The Effect of Tumor Size and Lymph Node Status on Breast Carcinoma Lethality

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Received May 6, 2003; revision received June 27, 2003; accepted June 30, 2003.

DOI 10.1002/cncr.11765

BACKGROUND. It has long been known that both tumor size and the presence of malignant disease in the regional lymph nodes are indicators of outcome for patients with invasive breast carcinoma; however, the way in which these two characteristics could be integrated into an overall assessment of prognosis has not been obvious.

METHODS. Kaplan–Meier survival estimates (15 years) according to tumor size and lymph node status were obtained for women with invasive breast carcinoma who were observed at the University of Southern California/Van Nuys Breast Center (Van Nuys, California) or at Massachusetts General Hospital (Boston, Massachusetts).

RESULTS. To isolate the individual contributions to death made by tumor size and lymph node status, data were sorted according to both of these variables. For women with tumors of equivalent size, lethality increased with increasing number of positive lymph nodes, such that there was an extra ≈6% chance of death associated with each positive lymph node. For women with equivalent lymph node status, tumor size was associated with increased lethality, such that each millimeter of tumor diameter was associated with an additional ≈1% chance of death. The overall lethality was equal to the sum of the contribution from lymph node status and the contribution from tumor size, and this finding led to the creation of a new technique (the *Size+Nodes* method) for predicting outcome.

CONCLUSIONS. The *Size+Nodes* method was shown to be capable of accurately estimating the risk of death due to invasive breast carcinoma from information on the size of the primary tumor and the number of positive lymph nodes. In addition, this method was used to stratify women into groups according to breast carcinoma lethality. In contrast, classification of women according to lymph node positivity, T status, or disease stage created groups with wide and overlapping levels of lethality. ***Cancer* 2003;98:2133–43.** © *2003 American Cancer Society.*

KEYWORDS: breast carcinoma, risk of death, tumor size, lymph node status.

The accurate staging of invasive breast carcinoma is a major objective in the management of this disease.[1–3] For example, it has long been known that both tumor size and the presence of malignant disease in the regional lymph nodes are indicators of outcome for patients with invasive breast carcinoma;[4–8] however, the way in which these two characteristics could be integrated into an overall assessment of prognosis has not been obvious. In the current report, we provide an assessment of the independent effects of tumor size and lymph node status on outcome for patients with breast carcinoma, and we present a new technique (the *Size+Nodes* method) for integrating these two variables into an overall prediction of survival.

TABLE 1
The *Size + Nodes* Method for Estimating the Risk of Invasive Breast Carcinoma Death from Information on Tumor Size and Lymph Node Status

Source of lethality	Method of estimation	Independent variable(s)	Parameters	Interpretation
Primary malignancy	$L_{primary} = 1 - e^{-Q_P D^Z}$ (Eq. 1)[a]	D (tumor diameter)	$Q_p = 0.0041$[b] $Z = 1.3243$	The lethal contribution of the primary mass increases gradually with increasing tumor size (1 mm in diameter ≈ additional 1% chance of death)
Malignant disease in lymph nodes	$L_{nodes} = 1 - e^{-(M*R)}$ (Eq. 3)	M (no. of positive lymph nodes)	$R = 0.0608$	There is approximately an additional 6% chance of death associated with each positive lymph node
Primary malignancy plus disease in lymph nodes	$L_{overall} = L_{primary} + L_{nodes} - (L_{primary}*L_{nodes})$ (Eq. 4)[c]	D (tumor diameter); M (no. of positive lymph nodes)	$Q_p = 0.0041$ $Z = 1.3243$ $R = 0.0608$[d]	

[a] Justification for the form of Equation 1 can be found in: Michaelson JS, Silverstein M, Wyatt J, et al. The prediction of breast cancer survival from tumor size. *Cancer*. 2002;95:713–723.[9]

[b] The 15-year Kaplan–Meier death rate was 20% for the 790 lymph node–negative patients in the University of Southern California/Van Nuys Breast Center population who were observed before 1990. Using the tumor size data for these patients, it was possible to estimate the value of Q_p by varying its value until $L_{primary} = 0.200$ when Equation 1 was summed over this patient group.

[c] The product $L_{primary} * L_{nodes}$ in Equation 4 prevents the double-counting of women who received lethal contributions from both the primary malignancy and from involved lymph nodes.

[d] The 15-year Kaplan–Meier death rate among the 443 lymph node–positive patients in the University of Southern California/Van Nuys Breast Center population was 48.62%. The average of all 443 values of $L_{overall}$ was estimated using Equation 4 along with data on tumor size and lymph node status for these 443 patients and the values of Q_p and Z that were determined previously. The value of R then was determined by adjustment until Equation 4 yielded an average value of $L_{overall}$ equal to 48.62%.

MATERIALS AND METHODS

Data were available for 2233 women with invasive breast carcinoma (excluding ductal carcinoma in situ) who were treated at the University of Southern California (USC)/Van Nuys Breast Center (Van Nuys, California) before November 1, 2000. Data on the subset of patients who were observed before December 31, 1990 ($n = 1233$), were used in most calculations for consistency with previous work performed by our group.[9] The average and median follow-up times for this subset, including women who died of breast carcinoma, were 9.0 and 8.9 years, respectively (standard deviation, 5.0 years). The average and median follow-up times excluding women who died of breast carcinoma were 9.8 and 9.6 years, respectively (standard deviation, 4.8 years). Data on tumor size, lymph node status, and survival also were available for 220 women with invasive breast carcinoma who were observed at Massachusetts General Hospital (MGH; Boston, Massachusetts) between 1980 and 1985. Survival rates used throughout the study were Kaplan–Meier estimates for 15 years; this time point was chosen because Karrison et al.[10] demonstrated that less than 10% of deaths due to breast carcinoma occur after 15 years. As in our previous study,[9] women were censored at the time of last follow-up (for those who were alive) or at the time of death (for those who died of causes other than breast carcinoma).

