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ORIGINAL ARTICLE

Tumour size predicts long-term survival among women with lymph node-positive breast cancer

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ABSTRACT

Background

The benefit of early detection of breast cancer is assumed to be achieved primarily by identifying disease before it has spread beyond the breast. In support of early detection, the survival experience of women with breast cancer decreases as the mean size of the cancer increases. It is not clear if women with regional spread (node-positive breast cancer) benefit from early detection to the same extent that women with node-negative breast cancer do.

Methods

A review was conducted of the survival experience of 1894 patients with invasive breast cancers 5.0 cm or less in size. Cases were divided into node-positive and node-negative, and tumours were categorized by size (0.1–1.0 cm, 1.1–2.0 cm, and 2.1–5.0 cm). After a mean follow-up of 9.9 years, 368 cancer-specific deaths had occurred in the cohort. The effect of tumour size on 15-year survival for subgroups of women with node-positive and node-negative breast cancer was estimated.

Results

Tumour size was a strong predictor of 15-year survival in both the node-positive and node-negative cancer subgroups. A decline of 1.0 cm in size was associated with a reduction in 15-year mortality of 10.3% in the node-positive group and of 2.5% in the node-negative group. A decline of approximately 1.5 cm was associated with a reduction in mortality of 23.0% in the node-positive group and of 10.8% in the node-negative group.

Conclusions

The impact of decreasing tumour size on 15-year survival is much greater for women with node-positive than for women with node-negative breast cancers. Contrary to expectation, the benefit of screening is likely to be greater for women with relatively advanced breast cancer than for women with early-stage disease.

KEY WORDS

Breast cancer, prognostic factors, node status, survivorship

1. INTRODUCTION

The goal of screening for breast cancer is to identify cancers when they are at a curable stage. The prospect for cure depends in turn on the extent to which the cancer has spread at diagnosis. If a breast cancer is entirely contained within the breast (that is, if no subclinical metastases have occurred), then complete excision through mastectomy or breast-conserving surgery is expected to be curative. If the cancer has spread to regional lymph nodes, cure is still the goal, but a proportion of women with node-positive cancer will also have subclinical metastatic disease that may or may not be cured by surgery and systemic chemotherapy. It is currently not possible to assay for the presence of subclinical metastases at diagnosis, but it is well established that the highest cure rates are achieved in women with small, lymph node-negative breast cancers[1].

Given the relationship between tumour size and survival, and given the conventional model of breast cancer spread, it seems logical that the principal goal of early detection should be to identify cancers when they are small and node-negative. Undoubtedly, the best outcome would be the detection of all breast cancers when they are small and node-negative. However, there may also be an advantage to identifying node-positive cancers when they are relatively small.

Follow-up data from the Henrietta Banting Database in Toronto was used to evaluate the relationship between tumour size and long-term survival in

women with and without lymph-node metastases at diagnosis. The absolute mortality benefit of finding small compared with medium-sized or large-sized breast cancers was determined for the two groups of women. The implications of the results, with regard to the differential benefit of screening in node-negative and node-positive women, are discussed.

2. METHODS

2.1 Study Subjects

The present study considers a cohort of 2310 patients with invasive breast cancer who were treated at Women's College Hospital in the Henrietta Banting Breast Centre between January 1987 and December 1999. Clinical characteristics (tumour size and lymph node status) were retrieved from the medical records. For 20 patients (1%), information for one or more key variables was missing, and those 20 women were excluded, leaving 2290 subjects in the study.

Follow-up has been maintained by the database coordinator through periodic review of the clinical charts and by contacting the patient or the patient's physician by telephone[2,3]. For deceased patients, the date and cause of death are obtained by review of medical records and by a mortality linkage with the Cancer Care Ontario database. Tumour size was taken as the largest dimension of the tumour (in centimeters) determined by pathology examination. Tumours larger than 5 cm in size were found in 110 patients, and those women were excluded. Node status was defined as positive or negative. For 286 women, a nodal dissection was not done, and those women were also excluded, leaving 1894 patients for the analysis.

This investigation involved human subjects, but informed consent was not required by the institution's ethics review board because no subject was contacted.

