

Predicting the Survival of Patients with Breast Carcinoma using Tumor Size

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Received September 5, 2001; revision received February 15, 2002; accepted April 1, 2002.

BACKGROUND. Tumor size has long been recognized as the strongest predictor of the outcome of patients with invasive breast carcinoma, although it has not been settled whether the correlation between tumor size and the chance of death is independent of the method of detection, nor is it clear how tumor size at the time of treatment may be translated into a specific expectation of survival. In this report, the authors provide such a method.

METHODS. A Kaplan–Meier survival analysis was carried out for a population of 1352 women with invasive breast carcinoma who were treated at the Van Nuys Breast Center between 1966 and 1990, and the data were analyzed together with survival data published by others.

RESULTS. The authors found that the survival of patients with invasive breast carcinoma was a direct function of tumor size, independent of the method of detection. The results showed that the correlation between tumor size and survival was well fit by a simple equation, with which survival predictions could be made from information on tumor size. For example, a comparison of three large populations studied over the last 5 decades revealed a marked improvement ($\approx 35\%$ absolute) in the survival of patients with invasive breast carcinoma diagnosed on clinical grounds that could be ascribed to a reduction in tumor size. However, the capacity of screening mammography to find smaller tumors remains the best way reduce breast carcinoma deaths, with the potential for adding an additional $\approx 20\%$ absolute reduction in breast carcinoma deaths. The mathematic correlation between tumor size and survival is consistent with a biologic mechanism in which lethal distant metastasis occurs by discrete events of spread such that, for every invasive breast carcinoma cell in the primary tumor at the time of surgery, there is approximately a 1-in-1-billion chance that a lethal distant metastasis has formed.

CONCLUSIONS. The correlation between tumor size and lethality is well captured by a simple equation that is consistent with breast carcinoma death as the result of discrete events of cellular spread occurring with small but definable probabilities.

Cancer 2002;95:713–23. © 2002 American Cancer Society.

DOI 10.1002/cncr.10742

KEYWORDS: breast carcinoma, tumor size, metastasis, survival, mammography.

Tumor size has been recognized as the strongest predictor of outcome for patients with invasive breast carcinoma,¹⁻⁷ although it has not been settled whether the correlation between tumor size and chance of death is independent of the method of detection,⁸⁻¹⁰ nor has it been clear how tumor size at the time of treatment may be translated into a specific expectation of survival. This article provides such a method in a simple equation for relating tumor size to survival with breast carcinoma, together with a plausible cellular mechanism of breast carcinoma death that can account for the form of that equation.

TABLE 1
Breast Carcinoma Survival by Tumor Size

| Tumor size (mm) | Median size (mm) | Fraction of surviving patients (%) ^a | | |
|-----------------|------------------|---|--------------------------|------------------------------------|
| | | Van Nuys (~ 1980–1990) | Tabar et al. (1977–1985) | Tubiana and colleagues (1954–1972) |
| 10–14 | 12 | 86 (248 patients) | 87 | — |
| 15–19 | 17 | 72 (222 patients) | 80 | — |
| 20–29 | 25 | 67 (318 patients) | 55 | — |
| 30–49 | 39 | 46 (222 patients) | 44 | — |
| 10–25 | 17 | 75 (757 patients) | — | 73 |
| 26–35 | 30 | 53 (175 patients) | — | 58 |
| 36–45 | 40 | — | — | 44 |
| 46–55 | 50 | — | — | 34 |
| 56–65 | 60 | — | — | 22 |
| 66–75 | 70 | — | — | 17 |
| 76–85 | 80 | — | — | 19 |
| 86–95 | 90 | — | — | 8 |

^a The 15-year survival rates for the Van Nuys data are shown (see Fig. 1). The Van Nuys data shown here are arranged into tumor size groups that were chosen to match those used by Tabar et al.^{1–3} and Tubiana and colleagues,^{4–7} as described in the text (see Materials and Methods). The values from Tabar et al.^{1–3} are for survival at 13.3 years, and the values from Tubiana and colleagues^{4–7} are for distant metastatic disease at 25 years; it was assumed that this was equivalent to survival (for further details, see Materials and Methods). There were not enough tumors measuring > 35 mm in the Van Nuys population to provide comparisons with the larger size groups studied by Tubiana and colleagues.^{4–7} Tumors in the Van Nuys populations measuring < 10 mm and > 49 mm are not shown here.

MATERIALS AND METHODS

Data on Tumor Size and Survival

Data on the correlation between tumor size and survival from the Van Nuys population^{11,12} are presented here for the first time and are shown in Table 1 and in Figures 1 and 2 together with comparable data from Tabar and colleagues^{1–3} and Tubiana and colleagues.^{4–7} The survival data for these three populations were obtained using slightly different methods. The Van Nuys data were obtained from 1352 patients with invasive breast carcinoma (patients with ductal carcinoma in situ were excluded from the analysis) who had tumors that were found between 1966 and December 31, 1990, with 95% of tumors found from 1980 to 1990. The Kaplan–Meier method was used to conduct a survival analysis, which was executed using Winstat software (A-Prompt Corporation). The data for the Van Nuys population shown in Table 1 are from the Kaplan–Meier survival analysis at 15 years. The decision to analyze the survival of patients with breast carcinoma in the Van Nuys data set who had tumors that were found before 1991 was made so that these values would be comparable to survival estimates made by Tabar and colleagues and Tubiana and colleagues, although similar survival calculations that included all tumors in the Van Nuys data set (up to the year 2000; results not shown) yielded essentially the

