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A Stochastic Numerical Model of Breast Cancer Growth That Simulates Clinical Data[1]

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ABSTRACT

A new stochastic numerical model of breast cancer growth is developed. First, the model suggests that Gompertzian kinetics does apply but that from time to time, in random fashion, there occurs a spontaneous change in the growth rate or rate of decay of growth, such that the overall growth pattern occurs in a stepwise fashion. According to the model, the average time for the tumor burden to increase from one cell to detection is probably in the range of 8 years. Secondly, the model suggests that there is a linear relationship between the number of axillary lymph nodes positive for metastasis at diagnosis and the number of other metastatic sites. This can be described mathematically by the equation $S = 0.24 + 0.35N$ where S is the number of other metastatic sites and N is the number of positive lymph nodes. The model has been verified by simulating three data sets: (*a*) the survival times of untreated breast cancer patients as described by Bloom *et al.* [Br. Med. J., *2:* 213–221, 1962]; (*b*) the growth rates of breast cancers immediately prior to diagnosis as described by Heuser and Spratt [Cancer (Phila.), *43:* 1888–1894, 1979]; and (*c*) the disease-free survival time postmastectomy as described by Fisher *et al.* [Surg. Gynecol. Obstet., *140:* 528–534, 1975]. This model could have implications concerning the overall treatment rationale for breast cancer.

INTRODUCTION

Results of breast cancer treatment have improved in the past 10 years. This has largely resulted from increased efforts at early detection and use of adjuvant chemotherapy after surgery for high-risk patients. Nonetheless, significant numbers of patients with local and regional disease at diagnosis go on to demonstrate recurrent disease and eventually die. This necessitates the development of even more effective treatment. To do so will require further refinements in our understanding of the disease process.

At present, the rationale for the postoperative use of so-called adjuvant chemotherapy in patients at high risk for recurrence is based on a group of "demiprinciples" derived from work on animal tumor models and from correlations with clinical human breast cancer data. These include the following: (*a*) patients who have recurrence after curative surgery have cancer cells that have spread to other sites in the body prior to surgery, thus establishing "micrometastases"; (*b*) micrometastases grow according to the Gompertzian pattern thought to be reasonably representative of how human cancers grow (14); (*c*) these rapidly growing micrometastases are more sensitive to the effects of chemotherapy than is more slowly growing clinical disease, thus making them more amenable to total eradication by systemic chemotherapy; (*d*) Gompertzian (almost exponentially)-growing small tumors are likely to undergo mutations similar to what is seen in exponentially growing bacteria, and this could give rise to clones of cells genetically resistant to chemotherapy (6). This mechanism is currently thought to be responsible for the majority of treatment failures, *i.e.*, patients who go on to relapse later in spite of surgery plus adjuvant chemotherapy.

Skipper *et al.* (20, 21) have done studies which demonstrate quantitative relationships between tumor burden, time of growth, and chemotherapy treatment effectiveness in L1210 leukemia and other animal tumor models. In their work, tumor growth rate is expressed as "average doubling times." While this approach has led to great insights, all agree that this representation has been a substitution for what is known to be a more complex phenomenon. Salmon (14) attempted to use the "log kill theory" of Skipper in conjunction with a Gompertz representation of tumor growth in order to develop a more realistic model of the effectiveness of surgical adjuvant chemotherapy. Thus, instead of an average tumor-doubling time, he used doubling times based on tumor kinetic data extrapolated from *in vivo* and *in vitro* human breast cancer studies. Calculations utilizing the Gompertz growth formula resulted in doubling time values ranging from 2 days for the fastest micrometastases to as long as 10 days when the tumor burden was relatively large, *i.e.*, in the range of 1×10^9 cells.

We became interested in considering new designs for surgical adjuvant chemotherapy and decided that computer-based simulations might provide valuable insights. We started by attempting to reproduce much of the work of Skipper with the Salmon modifications for tumor growth, but we were disturbed to find that some of the calculations obtained were not in keeping with our preconceived notions of the timing of the natural history for this disease. In particular, we were impressed that, if the parameter values used by Salmon were substituted into the Gompertz formula, the time required for a tumor to grow from one cell to a tumor large enough to be detected clinically, *i.e.*, 1×10^9 cells, would take about 4 months. This seems much shorter than we would expect, especially in light of the length of time to recurrence after mastectomy, which often takes a number of years. Therefore, we undertook a systematic reevaluation of the Gompertz equation as a valid representation of human breast cancer growth.

