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Important note: This document will remain archived as a technical appendix for publications. New versions will be added periodically as model refinements and updates are completed. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

READERS GUIDE

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5–10 minutes. Each contains links to more detailed information if required.

Model Purpose

This document describes the primary purpose of the model.

Model Overview

This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview

An overview of the basic assumptions inherent in this model.

Parameter Overview

Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview

A description of the basic computational building blocks (components) of the model.

Output Overview

Definitions and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

Key References

A list of references used in the development of the model.

Further Reading

These topics will provide a intermediate level view of the model. Consider these documents if you are interested gaining in a working knowledge of the model, its inputs and outputs.

JNCIMonograph Outline

This topic provides links to profile content organized according to the JNCI Monograph Outline for Model Description Chapters. Use this outline for comparisons focused on the CISNET Base Case simulations.

Advanced Reading

These topics denote more detailed documentation about specific and important aspects of the model structure

MODEL PURPOSE

SUMMARY

This document gives the general purpose of the model and other typical applications it might be used in.

PURPOSE

The purpose of the model is to predict the mortality associated with female breast cancer. The predictions may be by chronological year and/or age. Mortality may change by advances in treatment and/or changing dissemination of screening. The model incorporates the possibility that these latter two factors will change by chronological time and age. The model is general and enables the prediction of changes in mortality if technical advances are made by radiology or the discovery of other disease markers.

The probability model was developed to describe the early detection process for any chronic disease. The application to breast cancer requires knowledge of the relevant parameters associated with the natural history, diagnosis and treatment of breast cancer. Application to other chronic disease requires similar specialized inputs.

In addition to using the model to predict national mortality trends there are a number of other important applications of the model; i.e. (i) prediction of the outcome of early detection clinical trials without the necessity of long–term follow–up; (ii) evaluation of service programs on early detection; (iii) investigation of different screening schedules to compare mortality benefit. The screening schedules are a function of: age at first exam, number of exams, spacings between examinations and modality of diagnosis (physical exam, mammogram or both).

See Model Overview for deeper details and some limitations inherent in the model.

MODEL OVERVIEW

SUMMARY

This document provides an overview of the modeling effort including the reasons it was undertaken and the work it builds upon. It also contains a summary of the methodologies employed.

PURPOSE

The purpose of the model is to predict the mortality associated with female breast cancer. The predictions may be by chronological year and/or age. Mortality may change by advances in treatment and/or changing dissemination of screening. The model incorporates the possibility that these latter two factors will change by chronological time and age. The model is general and enables the prediction of changes in mortality if technical advances are made by radiology or the discovery of other disease markers. See Model Purpose for more details.

BACKGROUND

The model is a stochastic model of the natural history of the disease. A series of equations are derived that predicts the age specific probability of death which is the mortality rate. The introduction of screening in the model makes the mortality rate equations more complex as it is necessary to distinguish among screen detected and interval detected cases. Screen detected cases are those in which the woman is asymptomatic and the disease is diagnosed by an early detection screening examination; interval detected cases are those cases not detected at a screening examination, but there is a history of at least one negative screening examination. The model takes into account both lead time and length biased sampling biases. The assumption for the effect of screening assumes that diagnosis of screen detected cases changes the distribution of staging beyond what would be expected due to length biased sampling. We refer to this as a stage shift and is in the direction of having a higher proportion of more favorable prognostic cases.

The basic probability model requires the choice of a reference time point in chronological time. The model predicts the cumulative mortality relative to this reference time conditional on being a specific age at the reference time point. If the time point is chosen as a birth cohort year, then the model can predict the age specific mortality rate for a specific birth cohort year. The age specific mortality for any point in chronological time may be calculated by choosing a collection of birth cohort years. These may be averaged with respect to a weight function to give the overall mortality rate for a specific chronological year. Due to the generality of the model, predictions may be made for populations and sub populations.
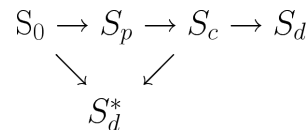
MODEL DESCRIPTION

The basic assumption of the model is that breast cancer is a progressive disease. Four or possibly five states of health are envisioned. These states are:

- S_0: A woman is disease free or has disease but it is asymptomatic and cannot be diagnosed by any modality;

- S_p: A woman has breast cancer, but it is asymptomatic and may be diagnosed by a special examination or examination program;
- S_c: A woman, having usual care, is diagnosed with invasive breast cancer;
- S_d: Death attributed to breast cancer;
- S_d^*: Death, not attributed to breast cancer

The progressive disease model may be described by the path:

$$S_0 \rightarrow S_p \rightarrow S_c \rightarrow S_d$$
$$\searrow \qquad \swarrow$$
$$S_d^*$$

The main output of the model is breast cancer specific mortality. Hence the transition into S_d^* may be ignored. See Component Overview for more details on the model's building blocks.

Inputs to the Model

The philosophy of the model is to have a probability model in which the parameters can be observed or can be directly estimated from existing data. The inputs required of the model are:

a. Age dependent incidence rates for a time period in which breast cancer screening was not widely used;

b. Age dependent transition rates into Sp (pre–clinical state);

c. Stage distribution for usual care cases and cases diagnosed by screening or having a history of screening exams. The stage distribution may be age related.

d. Survival distribution conditional by stage, chronological time and age. The reason for specifying chronological time is to account for advances in therapy. The dependence on chronological time will be a function of the dissemination of treatment advances in the general population.

e. Dissemination or pattern of screening;

f. Sensitivity of mammograms and physical exams by age,

g. Birth cohort year(s) to which mortality predictions will be made.

