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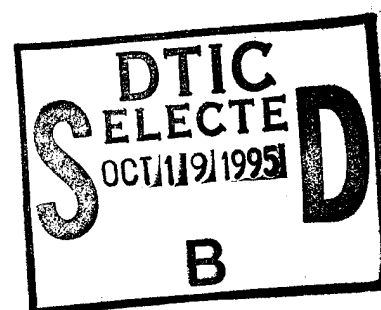
TITLE: Developing and Implementing the AJCC Prognostic System for Breast Cancer

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CONTRACTING ORGANIZATION: University of Nevada
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13. ABSTRACT (Maximum 200 words)

The TNM staging system for breast cancer has been in existence for over 35 years in America. Within the last ten years it has become clear that: (1) the TNM staging system is not highly accurate, and (2) if new breast cancer prognostic factors are to be integrated with the TNM variables to increase outcome prediction accuracy, a new prognostic system is required.

The goal of this project is the creation of a computer-based prognostic system for breast cancer that: (1) is significantly more accurate than the TNM staging system, (2) predicts survival over time based on therapy, (3) and presents its predictions in a manner that physicians can understand.

During the first year of the project, we made substantial progress on all 3 major tasks. We believe that we will be able to successfully meet our ultimate goal of providing a computer-based prognostic system that is more accurate than the TNM staging system and that is easy to use and understand, within the four year time frame of this grant.

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U.S. Army Midterm Report

INTRODUCTION

The TNM staging system for breast cancer has been in existence for over 35 years in America. Within the last ten years it has become clear that: (1) the TNM staging system is not highly accurate, and (2) if new breast cancer prognostic factors are to be integrated with the TNM variables to increase outcome prediction accuracy, a new prognostic system is required.

The goal of this project is the creation of a computer-based prognostic system for breast cancer that: (1) is significantly more accurate than the TNM staging system, (2) predicts survival over time based on therapy, (3) and presents its predictions in a manner that physicians can understand.

BODY: FIRST YEAR ACCOMPLISHMENTS

Task 1. Data analysis and prognostic factor evaluation.

1.01) Extend analysis of binary survival endpoint to 10 year survival.

We are currently analyzing SEER 10 year survival data. Preliminary results suggest that the predictors collected at disease discovery are less accurate in predicting 10 year survival than 5 year survival. It may be that predictors be collected at regular intervals after discovery and therapy, and these predictors be used to estimate 10 year survival. Additionally, conditional probability of survival can be calculated, i.e., if a woman survives for five years, what is her probability of living another five years.

1.02) Extend the analysis to recurrence as an endpoint.

We have analyzed recurrence as an end-point, see 1.08.1 for preliminary results

1.03) Comparison of prognostic models.

We have compared statistical method to artificial neural networks in terms of five year breast cancer-specific survival. Selected results are shown below.

NCDB/PCE 1983 Breast Cancer Data Set.

PREDICTION MODEL	ACCURACY*	SPECIFICATIONS
pTNM Stages	.720	Ø, I, IIA, IIB, IIIA, IIIB, IV
Principal Components Analysis	.714	one scaling iteration
CART, pruned	.753	9 nodes
CART, shrunk	.762	13.7 nodes
Stepwise Logistic Regression	.776	cubic splines
Fuzzy ARTMAP NN**	.738	54-F2a, 128-1
Cascade Correlation NN	.761	54-21-1
Conjugate Gradient Descent NN	.774	54-30-1
Probabilistic NN	.777	bandwidth = 16s
Backpropagation NN	.784	54-5-1

* The area under the curve of the receiver operating characteristic.

** NN, neural network.

These results were recently published.

Burke HB, Rosen DB, Goodman PH. Comparing the prediction accuracy of artificial neural networks and other statistical models for breast cancer survival. In G. Tesauro, D.S. Touretzky, T.K. Leen, eds. *Advances in Neural Information Processing Systems 7*. Cambridge, MA; MIT Press, 1995, 1063-68.

Additional publications related to statistical methods in breast cancer are listed below.

Burke HB. Statistical analysis of complex systems in biomedicine. In D. Fisher and H. Lenz, eds. *Learning from Data: Artificial Intelligence and Statistics V*. New York: Springer-Verlag, 1995, in press

Burke HB. Artificial neural networks for cancer research: outcome prediction. *Sem Surg Onc* 1994;10:73-79.

Burke HB, Goodman PH, Rosen DB. Artificial neural networks for outcome prediction in cancer. In *Proceedings of the World Congress on Neural Networks*. Hillsdale, NJ: Lawrence Erlbaum Assoc. Inc., 1994; 53-56.

Burke HB, Goodman PH, Rosen DB. Neural networks significantly improve cancer staging accuracy. *Proceedings 1994 IEEE Seventh Symposium on Computer-Based Medical Systems* 1994; 200.

Burke HB, Rosen DB, Goodman PH. Comparing the prediction accuracy of statistical models and artificial neural networks in breast cancer. *Preliminary Papers of the Fifth International Workshop on Artificial Intelligence and Statistics* 1995; 87.

Burke HB, Goodman PH, Rosen DB. Applying artificial neural networks to medical knowledge domain. *Proceedings of the International Symposium on Integrating Knowledge and Neural Heuristics* 1995, in press.

Burke HB. Artificial neural networks and biomedicine. *Proceedings of the Workshop on Environmental and Energy Applications of Neural Networks* 1995, in press.

Burke HB. The importance of artificial neural networks in biomedicine. *Proceedings of the World Congress on Neural Networks*. Hillsdale, NJ: Lawrence Erlbaum Associates Inc. 1995, 725-30.

Burke HB, Goodman PH, Rosen DB, Hellier JH, Weinstein JN, Winchester DP, Harrell Jr FE, Marks JR, Bostwick DG, Osteen RT, Zincke H, Henson DE. Improving breast cancer survival prediction accuracy. Submitted for publication.

1.04.2) Create a taxonomy of prognostic factors in breast cancer.

We have created a taxonomy of prognostic factors in breast cancer. The taxonomy was based on levels of analysis: demographic, anatomic/cellular, and molecular genetic. In addition, we collected, described, and cited the primary sources for the major breast cancer prognostic factors, of which there are over 76 at the current time (with a new putative prognostic factor reported almost every month). This work was recently published.

Burke HB, Hutter RVP, Henson DE. Breast Carcinoma. In P Hermanek, MK Gospadoriwicz, DE Henson, RVP Hutter, LH Sobin, eds. *UICC Prognostic Factors in Cancer*. Berlin: Springer-Verlag, 1995, 165-176.

1.04.3) Prognostic Factors in Breast Cancer book.