Tumor size was taken to be the largest diameter as determined on pathologic analysis. The number of lymph nodes examined for patients in the USC/Van Nuys Breast Center data set ranged from 1 to 47, with 90% of patients having more than 10 nodes examined and 98% having more than 5 nodes examined. The mean and median numbers of lymph nodes examined were 16.8 and 17, respectively (standard deviation, 7.2). For subsets of patients whose number of positive lymph nodes fell within a specified range, the average number of positive lymph nodes was calculated (e.g., the average number of positive lymph nodes among patients with 2 or more positive lymph nodes was 5.99). Data on tumor size and lymph node status also were available for 182 women with invasive breast carcinoma who were observed at the Lahey Clinic (Burlington, Massachusetts) between 1997 and 2000 and for 271 women who were observed at the MGH surgical practice between 1990 and 1999.

A summary of the mathematical expressions used can be seen in Table 1. Justification for the form of Equation 1 can be found in our previous report.[9] All studies had appropriate institutional review board approval, in accordance with human research study guidelines set forth by the National Institutes of Health.

RESULTS

Conflation of Tumor Size, Lymph Node Status, and Lethality

In agreement with many previous studies,[2–8] we found that in the USC/Van Nuys Breast Center population, breast carcinoma lethality increased with tumor size and with the presence of disease in the regional lymph nodes; however, it is not possible to use such data to gauge the magnitude of the individual contributions of size and lymph node status to lethality, because the two variables are conflated: as tumor size increases, so does the fraction of lymph node–positive women, and as the number of positive lymph nodes increases, so

TABLE 2
Fifteen-Year Kaplan—Meier Breast Carcinoma Death Rates and Mean Tumor Sizes, Sorted by Tumor Size or Lymph Node Status, for Women Observed before 1990 at the University of Southern California/Van Nuys Breast Center

Tumor characteristic	No. of patients	% LN-positive	Average no. of positive LNs	Mean tumor size (mm)	Fifteen yr Kaplan–Meier death rate (%)[a]
All invasive breast cancers	1233	36	1.9	26.2	30
Node negative invasive breast cancers	790	0	0	21.1	20
Node positive invasive breast cancers	443	100	5.3	35.3	49
1–9 mm, all nodal statuses	154	11	0.35	5.7	10
10–19 mm, all nodal statuses	429	30	0.97	13.5	20
20–29 mm, all nodal statuses	288	40	1.23	22.8	30
30–39 mm, all nodal statuses	144	50	2.87	31.8	50
40–49 mm, all nodal statuses	60	52	3.15	41.6	64
1 positive node, tumors of all sizes	130	100	1	25.7	26
2 positive nodes, tumors of all sizes	71	100	2	29.0	34
3 positive nodes, tumors of all sizes	46	100	3	30.7	37
4 positive nodes, tumors of all sizes	47	100	4	35.4	57

LN: lymph node.
[a] $P < 0.02$ for comparison of survival for women with 1 positive node, tumors of all sizes, in comparison to node negative women; $P < 0.001$ for comparison of survival for of all other groups of node positive women shown, in comparison to node negative women.

does tumor size (Table 2). To isolate the individual contributions of tumor size and lymph node status to breast carcinoma lethality, women were sorted by both tumor size and number of positive lymph nodes; doing so revealed that for women with equivalent lymph node status, lethality increases with increasing tumor size, and that for women with tumors of equivalent size, lethality increases with increasing number of positive lymph nodes (Figs. 1–3; Table 3).

Added Risk of Breast Carcinoma Death due to Each Increase in Primary Mass Size

The data shown in Figure 1 and Table 3 reveal that for women with equivalent lymph node status, lethality increases with increasing tumor size. This finding is most evident for lymph node–negative women (who make up the largest lymph node status category in the USC/Van Nuys Breast Center population), and the relation between tumor size and lethality is well fit by an equation of the form

$$L_{primary} = 1 - e^{-Q_p D^Z} \quad (1)$$

where $L_{primary}$ is the lethal contribution from the primary mass in lymph node–negative women, e is the exponential constant, D is the tumor diameter, Q_p is equal to 0.004113, and Z is equal to 1.3243 (Fig. 1; see Table 1 for details on the values of Q_p and Z).

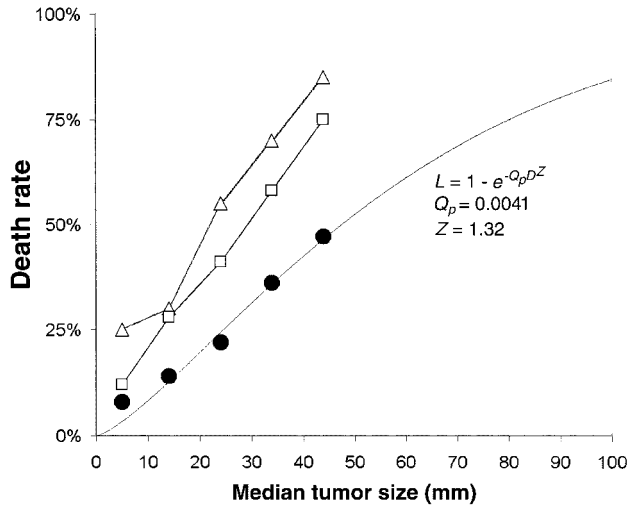

FIGURE 1. Fifteen-year Kaplan–Meier death rates by lymph node status for women in the University of Southern California/Van Nuys Breast Center population. Also shown is Equation 1, in which L is the fraction of women who died, e is the exponential constant, D is the tumor diameter, Q_p is equal to 0.004113, and Z is equal to 1.3243. See Table 1 for more information on these parameters. Open triangles: 3 or more positive lymph nodes; open squares: 1 or more positive lymph nodes; filled circles: no positive lymph nodes.

