although there has been a great deal of attention and controversy surrounding the survival of patients in randomized trials of breast carcinoma screening,[1–11] as well as in the population as a whole,[1,4–7,14] there has been less attention paid to the sizes at which screening identifies invasive breast carcinomas. Thus, while it has previously been possible to examine, in a trial, whether a screening intervention has had an impact on cancer death,[2–12,18–20,22–27] it has not been obvious how to relate these survival outcomes to the sizes at which the tumors were brought to medical attention. Similarly, studies have evaluated the impact of screening on the sizes at which tumors are brought to medical attention, but they have not been able to make inferences as to the likely health consequences of bringing smaller breast tumors to medical attention. The mathematical method used to evaluate the correlation between the size of an invasive breast tumor and the expectation of breast carcinoma lethality makes such estimates possible.[23] In the current study, we have assembled such size data and made survival calculations based on them.

A major limitation of the current analysis is that although it provides insight into the specific populations examined, it remains to be determined whether the conclusions drawn will be generalizable to the larger populations. It is fortunate that it should be possible to address these concerns by the simple accumulation of additional data from other populations.

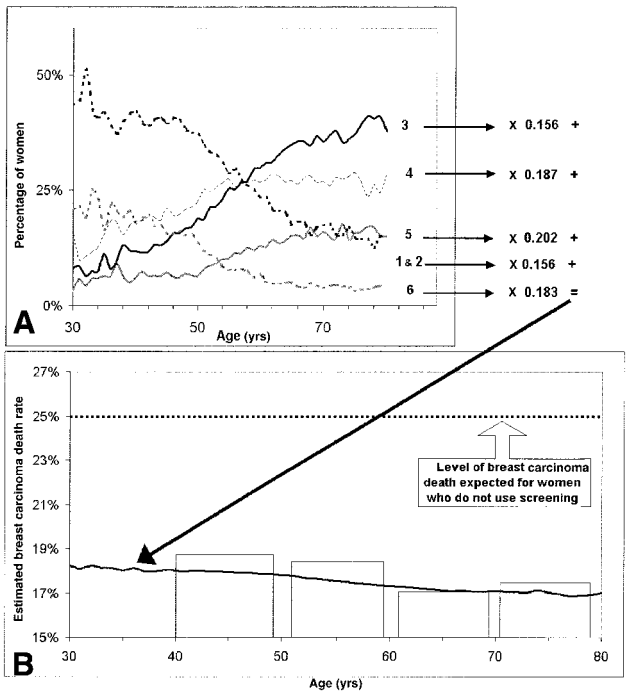

FIGURE 3. Impact of age on the effectiveness of mammographic screening. (A) Percentage of women in each of 5 breast density categories (Categories 1 and 2, 3, 4, 5, and 6; see Materials and Methods for definitions) and the estimated breast carcinoma death rates for screening populations comprising each of these density categories (15.6%, 15.8%, 18.7%, 20.2%, 18.3%; Table 2). (B) The dark line represents the survival rate expected after combining these two sources of information. Bars represent the estimated breast carcinoma death rates in the screening population sorted by age ($<$ 50 years, 50–59 years, 60–69 years, $\geq$ 70 years; Table 2).

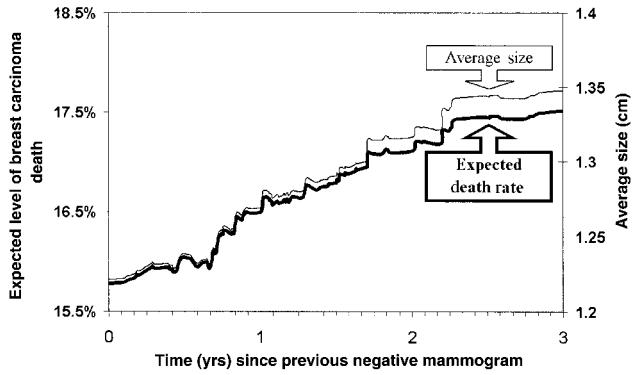

FIGURE 4. Average tumor size (thin line) and expected breast carcinoma death rate calculated using Equation 1 (thick line) for the Massachusetts General Hospital screening population versus screening interval. Values were calculated by considering all screen-detected tumors (first screen–detected and subsequent screen–detected cancers) and palpable tumors (intervening cancers) found within the various periods of time after the previous negative mammogram.

