FLEXKB DOCUMENT
Version: HI.001.07232013.57434
Document generated: 07/23/2013

STANFORD UNIVERSITY

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.

Stanford University
Readers 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

Definitons 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

The primary purpose of our simulation model is to explain the impact of breast cancer screening and treatment on US breast cancer incidence and mortality SEER trends from 1975–2000. We simulate breast–cancer specific events in the US female population and track related health outcomes using a natural history model of the disease.

PURPOSE

Our CISNET model (Model Overview) aims to reproduce population level breast cancer mortality rates from 1975 to 2000 by capturing breast cancer events that involve heterogeneity in disease progression, patient characteristics, compliance to screening and response to adjuvant treatment. The main purpose of our model is to quantify the impact of screening mammography and adjuvant therapy on breast cancer mortality trends from 1975 to 2000. In addition, our model can be extended to predict what the incidence and mortality trends would have been had alternative age–group been targeted for screening, had there been changes to the interval between screening examinations and/or changes to the groups targeted for adjuvant therapy.

Our specific aims are:

1. To develop and validate a stochastic natural history model of breast cancer.

We assume the tumor grows exponentially in the period that it can be screen detected. We assume that the growth rate is constant for a given individual but it can vary between individuals. We assume that the tumor progresses from local to regional to distant disease as it increases in volume. We aim to produce robust estimates of tumor growth rate distribution; the probability of the onset of the regional stage as a function of tumor volume; and the probability of the onset of the distant stage as a function of tumor volume.

2. To develop and validate a simulation model of the US female population undergoing screening and treatment.

We embed the natural history model described in Specific Aim 1 into a simulation

model of the US female population undergoing screening and treatment. For each individual, we simulate her age of birth, age and stage at breast cancer clinical detection, her age at breast cancer death and age at other–cause death. We assume that breast cancer death and other–cause death are independent, competing events. If the individual is screen detected, we will also simulate her age and stage at screen detection and age at breast cancer death from her screen detected tumor. We simulate individuals from every birth cohort since 1887 and aggregate the outcomes by calendar year. We estimate leadtime, lengthtime and overdiagnosis biases from screening.

3. To estimate the impact of breast cancer screening and treatment on SEER incidence and mortality rates.

We use the simulation model described in Specific Aim #2 together with a model of the dissemination of screening and treatment to estimate SEER trends in age–adjusted breast cancer incidence and mortality rates. We estimate: (i) the impact screening had on reducing breast cancer incidence and mortality, independent of treatment; (ii) the impact treatment had on breast cancer mortality, independent of screening; (iii) the impact treatment had as a result of early detection from screening programs.

* In this discussion, treatment refers to multi–agent chemotherapy and tamoxifen. It is assumed that breast cancer patients had mastectomy or breast conserving surgery followed by radiation.

Model Overview

Summary

This document provides a background and basic description of the simulation model that we developed to estimate the impact of screening and treatment on US breast cancer incidence and mortality SEER trends since 1975.

Purpose

The purpose of this simulation model is to explain the impact of breast cancer screening and treatment on SEER trends in age–adjusted breast cancer incidence and mortality since 1975.

Background

In the United States, approximately one out of every eight women will develop breast cancer in their lifetime and one out of every 29 women will die from breast cancer. Cancer control programs on prevention, screening and treatment aim to reduce breast cancer mortality. Yet the impact of past and current cancer control programs are hard to interpret. SEER–based analyses demonstrate that age–adjusted breast cancer mortality rates have been approximately stable from 1975 to 1989. From 1990 to 2000, breast cancer mortality rates fell 1.7% per year. Breast cancer incidence rates climbed between 1977 and 1987, and have approximately been level between 1990 and 1996. DCIS incidence rates are increasing. There is no widely accepted explanation for these trends.

Views on the battle against breast cancer vary. It can be argued that our current breast cancer control programs in screening and treatment (with multi–agent chemotherapy and tamoxifen) are working. In particular, the increasing fraction of local disease, as well as DCIS, is a result of screening. The increased incidence of DCIS would be positive outcome if DCIS were known to be a precursor to invasive breast cancer. Other positive news is that 5–year and 10–year survival probabilities have increased and breast cancer mortality has started to decrease. On the other hand, it can be argued that the benefits of breast cancer control programs are not obvious. Survival benefits (measured from the time of diagnosis) may be due to leadtime, length time and overdiagnosis biases. The measured mortality decline since 1990 may be due to changes in treatment alone. This perspective would not say that the screening programs are not essential, but might suggest that the most substantial benefit of screening is local control of the primary disease as opposed to its life–threatening metastases. Given these two divergent perspectives, an analytically rigorous explanation of the trends is needed for effective, and cost–effective, cancer control programs in the future. We are developing a computer model to simulate breast cancer specific event in the US female population in order to explain the impact of screening and treatment on SEER–observed breast cancer incidence and mortality trends.

Model Description

Our basic simulation model can be described by the following algorithm:

For birth cohorts from 1887 to 1970

For each woman in the birth cohort

Generate her natural history of breast cancer
Compute her life history without screening and adjuvant treatment
Compute her life history with screening but without adjuvant treatment
Compute her life history without screening but with adjuvant treatment
Compute her life history with screening and adjuvant treatment

End
End

Our model provides estimates for population–level breast cancer mortality trends by simulating the life history of individual patients then aggregating the breast cancer related outcomes at the population level. Via the Monte Carlo method, the following characteristics are generated for an individual breast cancer patient: (1) the date of her birth, (2) the age of her death of causes other than breast cancer, (3) the ages she undergoes screening examinations, (4) the age she would be detected with invasive breast cancer in the absence of screening, (5) the age she would be detected with invasive breast cancer in the presence of screening, (6) her primary tumor size, extent of nodal and distant involvement and ER status at the time of detection in the presence and absence of screening, (7) the adjuvant treatment she received in the presence and absence of screening (it is assumed that she received primary therapy which would include surgery and possibly radiation) (8) her breast cancer survival time given her disease stage, size, age at detection and mode of detection, (9) her cause of death (i.e. breast cancer, other causes).

Our model generates information that could never be observed in a single patient. For example, if a woman was screen detected with invasive breast cancer in a given stage, we could not know when she would have been clinically detected and her disease stage at clinical detection. Similarly, if the patient treated died of other causes, we could not know when she would have died and her cause of death in the absence of screening and/or adjuvant therapy. Outputs such as these enable us to estimate the

survival and mortality benefit of screening and adjuvant therapy alone, as well as estimate leadtime and overdiagnosis effects of screening on breast cancer survival.
In order to generate the breast cancer outcomes for an individual breast cancer patient in the presence and the absence of screening and/or treatment, we model the natural history of the disease. In particular, we model the tumor size and SEER historic stage (defined as local, regional or distant) of patient's tumor at and before the moment that the tumor clinically surfaces. By "clinically surfaces," we mean the tumor is detected upon clinical examination because the patient experiences symptoms such as breast pain or nipple discharge. The simulation model traces the tumor from the moment it clinically surfaces "backwards" in time and provides estimates of the size and stage of the tumor at any time during the preclinical phase of the disease. A screening schedule that specifies the patient's age at the time of screening mammography is superimposed on the patient's disease history. A patient is screen detected only if the size of her tumor is at or above the tumor size detection threshold of mammography at the time of screening. Once the patient is detected, she is assigned a breast cancer specific survival time dependent on her age, tumor size, SEER historic stage mode of detection and her use of adjuvant treatment. Her age of death is the minimum age of breast cancer death and the age of other cause death. Individual level outcomes are aggregated and summarized as population level outcomes in terms of age–adjusted breast cancer incidence and mortality.

