

## Quantitative Target Sizes for Breast Tumor Detection Prior to Metastasis: A Prerequisite to Rational Design of 4D Scanners for Breast Screening

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It is important to determine a breast cancer tumor target size for new screening equipment and molecular detection. Records of women aged 40-69 years diagnosed in 1988-1997 with a nonmetastasized, node-negative, or node-positive T1-stage breast cancer were abstracted from the Surveillance, Epidemiology, and End Results (SEER) public-use database. The linear, Gompertzian, lognormal, and power-exponential models of the effect of tumor size on breast cancer specific mortality were compared using corresponding transforms of size in multivariate Cox proportional hazard models. Criteria for comparison were the linearization of the size transforms and the Nagelkerke  $R^2_N$  index for the Cox models. Our results show that the assumption of a linear effect of tumor size was rejected by the linearity test ( $P=0.05$ ). The Gompertzian, lognormal, and power-exponential transforms satisfied the test with  $P$ -values of 0.08, 0.29, and 0.14, respectively. The corresponding  $R^2_N$  were 0.08410, 0.08420, and 0.08414, respectively, showing a marginally best fit with the lognormal model, which was selected as a model for small tumors. The lognormal function with unadjusted crude death rates gave a lognormal-location parameter of 25 and shape parameter of 1.7, while the corresponding values in multivariate models were 18 and 2, respectively. The derivation of the lognormal model indicates tumor growth acceleration starting at 3 mm (unadjusted crude data) or 2 mm (multivariate model). The breast cancer tumor target size for screening equipment, whether by imaging or molecular detection, is therefore 2 mm.

Key words: Breast cancer detection, Screening.

### Introduction

One in eight women in North America will develop breast cancer during her lifetime, and the incidence is increasing in most countries (1). Currently, screening mammography is the primary imaging technique for the early detection and diagnosis of breast lesions. However, mammographers miss 10-30% of all lesions (2). The overall yield of breast cancers per breast biopsy is 15 to 40% (3, 4). Even among women known to be at high-risk of breast cancer who were monitored closely with the help of MRI, the median size of detected tumors exceeded 1 cm (5).

There has been a major controversy over the effectiveness of breast cancer screening via standard mammography in reducing mortality (6-17), which is perhaps beginning to be resolved (18). This debate over standard projection mam-

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**Abbreviations:** GAM, Generalized additive models; PH, Proportional hazards; SEER, Surveillance, Epidemiology, and End Results.

mography and the tumors it misses (2) has led several research groups to investigate alternate techniques to image the breast. A long-range program has been undertaken to design scanners to detect breast tumors “before metastasis” (19). The design of such equipment requires a “target” size, *i.e.*, a tumor size for which: a) detection is feasible; and b) detection is effective in terms of ultimate reduction of mortality, if the tumors are treated. As the latter cannot be known until the equipment is built and tested epidemiologically over a 10-15 year period, the investigators are in a Catch-22 that can only be escaped by extrapolation of effect versus tumor size to smaller tumor diameters. Similar considerations apply to molecular detection. We have previously extrapolated the “linear” breast cancer data of Koscielny *et al.* (20) (linear on a probit vs. log tumor diameter plot) and predicted a 99.6% cure rate (with a 95% confidence interval of 98.2% to 99.8%) if 100% of tumors could be detected and treated before they reached a 4 mm diameter (21). Thus the very design of scanners for 4D screening (22) (digital subtraction of longitudinal 3D images) and early treatment is critically dependent on the mortality vs. diameter relationship.

The question of a target size is important, not only to address whether a minimum requirement of screening size detection capability is worthwhile or not, but also as a decision tool for women at high-risk who might need to face the choice between alternative surveillance modalities.

Verschraegen *et al.* recently investigated how tumor size relates with all-cause mortality in T1-T2 stage breast cancer, that is cases diagnosed and treated for tumors  $\leq 50$  mm (23). Using extended survival analysis, the authors found that tumor size was an important independent prognostic factor (*cf.* also (24)), that its effect was maintained irrespective of nodal status, that the relationship between tumor size and mortality was nonlinear, and that this relationship could be expressed as a Gompertzian function. The authors noted, however, that within the data range investigated, there was a problem of indeterminacy. Several functions, such as the lognormal or a power-exponential function, also provided a good fit. If the relationship cannot be determined, then it would imply that the problem of target size has no unique solution. One might, however, argue that the mortality from any cause used by the authors as end-point does not reflect the biological effect of breast cancer, *i.e.*, that the function fit might have been confounded by conditions unrelated to breast cancer. It might also be argued that by including T2-stage tumors, *i.e.*, worse prognosis, their models gave more weight to the more unfavorable advanced stages, thus obscuring finer details in the T1 stage. Furthermore, though the functions gave similar model fits, the extrapolation to small tumors differed substantially.