Some of these parameters may be estimated from the eight randomized trials investigating mammography; e.g. stage distribution by modality of diagnosis, sensitivity. Others can be obtained from databases such as SEER (survival conditional on stage, stage distributions with usual care). The age dependent transition rates into S_p may be obtained from the age incidence rates using the methods earlier derived by Lee and Zelen. See Parameter Overview for more details.

Outputs

The outputs of the model are: overall breast cancer mortality for chronological time and reduction in mortality relative to some base. We believe that the reduction in mortality may be the most accurate prediction. Our reasoning is that if there are other factors influencing breast cancer mortality, which do not interact with treatment and/or early detection modalities, their effect on mortality reduction will be negligible as their contribution to the hazard function will be additive. The reductions in mortality may

be relative to a base year, a screening strategy (before and after) or a reduction in lag time between a clinical trial showing the benefit of a new therapy and the time when the new therapy is widely adopted.

The mortality outputs may also be age specific. Furthermore, the model outputs may be cause specific or total mortality. See Output Overview for more details.

Limitations of the Model

The basic assumptions of the model are: (i) breast cancer is a progressive disease and (ii) the benefit of early detection is through a stage shift in diagnosis. See Assumption Overview for a more detailed list of assumptions. Current views of the natural history of the disease agree that breast cancer is a progressive disease. However there is less agreement on the reasons earlier diagnosis may result in reducing mortality. There is a group of investigators who believe that early detection by mammography confers no benefit. However it is now generally accepted that the criticisms of the scientific evidence have been satisfactorily answered, discredited or are peripheral. Our model, suitably modified, can be used to predict the outcome of the early detection clinical trials. It was applied to the eight randomized early detection breast cancer clinical trials and was able to predict the outcome of seven of the trials. The agreement with the breast cancer early detection randomized trials indicates that the stage shift assumption may be a valid assumption to explain benefit. Our findings were presented at the Global Summit on Mammography held in Milan, Italy in early June 2002.

Another possible criticism of our model is that survival depends on modality of detection as well as disease stage. However there is no clinical data to support this conjecture.

CONTRIBUTORS

ASSUMPTION OVERVIEW

SUMMARY

In this section we summarize the main assumptions fo the model

BACKGROUND

The basic assumptions of the model are: (i) breast cancer is a progressive disease and (ii) the benefit of early detection is through a stage shift in diagnosis. A more detailed list follows.

It is widely believed that breast cancer is a progressive disease. The stage shift assumption is the only reasonable hypothesis as to why early detection may be beneficial.

The prediction of the mortality reduction in the eight randomized early detection trials indicated no benefit for the two canadian trials. These were the only two trials that did not show a stage shift.

There is no intreaction between the progressive disease model and stage shift. However there are interactions with age.

ASSUMPTION LISTING

a. Progressive disease model is basic to the model. The natural history of disease progresses from no disease (or disease which cannot be detected) to pre–clinical disease to clinical disease. The natural history will depend on age.

b. The process by which early detection changes prognosis is by a stage shift in that a higher proportion of screened detected cases will have disease stages with better prognosis. The stage shift may be age dependent.

c. Women who are interval–detected cancers have the same stage distribution as those not participating in a screening exam. This is an observation from the eight early detection trials. However this assumption is not necessary.

d. The survival distribution consists of a mixture of survival distribution conditional on stage. The weights correspond to the probability of being diagnosed in a particular stage. They will change according to a stage shift for screen–detected cases. The conditional survival distributions will change with chronological time corresponding to the introduction of advances in treatment.

e. The sensitivity of the exams (mammograms, physical and the combination) will be age–related with lower mammogram sensitivities for younger women.

f. The sojourn time distribution is assumed to follow the exponential distribution with a mean which is age dependentNOte that this distribution is not observed. Older women are assumed to have longer mean sojourn times than younger women. The expinential assumption is based on the results of the HIP trial in which full data is available. We have shown that a necessary and suficient condition for the sojourn time to be exponential is that the mean ages of those diagnosed at the first exam is equal to the mean age of a diagnosed control group. This condition was true for the HIP study.

g. We have assumed that the sensitivity of a mammogram is age dependent with higher sensitivities for the women over 50. This age dependence has been illustrated in many of the early detection trials.

PARAMETER OVERVIEW

SUMMARY

This document describes the basic parameters used by the model as well as provides current estimates for each.

BACKGROUND

The key assumptions are outlined in Assumption Overview . These are that (i) breast cancer is a progressive disease and (ii) the benefit from early detection is due to a stage shift in screen–detected cases. The stage shift is by definition beyond that expected from length biased sampling.

Our model requires input data which may come from various sources. They include: survival conditional on stage, sensitivity of mammograms, sojourn time distribution in the pre–clinical stage, stage distribution with and without screening, dissemination of screening and therapy in the 1975–1999 period and the estrogen receptor (ER) status. Many of these inputs may be age–related. In this section we discuss the values of these inputs.

The philosophy of the model is that the input data may be observed or can be estimated from existing data. Examples of the latter are the sensitivity of the screening modality and the transition probabilities into S_p. The model does not contain parameters which are estimated to fit existing mortality. In this section the sources of the basic input data and applications to our model are described. The notation used in this section is previously defined in Natural History Component . We have used the software, Mathcad 2001i from Mathsoft Inc., to carry out the calculations of the breast cancer mortality in the U.S. women in the chronological time period 1975–1999.

PARAMETER LISTING OVERVIEW

The model requires numerical values of various parameters. In this section we summarize our estimates and discuss various data sources.