2.2 Survival Analysis

The patients were followed for breast cancer–specific survival from diagnosis until either death from breast cancer, death from another cause, or date of last contact. Death from breast cancer occurred in 368 patients, and death from another cause, in 38. Using the Kaplan–Meier method, breast-specific survival was determined from the time of diagnosis until death from breast cancer. The log-rank test was used to examine the statistical significance of the differences observed between groups. All analyses were carried out using the SAS software application (version 9.1.3: SAS Institute, Cary, NC, U.S.A.).

3. RESULTS

Table I describes the study cohort. The mean follow-up period was 9.9 years (range: 1–15 years). Tumours

TABLE I Description of the study patients

Variable	*Value*
Patients (*n*)	1894
Year of birth	
Mean	1939.4
Range	1897–1970
Age at diagnosis (years)	
Mean	54.3
Range	22–100
Tumour size [*n* (%)]	
0.1–1.0 cm	457 (24.1)
1.1–2.0 cm	725 (38.3)
2.1–5.0 cm	712 (37.6)
Mean tumour size in cohort (cm)	2.0
Nodal status [*n* (%)]	
Negative	1175 (62.0)
Positive	719 (38.0)
Surgery [*n* (%)]	
Lumpectomy	1490 (78.7)
Mastectomy	404 (21.3)
Chemotherapy [*n* (%)][a]	
No	1235 (66.1)
Yes	632 (33.9)
Radiotherapy [*n* (%)][a]	
No	591 (31.7)
Yes	1273 (68.3)
Tamoxifen[a]	
No	955 (51.4)
Yes	904 (48.6)
Estrogen receptor [*n* (%)][a]	
Negative	535 (30.0)
Positive	1247 (70.0)
Missing	112
Progesterone receptor[a]	
Negative	705 (40.5)
Positive	1034 (59.5)
Missing	155
HER2 status [*n* (%)][a]	
Negative	829 (75.5)
Positive	269 (24.5)
Missing	796
Local recurrence [*n* (%)][a]	
No	1660 (87.6)
Yes	234 (12.4)
Distant recurrence [*n* (%)]	
No	1481 (78.2)
Yes	413 (21.8)
Death from breast cancer [*n* (%)]	
No	1526 (80.6)
Yes	368 (19.4)

[a] Percentages calculated using only patients with a known status as the denominator.

of 1 cm or less in size (small cancers) were found in 457 patients; tumours of 1–2 cm in size (intermediate cancers), in 725 patients; and tumours of 2–5 cm size (large cancers), in 712 patients.

Size was a strong predictor of 15-year survival, both for women with node-negative breast cancer and for those with node-positive breast cancer (Table II, Figures 1 and 2). The decline in survival attributable to positive nodal status increased with tumour size. The 15-year actuarial breast-cancer-specific survival rates for women with small node-negative cancers was 92%, and for women with small node-positive cancers, it was 80%—a difference of 12 percentage points (Table II). The 15-year breast-cancer-specific survival rates for women with medium-sized node-negative cancers was 89%, and for women with medium-sized node-positive cancers, it was 70%—a difference of 19 percentage points. The 15-year actuarial breast-cancer-specific survival rates for women with large-sized node-negative cancers was 79%, and for women with large-sized node-positive cancers, it was 47%—a difference of 32 percentage points.

Figure 3 presents the association between tumour size and survival in graph form. In the present analysis, a moving average consisting of patients with tumours that were within 0.5 cm of the mean value was constructed. The slope of the curve is greater for node-positive than for node-negative cancers, indicating that a given change in tumour size is associated with a greater difference in mortality for node-positive than for node-negative cancers. Figure 4 presents the net difference in 15-year mortality attributable to the effect of node positivity by tumour size.

A decline of a given magnitude in the mean size of a breast cancer was associated with a much larger decline in mortality for the node-positive group of women than for the node-negative group. For example, the difference in survival between women with medium-sized and small tumours (a decline of 1.0 cm) was 2.5% for the node-negative group and 10.3% for the node-positive group (Table II). The difference in survival between women with large- and medium-sized tumours (a decline of roughly 1.5 cm) was 10.8% for the node-negative group and 23.0% for the node-positive group.