Since the issue of identifying a target size for screening is concerned with small tumors, it is important to reexamine which functional form (mathematical statement of the relationship between mortality and tumor size at detection) is the most appropriate for small tumors. The present study will try to make this determination in T1-stage breast cancer, using breast cancer specific mortality as the endpoint. Once an appropriate functional form is identified, we will examine the implication for screening target size.

### Materials and Methods

Patients' data were extracted from the 9-registries dataset of the Surveillance, Epidemiology, and End Results Program (SEER) of the United States (25): San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, and Metropolitan Atlanta. Selected patients were women aged from 40 to 69 years without previous history of cancer presenting with a noninflammatory invasive breast carcinoma, histologically confirmed, and diagnosed between 1988 and 1997, with pathological tumor size recorded and no larger than 20 mm, strictly confined to one breast without distant metastasis, in which curative surgery and axillary lymph node dissection were performed with at least one node removed. Node-positive cases were included, considering that node-positive patients also benefited from screening (26). Exclusion criteria for data quality concern or for scarce and extreme values have been described elsewhere (23, 27, 28). Follow-up cut-off date of the present data was December 31, 1999. The survival end event was defined as death from breast cancer.

Three functional forms of tumor size (in mm) were considered: Verschraegen's Gompertzian (23, 29),  $\exp(-\exp(-(size-15)/10))$ ; Koscielny's lognormal (20, 21), using the cumulative distribution function with lognormal-location (“mean”) parameter  $\log_e$  (18) and shape (“standard deviation”) parameter  $\log_e$  (2); Michaelson's power-exponential function (30, 31),  $1-\exp(-0.006*size^{1.7})$ . The base parameters were derived from the previous study (23), in particular to avoid over-optimism when fitting data and as a validity check by eventually detecting inconsistencies.

Cox proportional hazards models (32) were used to adjust for the effect of other known prognostic factors. Variables included were: registry area, race, marital status, tumor topography, histological type and grade, estrogen and progesterone receptor status, type of primary surgery, and administration of postoperative radiotherapy, which were modeled as qualitative variables, converted into dummy variables to allow binary coding, *e.g.* “married” versus “not married”, “high grade” versus “not high grade”, *et cetera*. Age at diagnosis, period of diagnosis, nodal involvement, and tumor size, or functions of tumor size, were modeled as

continuous (noncategorized) variables. The nodal covariate used the log-odds of nodal involvement computed by the sample logit,  $\ln[(\text{number of involved nodes}+0.5)/(\text{number of excised nodes}+0.5)]$  (33), to adjust against the variability of node dissection (34, 35). Age and period of diagnosis were used as untransformed covariates.

The binary codings of the qualitative covariates were selected after verifying that more complex factor groupings as done in earlier work were not necessary (27), and by noting that expanding or changing the grouping of major covariates did not change substantially the estimates for the variable of interest (36).

Verification of the covariates found departures from the proportional hazard assumption as have been described by other authors (27, 37-39), but there was no notable impact on the results when alternative categorizations or subset analyses were performed.

The age range was limited to 40-69 years to limit the influence of treatment variability and co-morbid conditions associated with extreme age, as has been done in another study (36), and to avoid complex modeling to adjust for the biphasic functional form of the effect of age (40-43).