Gompertz Model of Tumor Growth

Gompertz (7), a 19th-century actuarial scientist, formulated a mathematical expression which has been used as a growth representation (25). Beginning essentially as exponential growth, as time goes on, the process becomes damped and eventually stops. It can be represented by the mathematical formula:

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$$N = \exp\left[(A_0/\alpha)\,(1 - \exp(-\alpha t))\right]$$

where N is the number of cells at some time after growth starts, A_0 is the initial specific growth rate, α is the proportional rate of decay of A_0, and t is the time after the start of growth.

Laird (10) published convincing evidence that Gompertzian growth is representative of all biological growth. It is considered to be the best mathematical descriptor of tumor growth, although many other growth equations exist (17).

A New Model of Breast Cancer Growth

While Gompertzian growth "fits" intuitively with much of our clinical experience, *i.e.*, smaller tumors grow rapidly, large tumors grow slowly as indicated previously, we became suspicious of its validity. As a further attempt to consider its usefulness, we decided to evaluate Gompertzian growth with a range of values for A_0 and α. Values used by Salmon were based on his work with human myeloma (23) and breast cancer cells grown in soft agar (14). The myeloma data show a duration of subclinical disease ($\leq 2.5 \times 10^{11}$ cells) to range from 91 to 575 days, with an average of 223 days. As stated previously, when Salmon did his breast cancer modeling, he used $A_0 = 0.3$ (1/days) and $\alpha = 0.011$ (1/days) resulting in growth to 1×10^9 cells in approximately 120 days (4 months). Since this intuitively seems too rapid, we substituted the published range of values for both A_0 and α (23) into the Gompertz equation and generated the family of curves illustrated in Chart 1. Unfortunately, as can be seen, none of the curves result in growth from one cell to 1×10^9 cells in times in excess of 1 year, the minimum time we believed necessary in order for the growth model to be a reasonable representation.

We thus undertook to devise a new way to mathematically represent growth. First of all, we decided to accept Laird's observations that, when tumors do grow, Gompertzian kinetics describes them satisfactorily. Secondly, we considered that tumors might grow in "spurts" instead of steadily, which is not incompatible with what we can imagine biologically. It can be shown that the factor which governs the ultimate size of the tumor using the Gompertz equation is the rate A_0/α. Any increase in this ratio will result in an upward "translation" or a step in the curve. After a mathematical evaluation, we found that it makes little difference if A_0 increases or α decreases. We arbitrarily chose to decrease α as a method of producing a new growth "spurt." Furthermore, we postulated that growth spurts would occur in a stochastic or random fashion. The new model differs from other models (3, 5, 11, 13, 16, 19, 22, 24) in that it is stochastic, is numerical, and also generates individual tumors to comprise a population. The model begins with one cell at zero time and has specified values of A_0, α, A_4, the probability that α will undergo a change in a 5-day period, and A_3, a determinant of the amount of change in α. α and A_0 are in units of reciprocal days, and A_3 and A_4 are dimensionless. Time (t) is expressed in days.

The program allows variations in the size at which detection of the tumor will occur. Detection sizes, which were set to vary from 1×10^9 to 5×10^9, correspond to usual clinical experience. The lethal size was arbitrarily set at 1×10^{12}. A tumor of 1×10^9 cells has a mass of about 1 g and a volume of about 1 ml, while a tumor of 1×10^{12} cells has a mass of about 1 kg and a volume of about 1 liter.

The program evaluates the tumor burden using the Gompertz equation and then inquires if the tumor burden is detectable. Time is incremented by 5 days, and a random number between 0 and 1 is generated and compared to A_4. If A_4 is smaller, the tumor continues to grow at the prior rate. If not, the program reduces α by an amount depending on A_3 and another random (0 to 1) number [$\alpha = \alpha/(1 + \text{random number} \times A_3)$]. Growth continues in this fashion recording time of detection until a lethal tumor burden is achieved or a preset time has elapsed (40 years was used). Typical growth of 3 tumors is displayed in Chart 2. It is important to note that, although each curve is different, each was generated by running the identical program. The differences are accounted for by the random chance of change and the randomly determined amount of change.

Evaluation of the Model

Mathematical models are not reality, but they can be useful in experimentation if they simulate reality. This section will cover how closely this mathematical model simulates clinical data. In order to evaluate the model, we decided to test it against a wide spectrum of clinical data. Chart 3 summarizes the 3 data sets