Survival, Sensitivity, Sojourn Time in the Pre–clinical State and Stage Distribution

The SEER database provides breast cancer incidence, staging and survival for the period 1975–1979. We have chosen this time period for the input data as breast cancer screening was not common at that time. Choosing a later period would result in these data sources being influenced by screening. The estimate of the age–specific breast cancer mortality for birth cohort year v without screening history ($d_v(T)$, defined in equation (2.5) has utilized the input data $S_v(t)$ and $I_v(\tau)$ for birth cohort v which was provided by the CISNET NCI group. In our model, Ductal Carcinoma In Situ (DCIS) cases were not included.

Table 1 summarizes the stage distribution without screening (θ_i) based on the SEER data. The CISNET NCI group has estimated the AJCC stage distributions using the SEER extent of disease data for the years 1975–1979. Age–specific breast cancer survival, conditional on the AJCC stage, has also been provided by the CISNET NCI group. We estimated the annual hazard rate and cumulative survival conditional on stage and age. By multiplying these two quantities, the p.d.f of age–specific breast cancer survival conditional on stage was estimated. Then the p.d.f of breast cancer specific survival as defined in equation (2.1) was generated using the stage distributions (θ_i) and the p.d.f. of breast cancer survival conditional on stage.

TABLE 1. Summary on Stage Distribution without Screening

AJCC Stage Distribution from SEER 1975–1979					
Age	Stage I	Stage II–	Stage II+	Stage III	Stage IV
30–39	0.31	0.23	0.31	0.09	0.06
40–49	0.30	0.23	0.31	0.10	0.06
50–59	0.29	0.22	0.31	0.10	0.08
60–69	0.30	0.22	0.27	0.10	0.11
70–84	0.32	0.27	0.22	0.10	0.10

Our model requires further input data to incorporate screening history and advances in treatment over chronological time. Using the age–specific incidence data $I_v(\tau)$ for birth cohort v, we have estimated transition probabilities between S_0 to S_p and between S_p to S_c. We have further assumed that the pre–clinical sojourn time follows an exponential distribution with an age dependent mean. The mean sojourn times ($m(t)$) serving as input to the model are:

$$m(t) = \begin{cases} 2 & \text{for } t \leq 40 \\ -6 + 0.2t & \text{for } 40 < t \leq 50 \\ 4 & \text{for } t > 50 \end{cases}$$

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Parameter Overview
Parameter Listing Overview

These values are based on data from the early detection in randomized clinical trials. The Breast Cancer Surveillance Consortium (BCSC) published the age–dependent sensitives of screening mammograms in the U.S. administered in 1996–1998[1]. We used their estimates in the model. (The BCSC project was founded by NCI in 1994 to evaluate mammogram screening practices in the U.S. population.) The BCSC database currently contains mammogram screening data and follow–up for approximately one million U.S. women beginning in 1994. Specifically the age–dependent estimated sensitivities ($\beta(t)$) for screening exams from the BCSC data are:

$$\beta(t) = \begin{cases} 0.55 & \text{for } t < 40 \\ 0.65 & \text{for } 40 \leq t < 45 \\ 0.70 & \text{for } 45 \leq t < 50 \\ 0.75 & \text{for } 50 \leq t < 70 \\ 0.8 & \text{for } t \leq 70. \end{cases}$$

Shen and Zelen[2] estimated sensitivities of screening examinations and mean pre–clinical sojourn times from the randomized clinical trials evaluating the benefit of mammography. In their calculations, the mammogram sensitivities had an improving trend over time for screening clinical trials conducted in 1963 – 1990's. Therefore the sensitivities presented above were applied to screening exams conducted in 1995–1999 and the sensitivities for the previous years were lowered. For 1985–1995, the sensitivities were lowered by 0.10 for ages Finally the assumption of exponential sojourn times in the pre–clinical state can be justified from two sources. Zelen and Feinleib[3] have proved that the necessary and sufficient condition for the sojourn time to follow an exponential distribution is that the mean age of diagnosis for the initial early detection exam be the same age as those diagnosed in a control group. This condition was verified in the HIP randomized trial. The second source is the empirical study carried out by Day and Walter[4] in which they investigated various distributions for the pre–clinical sojourn time in the HIP trial and found that the exponential distribution gave the best fit.

Stage Shift

The BCSC has provided data on AJCC stages at diagnosis for screen–detected and interval cases. In the BCSC data, a screen detected cancer was defined as cancer diagnosed within 4 months of a positive screening mammogram (bilateral mammograms indicated by the radiologist to be done for routine screening). An interval cancer was defined as cancer diagnosed within 4 months of a diagnostic mammogram (mammogram indicated by the radiologist to be done for evaluation of a breast problem). A mammogram was considered positive if it was given a final BI–RADS assessment code of 0 (need additional imaging evaluation), 4 (suspicious abnormality), 5 (highly suggestive of malignancy), or 3 (probably benign finding) with a recommendation for immediate follow–up. Time since prior mammography was determined using dates of prior examinations in the mammography registry or self–reported information. We have categorized the time since prior mammogram as one–year and longer than one–year.