For the comparison of the modeling performance of the functional forms of survival versus tumor size, we used two criteria. i) The results of the linearity test of tumor size from the procedure of generalized additive models (GAM) (32). Intuitively, the procedure can be considered as the multivariate computational analogue of using special scale grid papers to fit nonlinear models. For example, the introduction cited the probit vs. log tumor diameter plot (21). Correspondingly, with the proportional hazards and GAM procedure, if the lognormal functional form is appropriate, then size, replaced by a lognormal function, would test and display as linear. Linearity (for the log hazard ratio) is required for continuous variables in proportional hazards models (32). ii) An  $R^2$  type measure, the Nagelkerke  $R^2_N$  index.  $R^2$  in Cox models is derived from the maximum partial likelihood contributed by covariates. The  $R^2_N$  index divides  $R^2$  by its maximum attainable value to scale it within a range of 0-1.  $R^2_N$  is close to zero for a model that does not discriminate between short and long survival times, and close to one for a perfectly predictive model (44).  $R^2$  is given by  $(LR-2p)/(L^0-L^*)$  where  $LR$  is the log likelihood ratio,  $p$  is the number of parameters, and  $L^0$  is the  $-2$  log likelihood when there are no predictors.  $R^2_{max}$  is given by  $1-\exp(-L^0/n)$  where  $n$  is the sample size.  $R^2_N$  is given by  $R^2/R^2_{max}$ . The meaning of  $R^2$  for proportional hazards is similar to the  $R^2$  proportion of explained variation in ordinary regression, but not identical because of censoring. Readers interested in clinical applications of pseudo- $R^2$  measures might consult for example (35, 45-47)

(the list is not exhaustive). For alternative approaches to modeling tumor size, one might also consider the excellent software Adjuvant! (<http://www.adjuvantonline.com>).

A note about the terminology: throughout the paper we will use the qualificatives Gompertzian, power exponential model, or lognormal model, in the sense that the corresponding functions are used to transform a predictor (tumor size) which is used in a proportional hazards model, in the same way a fractional polynomial can be used to transform a predictor (42). This should not be confused with other parametric approaches which model survival time such as for example Tai *et al.*'s lognormal modeling (48).

Statistical analyses were performed using Splus (Insightful Corporation, Seattle, WA, USA).

## Results

A total of 37,765 patients were selected and constitute the study population. Characteristics and corresponding crude death rates (number of deaths divided by number of patients at risk) are summarized in Table I (some characteristics are not detailed, they can be computed from the totals). The median follow-up was 72 months (range 1-143, mean 74). The median time to death among patients who died of breast cancer was 48 months (range 1-143, mean 53). The table shows no unexpected features. Death rates higher than the overall average are observed in patients with known poor prognostic factors (race, histological grade, negative receptor status, nodal involvement). Lower death rates are observed with node-negative and smaller tumors.

Table II shows the basic proportional hazards model and results of the modeling assuming linearity of the histopathological tumor size effect on mortality. There are no major unexpected results. Period of diagnosis suggests an improvement over time. Age appears nonsignificant, indicating that the variation of breast cancer specific mortality with age is small in the selected age range 40-69 years. The interaction term for radiotherapy and breast conserving surgery is significant (49).

Table III shows the comparison between different functional forms of tumor size. The "null" column indicates a Cox proportional hazards model identical to Table II but without a tumor size covariate. Including a tumor size covariate (any functional form) provides a 6% improvement to the Cox model (increase of  $R^2_N$  from 0.079 to 0.084).

The "linear" column indicates a Cox model identical to Table II using tumor size as an untransformed covariate. The GAM test shows that the assumption of linearity is inappropriate, since it just significantly fails the test with  $P=0.0546$ . Figure

**Table I**  
Selected patient characteristics

	n	% of total	crude death rate (%)
	(total=37765)		(overall=5.6%)
Registry area			
East states	14473	38.3	6.2
Central states	8543	22.6	6.2
Western states	14749	39.1	4.8
Year of diagnosis			
1988-1992	17737	47.0	8.6
1993-1997	20028	53.0	3.0
Age at diagnosis			
40-49 year	10253	27.1	6.0
50-59 year	12491	33.1	5.6
60-69 year	15021	39.8	5.4
Race black	2324	6.2	9.3
Married status	25935	68.7	5.5
Tumor localization inner quadrant	6167	16.3	5.9
Histology ductal	29298	77.6	5.9
Pathological grade 3-4	9337	24.7	9.6
Hormone receptor (from 1990)			
Estrogen negative	5602	14.8	9.2
Progesterone negative	7315	19.4	8.3
Local regional treatment			
Breast conserving surgery (BCS)	19012	50.3	3.8
Total mastectomy	18753	49.7	7.5
Post-BCS radiotherapy	16871	44.7	3.5
Post-mastectomy radiotherapy	1081	2.9	16.0
Number of involved nodes (npos)			
npos = 0	28976	76.7	3.3
npos = 1-3	6363	16.8	9.1
npos = 4-9	1753	4.6	19.3
npos >= 10	673	1.8	35.5
Number of excised nodes (nex)			
nex = 1-9	6259	16.6	5.6
nex = 10-19	22550	59.7	5.4
nex = 20-50	8956	23.7	6.3
Tumor size			
T1a (<= 5 mm)	2300	6.1	2.7
T1b (6-10 mm)	11360	30.1	3.2
T1c (11-20 mm)	24105	63.8	7.0

