



UNIVERSITY OF TEXAS MDACC

FLEXKB DOCUMENT
Version: HI.001.07232013.57428
Document generated: 07/23/2013

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.



- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References

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 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 provides a description of the problems our model was designed to address.

PURPOSE

The decade from 1990 to 2000 has seen an over-all decrease in breast cancer mortality within the United States¹. This encouraging trend has also been observed in a number of other countries including Canada and the United Kingdom². While there are a variety of possible explanations for this decline in mortality, two of the most likely reasons are earlier detection and improved treatment.

The principal goal of our model is to provide estimates (and their associated uncertainties) of the relative contributions of screening mammography, tamoxifen use, and improvements in chemotherapy to the observed decrease in U.S. breast cancer mortality since 1990. We will also address the potential impact on future U.S. breast cancer mortality of changes in screening mammography schedules, increased use of tamoxifen, and improvements in chemotherapy.

REFERENCES:

-
- ¹ Cancer Surveillance Research Program, National Cancer Institute. "The Surveillance, Epidemiology, and End Results (SEER) Program" 1998;
- ² IARC "The CANCER-Mondial website" in International Agency for Research on Cancer 1999;
-



MODEL OVERVIEW

SUMMARY

This document describes the methods we use to simulate the US population of women from 1975 through 2000 and estimate the breast cancer mortality for these years.

PURPOSE

Our principal goal is to provide estimates (and their associated uncertainties) of the relative contributions of screening mammography, tamoxifen use, and improvements in and greater use of chemotherapy to the observed decrease in U.S. breast cancer mortality since 1990. We also address the potential impact on future U.S. breast cancer mortality of changes in screening mammography prevalence, increased use of tamoxifen, and further improvements in chemotherapy.

BACKGROUND

The decade from 1990 to 2000 has seen an overall decrease in breast cancer mortality within the United States¹. This encouraging trend has also been observed in a number of other Western countries including Canada and the United Kingdom². While there are a variety of possible explanations for such a decline, two of the most likely are earlier detection and improved treatment.

MODEL DESCRIPTION

Using innovative modeling and simulation techniques and available information we assess the impact that breast cancer interventions have had in the U.S. We use Bayesian updating⁴ to estimate the contributions of mammography, chemotherapy, and tamoxifen use to the observed decline in breast cancer mortality in the United States since 1990. Computations of posterior distributions are effected using the "rejection method"⁶: an observation from the prior distribution is included in the posterior distribution depending on the value of its likelihood. In our application the likelihood function is very complicated and cannot be exhibited in closed form.

We begin with a cohort of women in 1975. We then follow this cohort until 2000, simulating the various breast cancer events on an annual basis. Our cohort is dynamic in that we allow women to enter (births, immigration) and leave (deaths, emigration) the population each year.



Breast cancer events depend on each woman's age, mammography use, and treatment (for those detected with breast cancer), all of which change over time. Each year each woman is assigned to be screened or not, depending on the patterns of screening by age in that year. Whether a woman is screened in any given year also depends on her screening history. Breast cancer is diagnosed (or not) depending on the woman's age, mode of detection, the time since her last mammogram, and the calendar year. If she is diagnosed with breast cancer, then her cancer is assigned a stage, nodal status, and estrogen-receptor status with frequencies appropriate for her age, mode of detection, and time since her last mammogram. Therapy is assigned according to the standards of the day, depending on the woman's and the cancer's characteristics. The effects of therapy are based on the observations sampled from the prior distributions for these effects.

We determine which women die depending on actuarial survival data, and we observe breast cancer mortality for the cohort of women to estimate breast cancer mortality from 1975 to 2000. This estimate is compared to the observed breast cancer mortality in the U.S. for each year from 1975 through 2000.

Further details of the model are described in [Component Overview](#) .

CONTRIBUTORS

Donald A. Berry, Ph.D.

Principal Investigator

University of Texas M.D. Anderson Cancer Center
Department of Biostatistics & Applied Mathematics
1515 Holcombe Boulevard, Box 447

Houston, TX 77030

Telephone: (713) 794-4141

Fax: (713) 745-4940

E-mail: dberry@odin.mdacc.tmc.edu

Melissa Bondy, Ph.D.

Co-Principal Investigator

University of Texas M. D. Anderson Cancer Center
Telephone: (713) 794-5264

E-mail: mbondy@mdanderson.org

Lurdes Inoue, Ph.D.

Assistant Professor

University of Washington
Seattle, Washington

Telephone: (206) 616-6398

E-mail: linoue@u.washington.edu

Mark Munsell, M.S.