We estimated the distribution of AJCC stages for screen detected cases in age groups of

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Parameter Overview
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TABLE 2A. Summary of Stage Distribution for Screen Detected Cases

	AJCC Stage Distribution with Annual Screening (from BCSC)				
Age	Stage I	Stage II–	Stage II+	Stage II	Stage IV
	0.62	0.11	0.21	0.04	0.01
50–59	0.67	0.11	0.19	0.03	
60–69	0.76	0.07	0.14	0.02	
70+	0.78	0.09	0.11	0.02	0.01

	AJCC Stage Distribution with Screening Interval				
Age	Stage I	Stage II–	Stage II+	Stage III	Stage IV
	0.58	0.12	0.24	0.04	0.015
50–59	0.62	0.15	0.17	0.04	0.016
60–69	0.66	0.13	0.18	0.03	0.007
70+	0.73	0.13	0.11	0.01	0.014

TABLE 2B. Summary of Stage Distribution for Interval Cases

	AJCC Stage Distribution with Annual Screening (from BCSC)				
Age	Stage I	Stage II–	Stage II+	Stage III	Stage IV
	0.46	0.19	0.26	0.07	0.02
50–59	0.45	0.17	0.30	0.07	0.01
60–69	0.54	0.15	0.23	0.06	0.01
70+	0.54	0.23	0.16	0.05	0.01

	AJCC Stage Distribution with Screening Interval				
Age	Stage I	Stage II–	Stage II+	Stage III	Stage IV
	0.37	0.22	0.31	0.08	0.02
50–59	0.29	0.26	0.26	0.12	0.06
60–69	0.41	0.22	0.27	0.07	0.03
70+	0.43	0.29	0.18	0.07	0.03

The stage distribution in the absence of screening can be compared to the stage distribution estimated from the BCSC data. For example, for women under the age of 50 years, 54% were diagnosed with Stage I/II– disease when no screening was conducted. (Stage I/II–disease is essentially node negative or local disease stage). However 73% of the same age group were detected at screening with stage I/II– with annual mammograms and 70% with exams having longer than a one–year interval between exams. This shift of 54% to 73% in finding more cases at an earlier stage (stage I/II–), when women were screened annually, results in a mortality reduction.

This staging information compared to the SEER stage distribution presented in Table 1 allows comparison of stage shift data for screening versus usual care. There is a larger

proportion of women detected at earlier stages when diagnosed by screening. Furthermore the stage shift is slightly more pronounced with a shorter screening interval. Similar stage shift data are available from the eight randomized early detection clinical trials and are in close agreement (see Discussion). Finally, the p.d.f. of disease–specific survival for screening exam diagnosed groups were estimated using the stage distributions presented in Tables 2a and 2b combined with the 1975–79 SEER survival data.

It is interesting to note that the interval cases had a slightly better prognostic stage distribution than the control group. The stage shift distribution for interval cases depends slightly on the screening intervals.

Screening Dissemination

Screening patterns for each birth cohort year have been modeled by the CISNET NCI group using the data from the National Health Interview Survey (NHIS) and BCSC. This effort provides information on the probability of the first screening examination for birth cohorts 1891–1970 at chronological years 1975–1999. This information is directly incorporated into our model. In addition, the information on screening patterns, conditional on the age at the first screening examination, was available. The screening pattern was incorporated into our model using the age intervals 18–39, 40–49, 50–59, 60–69 and 70–79. In addition, the screening patterns are summarized using three idealized screening intervals; i.e., short (1 year), medium (2 years) and long (5 years). For women starting the first screening examination at ages 50–59, the possible screening patterns and probabilities of observing specific patterns are summarized in Table 3. If women die of breast cancer before age 70, screening patterns up to age 69 and the corresponding probabilities are utilized.

TABLE 3. Screening Patterns for Women with First Screening Exam at Ages 50–59 Years

Screening during Ages			
50–59	60–69	70–79	Probability
s	s	s	0.369
s	s	m	0.033
m	s	m	0.012
m	m	m	0.259
m	m	l	0.034
m	l	l	0.001
l	l	l	0.292

s=1 year, m=2 years, l=5 years

For the purpose of illustration, we have displayed only a summary of screening patterns for women who had their first screening examinations between ages 50–59. However we have created similar tables for all of the age categories described above. The combinations of various screening patterns (H_i for $i = 1, ..., k$) together with disease–specific survival data and stage shift information have been incorporated into equation (2.8) to assess the disease–specific mortality for the screened population. The

stage distributions used in the model correspond to the screening patterns summarized in Tables 2a and 2b. For women following screening exams with mixed intervals (1,2 and 5 years), the stage distribution associated with screening interval greater than one–year was used. When all the screening exams are 5 years apart, the stage shift associated with screening interval greater than one–year interval was lowered by combining it with the stage distribution of the control group in Table 1. These adjustments were made to take into account the empirical observation that the magnitude of the stage shift is associated with actual screening intervals.

Treatment Dissemination

The dissemination of adjuvant therapies for breast cancer has also been modeled by the NCI CISNET group. The patterns of care data has been utilized to model the dissemination of breast cancer treatments in the U.S. between the years 1975–1999[5]. The CISNET NCI group has provided the data on the proportion of women receiving Tamoxifen, multi–chemotherapy or both by age groups (69) and the AJCC stages for the years 1975–1999. For each treatment option, a median smoothing technique was applied to model the proportion of women receiving therapy as a function of chronological years 1975–1999. The smoothed function of the dissemination pattern for each treatment option has been directly incorporated into our model.

We have utilized the survival benefit of multi–chemotherapies reported by the Early Breast Cancer Trialists' Collaborative Group[6]. The EBCTCG reported the proportional reduction in the annual odds of death for multi–chemotherapies by age groups A similar adjustment was made for the survival benefit attributed to Tamoxifen. The EBCTCG[7] reported the proportional reduction in the annual odds of death ratio for tamoxifen use of 2 years and 5 years of continuous use. Again the disease specific survival from the SEER 1975–1979 database has been appropriately adjusted using the reported annual odds of death for 2 year or 5 year Tamoxifen course of therapy. We have estimated the age specific ER positivity using the 1988–1993 SEER data (ER status data became available in the SEER database beginning in 1988). Table 4 summarizes the age specific ER status data used in our model. The benefit of Tamoxifen was applied only to ER+ women. In addition, the dissemination and benefit of Tamoxifen have been modeled separately for the 2 year vs. 5 year use of Tamoxifen.