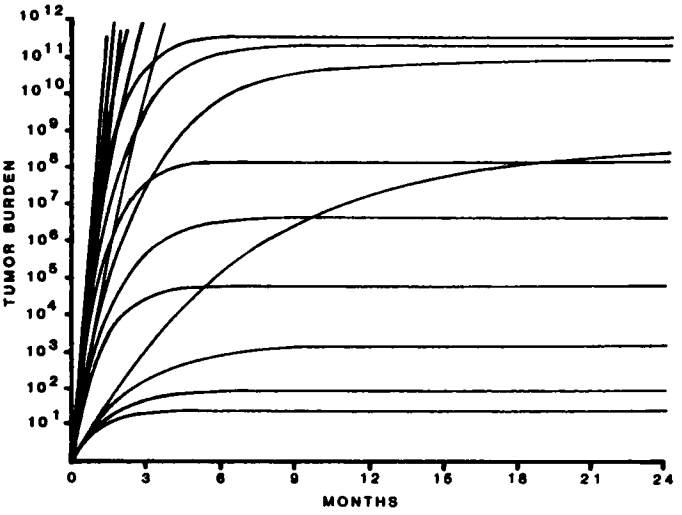


Chart 1. Gompertz growth curves for the range of A_0 and α as reported by Sullivan and Salmon (23) for IgG myeloma.

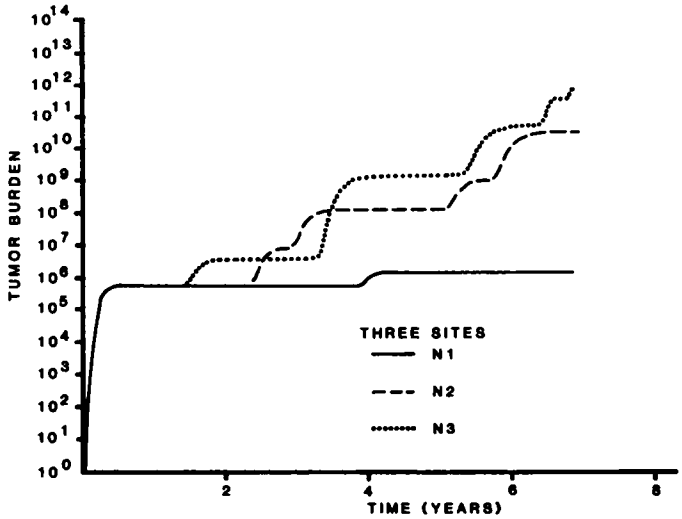


Chart 2. Computer run generating 3 typical tumors. Program was terminated when one tumor reached the lethal limit set at 1×10^{12} cells.

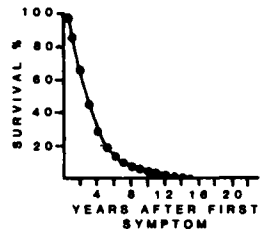
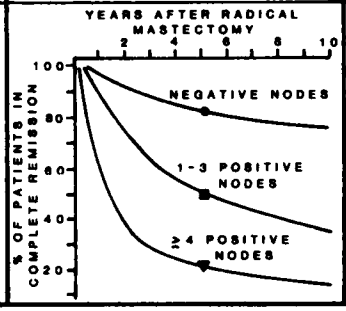
REFERENCE	DESCRIPTION OF DATA	COMMENTS
BREAST CANCER Henderson/Canellos Vol 302, No. 1, 1980 "Medical Progress" Bloom, Richardson Harries Br. Med. J. 1962 2: 213-21		END STAGE DISEASE A_3 AND A_4 DETERMINED
GROWTH RATES OF PRIMARY BREAST CANCERS L.Heuser, J. Spratt, H. Polk Cancer 43: 1888-94, 1979	DATA: 10120 SUBJECTS 30000 MAMMOGRAMS OVER 3 YEAR PERIOD 109 CANCERS DETECTED PREVIOUS MAMMOGRAMS WERE EXAMINED TO TRY TO DETERMINE GROWTH RATES OF TUMORS. 32 WERE DETERMINABLE 17 GREW TOO FAST 15 DETECTED BUT UNMEASURABLE 45 DETECTED ON 1ST MAMMOGRAM	EARLIEST CLINICAL DISEASE A_0 DETERMINED
QUANTITATIVE & CYTOKINETIC STUDIES IN EXPERIMENTAL TUMOR SYSTEMS H. Skipper & F. Schabel Cancer Medicine 2nd Edition Ref: Fisher data		STAGE II POST OP DISEASE DETERMINED: 1. $S = C_1 + C_2 N$ 2. C_1 & C_2 VALUES OF CLINICAL SIGNIFICANCE

Chart 3. Summary of 3 data sets used to establish the model. *POST OP*, postoperative.

we used. The first is the plot of natural history of untreated breast cancer patients reported by Bloom *et al.* (2) and Henderson and Canellos (8). The survival curve is shown for 250 subjects who refused treatment for diagnosed breast cancer between 1805 and 1933 in England.