Research Statistician

University of Texas M. D. Anderson Cancer Center
Telephone: (713) 794-4179

E-mail: mfmunsell@mdanderson.org



Yu Shen, Ph.D.
Associate Professor
University of Texas M. D. Anderson Cancer Center
Telephone: (713) 794-4159
E-mail: yushen@odin.mdacc.tmc.edu

Richard L. Theriault, D.O., M.B.A.
Co-Principal Investigator
University of Texas M. D. Anderson Cancer Center
Telephone: (713) 745-3315
E-mail: rtheriau@mdanderson.org

John Venier, M.S.
Systems Analyst III
University of Texas M. D. Anderson Cancer Center
Telephone: (713) 794-5985
E-mail: venier@mdanderson.org

Acknowledgements

We gratefully acknowledge the National Cancer Institute's Breast Cancer Surveillance Consortium for working with us to provide invaluable data for this project. We acknowledge the Centers for Disease Control and Prevention (CDC) and the state, territorial, and tribal organizations that are part of the National Breast and Cervical Cancer Early Detection Program (NBCCEDP) for their commitment to providing high-quality breast and cervical cancer screening, follow-up and treatment to women in medically underserved populations throughout the United States. The NBCCEDP was created by Congress with the passage of the Breast and Cervical Cancer Mortality Prevention Act in 1990 (Public Law 101-354), authorizing funds for a national screening program for breast and cervical cancer for medically underserved women. The NBCCEDP is implemented through cooperative agreements with qualifying health agencies that provide free or low-cost screening to uninsured or underinsured low-income women, develop and disseminate public and professional education strategies, establish quality assurance systems, engage in surveillance and evaluation activities, and develop coalitions and partnerships

REFERENCES:

- ¹ Cancer Surveillance Research Program, National Cancer Institute. "The Surveillance, Epidemiology, and End Results (SEER) Program" 1998;
- ² IARC "The CANCER-Mondial website" in International Agency for Research on Cancer 1999;
- ³ Berry, DA. "Statistics: A Bayesian Perspective" 1996;
- ⁴ Berry, DA & Stangl, DK. "Bayesian Biostatistics" 1996;
- ⁵ Spiegelhalter, DJ, Abrams KR, Myles JP. "Bayesian Approaches to Clinical Trials and Health-Care Evaluation." 2004;
- ⁶ Tanner, MA. "Tools for Statistical Inference: Methods for the Exploration of Posterior Distributions and Likelihood Functions" 1996;



ASSUMPTION OVERVIEW

SUMMARY

This document describes the key assumptions behind our model.

BACKGROUND

Population Dynamics

Our model allows for women to be born into our population or migrate into and out of our population.

Intervention Effects

Because we do not know the impact of adjuvant tamoxifen or adjuvant chemotherapy on the reduction in risk of breast cancer mortality, we impose separate and independent prior distributions on the reduction in the risk of breast cancer mortality due to these two interventions. We allow for the possibility of an additional survival benefit (beyond stage shift) due to mammography screening. More information on the assumptions regarding these intervention effects can be found in the [Parameter Overview](#).

Tumor Characteristics

If breast cancer is detected in a woman, we base the tumor's characteristics on data from the Breast Cancer Surveillance Consortium¹, the National Breast and Cervical Cancer Early Detection Program², the Canadian National Breast Screening Studies⁴, and the Health Insurance Plan Project⁵, depending on the mode of detection. However, there are a few assumptions that we make regarding tumor characteristics.

ASSUMPTION LISTING

In our model we assume:

Population Dynamics

1. Women in the population are born on January 1 of their birth year.
2. Women age in discrete increments of 1 year.
3. Immigrants have had no screening mammograms before entering the population.
4. Emigrants are lost to follow-up as of the year they leave the population.

Intervention Effects

1. Observed decrease in mortality is caused by screening and treatment.





2. A priori, screening and treatment have independent effects.
3. All adjuvant chemotherapy regimens have the same effect.
4. A prior distribution of the reduction in risk of breast cancer mortality due to adjuvant tamoxifen.
5. A prior distribution of the reduction in risk of breast cancer mortality due to adjuvant chemotherapy.
6. A prior distribution on the reduction in risk of breast cancer mortality beyond stage shift.
7. Women with stage IV disease receive no survival benefit from chemotherapy or hormonal therapy.
8. Women aged 50 or younger receive an additional 10% reduction in the hazard of breast cancer mortality due to chemotherapy. (Based on the Overview results⁶.)
9. Women with stage IV disease do receive no survival benefit from treatment with chemotherapy or hormonal therapy.
10. Women who are treated with taxanes receive an additional 14% survival benefit⁷.

Tumor Characteristics

1. Given tumor characteristics, there is no race effect.
2. ER status is dependent on mode of detection.
3. Tumors detected more than 3 years after a screening mammogram have the same characteristics as clinically detected tumors.

REFERENCES:

-
- ¹ National Cancer Institute. "Breast Cancer Surveillance Consortium (BCSC)" 2003;
 - ² Centers for Disease Control and Prevention. "National Breast and Cervical Cancer Early Detection Program (NBCCEDP)" 2002;
 - ³ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years." in Canadian Medical Association Journal 1992; 147: 1459-1476
 - ⁴ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years." in Canadian Medical Association Journal 1992; 147: 1477-1488
 - ⁵ Shapiro, S, Venet, W, Strax, P, et al. "Periodic Screening for Breast Cancer: The Health Insurance Plan Project and its Sequelae, 1963-1986" 1988;
 - ⁶ Early Breast Cancer Trialists' Collaborative Group. "Polychemotherapy for early breast cancer: an overview of the randomized trials." in The Lancet 1998; 352: 930-942
 - ⁷ Theriault R, Carlson R, Stockdale F. "(Personal communication)" 2003;
-



PARAMETER OVERVIEW

SUMMARY

This document describes the 6 parameters included in our model.