1 shows the smoothed plot from the GAM analysis. The non-linearity of tumor size is apparent in Figure 1A which corresponds to the untransformed size covariate in the Cox model. The nonlinearity is also apparent in a plot of the crude unadjusted death rates as a function of tumor size (Figure 2).

The three other functional forms improve on the linear assumption with  $P$ -values that do not reject the linearization (all  $P$ 's > 0.05). The graphical effect of the transforms is shown in Figure 1B-D. All three plots are closer to a straight line than the plot for the untransformed tumor size (Figure 1A). The lognormal appears to perform best, with the largest GAM  $P$ -value ( $P=0.2934$ ) and straightest plot (Figure 1C).

The contribution of the lognormal transform to global model fit is very small, 0.2% increase of  $R^2_N$  ( $R^2_N=0.08420$ ) as compared with the model using an untransformed size covariate ( $R^2_N=0.08407$ ) (Table III). But the results of the linearity test and the graphical display indicate that the lognormal is an appropriate functional form. A check was therefore performed on unadjusted death rates to verify how the lognormal performs with crude data. A satisfying fit was obtained (plot Lognorfit, Figure 2), but required changing the base location and shape parameters to 25 and 1.7, respectively, instead of the initial values 18 and 2.

To examine the implication of the lognormal functional form, we looked at the impact of unit increments of tumor size on

**Table II**

Proportional hazards basic model, T1-stage breast cancer. Hazards ratios of breast cancer specific mortality, >1 indicates increased relative mortality. For an explanation of the interaction term BCS x RT, see work by Burzykowski and others (49).

Terms	Hazard Ratio	95% confidence interval
Registry area		
Central states / East	0.941	0.842 —1.053
Western states / East	0.787	0.711 —0.871
Race black / non black	1.422	1.226 —1.648
Marital status married / non married	0.910	0.829 —0.997
Topography inner quadrant (innerkw) / non inner	1.243	1.109 —1.393
Histology ductal (histduct) / non ductal	1.180	1.057 —1.317
Pathological grade 3-4 / other	1.791	1.634 —1.964
Hormone receptor		
Estrogen negative (ERneg) / non neg.	1.456	1.262 —1.679
Progesterone negative (PRneg) / non neg.	1.571	1.373 —1.799
Local regional treatment		
Breast conserving surgery (BCS)	0.988	0.816 —1.195
Postoperative radiotherapy (RT)	1.176	0.994 —1.392
Interaction BCS x RT	0.657	0.505 —0.853
Continuous terms		
Age at diagnosis [year]	1.002	0.997 —1.007
Log-odds of nodal involvement [dimensionless]	1.550	1.514 —1.588
Year of diagnosis [year]	0.911	0.892 —0.930
Tumor size [mm]	1.061	1.051 —1.072

mortality, as a function of where the increment occurs. This is the first derivative of the function, *i.e.*, the “speed” of mortality change as a function of tumor size. For a tumor size < 5 mm, size increase has almost no effect; this is the initial flat portion of the curve Lognorfit. For tumor size > 5 mm, each millimeter size increment has increasingly larger impact on mortality up to 10 mm, then afterwards the impact becomes less marked (curve LognorSpeed, Figure 3). The pattern of “speed” indicates an “acceleration” that starts at 3 mm and peaks at 10 mm, and afterwards a deceleration. This is the second derivative, shown as curve LognorAccel in Figure 3. Figure 3 was built using the “unadjusted” lognormal function with base location and shape parameters 25 and 1.7. The

curves are similar when using the “multivariate” lognormal function with base parameters 18 and 2, except for a shift towards earlier acceleration that starts at 2 mm and peaks at 5 mm. The target sizes are most clearly indicated by the slope of the acceleration curve, *i.e.*, the third derivative, in Figure 4. These curves seem to rise from zero at these tumor sizes. Any quantitative choice for a threshold would seem arbitrary, so we leave these estimates to visual judgement.