CONTRIBUTORS

PlevritisSylvia
RaiSanatan
GlynnPeter
SalzmanPeter
RosenbergJarret
SigalBronislava

ASSUMPTION OVERVIEW

SUMMARY

We describe the assumptions in our model.

BACKGROUND

In order for the model to be mathematically tracktable we need to make certain assumptions. We subdivide the assumptions we make into sevaral categories, i.e. the ones related to patients characteristics, tumor characteristics, screening, adjuvant treatment (Component Overview).
Some assumptions regarding background cancer incidence are required, since, for example, incidence for later years is contaminated by screening and hence background rates are unobservable. The natural history of breast cancer is also unobservable. Existing measurements of the growth rate are biased toward slower growing tumors. The onset of regional and metastatic disease is not known. Finally, the rate that the tumor advances in stage is not known. Size of the tumor at which it becomes detactable by mammography is unobservable as well and requires modeling.

ASSUMPTION LISTING

Patient Characteristics

- The age– and cohort–specific incidence of breast cancer in the absence of screening is provided by NCI. It is assumed to be zero for women under 25 years of age and over 84 years. We treat this incidence as the hazard rate of the first cancer and apply it to our estimated cancer–free population.
- A woman is screen detected with breast cancer only if the size of her tumour at a screening exam is greater than the *screening threshold* (SD threshold). If this tumor would have been clinically detected after her natural death, then she is "overdiagnosed."
- Regardless of the mode of detection, breast cancer survival is based on SEER–derived breast cancer age, size and stage specific survival curves for cases detected in 1975–1979 (ie before screening).
- Death from causes other than breast cancer and death from breast cancer assumed to be two independent events.

Tumor Characteristics

- The tumour grows exponentially.
- The tumour volume doubling time has gamma distribution.

- The tumor begins in the local stage and progresses through the regional stage before enters the distant stage. We define the onset of the regional stage as the point at which nodal involvement first becomes detectable by techniques commonly used in clinical practice. Similarly, we define the onset of the distant stage as the point at which distant disease first becomes detectable by techniques commonly used in clinical practice. If the tumor is clinically detected before the onset of the regional or distant disease, it is staged as local disease. If the tumor is clinically detected after regional transition but before distant transition, it is staged as regional disease. If the tumor is clinically detected after the distant transition, it is staged as distant disease.
- The hazard of clinical detection at time t is proportional to the volume of the tumor at time $t, V(t)$. The onset of regional disease and the onset of distant disease are each modeled as the time to the first out of the two independent competing events. The hazard of the first event is constant over time and the hazard of the second event is proportional to the volume of the tumor at time $t, V(t)$. Clinical detection, and onset of the regional stage are independent of each other given the tumor volume doubling time. Onset of the distant stage is independent of the clinical detection given doubling time and tumor size at transition to regoinal stage.
- Tumor doubling time, hazard of clinical detection and stage transition are independent of the birth cohort.

Operating Characteristics of Mammography

- The detection threshold is defined as first tumor size that can be detected by the screening examination; tumors below this size will be missed and tumors above this size will be detected.
- We assume that detection threshold dose not depend on the year in which mammography is performed.

Mammography Dissemination

- Model for generating woman's ages at screening mammography is provided by NCI.

Treatment Efficacy

- We assume proportional benefits due to adjuvant treatment using hazard ratios published by Early Breast Cancer Trialists' Collaborative Group[2].

Treatment Dissemination

- Model for generating treatment (adjuvant chemotherapy, adjuvant tamoxifen, both or no treatment) recieved for given age, stage, size and ER status at detection is provided by NCI.

Breast Cancer Survival

- In the absence of screening and adjuvant treatment breast cancer cause specific survival stratified by tumor size, stage and patient's age at detection is assumed to be independent of the year of diagnosis.

REFERENCES:

1 Early Breast Cancer Trialists' Collaborative Group. “Tamoxifen for early breast cancer: an overview of the randomised trials.” in Lancet 1998; 351: 9114: 1451-67

2 Early Breast Cancer Trialists' Collaborative Group. “Polychemotherapy for early breast cancer: an overview of the randomised trials.” in Lancet 1998; 352: 9132: 930-42

PARAMETER OVERVIEW

SUMMARY

This document describes our modeling philosophy and the input parameters of our model.

BACKGROUND

Our model building process involves the following steps: we (1) decomposed the factors that drive population level breast cancer outcomes into distinct, less complex, physically meaningful components at the individual patient level; (2) analytically formulated the model components with a small number of parameters using basic biological, clinical and epidemiological principles and widely–held assumptions; (3) estimated the parameters from the best available national data; the parameters are classified as either: (i) observable parameters, meaning that they are directly observed, typically from clinical trials or (ii) unobservable parameters, meaning that they cannot be directly observed but may be estimated based on modeling assumptions; (4) merged all the components into a simulation algorithm that generates the population level breast cancer outcomes across a large range of calendar years; (5) validated the population level simulation model by measuring how well it reproduces data on breast cancer trends that were not used in parameter estimation or model calibration; (6) evaluated uncertainty in the estimated breast cancer trends due to uncertainty in the estimates of the parameters of the model components; (7) performed sensitivity analysis to modeling assumptions and (8) identified worthy refinements to the model should the appropriate data become available.

The step that is perhaps the most critical in our model building process is that of model validation. From the start of this project, we intended to validate the model by analyzing how well it reproduces the observed SEER incidence and mortality trends, particularly in the post–screening period. For this reason, we required that no parameter estimation should rely on calibrating to the observed population trends, particularly in the post–screening period. We needed to moderately relax this requirement in the current version of the model.

PARAMETER LISTING OVERVIEW

Patient Characteristics

- Age–specific incidence rate of breast cancer with secular trend across birth cohorts.
- Other–cause death by birth cohort
- Kaplan–Meier breast cancer specific SEER survival curves stratified by age, tumor size and stage.

Tumor Characteristics

- Mean growth rate is estimated together with mammography detection threshold by calibrating to SEER incidence and BCSC data on size distribution of screen detected cancers.

- Parameters of the natural history model, i.e. hazard of clinical detection, hazard of transition from local to regional and from regional to distant stages, are estimated from SEER 1975–1981 data (prescreening period) on tumor size and stage at detection using only cases which are the first malignant tumor in a patient.
- Probability of having ER+ tumor is estimated from SEER 1990–1994 data.