The second data set, reported by Heuser *et al.* (9), demonstrates unperturbed growth at the smallest detectable tumor sizes. In Kentucky, 10,120 subjects were given yearly mammograms. When cancer was detected, previous mammograms were reexamined to determine if in retrospect tumor could be identified and measured so that the growth rate could be calculated.

The third set from Fisher *et al.* (4) addresses the regrowth of tumor following surgical resection of primary disease. The percentage of patients in complete remission following radical mastectomy is plotted separating groups by extent of nodal involvement.

This collection of clinical data covers the range from tumors too small to be detected to those large enough to cause death. Subjecting a growth model of breast cancer to these situations was considered to be essential in determining the ability of the model to simulate a group of patients.

The Bloom data were actually used to determine the best values for A_3 and A_4. A systematic search routine in the A_3, A_4 plane was used to find the best fit to the Bloom data. The figure of merit used for comparison of fit was the absolute value of the average error between the Bloom data and the model calculation based on a sample of 480 patients per calculation.

Using this approach, we found optimized values for $A_3 = 0.3$ and $A_4 = 0.008$, and this was true for any value of A_0 from 0.1/days to 0.7/days. Two such examples are illustrated in Chart 4 ($A_0 = 0.3$ and $A_0 = 0.7$). For illustrative purposes, one curve resulting from minimally different values ($A_3 = 0.4$ and $A_4 = 0.009$) is also shown, demonstrating a significant deviation from the Bloom data.

It is interesting to note that, if the optimum value of A_4 would have been zero, then the resulting growth curve would have been the classical Gompertzian pattern which, in fact, is thus refuted on empirical grounds.

The fact that optimum values for A_3 and A_4 are independent of the initial specific growth rate (A_0) is worth further consideration. What this observation means is that tumor growth from detection to death, *i.e.*, the time of clinical disease, is independent of the initial specific growth rate of the tumor. A_0 does make a difference in the total life history of the cancer. This is shown in Table 1, which indicates that the average time from detection to death is fairly constant, approximately 3.3 ± 2.6 (S.D.) years, whereas the time from one cell to detection varies from 0.2 to 26 years dependent on A_0. Thus, A_0 determines the preclinical lifetime of the tumor.

While our initial intuitive impression led us to reject the straight Gompertzian model because the preclinical lifetime of the tumor was too short, we likewise believed that the range from 0.2 to 26 years was not specific enough. This led us to further attempt to determine a more precise and meaningful range of time for the preclinical life span of breast cancers. This was done by considering the Heuser data.

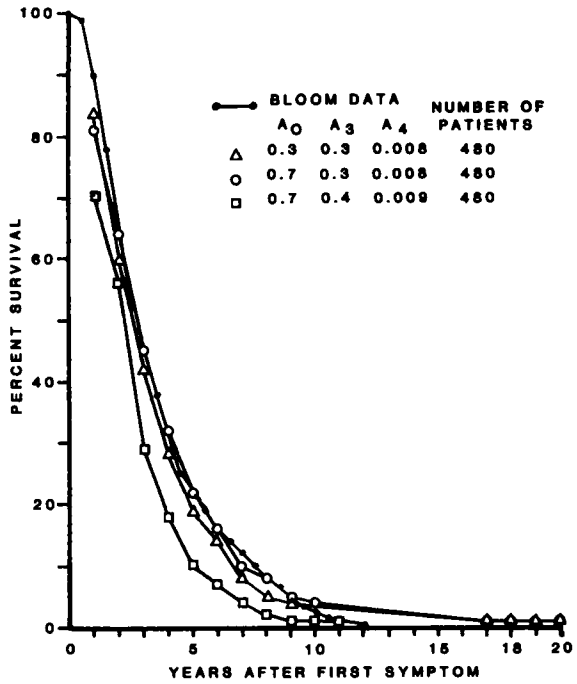


Chart 4. Comparison of model results and Bloom data.

Table 1

Natural history of breast cancer from the model for various values of A_0

A_0 (1/days)	Time to detection (yr)	Time to 1×10^{12} cells (yr)	Time from detection to 1×10^{12} cells (yr)
0.1	26.2 ± 6.9[a]	29.6 ± 6.8	3.4 ± 2.7
0.2	16.6 ± 5.4	19.9 ± 5.9	3.3 ± 2.6
0.3	11.5 ± 5.2	14.8 ± 5.7	3.3 ± 2.8
0.4	7.8 ± 3.9	11.3 ± 5.0	3.5 ± 3.0
0.5	4.7 ± 2.9	8.0 ± 3.8	3.3 ± 2.7
0.6	2.3 ± 2.0	5.5 ± 3.3	3.1 ± 2.6
0.7	0.2 ± 0.04	3.5 ± 2.5	3.2 ± 2.5

[a] Mean ± S.D.