**Discussion**

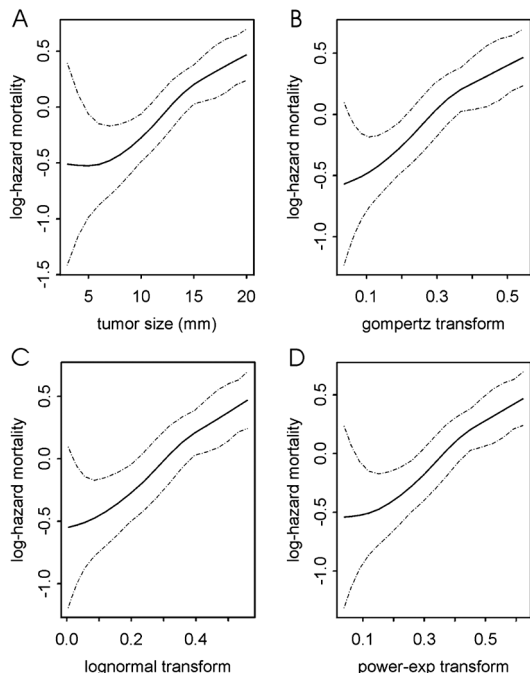
Limitations and caveats of the SEER data have been discussed previously (23, 27). The data is heterogeneous and

**Table III**

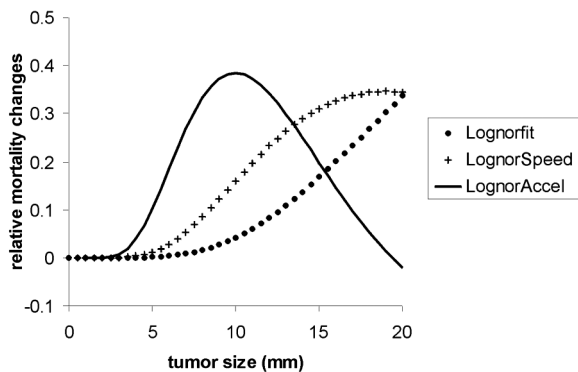
Effect of tumor size in T1-stage breast cancer evaluated by proportional hazards (PH) models (cf. template in Table II). The PH models differed only by the tumor size covariate, which was either not included in the PH analysis, or included as untransformed covariate (linear assumption), or included after transform with the gompertz, lognormal, or power-exponential function. Total = 37765 patients, 2123 breast cancer deaths.

	Functional forms of tumor size				
	null (PH without size variable)	linear (size variable as is)	gompertz	lognormal	power exponential
Coefficient	n.a.	0.0596	1.7591	1.6765	1.6583
std.error coefficient	n.a.	0.0051	0.1494	0.1422	0.1412
GAM <i>P</i> (nonlinearity)	n.a.	0.0546	0.0769	0.2934	0.1406
Sum squares deviance residuals	13637.63	13507.43	13506.98	13503.91	13505.52
$R^2_N$	0.07884	0.08407	0.08410	0.08420	0.08414

*Coefficient*: Log-hazard ratio of breast cancer mortality for the tumor size variable. *n.a.*: Not applicable (PH model without size variable). *GAM P*(nonlinearity): *P*-value for departure from linearity. Larger values indicate better concordance with PH modeling assumption of linearity. *Sum squares deviance residuals*: Smaller values indicate improved model.  $R^2_N$ : Nagelkerke’s  $R^2$  measure of predictive ability, 0 indicate nonpredictive model, 1 indicate perfect prediction.

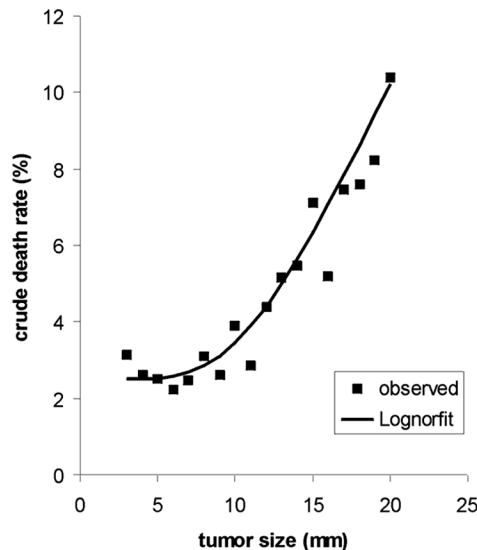


**Figure 1:** Effect of tumor size on breast cancer mortality estimated in multivariate proportional hazards models. **A:** tumor size (mm) as untransformed variable. **B:** Gompertz transform. **C:** lognormal cumulative distribution function. **D:** power exponential. Dotted lines: 95% confidence interval. The best linearization relating tumor size to the log hazard of mortality is obtained with the lognormal transform.