Mammography Operating Characteristics

- The distribution for the mammography threshold was modeled by assuming that the hazard function for "screen–detectability", i.e. the transition from a nonscreen detectable tumor to a screen detectable tumor, is proportional to the cross–sectional area of the tumor, which is in turn proportional to the tumor volume raised to the two–thirds power.

Mammography Dissemination

- Model for generating woman's ages at screening mammography is provided by NCI.

Treatment Dissemination

- Model for generating treatment (adjuvant chemotherapy, adjuvant tamoxifen, both or no treatment) recieved for given age, stage, size and ER status at detection is provided by NCI.

Treatment Efficacy

- We assumed proportional benefits due to adjuvant treatment using hazard ratios published by Early Breast Cancer Trialists' Collaborative Group (1998).

See also Component Overview .

COMPONENT OVERVIEW

SUMMARY

We describe the components of the model.

OVERVIEW

The following briefly describes the model algorithm and the model components involved at each step.

We start by generating woman's date of birth and age at death from other causes given her year of birth. Then her age at clinical detection of breast cancer is generated. Given parameter estimates for the stage–shift natural history model and age at clinical detection, we sample from estimated distributions of the tumor volume doubling time, tumor size at detection and tumor size at onset of the regional and the distant stage conditioned on the doubling time. In the next step we compute tumor stage at clinical detection in the absence of screening. If the tumor is clinically detected before the onset of the regional disease, after the onset of the regional disease but before the onset of the distant disease, after the onset of the distant disease, it is staged as local, regional or distant respectively. Given age, size and stage at clinical detection we compute the age at breast cancer death following clinical detection using survival curves estimated from 1975–1979 SEER data. Screening schedule is generated using either model provided by NCI or custom schedule, i.e. screening interval can be kept constant or set arbitrarily. Tumor–size detection threshold of the screening examination is generated using approach in [ref]. Based on woman's screening schedule and detection threshold we compute age, tumor size and stage at screen detection. A patient is screen detected only if the size of her tumor is at or above the tumor size detection threshold of mammography at the time of screening. The tumor size at the time of screening is determined knowing the size of the tumor at clinical detection, the tumor volume doubling time and the difference in the woman's age at the time of screening and her age at the time of clinical detection in the absence of screening. Next, using the model provided by NCI we generate type of the adjuvant treatment recieved by the woman given her year of diagnosis, age at diagnosis, tumor size and stage. Once the patient is detected, she is assigned a breast cancer specific survival time dependent on her age, tumor size, SEER historic stage mode of detection and her use of adjuvant treatment. Her age of death is computed as the minimum of the age at breast cancer death and the age at death from other causes.

COMPONENT LISTING

Our model consists of six underlying components: population, breast cancer incidence, breast cancer survival, natural history model, screening intervention and adjuvant treatment intervention. The components themselves contain subcomponents, some of which are referred to as "CISNET base case inputs" because they were defined by CISNET Breast Cancer Working Group as common inputs that would facilitate comparison among the seven different models.

Below is the pseudocode for our simulation model.

For birth cohorts 1887:1970,
For individuals 1:2,000,000

Step 1: Generate date of birth (Population Component)
Step 2: Generate age at other–cause death given birth cohort (Population Component)
Step 3: Generate age at clinical detection (Cancer Incidence Component)
Step 4: Generate tumor volume doubling time (Natural History Component)
Step 5: Generate tumor size at clinical detection given the tumor volume doubling time (Natural History Component)
Step 6: Generate tumor size at the onset of regional and distant stage (Natural History Component)
Step 7: Compute stage of the tumor at clinical detection
Step 8: Generate age at breast cancer death following clinical detection given age and stage at clinical detection (Survival And Mortality Component)
Step 9: Generate the ages undergoing screening given birth cohort (Screening Component)
Step 10: Generate the tumor size detection threshold of mammography (Screening Component)
Step 11: Compute age, tumor size and stage at screen detection
Step 12: Generate type of adjuvant therapy (Treatment Component)
Step 13: Generate age at breast cancer death following screen detection given age and stage at detection (Survival And Mortality Component)
Step 14: Compute age of death as min{age of breast cancer death, age of other cause death} (Survival And Mortality Component)

Repeat for next individual
Repeat for next birth cohort

OUTPUT OVERVIEW

SUMMARY

We describe the output of breast cancer population simulation model.

OVERVIEW

The following outputs are produced by our model to help answer CISNET questions: age specific annual breast cancer incidence, age specific annual breast cancer deaths, mid–year population. The different type of output is used to estimate operational mammography characteristics, and such unobservable quantities as lead time and overdiagnosis.

OUTPUT LISTING

Breast cancer incidence and mortality:

- Age–specific (5–year) annual counts of detected breast cancers.
- Age–specific (5–year)annual counts of breast cancer deaths.
- Age–specific (5–year) annual counts of breast cancer prevalence cases.
- Age–specific (5–year) annual counts of detected breast cancers by size and stage.
- Age–specific (5–year) annual mid–year population.

The above outputs could be used to compute age–specific and age–adjusted annual breast cancer incidence rates by year of diagnosis, breast cancer mortality rates by year of death and prevalence rates.

Screening program characteristics based on cancers generated in years 1975–2000:

- Mean leadtime by 5–year age groups.
- Mean overdiagnosis by 5–year age groups.
- Mammography detection rates by 5–year age groups for the first screen and for the all subsequent screens.
- Program sensitivity by 5–year age groups.

All of the above outputs could be produced under the four scenarios (where appropriate):

- Background risk only
- Treatment only
- Screening only
- Screening and treatment

RESULTS OVERVIEW

SUMMARY

In this section we present the results that could be derived from our program outputs as well as the results of sensitivity analysis.

OVERVIEW

In order to answer CISNET base case question : "What are the contributions of screening and treatment to mortality reduction?", we predict age–adjusted breast cancer mortality trends from 1975 to 2000. We also perform one–way sensitivity analysis of the age–adjusted mortality trends with respect to changes in the various input parameters of our model.

RESULTS LIST

Fit to the Age–adjusted Mortality Trend for Years 1975–2000

Comparison of the predicted and actual age–adjusted breast cancer mortality rates from 1975 to 2000 as reported by the National Center for Health Statistics (NCHS) are shown in Figure 1 (Age Adjusted Mortality).

Uncertainty analysis

We assessed uncertainty in the annual breast cancer mortality due to the estimated uncertainty in the scaled parameters of the natural history model (see Uncertainty Sensitivity Analysis)

Sensitivity Analysis

Because our model predicts a higher mortality rate than observed and does not predict the continued decline in mortality after 1995, a sensitivity analysis was especially critical. We performed the following one–way sensitivity analyses:

1. Varying the secular trend in breast cancer incidence.
2. Adding a temporal improvement in mammography detection.
3. Adding a temporal trend to treatment efficacy.
4. Adding a temporal improvement in baseline survival.
5. Allowing a fraction of screen detected invasive tumors to be screen detected as DCIS.

For details see Uncertainty Sensitivity Analysis .