BACKGROUND

Because we do not know the impact of adjuvant tamoxifen or adjuvant chemotherapy on the reduction in risk of breast cancer mortality, we impose separate and independent prior distributions on the reduction in the risk of breast cancer mortality due to these two interventions. Because of the lead time and the stage shift associated with screening mammography, women whose cancers are detected mammographically tend to have longer survival than those with cancers detected otherwise. We allow for the possibility of an additional survival benefit (beyond stage shift) due to mammography screening. We include separate prior distributions for the reduction in the risk of breast cancer mortality beyond stage shift for AJCC stages I–II and for AJCC stages III–IV.

We also allow for uncertainty in the underlying survival distributions by AJCC stage and age group by placing a prior distribution on the baseline hazard. An age–period–cohort (APC) model is used to estimate breast cancer incidence over time. We also impose a prior distribution on a parameter used to allow for uncertainty in the APC model.

PARAMETER LISTING OVERVIEW

1. Effect of Adjuvant Tamoxifen

The prior distribution of the reduction in risk of breast cancer mortality due to adjuvant tamoxifen follows a beta distribution with mean 0.28 and standard deviation 0.15 (i.e., $\text{beta}(2.23, 5.73)$). The mean for this prior distribution is from the 1998 report by the Early Breast Cancer Trialists' Collaborative Group¹. Because this report is based on the results of randomized clinical trials, we incorporated additional uncertainty into our prior distribution and used a standard deviation that was three times the standard error in this report.

2. Effect of Adjuvant Chemotherapy

The prior distribution of the reduction in risk of breast cancer mortality due to adjuvant chemotherapy follows a beta distribution with mean 0.14 and standard deviation 0.16 (i.e., $\text{beta}(0.52, 3.18)$). The mean for this prior distribution is from the 1998 report by the Early Breast Cancer Trialists' Collaborative Group². Again, we inflated the standard error of the effect of chemotherapy in determining the standard deviation of our prior distribution.

3–4. Effect of Screening Mammography Beyond Stage Shift

In addition to any stage shift, we allow for an effect on survival beyond stage shift. We estimate the effects beyond stage shift from the Health Insurance Plan Project (HIP)³ and the Canadian National Breast Screening Study (CNBSS)⁵, and we use these data to derive the means and standard deviations of our prior distributions for our two



beyond-stage-shift parameters.

3. AJCC Stages I-II

We assume the prior distribution for the parameter estimating the effect beyond-stage-shift for AJCC stages I-II to be uniform(0, 0.80), having mean 0.40 and standard deviation 0.23.

4. AJCC Stages III-IV

We assume the prior distribution for the parameter estimating the effect beyond-stage-shift for AJCC stages III-IV to be uniform(0, 0.50), having mean 0.25 and standard deviation 0.14.

5. Underlying Breast Cancer Survival

We have an underlying survival distribution for non-screen-detected breast cancer for each AJCC stage I-IV and age group⁶ that is not treated with either chemotherapy or tamoxifen. Because of the uncertainty in these underlying survival distributions, we allow for the data to modify them. We do this by imposing a uniform(0.8,1) prior distribution on the baseline hazard function of these survival distributions.

6. Age-Period Cohort Model

Women who have never had a screening mammogram have breast cancer detected with a probability that depends on her age and year of birth. The probabilities incorporate the secular trend in incidence from the age-period-cohort (APC) model developed by Holford⁷. However, this model is an estimate, and like all estimates is subject to uncertainty. To reflect this uncertainty we impose a uniform(0,1) prior distribution on the impact of the APC model. The alternative we consider to the APC model is constant background incidence over time. This method allows for the possibility that the APC is not correct, and lets the actual observed mortality determine the weight attributed to the APC model.

REFERENCES:

- ¹ Early Breast Cancer Trialists' Collaborative Group. "Tamoxifen for early breast cancer: An Overview of the randomised trials" in *The Lancet* 1998; 351: 1451-1467
- ² Early Breast Cancer Trialists' Collaborative Group. "Polychemotherapy for early breast cancer: an overview of the randomized trials." in *The Lancet* 1998; 352: 930-942
- ³ Shapiro, S, Venet, W, Strax, P, et al. "Periodic Screening for Breast Cancer: The Health Insurance Plan Project and its Sequelae, 1963-1986" 1988;
- ⁴ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years." in *Canadian Medical Association Journal* 1992; 147: 1459-1476
- ⁵ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years." in *Canadian Medical Association Journal* 1992; 147: 1477-1488
- ⁶ CISNET. "Modeling impact of mammography and adjuvant treatment on U.S. breast cancer mortality rates: collective results from the Cancer Intervention and Surveillance Modeling Network." in *Journal of the National Cancer Institute Monograph* 2004;
- ⁷ Holford, T. "Cancer Intervention and Surveillance Modeling Network; Base Case" 2003;



COMPONENT OVERVIEW

SUMMARY

This document provides an overview of the major components in the model.

OVERVIEW

Population Component

We recognize that in 1975, the initial year of our simulation, that there are women living with breast cancer. We must first identify these prevalent cases.

We then simulate a cohort of 2,000,000 women with an age distribution appropriate for 1975, allowing for prevalent cases. We then follow this cohort to 2000, allowing for births, deaths, and migration. Each year we identify which women are diagnosed with breast cancer. See the [Cancer Incidence Component](#) for details on how we diagnose breast cancer.