In the Heuser study, 10,120 women had annual screening mammograms for 3 years. One hundred nine cancers were detected, of which 45 were diagnosed on the first mammogram. Of the 64 diagnosed on subsequent mammograms, 17 were not visible in retrospect on previous mammograms, 15 were visible but not measurable, and 32 were both visible and measurable allowing for the determination of growth rates. Tumors that grew to visible size in less than 1 year, specifically between mammograms, were not measurable, causing a bias in the results. The average tumor burden was $1 \times 10^{9.12}$ at detection; on the previous mammogram 313 days earlier, the average size was $1 \times 10^{8.81}$. These data are summarized in Chart 5.

To test our model, we calculated the growth rate for 313 days past the time when the tumor burden was $1 \times 10^{8.81}$ cells. The results are shown on Chart 6 together with the similarly analyzed clinical data. The 32 measured tumors are displayed in the histogram in Chart 6*a*. The question mark (?) is there to remind us that there are at least 17 more tumors that grew too rapidly to be measured and would show up as having faster growth rates than did the 32 displayed tumors. Chart 6, *b* to *d*, shows the calculated similar situations for various A_0 values as indicated.

With a significant fraction of the tumors not measurable and the data biased, it would be guesswork to specify precisely which A_0 in our model would best represent the complete situation. $A_0 = 0.4$ may best represent the case for all 64 tumors that Heuser tried to measure.

Curiously enough, 9 of Heuser's tumors did not grow by a measurable amount in the year between mammograms, as can be seen in Chart 5. Likewise, as illustrated in Chart 2, our model

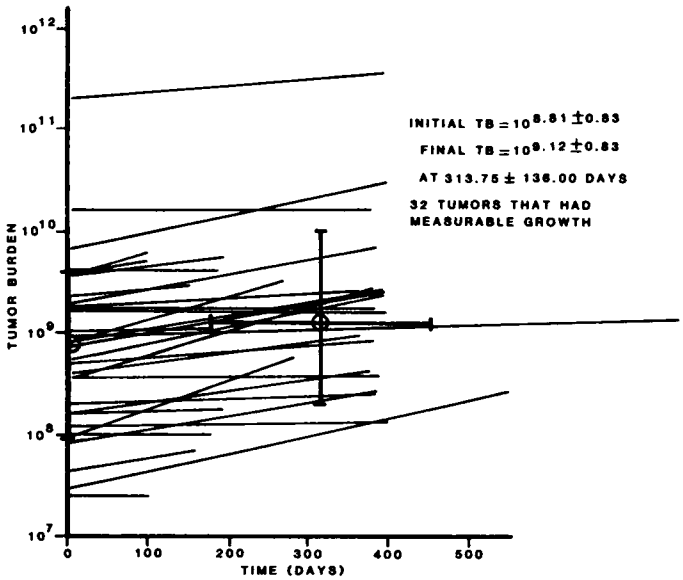


Chart 5. Summary of Heuser data. The data for each tumor consist of a determination of tumor size at 2 different times approximately 1 year apart. The first tumor size is plotted on the time = 0 axis. A *straight line* connects the initial point and the final point for each tumor. *TB*, tumor burden.

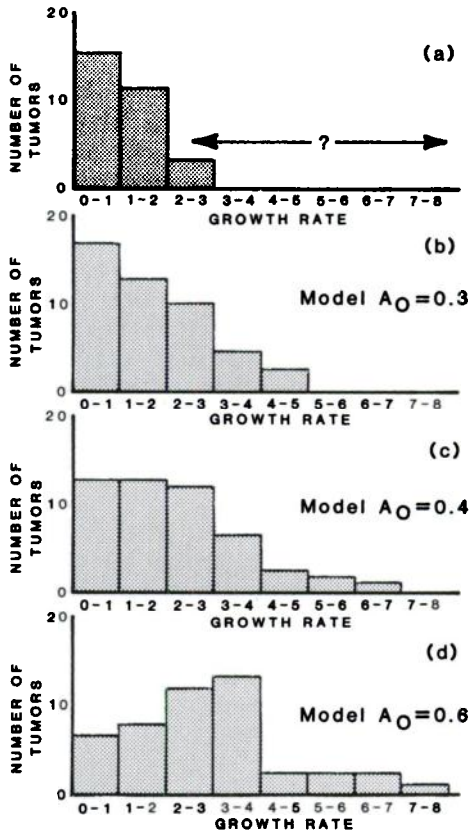


Chart 6. Histogram of the growth rate of the tumors from the Heuser data are shown in *a*. Growth rate is defined as $10^9 \times [\Delta \log (\text{tumor burden})]/\text{days}$. *b*, *c*, and *d* show the equivalent model results for various values of A_0.

generates tumors that exist in a steady state for years at a time.