There are many problems and pitfalls in the discovery, analysis, and use of prognostic factors. A book, that uses breast cancer as its cancer site, will be helpful in prognostic factor research for all cancers. Although we have not yet reached an agreement with a publisher regarding a book on prognostic factors in breast cancer, we are actively publishing on the subject. (See also 1.03 for statistical publications.)

Burke HB. *Multiple markers to enhance clinical utilities of cancer tests*. In M Hanausek, Z Walaszek, eds. *Methods in Molecular Biology: Tumor Marker Protocols*. Humana Press Inc., in preparation.

Burke HB. *Increasing the power of surrogate endpoint biomarkers: the aggregation of predictive factors*. *J Cell Biochem*, 1994;19S:278-82.

Burke HB. *The future of the TNM staging system*. In preparation.

Burke HB, and collaborators. *A proposal for the structured reporting of cancer prognostic factor studies*. In preparation.

Burke HB. *Prognostic methods in cancer: a review*. In preparation.

1.06.3) Determining minimum data set size.

We have found that for predicting five year breast cancer-specific survival, using currently collected prognostic factors and a 30% five-year breast cancer-specific mortality rate, we found that approximately 2,300 patients are required for maximum accuracy. More than 2,300 cases does not provide any improvement in prediction accuracy. We have not yet reported these results because we are working with Memorial Sloan-Kettering Cancer Center on extending it to molecular-genetic prognostic factors.

1.08.1) Recurrence analysis.

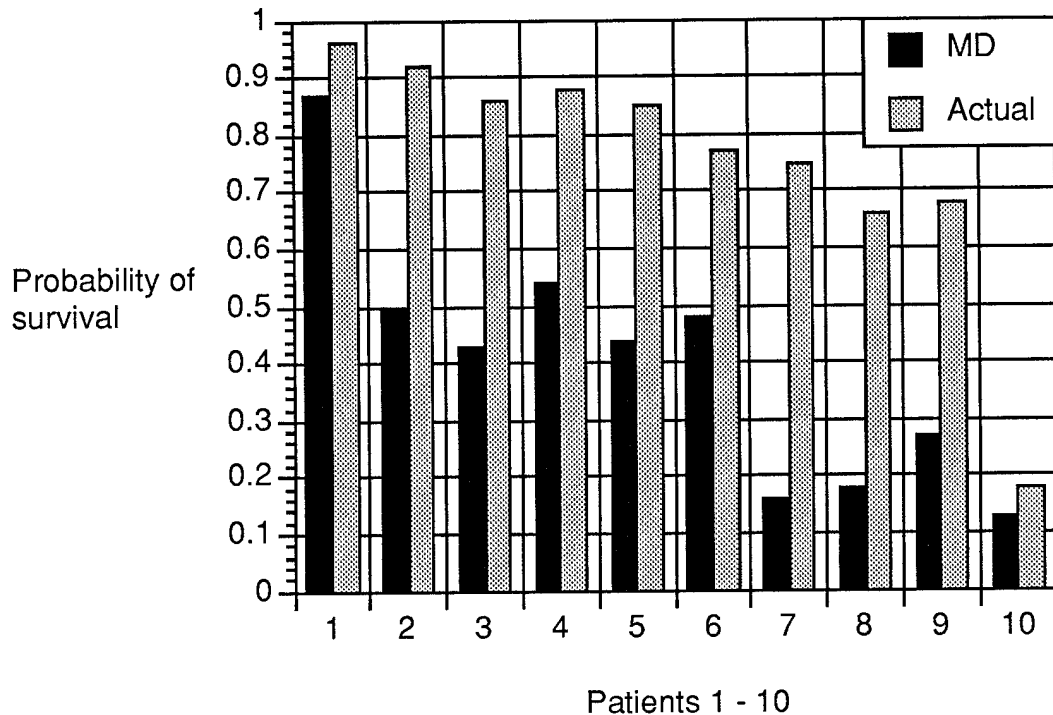
There are two types of recurrence analyses; predicting recurrence based on data at discovery, and predicting survival based on there having been a recurrence. We are primarily interested in predicting recurrence at discovery. In other words, at this time, we are interested in using recurrence as an endpoint rather than as a prognostic factor for survival.

The accuracy (area under the receiver operating characteristic curve) of the probability of recurrence predictions at three, four and five years, for those women who are alive at each time period, is .731, .714, and .701, respectively. We can make two observations regarding these results. (1) Based on our analysis of five year breast cancer-specific survival, predicting recurrence from data collected at the discovery of disease is less accurate than predicting survival from the same data. (2) Predictive accuracy declines as the prediction extends further into the future.

1.11) Patient information and physician credibility.

We have performed a small, preliminary survey of oncologists' assessment of five year breast cancer specific survival. The survey is preliminary because

we want to survey more oncologists, and we want to survey oncologic surgeons, pathologists, and radiation oncologists. Oncologists were asked to estimate ten patient's five year breast cancer specific survival. (Survey instrument is presented in Appendix B). The mean of the oncologist's predictions for each patient was compared with the patient's actual survival. (see Figure below)



Oncologists tended to be pessimistic regarding breast cancer patient prognosis. Since the therapy for patients with poor prognoses is different therapy from that of patients with a good prognosis, this finding (currently unpublished) has important implications for patient care.

As shown in 1.05 above, the TNM staging system's accuracy is .720. This is only approximately 44% better than chance in predicting whether a woman with breast cancer will survive five years. Our prognostic system is significantly more accurate than the TNM staging system. This result has been submitted for publication.

Burke HB, Goodman PH, Rosen DB, Hellier JH, Weinstein JN, Winchester DP, Harrell Jr FE, Marks JR, Bostwick DG, Osteen RT, Zincke H, Henson DE. Improving cancer survival prediction accuracy. Submitted for publication.

Task 2. Developing the prognostic model.

2.1) Survival curves for individual patients and for groups of patients:

2.1.1) Generate survival curves for 10 year data.

Our work on 5 year survival is directly applicable to 10 year survival.

2.1.2) Generating survival curves.

We have compared the accuracy of the major statistical methods to artificial neural networks in predicting cancer-specific five-year survival for breast cancer (1.03). We extend this work by creating an artificial neural network that predicts individual patient survival over time (survival curves).

Ideally, a model that estimates the probability of survival over time should: (1) Generate an accurate estimate of an individual patient's probability of survival over time, i.e., an accurate survival curve. (2) Accommodate censored cases (with a minimum of assumptions). (3) Capture the predictive power of nonlinear and interacting prognostic factors. (4) Allow prognostic factors to have different effects on the probability of survival over time, i.e., proportional hazards is not assumed.

The methods discussed below accommodate censored cases, some more successfully than others.