Screening Component

We assign each woman a screening schedule that she follows throughout her life. We assume that immigrants have had no screening mammograms before entering our cohort. As we follow the cohort from 1975 to 2000, each year we determine whether the woman had a screening mammogram based on her screening schedule.

Cancer Incidence Component

Each year we determine whether a woman is diagnosed with breast cancer. The probability of breast cancer detection depends on whether or not the woman has had a screening mammogram. If the woman has had a screening mammogram the probability of breast cancer detection depends on how long it has been since her last screening mammogram. We also allow for interval cases, which occur between screening mammograms. Tumor characteristics depend on how the breast cancer was detected, and our model recognizes this dependency.

Treatment Component



Treatment depends on a woman's and the tumor's characteristics. Treatment also depends on the calendar year, as there have been changes in treatment over time. Refer to the [Survival And Mortality Component](#) to see how treatment impact survival.

[Survival And Mortality Component](#)

Each woman who is diagnosed with breast cancer is assigned a lifetime with cause of death from breast cancer. Each woman also has a "natural" lifetime assigned to her when she enters the cohort. A woman's survival is defined as the shorter of these two lifetimes.

[Results Component](#)

Our model parameters are selected from prior distributions, which are based on available information from the literature and other sources (see [Parameter Overview](#)). We use Bayesian updating to populate the posterior distributions of these parameters. We are also able to obtain the joint posterior distributions of parameters, and from these parameters we estimate the impact of treatment and screening mammography on breast cancer mortality.

COMPONENT LISTING

- [Population Component](#)
- [Screening Component](#)
- [Cancer Incidence Component](#)
- [Treatment Component](#)
- [Survival And Mortality Component](#)
- [Results Component](#)

For a more detailed listing of the steps in the simulation see [Component Listing](#) .



OUTPUT OVERVIEW

SUMMARY

This document describes the outputs generated by the model. Our model generates intermediate outputs that can be used to assess the operation of the model, as well as the primary outputs that are used to meet our principle goal (see [Model Purpose](#)).

OVERVIEW

Intermediate Outputs:

1. age distribution of women in the U.S. for each year 1975–2000
2. prevalence of breast cancer in 1975
3. tumor characteristics of breast cancer detected in each year 1975–2000
4. survival distribution for women diagnosed with breast cancer
5. survival distribution for women not diagnosed with breast cancer
6. screening mammography schedules
7. proportion of women who have ever had a screening mammogram
8. incidence of breast cancer by stage and by mode of detection, by age and year, and age-adjusted by year
9. breast cancer mortality by year of detection, prevalent in 1975, or incident in 1975 or later

Primary Outputs:

1. age-adjusted breast cancer mortality for each year 1975–2000
2. age-adjusted total mortality for each year 1975–2000
3. posterior distributions for parameters drawn from prior distributions such as the benefits of adjuvant tamoxifen and adjuvant chemotherapy

OUTPUT LISTING

All of the outputs are used in some form of testing and validation at one time or another, but the "intermediate outputs" listed above are primarily used for testing and validation.

Breast Cancer Mortality:

Our model yields estimates of breast cancer mortality for each year 1975–2000. Our modeling approach validates these estimates by comparing them to the known breast cancer mortality for each year 1975–2000.

Breast cancer mortality is also be used as the basis for the acceptance/rejection method² for determining the posterior distributions of the parameters which were drawn from the prior distributions. See the [Parameter Overview](#) for more details of these prior distributions.



REFERENCES:

-
- ¹ Spiegelhalter, DJ, Abrams KR, Myles JP. "Bayesian Approaches to Clinical Trials and Health-Care Evaluation." 2004;
 - ² Tanner, MA. "Tools for Statistical Inference: Methods for the Exploration of Posterior Distributions and Likelihood Functions" 1996;
-



RESULTS OVERVIEW

SUMMARY

This document describes the results obtained from our model to address our principle goal (see [Model Purpose](#)).

OVERVIEW

We simulated approximately 80,000 populations in 1975 and followed them through the year 2000. For each of these 80,000 populations we simulated one set of parameters from our posterior distributions, as described above. Of these simulations we accepted 176 for our posterior distributions by the criteria illustrated in *Figure 1* (see [Figures](#)) and described above, using an acceptance window on each year of ± 2.5 and a window on the slope of ± 0.17 . The average of the breast cancer mortality estimates from these 176 accepted simulations is shown in *Figure 2* (see [Figures](#)).

RESULTS LIST

Posterior Distributions of Model Parameters

The prior and posterior distributions for the 4 intervention parameters are shown in *Figure 3* (see [Figures](#)). The means and standard deviations of the posterior distributions of these 4 intervention parameters are summarized in *Table 2*. Also included in *Table 2* are the means and standard deviations of the other 2 parameters that we sample from prior distributions and discussed above. Recall that we place a prior distribution on the underlying survival distribution in the absence of treatment and on the impact of the age–period–cohort (APC) model for determining incidence of disease (see [Parameter Overview](#)).

