A Gompertzian Model of Human Breast Cancer Growth

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ABSTRACT

The pattern of growth of human breast cancer is important theoretically and clinically. Speer et al. (Cancer Res., 44: 4124–4130, 1984) have recently proposed that all individual tumors initially grow with identical Gompertzian parameters, but subsequently develop kinetic heterogeneity by a random time-dependent process. This concept has elicited interest because it fits clinical data for the survival of untreated patients, for the progression of shadows on serial paired mammograms, and for time-to-relapse following mastectomy. The success of these curve-fits is compelling, and the model has been applied to clinical trials. However, the assumption of uniform nascent growth is not supported by theory or data, and individual cancers have not been shown to follow the complex growth curves predicted by the Speer model. As an alternative, if kinetic heterogeneity is understood to be an intrinsic property of neoplasia, the same three historical data sets are fit well by an unadorned Gompertzian model which is parsimonious and has many other intuitive and empirical advantages. The two models differ significantly in such clinical projections as the estimated duration of silent growth prior to diagnosis and the anticipated optimal chemotherapy schedule postsurgery.

INTRODUCTION

Many models of tumor growth have been proposed to fit clinical data and to offer therapeutic guidance (1, 2). Each model is to some extent dependent on the assumption of a certain pattern of growth of the unperturbed tumor. The landmark work of Skipper and colleagues, for example, was based on exponential kinetics (3). In exponential growth the cell number \( N \) is a function of the starting size \( N(0) \), the time of growth \( t \), and a constant \( b \), by the formula:

\[
N(t) = N(0) \cdot \exp(b \cdot t)
\]

Hence, the time \( t_d \) required for \( N(t_d) \) to double, i.e., \( N(t_d) = 2N(0) \), is always constant at \( \log_2(2)/b \). The Skipper model, developed principally for experimental murine leukemia, continues to yield valuable insights into the relationship between tumor size, growth characteristics, and therapeutic response (4). More recent models have also depended upon the exponential curve. An example is the reconsideration by Goldie and Coldman (5) of the Delbruck-Luria mutagenesis model (6) as extended by Law from bacteria to cancer (7).

The exponential pattern of growth can be useful if it fits actual data, but it is now known not to be universally appropriate. In particular, in many types of growth—normal and neoplastic—\( t_d \) is not constant, but increases as the population size increases. To many of these cases Laird (8) successfully applied Gompertz' equation, originally developed for actuarial analysis, but later proposed as a growth curve (9). In Gompertzian growth \( N(t) \) is a function of \( N(0), t \), and \( b \), but also a limiting size \( N(\infty) \), by the equation:

\[
N(t) = N(0) \cdot \exp(k \cdot (1 - \exp(-bt)))
\]

where \( k = \log[N(\infty)/N(0)] \).

This equation fits experimental (10) and clinical data (11), and uncovers growth-regulatory mechanisms in animal (12, 13) and human (14) cancers. In addition, when used to relate a tumor's size to its rate of regression in response to therapy (15), Gompertz' equation has aided in the design of successful clinical trials (16, 17).

Recently, however, the validity of the assumption of Gompertzian growth for clinical breast cancer has been challenged by the provocative new model of Speer et al. (18). These authors propose a stochastic process in which growth is fundamentally Gompertzian, but with random, spontaneous alterations in the parameters such that \( b \) decreases and \( N(\infty) \) increases in a functionally related manner. This results in growth "spurts." They postulate that both \( b \) and \( N(\infty) \) are constant for all tumors at inception, and the probability of random change is independent of \( N(t) \), i.e., a large tumor has the same chance of undergoing an alteration as a small tumor. Tumor heterogeneity is a consequence of the randomness of the process. This model was constructed so as to reconcile the Gompertzian parameters described for multiple myeloma and in vitro breast cancer cells (19) with "preconceived notions of the timing of the natural history" of clinical breast cancer. It predicts an average of 8 years of growth from one cell to clinical recognition at \( 1 \times 10^9 \) to \( 5 \times 10^9 \) cells. Of greatest interest, the model fits two-point volume data for early (mammographically discernible) tumors (20), survival data for untreated cancers (21), and remission duration data post-mastectomy (22). It suggests that the shorter time-to-relapse after mastectomy for those patients who had more axillary nodal involvement is due to a positive linear relationship between number of involved nodes and number of metastatic sites. This view of theirs is in contrast to a previously hypothesized and widely accepted relationship, that patients with more involved nodes have a greater total-body tumor cell burden (4). Additionally, the Speer model anticipates merit in long-term maintenance chemotherapy in the postsurgical adjuvant setting, as opposed to current short-term, intensive approaches.