Increased Risk of Death Is Determined by the Number of Positive Lymph Nodes

Data from the USC/Van Nuys Breast Center population as a whole (Fig. 2; Table 3) and from a subset of 494 patients in the USC/Van Nuys Breast Center population who had not received adjuvant chemotherapy (Fig. 3) revealed that it is not simply the presence of malignant disease in the lymph nodes per se that determines lethality, since women with only 1 or 2

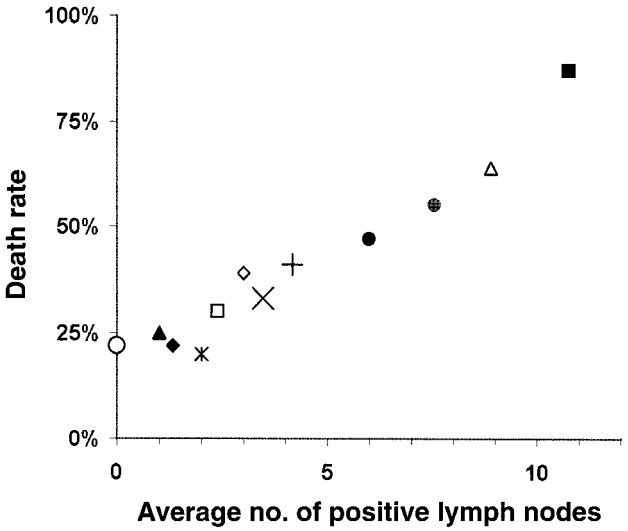

FIGURE 2. Fifteen-year Kaplan–Meier death rates for women in the University of Southern California/Van Nuys Breast Center population with tumors measuring 20–29 mm in diameter. See Table 3 for numeric values. Open circle: no positive lymph nodes; filled triangle: 1 positive lymph node; star: 2 positive lymph nodes; open diamond: 3 positive lymph nodes; filled diamond: 1 or 2 positive lymph nodes; open square: 2 or 3 positive lymph nodes; ×: 3 or 4 positive lymph nodes; +: 1 or more positive lymph nodes; filled circle (black): 2 or more positive lymph nodes; filled circle (gray): 3 or more positive lymph nodes; open triangle: 4 or more positive lymph nodes; filled square: 5 or more positive lymph nodes.

positive lymph nodes had similar death rates compared with lymph node–negative women with tumors of a similar size. It was only as the number of positive lymph nodes increased that additional lethality became evident. In none of the size groups examined did women with 1 positive lymph node have a statistically significantly greater death rate compared with lymph node–negative women with tumors of the same size, and in only 1 size group (women with tumors measuring 10–19 mm) was there a statistically significant increase in lethality (6%) for women with 2 positive lymph nodes (Table 3). Only for women with large numbers of positive lymph nodes was there a dramatic increase in death rates compared with lymph node–negative women with tumors of the same size (Figs. 1–3). For example, women who had 3 or more positive lymph nodes (mean, 7.52 positive lymph nodes) had a greater risk of death by ≈25% compared with lymph node–negative women with tumors of the same size, and women who had 5 or more positive lymph nodes (mean, 10.75 positive lymph nodes) had a greater risk of death by ≈30%. These findings suggest that it is not lymph node positivity itself, but rather the number of positive lymph nodes, that determines the magnitude of the added risk of death.

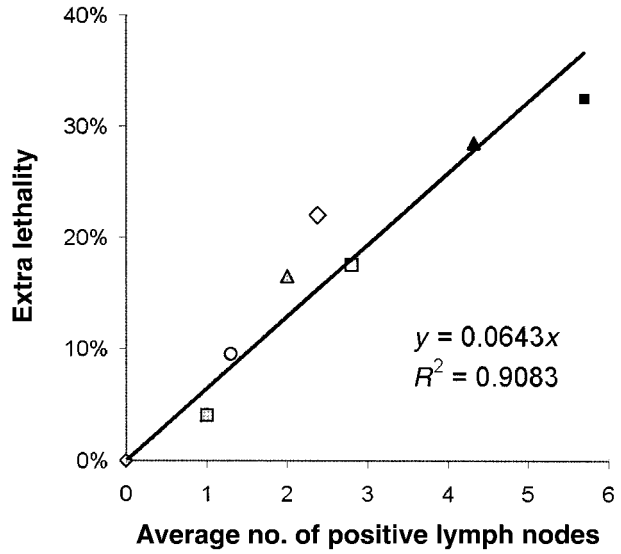

FIGURE 3. Added lethality for women with various numbers of positive lymph nodes compared with lymph node–negative women with tumors of the same size. Data were obtained from a subset of 494 patients in the University of Southern California/Van Nuys Breast Center population who had not received adjuvant chemotherapy. The additional lethality observed among women with a specified number of positive lymph nodes (e.g., 1 positive lymph node, 2 positive lymph nodes, 1 or more positive lymph nodes, etc.), calculated as an average over 2 tumor size categories (10–19 mm and 20–29 mm), was evaluated relative to the risk of death for lymph node–negative women and graphed against the average number of positive lymph nodes. Comparable results also were obtained for the entire study population (Table 3). Filled diamond (gray): no positive lymph nodes; filled square (gray): 1 positive lymph node; filled triangle (gray): 2 positive lymph nodes; open circle: 1 or 2 positive lymph nodes; open diamond: 2 or 3 positive lymph nodes; open square: 1 or more positive lymph nodes; filled triangle (black): 2 or more positive lymph nodes; filled square (black): 3 or more positive lymph nodes.