TABLE 4. Distribution of ER Status by Age Group in SEER 1988–1993

Age	ER+	ER–
	63%	37%
50–69	77%	23%
$\geq$ 70	85%	15%

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[2] Shen, Y, Zelen, M "Screening sensitivity and sojourn time for breast cancer early detection trials: mammograms and physical exams." in J Clin Oncol 2002 2002; 19: 3490-3499

[3] Zelen, M, Feinleib, M "On the theory of screening for chronic diseases" in Biometrika 1969; 56: : 601-614

[4] Day, NE, Walter, SD. "Simplified models of screening of chronic disease: estimation procedures from mass screening programmes" in Biometrics 1984; 40: : 1-13

[5] Mariotto, A, Feuer, EJ, Harlan, LC, Wun, LM, Johnson, KA, Abrams, J "Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999" in JNCI 2002; 94: : 1626-1634

[6] EBCTCG "Polychemotherapy for early breast cancer: an overview of randomized trials" in Lancet 1998a; 352: : 930-942

[7] EBCTCG "Tamoxifen for early breast cancer: an overview of the randomized trials" in Lancet 1998b; 351: : 1451-1467

COMPONENT OVERVIEW

SUMMARY

Describes major model components.

OVERVIEW

In this section we describe the major components of the model. Since our models are probability models we will describe the elements in minimal technical language. The development of the model requires that individuals without a screening history be treated differently than those with a screening history. The equations for individuals with screening history are more complex.

COMPONENT LISTING

Natural History Component
Survival And Mortality Component

OUTPUT OVERVIEW

SUMMARY

A Stochastic model has been developed for predicting U.S. breast cancer mortality as a function of chronological time and/or age.The model takes into account the changinging disemination of new therapies and screening patterns using mammography.

OVERVIEW

The output from this model may consist of: annual breast cancer mortality for specified chronological times and age specific breast cancer mortality for specified chronological times. Reductions in breast cancer mortality can also be similarly generated relative to a base year. In addition the model will be able to partition the reduction in breast cancer mortality according to changes in treatment and changes in the dissemination of mammography use. In general the output for the model will will be mortality as a function of the inpput parameters; i.e.age distribution of population, screening schedules, survival conditional on stage and treatment, stage distribution. In many cases the output will be the proportional reduction in mortality relative to a control group.

OUTPUT LISTING

Important outputs: mortality by chronological time and/or age, reduction in proportional mortality by age or chronological time. The mortality can be standardized to any base year. Finally, our overall model has been used to predict the outcomes of the eight randomized early detection breast trials. We have been able to verify the reduction in mortality reported by seven of the eight trials.

RESULTS OVERVIEW

SUMMARY

This contains the outputs of the model

OVERVIEW

Eventually the application of model will generate:

1. Mortality predictions

2. Predictions of mortality reduction for proposed screening schedules

3. Reductions in mortality associated with screening dissemination, advances in therapy and a combination of both.

4. Prediction of probability of over diagnosis by age.

5. Test of model by predicting outcomes of eight early detection breast cancer trials

RESULTS LIST

Several results have been generated by this modeling effort. We list a few of them below.

Model Validation Procedures

Describes model validation and sensitivity analysis used in this effort.

Predicted Mortality Reductions

A table of predictions of the outputs for the eight randomized breast cancer early detection trials.

Natural History Component

Summary

This document overviews the models treatment of the natural history of the disease.

Overview

The theoretical model builds on the natural history of the disease. The basic assumption of the natural history is that breast cancer is a progressive disease. Four or possibly five states of health are envisioned. The states are:

S_0 : A woman is disease free or has disease but it is asymptomatic and cannot be diagnosed by any modality;
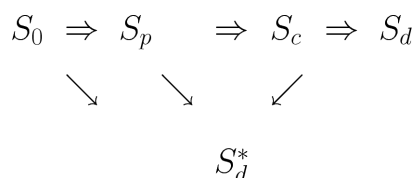
S_p : A woman has breast cancer, but it is asymptomatic and may be diagnosed by a special examination;

S_c : A woman having usual care is diagnosed with invasive breast cancer;

S_d : Death attributed to breast cancer;

S_d^* Death, not attributed to breast cancer.

The progressive disease model may be described by the path:

$$S_0 \Rightarrow S_p \quad \Rightarrow S_c \Rightarrow S_d$$
$$\searrow \qquad \searrow \qquad \swarrow$$
$$S_d^*$$

The main interest is the reduction in breast cancer specific mortality. Women diagnosed with breast cancer who eventually die of other causes are regarded as right–censored observations. Hence the transition into S_d^* may be ignored.

The goal of a breast cancer screening program is to diagnose women who are asymptomatic for breast cancer. Hence by definition women diagnosed by a screening exam are in the pre–clinical state. It is necessary to distinguish among cases which are diagnosed: (i) by a screening exam, (ii) after a negative exam when the disease becomes symptomatic and (iii) by usual care. *Screen detected* cases are those in which the women are asymptomatic and the disease is diagnosed by an early detection examination. *Interval cases* are those not detected at a screening examination, but there is a history of at least one negative screening examination. An *incident case* refers to women who have no history of screening exams but are diagnosed by usual care; i.e., the disease has generated signs/symptoms which makes the women seek medical attention. Interval and incident cases are assumed to be diagnosed in the clinical state. Note that mammography and/or a physical exam may be used to aid in the diagnosis of breast cancer when there are signs/symptoms as well as being used to detect cases in which there are no signs/symptoms. The latter is referred to as a screening exam whereas the former is a diagnostic exam even though the same examination modality is used. In addition to the assumption that breast cancer is a progressive disease, the other basic assumption is that the potential reduction in breast cancer specific mortality from screening is due to a favorable stage shift in diagnosis relative to the distribution of stages when diagnosis is by usual care. We have used the AJCC classification for breast cancer staging. However any system of disease staging may be used in the model.