The Speer model is theoretically intriguing. The concept of random spontaneous change in growth rate recalls the powerful theory of tumor progression (23, 24). The inverse relationship between \( b \) and \( N(\infty) \) has indeed been previously described (12). Nevertheless, curves consistent with the Speer model have not been fit in individual cases, as has been done innumerable times for the Gompertzian model. Additionally, the assumption of a uniform \( b \) and \( N(\infty) \) for all primary breast cancers at onset of growth is not consistent with the known biological heterogeneity of breast cancer on the cellular or even molecular level (2, 25, 26). Indeed, the construction of such complicated curves as found in the Speer model is made necessary only if a uniform initial \( b \) is hypothesized. If variability in \( b \) is allowed, the unmodified Gompertzian model is sufficient to fit clinical data. This is shown below by the analysis of the same three data sets used by Speer.
MATERIALS AND METHODS

The first data set used by Speer was provided by Bloom et al. who collected data for 250 women with untreated breast cancer followed at the Middlesex Hospital, London, during the period 1805 to 1933 (21). All patients had confirmation of the histological diagnosis at necropsy. 58% of the women were over the age of 50. The initial symptom for 83% was a breast lump; and for 71% there was a delay between first symptom and presentation to hospital of more than 1 year. The duration of life from onset of symptoms to death is graphed as square points in Fig. 1A: median survival is 2.7 years, and fewer than 1% of patients survived for more than 15 years. These results are similar to earlier reports (27, 28).

These data are analyzed here as follows: N(t) is an individual patient's tumor size at a time t measured from the onset of symptoms at time 0. The tumor size at onset of symptoms is N(0) and N(∞) is held constant. Parameter b is allowed to vary, which produces a family of Gompertzian curves which intersect only at N(0). For the group of 250 patients P5(t) is the proportion of patients who have died by or at time t because their tumors sizes had reached a lethal tumor size Nl at some time less than or equal to t. By rearrangement of the Gompertz equation

$$ t_i = \frac{-1}{b_i} \log \left( 1 - \frac{1}{8} \log \left( \frac{N_i}{N(0)} \right) \right) $$

where P5(ti) is the fraction of the 250 cancers which have Gompertzian parameters b less than or equal to bi. This process defines the probability distribution of b. Using P5(t) from Bloom and reasonable initial values of N(0), Nl, and N(∞), the distribution was found to be approximately log-normal. By iteration, values of N(0), Nl, N(∞), and the mean and standard deviation of b were found so as to minimize the least-squares fit of log(bi) to the log(b) values calculated above. The fit to the actual data of the model so generated was confirmed by simulation of individual growth curves. The model is as follows: A value of b is chosen randomly from the derived log-normal distribution and ti is calculated such that N(ti) = Nl. The array of values of ti is used to estimate P5(t) by standard actuarial methods (29), and is graphically compared with P5(t) from the Bloom data.

The second data set used by Speer is from Heuser et al. who present data for 109 primary breast cancers (108 women) diagnosed among 10,120 screening mammograms (20). 45 lesions were discovered on initial examination. Of the 64 remaining cases with diagnostic mammograms, 32 had had previous mammograms that retrospectively demonstrated measurable tumors. The authors estimate that these 32 examples represent the slowest-growing 23% of cancers in their series, with the remaining 77% growing too rapidly to remain undiagnosed clinically between two widely spaced mammograms. Nine of the 32 had such consistent findings in the two consecutive examinations that growth could not be documented. For the 23 cancers that did grow to a measurable degree the authors provide mutually perpendicular diameter values (L for length and W for width, such that L ≥ W) and the date of each of the first and second measurements.

The Heuser data are analyzed here as follows: The time between dates ti is calculated in months; each tumor volume is estimated as the volume of revolution of an ellipse by \( \pi/6 \cdot L_i \cdot W_i^2 \); N(0) is set at the first volume; N(ti) is set at the second volume; using the value of N(∞) determined by the Gompertzian fit to the Bloom data, bi is calculated by the Gompertz equation.