Each Positive Lymph Node Results in an Additional ≈6% Risk of Breast Carcinoma Death

To characterize the correlation between the number of positive lymph nodes and lethality, the added lethality found among women with a specified number of positive lymph nodes was graphed against the average number of positive lymph nodes per woman within that group. Doing so revealed a linear relation with a slope of ≈6%, which represents the added lethality per positive lymph node (Fig. 3). A similar indication that each positive lymph node contributes a small amount of additional lethality can be seen in the four columns in Table 3 that fall under the heading "Extra lethality per positive lymph node." Thus, the lethality contributed by positive lymph nodes, L_{nodes}, is well captured by the product of the number of positive nodes (M) and a constant (R).

$$L_{nodes} \approx * R \qquad (2)$$

TABLE 3
Fifteen-Year Kaplan—Meier Breast Carcinoma Death Rates and Mean Tumor Sizes for Women in the University of Southern California/Van Nuys Breast Center Population, by Tumor Size and Lymph Node Status

No. of positive LNs	Average no. of positive LNs	*n*				Fifteen yr Kaplan–Meier death rate (%) [P^a]				Extra lethality for LN-positive women[b] (%)				Extra lethality per positive LN (%)			
		1–9 mm	10–19 mm	20–29 mm	30–39 mm	1–9 mm	10–19 mm	20–29 mm	30–39 mm	1–9 mm	10–19 mm	20–29 mm	30–39 mm	1–9 mm	10–19 mm	20–29 mm	30–39 mm
0	0	264	535	273	108	8 [—]	14 [—]	22 [—]	36 [—]	—	—	—	—	—	—	—	—
1	1	16	85	72	31	0 [0.4]	25 [0.08]	23 [0.18]	18 [0.54]	−8	11	1	18	−8	11	1	18
2	2	4	44	32	14	— [—]	20 [0.03]	22 [0.13]	49 [0.13]	—	6	0	13	—	3	0	7
3	3	2	21	23	8	— [—]	41 [0.0001]	39 [0.001]	17 [0.6]	—	27	17	−19	—	9	6	6
4	4	1	8	19	15	— [—]	0 [0.45]	25 [0.36]	75 [0.01]	—	−14	3	39	—	−4	1	10
1 or 2	1.32	20	129	104	45	0 [0.015]	24 [0.015]	22 [0.19]	29 [0.77]	−8	10	0	−7	−6	8	0	−5
2 or 3	2.38	7	65	55	22	0 [0.5]	27 [< 0.0001]	30 [0.003]	41 [0.4]	−8	13	8	5	−3	5	3	2
3 or 4	3.48	7	29	42	23	0 [0.5]	23 [0.002]	33 [0.006]	65 [0.11]	−8	9	11	29	−2	3	3	8
4 or 5	4.35	3	13	30	24	50 [0.009]	0 [0.3]	55 [0.0001]	71 [0.016]	42	−14	33	35	10	−3	8	8
1 or more	4.16	29	186	186	112	40 [0.64]	28 [< 0.0001]	41 [< 0.0001]	58 [0.003]	32	14	19	22	8	3	5	5
2 or more	5.99	14	101	114	81	17 [0.15]	26 [< 0.0001]	47 [< 0.0001]	67 [< 0.0001]	9	12	25	31	2	2	4	5
3 or more	7.52	9	57	82	67	25 [0.036]	30 [< 0.0001]	55 [< 0.0001]	70 [< 0.0001]	17	16	33	34	2	2	4	5
4 or more	8.89	7	36	59	59	34 [0.003]	25 [0.004]	64 [< 0.0001]	76 [< 0.0001]	26	11	42	40	3	1	5	4
5 or more	10.75	6	28	40	44	40 [0.0004]	30 [< 0.0001]	87 [< 0.0001]	74 [< 0.0001]	32	16	65	38	3	1	6	4

LN: lymph node.

[a] For comparison with lymph node–negative women (Cox–Mantel test).

[b] Compared with lymph node–negative women with tumors of the same size.

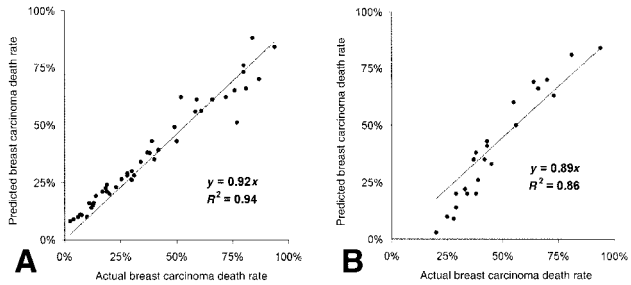

FIGURE 4. Scatter plot of the risk of death estimated from data on tumor size and lymph node status using the *Size+Nodes* method (Eq. 4) versus the actual 15-year Kaplan–Meier death rates for various subgroups of the (A) University of Southern California/Van Nuys Breast Center and (B) Massachusetts General Hospital populations. Subgroups represented in (A) are listed in Table 4. Subgroups represented in (B) are *all malignancies*; *lymph node–negative*; *lymph node–positive*; *1–4 positive lymph nodes*; *5–51 positive lymph nodes*; Stage I disease; Stage II disease; Stage III disease; Stage IV disease; T1 (all); T1a; T1b; T1c; T2; T3/T4; *estimated lethality (Eq. 4), 1–24.99%*; *estimated lethality, 25–49.99%*; *estimated lethality, 50–75.99%*; *estimated lethality, 75–100%*; first quartile according to estimated lethality; second quartile according to estimated lethality; third quartile according to estimated lethality; and fourth quartile according to estimated lethality.