We summarize the relationship between our model and Heuser's data as follows. Our model with $A_0 = 0.4$ seems to agree with the clinical data. More specifically, the model generates tumors that grow at the same rate as the clinical data indicated. Also clinically and from the model, some tumors did not grow at all in 1 year.

Referring to Table 1, it might be reasonable to conclude that our model indicates that breast tumors grow for 7.8 ± 3.9 years before detection. The model would simultaneously agree with both Bloom and Heuser under these conditions.

At the suggestion of S. Piantadosi,[3] we examined variations of the Gompertz equation to evaluate the sensitivity of our model to the exact shape of the growth curve.

We decided to try various growth patterns while retaining both the initial exponential growth and the ultimate cessation of growth. This was done by using the Gompertz equation and varying A_0 and α (initial) while restricting (A_0/α) to be constant. All of the growth curves matched the Bloom data with the same values of $A_3 = 0.3$ and $A_4 = 0.008$. We concluded that the model shows little sensitivity to the exact form of the equation. Thus, the essence of our model is in the random change of the growth parameters.

The final data set which we considered in the development of this model was the disease-free survival time of patients following mastectomy where varying numbers of axillary lymph node metastases existed, as reported by Fisher *et al.* (4). Skipper *et al.* (20, 21) reasoned that these data were similar to data that they generated in mice inoculated with varied but precisely defined quantities of L1210 leukemia. Their conclusion was that time to recurrence (disease-free survival) is related to the quantity of tumor left behind in micrometastatic deposits. Furthermore, they then concluded that on the average there is a relationship between the number of nodes positive and the average quantity of tumor remaining postoperatively. Thus, more positive nodes predict a shorter time to recurrence.

Our model is also intuitively compatible with Fisher's data; with more positive nodes, disease-free survival is shorter. However, in our model, this occurs for an entirely different reason. The statistical nature of our model implies that the time interval between individual sites reaching a detectable size decreases as the number of sites increases. Thus, if 2 tumors started growing at approximately the same time, they would not necessarily reach the detection level simultaneously. Rather, one would be detected first. Likewise, if 3 tumors started growing at approximately the same time, the likelihood is that the time between the first and second tumors reaching detection would be shorter than the previous example.

From repeated clinical studies, it is absolutely clear that the more numerous the positive lymph nodes, the shorter will be the disease-free interval. As we have demonstrated with our model, there is also a relationship between the number of sites and the disease-free interval, implying that there must be a relationship between the number of sites and the number of positive lymph nodes. The simplest expression of this relationship is

$$S = C_1 + C_2 \times N$$

where S is the average number of individual metastatic sites, C_1 and C_2 are constants, and N is the number of positive nodes at diagnosis. In order to evaluate this hypothesis, we chose to test it empirically, considering the probability of disease-free survival at any point in time for various subsets of patients, *i.e.*: those with no positive nodes; those with 1 to 3 positive nodes; and those with ≥4 nodes. Thus, the probability of a single metastatic site not growing to $\geq 1 \times 10^9$ cells at any point along one of the disease-free survival curves can be expressed as $P_1(t)$. Likewise, the likelihood of none of the S sites reaching 1×10^9 cells at time t is $P_S(t)$. Because each metastatic site is independent of each other, it follows that $P_S(t) = P_1^S(t)$. By substitution, this expression becomes $P_1^{(C_1 + C_2N)}(t)$ which can be restated as $P_1^{C_1}(t) * P_1^{C_2N}(t)$.

In considering Fisher's data, we have defined the node-negative population as Data Set 0. Likewise, in this analysis, we have arbitrarily represented all patients with 1 to 3 nodes positive as Data Set 2 and those with ≥4 nodes positive as Data Set 5. Thus,

$$\text{Data } 0 = P_1^{C_1}(t) * P_1^{C_2N}(t) = P_1^{C_1}(t)$$

since $N = 0$,

$$\text{Data } 2 = P_1^{C_1}(t) * P_1^{C_2N}(t) = P_1^{C_1}(t) * P_1^{2C_2}(t)$$

since $N = 2$, and likewise,

$$\text{Data } 5 = P_1^{C_1}(t) * P_1^{5C_2}(t)$$

because $N = 5$. By substitution

$$\text{Data } 2 = \text{Data } 0 * P_1^{2C_2}(t)$$

and

$$\text{Data } 5 = \text{Data } 0 * P_1^{5C_2}(t)$$

Thus, the empiric prediction

$$\left(\frac{\text{Data } 2}{\text{Data } 0}\right)^{1/2} = \left(\frac{\text{Data } 5}{\text{Data } 0}\right)^{1/5}$$