The Kaplan-Meier method (Kaplan, 1958) is a descriptive method for prediction over time based on covariate "bins". Bins can range from one, all patients, to a bin for each covariate or level of covariate. The Kaplan-Meier can accommodate censored cases, and, like most methods that accommodate censoring, its accuracy can suffer as censoring increases because there are fewer cases to base prediction upon. The Kaplan-Meier can be less accurate than inferential models because it assumes independence, whereas most inferential models only assume conditional independence (any dependence is explained by the covariates). The Kaplan-Meier's problems are those of a bin model, including; an exponential increase in the number of bins as the number of covariates increase, it loses information by requiring that continuous variables be cut into ranges, and there is no optimization strategy for finding the most accurate combination of bins.

The Cox proportional hazards model (Cox, 1972) is a linear effects model. It estimates the importance of each covariate, and it handles censored cases. It assumes proportional hazards and it does not provide a survival curve without the imputation of a baseline survival curve.

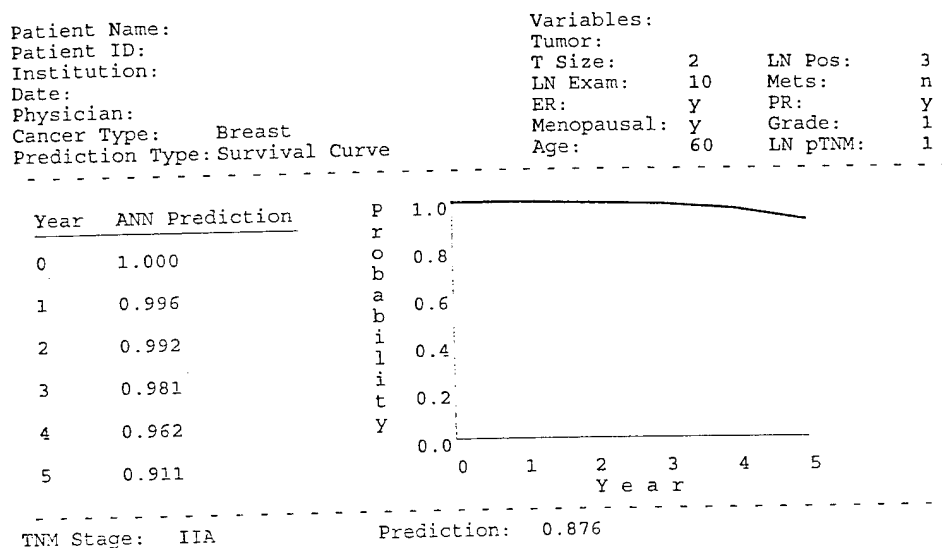
Faraggi and Simon (1994) nest an artificial neural network in the Cox proportional hazards model, replacing the linear combination of covariates with an artificial neural network. This solves the problem of capturing nonlinear and interactional covariates, while handling censored cases. As an artificial neural network generalization of the Cox proportional hazards model, it retains the assumption of proportional hazards and it does not provide a survival curve unless a baseline survival curve is imputed.

The simplest approach to a full artificial neural network implementation of a probability of survival over time model is to create a artificial neural network for each time interval. Data would be time interval specific; the censored cases would be dropped from the analysis, i.e., not included in the subsequent time interval artificial neural networks, at the time of censoring. Survival probabilities can be generated by each time-interval-specific artificial neural network, and they can be multiplied in succession to provide a survival prediction for each time interval. A problem with this approach is that the information contained in variables over several time periods is lost, because each time period is a separate artificial neural network. One artificial neural network spanning all time intervals partially solves this problem. This approach, with a two layer neural network, is similar to a series of logistic regression models, one for each time interval. (Cox vs. LR comparison here).

Ravdin and Clark (1992), provide the earliest attempt to create a probability of survival artificial neural network. Employing a commercial artificial neural network, Ravdin and Clark generate a prognostic index, which is roughly proportional to the survival probability, which they stratify into four groups by predicted prognosis. They code time as an input variable, each patient's data is reproduced for each time interval, in order to represent censored outcomes. Thus, for four time intervals there are four representations of each patient, with each representation differing only in its time interval failure information, i.e., outcome status (alive/dead), and censored status. Ravdin and Clark drop censored cases from the analysis at the time interval at which censoring occurs. Since only alive or dead remain in the analysis, as time continues, the ratio of dead to alive increases dramatically, resulting in too many patients dead and too few patients alive in the later time intervals. In order to rectify this imbalance, at each time interval the authors use the Kaplan-Meier product-limit estimate to determine the overall ratio of survivor to nonsurvivor. They use this ratio, based on the independence assumption, to determine the number of dead to randomly remove from the study in later time intervals. But the Kaplan-Meier estimate is itself sensitive to censoring, and the independence assumption must be justified. When faced with this situation, a better response might be to use the predictors to determine who to remove from the study. Also, throwing out patients removes predictive information from the study.

Liestold and Anderson (1994) create an artificial neural network that estimates the probability of survival over time. Their model creates one artificial neural network, and represents each time interval as a separate output node. Each output node generates a conditional survival probability. A possible problem with generating conditional survival probabilities is that the error of each prediction (variance) may accumulate when the predictions are multiplied together to create the survival estimate over time. Further, there is the problem of equal training of the nodes resulting in unequal accuracy, as some nodes are overfitted and some underfitted. Although their model retains the proportional hazards assumption, they suggest stratifying the covariates in order to remove this assumption. The authors go on to add a penalty term to the model, to penalize for deviations from proportionality.

We have implemented a new artificial neural network, one that achieves the four objectives stated above for estimating survival over time. We have also created a Windows-based interface for online prediction of individual patient survival. (see below)



The figure at the right is an individual patient's five year breast cancer-specific survival curve, based on the ten prognostic factors shown in the upper right. At the left are the numerical values associated with the curve at each year. At the bottom is a computerization of the TNM staging system. Given the TNM variables, it automatically generates the TNM stage. In addition, it also presents the probability of five year breast cancer-specific survival associated with that stage. This work has been published.

Burke HB, Hoang A, Rosen DB. Survival function estimates in cancer using artificial neural networks. Proceedings of the World Congress on Neural Networks. Hillsdale, NJ: Lawrence Erlbaum Assoc. Inc. 1995, 742-7.

Burke HB, Goodman PH, Rosen DB. A computerized prediction system for cancer patient survival that uses an artificial neural network. Proceedings of the First World Congress on Computational Medicine and Public Health 1995, in press.

2.1.3) Determining the accuracy of the survival curves.