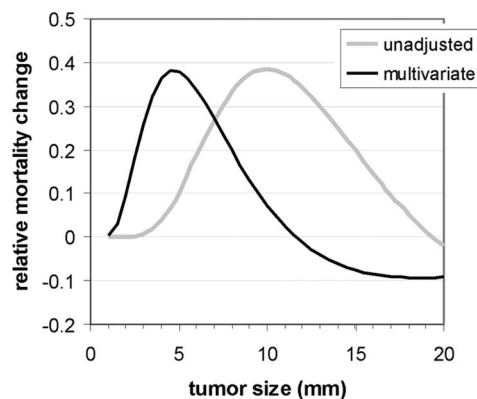


**Figure 3:** Implications of the lognormal model. Lognorfit = fit of unadjusted crude breast cancer mortality (parameters from Figure 2). LognorSpeed = slope of Lognorfit, indicates the impact of each unit increment of tumor size on mortality. LognorAccel = slope of LognorSpeed, indicates the “acceleration” pattern. Arbitrary vertical scale to allow plots on the same graph.

retrospective. The selection of cases implies the most complete records, and thus might not be representative of the population. The lack of data on systemic treatment might have confounded some results. Pathological review was not performed. Measurements of tumor size and other parameters might be subject to errors, from the initial clinical assessment, through abstraction to recording of the data. The differences between the different models are extremely



**Figure 2:** Unadjusted crude mortality from breast cancer as a function of tumor size (observed) and lognormal fit (Lognorfit) with location parameter  $\log_e(25)$  and shape parameter  $\log_e(1.7)$ .



**Figure 4:** Slope of the acceleration curves LognorAccel (third derivative) for the unadjusted crude data and multivariate models, most clearly showing that the target sizes for screening of breast tumors are of 2 mm and 3 mm, respectively.

small and the confidence intervals are wide, they can provide no certainty. Other modeling approaches have not been explored (42). Many issues such as problems of breast texture, anatomical variability, shape irregularity of tumors, and time frame to schedule surveillance are beyond the scope of the paper. The terms “speed” and “acceleration” make the assumption that the impact of increases of tumor size on mortality reflects tumor growth rates. Without a time scale for successive measurements of tumor size, we cannot verify whether or not the impact on mortality correlates with growth rates. For all these reasons, the results need to be weighted in view of the literature.

The concordance with cell kinetics studies was mentioned elsewhere (23). Of more immediate interest are the clinical

studies that have reported the growth rate of breast tumors based on the direct observation of untreated tumors over time (50-52). One of the earliest reports was von Fournier *et al.*'s observation of 53 cases of mammary carcinomas for which the tumor could be retrospectively identified on serial mammographies (53). Measurements over time showed changes in growth rates, 33% of the carcinomas accelerating, 66% decelerating. Later, Spratt and von Fournier studied the serial mammographies in 448 patients from Heidelberg and Louisville, in whom the tumor was retrospectively identified on the initial mammogram, or in whom the patients refused treatment but consented to serial mammograms (52). Two observations were made in each of 335 patients. A mean of 3.4 observations were made in the remaining 113 patients. The measurements over time showed that initially, growth was nearly exponential, but growth retardation became progressively more pronounced. Modeling indicated a decelerating growth (51). The authors used the term "decelerating" in referring to equations as a function of time that are S-shaped curves, have an inflection point, and describe initially rapid growth that slows progressively. Generalized logistic curves, which belong to the family of transition functions like the Gompertzian or the lognormal, were used to fit the growth rates (52, 54).