Again, substituting actual values from Fisher's disease-free survival probability curves, we obtain at 5 years:

$$\left(\frac{\text{Data } 2}{\text{Data } 0}\right)^{1/2} = \left(\frac{0.5}{0.82}\right)^{1/2} = 0.78$$

and

$$\left(\frac{\text{Data } 5}{\text{Data } 0}\right)^{1/5} = \left(\frac{0.21}{0.82}\right)^{1/5} = 0.76$$

and repeating the same calculations at 10 years:

$$\left(\frac{\text{Data } 2}{\text{Data } 0}\right)^{1/2} = \left(\frac{0.35}{0.76}\right)^{1/2} = 0.68$$

and

$$\left(\frac{\text{Data } 5}{\text{Data } 0}\right)^{1/5} = \left(\frac{0.13}{0.76}\right)^{1/5} = 0.70$$

Thus, since this empiric test of our theoretical prediction $S = C_1 + C_2N$ was reasonably accurate, we decided to evaluate it further.

[3] S. Piantadosi, personal communication, 1982.

Chart 7 shows the disease-free survival for 0, 1, 2, and 3 metastatic sites from our model (using A_0, α, A_3, and A_4 values as determined previously). Combining the data from Chart 7 and Fisher's data, Chart 8 was generated showing the relationship between the number of metastatic sites and the number of positive nodes. All of these data may be represented by a single, best-fit straight line with the y-axis intercept at 0.24 ± 0.05 and a slope of 0.35 ± 0.10. Thus, according to the relationship between metastatic sites and positive nodes previously developed, we have

$$S = 0.24 + 0.35N$$

The value of S for zero positive nodes is 0.24 which implies that 24% of the persons with zero positive nodes actually have a metastatic site growing. This agrees with the asymptotic limit of Fisher's $N = 0$ curve (24% treatment failures at 10 years). We can use these values for C_1 and C_2 to further develop the numerical relationship between disease-free survival and nodal involvement. Continuing from the previous development,

$$\text{Data } N = P_1^{C_1 + C_2 N}(t)$$

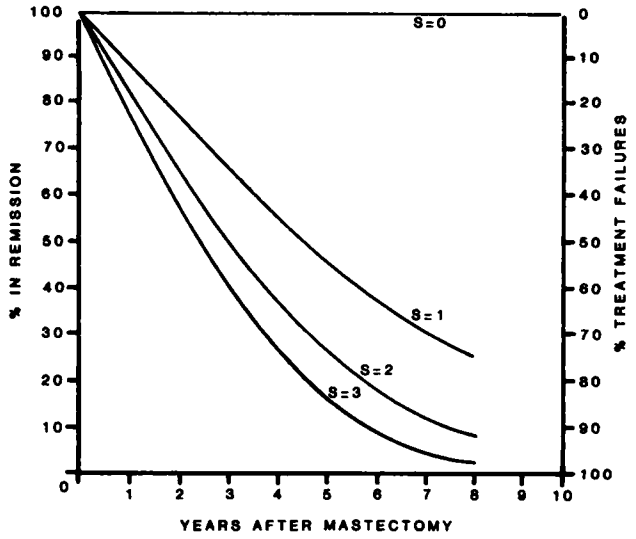


Chart 7. Remission *versus* time for the model with number of sites as parameter.

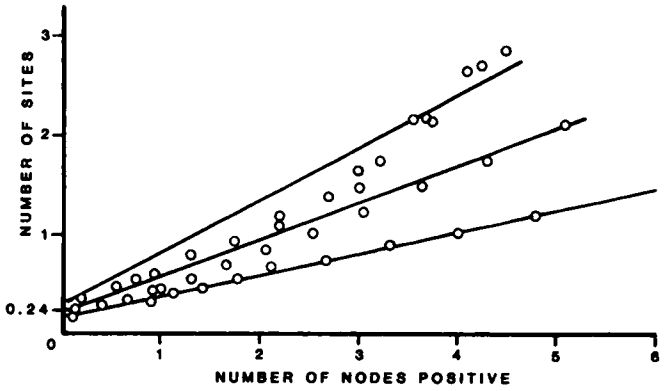


Chart 8. Relationship between the number of metastatic sites and number of positive nodes as derived from our model and Fisher's data. This was done by eliminating time as a variable.