Of course, no woman can die twice due to two separate lethal metastases, and thus, for all women, including those with large numbers of positive lymph nodes, a more accurate estimate of L_{nodes} might be

$$L_{nodes} = 1 - e^{-(M*R)} \quad (3)$$

As can be seen in Table 1, based on the survival data for all lymph node–positive patients, $R = 6.08\%$.

The *Size+Nodes* Method

It follows that the combined effect of the two contributors to lethality will be

$$L_{overall} = L_{primary} + L_{nodes} - (L_{primary} * L_{nodes}) \quad (4)$$

Equation 4 provides a new approach, which we call the *Size+Nodes* method, for estimating the risk of breast carcinoma death. To test the method, calculations were made using Equation 4 for each of the 1233 women with invasive breast carcinoma in the USC/Van Nuys Breast Center population who were observed before 1990 and for each of the 220 women with invasive breast carcinoma who were observed at MGH between 1980 and 1985. The women then were grouped in various ways, and each group's average expected death rate as calculated using Equation 4 was compared with the actual 15-year death rate as estimated by Kaplan–Meier analysis (Fig. 4; Table 4). Of the 46 such comparisons made for the USC/Van Nuys Breast Center population, more than three-fourths (36 of 46) agreed to within 5%, and more than nine-tenths (42 of 46) agreed to within 10%. Of the 23 such comparisons made for the MGH population, almost half (9 of 23) agreed to within 5%, and almost two-thirds (14 of 23) agreed to within 10% (Fig. 4). The largest disagreements tended to occur for comparisons involving the smallest numbers of women.

Cumulative distributions of the risk values calculated using the *Size+Nodes* method (Eq. 4) revealed wide risk distributions in each of 4 populations of women with invasive breast carcinoma, with approximately 10% of women having less than a 10% estimated risk of death and another 10% having greater than a 60% estimated risk of death (Fig. 5). In fact, a small number of women (≈2%) had either less than a 5% estimated risk of death or greater than a 90% risk of death. This predicted variation in the risk of death was borne out by the actual survival data for the groups of women generated by Equation 4 (Fig. 5). Thus, the 82 women in the USC/Van Nuys Breast Center data set who had risk values of 5% or less as calculated by Equation 4 had an actual 15-year breast carcinoma death rate of 8% according to Kaplan–Meier analysis, whereas the 30 women with estimated risk values of 90% or greater had an actual 15-year death rate of 84% (Table 4). It also is noteworthy that the groups with intermediate degrees of lethality that were generated by the *Size+Nodes* method (Eq. 4) exhibited finer gradations in lethality than did the groups generated using the more conventional T classification and disease stage categories[2] (Fig. 6; Table 4).

The groupings generated by the *Size+Nodes* method (Eq. 4; Figs. 4, 5) were constructed with the aim of avoiding overlapping levels of lethality; this goal appeared not to be met for groups generated according to lymph node postivity, T classification, or disease stage[2] (Fig. 7). For example, among women with a 75% risk of death as calculated using Equation 4, there were both lymph node–negative and lymph node–positive patients; patients with T1a, T1b, T1c, T2, and T3 lesions; and patients with Stage IIA, Stage IIIA, and Stage IIIC disease (Fig. 8). Conversely, within the categories generated using conventional methods, there was great variation in terms of the risk of death as estimated using Equation 4 (Fig. 7B–D). Thus, the lymph node–negative group contained women with calculated risks of death ranging from 0.4% to 97%, whereas the lymph node–positive category contained women with calculated risks of death ranging from 8% to 99% (Fig. 7D). These wide and overlapping levels of lethality as predicted by Equation 4 were borne out by actual survival data (Fig. 7). For example, although lymph node–negative patients fared better as a group than did lymph node–positive patients (15-year

TABLE 4
Estimated Risk of Death Generated by the *Size + Nodes* Method Compared with the Actual (Kaplan–Meier) Death Rate for Various Groups of Women Seen before 1990 at the University of Southern California/Van Nuys Breast Center

Group	Estimated risk of death (Eq. 4) (%)	Actual 15 yr Kaplan–Meier death rate (%)	No. of women
All patients	30	30	1233
LN-negative	20	20	443
LN-positive	49	49	790
1 positive LN	30		130
2 or 3 positive LNs	40	35	117
4–7 positive LNs	52	62	97
8–36 positive LNs	80	76	99
Stage I	11	16	526
Stage IIA	28		348
Stage IIB	50	43	128
Stage IIIA	59	61	149
Stage IIIC	84	88	81
T1a	4	9	69
T1b	10		190
T1c	19	21	434
T2	39	43	398
T3	77	51	106
T4	80	73	36
Estimated lethalities between 1% and 24.99%	13	16	629
Estimated lethalities between 25% and 49.99%	34	34	366
Estimated lethalities between 50% and 75.99%	61	56	131
Estimated lethalities between 75% and 100%	87	70	107
Estimated lethalities between 1% and 4.99%	3	8	82
Estimated lethalities between 5% and 9.99%	8	11	153
Estimated lethalities between 10% and 14.99%	13	15	167
Estimated lethalities between 15% and 19.99%	18	23	168
Estimated lethalities between 20% and 29.99%	25		186
Estimated lethalities between 30% and 49.99%	38	38	182
Estimated lethalities between 50% and 69.99%	58	56	112
Estimated lethalities between 70% and 89.99%	81	66	153
Estimated lethalities between 90% and 100%	94	84	30
First quartile, by estimated lethality	7		308
Second quartile, by estimated lethality	17	21	308
Third quartile, by estimated lethality	31	28	308
Fourth quartile, by estimated lethality	66	61	309
First quintile, by estimated lethality	6	10	245
Second quintile, by estimated lethality	14		245
Third quintile, by estimated lethality	23	23	245
Fourth quintile, by estimated lethality	37	38	245
Fifth quintile, by estimated lethality	72	62	253
First hexile, by estimated lethality	6	10	205
Second hexile, by estimated lethality	12		205
Third hexile, by estimated lethality	19	24	205
Fourth hexile, by estimated lethality	28	29	205
Fifth hexile, by estimated lethality	42	39	205
Sixth hexile, by estimated lethality	76	65	208