same results as the calculations that included tumors that were found before 1991. The data from Tabar et al. shown in Table 1 and Figure 2 are survival values at 160 months² (13.33 years) for patients with invasive breast carcinoma who had tumors that were found from 1977 to 1985 and were analyzed in December, 1990. The data from Tubiana and colleagues shown in Table 1 and Figure 2 are for patients with breast carcinoma who had tumors that were found from 1954 to 1972: The precise time of these calculations was not given; however, this work was submitted in December, 1983, and we assume the calculations were made in the previous year. The values from Tubiana and colleagues are from the Kaplan–Meier survival analysis at 20 years for the appearance of distant metastatic disease, which we assume closely reflects ultimate mortality. Karrison and colleagues,¹³ in their 1999 analysis of 1547 patients with breast carcinoma who underwent surgery between 1945 and 1987, found that most deaths from breast carcinoma occurred within 10 years of surgery; only 12% of deaths occurred after 13 years, at which time, the hazard rate had declined \approx 7-fold. Thus, it is not unreasonable to compare the 15-year survival rates of the women in the Van Nuys population^{11,12} with the 13.33-year survival rates reported by Tabar and colleagues^{1–3} and the 25-year recurrence rates reported by Tubiana and colleagues,^{4–7} as shown in Table 1.

Note that the data from Tubiana and colleagues are largely from the premammography era (1954–1972), whereas half of the women in the population studied by Tabar and colleagues were offered mammography as part of the Two-County Trial of Breast Cancer Screening (1977–1985). Among 1352 women with invasive breast carcinoma in the Van Nuys population who had tumors that were found before 1991, 1132 tumors were palpable, 216 tumors were nonpalpable (i.e., detected with mammography), and 4 tumors were unspecified in the data base. Data on the size of all 1352 invasive breast tumors that were found before 1991 in the Van Nuys population also were from measurements made at the time of pathologic analysis.

Tumor size data also were available on 182 women with invasive breast carcinoma who were seen at the Lahey Clinic from 1997 to 2000.^{14,15} Data on the sizes of the invasive breast tumors that were seen in earlier decades were derived from information provided by Tabar et al.^{1–3} and Tubiana and colleagues.^{4–7} In those reports, tumors were lumped into groups by size; thus, the inferences made from these data, by necessity, are less precise than inferences that we could make from the Van Nuys data sets.^{11,12} However, the general trends from these data were clear.

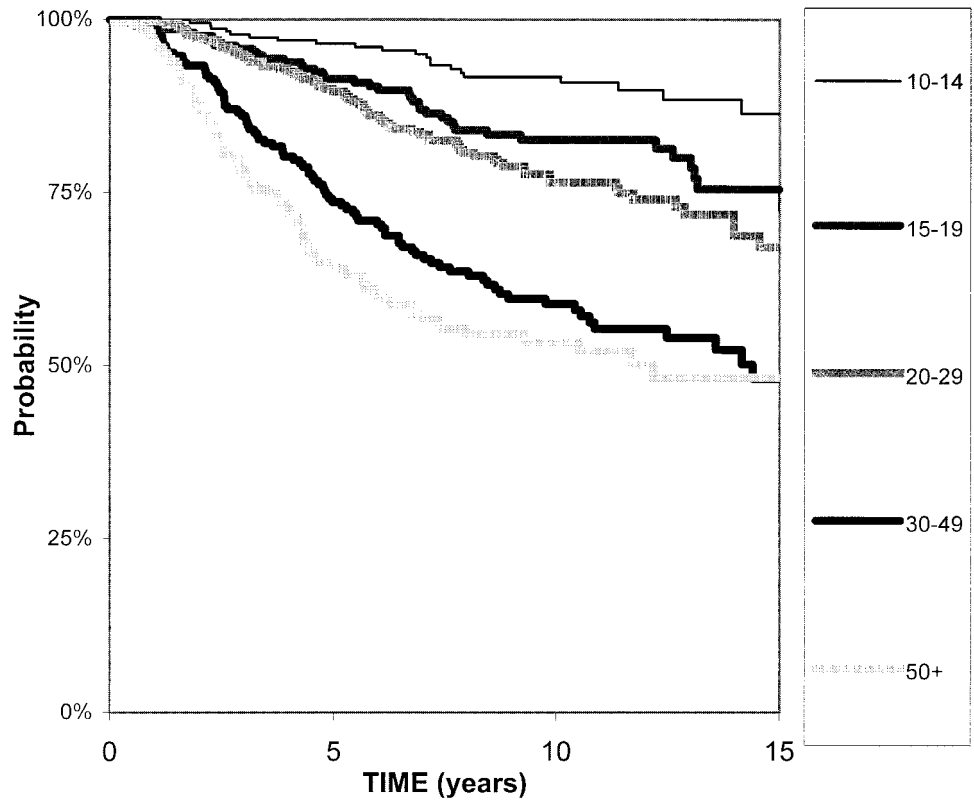


FIGURE 1. Kaplan–Meier survival curves for women who were diagnosed with breast carcinoma before 1991 in the Van Nuys populations by size (in mm). Units of time in are shown in years.