CISNET Base Case Result

In answering the CISNET base case question: "What are the contributions of screening and treatment to mortality reduction?", we predict age–adjusted breast cancer mortality trends from 1975 to 2000 under the following four scenarios:

1. in the absence of screening and adjuvant therapy

2. in the presence of screening only
3. in the presence of adjuvant therapy only
4. in the presence of both screening and adjuvant therapy.

See Base Case Results for details.

POPULATION COMPONENT

DETAIL

Our population component specifies the birth cohorts for our population level simulation analysis. To reproduce the outcomes of women ages 30 to 84 years in the US from the years 1975 to 2000, a representative sample of women born in the US between the years 1887 and 1970 is generated. Each birth cohort consists of two million women, which we found was a sufficiently large number to reduce the variability associated with the Monte Carlo method. Even though factors such as population immigration and emigration are likely to vary the relative sizes of the birth cohorts, the size of each birth cohort is kept constant in our simulation because the incidence and mortality trends are reported as age–adjusted rates. Each woman is assigned a birth date and an age at death from other causes. Death from breast cancer and other–causes are assumed to be independent. The other–cause death rate is a NCI base–case input and based on the Berkeley Mortality Database which start with the 1900 birth cohort[2]. For birth cohorts before 1900, we assume 1900 other–cause mortality rates.

REFERENCES:

[1] The Berkeley Mortality Database. Department of Demography at the University of California, Berkely. "BerkeleyMortality"

[2] Rosenberg, M. "Annual probabilities of death from causes other than breast cancer." in Cancer Intervention and Surveillance Modeling Network; Base Case. Unpublished data.

CANCER INCIDENCE COMPONENT

DETAIL

The breast cancer incidence component determines whether or not an individual from a particular birth cohort would become clinically detected with invasive breast cancer in the absence of the screening and other–cause mortality. The breast cancer patient is assigned the age at which her first primary invasive tumor clinically surfaces.
This component relies on a CISNET base case input commonly referred to as the "secular trend in breast cancer incidence" and is estimated from the historic Connecticut Tumor Registry (CTR) and SEER[1]. The base case input estimates breast cancer incidence (invasive and in situ) in the absence of screening for annual birth cohorts starting 1891 by single year of age, for ages 25 to 84 years. The base case incidence is assumed to be zero for women under 25 years old and over 84 years old.

We treat the base case incidence as the hazard rate of the first cancer and apply it to our estimated cancer–free population. For each birth cohort we interpret the given incidence per 100,000 women (h_a) as the hazard rate for age a . To reduce the execution time for multiple runs, we generate and sample from a distribution function for the clinical detection age (A_{BC}) at symptomatic detection of the first invasive breast cancer for each birth cohort in the following way:

$$P(A_{BC} \leq a) = 1 - \prod_{i=25}^{a} (1 - h_i/100,000)$$

where the age a is an integer. Because this is a discrete distribution function of the woman's age at the first symptomatic detection, we generate the exact age by assuming a uniform distribution within a year. The same calculation is made for all the birth cohorts.
Two limitations with the breast cancer secular trend exist. First, we are likely overestimating the true hazard of the first primary, particularly in the older age groups. The base–case incidence was approximated as the observed count of "new cancers" divided by the size of the mid–year population based on data from the CTR and SEER, whereas the true incidence is defined as the count of "first cancers" divided by the size of the cancer free population[2]. This approximation is made because SEER does not include the size of the cancer free population. It would produce the true incidence if women are equally at risk for breast cancer regardless of their history of breast cancer; however, the risk of breast cancer likely increases with a prior history of primaries as evidenced by the Gail model[3].
The second limitation with our use of base case incidence is that we had to modify it in order to estimate the incidence for clinically detected invasive cancers only. The base case input provides the estimated trend for the sum of clinically detected in situ and invasive disease. We adjusted it by removing an estimated proportion of in situ cases as a function of age, which was estimated from SEER 1975–1979 data. The same correction factor was applied to all birth cohorts.

REFERENCES:

[1] Holford, T.R., et al. "Changing Patterns in Breast Cancer Incidence Trends." in J Clin Epi. submitted.

[2] Merrill, R.M. and E.J. Feuer "Risk-adjusted cancer-incidence rates (United States)." in Cancer Causes Control 1996; 7: 5: 544-52.

[3] Gail MH,et al. "Projecting individualized probabilities of developing breast cancer for white females who are being examined annually." in J Natl Cancer Inst 1989; 81: 24: 1879-86.

NATURAL HISTORY COMPONENT

OVERVIEW

Our natural history component specifies the size of a breast cancer patient's first primary invasive breast tumor and its SEER historic stage during the preclinical phase of the disease mechanism under which the first primary invasive tumor is clinically detected[1]. Herein, the preclinical phase is defined from the moment the tumor is invasive and 2mm in diameter to the moment it clinically surfaces. We trace the tumor size backwards in time from the time it would have been clinically detected. (We are not modeling the tumor forward in time by estimating the onset of the first malignant cell or the onset of a tumor mass of a fixed size.)

DETAIL

Doubling time distribution of the primary tumor

The tumor is assumed to be spherical and grow exponentially, at a constant rate, in the preclinical phase. The volume of the tumor at time t is expressed as $V(t) = c_0 \exp^{t/R}$, where the inverse growth rate R (which is doubling time divided by ln(2)) has gamma distribution with rate α and shape β.

Stage transition of the primary tumor

The disease is assumed to start in the local stage, and progress to regional and distant stages as it increases in size. We define the onset of the regional stage as the point at which nodal involvement first becomes detectable by methods commonly used in clinical practice. Similarly, we define the onset of the distant stage as the point at which distant disease first becomes detectable by techniques commonly used in clinical practice. If the tumor is clinically detected before the onset of the regional or distant disease, it is staged as local disease. If the tumor is clinically detected after regional transition but before distant transition, it is staged as regional disease. If the tumor is clinically detected after the distant transition, it is staged as distant disease.

The onset of regional disease and the onset of distant disease are each analytically modeled as the time to the first out of the two independent competing events. The hazard of the first event is constant over time and the hazard of the second event is proportional to the volume of the tumor at time $t, V(t)$. In mathematical terms the hazard of the time to onset of observable nodal involvement (T_N) has the form,

$$P(T_N \in [t, t+dt) | T_N \geq t) = (\eta_0 + \eta_1 V(t))dt + o(dt).$$

The hazard of the time to onset of observable distant metastasis (T_M) is

$$P(T_M \in [t, t+dt) \ | T_M \geq t, T_N = t_N)$$

$$= \begin{cases} (\omega_0 + \omega_1 V(t))dt + o(dt), & t \geq t_N \\ 0, & t < t_N. \end{cases}$$

We do not include a temporal trend in the stage–transitions due to the lack of data to support parameter estimation. Yet it is reasonable to assume that technology advancements have caused a stage migration[2].

Clinical detection function

The hazard of the time to clinical detection (T_D) is assumed to be proportional to the current tumor volume,

$$P(T_D \in [t, t+dt) | T_D \geq t) = \gamma V(t) dt + o(dt).$$

This clinical detection function was introduced previously for breast cancer[3]. We do not vary the clinical detection function by calendar year due to lack of data to support estimation. Yet the clinical detection function has probably changed over time, yielding smaller median tumor sizes as increasing numbers of women are becoming aware of early breast cancer symptoms through greater education and outreach programs.