From *Table 2* we see that the posterior mean effect of tamoxifen is 0.37, suggesting a 37% decrease in the hazard of breast cancer mortality due to treatment with tamoxifen. The posterior mean effect of screening mammography beyond stage shift for stages I–II is 0.28. This implies that screening mammography provides an additional reduction in hazard of 28% for those women who are diagnosed with stage I–II disease through screening. This reduction is in addition to any benefit that would be achieved due to the cancer being detected at an earlier stage than it might have been if detected clinically.

TABLE 2. Posterior Estimates of Model Parameters

	Mean	Std Dev
Tamoxifen	0.37	0.14
Chemotherapy	0.15	0.14
Beyond Stage Shift I–II	0.28	0.19
Beyond Stage Shift III–IV	0.23	0.14
Underlying Survival Dist	0.87	0.04
APC Incidence	0.61	0.29

The posterior means of the effect of chemotherapy and the benefit of screening

THE UNIVERSITY OF TEXAS
MDANDERSON
CANCER CENTER
Making Cancer History™

- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References



mammography beyond stage shift for stage III–IV disease are similar to the prior means. That is, we estimate that chemotherapy provides a 15% reduction in the hazard of breast cancer mortality, and the reduction in the hazard due to mammography beyond stage shift for stage III–IV disease is 23%.

Our model also estimates the adjustment to the hazard of the underlying survival distribution for women with breast cancer in the absence of treatment has a mean of 0.87 with a standard deviation of 0.04. That is, each underlying survival distribution $S_{ij}(t)$, for non–screen detected breast cancer of stage i , for $i = 1, 2, 3, 4$, and age group j in the absence of treatment is adjusted as $S_{ij}^*(t) = S_{ij}(t)^\lambda$, where λ has a distribution with mean 0.87 and standard deviation 0.04. The estimates of the effect of screening and treatment are in addition to this initial adjustment.

We discount the impact of the age–period–cohort (APC) model on estimating incidence of breast cancer by an average of 0.61 (sd=0.29). Recall that we placed a uniform(0, 1) distribution on the impact of the APC model. So, on average our model includes only 61% of the incidence estimated by the APC model.

Posterior Estimates of Intervention Effects

From each of our 176 accepted simulations we estimate the percent reduction in breast cancer mortality since 1990, and we estimate the contribution of treatment and screening to this reduction. By ignoring the effect of treatment in our model we estimate the impact of screening mammography on breast cancer mortality. Similarly, by ignoring the effect of screening we estimate the impact of treatment (both chemotherapy and tamoxifen) on breast cancer mortality.

The joint distribution of the contribution of screening and treatment is illustrated in Figures 4a and 4b (see [Figures](#)). It is clear from these figures that there is a negative correlation between the percent reduction in breast cancer mortality due to screening and due to treatment. Our model estimates this correlation to be -0.40 .

Using our model we estimate a 0.90 posterior probability of a benefit of screening mammography. We estimate a 0.90 posterior probability of a benefit of treatment of at least 9.5%.



POPULATION COMPONENT

SUMMARY

This document describes how our model builds the initial cohort of women and follows this cohort over time.

OVERVIEW

We must first determine which women are living with breast cancer in 1975 (prevalent cases). Once we've identified these women, we simulate a cohort of women in 1975 with an age distribution appropriate for that year, including the prevalent cases. We then age our cohort in discrete yearly intervals, allowing for births, deaths, and migration.

DETAIL

Determining Prevalent Cases

To determine which women are the prevalent cases in 1975 we begin by simulating an initial cohort of 2,000,000 women in 1940. We follow this cohort to 1975, diagnosing women with breast cancer each year based on the incidence by age and stage for each year from 1940 to 1974. We assign each woman in this initial cohort a lifetime where cause of death is anything other than breast cancer¹. Call this her "natural lifetime". We also simulate a lifetime with breast cancer as the cause of death², and we determine the cause of death from the shorter of these 2 lifetimes.

We do not allow women to enter this cohort, and women may exit this initial cohort only by dying (of any cause). The women in this cohort who have breast cancer in 1975 are the prevalent cases. We construct a new population of women in 1975 having the corresponding distribution of prevalent cases. We repeat this procedure for each simulation of the model.

Simulating Population of Women

Once we have identified the prevalent cases we simulate a population of 2,000,000 women with the age distribution appropriate for 1975 based on data from the 2001 Regional Database, Woods & Poole Economics, Inc.³, including the prevalent cases. For each woman we simulate a natural lifetime¹, where cause of death is anything other than breast cancer. As we follow the population in discrete yearly intervals, each woman gets one year older and we determine whether she is diagnosed with breast cancer depending on the incidence of the disease for women her age in that year, and also depending on whether she had a screening mammogram in that year.



Each year we allow for births, deaths, and migration. Those women born into the population from 1975 on are not likely to develop breast cancer, but they do contribute to the size and age distribution of the population. We use the data from Woods & Poole Economics, Inc.³ to define migration patterns by comparing the U.S. female age distributions in consecutive years. We assign a natural lifetime to each woman who immigrates into our population. We also assign her breast cancer events following the same procedure as for women who were initially in the population in 1975, as described in the [Cancer Incidence Component](#) .