Method for Predicting the Survival of Patients with Invasive Breast Carcinoma from Information on Tumor Size

It long has been appreciated that the larger the tumor size, the greater the chance of dying from breast carcinoma. Here, we have fit the correlation between tumor size (in mm), in terms of the *greatest tumor dimension (D)*, and the *fraction of women surviving breast carcinoma (F)*, as estimated at ≈ 15 years post-treatment, to the expression

$$F = e^{-QD^Z} \tag{1}$$

where *Q* and *Z* are constants (*Z* is dimensionless, and *Q* has units of mm^{-Z}). The form of this expression arose from the model shown below for the probability of metastasis in individual tumor cells (see Eqs. 4–16 below), although its practical advantage arises solely from its simple form and close fit to the data (for example, see Fig. 2, right).

Excel spreadsheet software (Microsoft Corporation, Redmond, WA) does not have the capacity to fit data to this function easily, although it will fit data points to a power function if the values are positive, thus transforming Equation 1,

$$-\ln(F) = QD^Z \tag{2}$$

provides a way to estimate the values of *Q* and *Z* (for example, see Fig. 2, left). We called *F_W* the fraction (*F*) of surviving patients among *W* women with invasive breast carcinoma. It follows from Equation 1 that the average survival among such a group of women will be

$$F_w = (1/W) \sum_{i=1}^W e^{-QD_i^Z}, \tag{3}$$

where *D_i* is the greatest tumor dimension in Patient *i*. The actual calculation of the value of *F_W* was carried out using Excel spreadsheet software.

Modeling Survival in Terms of the Probability of Lethal Metastatic Spread per Cell and per Cell-Day

Let us say that tumors are made of *N* components. *N* can be thought of in units of *tumor volume* or in units of *cell number*. Let *p* represent the probability of a single event of lethal spread prior to surgery for each of the *N* cells, as we proposed previously.^{16,17} This definition of *p* does not consider events of distant spread that do not lead to death or nonlethal events of spread to the local lymph nodes. It also does not assume that *p* is constant, and the data will show that it decreases in a predictable fashion with *N*. The probability that any given cell does not produce a distant

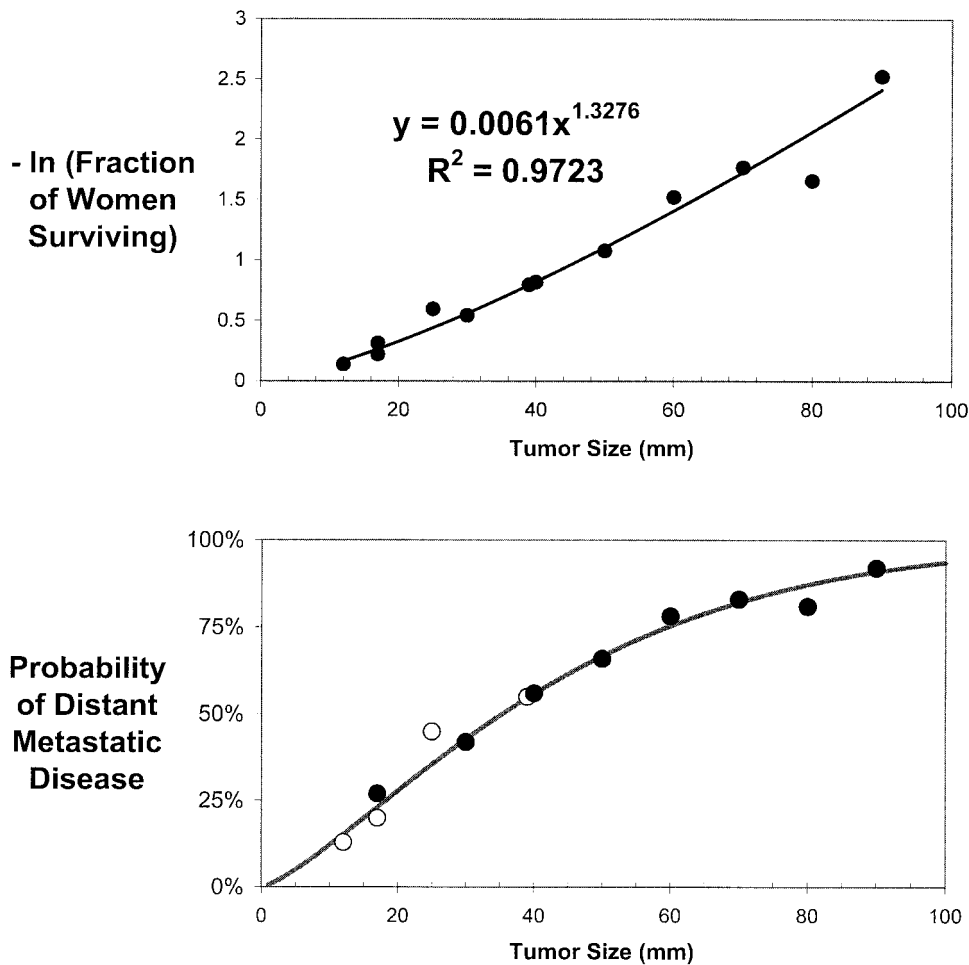


FIGURE 2. (Top) Best-fit form of Equation 2 [$-\ln(F) = Q(D)^2$] showing the correlation between survival (F) and greatest tumor dimension (D). Data points are from Tabar et al.¹⁻³ and Tubiana and colleagues⁴⁻⁷ (other estimates are shown in Table 2). (Bottom) The correlation between tumor size and the probability of surviving breast carcinoma, as reflected in Equation 1, using the values derived from the top graph ($F = e^{-0.0061D^{1.3267}}$; solid line). Open circles indicate data from Tabar et al.,¹⁻³ and solid circles indicate data from Tubiana and colleagues.⁴⁻⁷ R^2 : correlation coefficient.