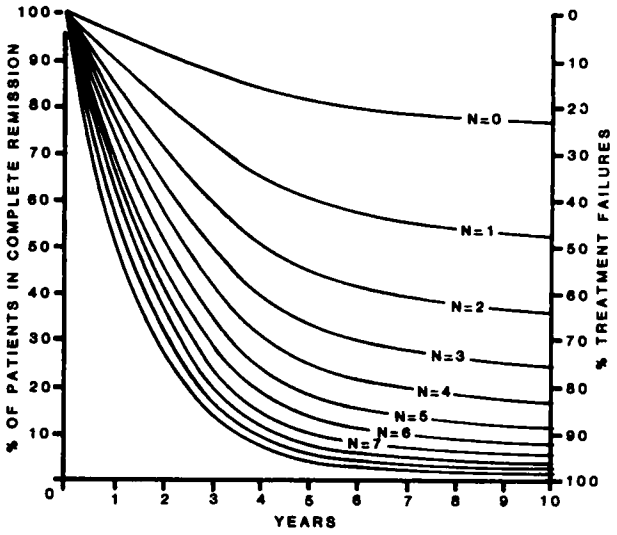


Chart 9. Family of curves generated by the model using the equation data N = data $0^{(1+1.46N)}$. This is the model simulation of remission *versus* time with number of positive nodes (N) as parameter and may be compared directly to Fisher's data.

which may be rewritten as

$$\text{Data } N = P_1^{C_1(1 + C_2 N/C_1)}(t)$$

or

$$\text{Data } N = \text{Data } 0^{(1+1.46N)}$$

Thus, Data 0 = Data 0^1, Data 1 = Data $0^{2.46}$, Data 2 = Data $0^{3.92}$, Data 3 = Data $0^{5.38}$, etc. Finally, from these relationships, it is possible to recreate Fisher's data curves as well as data curves for patient populations with each individual number of nodes positive as shown in Chart 9.

The development described above is compatible with the actual disease-free survival as documented by Fisher. Its major significance lies in showing that our model suggests that the number of positive lymph nodes at diagnosis predicts the number of other metastatic sites rather than the number of tumor cells left behind following curative surgery.

Fisher's data may be very accurately represented by a mathematical power series as illustrated in Chart 9. This indicates to us that probabilistic effects, such as used in our model, dominate tumor kinetics.

DISCUSSION

The model of breast cancer kinetics developed above can be important in a number of ways.

1. It represents a different approach in that it is both stochastic and numerical, contrary to other models which are based on differential equations. We used this approach because it offered us more versatility than did the differential equation method. Thus, we were able to develop mathematical representations of concepts expressed from words rather than formal equations. Our model generates every individual in the population rather than a group of means or averages representing the population.

2. It fits human breast cancer data in a unique fashion. Although it was developed to match published statistical data, it

does so by counting the sum of every individual in the model. It is a model of individuals. Thus, the individuals generated by the model are a meaningful representation of a clinical population of breast cancer patients both individually and collectively.

3. It adequately accounts for the heterogeneity seen in human breast cancers. It is well known that the natural history of breast cancer can vary by several orders of magnitude between patients with essentially identical clinical presentations. Our model creates a population of individuals that encompasses the entire spectrum of the disease commonly referred to as "heterogeneous."

4. It suggests that a major cause for resistance to adjuvant chemotherapy could be due to large numbers of nonproliferating cells. In particular, this model suggests that, during the natural history of the disease, a number of time periods can exist during which the tumor is not changing in size. This could be the result of one of 3 possibilities: (*a*) tumor is growing at exactly the same rate as the rate of cell decay; (*b*) the growth fraction is zero; and (*c*) some combination of *a* and *b*. In any case, the implication exists that if cells were present in a nonproliferating state they would be resistant to adjuvant therapy as suggested by Alexander (1). If this is so, our model implies that current approaches to adjuvant chemotherapy based on simpler growth models (6, 12, 14, 15, 18, 20, 21, 26) could be inadequate. It further suggests that some form of long-term maintenance therapy could be more effective.

In summary, we have developed a stochastic numerical model representing the growth of breast cancer. The model suggests that Gompertzian kinetics does apply but that from time to time, in random fashion, there occurs a spontaneous change in the growth rate or rate of decay of growth, such that the overall growth pattern occurs in a stepwise fashion. Time from one cell to detection, according to this model, is variable depending on the initial growth rate but probably is in the range of 8 years. Also, the model suggests that there is a linear relationship between the number of axillary lymph nodes positive for metastases at diagnosis and the number of other metastatic sites as described by the equation $S = 0.24 + 0.35N$.

Data from clinical disease studies are simulated well by our model. Due to the excellent fit of this model to clinical data, it is not unreasonable to assume that it applies to smaller tumor burdens as well. If this is the case, there are significant implications about adjuvant chemotherapy. Resistance in patients with resected breast cancer who are at high risk for recurrence may be due in part to nonproliferating cells rather than entirely to other mechanisms of resistance. Thus, further work with this model in conjunction with a model for treatment effect could provide new insights in designing therapy trials.

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