The accuracy of predicted survival curves, with respect to the actual times of death (or of censoring) of the patients in a data set, can be evaluated in terms of accuracies of the survival or hazard probabilities at each point in time. The accuracy of these component probability predictions should be assessed using a (strictly) proper scoring rule, such as the quadratic (e.g. Brier) or logarithmic score, whose expectation is maximized by (and only by) predicting the true probability (Winkler, 1969; Savage, 1971). Our recent work has shown that such scoring rules are in fact averages of actual decision-making loss or regret (Rosen, 1995, 1996). These averages are over the potential decision problems in which the probability predictions might be used, each such decision problem being characterized by the regret associated with a false positive vs. that associated with a false negative. This theory also suggests an ROC curve alternative whose area is a proper scoring rule.

We also seek a measure of the extent to which the predictions are in the correct relative order, regardless of their numerical values. Such indices (Somers' D_{yx} , c index, ...) are often called measures of ordinal discrimination, or of concordance (the number of pairs of predictions in the correct order), and in the dichotomous-outcome case, can arise from the empirical ROC curve. When a proper scoring rule is used to evaluate the overall correspondence of the predictions with the outcome, we wish to know how much of this inaccuracy could be due to miscalibration, and how much is unequivocally due to mis-ordering. This question is difficult to answer using concordance or ROC-based indices without strong parametric assumptions. We have introduced (Rosen 1994; Rosen, Burke, & Goodman, 1995a) a procedure identifying an unequivocal misdiscrimination component in any proper score, including logarithmic (binomial log-likelihood or Kullback-Liebler).

The procedure calibrates the predictions on a given data set so that all proper scores are simultaneously optimized on that data subject to the constraint that the ordering of the predictions not change (though ties can be produced). This constraint is very strong; without it such a calibration could often achieve a perfect score. The resulting score of interest (log-likelihood, Brier, etc.) on these self-calibrated predictions tells how much of the original score cannot possibly be improved by any order-preserving recalibration, and is thus an index of ordinal discrimination. The method can also be applied to predictions of a continuous dependent variable's mean.

This work has recently been published.

Rosen DB. Ordinal discrimination index for any proper scoring rule. Published Abstract. *Medical Decision Making* 1994;14:440.

Rosen DB. How good were those probability predictions? The expected recommendation loss (ERL) scoring rule (8 pp.). To appear in *Maximum Entropy and Bayesian Methods: Proceedings of the Thirteenth International Workshop (August 1993)*, G. Heidbreder, ed., Kluwer, Dordrecht, The Netherlands, 1995a.

Rosen DB, Burke HB, Goodman PH. Improving prediction accuracy using a calibration postprocessor. Submitted for publication, 1995b.

Rosen DB. Issues in selecting empirical performance measures for probabilistic classifiers. In *Maximum Entropy and Bayesian Methods: Proceedings of the Fifteenth International Workshop (July/August 1995)*, K. Hanson and R. Silver, eds., Kluwer, Dordrecht, The Netherlands, 1996, in press.

2.1.4) Comparison of artificial neural networks with Cox proportional hazards model.

We are currently performing these comparisons, using several different measures of accuracy. (see 2.1.3)

2.2) Missing data.

Most data analyses either drop cases with missing data or impute some measure of central tendency for the missing data. Dropping cases has at least two negative effects: the remaining data may be biased, and it reduces the amount of data available for analysis. It may be possible to impute a central tendency value for missing data. But there are a number of statistical problems with the imputation of a central tendency, especially when there are many cases with missing data or when the important predictor variables contain much of the missing data..

The current cancer prediction system, the TNM staging system, does not provide a stage if one of the TNM variable is missing, nor does it provide guidance regarding prediction with missing variables (Beahrs, 1992).

In cancer prognostic factor research, many large data sets, both retrospective and prospective, suffer from missing data, i.e., missing prognostic factor information (Burke, 1993, 1995b, 1995c). We estimate that 75 - 80% of cases in some national data sets contain missing data. The usual approach to missing data is to remove the entire case, but this reduction in data set size, combined with the further reduction caused by splitting the data set into training and testing subsets, can significantly reduce the accuracy of statistical models. As Little and Rubin [1987] note:

"Statistical packages typically exclude units that have missing value codes for any of the variables involved in an analysis. This strategy is generally inappropriate, since the investigator is usually interested in making inferences about the entire target population, rather than the portion of the target population that would provide responses to all relevant variables in the analysis."

Moreover, when one is predicting an individual patient's outcome in a clinical situation, there is no guarantee that values for every predictive factor will be known for that individual; clearly "removing the case" is not an option in clinical situations. The result of a missing prognostic factor in clinical practice is usually an ad hoc guess of prognosis. For example, in the TNM staging system, if one of the covariates is not available no stage can be assigned, so the clinician must guess the patient's prognosis.

The missing data problem is especially severe in small data sets, where all data is precious. Here the problem can be enough to preclude the analysis of the data set. For example, in the Duke University breast cancer data set, which contains several of the new molecular-genetic prognostic factors, of the 230 cases in the data set, only 98 cases have no missing data. Given the number of covariates and the event rate (death from breast cancer), 98 cases are not sufficient for an analysis of these data. Because the new molecular-genetic prognostic factors are not always collected, and because molecular-genetic prognostic factors can be very powerful predictors of survival, it is essential that the problem of missing data be solved so that outcome prediction in cancer can advance.

When constructing a statistical model to predict a cancer outcome, e.g. survival, missing data (incomplete feature vectors) can cause a decrease in predictive accuracy (compared to the data set which does not contain missing data) because: (1) the missing data itself reduces the amount of data available to serve as a basis for prediction, and (2) the usual practice of removing cases with missing data, which reduces sample size, and therefore accuracy, reduces the amount of usable data to a level below that required to maintain predictive accuracy. One can never predict the true values of the missing data, but unless there are a great many missing values for a particular covariate, substituting values generated by an efficient method should improve prediction accuracy, compared to removing the cases with missing data. In other words, the problem we address is what method best deals with missing data, allowing us to retain the rest of the patient's data. Best means the method that produces the least biased estimates of the missing data values. Commonly used methods for estimating the missing values, e.g., imputing the mean covariate value or zero for the missing data, create strong biases and should be avoided (Little, 1992; Little and Rubin, 1987).

To be more precise, there are two missing data problems. One involves covariate values missing in the data sets used to train and test statistical prediction methods, such as logistic regression or Cox proportional hazards. The other involves missing predictors in a clinical situation; the patient's chart does not contain all the expected prognostic factors. For missing values, we prefer a method that uses all the information in the data set to estimate the missing values. This approach contrasts with, and is more accurate than, the simple insertion of a descriptive value (usually some measure of central tendency) of the covariate (e.g., a mean or median value) (Vamplew and Adams, 1992).

We are developing an artificial neural network approach for solving the missing data problem, using Normalized Radial Basis Functions. Normalized Radial Basis Functions based on estimating the joint input-output data distribution using a network representing mixtures of many multivariate gaussians.