lethal metastasis before surgery is then $(1 - p)$. Assuming that tumor cells metastasize independently, the overall probability that a tumor of N cells has not given rise to one or more such lethal metastases will then be $(1 - p)^N$. For a population of women who all have tumors of identical size with N cells, the expected (i.e., average) fraction (F) of women who have not had an event of lethal spread is just this probability, i.e.,

$$F = (1 - p)^N \tag{4}$$

It can be shown that, for small values of p , this can be approximated very well by

$$F = e^{-Np} \tag{5}$$

or

$$p = -\ln(F)/N \tag{6}$$

This provides a way to estimate the value of p from information on the survival of women with tumors of various sizes. Of course, tumor size is not generally available in terms of cell number (N) but, rather, in

terms of greatest tumor dimension (D). However, values of D are converted easily into values of cell numbers (N) by assuming a density of s (in cells per mm^3):

$$N = sV \tag{7}$$

and spherical geometry, i.e.,

$$V = \frac{4}{3} \pi \left(\frac{D}{2}\right)^3 \tag{8}$$

Using this approach, it is apparent from the data discussed below on the survival of patients with invasive breast carcinoma that the value of p declines gradually with increasing tumor size and, indeed, can be fit closely by a power function (see Fig. 3). That is,

$$p = aN^b, \tag{9}$$

where a can be thought of as the chance that very first cell in the tumor will spread (i.e., when $N = 1$), whereas b is a reflection of how much that value changes as the tumor grows larger. In the equations

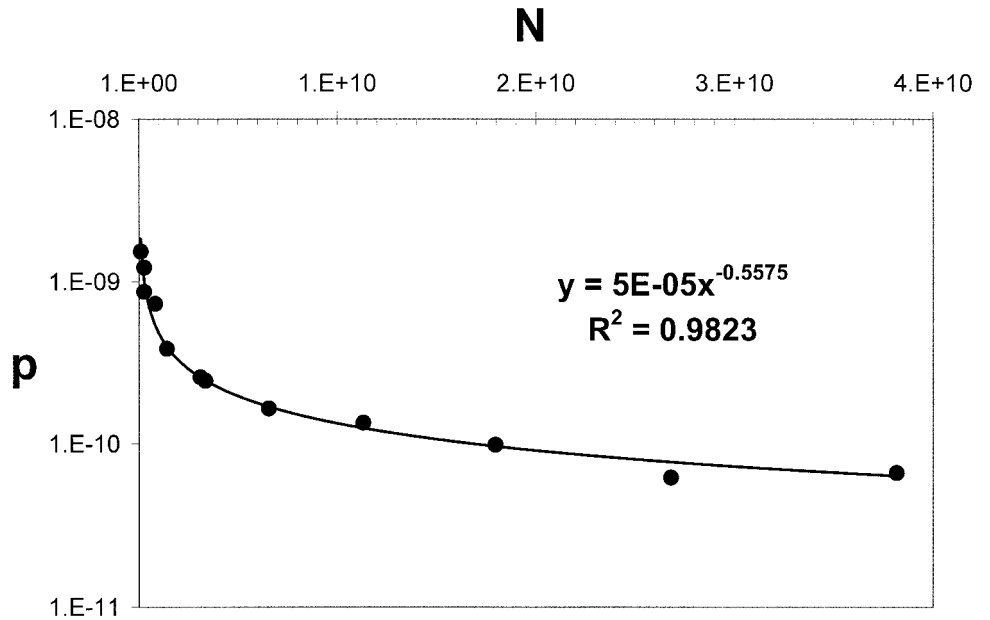


FIGURE 3. Estimation of the probability (p) of distant lethal spread per cell in the primary tumor as a function of cell number at the time of surgery using Equation 5 [$p = -\ln(F/N)$], where N is the cell number, assuming spherical geometry; cell density $s = 10^8$ cells per cc; and F is the fraction of patients who survived breast carcinoma. R^2 : correlation coefficient. The data points are from Tabar and colleagues¹⁻³ and Tubiana and colleagues.⁴⁻⁷

below, b takes on a negative value, indicating that the value of p declines as tumors grow larger (Fig. 3). The constant b is dimensionless, and the constant a has units of cell^($b = 1$).

Note that combining Equation 9 with Equation 5 (together with Eqs. 7 and 8 to convert from units of cell number into units of greatest tumor dimension) leads to Equation 1, in which

$$a = (Z/3) - 1 \tag{10}$$

and

$$b = Q/[(\pi/6)s]^{2/3}, \tag{11}$$

thus revealing that Equations 1 and 3 are consistent with a mechanism of death from breast carcinoma caused by distant lethal metastasis occurring as a discrete event of cellular spread. However the practical application of Equation 1 in this report for predicting survival in patients with breast carcinoma is strictly empiric: It remains valid even if the actual mechanism of death from breast carcinoma is other than that suggested by this model.