The third data set cited by Speer concerns the growth of micro-metastatic foci of breast cancer following removal of a primary tumor by Halsted radical mastectomy. In 1975 Fisher et al. (22) published the 10-year results of a National Surgical Adjuvant Breast Project trial of postoperative chemotherapy compared with placebo for patients with Stages I or II disease (regional disease not advanced and no evidence of metastases except to axillary lymph nodes in Stage II). For 370 placebo-treated women at 5 years and 333 at 10 years the percentage of free local or regional recurrence or metastases were estimated by the method of Cutler and Ederer (30). These are graphed in Fig. 3 for three subgroups by axillary lymph node positivity at the time of mastectomy: all nodes negative, one to three positive, or four or more positive. The model of this paper is applied to the Fisher data by the same method of simulation used to confirm the fit of the model to the Bloom data, with three exceptions. The limiting event, recurrence, is set at a tumor size N0 < Nl; a variable percentage of patients are assumed to be cured (i.e., N(0) = 0) by mastectomy; for the individuals who are not cured N(0) is allowed to vary so as to give the best least-squares curve fit to the probability of recurrence P5(t) as a function of time t after mastectomy.

RESULTS

By the above methods the Bloom data are found to be consistent with the Gompertz equation with N(0) = 4.8 × 10^9 cells (almost 5 cc of densely packed tumor cells), N(∞) = 3.1 × 10^12 cells (3.1 liters), a lethal tumor cell number of Nl = 10^13 cells (one liter), and, expressing t in units of months, a log-normal distribution of parameter b with mean log(b) of −2.9 and a standard deviation of log(b) of 0.71. The line in Fig. 1A is the fit of this model to the Bloom data. Precise fit is seen at all data points except the 86%-alive point at 1 year, where the model predicts a 91.6% point. The Speer model underpredicts this point to a comparable degree. Hence, the simple Gompertz equation fits data for unperturbed breast cancer growth from onset of breast mass to lethal tumor size.

Fig. 1B presents sample growth curves simulated by the Gompertzian model. Chosen for illustrative purposes are representatives of the 10th, 50th, 70th, 90th, and 99th percentiles, ordered by rapidity of growth. These curves may be compared directly with the points of 90, 70, 50, 30, 10, and 1% survival in Fig. 1A.

The probability density curve for log(b) from the Gompertzian fit to the Bloom data is shown in Fig. 2. Graphed for comparison are the 23 values for b calculated by the method described above using the Heuser data. These values fit within the lower 15% of the distribution of b, which corresponds well with Heuser's estimate of 23%.

Fig. 3 presents P5(t) postmastectomy. The points are the actual data and the lines are the predictions of the Gompertzian model using the same probability density of log(b) and the same N(∞) as derived for the Bloom data. The tumor size at diagnosis of relapse is set at N0 = 10^11 cells. For node-negative patients the best-fit parameters are N(0) = 10^7, 74.7% cured; for the one to three positive node group N(0) = 10^5, 33.5% cured; for patients with four or more involved nodes, N(0) = 1.7 × 10^5, 12.5% cured. The model not only fits the data points well, but does so with sigmoid curves that simulate the shape of actual clinical observations (31).

DISCUSSION

The ability of the Gompertzian model with variable parameter b to simulate clinical data demonstrates that the complexities of the Speer model, which are unconfirmed experimentally, are unnecessary theoretically as well. Even with fixed N(0), N(∞), and fixed tumor size at event (recurrence, death), the Gompertzian model provides a remarkably close fit to actual observations. These fixed values are simplifying assumptions that may account for the slight deviations from the model from the data. While it has been previously observed in experimental animals that b varies more widely than does N(∞) between individual tumors of given histological type, N(∞) does, nevertheless, vary. Indeed there may be a nontrivial functional relationship between b and N(∞) (12). In addition it is clear from clinical experience that N(0) at first symptom is variable, and it is unreasonable to assume that N(0) after mastectomy should be constant in all individuals. Also, the tumor size N(t) at