A second limitation concerns the finding that smaller invasive breast tumors are not the only way that screening is believed to reduce the death rate among women with breast carcinoma. Screening is also believed to benefit patients by identifying DCIS before ir progresses to invasive carcinoma. Approximately 80% of breast tumors detected are invasive.[40] Of the approximately 20% that are DCIS, it has been estimated that one-third to one-half would have developed into invasive breast carcinomas had the disease been left untreated.[41] These values suggest that the greatest benefit of screening is received by patients with invasive breast carcinoma. There also may be a small additional benefit for patients with DCIS, whose contribution to the risk of death was not estimated with Equation 1. The approach used in the current study to estimate the health consequences of finding invasive breast tumors of various sizes probably provides a conservative estimate of the life-sparing benefit of screening.

The data presented in the current study reveal that screening substantially reduced the sizes of the invasive breast tumors in the Swedish Two-County trial,[18–20] which reported a reduction in the death rate. However, the data showed that there was little reduction in the sizes of the tumors detected in the screening populations of either of the two Canadian trials,[21,22] which reported no reductions in the death rate. According to data on tumor size in the intervention and control arms of the two Canadian studies, the Canadian Study-1 trial (women ages 40–49 years) was expected to yield a 5% reduction in the death rate, whereas the Canadian Study-2 trial (women ages 50–59 years) was expected to yield a 13% reduction in the death rate. It is unfortunate that neither study had enough women to detect these levels of benefit.[21,22,32] The technical quality of the mammography in the Canadian trials has been questioned,[32,42–44] in agreement with the disappointing reductions in the size of the tumors in these two studies. Analysis of the sizes of the tumors detected in the screening populations of both the Swedish Two-County trial and the MGH Breast Imaging Division further indicates that mammography has the potential to reduce the size at which tumors come to medical attention, and thus the lethal burden of breast carcinoma. The absence of a reduction in the death rate in the two Canadian trials should be considered as evidence of the low level of benefit that screening provided in those trials, but not as evidence of an absence of the actual potential for reducing death from breast carcinoma when screening is practiced rigorously.

The analysis of invasive breast tumor size among various subgroups of women in the MGH screening population leads to three striking conclusions. First, mammography has the potential to reduce the size at

which invasive breast tumors are brought to medical attention, with an equivalent potential to reduce the death rate among women with breast carcinoma, in all age and tissue density categories. It has long been recognized that screening is less effective in younger women than in older women, presumably because of the change with age in the radiologic density of the breast. The tumor size data in the current study confirm this belief. However, these data also reveal that the actual magnitude of this age-associated effect is remarkably small, such that neither age nor density provides a practical barrier to the effectiveness of screening mammography. For example, the calculations outlined in the current study indicate that women age 70 years who utilize screening can expect an absolute 8% reduction in breast carcinoma lethality compared with women who do not use screening. Women age 30 years who undergo screening should expect only a marginally smaller absolute reduction in the death rate from breast carcinoma (7%). These findings suggest that only the incidence of breast carcinoma, rather than the practical effectiveness of mammography, should provide an age-associated barrier to screening in younger women. Second, the data from the MGH population suggest that women who returned promptly for their annual examination have a markedly smaller distribution of tumor sizes and thus can expect a lower level of breast carcinoma lethality relative to women who returned less promptly. The tumor size data suggest that women in the MGH screening population as a whole (who exhibit a disappointing level of variation in their return times[31]) can expect an 18% breast carcinoma death rate, whereas women who returned promptly for their annual exams can expect a death rate of 16.5%. Third, the tumor size data also suggest that there may be some additional benefit gained from screening more frequently than once a year, with the potential for additional reductions in breast carcinoma death rates resulting from a reduction in the screening interval to approximately 6 months. These findings generally agree with computer simulation studies, which have suggested that prompt annual screening has the potential to lead to considerable reductions in breast carcinoma death and that there may well be a small but not insignificant reduction in breast carcinoma death that can be achieved with twice-yearly screening from age 30 years onward.[13,16,17]

Although the findings of the current study suggest that additional benefit may result from screening more aggressively than the American Cancer Society (ACS) recommendation of once yearly from age 40 years onward, we regard this as only an intriguing hypothesis, whose value must be tested with additional data. We believe that such a possibility should not detract from the most noteworthy conclusion: an enormous health benefit appears to be attainable simply by more widespread compliance with the ACS recommendation. The data suggest that prompt annual screening from age 40 years onward, when performed in a technically rigorous fashion, can reduce the death rate among women with invasive breast carcinoma to less than 17%, in comparison to the 25–50% death rate in the population as a whole.[45,46] Such a reduction in the death rate, if achieved, would represent an enormous reduction in the burden of death resulting from this disease.

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