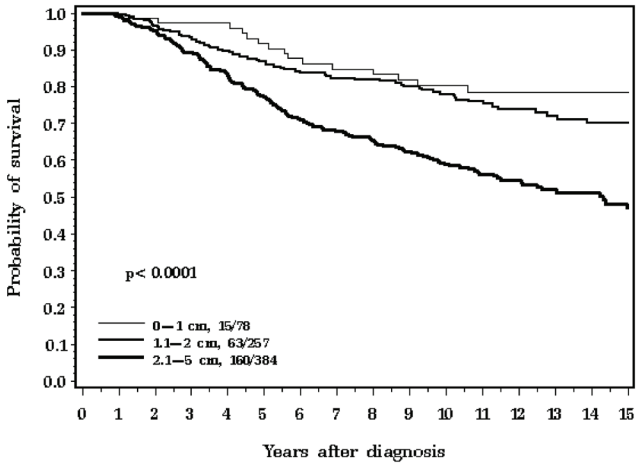

FIGURE 1 Survival after breast cancer in node-positive patients, by tumour size.

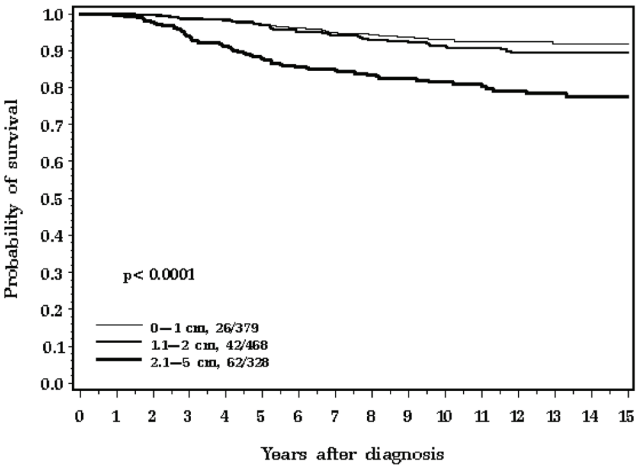

FIGURE 2 Survival after breast cancer in node-negative subjects, by tumour size.

4. DISCUSSION

In the present work, data on tumour size, nodal status, and survival in a large cohort of breast cancer patients were collected and examined with the goal of asking whether the benefits of early detection are

TABLE II Tumour size at diagnosis and survival at fifteen years by lymph node status

Tumour size group	*Mean tumour size (cm)*		*Survival after 15 years [% (95% CI)]*	
	Node-positive	*Node-negative*	*Node-positive*	*Node-negative*
0.1–1 cm	0.7	0.6	80.4 (71.2 to 89.6)	91.8 (88.7 to 94.9)
1.1–2 cm	1.7	1.6	70.1 (63.4 to 76.8)	89.3 (86.2 to 92.4)
2.1–5 cm	3.3	3.0	47.1 (40.4–53.8)	78.5 (73.4–83.6)

CI = confidence interval.

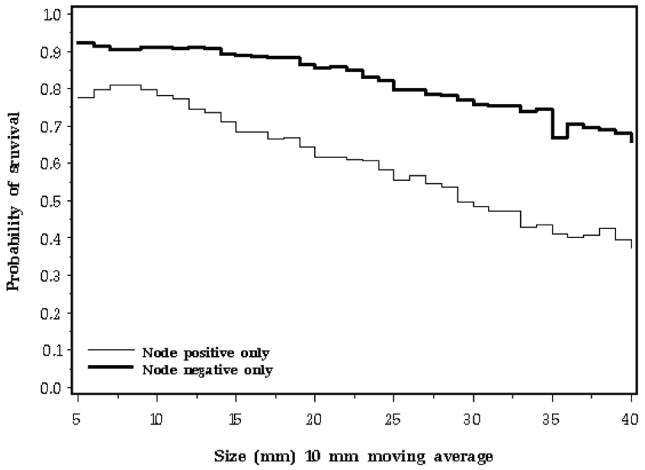

FIGURE 3 Fifteen-year survival after breast cancer diagnosis, by mean tumour size.