Parameter estimation

Estimation of scaled rate parameters

In total, our natural history model has seven parameters: $\alpha, \beta, \gamma, \eta_0, \eta_1, \omega_0, \omega_1$ which are specified above. Maximum likelihood estimates for these parameters are based on SEER data of the tumor size and stage of invasive cancers that were clinically detected in the absence of screening[4]. Only tumors detected between 1975 and 1981, which represents a period of no to little screening, were considered, and of these only the breast tumor which is the first primary tumor in a women with multiple primaries were selected. Because we do not use any data that contains temporal information (such as age), the rate parameter estimates are dimensionless and scaled by the mean doubling time. The scaled natural history parameters estimates are stratified by age–groups (20 – 39 years old, 40 – 49 years old, 50 – 69 years old, 70 – 84 years old).

Estimation of the mean volume doubling time and screening detection threshold

We estimated two unobservable parameters, namely the median tumor size detection threshold of mammography and mean tumor volume doubling time simultaneously, by calibrating to the SEER incidence trends and data from the Breast Cancer Surveillance Consortium (BCSC)[5] using a two–step procedure. In the first step, each of five–year age–specific SEER incidence curves were smoothed with respect to the year of diagnosis using natural splines (SPLUS 6.1) in terms of the number of new cancers divided by the mid–year population. Using our simulation program we estimated incidence as a number of first cancers divided by the mid–year population minus the prevalence. Sum of squared difference between age–specific smoothed SEER incidence and simulated incidence was used as a goodness of fit measure, thus assuming the same weight for each age group and each calendar year. This measure was computed over the two–dimensional parameter grid with increments of 0.05 year for the mean doubling time and 0.05 cm for the median threshold. The mean doubling time was varied between 0.2 year and 1.1 year and median detection threshold was varied between 6mm to 12mm. Various combinations of the parameters produced similar

goodness of fit measures. In the second step, for each fixed threshold we selected the best mean doubling time. Using thus created "pairs" we selected the one that produced better fit to the median size at detection for screen detected cases in BCSC 1994–2000 data of cancers screen detected within three years of the previous screening mammogram for women 50–69 years old. The resulting estimates currently used in the program are 0.75 year for mean doubling time and 1.0 cm for the median threshold of screening mammography.

This estimation procedure counters our intention to avoid calibration to post–screening SEER trends. However, it is limited to two parameters and calibration to incidence trends only. Through sensitivity analysis, we found these two parameters largely impact the change in breast cancer incidence rate once screening was introduced. In future work, this calibration procedure can be avoided because, in theory, these parameters along with the other parameters underlying the natural history can be simultaneously estimated from screening trial data.

Natural history model validation

After estimating the scaled rate parameters, we generate the goodness–of–fit measure by comparing the observed versus estimated tumor size distribution and the stage distribution conditioned on tumor size, for each age–group.

REFERENCES:

[1] Plevritis, S.K., et al. "A Natural History Model of Stage Progression Applied to Breast Cancer." in (Submitted).

[2] Feinstein, A.R., D.M. Sosin, and C.K. "Wells, The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer." in N Engl J Med 1985; 312: 25: 1604-8

[3] Bartoszynski, R. "A modeling approach to metastatic progression of cancer Cancer Modeling." in Cancer Modeling, J.R.a.B. Thompson, B. W., Editor. 1987; : 237

[4] Surveillance, E., and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public–Use, Aug 2000 Sub (1973–1998) "SEERStat" in National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch.

[5] Ballard–Barbash, R., et al. "Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database." in AJR Am J Roentgenol 1997; 169: 4: 1001–8

Survival And Mortality Component

Overview

Survival is determined by age, size, stage, mode of detection and use of adjuvant therapy. For clinically detected cancer cases (in the absence of screening and treatment), we use age, stage and cause–specific survival curves obtained from SEER for women detected between the years 1975–1979 for which breast cancer was the first primary tumor. This is an NCI base case input for tumor size categories

Detail

Baseline breast cancer survival

Breast cancer survival curves for patients detected in the absence of screening and adjuvant therapy are a CISNET base case input, referred to as baseline breast cancer survival curves. These are Kaplan–Meier estimates obtained from SEER for female breast cancer patients who were detected between the years 1975–1979 and for whom breast cancer was their first primary tumor. Because the period from 1975 to 1979 is associated with minimal levels of screening and adjuvant therapy, the baseline survival curves are assumed to only capture the effects of primary breast cancer treatment, namely surgery with the possibility of radiation. The curves are stratified by age at detection (30 – 39 years old, 40 – 49 years old, 50 – 59 years old, 60 – 69 years old, 70 – 84 years old), SEER historic stage (i.e. local, regional, distant), for local and regional stages curves are further stratified by tumor size (i.e. We do not include temporal variation in these curves, although improvements in primary treatment may have improved survival[1]. In addition, baseline survival may be impacted by temporal variation in the proportion of disease histology[2].

Breast cancer survival post screen detection without adjuvant therapy

The breast cancer survival curve post screen detection is taken to be the maximum of two curves: (1) the baseline survival curve that corresponds to the age, size and stage at screen detection and (2) the baseline survival curve that corresponds to the age, size and stage at clinical detection. Both survival curves are initiated at the corresponding age of detection and survival probability for curve that corresponds to clinical detection is set to be 100% during the leadtime. This approach rules out the possibility of death during the leadtime.

The assignment of breast cancer survival post–screen detection is arbitrary. Better breast cancer mortality outcomes would be obtained by using the baseline breast cancer survival curve that corresponds to the screen detected tumor characteristics initiated at the age of clinical detection. Worse outcomes would be obtained by using the baseline breast cancer survival curve that corresponds to the screen detected tumor characteristics initiated at the age of screen detection, because it would allow for death in the leadtime. In a sensitivity analysis, we found that these two extremes do not deviate significantly from the decision rule that we applied.

Breast cancer survival following adjuvant therapy with and without screening

We assume a proportional hazard reduction in breast cancer mortality due to adjuvant

treatment (Treatment Component). In the absence of screening, the hazard ratio is applied to the base case baseline breast cancer curves. In the presence of screening, the hazard ratio is applied to the resulting survival curve obtained earlier.

Other cause mortality

Other cause mortality and cause–specific mortality are assumed to be independent. Age and cause of death is then determined as the minimum of the cause–specific and other cause mortality.

What is the effect of not modeling in–situ disease?

DCIS is not included in our natural history model because there is little known about its progression. Some forms of in situ (in particular, high–grade DCIS) have been suggested to progress to invasive disease[3], but exactly what percent progresses and how fast it progresses is not known. For this reason, our model is limited to disease that would have been clinically detected as invasive. By not including clinically detected in situ disease we are implicitly making the assumption that DCIS does not contribute to breast cancer mortality. We are also not considering disease that would have been clinically detected as invasive but is screen detected as in situ. In our model, DCIS is likely screen detected as localized, small invasive tumor and as such would have good prognostic outcome. Should this assumption lack validity, we expect a poor prediction of breast cancer mortality since DCIS is a substantial fraction of incident breast cancer in the screening period[4].