Tumors grow over time. Let us define C as the number of cells present for the number of days that a tumor has accumulated from any point in time, that is, the number of *cell-days* a tumor has accumulated. Because there is abundant evidence that, over the range of sizes for which most tumors are seen ($\approx 1-2$ cm), the growth of invasive breast carcinoma is exponential,¹⁷⁻¹⁹ the correlation between the number of cells in a tumor (N) and time (t) can be expressed as follows:

$$N = N_0 e^{rt} \tag{12}$$

where N_0 is the number of cells at time $t = 0$, e is the exponential constant, t is time, and r is a constant, such that

$$r = \ln(2)/t_D, \tag{13}$$

where t_D is the tumor doubling time. It follows that C will equal the integral of Equation 1, evaluated from $t = 0$ (where $N = N_0$) to $t = (\ln N)/r$:

$$C = \int e^{rt} dt = (N - N_0)/r \approx N/r \quad \text{if } N_0 \ll N. \tag{14}$$

It has been noted often that, although the growth of breast carcinoma is approximately exponential over the range that it is evident clinically ($\approx 1-2$ cm), it may display faster growth when the tumors are smaller, a growth pattern often called Gompertzian, reflecting one type of equation that captures such growth.¹⁷⁻¹⁹ However, as shown in Equation 14, as long as exponential growth occurs between values N_0 and N , $N_0 \ll N$, and $F \approx 1$ at $N = N_0$, all three conditions of which are fulfilled for breast carcinoma for $N_0 \approx 5 \times 10^4$, which roughly corresponds to a tumor that measures 1 mm, then such Gompertzian growth will not affect the values of C materially.

We also may want to estimate the probability of spread in terms of C . In analogy to the treatment used above, let us define p' as the probability of a single event of lethal spread per C cell-days, such that

$$F = (1 - p')^C. \tag{15}$$

Together with Equation 14 and with a treatment analogous to that used for Equations 4–6, it follows that

$$p = rp. \tag{16}$$

Note that it is simply a matter of preference whether we wish to estimate the probability of spread in terms of p per cell (N), or in terms of p' per cell-day (C). However, these two values probably are relevant to two different types of biologic mechanisms of tumor spread. Biologic mechanisms that occur once per cell, such as mutational events that occur at cell division,²⁰ should be expected to occur with a probability, such as p , that is calculated in terms of N, the number of cells in the tumor at the time of surgery. Conversely, biologic mechanisms of a more mechanical nature, such as cell detachment, re-engraftment, evasion of immune attack, or successful angiogenesis,^{21–24} may occur at any time and should be expected to occur with a probability such as p' , which is calculated in terms of the number of cell-days (C) that a tumor of N cells has accumulated. Note, however, that whether the mechanism of spread occurs by events that can occur once per cell (p) or continuously (i.e., per cell per day; p'), both lead to Equation 1 (with the values of a and b shown in Eqs. 10 and 11), which, as shown below, provides a remarkably good capture of the correlation between tumor size and survival. This reveals that the actual survival data are equally compatible with biologic mechanisms that would occur once per cell (p) or continuously in time (p').

RESULTS

Kaplan–Meier survival curves for women in the Van Nuys population^{11,12} revealed that, as shown in many previous reports,^{1–7,25–31} survival decreases as tumors become larger (Fig. 1, Table 1). The 15-year survival values from the Van Nuys population, together with comparable estimates from the populations reported by Tabar et al.,^{1–3} and Tubiana and colleagues,^{4–7} are shown in Table 1. Table 2 shows that the correlation between tumor size (D) in mm and survival (F) found in those studies (Table 1) is well described by Equation 1:

$$F = e^{-QD^Z}, \tag{1}$$

where Q and Z are constants with values that can be determined from survival data using Equation 2. Note that the correlation coefficient (R^2) values are high (see Table 2, Fig. 2). This indicates that Equation 1 provides a good description of the correlation be-

TABLE 2
Best-Fit Coefficients for Equation 2: The Correlation between Survival and Greatest Tumor Dimension^a

| Data source | Q | Z | R ² | No. of data points |
|---|---------------------------|---------------------------|----------------|--------------------|
| Tabar et al. and Tubiana and colleagues | Q _{TT} = 0.0061 | Z _{TT} = 1.3276 | 0.97 | 11 |
| Van Nuys data | Q _V = 0.0067 | Z _V = 1.2980 | 0.95 | 4 |
| Tabar et al., Tubiana and colleagues, and Van Nuys data | Q _{TTV} = 0.0062 | Z _{TTV} = 1.3243 | 0.97 | 15 |

R²: correlation coefficient; Q_{TT}, Z_{TT}: taken from the data sets of Tabar et al.^{1–3} and Tubiana and colleagues^{4–7}; Q_V, Z_V: taken from the Van Nuys data set^{11,12}; Q_{TTV}, Z_{TTV}: taken from the data sets of Tabar et al.,^{1–3} Tubiana and colleagues,^{4–7} and the Van Nuys data set.^{11,12}

^a In Equation 2 (see text), Z is a dimensionless constant, and Q is a constant with units of mm^{-Z} (see Fig. 2, left).

tween invasive breast carcinoma tumor size and survival in patients with breast carcinoma.