Normalized Radial Basis Function (NRBF) networks (Moody and Darken, 1988, 1989; Poggio, 1989; Nowlan, 1990) model the output as a weighted average of an output value associated with each hidden unit. A given hidden unit also has

an associated position in the input space, and a "width" in each input dimension specifying how fast the weighting (importance in the weighted average) falls off in that dimension. Thus each hidden unit, or term in the model, is radial (or ellipsoidal) in that its influence decreases in all directions from its center. This is in contrast to conventional sigmoidal-projective neural networks, which do not use a weighted average, and in which each hidden unit has no "center" point, but rather selects (through its input weight vector) an arbitrary direction (linear projection) in the input space, where its contribution to the final prediction is a sigmoidal function along this direction. Training of the NRBF is accomplished using any of the standard neural network algorithms based on backpropagation of errors for calculation of the gradient of the log-likelihood with respect to the parameters (weights) of the network.

An advantage of a trained NRBF (when using gaussians as the radial weighting functions) is its ability to easily handle missing inputs during performance (i.e. prediction or recall), since merely ignoring those input components that are missing in a given input vector is equivalent to the correct Bayesian marginalization over the missing components.

The nonparametric form of the NRBF is known as a kernel estimator or Probabilistic Neural Network (Rosenblatt, 1956; Parzen, 1962; Nadaraya, 1964; Watson, 1964; Specht, 1990, 1991). Here, instead of using an optimization criterion to set the parameters of the network, there is a single hidden unit corresponding to each training case, whose location in the input space, as well as output value, is taken directly as those input and output values defining the case. These methods are sometimes called memory-based or case-based, since they store all the training data but require little or no computation during training. Thus these methods are attractive where training time is expensive but storage space during performance is not limiting, and they retain the ability to handle missing data during performance.

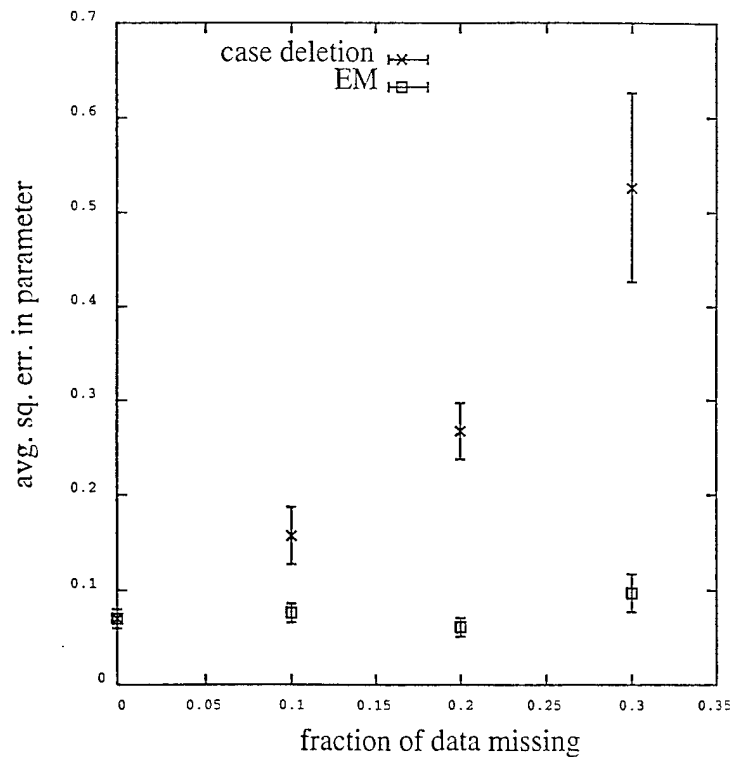
The NRBF can be generalized to form a Gaussian Mixture Network (Tresp, et al., 1994, Ghahramani and Jordan, 1994) for the joint (input-output, i.e. predictor-response) probability density. This can use basis functions with non-diagonal variance-covariance matrices, thus incorporating some of the projective aspects of conventional sigmoidal neural networks. More importantly, they can be trained using the maximum-joint-likelihood (probability of observed training data inputs and outputs given parameters) criterion, enabling training on cases with arbitrary missing data (even if every case has some missing) using the iterative Expectation and Maximization (EM) algorithm (McKendrick, 1926; Hartly 1958; Orchard and Woodbury, 1972; Dempster, Laird, and Rubin, 1977).

It has been suggested by Efron and others that, ignoring the question of missing data, maximum-joint-likelihood estimation is less efficient than conventional maximum-likelihood estimation (probability of observed training data outputs given training data inputs and the parameters). Therefore, as our first missing-data method, we will examine the use of mixture networks to perform multiple imputation of missing values, as a preprocessor to be followed by a separate conventional feedforward neural network for prediction using these imputed values. A nonparametric (memory-based) form of this method has been proposed (Tresp, et al., 1995]) but has the disadvantage of requiring that a good fraction of the training cases are complete, i.e. have no missing inputs.

The figure below demonstrates that, compared to the most common approach of removing cases with missing data, where accuracy decreases as missing data

increases, the accuracy of our approach is stable across a wide range of missing data.

100 training observations from known distribution
(mean results of 10 trials)



Preliminary results were presented at the National Cancer Institute.

Burke HB, Rosen DB. Missing data solutions using artificial neural networks. Division of Cancer Prevention and Control Seminar Series, National Cancer Institute, Bethesda MD, June 21, 1995.

2.3) Censored cases

Discussed in detail in 2.1.2.

Task 3. Implementation of a clinically useful prognostic system

3.1) Computer code for artificial neural networks.

All our work is written in either C, C++, or XLISP-STAT.

3.2) Physician interface.

It is very important that physicians find the new prognostic system easy to use and useful. To this end we have implemented the prognostic system on a DOS platform with a Windows interface. We are presenting the system to clinicians

3.2) Physician interface.

It is very important that physicians find the new prognostic system easy to use and useful. To this end we have implemented the prognostic system on a DOS platform with a Windows interface. We are presenting the system to clinicians and receiving feedback regarding what is important to them in terms of information and the graphical display of the information. (see 2.1.2)

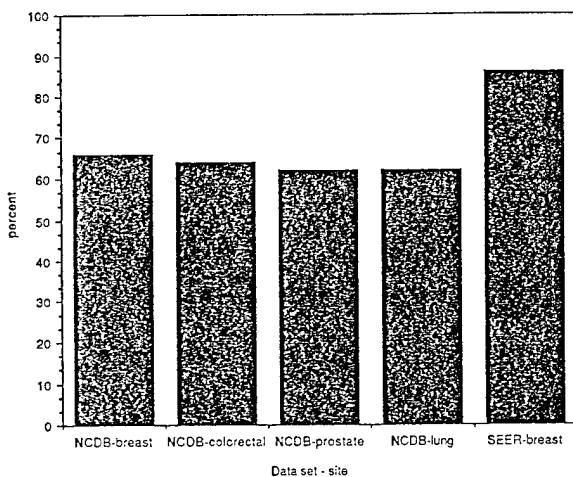
Tasks added to the project

We have added three tasks to the project. (1) A comparison of the NCDB and the SEER data sets, (2) an examination of methods for dealing with censoring bias (cases not missing at random) and competing risks, and (3) the computerization of the TNM staging system for breast cancer.