REFERENCES:

[1] Bartelink, H., et al. “Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation.” in N Engl J Med 2001; 345: 19: 1378-87

[2] Li, C.I., et al. “Trends in incidence rates of invasive lobular and ductal breast carcinoma.” in Jama 2003; 289: 11: 1421-4

[3] Kerlikowske, K., et al. “Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy.” in J Natl Cancer Inst 2003; 95: 22: 1692-702

[4] Ernster, V.L., et al. “Detection of ductal carcinoma in situ in women undergoing screening mammography.” in J Natl Cancer Inst, 2002. 94(20): p. 1546-54. 2002; 94: 20: 1546-54

SCREENING COMPONENT

OVERVIEW

Our screening component specifies the screening schedule of a given individual and the criterion upon which a patient is screen detected.

DETAIL

Screening Dissemination Module

We use the CISNET base–case input for mammography dissemination to specify the ages at which a given individual undergoes screening, given her birth cohort.[1] The screening schedule is truncated at the age of clinical detection or death of other causes, whichever occurs first.

Screen Detection Mechanism

Each woman who receives at least one screening examination is randomly assigned a mammographic detection threshold. The mammography detection threshold is defined as smallest tumor diameter detectable on screening mammography. Tumors below this diameter will be missed and tumors above will be classified as screen detected if they have not clinically surfaced before the time of the screening examination. Because the tumor size increases between screening examinations, the probability of screen detection increases. Once a patient is screen detected, her age, tumor size, SEER historic stage at detection are recorded. A patient is classified as an "interval case" if her tumor is clinically detected between two scheduled screening examinations.
The distribution for the mammography threshold was modeled by assuming that the hazard function for "screen–detectability", i.e. the transition from a nonscreen detectable tumor to a screen detectable tumor, is proportional to the cross–sectional area of the tumor, which is in turn proportional to the tumor volume raised to the two–thirds power, i.e.

$$P(V_{TH} \in [v, v+dv) | V_{TH} \geq v) = \lambda v^{2/3} dv + o(dv)$$

In terms of the tumor diameter, the resulting cumulative distribution function is $\mathrm{F}_{TH}(d) = 1 - \exp^{-0.6\lambda d^5}$. In our simulations, the distribution was truncated at diameter d = 2mm i.e. we set $\mathrm{F}_{TH}(d) = 0$ for d
Our mammography detection function has the advantage that it is fully specified by one unobservable parameter, but the disadvantage that it produces a narrow distribution. A wider distribution is more plausible however, it would require an additional unobservable parameter that could not be identifiable from the available data. Temporal variation in the screening detection function was not modeled because its estimation would rely on data that are not available (other than data from the SEER post–screening period which is being reserved for model validation).

REFERENCES:

[1] Cronin, K.A., et al. "Modeling the dissemination of mammography in the United States. Cancer Causes Control, in press." in Cancer Causes Control, in press.

TREATMENT COMPONENT

OVERVIEW

Our adjuvant treatment component assigns adjuvant treatment and its corresponding survival benefit to a breast cancer patient.

DETAIL

Treatment Dissemination

Each breast cancer patient is assigned adjuvant treatment (tamoxifen, multiagent chemotherapy, both, neither) depending on the patient's age, tumor size, disease stage, ER status, and year at detection, as specified by the NCI treatment dissemination base case input[1].

Tamoxifen dissemination targets ER–positive women in more recent years. Because ER status was not part of the natural history model, we assume that ER status does not vary over the preclinical course of the disease and does not impact the probability of screen detection. The probability that a given breast cancer patient is ER–positive was based on the proportion of women with ER–positive disease in the SEER data for years 1990–1994: the proportion of ER+ is 62%, 75%, and 83% for women

Survival Benefit from Adjuvant Treatment

We assumed proportional benefits due to adjuvant treatment using published hazard ratios[3]. For chemotherapy, the hazard ratio for the breast cancer specific survival depends on the age at detection: 0.72 for women 2 to convert it to a breast cancer specific mortality benefit. Ideally, this correction should depend an age and nodal status. If a woman receives both treatments, the product of hazard ratios is applied.

REFERENCES:

[1] Mariotto, A., et al. "Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999." in J Natl Cancer Inst 2002; 94: 21: 1626-34

[2] Early Breast Cancer Trialists' Collaborative Group. "Tamoxifen for early breast cancer: an overview of the randomised trials." in Lancet 1998; 351: 9114: 1451-67

[3] Early Breast Cancer Trialists' Collaborative Group. "Polychemotherapy for early breast cancer: an overview of the randomised trials." in Lancet 1998; 352: 9132: 930-42

AGE ADJUSTED MORTALITY

A comparison of the predicted and actual age–adjusted breast cancer mortality rates from 1975 to 2000 as reported by the National Center for Health Statistics (NCHS) are shown in Figure 1. Because a measure for goodness of fit is not clear for our purposes, we proceed with a qualitative assessment. The general shape of the predicted mortality curve is similar to the actual curve. The mortality trend has a dominant downward trend in mortality approximately starting in the year 1990. However, two significant discrepancies exist between the modeled and actual curves. First, the predicted mortality rates are higher than the actual rates on an absolute scale. Second, the predicted mortality curve levels off starting in the year 1995 but the actual mortality curve shows a continued decrease. Both of these discrepancies were anticipated. The mortality is systematically higher than expected because the incidence for the first primary may be too high (see Cancer Incidence Component). The predicted trends are fairly flat after 1995 because there is little temporal variation in the model inputs just before and during this period. Also, as expected, we find that both of these discrepancies are most dominant among women over age 60 at death. The differences, if any, are minor among the younger women, for whom the incidence of breast cancer is relatively low.

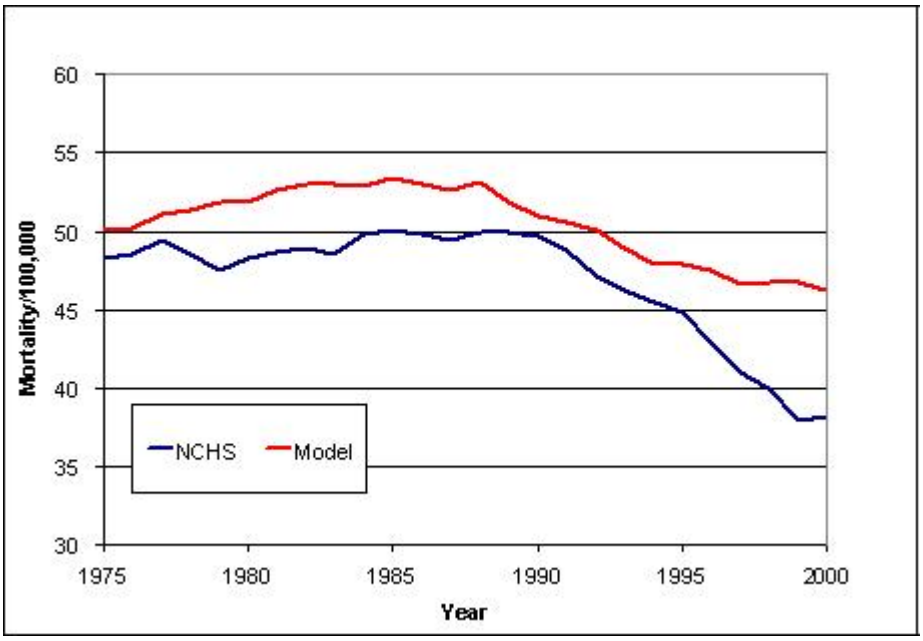

FIGURE 1. Comparison of age–adjusted US breast cancer mortality: NCHS data versus simulation model.