GOMPERTZIAN BREAST CANCER MODEL

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overdetermination. Analyzed, actual observations, so as to avoid the dangers of additional parameters, however, must be based on carefully observed data: the diameter measurements from the first mammogram of 250 women with untreated breast cancer (21). The solid line is the fit of the Gompertzian model detailed in the text. Excellent fit is evident. B, solid lines represent growth curves (tumor cell number as a function of time of growth) for selected individual cancers simulated by the Gompertzian model which generated the curve-fit in A. Ranking the simulated tumors in order of rapidity of growth, the illustrations represent the 10th, 30th, 50th, 70th, 90th, and 99th percentiles. Each tumor is assumed to be lethal at 10^12 cells (1 liter). Since 90% of the tumors reach lethal size after the tumor representing the 10th percentile does, 90% of patients would be expected to survive past the time point at which the 10th percentile tumor reaches 10^12 cells, etc. Using this relationship the growth curves of B should be directly compared with the survival estimates of the line in A.

Relapse or death varies between individuals, and might, in fact, be partially dependent on the tumor growth rate. For example, the slight overprediction by the Gompertzian model of the percentage of Bloom's patients surviving at least 1 year may be because rapidly growing tumors are lethal at a smaller size than indolent cancers. The failure to demonstrate growth on serial mammograms for nine tumors in the Heuser data set may illustrate the imprecision of the estimation of N(0) from clinical data: the diameter measurements from the first mammogram may have included benign or premalignant tissue, or edema, with only a component of actual neoplastic cells. Since breast cancers frequently arise from areas of carcinoma-in-situ or hyperproliferative fibrocystic disease, this possibility is tenable. Allowance for variability in N(0), N(∞), and N(t) at relapse or death could permit the Gompertzian model to simulate clinical observations even more accurately than seen here. The inclusion of additional parameters, however, must be based on carefully analyzed, actual observations, so as to avoid the dangers of overdetermination.

The Gompertzian parameters used here to fit the Bloom data, and shown to be consistent with the Heuser and Fisher data sets, are appropriate for an in vivo model, and must not be compared too strictly with such in vitro estimates as provided by Salmon (19). Intact host mechanisms in vivo may add significantly to the cell-loss factor, which serves to slow clinical growth (32). Indeed, the relationship between in vitro measurements and in vivo growth characteristics of the same neoplastic tissue may be a novel approach to the estimation of cell loss and perhaps the efficacy of host defense.

The Gompertzian model simulates time-to-recurrence curves after mastectomy by assuming that N(0) and cure rate is a function of the number of involved nodes at the time of surgery. The analysis presented here thereby agrees with Skipper that the residual N(0) after mastectomy is greater when the number of positive nodes is greater (33). The Speer model, in contrast, attaches greater importance to the hypothesis of a positive linear relationship between the number of micrometastatic sites and the degree of nodal positivity. While a positive relationship between N(0) and the number of different metastatic sites is plausible, the Gompertzian model finds this hypothesis unnecessary to explain the data. It is of note that Speer's linear relationship was fit by the assumption of an average of two
involved nodes in the group of patients with one-to-three positive nodes, and five involved nodes in the four-or-more node category. This assumption may be gratuitous. In addition, clinical experience with Stage IV disease discloses no major difference in the spectrum of metastatic sites involved as a consequence of the prior nodal status (31, 34).

The Speer model advises postsurgical adjuvant chemotherapy of prolonged duration so that chemotherapy exposure may coincide with the hypothesized growth spurs. This recommendation has influenced the interpretation and design of clinical trials (35). Yet prudence in this regard is indicated by several considerations. Exponential and Gompertzian tumors should be treated early and intensively for best results (15). For breast cancer the parsimonious Gompertzian model is here shown to simulate clinical data as well or better than alternative models, which must afford it at least equal credence as regards clinical extrapolations. Secondly, pending the completion of ongoing clinical studies (36), currently available data fail to demonstrate significant advantage from prolonged adjuvant chemotherapy with a single drug combination, although some finite limit to regimen brevity without loss of efficacy may well be defined by future research (37, 38). Lastly, if the growth spurt postulated by Speer were to occur, it would more likely be due to the emergence of an aberrant clone than a change in the growth kinetics of the entire population. While it is conceivable that this aberrant clone might be more chemotherapy sensitive than the parental cells by virtue of a higher growth fraction, it might also be more insensitive as a consequence of randomly acquired biochemical drug resistance (2). Hence, attempts toward eradication of the parent population prior to the emergence of this potentially resistant clone would seem to be more fruitful than delays in therapy. Indeed, there is no reason to suppose that the parent population itself would be more sensitive to therapy at a time after the emergence of the more rapidly growing clone than before, so that even if the new clone were chemotherapy responsive, the parent population would be no easier to cure later rather than sooner. Therefore, even if the Speer model was valid phenomenologically, intensive chemotherapy applied immediately against minimal disease would still be more reasonable than prolonged low-dose or delayed treatment. Arguments in favor of immediate, intensive induction chemotherapy followed by cross-over, intensive consolidation have been presented elsewhere (2).