Determining Cause of Death

For each woman who is diagnosed with breast cancer, her survival depends on her tumor's characteristics, the mode of detection of the tumor, and the treatment she received, as described in the [Survival And Mortality Component](#) . We compare this survival time to her natural lifetime simulated when she entered the population. If the survival time from breast cancer is shorter than her natural lifetime, then the woman is considered to have died from breast cancer and contributes to the breast cancer mortality. If the survival time from breast cancer is longer than her natural lifetime, then the woman is considered to have died from causes other than breast cancer. If a woman dies of other causes or emigrates she is censored as of that time.

RELEVANT COMPONENTS

[Cancer Incidence Component](#)

[Survival And Mortality Component](#)

REFERENCES:

-
- ¹ Rosenberg, M. "Annual probabilities of death from causes other than breast cancer; Base Case" 2002;
 - ² CISNET. "Modeling impact of mammography and adjuvant treatment on U.S. breast cancer mortality rates: collective results from the Cancer Intervention and Surveillance Modeling Network." in Journal of the National Cancer Institute Monograph 2004;
 - ³ Woods & Poole Economics Inc. "2001 Regional Database: Estimated July 1 population by race, sex and single year and 5-year age groups based on 1990 Census and post-censal Census Bureau estimates." 2001;
-



CANCER INCIDENCE COMPONENT

SUMMARY

This document describes how our model determines whether a woman is detected with breast cancer in a given year.

OVERVIEW

This component serves to determine if a woman has a breast cancer detected in the current year being simulated. The probability of detection (clinical or by screening) depends on an age–period–cohort model as well as the woman's screening status.

DETAIL

Breast Cancer Detected Clinically

In each year starting in 1975, we consider every woman who is at least 20 years old and determine whether or not she has a breast cancer detected. If she has not yet had a screening mammogram, she is detected with breast cancer with a probability that depends on her age and year of birth. These probabilities incorporate the secular trend in incidence estimated from the age–period–cohort model¹. However, we impose a uniform(0, 1) prior distribution on the impact of the age–period–cohort model, and sample one value from this prior distribution for each population we simulate (see [Parameter Overview](#)).

Characteristics of tumors that are clinically detected are determined from the 1975 data in SEER² as adjusted and described in the Chapter 4 of CISNET³. These data provide a mechanism for assigning AJCC disease stage. We determine whether or not there were positive nodes based on data from HIP⁴, and we determine ER status based on data from SEER².

Breast Cancer Detected by Screening Mammogram



For a woman who has a screening mammogram in the current year, the probability of breast cancer detection, depending on her age, is based on data from the National Breast and Cervical Cancer Early Detection Program (NBCCEDP)⁵. This probability also depends on whether it was her first mammogram, and if it was not, then it depends on the amount of time since her last screening mammogram. If it has been more than 3 years since her last screening mammogram, the probability of detecting breast cancer is the same as for a first screening mammogram.

Breast Cancer Detected in an Interval Between Screening Mammograms

We also simulate breast cancer incidence during intervals between screening mammograms (interval cases) by time since last screening mammogram, age and the current year. The tumor stage for these interval cases is assigned using data from a variety of sources. We used a hierarchical model based on data from the BCSC, the NBCCEDP, the Breast Cancer Detection Demonstration Project (BCDDP)⁶, HIP⁴, CNBSS⁸, and data from 2 Scandinavian studies¹⁰ to estimate the probability of an interval cancer being a given stage. Nodal status and estrogen receptor status was assigned based on data from the BCSC¹¹. For those tumors detected more than 3 years after a screening mammogram, we assign tumor characteristics as if they were clinically detected tumors.

RELEVANT ASSUMPTIONS

1. Immigrants have had no screening mammograms before entering the population.
2. Tumors detected more than 3 years after a screening mammogram have the same characteristics as clinically detected tumors.

See [Assumption Overview](#) .

RELEVANT PARAMETERS

Age-Period-Cohort (APC) Model Parameter

Because the APC model is an estimate it is subject to uncertainty. To reflect this uncertainty we impose a uniform(0,1) prior distribution on the impact of the APC model. The alternative we consider to the APC model is constant background incidence over time. This method allows for the possibility that the APC is not correct, and lets the actual observed mortality determine the weight attributed to the APC model. See [Parameter Overview](#) .

RELEVANT COMPONENTS

[Screening Component](#)

[Survival And Mortality Component](#)

REFERENCES:

¹ Holford, T. "Cancer Intervention and Surveillance Modeling Network; Base Case" 2003;

² Cancer Surveillance Research Program, National Cancer Institute. "The Surveillance, Epidemiology, and End Results (SEER) Program" 1998;



- ³ CISNET. "Modeling impact of mammography and adjuvant treatment on U.S. breast cancer mortality rates: collective results from the Cancer Intervention and Surveillance Modeling Network." in *Journal of the National Cancer Institute Monograph* 2004;
- ⁴ Shapiro, S, Venet, W, Strax, P, et al. "Periodic Screening for Breast Cancer: The Health Insurance Plan Project and its Sequelae, 1963-1986" 1988;
- ⁵ Centers for Disease Control and Prevention. "National Breast and Cervical Cancer Early Detection Program (NBCCEDP)" 2002;
- ⁶ Smart, CR, Byrne, C, Smith, RA, et al. "Twenty-year follow-up of the breast cancers diagnosed during the breast cancer detection demonstration project" in *A Cancer Journal for Clinicians* 1997; 47: 134-149
- ⁷ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years." in *Canadian Medical Association Journal* 1992; 147: 1459-1476
- ⁸ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years." in *Canadian Medical Association Journal* 1992; 147: 1477-1488
- ⁹ Hakkama, M, Holli, K, Isola, J, et al. "Aggressiveness of screen-detected breast cancers" in *The Lancet* 1995; 345: 221-224
- ¹⁰ Frisell, J Eklund, G, Hellstrom, L, Somell, A "Analysis of interval breast carcinomas in a randomized screening trial in Stockholm" in *Breast Cancer Research and Treatment* 1987; 9: 3: 219-225
- ¹¹ National Cancer Institute. "Breast Cancer Surveillance Consortium (BCSC)" 2003;



SCREENING COMPONENT

SUMMARY

This document describes how screening is modeled.