Equation 1 can be used to predict the survival (F) of groups of women with tumors of the same size (D), whereas the overall survival (F_w) of a group of women (W) with tumors of various sizes is given by

$$F_w = (1/W) \sum_{i=1}^W e^{-QD_i^Z}, \tag{3}$$

where D_i is the greatest tumor dimension in Patient i . Survival predictions made with Equation 3 using the estimates of Q and Z from the data sets of Tabar et al.^{1–3} and Tubiana and colleagues^{4–7} and using tumor size data from women in the Van Nuys population^{11,12} proved to be remarkably close to the actual survival of women in the Van Nuys population (see Table 3, All tumors). Conversely, survival predictions made with Equation 3 using the estimates of Q and Z from the Van Nuys data set and tumor size data from women in the populations studied by Tabar et al.^{1–3} and Tubiana and colleagues^{4–7} also proved to be very close to the actual survival values (Table 3). These and similar results shown in Table 3 confirm the predictive power of Equation 3.

Equation 3 provides a practical tool for relating tumor size to expected survival (Table 3). For example, survival was ≈ 40% in the population studied by Tubiana and colleagues^{4–7} (1954–1972) and ≈ 70% in the Van Nuys population^{11,12} (≈ 1980–1990) and in the population studied by Tabar et al.^{1–3} (1977–1985), whereas the median tumor dimension was twice as large in the population studied by Tubiana and colleagues compared with the population studied by Tabar et al. and the Van Nuys population (see Table 3, All

TABLE 3
Expected Survival and Observed Survival of Women with Breast Carcinoma Compared with Other Populations Based on Tumor Size Data and Equation 3

| Tumor type by data source | Expected survival of women with breast carcinoma based on Equation 3 (%) ^a | | | Median tumor size (mm) | Observed survival (%) |
|--|---|------------|--------------------|------------------------|-----------------------|
| | Q_{TT}, Z_{TT} | Q_V, Z_V | Q_{TTV}, Z_{TTV} | | |
| Van Nuys data (~ 1980–1990) | | | | | |
| All tumor types | 67 | 67 | 67 | 20 | 68 |
| Screening mammography-detected tumors | 83 | 83 | 83 | 11 | 88 |
| Clinically detected tumors | 64 | 64 | 64 | 20 | 65 |
| Tabar et al. (1977–1985) | | | | | |
| All tumor types | 71 | 71 | 71 | 17 | 68 |
| First screening (mammography-detected tumors) | 78 | 78 | 78 | 12 | 85 |
| Later screenings (mammography detected tumors) | 80 | 80 | 80 | 12 | 88 |
| Intervals (clinically detected tumors) | 67 | 68 | 67 | 20 | 64 |
| Controls | 64 | 64 | 64 | 18 | 63 |
| Tubiana and colleagues (1954–1972) | | | | | |
| All tumors | 40 | 40 | 40 | 40 | 40 |

Q_{TT}, Z_{TT} : taken from the data sets of Tabar et al.^{1–3} and Tubiana and colleagues^{4–7}; Q_V, Z_V : taken from the Van Nuys data set^{11,12}; Q_{TTV}, Z_{TTV} : taken from the data sets of Tabar et al.,^{1–3} Tubiana and colleagues,^{4–7} and the Van Nuys data set.^{11,12}

^a In Equation 3 (see text), Z is a dimensionless constant, and Q is a constant with units of mm^{-2} .

tumors). The results of the calculations made with Equation 3 reveal that the observed change in survival is essentially what should be expected for the reduction in tumor size (Table 3). Two forces appear to have contributed to this overall reduction in breast tumor size: a reduction in the sizes at which clinically detected tumors come to medical attention, perhaps due to a greater awareness of breast carcinoma,³⁴ and an increased use of screening.³² The changes in the size of clinically detected tumors can be seen by comparing the data from the population studied by Tubiana and colleagues, which were collected largely in the premammographic era (1954–1972; median tumor size, 40 mm), with the data from clinically detected tumors in the population studied Tabar et al. (1977–1985; median tumor size, 20 mm) and in the Van Nuys population (\approx 1980–1990; median tumor size, 20 mm) (Table 3). The corresponding survival rates for the patients with clinically detected tumors were \approx 40% for the population described by Tubiana and colleagues and \approx 65% for the population described by Tabar et al. and for the Van Nuys population (Table 3). Again, the finding that the improvement in survival was the result of a reduction in tumor size can be seen from the agreement of the results of Equation 3 with the actual survival rates (Table 3). A comparison of the survivability of patients who had mammographically detected tumors, compared with patients who had clinically detected tumors, further reveals that the smaller size of the mammographically detected tumors resulted in greater survival. Thus, in the Van

Nuys data set, the patients with mammographically detected tumors (median size, 11 mm) had a survival rate of 88%, whereas the patients with clinically detected tumors (median size, 20 mm) had a survival rate of 65%. Similarly, in the data set of Tabar et al., the patients with mammographically detected tumors (median size, 12 mm,) had a survival rate of 85–88%, whereas the patients with clinically detected tumors (median size, 20 mm) had a survival rate of 64%. Again, this can be ascribed to the effect of mammography's capacity to find tumors at smaller sizes, as indicated by the agreement of the actual survival with the results of Equation 3, which is based on tumor size alone.