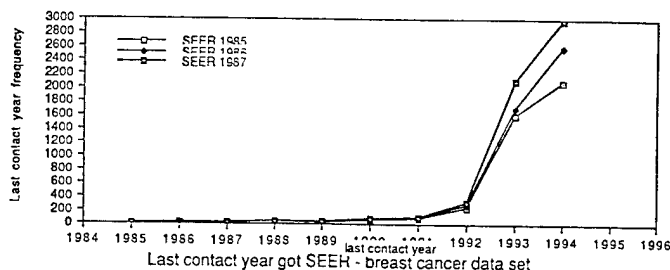
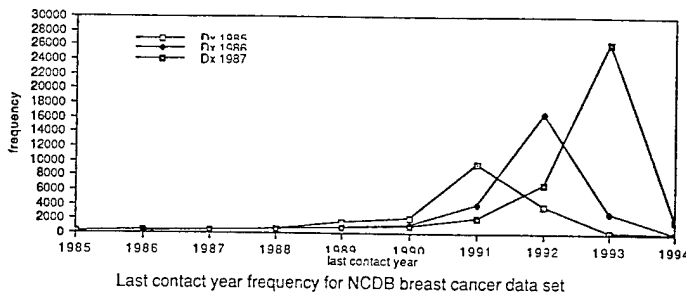
(1) Comparison of the NCDB and the SEER data sets.

To the best of our knowledge no one has performed a comprehensive comparison of the National Cancer Data Base (NCDB) and its associated Patient Care Evaluation (PCE), and the Surveillance, Epidemiology, and End Results (SEER) data sets. It is commonly felt that the SEER, which is population based rather than hospital based, is more accurate than the NCDB. But the NCDB is five-times larger than the SEER and the SEER over represents certain minorities. We are examining these data sets in terms of missing data, censoring, and the prognostic and outcome variables. This work is very time consuming, but it is necessary to determine which is the better data set for the prognostic system. Shown below are (1) a comparison of missing data, (2) a comparison of censoring, and (3) a Kaplan-Meier comparison of the NCDB and the SEER, for five year breast cancer-specific survival.

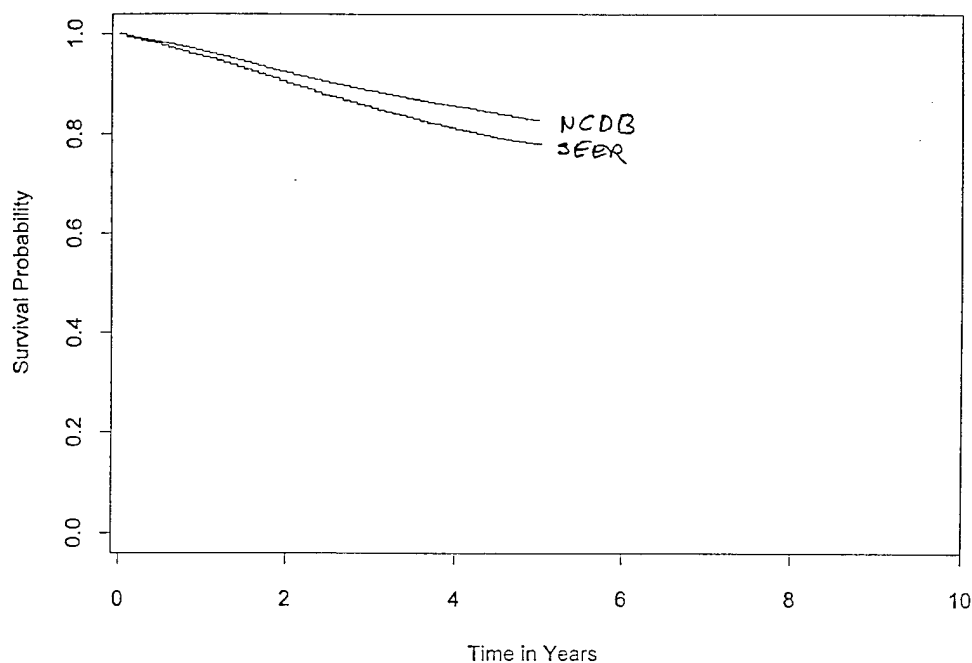
1. So far, for breast cancer, we have not found any significant demographic variable differences between the SEER and NCDB.
2. For breast cancer, the NCDB does have significantly more missing data than the SEER.



Percentage of data, by data set and site, that contains valid and known responses



3. The NCDB and the SEER do exhibit differences in censoring. We have not yet determined how important these differences are.



This work is being prepared for publication.

Hoang A, Burke HB, Rosen DB. Comparison of the two national cancer data sets: SEER and NCDB. In preparation.

(2) Censoring bias and competing risks.

It is well known that censoring (lost-to-follow-up) can be biased in cancer, that cases are not missing at random. This is important because most statistical methods in use to day assume that censored cases are missing at random. We are developing analytic and empirical methods for (i) determining if there is a bias, and (ii) adjusting for the bias.

Hoang A, Burke HB, Rosen DB. Survival analysis with some cases nonrandomly lost-to-follow-up. In preparation.

It is also important to recognize that other causes of death affect the probability of death from breast cancer. The prognostic system must model other causes of death, in addition to modeling breast cancer mortality and censoring.

(3) Computerization of the TNM staging system

Although there have been plans for computerizing the TNM staging system for breast cancer, our implementation (see 2.1.2) is the first PC-based program for: (i) determining the breast cancer TNM stage from the breast cancer TNM variables, and (ii) predicting five year breast cancer specific survival based on TNM stage.

CONCLUSION

We have made substantial progress during the last year. We believe that we will be able to successfully meet our goal of providing a computer-based prognostic system that is more accurate than the TNM staging system and that is easy to use and understand, within the four year time frame of this grant.