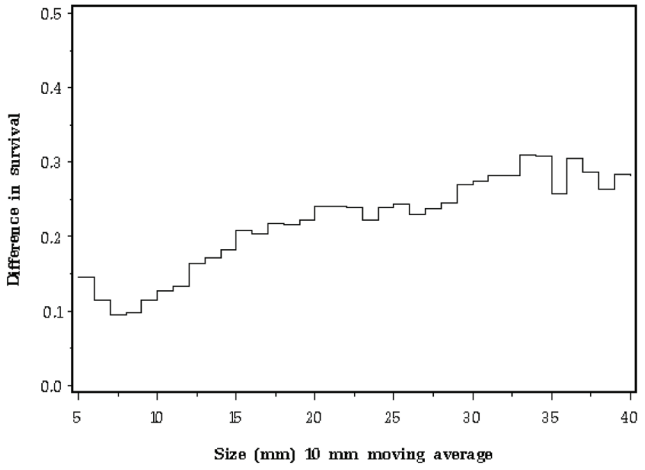

FIGURE 4 Difference in fifteen-year survival associated with node-positivity, by mean tumour size.

likely to accrue to women with node-positive as well as node-negative breast cancer. Two key observations were made: First, the adverse impact of positive nodal status on survival increased with the mean size of the tumour. Second, the decrease in mortality associated with a decrease in mean tumour size is much greater for women with node-positive cancer than for those with node-negative cancer.

If the mortality rates observed here are similar to those for a population of women with screen-detected breast cancer, then screening would be expected to benefit women with both node-positive and node-negative cancer.

The populations that might benefit most from screening can be speculated. Undoubtedly, the best outcome would be achieved if all breast cancers were to be detected when small and node-negative. However, in a population in which most cancers are detected at 2.0 cm or smaller and when they are node-negative, the expectation of benefit from mammographic screening (or another form of early detection) would be small (Figure 2) because baseline mortality is already low and the relationship between tumour size and survival is attenuated for cancers less than 2 cm in size. On the other hand, in a population in which cancers typically present when they are 2–5 cm and node-positive, a reduction in mortality of approximately 50% would be expected if a screening program resulted in a reduction of the mean tumour size to 2.0 cm, even if the proportion of node-positive cancers stayed the same. This situation resembles circumstances in the developing world, and it is a rational goal to try to find all breast cancers at 2.0 cm or less throughout the world.

Similarly, the circumstances in which a randomized screening trial is likely to show a significant benefit can be speculated. Assume that standard mammography is to be applied uniformly in a screening arm and that imaging reduces the size of every breast cancer at diagnosis by 1 cm. The net reduction in cancer mortality would therefore be approximately 10% in a population in which most cancers (that is, those in the control arm) present at above 2 cm and are node-positive, but less than 3% in a population in which most cancers present at less than 2 cm and are node-negative. Thus, the nature of the control group is critical to the power of a screening trials, and trials conducted earlier on were *a priori* more likely to be successful than trials conducted in the modern era[4,5].

That argument is perhaps simplistic in that it is based purely on the statistics derived from a single cohort of women. Also, I have not taken into account histologic features of the breast cancers that may be relevant—in particular, estrogen-receptor (ER), progesterone receptor, and HER2 status[6–8]. The relationship between tumour size and survival is much stronger for ER-positive breast cancers than it is for triple-negative breast cancers or for HER2-positive breast cancers[6], and the benefit of screening may accrue differently for patients with different cancer subsets.

It is important to note here that 5-year survival is not a reliable surrogate for ultimate cure when various cancer subsets are compared. Tumour size and nodal status are independent predictors of recurrence, but again, the relationship is inconstant and the correlation is strongest for the ER-positive cancers. In the extreme case, cancers that are very small in size, but that are associated with 2 or more positive lymph nodes appear to be particularly aggressive[9]. For those reasons, the expected benefit of detecting cancers by screening is not determinable solely by considerations of tumour size.

Other factors relevant to an evaluation of screening policy, such as the various biases associated with screening (lead-time bias and length-time bias, for instance), test sensitivity and specificity, costs, and the possibility of overdiagnosis are not discussed here. The analysis presented here is purposefully

simple, and I have chosen not to take into account other pathologic features, screening history, and treatment; however, lack of detail on those features should not detract from the central argument. In the present study, nodal status is dichotomized, which does not capture the variability in survival rates associated with the number of positive nodes in women with node-positive breast cancer[1].

5. CONCLUSIONS

A reduction in mean tumour size on diagnosis is important for women with node-positive breast cancer, and screening is likely to benefit women even after regional spread. A mammography screening program is likely to have a significant impact in a community where breast cancer typically presents at 2.0 cm or greater, particularly if most of those cancers are lymph-node positive.

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7. CONFLICT OF INTEREST DISCLOSURES

The author declares that he has no financial conflicts of interest.

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