Uncertainty Sensitivity Analysis

Uncertainty Analysis

The uncertainty in the annual breast cancer mortality due to the estimated uncertainty in the scaled parameters of the natural history model (Natural History Component) is less than 1 death per 100,000 women. We estimated this uncertainty by bootstrapping the model with a new set of scaled natural history parameters. Parametric bootstrap was used to approximate joint distribution of the maximum likelihood estimates. The new parameter sets were generated by sampling from this joint distribution. This uncertainty does not fully account for differences between the modeled and actual breast cancer mortality.

Sensitivity Analysis

Because our model predicts a higher mortality rate than observed and does not predict the continued decline in mortality after 1995, a sensitivity analysis was especially critical. We proceed as follows:

1. *Varying the secular trend in breast cancer incidence:* Our breast cancer mortality rate may be too high because we may be overestimating the true hazard of first cancer (see Cancer Incidence Component). We adjust the number of new first cancer patients as follows: (1) we determine if a patient has been diagnosed previously given her age and stage, based on data from the CTR from the years 1975–1979; (b) if yes, then we return her to the healthy population. While this adjustment may underestimate incidence of first cancer, we find that it does not change the shape of the predicted mortality trend, but reduces its absolute level closer to the observed level, as shown in Figure 1(a). These desirable features warrant further investigation with alterations to the CISNET base case input for the secular trend in incidence.

1. *Adding a temporal improvement in mammography detection:* We introduced a stepwise change in the median tumor size detection threshold of mammography by reducing it from 1.0 cm to 0.5 cm at a specified calendar year and thereafter. The results from a step–wise change in the years 1985, 1990 and 1995 are shown in Figure 1(b). A noticeable reduction in breast cancer mortality begins approximately three years after the step–wise change. Despite the significant reduction in the detection threshold, the reduction in mortality is not large enough to account for continued mortality decline after the year 1995. For this reason, we do not suspect that we are significantly underestimating the benefit of screening mammography.

1. *Adding a temporal trend to treatment efficacy:* The efficacy in adjuvant treatment was assigned a stepwise change by improving the efficacy by 2 standard deviations based on published meta–analysis[2] in a specified calendar year and thereafter. The results following a stepwise change in 1985, 1990 and 1995 are shown in Figure 1(c). The response in mortality was immediate. If one were to consider a more gradual change in efficacy, such change in the 1990's could predict a continued mortality decline after 1995 without compromising the agreement between the predicted and actual mortality trends before 1995. Because a gradual improvement in multi–agent chemotherapy is likely due to changes in prescribed agents, it is possible that we are currently underestimating the benefit of adjuvant therapy in the later years. Future refinements to the treatment efficacy are warranted.

1. *Adding a temporal improvement in baseline survival:* We introduced a stepwise change in the baseline survival by forcing a 20% increase in a specific calendar year and thereafter. The results from a step–wise change in years 1985, 1990 and 1995 are shown in Figure 1(d). The response in mortality was immediate. Even a more modest improvement in baseline survival could significantly alter the shape of the predicted mortality curve before the year 1995 since it affects all cancer patients, so we do not expect it to be the major factor between 1975 and 1995 and hence after 1995.

1. *Allowing a fraction of screen detected invasive tumors to be screen detected as DCIS:* We assumed that a fraction p of tumors screen detected in local stage and below 1cm would be in situ disease with no risk of death from breast cancer. This was done by re–calibrating the remaining invasive cases to incidence while keeping mammography threshold fixed at 1 cm (see Natural History Component). As the percent of in situ disease varied from 5%, 10%, 20%, and 50%, the mortality reduction in the year 2000 varied from 0.2%, 1.1%, 1.4%, and 3.1% respectively. Even if 100% of all less than 1cm, local tumors were screen detected as in situ disease, breast cancer mortality in the year 2000 would decrease by only 6%, which is not large enough to explain the unaccounted for decline in mortality. We suspect that mortality is not greatly impacted because small, local tumors already have good prognosis.

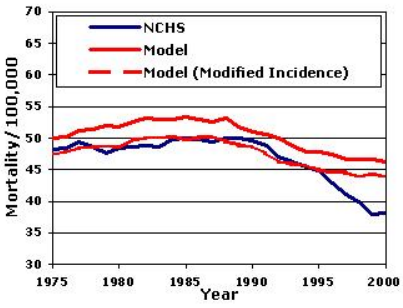

Figure 1(a). Comparison of the age-adjusted mortality: the observed data, the simulation model and the simulation model with the incidence modified.

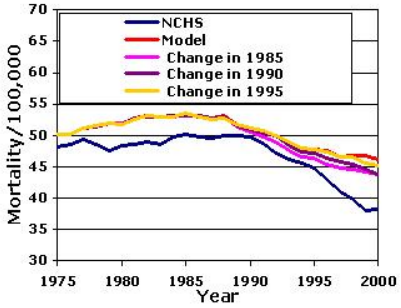

Figure 1(b). Age-adjusted mortality due to a stepwise change in mammography tumor size detection threshold in 1985, 1990 and 1995.

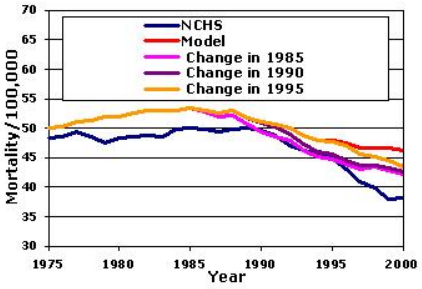

Figure 1(c). Age-adjusted mortality following a step-wise change in treatment efficacy in 1985, 1990 and 1995.

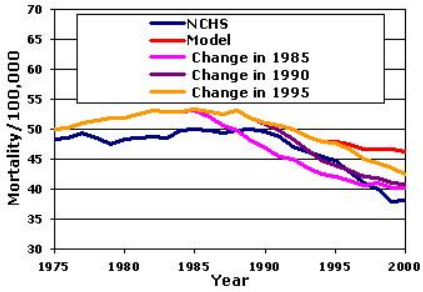

Figure 1(d) Age-adjusted mortality due to stepwise change in baseline breast cancer survival in 1985, 1990 and 1995.