References

- Bamber D. The area above the ordinal dominance graph and the area below the receiver operating graph. *J Math Psych* 1975;12:387-415.
- Bearhrs OH, Henson DE, Hutter RVP and Kennedy BJ (1992). Manual for staging of cancer. Philadelphia: J B Lippincott.
- Breslow NE. Covariance analysis of censored survival data. *Biometrics* 1974; 30:89-99.
- Burke HB, Henson DE. Criteria for prognostic factors and for an enhanced prognostic system. *Cancer* 1993;72:3131-5.
- Burke HB. Artificial neural networks for cancer research: outcome prediction. *Sem Surg Onc* 1994;10:73-79.
- Burke HB, Hutter RVP, Henson DE. Breast Carcinoma. In P. Hermanek, L.H. Sobin, D.E. Henson, R.V.P. Hutter, M. Gospadoriwicz, eds. *UICC Prognostic Factors in Cancer*. Berlin: Springer-Verlag, 1995a, 165-176.
- Burke HB, Rosen DB, Goodman PH. Comparing the prediction accuracy of artificial neural networks and other statistical models for breast cancer survival. In G. Tesauro, D.S. Touretzky, T.K. Leen, eds. *Advances in Neural Information Processing Systems 7*. Cambridge, MA; MIT Press, 1995b, 1063-67.
- Burke HB, Goodman PH, Rosen DB, Hellier JH, Weinstein JN, Winchester DP, Harrell Jr FE, Marks JR, Bostwick DG, Osteen RT, Zincke H, Henson DE. Improving cancer survival prediction accuracy. Submitted for publication, 1995c.
- Centor RM (1991). Signal detectability: the use of ROC curves and their analyses. *Medical Decision Making* (11):102-106.
- Cox DR. Regression models and life tables (with discussion). *J Royal Stat Soc, Ser. B*, 1972;34:187-220.
- Crawford SL, Tennstedt SL and McKinlay JB (1995). A comparison of analytic methods for non-random missingness of outcome data. *Journal of Clinical Epidemiology* (2):209-19.
- Dempster AP and Rubin DB (1983). Overview. In: Madow WG, Olkin I and Dubin DB (eds.) *Incomplete data in sample surveys, Vol II: Theory and annotated bibliography*. New York: Academic Press. pp. 3-10.
- Dempster AP, Laird NM and Rubin DB (1977). Maximum likelihood estimation from incomplete data via the EM Algorithm (with discussion). *J. Roy. Statist. Soc. (B39)*:1-38.
- Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York: Chapman & Hall, 1993.
- Efron B. Bootstrap methods: another look at the jackknife. *Am Statist* 1979;7:1-26.
- Gallant SI (1993). *Neural Network Learning and Expert Systems*. Cambridge, MA: MIT Press.

- Ghahramani Z and Jordan MI (1994). Supervised learning from incomplete data via an EM approach. In: Cowan JD, Tesauro G and Alspector J (eds.) Advances in neural information processing systems. San Francisco, CA: Morgan Kaufman. pp. 120-27.
- Hanley JA, McNeil BJ. The meaning and use of the area under the receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
- Harrell FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. JAMA 1982;247:2543-46.
- Hartley HO (1958). Maximum likelihood estimation from incomplete data. Biometrics (14):174-194.
- Healy MJR and Westmacott M (1956). Missing values in experiments analyzed on automatic computers. Appl. Statist. (5):203-206.
- Hilden J (1991). The area under the ROC curve and its competitors. Medical Decision Making (11):95-101.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
- Liestol K, Anderson PK, Anderson U. Survival analysis and neural nets. Stat Med 1994; 13:1189- 1200.
- Little R and Rubin D (1987). Statistical analysis with missing data. New York: John Wiley & Sons.
- Little RJA. Regression with missing X's: a review. JASA 1992;87:1227-37.
- Marks JR, Humphrey PA, Wu K, Berry D, Bandarenko N, Kerns BM, Inglehart JD. Overexpression of the p53 and HER-2/neu proteins as prognostic markers in early stage breast cancer. Ann Surg 1994;219:332-41.
- McKendrick AG (1926). Applications of mathematics to medical problems. Proc. Edinburgh Math. Soc. (44):98-130.
- Moody J and Darken C (1988). Learning with localized receptive fields. In: Touretzky D, Hinton G and Sejnowski T (eds.) Connectionist Summer School. San Mateo, CA: Morgan Kaufmann. pp. 133-143.
- Moody J and Darken C (1989). Fast learning in networks of locally-tuned processing units. Neural Computation 1:281-294.
- Orchard T and Woodbury MA (1972). A missing information principle: theory and applications. Proceedings of the 6th Berkeley Symposium on Mathematical Statistics and Probability pp. 697-715.
- Parzen E (1962). On estimation of a probability density and mode. Annals of Mathematical Statistics 35:1065-1076. Poggio T and Girosi F (1990). Networks for approximation and learning. Proc IEEE pp. 1481-97.
- Ravdin PM, Clark GM. A practical application of neural network analysis for prediction outcome of individual breast cancer patients. Breast Cancer Res Treat 1992; 22:285-293.
- Rosen DB. Ordinal discrimination index for any proper scoring rule.

Published Abstract. Medical Decision Making 1994;14:440.

Rosen DB. How good were those probability predictions? The expected recommendation loss (ERL) scoring rule (8 pp.). To appear in Maximum Entropy and Bayesian Methods: Proceedings of the Thirteenth International Workshop (August 1993), G. Heidbreder, ed., Kluwer, Dordrecht, The Netherlands, 1995a.

Rosen DB, Burke HB, Goodman PH. Improving prediction accuracy using a calibration postprocessor.
Submitted for publication, 1995b.

Rosen DB. Issues in selecting empirical performance measures for probabilistic classifiers. To appear in Maximum Entropy and Bayesian Methods: Proceedings of the Fifteenth International Workshop (July/August 1995), K. Hanson and R. Silver, eds., Kluwer, Dordrecht, The Netherlands, 1996, in press.

Rosenblatt M (1956). Remarks on some non-parametric estimates of a density function. Annals of Mathematical Statistics 27:642-669.

Savage LJ. Elicitation of personal probabilities and expectations.
J Am Stat Assoc 1971;66:783-801.

Schneiderman ED, Kowalski CJ and Willis SM (1993). Regression imputation of missing values in longitudinal data sets. Int J Biomed Comput (32):121-33.

Specht DF (1990). Probabilistic neural networks. Neural Networks 3:109-118.

Specht DF (1991). A general regression neural network. IEEE-TR-NN 2(6):568-576.

Steele GD, Jr, Winchester DP, Menck HR, Murphy GP. National Cancer Data Base, 1993. Atlanta, GA; American Cancer Society, 1993.

Tierney L (1990). LISP-STAT: An object-oriented environment for statistical computing and dynamic graphics. New York: John Wiley & Sons.

Tresp V, Ahmed S, Neuneier R. Training neural networks with deficient data. In JD Cowan, G Tesauro, J Alspector (eds.), Advances in Neural Information Processing Systems, 6. San Francisco, CA: Morgan Kaufman, 1994, 128-35.