OVERVIEW

Tumor characteristics, and thus survival, depend on the mode of detection of breast cancer. We determine each year whether a woman has a screening mammogram, and if she does, we determine whether breast cancer was detected.

DETAIL

Screening Dissemination

We use the screening mammogram dissemination model¹ to determine whether a woman will have screening mammograms. If so then we use the screening mammography dissemination model to determine her screening schedule.

Our model allows for immigration into our population. For a woman who is an immigrant, it is possible that the screening dissemination model would assign screening mammograms for her before she entered our population. Any such mammograms are ignored.

RELEVANT ASSUMPTIONS

Immigrants had no screening mammograms before entering our population.

RELEVANT COMPONENTS

[Cancer Incidence Component](#)

REFERENCES:

¹ Cronin, K, Krapcho, M. "Cancer Intervention and Surveillance Modeling Network; Base Case; unpublished data." 2003;



TREATMENT COMPONENT

SUMMARY

This document describes how treatment is assigned in our model.

OVERVIEW

We assign chemotherapy and tamoxifen to women who are detected with breast cancer, depending on the characteristics of the tumor. These treatment assignments will have an impact on survival, as described in the [Survival And Mortality Component](#).

DETAIL

We use the treatment dissemination model developed by¹ to determine treatment for women who are diagnosed with breast cancer. The treatment depends on the tumor characteristics, as well as the woman's age and the year of detection.

In addition to polychemotherapy and tamoxifen, we consider the use of taxanes that were introduced into standard clinical practice in the late 1990s. Taxanes are not represented in the treatment dissemination model. Beginning in 1998 we allow any woman receiving chemotherapy to also receive a taxane. The proportion of women who receive a taxane depends on the stage of disease, and is based on expert opinion². We assign an additional 14% survival benefit for women receiving taxanes.

RELEVANT ASSUMPTIONS

Women who are treated with taxanes receive an additional 14% survival benefit.



RELEVANT PARAMETERS

1. Effect of Adjuvant Tamoxifen

The prior distribution of the reduction in risk of breast cancer mortality due to adjuvant tamoxifen follows a beta distribution with mean 0.28 and standard deviation 0.15 (i.e., beta(2.23, 5.73)). The mean for this prior distribution is from the 1998 report by the Early Breast Cancer Trialists' Collaborative Group³. Because this report is based on the results of randomized clinical trials, we incorporated additional uncertainty into our prior distribution and used a standard deviation that was three times the standard error in this report.

2. Effect of Adjuvant Chemotherapy

The prior distribution of the reduction in risk of breast cancer mortality due to adjuvant chemotherapy follows a beta distribution with mean 0.14 and standard deviation 0.16 (i.e., beta(0.52, 3.18)). The mean for this prior distribution is from the 1998 report by the Early Breast Cancer Trialists' Collaborative Group⁴. Again, we inflated the standard error of the effect of chemotherapy in determining the standard deviation of our prior distribution.

See [Parameter Overview](#) .

RELEVANT COMPONENTS

Survival And Mortality Component

REFERENCES:

-
- ¹ 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 Journal of Epidemiology and Community Health 2002; 57: 7: 525-6
 - ² Theriault R, Carlson R, Stockdale F. "(Personal communication)" 2003;
 - ³ Early Breast Cancer Trialists' Collaborative Group. "Tamoxifen for early breast cancer: An Overview of the randomised trials" in The Lancet 1998; 351: 1451-1467
 - ⁴ Early Breast Cancer Trialists' Collaborative Group. "Polychemotherapy for early breast cancer: an overview of the randomized trials." in The Lancet 1998; 352: 930-942
-



SURVIVAL AND MORTALITY COMPONENT

SUMMARY

This document describes how survival and mortality from cancer are determined in the model.

OVERVIEW

This critical component of the model determines survival from cancer after both clinical and screen detection. Survival depends on several factors including mode of detection, stage, age, treatments used, and ER status.

For each woman who is diagnosed with breast cancer, her survival depends on her tumor's characteristics, the mode of detection of the tumor, and the treatment she received. We compare this survival time to her natural lifetime simulated when she entered the population. If the survival time from breast cancer is shorter than her natural lifetime, then the woman is considered to have died from breast cancer and her death contributes to breast cancer mortality. If the survival time from breast cancer is longer than her natural lifetime, then the woman is considered to have died from causes other than breast cancer. If a woman dies of other causes or emigrates she is removed from the at-risk population as of that time.