LN: lymph node.

Kaplan–Meier death rate, 21% vs. 44%), the 75 lymph node–negative patients with the greatest estimated risk of death according to Equation 4 had a worse actual Kaplan–Meier outcome (death rate, 32%) than did the 75 lymph node–positive women with the lowest estimated risk of breast carcinoma death (death rate, 21%; $P = 0.002$). Similarly, although women with T2 lesions had lower estimated and actual death rates as a group compared with women with T3 lesions, the 15 women with T2 lesions who had the greatest risk of

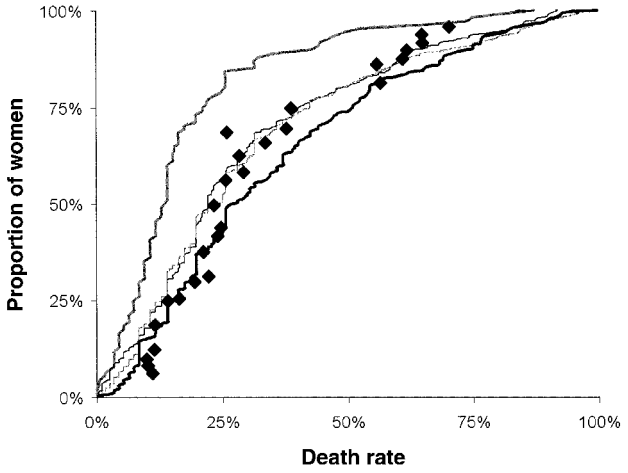

FIGURE 5. Cumulative distributions of the estimated risk of death using the *Size+Nodes* method (Eq. 4) for four different populations of women with invasive breast carcinoma. Diamonds indicate actual 15-year Kaplan–Meier death rates for various subgroups of the University of Southern California (USC)/Van Nuys Breast Center population generated by the *Size+Nodes* method. Represented subgroups are listed in Table 4. Gray line: Lahey Clinic, 1997–2000; thin black line: Massachusetts General Hospital (MGH), 1990–2000; dashed line: USC/Van Nuys Breast Center, ≈1970–1990; thick black line: MGH, 1980–1985.

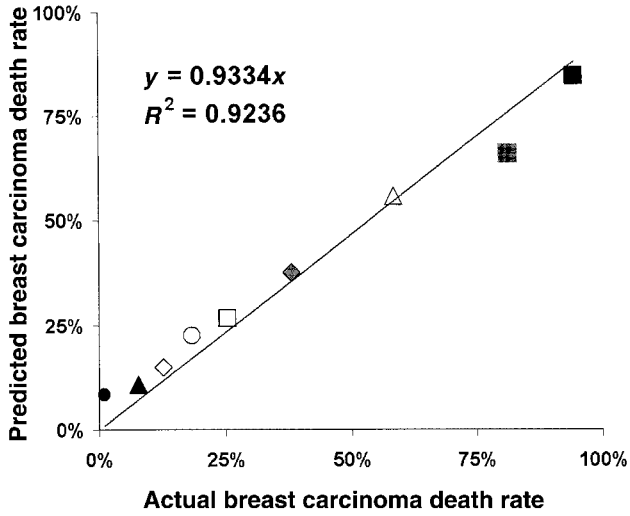

FIGURE 6. Scatter plot of the risk of death estimated from data on tumor size and lymph node status using the *Size+Nodes* method (Eq. 4) versus the actual 15-year Kaplan–Meier death rates for 9 subgroups, all stratified based on the risk of death calculated using the *Size+Nodes* method. See Table 4 for numeric values. Filled circle: 1—4.99%; filled triangle: 5—9.99%; open diamond: 10—14.99%; open circle: 15—19.99%; open square: 20—29.99%; filled diamond: 30—49.99%; open triangle: 50—69.99%; filled square (gray) with cross: 70—89.99%; filled square (black): 90—100%.

death as determined by Equation 4 fared far worse (15-year Kaplan–Meier death rate, 90%) than did the 15 women with T3 lesions who had the lowest risk of death according to Equation 4 (15-year Kaplan–Meier death rate, 33%; $P = 0.0006$). In fact, the 75 women with T2 lesions who had the greatest estimated risk of death fared markedly worse (15-year Kaplan–Meier death rate, 73%) than did the 75 women with T3 lesions who had the smallest estimated risk of death (15-year Kaplan–Meier death rate, 38%; $P = 0.002$) (Fig. 7C). Similar overlap also was evident among groups generated according to disease stage 2 (Fig. 7D), although this overlap had a lower level of statistical significance. As a group, women with Stage IIB disease had lower estimated and actual death rates than did women with Stage IIIA disease (Table 4); however, the 10 women with Stage IIB disease who had the greatest risk of death according to Equation 4 actually had a far worse outcome (15-year Kaplan–Meier death rate, 80%) compared with the 10 women with Stage IIIA disease who had the smallest risk of death according to Equation 4 (15-year Kaplan–Meier death rate, 20%; $P = 0.08$).