Since the sole intention of this paper is to demonstrate that an unadorned Gompertzian model is sufficient to simulate clinical data, a high degree of confidence in the precision of the estimated parameters is neither meant nor justified. Such refinements as the inclusion of variable $N(0)$, $N_{r}$, and $N_{o}$ would seem to be required to produce a more intuitively satisfactory model. The impact of such modifications on the probability density of $b$ remains to be determined by further research. Nevertheless, it is of speculative interest to note that setting $N(0) = 1$ and $N_{r}(t) = 4.8 \times 10^{5}$, with $N(0)$ and the probability density of $\log_{2}(b)$ as above, that the 95% confidence limits of $t_{i}$ range from about 6 or 7 months to about 9 years, with a median of about 2.25 years. This is a shorter duration of preclinical growth than is usually assumed. Epidemiological data relating the carcinogenic influence of short-exposure radiation to the incidence of breast cancer would suggest a longer lag period (39). This divergence is consistent with the concept of a time-consuming precancerous state induced by the radiation, followed by a second, perhaps random, event associated with the initiation of the Gompertzian growth of the actual malignancy. Primary carcinogens other than radiation could also operate according to this paradigm (23). Such a concept could relate directly to attempts to alter or reverse the precancerous state with pharmacological or micronutrient interventions.

The Speer model is innovative and thought provoking. At present, however, there is insufficient evidence to abandon the Gompertzian model for human breast cancer. Further refinements of the model presented here may well yield better estimates of the volume of the tumor residual after surgery or of the average duration of growth preceding clinical presentation. Nevertheless, no current model fits human or animal data better than unadorned Gompertzian growth. The therapeutic implications of other models in general, and the Speer model in particular, should be interpreted and applied with caution.

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REFERENCES

21. Foulds, L. The histologic analysis of mammary tumors of mice. II. The
cells from a single mouse mammary tumor. Cancer Res., 38: 3174-3181,
1978.
producing tumor cell line from a heterogeneous strain BALB/cfC3H mouse
27. Greenwood, M. A report on the natural duration of cancer. His Majesty's
28. Nathanson, I. T., and Welch, C. E. Life expectancy and incidence of mali-
29. Kaplan, E. I. . and Meier, P. Non-parametric estimation from incomplete
30. Cutler, S. J., and Ederer, F. Maximum utilization of the life table method in
31. Valagussa, P., Bonadonna, G., and Veronesi, U. Patterns of relapse and
33. Skipper, H. E. Comparison of the response of MAM 16/C tumors in mice
and breast cancer in women to the same three-drug combination (CAF),
using the same dose intensity unit and the same normalization standard.
34. Lee, Y-TN. Breast carcinoma: pattern of recurrence and metastasis after
36. Rivkin, S. E., Knight, W. A. III, McDivitt, R., Cruz, T., Foulkes, M.,
Osborne, C. K., Fabian, C. J., and Constanzi, J. J. Adjuvant therapy for
breast cancer with positive axillary nodes designed according to estrogen
37. Bonadonna, G., Valagussa, P., Rossi, A., Tancini, G., Brambilla, C., Zambetti,
M., and Veronesi, U. Ten-year experience with CMF-based adjuvant
chemotherapy in resectable breast cancer. Breast Cancer Res. Treat., 5: 95–
38. Henderson, I. C., Gelman, R. S., Harris, J., and Canellos, G. P. Duration of
98, 1986.
39. Tokunaga, M., Norman, J. E., Asano, M., Tokuoka, S., Ezaki, H., Nishimori,
I., and Tsuji, Y. Malignant breast tumors among atomic bomb survivors;
1979.
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