DETAIL

See Survival And Mortality Component for details on the modeling of mortality reduction.

SURVIVAL AND MORTALITY COMPONENT

SUMMARY

This document describes development of mortality reduction models for screening and non–screening individuals.

OVERVIEW

In this section we describe the major components of the model. The development of the model requires that individuals without a screening history be modeled differently than those with a screening history. Our formulation allows us to follow a specific birth cohort and predict the age–specific breast cancer mortality in any chronological year for the birth cohort.

DETAIL

No Screening History Model

Define:

v = year of birth cohort

τ = age of incidence

T = age at death

$S_v(t)$ = probability of normal population surviving to year t for birth cohort v

$I_v(\tau)$ = age specific disease incidence for birth cohort v

$g(t|\tau + v)$ = probability density function (p.d.f.) of disease specific survival for subject incident at age τ in chronological year $\tau + v$;

$d_v(T)$ = probability of disease–specific death at age T for birth cohort v.

$M_v(T)$ = age–specific mortality rate for birth cohort v.

The p.d.f. $g(t|\tau + v)$ is a mixture of distributions weighted by the probability of being diagnosed in a particular stage. Specifically

$$g(t|\tau + v) = \sum_{i=1}^{k} \theta_i g_i(t|\tau + v),$$

(2.1)

where θ_i is the probability of being diagnosed in stage i

$(i = 1, 2, \ldots, k)$

and $g_i(t|\tau + v)$ is the survival distribution p.d.f. for stage i for a subject diagnosed in chronological time $(\tau + v)$ for a subject having incidence at age τ.

In the chronological year of diagnosis $(\tau + v)$, there may be several treatment options which may have different survival outcomes.

In this case $g_i(t|\tau + v)$ may be written as the mixture

$$g_i^*(t|\tau + v) = \sum_{r=1}^{R} \phi_i(r|\tau + v) g_{ir}(t|\tau + v),$$

(2.2)

where $\phi_i(r|\tau + v)$ = probability of treatment r for a subject diagnosed in stage i at chronological time $\tau + v$ and $g_{ir}(t|\tau + v)$ is the corresponding survival p.d.f. Then the p.d.f. of the disease–specific survival for a subject diagnosed at age τ in chronological year $\tau + v$ and receiving available treatments at that time is

$$g^*(t|\tau + v) = \sum_{i=1}^{k} \theta_i g_i^*(t|\tau + v).$$

(2.3)

The age–specific mortality rate for a subject from birth cohort year v is defined as

$$M_v(T) = \frac{d_v(T)}{S_v(T)} \times 100,000,$$

(2.4)

where

$$d_v(T) = \int_T^{T+1} \int_0^y S_v(\tau) I_v(\tau) g(T - \tau | \tau + v) d\tau dy.$$

(2.5)

That is, the age–specific mortality rate represents the number of disease–specific deaths between ages (T, T+1) in a population of 100,000 from birth cohort year v.
One aim of the model is to estimate the age specific mortality by chronological year. If t refers to chronological year and T denotes the age of death, then $t = T + v$. Hence by choosing a birth cohort year, estimates can be made about age specific mortality corresponding to chronological time t.
Overall disease–specific mortality rate for a chronologic year t may be calculated with reference to some base year. Suppose $p_0(T)$ represents the distribution of ages for a chosen base year. Then the age–adjusted disease–specific mortality rate for chronological year t is

$$M(t) = \int M_{t-T}(T)p_0(T)dT.$$

The range of integration will be over the values of T in which $p_0(T)$ is non–negligible.

Screening History Model

Subjects undergoing screening require a more complex model than those without a screening history. Furthermore it is necessary to distinguish between cases diagnosed at a screening examination (screen detected cases) and those diagnosed at other than a screening exam (interval cases). Suppose a subject from cohort year v has a history of screening exams H_i at ages $t_1 < t_2 < \cdots < t_n$.

Screen detected cases get diagnosed at any exam given at ages $t_1, t_2, \cdots, t_n$. It is assumed that no further exams are given after a diagnosis. Interval cases get diagnosed in between exams (t_i, t_{i+1}) for $i = 1, \cdots, n-1$ or after the last exam at t_n.

The probability of disease–specific death at age T for birth cohort v who follows a screening pattern H_i has a more complicated expression than the probability expression (??) of the non–screened population. It can be written as

$$d_v(T|H_i) = \int_T^{T+1} \int_0^y \{D_v(\tau|H_i) + I_v(\tau|H_i)\}d\tau dy,$$

where

$$D_v(\tau|H_i) = \text{Probability of disease–specific death at age } \tau$$
$$\text{for screen detected cases with screening history of } H_i;$$

$$I_v(\tau|H_i) = \text{Probability of disease–specific death at age } \tau$$
$$\text{for interval cases with a screening history of } H_i$$

These probabilities are a function of many parameters involved in the case finding process and have complicated expressions. Details of the derivations and expressions will be published in another paper[1]. In calculating these probabilities, it is necessary to introduce a sensitivity parameter which may be age dependent and two new probability distributions. One of the distributions corresponds to the age–specific probability of entering the pre–clinical state and the other denotes the sojourn time in the pre–clinical state. Both may be age–related.