Galante *et al.* measured the doubling time of 196 consecutive breast cancers by means of two successive mammographies at an average interval of 30 days (55). Their preliminary report found a correlation between faster growing tumors and the proportion of recurrences. An updated analysis later confirmed the association between faster growth rate and poorer prognosis (56). Galante *et al.* concluded from their analysis that growth rate and metastatic potential are not the same in primary breast cancers (56). Verschraegen *et al.* remarked too that tumor growth and metastasis appeared to be distinct phenotypic manifestations (23). The correlation between growth rate computed from mammography measurements taken at different points in time and prognosis was confirmed in another study by Kuroishi *et al.* (57).

Our results are concordant with these direct observations of growth rate (51, 54-57), as well with indirect estimations of growth rate (20, 21, 23, 30, 31). The concordance, despite the many different endpoints used in the literature to investigate tumor size (23), can be explained by the fact that breast cancer mortality is the major cause of death among patients diagnosed with breast cancer, and by the fact that various measures such as recurrence, metastases, and disease free survival, are expressions of the intensity of the disease.

Of particular notice is the lognormal model that might give an additional insight into tumor growth latency and acceleration. Investigating the lag time between treatment and recurrence to determine whether a tumor that recurs after

mastectomy grows at a constant rate or whether it grows rapidly following a period of tumor dormancy, Demicheli and others observed that the hypothesis of uninterrupted constant growth could not be supported (58, 59). The model of latency and acceleration summarized in Figures 3 and 4 parallels Demicheli's description of a period of tumor dormancy followed by more rapid growth.

The  $R^2_N$  values of Table III are small. Schemper has remarked that often in practice, covariates can explain only a small fraction of the variation among outcome values, regardless of the type of regression model (60). Therefore it is important to know that even strong and highly significant covariates of a study may not automatically translate into sufficiently accurate prediction or close determination of individual outcome. We believe that the use of the  $R^2$  type of measure rather than  $P$ -values provide a more realistic view of the results of the data analysis.

In a strict sense the problem of indeterminacy of the functional form of the effect of tumor size remains unsolved. The confidence intervals are wide due to the small number of events (Figure 1). The linear functional form of tumor size could be considered as a satisfying approximation. But, for an investigation of fine details, it is insufficient. The three nonlinear functional forms of tumor size improved on the linear form by a hairsbreadth. Among the three nonlinear forms, Table III and the review of the literature suggest that for small tumors, the lognormal is likely the most appropriate function.

Based on the lognormal, we conclude that 2 mm (from a multivariate model) or 3 mm (from a crude unadjusted model) should be the target size for improved screening. In designing imaging modalities (1, 19) and molecular detection (61-66) or molecular imaging (67) for screening, the more conservative estimate of 2 mm target size would seem warranted.

There are three questions that our quantitative target size raises:

- I. *What is the relationship of target size to angiogenesis?* Tumor angiogenesis, *e.g.* high microvessel density, is associated with increased risk of metastasis (68) and decreased survival (69). Until tumor angiogenesis occurs, tumors grow no larger than 2-4 mm in diameter (70). But at the same time, it was found (71) that microvessel density decreased as tumor volume increased, though this has to be tempered with the discovery of pseudovascularization or "vascular mimicry" of certain tumors (72), which has been found to apply to some breast tumors (73-76). Thus there is nothing in the data or the functional form of tumor size that suggests a thresh-

old for sudden growth or metastasis (77), perhaps due to angiogenesis. On the other hand, there may be such a threshold for each individual tumor, which is blurred out in a population average. This raises the possibility that the functional form of tumor size for an individual tumor may be quite different from the average functional form of tumor size for the population.

- II. *Can we combine target size with cellular and cytogenetic models for tumor growth?* At a tissue level, tumor growth requires an exquisite set of microenvironmental factors for the cells to express their malignant phenotype or for the tumor to progress (78-84). But as the tumor grows, the tumor-microenvironment factors that were in favor of growth are disrupted and become less favorable to tumor growth.
- III. *Which imaging modalities can achieve the required resolution, safely for screening?* This is the theme of most of the contending papers in this special issue of *Technology in Cancer Research and Treatment*. A target of 2-3 mm will push most imaging modalities to their limits, which, fortunately, have not yet been reached, leaving room for research and improvement. Thus this target can provide a goad to technical and mathematical advancements.

Once a small tumor is found, its destruction can presumably lead to cure, if it hasn't yet metastasized and if more small tumors don't form. Various technologies are in contention for destroying small tumors by ultrasound, laser, microwave or radio wave ablation (85-104).

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