Why is the correlation between tumor size and survival fit so well by expressions of the form of Equations 1 and 3? Some insight into this question can be gained by considering that death from breast carcinoma usually is a result of the spread of cells from the primary mass, thus rendering the patient incurable by local treatment.³³ The probability (p) per cell of such events of lethal distant spread can be calculated using Equation 9 (Fig. 3), revealing that, for tumors measuring < 2 cm in greatest dimension, p is roughly 10^{-9} . In other words, the risk of spread for most tumors is approximately 1 metastasis for every 1 billion cells at the time of surgery (the value of such a probability, when estimated per cell per day [i.e., in terms of p' in Eq. 16], is roughly 10^{-11}). Figure 3 shows that, as tumor size increases, the per cell risk of spread gradually declines until p is closer to 10^{-10} (1 metastasis

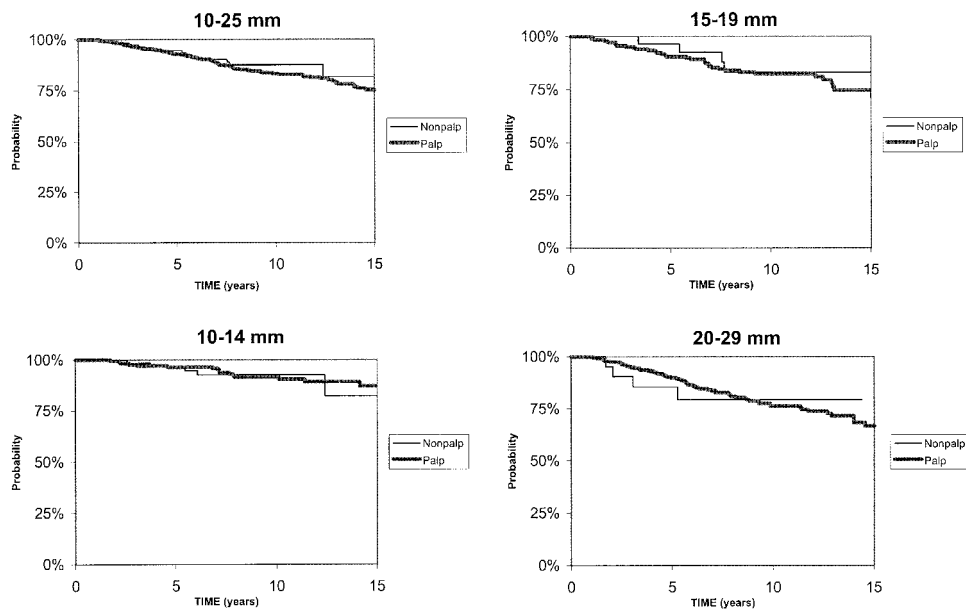


FIGURE 4. Kaplan–Meier survival curves for women who were diagnosed with breast carcinoma before 1991 in the Van Nuys populations by tumor size and method of detection. Curves labeled *Nonpalp* indicate nonpalpable, mammographically detected tumors, and curves labeled *Palp* indicate palpable, clinically detected tumors. Cox–Mantel log-rank tests for comparisons of survival between women with palpable tumors and women with nonpalpable tumors showed the following curves: tumor size 20–29 mm, $p = 0.973$; tumor size 15–20 mm, $p = 0.615$; tumor size 10–14 mm, $p = 0.864$; and tumor size 10–25 mm, $p = 0.397$. The curves for the nonpalpably detected tumors were less smooth because there were only 216 mammographically detected, nonpalpable tumors compared with to 1352 clinically detected, palpable tumors.

per 10^{10} cells) for tumors measuring < 5 cm in greatest dimension. This decline can be estimated more precisely by fitting a power function to the data in Figure 3, thus producing an empiric estimate of the correlation between p and N :

$$p = 0.00005 * N^{-0.5575} . \quad (9A)$$

It is shown above (see Materials and Methods) that, if the lethal spread of breast carcinoma cells occurs with such a probability, then the correlation between tumor size and survival will take the form of Equations 1 and 3. Thus, Equations 1 and 3 are consistent with a mechanism of death from breast carcinoma caused by distant lethal metastasis occurring as discrete events of cellular spread, although other biologic mechanisms also may give rise to expressions of this form.

Equation 3 also can be used to predict the survival of patients with breast carcinoma for whom actual survival data are not available. For example, from an analysis of 182 women with invasive breast tumors who were seen at the Lahey Clinic from 1997 to 2000, it is apparent that there have been further reductions in the sizes of breast tumors seen in women who had not used screening (median tumor size, 15 mm) as well as increases in the fraction of tumors that were found by mammographic screening (50%; data not

shown). Using tumor size data from these 182 women, Equation 3 yields a prediction of an overall survival rate of 81%, with an expected 86% survival rate for women with mammographically detected tumors and an expected 76% survival rate for women with clinically detected tumors.