Tresp V, Neuneier R and Ahmed S (1995). Efficient methods for dealing with missing data in supervised learning. In: Tesauro G, Touretsky DS and Leen TK (eds.) Advances in neural information processing systems. Cambridge, MA: MIT Press.

Vamplew P and Adams A (1992). Real world problems in backpropagation: missing values and generalizability. Third Australian Conference on Neural Networks.

White H (1989). Learning in artificial neural networks: a statistical perspective. Neural Computation (1):425-64.

Winkler RL. Scoring rules and the evaluation of probability assessors.
J Am Stat Assoc 1969;64:1073-1078.

APPENDIX A - PRESENTED PAPERS

Burke HB, Rosen DB, Goodman PH. Comparing the prediction accuracy of artificial neural networks and other statistical models for breast cancer survival. Neural Information Processing Systems (NIPS 94): Medical Applications of Neural Networks (postconference workshop), Denver CO, November 28 - December 3, 1994.

Rosen DB, Burke HB, Goodman PH. Local methods in high dimension: are they surprisingly good but miscalibrated? Neural Information Processing Systems (NIPS 94): Local Methods in High Dimensions (postconference workshop), Denver CO, November 28 - December 3, 1994.

Burke HB. The science of medical prediction. National Coordinating Workshop on Prognostic Factors in Cancer, National Cancer Institute, Bethesda MD, January 4 - 5, 1995.

Burke HB, Rosen DB, Hoang A. Prototype cancer prognostic system with survival curves. National Coordinating Workshop on Prognostic Factors in Cancer, National Cancer Institute, Bethesda MD, January 4 - 5, 1995.

Burke HB, Rosen DB, Goodman PH. Comparing the predictive accuracy of statistical models and artificial neural networks in breast cancer. Fifth International Workshop on Artificial Intelligence and Statistics, Ft. Lauderdale FL, January 4 - 7, 1995.

Burke HB, Rosen DB, Hoang A. Cancer survival curve prediction using artificial neural networks. American Joint Committee on Cancer National Meeting, Scottsdale, AZ, January 14, 1995.

Burke HB. Survival curve analysis of cancer data. Grand Rounds, Department of Radiation Oncology, Cornell Medical Center - New York Hospital, New York NY, January 26, 1995.

Burke HB. The importance of artificial neural networks in biomedicine. Workshop on Environmental and Energy Applications of Neural Networks, Battelle - Pacific Northwest Laboratories, Richland WA, March 30 -31, 1995.

Burke HB, Rosen DB, Hoang A. Survival prediction in cancer using artificial neural networks. Grand Rounds, Center for Devices and Radiological Health, Division of Electronics and Computer Science, Food and Drug Administration, Rockville MD, April 3, 1995.

Burke HB, Rosen DB, Hoang A. Survival analysis. Radiation Therapy Oncology Group, Philadelphia PA, April 10, 1995.

Burke HB. Predicting survival in cancer. Grand Rounds, Division of Hematology-Oncology, New York Medical College, Valhalla NY, June 1, 1995.

Burke HB. The past, present, and future of cancer prognostic factor research. Prognostic Factors in Cancer, Cambridge Healthtech Institute, Arlington VA, June 7 - 8, 1995.

Burke HB. Computer-based prognostic system in cancer. Prognostic Factors in Cancer, Cambridge Healthtech Institute, Arlington VA, June 7 - 8, 1995.

Burke HB. Outcome prediction in cancer. Grand Rounds, Division of Solid Tumor Oncology Conference, Memorial Sloan-Kettering Cancer Center, New York, NY, June 19, 1995.

Burke HB, Rosen DB. Missing data solutions using artificial neural networks. National Cancer Institute, Bethesda MD, June 21, 1995.

Burke HB. Artificial neural networks and biomedical research. World Congress on Neural Networks. Washington D.C., July 17 - 21, 1995.

Burke HB, Rosen DB, Hoang A. Survival function estimation in cancer using artificial neural networks. World Congress on Neural Networks. Washington D.C., July 17 - 21, 1995.

Burke HB. Artificial neural networks significantly improve outcome prediction in breast cancer. Operations Research and Information Conference. New Orleans LA, October 29 - November 1, 1995.

APPENDIX B - PHYSICIAN SURVEY

SURVEY OF PHYSICIAN ESTIMATES OF FIVE YEAR BREAST CANCER-SPECIFIC SURVIVAL

We are interested in your estimate of the breast cancer-specific survival of women diagnosed in the United States in 1985 .

You are a (check one): _____ oncologist, _____ oncologic surgeon, _____ pathologist,
_____ radiation oncologist .

You graduated from medical school: _____ years ago.

Assume that each of the patients listed below is in your office, and asks you what her chances are, from date of diagnosis, of living five years. What is your estimate (% alive) of each patient living five years (not including those patients who died from causes other than breast cancer), over all primary and adjuvant therapies? Base your estimates on 1985 patients. (Note: for purposes of TNM staging, all patients with positive lymph nodes have been classed as T1).

PATIENT DESCRIPTION	% PATIENTS SURVIVING 5 YRS
Patient 1. Fifty-five year old, postmenopausal, 2 cm tumor, 0 positive lymph nodes, no distant metastasis, ER and PR positive, Grade 1.	
Patient 2. Thirty-five year old, premenopausal, 1 cm tumor, 3 positive lymph nodes, no distant metastasis, ER and PR negative, Grade 1.	
Patient 3. Fifty-five year old, postmenopausal, 5 cm tumor, 3 positive lymph nodes, no distant metastasis, ER and PR negative, Grade 1.	
Patient 4. Fifty-five year old, postmenopausal, 6 cm tumor, 0 positive lymph nodes, no distant metastasis, ER and PR negative, Grade 1.	
Patient 5. Forty-five year old, premenopausal, 6 cm tumor, 3 positive lymph nodes, no distant metastasis, ER and PR positive, Grade 1.	
Patient 6. Sixty-five year old, postmenopausal, 6 cm tumor, 3 positive lymph nodes, no distant metastasis, ER and PR negative, Grade 1.	
Patient 7. Forty-five year old, premenopausal, 1 cm tumor, 3 positive lymph nodes, positive distant metastasis, ER and PR positive, Grade 3.	
Patient 8. Forty-five year old, premenopausal, 3 cm tumor, 1 positive lymph node, positive distant metastasis, ER and PR positive, Grade 3.	
Patient 9. Sixty-five year old, postmenopausal, 3 cm tumor, 1 positive lymph node, positive distant metastasis, ER and PR positive, Grade 3.	
Patient 10. Forty-five year old, premenopausal, 6 cm tumor, 7 positive lymph nodes, positive distant metastasis, ER and PR positive, Grade 3.	