In contrast to the groups generated according to lymph node postivity, T classification, or disease stage[2] (Fig. 7B–D), the groups generated using the *Size+Nodes* method (Eq. 4; Fig. 7A) showed little indication of overlap in terms of death rates, as is evident from the quartile data that resulted from the division of the USC/Van Nuys Breast Center population into 4 groups containing roughly equivalent numbers (~300) of women (Table 4). Not once did the 20 women with the most-lethal phenotypes (as determined by tumor size, number of positive lymph nodes, or disease stage)[2] in any quartile have a significantly worse Kaplan–Meier outcome compared with the 20 women in the next highest quartile who had the least lethal phenotypes (data not shown).

DISCUSSION

The data presented in the current study reveal that both tumor size and the number of positive lymph nodes make independent contributions to the lethality of invasive breast carcinoma. The data also reveal that it is not simply the presence of malignant disease in the lymph nodes that determines lethality, as women with only one or two positive lymph nodes had survival rates that were very similar to those observed among lymph node–negative women with tumors of a similar size. Only as the number of positive lymph nodes increased did the added lethality ascribable to each positive lymph node become apparent.

It was possible to place these findings into quantitative terms. For women with equivalent lymph node status, tumor size was associated with increased lethality, and this association was described by a simple

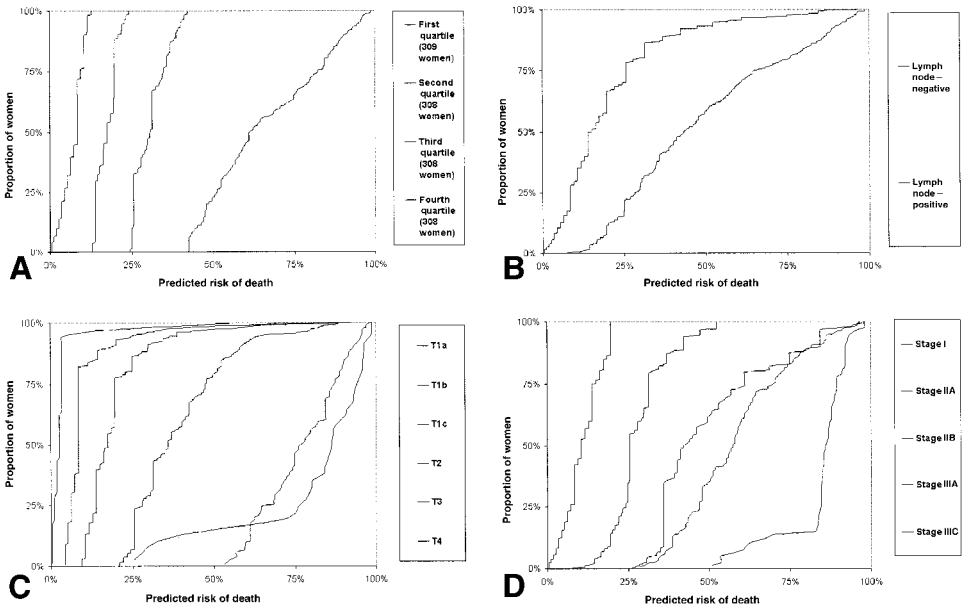

FIGURE 7. Cumulative distributions of the estimated risk of death (Eq. 4) for subgroups of women in the University of Southern California/Van Nuys Breast Center population who were observed before 1990. Subgroups were constructed according to (A) quartiles based on estimated risk of death, (B) lymph node positivity, (C) T classification, and (D) disease stage. The order of the labels in the symbol key (from top to bottom) corresponds to the order of the cumulative distributions (from smallest to greatest estimated risk of death).

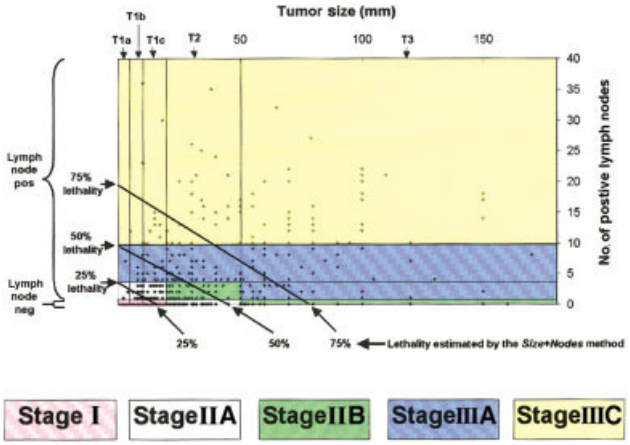

FIGURE 8. Scatter plot of tumor size versus number of positive lymph nodes for women with invasive breast carcinoma in the University of Southern California/Van Nuys Breast Center population, with boundaries (25%, 50%, and 75%) between regions of differing risk of breast carcinoma death as estimated using Equation 4. Also shown are regions containing women classified by lymph node status, T status, and disease stage. The Stage IIIB group, which is not shown, corresponds to all patients except those with N3 disease (10 or more positive lymph nodes) and direct extension to the chest wall or skin. Note that some data points represent multiple women with tumors of the same size and the same number of positive lymph nodes. Boundary lines based on Equation 4 are approximate and exhibit a small amount of curvature when examined on a finer scale than can be seen in the figure. Pos: positive; Neg: negative.