One of the implications of both the empiric validity of Equation 3 and of the finding that the probability of spread occurs with a definable value per cell (Eq. 9a) is that women with tumors of the same size but with differing methods of detection should not differ in survival. This prediction was confirmed using survival data from the Van Nuys data set, which revealed no difference in survival of women with clinically detected or mammographically detected tumors of the same size (Fig. 4). Yet another indication that women with tumors of the same size have about same survival, regardless of how the tumors are detected, can be seen by comparing data from the Van Nuys population with previously published data from Tabar et al.^{1–3} and Tubiana and colleagues.^{4–7} Some of the tumors among patients in the Van Nuys population and many of the tumors among patients in the study carried out by Tabar and colleagues were found by screening mammography and, thus, were found at smaller sizes compared with the tumors among pa-

tients in the earlier study by Tubiana and colleagues, which occurred largely in the premammography era. Nonetheless, patients with tumors of the same size appeared to have approximately the same survival in all three populations (Table 1).

DISCUSSION

The survival data presented here provide the first demonstration that, in the absence of additional information, the survival of patients with invasive carcinoma is a direct function of tumor size, independent of the method of detection. Furthermore, we have been able to capture this function in the form of a simple equation (Eq. 3). The independence of survival from the method of detection was seen from two observations: 1) populations of women with invasive breast tumors of the same size had the same survival, regardless of how the tumors were detected; and 2) the survival values derived with Equation 3 were equally accurate for women with clinically detected tumors and women with mammographically detected tumors. These findings appear to exclude the possibility, expressed by a number of authors,⁸⁻¹⁰ that mammographic screening may be revealing some tumors that, although they are identifiable histologically as invasive breast carcinoma, may have less lethality compared with tumors of the same size that are found on clinical grounds.

The nature of detecting breast tumors has changed over the last decades,³² and Equation 3 makes it possible to assess the relative effect of various forces behind these changes. For example, the sizes at which tumors are found in the absence of screening have decreased dramatically over the last decades, perhaps due to a generally greater popular awareness of the importance of prompt attendance to the signs of breast carcinoma.³⁴ If the populations studied by Tubiana and colleagues⁴⁻⁷ (1954–1972) and Tabar et al.¹⁻³ (1977–1985) and the Van Nuys population^{11,12} (\approx 1980–1990) are representative of the larger population of women with breast carcinoma during those periods, then the reduction in the size of clinically detected tumors may have had a major (\approx 35%, absolute) effect on the survival of patients with breast carcinoma. Indeed, this reduction in the sizes of tumors seen in the absence of screening may well be the major determinant in the reduction in deaths from breast carcinoma seen in the last decade.^{35,36} Nonetheless, it is also apparent that screening mammography remains the best way for women with breast carcinoma to achieve the highest level of survival, with the potential to add yet an additional 20% (absolute) increase in survival.

Building on our previous suggestions,^{16,17} and as

also shown here, the data on the correlation between tumor size and death can be ascribed to the biologic mechanism of discrete events of the spread of tumor cells from the primary site to the periphery, thus rendering the patient incurable by local treatment. From the data outlined here, we have been able to estimate that this probability, p , has a value of about 1 event of spread per 1 billion cells in the primary tumor. That spread should occur in such a discrete fashion is not a surprise, because most of the commonly hypothesized mechanisms of metastasis, such as mutation or events of a simple mechanical nature (e.g., detachment, engraftment, evasion of immune attack, re-engraftment, and successful angiogenesis), would be expected to have a definable probability per cell.²¹⁻²⁴ What was not expected was the decline in the value of p as tumors became larger. Indeed, we found that the magnitude of this decline appeared to occur to the 0.56 power of the number of cells in the tumor. One possible explanation for this may be that it is more likely that a cell will leave a tumor if it is located at the periphery than if it is buried inside the tumor. Another explanation may be that the density of living cells declines as tumors grow, such as what may be expected from the accumulation of necrotic material; and yet another possibility may be the development of immune resistance to the survival of tumor cells.

In addition to the lethal events of distant spread, there also may be local events of spread to the lymph nodes that are not lethal. Preliminary analysis has suggested that these local events of spread also occur with a definable probability, although with a value that is somewhat greater than the value of p for distant spread (data not shown). Whether local and distant spread are independent events or are related in some way remains to be determined.

It has been suggested that adjuvant chemotherapy may be reducing deaths from breast carcinoma by eradicating some of the individual events of spread before they become established.³⁷⁻³⁹ It follows that the effect of adjuvant chemotherapy should be reflected in a decrease in the value of p that should be measurable by using the methods outlined here.

The estimates made here are for the population with invasive breast carcinoma as a whole, although it is likely that there are differences in lethality between tumor types based on characteristics such as histology, lymph node status, and molecular markers. A number of studies have examined the survival of women with tumors that differed by histologic subtypes or tumor markers, such as p53, HER-2, estrogen and progesterone receptors, etc.⁴⁰⁻⁴³ However, in many of those studies, comparisons were made between patient groups with a wide range of tumor sizes.

This may have clouded the actual association of these phenotypic characteristics with the propensity for spread. Estimating the values of D and Z (Eq. 2) associated with various tumor markers may provide a way to isolate and define their prognostic consequences. Precision in the measurement of tumor size,⁴⁴ together with estimates of the value of D and Z for specific subtypes of invasive breast tumors based on histology, patient history, and tumor markers, should allow for more accurate predictions of prognosis.^{45,46}

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