The survival distribution for screen–detected cases is assumed to be a mixture of distributions as described in equation (1), except that the probabilities (θ_i) of being diagnosed in the various disease stages have changed due a possible stage shift. In our model the stage shift is represented by the new values of θ_i. Generally larger values (θ_i) are expected for better prognostic stages when screening is involved. The lead time, which is defined to be the difference between the age transitioning into the clinical state and the age of earlier diagnosis, is a random variable, which is not observed. It is equivalent to having a random guaranteed survival time; i.e., the subject will live at least to the age at which clinical diagnosis is made. The model accounts for the guaranteed survival time. Otherwise there will be a lead time bias when compared to non–screened cases.

The age–specific mortality rate for a birth cohort v having a screening history H_i is

$$M_v(T|H_i) = \frac{d_v(T|H_i)}{S_v(T)} \times 100,000.$$

The quantity $M_v(T|H_i)$ is a basic element in estimating various screening scenarios. Weighted linear combinations of this quantity can be used to predict the age–specific mortality rate for birth cohort v having a variety of screening histories. The screening histories consist of various combinations of the age at the first screening, frequencies of the screening examinations and the total number of exams. Then the age–specific mortality rate of birth cohort v with screening histories H_i; for $i = 1, ..., k$ is defined as

$$M_v(T|H) = \sum_{i=1}^{k} h_i M_v(T|H_i),$$

(2.7)

where h_i is the probability of screening history H_i.

The age–specific mortality rate for chronological year t can be calculated using the relation $t = v + T$ to identify the appropriate birth cohort year. The overall disease–specific mortality rate for chronological year t for a population with screening histories H, standardized to a population having ages $p_0(T)$, is then

$$M(t|H) = \int M_{t-T}(T|H)p_0(T)dT,$$

(2.8)

where the limits of integration are over the range of T which has non–negligible probabilities $p_0(T)$.

Mortality Reduction

We have formulated the expressions for the overall disease–specific mortality rate at chronological year t. This formulation can be used to estimate the mortality reduction due to treatment, screening or to both treatment and screening disseminated in the population over years. Using the expressions in equations (2.6) and (2.8), one can estimate the overall disease–specific mortality reduction at chronological year t due to screening as

$$MR_{sc}(t|H) = \int \{M_{t-T}(T) - M_{t-T}(T|H)\}p_0(T)dT/ \; M(t).$$

(2.9)

The mortality reduction due to treatment disseminated in the population is given by

$$MR_{rx}(t) = \int \{M_{t-T}(T) - M_{t-T}^*(T)\}p_0(T)dT/ \; M(t),$$

(2.10)

where $M_{t-T}^*(T)$ can be estimated from equation (2.6) using the treatment incorporated survival p.d.f. described in (2.3).

Lastly, the mortality reduction due to both screening and treatment disseminated in the population is formulated as

$$MR_{sc*rx}(t|H) = \int \{M_{t-T}(T) - M^*_{t-T}(T|H)\}p_0(T)dT/\ M(t).$$

(2.11)

REFERENCES:

[1] Lee, SJ, Zelen, M "Mortality modeling of early detection programs" in (in manuscript) 2004;

MODEL VALIDATION PROCEDURES

SUMMARY

This document describes some preliminary validation and sensitivity analysis work done with the model.

RESULT TYPE

Validation

OVERVIEW

Model Validation and Sensitivity Analysis

The stochastic model we proposed has two basic assumptions: (i) natural history is progressive and (ii) gains from screening are attributed to a stage shift. In order to validate our model, we applied it to the eight randomized trials investigating the benefits of mammography. The application used input parameters from the trials; e.g., stage shift distribution, exam sensitivities, frequency and spacing of examinations, age distributions and mean sojourn time in the pre–clinical state. These parameters would generally be available during the first few years of the trial. The survival, conditional on stage, was obtained from the 1975–79 SEER data base. The follow–up period for the trials ranged from seven to nineteen years. The follow–up times coincided with the last published follow–up time. Our model predictions for mortality reduction were within the reported confidence intervals for seven of the trials (c.f. Lee and Zelen[1]). The other trial did not report a confidence interval for the reported mortality reduction.

A sensitivity analysis for the model has also been carried out. We have varied two of the input parameters specific to our model (mammogram sensitivities and stage distributions) to evaluate the impact on disease–specific mortality. In particular we have: (i) increased the sensitivity of mammograms to $\beta(t) = 1$ for all ages in the period 1975–1999, (ii) lowered the age–dependent sensitivities to 0.35–0.70 in the period 1975–1999, (iii) changed the stage shift for women following a 5 year screening pattern to the stage distribution from the BCSC for screening with more than one–year and (iv) lowered the stage shift of women following a 5 year screening pattern to the stage distribution of the control group. The results are displayed in Figures 1 and 2.