expression, Equation 1. For women with tumors of the same size, each positive lymph node appeared to contribute approximately an additional 6% to the risk of death (Eq. 3). These equations are driven by three parameters, *Q*, *Z*, and *R*, whose values were determined based on data from the USC/Van Nuys Breast Center population regarding tumor size, lymph node status, and survival. The overall lethality was found to equal the sum of the contributions from tumor size and the number of positive lymph nodes (Eq. 4); this finding led to a new technique (the *Size+Nodes* method) for estimating the risk of death using information on tumor size and lymph node status. The validity of the *Size+Nodes* method was confirmed by the analysis of two separate populations (MGH and USC/Van Nuys Breast Center) of women with invasive breast carcinoma. Thus, although the values of *Q*, *Z*, and *R*, which drive the *Size+Nodes* equation, were estimated using data from the USC/Van Nuys Breast Center population, their validity was confirmed by their ability to predict survival accurately in the MGH population.

The finding that tumor size and lymph node status are associated with lethality agrees with the findings of many previous studies.[2–8] In addition, our findings on the independent lethal contributions of the primary site and of the lymph nodes agree with the findings of Carter et al.[5] and Fisher et al.[6] Furthermore, the magnitude of the relation between tumor size and survival in lymph node–negative patients in the USC/Van Nuys Breast Center population roughly agrees with the result of a similar measurement made by Rosen et al.[7] and with the findings of Quiet et al.,[8] who also observed an increase in lethality as the number of positive lymph nodes increased. The large number of patients in the USC/Van Nuys Breast Center population, together with the long follow-up time in the current data set, permitted the fine level of sorting

by size and lymph node status that was required to isolate the magnitudes of the independent contributions of tumor size and lymph node status to breast carcinoma lethality.

Over much of its domain, Equation 1 is roughly linear, such that each millimeter increase in tumor diameter is associated with approximately a 1% increase in lethality (Fig. 1). Furthermore, as noted above, each positive lymph node is associated with approximately an additional 6% risk of death. These findings allow a rough estimate of the *Size+Nodes* calculation to be made using simple multiplication and addition. Thus, a woman with a 21 mm tumor and 2 positive lymph nodes is estimated to possess an approximately 33% ($21 \times 1\% + 2 \times 6\%$) risk of death. (The more exact estimate [Eq. 4] is 31%.) This rough approximation, which breaks down for the ≈20% of women with tumors larger than 50 mm or more than 3 positive lymph nodes, provides a convenient mnemonic for the *Size+Nodes* method.

Although the *Size+Nodes* method requires data on only tumor size and the number of positive lymph nodes, the general method has the potential to extend beyond the calculations described in the current report and make estimates that are even more accurate using information on other prognostic factors, such as patient age, genotype, family history, occurrence of previous malignancy, tumor histologic subtype, and tumor markers (e.g., *p53*, HER-2, estrogen/progesterone receptors, gene array signatures, etc.[11–15]). This type of refinement to the *Size+Nodes* method should be accomplishable by estimating the *Size+Nodes* parameters *Q*, *Z*, and *R* for subgroups of women with such prognostic factors and then using Equation 4 to calculate survival rates for these subgroups. For example, by estimating the values of *Q*, *Z*, and *R* in a population of women treated before the use of chemotherapy was commonplace,[6,7] it should be possible to estimate the intrinsic lethality associated with tumor size and lymph node status; any subsequent reduction in lethality for women receiving chemotherapy could be expected to reflect the impact of the treatment. In this way, the *Size+Nodes* method provides an approach for measuring the impact of chemotherapy even in populations not involved in randomized trials. The same general approach should be applicable to other prognostic features, such as extension of the tumor to the chest wall and local recurrence.

Of course, the accuracy of a survival estimate based on tumor size and the number of positive lymph nodes will depend on the accuracy with which these features are measured. Abner et al.[16] demonstrated that considerable improvement in the estimation of the size of primary breast lesions can result from careful measurement on the microscope slide. Inaccuracy in determining the number of positive lymph nodes can result from incomplete sampling. Another area of uncertainty concerns whether all positive lymph nodes make the same lethal contribution.[17] We recently used digital microscopy to analyze the sizes of metastatic deposits in a series of 49 positive lymph nodes and found that they ranged from 0.3 mm to 15 mm in diameter (unpublished data, 2003). Whether all such positive lymph nodes, or lymph nodes with only micrometastases,[17] make equivalent lethal contributions remains to be investigated further. In this regard, it is noteworthy that the mean size of the metastatic deposits that we have examined in lymph nodes is 5.95 mm (unpublished data, 2003). The data outlined in the current report indicate that the lethal contribution from a positive lymph node (≈6%) is roughly equal to the lethal contribution from a primary mass in the breast when the mass measures 6 mm in diameter (Eq. 1); this finding raises the question of whether the presence of malignant disease in the lymph nodes leads to extra lethality because of the additional tumor bulk located there rather than because of an intrinsic biologic change in the nature of the malignancy signaled by lymph node invasion.

The *Size+Nodes* method, described by Equation 4, offers the potential to add an extra level of precision and flexibility to the current TNM staging system. For example, whereas sorting women by lymph node positivity, disease stage,[2] or T classification leads to groups of patients with broad, overlapping levels of risk of death, sorting these patients according to the survival predictions made using Equation 4 generates groups that do not possess such overlap. Furthermore, Equation 4 allows the creation of groups with boundaries defined by any desired level of lethality or even the individual assessment of patients. Thus, the *Size+Nodes* method offers the potential to provide more accurate estimates of breast cancer prognosis, in quantitative terms, which can allow the risks of various interventions to be weighed against the benefits that might be achieved.

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