REFERENCES:

[1] Early Breast Cancer Trialists' Collaborative Group. "Tamoxifen for early breast cancer: an overview of the randomised trials." in Lancet 1998; 351: 9114: 1451-67

[2] Early Breast Cancer Trialists' Collaborative Group. "Polychemotherapy for early breast cancer: an overview of the randomised trials." in Lancet 1998; 352: 9132: 930-42

BASE CASE RESULTS

CISNET Base Case Result

In answering the CISNET base case question: "What are the contributions of screening and treatment to mortality reduction?", we predict age–adjusted breast cancer mortality trends from 1975 to 2000 under the following four scenarios:

(1) in the absence of screening and adjuvant therapy,
(2) in the presence of screening only,
(3) in the presence of adjuvant therapy only, and
(4) in the presence of both screening and adjuvant therapy.

The results are shown in Figure 1. In the absence of screening and treatment, we predict a steady increase in age–adjusted breast cancer mortality due to the secular trend in incidence. Compared to the predicted mortality rate in the absence of screening and adjuvant therapy in the year 2000, the mortality rate in the presence of both screening and adjuvant therapy is reduced by a total of 29.9%, which is decomposed as follows: 16.9% due to screening, 6.9% due to chemotherapy and 8.9% due to adjuvant therapy. The estimated relative contributions of screening and adjuvant therapy to the mortality reduction were similar in magnitude: 53% due to screening versus 47% due to adjuvant therapy. Based on a sensitivity analysis, we found little difference in the relative contributions of screening and adjuvant therapy with the variation in the breast cancer secular trend (see Uncertainty Sensitivity Analysis). However, we may be underestimating the contribution due to adjuvant therapy given a likely temporal improvement in treatment efficacy (see Uncertainty Sensitivity Analysis). If we allow death in the leadtime (analysis not shown), we would be allowing the possibility that screening impacts only survival but not mortality, yet we still find a decline in breast cancer mortality.

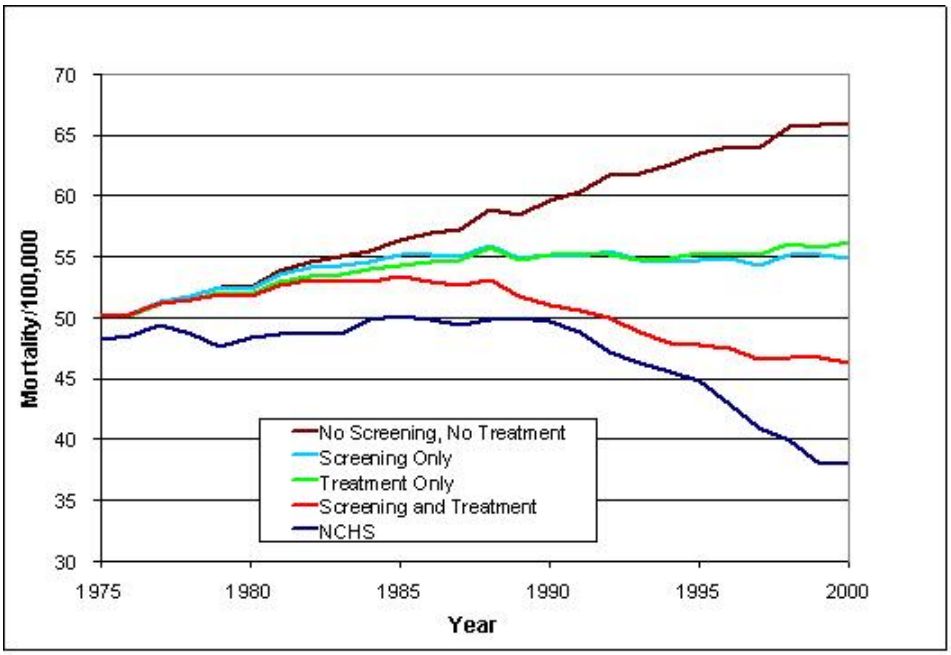

FIGURE 1. Simulated age–adjusted breast cancer mortality under four scenarios: (1) absence of screening and adjuvant therapy; (2) presence of screening only; (3) presence of adjuvant therapy only; and (4) presence of screening and adjuvant therapy. Observed NCHS age–adjusted breast cancer mortality is plotted for comparison.

KEY REFERENCES

Ballard-Barbash, R., et al. (1997) Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. in *AJR Am J Roentgenol* 169:4, p 1001-8

Bartelink, H., et al. (2001) Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. in *N Engl J Med* 345:19, p 1378-87

Bartoszynski, R. (1987) A modeling approach to metastatic progression of cancer Cancer Modeling. in *Cancer Modeling, J.R.a.B. Thompson, B. W., Editor.*, p 237

Bartoszynski, R., et al. (2001) Modeling cancer detection: tumor size as a source of information on unobservable stages of carcinogenesis. in *Math Biosci* 171:2, p 113-42

Cronin, K.A., et al. Modeling the dissemination of mammography in the United States. Cancer Causes Control, in press. in *Cancer Causes Control, in press.*,

Early Breast Cancer Trialists' Collaborative Group. (1998) Polychemotherapy for early breast cancer: an overview of the randomised trials. in *Lancet* 352:9132, p 930-42

Early Breast Cancer Trialists' Collaborative Group. (1998) Tamoxifen for early breast cancer: an overview of the randomised trials. in *Lancet* 351:9114, p 1451-67

Ernster, V.L., et al. (2002) Detection of ductal carcinoma in situ in women undergoing screening mammography. in *J Natl Cancer Inst, 2002. 94(20): p. 1546-54.* 94:20, p 1546-54

Feinstein, A.R., D.M. Sosin, and C.K. (1985) Wells, The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. in *N Engl J Med* 312:25, p 1604-8

Gail MH,et al. (1989) Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. in *J Natl Cancer Inst* 81:24, p 1879-86.

Holford, T.R., et al. Changing Patterns in Breast Cancer Incidence Trends. in *J Clin Epi. submitted.*,

Kerlikowske, K., et al. (2003) Characteristics associated with recurrence among women with ductal carcinoma in situ treated by lumpectomy. in *J Natl Cancer Inst* 95:22, p 1692-702

Li, C.I., et al. (2003) Trends in incidence rates of invasive lobular and ductal breast carcinoma. in *Jama* 289:11, p 1421-4

Mariotto, A., et al. (2002) Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999. in *J Natl Cancer Inst* 94:21, p 1626-34

Merrill, R.M. and E.J. Feuer (1996) Risk-adjusted cancer-incidence rates (United States). in *Cancer Causes Control* 7:5, p 544-52.

Plevritis, S.K., et al. A Natural History Model of Stage Progression Applied to Breast Cancer. in *(Submitted).*,

Rosenberg, M. Annual probabilities of death from causes other than breast cancer. in *Cancer Intervention and Surveillance Modeling Network; Base Case. Unpublished data.*,

Surveillance, E., and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER 9 Regs Public–Use, Aug 2000 Sub (1973–1998) in *National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch.*,

The Berkeley Mortality Database. Department of Demography at the University of California, Berkely. ,