RESULT

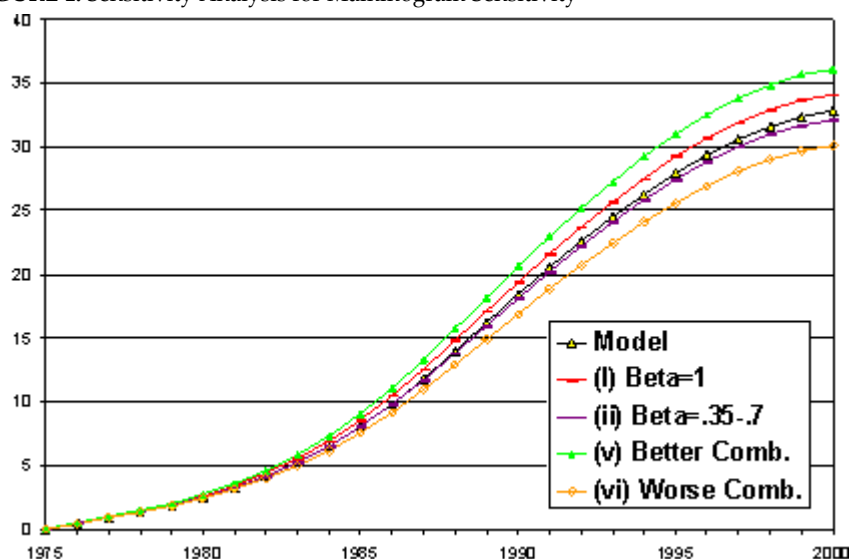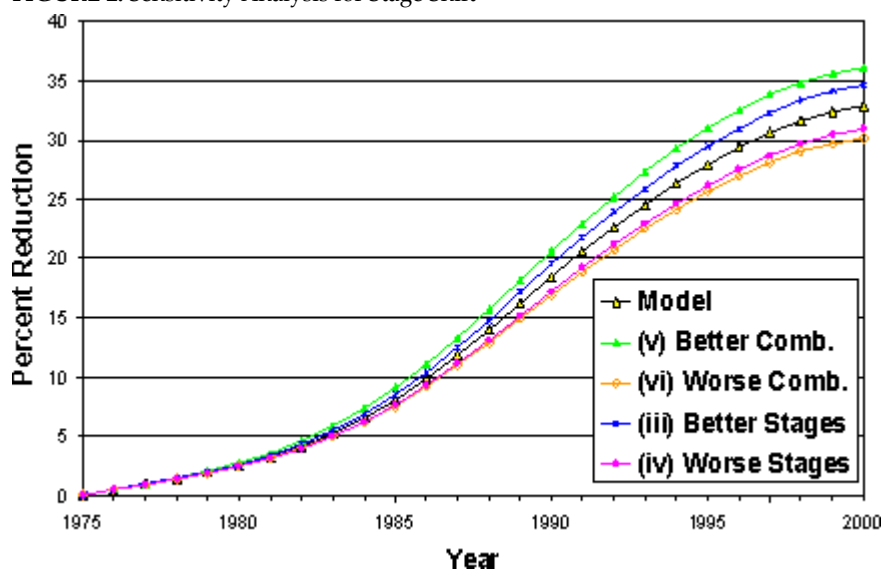**FIGURE 1.** Sensitivity Analysis for Mammogram Sensitivity

FIGURE 2. Sensitivity Analysis for Stage Shift

The curve labled "Model" in Figures 1 and 2 represents our final model prediction (equation 2.11). The other curves represent the changes by varying the input parameters. The curve labeled "Worse Comb" represents a combination of (ii) and (iv); and the curve labled "Better Comb" represents a combination of (i) and (iii). The magnitude of the reduction depends on the dissemination patterns. Generally the mortality reduction (MR) increases over time as screening and modern treatment become more widely disseminated in the population. Note that the MR ranged from 0% to 34% in the 25 year period 1975 to 1999 in the CISNET model.

As displayed in Figure 1, if the sensitivity of the screening examination was increased to 1, the MR increased. In the year 1999, it increased to 34% compared to 33% from the lower sensitivities in the base case model. When the mammogram sensitivities were

lowered, the MR in 1999 was lowered to 32%. Figure 1 also displays the better and worse combinations of mammogram sensitivities and stage shifts. In the year 1999, the maximum MR with a better combination of mammogram sensitivities and stage shift was 36% and the minimum MR was 30% with a poorer prognosis combination. Our sensitivity analysis indicates that the deviation from the model predictions was always less than 3%.

The mammogram dissemination patterns modeled by the NCI that indicated approximately 30% of U.S. women, who have started screening, followed a screening schedule of exams 5 years apart. In calculations, a combination of stage distributions from the BCSC estimate for screening with more than a one–year scheduling interval and SEER (1975–1979, no screening exams) was used for this group. The stage shift for this group has been changed to assess the impact of the stage distribution on MR. Figure 2 displays the results. A more favorable stage distribution was utilized by using the BCSC estimate of screening with a more than one–year screening interval; a less favorable stage distribution was utilized by using the stage distribution of SEER. The better stage shift improved the MR in the year 1999 to 35% and the control stage distribution lowered the MR in the year 1999 to 31%. Thus these sensitivity calculations show that there are small deviations between the model predictions and the predictions based on alternative stage shift distributions.

REFERENCES:

[1] Lee, SJ, Zelen, M. "Modeling the early detection of breast cancer" in Annals of Oncology 2003; 14: : 1199-1202

PREDICTED MORTALITY REDUCTIONS

RESULT TYPE

Validation

RESULT

Below is the predictions of the outputs for the eight randomized breast cancer early detection trials.

TABLE 1. Summary of Reported and Predicted Mortality Reductions (MR)

Trial	FU(yrs)	Reported	MR(CI)	Prediction MR
Malmo–1	19	19%	(0,34%)	17%
Stockholm	15	10%	(–28%,37%)	21%
Gothenburg	13.5	22%	(–7,43%)	20%
Ostergotland	17	11%	(–9,28%)	22%
Edinburgh	14	17%	(–18,42%)	11%
HIP	10	30%	(?)	3%
Canada–1 (40–49)	7	–36%	(–121,16%)	1%
Canada–2 (50–59)	7	3%	(–52,38%)	1%

KEY REFERENCES

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