DETAIL

Baseline Survival

We have an underlying survival distribution, $S_{ij}(t)$, for non-screen detected breast cancer of stage i , for $i = 1, 2, 3, 4$, and age group j (Chapter 4 of CISNET, 2004¹) that is not treated with either chemotherapy or tamoxifen. Because of the uncertainty in these underlying survival distributions, we allow for the data to modify them. We do this by imposing a uniform(0.80, 1) prior distribution on the hazard function of $S_{ij}(t)$. That is, for the simulation we sample a value, say λ , from a uniform(0.80, 1) distribution and adjust each of these underlying survival distributions as $S_{ij}^*(t) = S_{ij}(t)^\lambda$. This parameter λ is handled just like other unknown model parameters: it will be accepted as part of the posterior distribution if the resulting simulated breast cancer mortality is sufficiently close to the observed breast cancer mortality.

Impact of Interventions on Survival

We impose separate and independent prior distributions on the reduction in the risk of breast cancer mortality due to (1) adjuvant tamoxifen use, (2) adjuvant chemotherapy, and survival benefit beyond stage shift due to screening mammography. We have separate prior distributions for the reduction in the risk of breast cancer mortality beyond stage shift for (3) AJCC stages I–II and for (4) AJCC stages III–IV. The prior distributions are summarized in *Table 1*.



TABLE 1. Prior Distributions for Intervention Effects

		Mean	Std Dev
Tamoxifen	Beta(2.23, 5.73)	0.28	0.15
Chemotherapy	Beta(0.52, 3.18)	0.14	0.16
Beyond Stage Shift I-II	Uniform(0, 0.80)	0.40	0.23
Beyond Stage Shift III-IV	Uniform(0, 0.50)	0.25	0.14

Refer to the [Parameter Overview](#) for details on how these prior distributions were determined.

We sample once from each prior distribution to determine the reduction in risk of dying of breast cancer for each woman who is detected with the disease, depending on the tumor characteristics, whether the tumor was detected by a screening mammogram, and the treatment received. This parameter set is used in the simulation of the population from 1975 through 2000. Each time the population is simulated, we sample again from each prior distribution to obtain a parameter set to use for that population.

RELEVANT ASSUMPTIONS

1. Observed decrease in mortality is caused by screening and treatment.
2. A priori, screening and treatment have independent effects.
3. All adjuvant chemotherapy regimens have the same effect.
4. A prior distribution of the reduction in risk of breast cancer mortality due to adjuvant tamoxifen.
5. A prior distribution of the reduction in risk of breast cancer mortality due to adjuvant chemotherapy.
6. A prior distribution on the reduction in risk of breast cancer mortality beyond stage shift.
7. Women with stage IV disease receive no survival benefit from chemotherapy or hormonal therapy.
8. Women aged 50 or younger receive an additional 10% reduction in the hazard of breast cancer mortality due to chemotherapy. (Based on the Overview results².)
9. Women with stage IV disease do receive no survival benefit from treatment with chemotherapy or hormonal therapy.

RELEVANT PARAMETERS

1. Effect of Adjuvant Tamoxifen

The prior distribution of the reduction in risk of breast cancer mortality due to adjuvant tamoxifen follows a beta distribution with mean 0.28 and standard deviation 0.15 (i.e., beta(2.23, 5.73)). The mean for this prior distribution is from the 1998 report by the Early Breast Cancer Trialists' Collaborative Group³. Because this report is based on the results of randomized clinical trials, we incorporated additional uncertainty into our prior distribution and used a standard deviation that was three times the standard error in this report.



2. Effect of Adjuvant Chemotherapy

The prior distribution of the reduction in risk of breast cancer mortality due to adjuvant chemotherapy follows a beta distribution with mean 0.14 and standard deviation 0.16 (i.e., $\text{beta}(0.52, 3.18)$). The mean for this prior distribution is from the 1998 report by the Early Breast Cancer Trialists' Collaborative Group². Again, we inflated the standard error of the effect of chemotherapy in determining the standard deviation of our prior distribution.

3–4. Effect of Screening Mammography Beyond Stage Shift

In addition to any stage shift, we allow for an effect on survival beyond stage shift. We estimate the effects beyond stage shift from the Health Insurance Plan Project (HIP)⁴ and the Canadian National Breast Screening Study (CNBSS)⁶, and we use these data to derive the means and standard deviations of our prior distributions for our two beyond–stage–shift parameters.

3. AJCC Stages I–II

We assume the prior distribution for the parameter estimating the effect beyond–stage–shift for AJCC stages I–II to be $\text{uniform}(0, 0.80)$, having mean 0.40 and standard deviation 0.23.

4. AJCC Stages III–IV

We assume the prior distribution for the parameter estimating the effect beyond–stage–shift for AJCC stages III–IV to be $\text{uniform}(0, 0.50)$, having mean 0.25 and standard deviation 0.14.

5. Underlying Breast Cancer Survival

We have an underlying survival distribution for non–screen–detected breast cancer for each AJCC stage I–IV and age group⁷ that is not treated with either chemotherapy or tamoxifen. Because of the uncertainty in these underlying survival distributions, we allow for the data to modify them. We do this by imposing a $\text{uniform}(0.8, 1)$ prior distribution on the baseline hazard function of these survival distributions.

RELEVANT COMPONENTS

Cancer Incidence Component

Screening Component

Treatment Component

Results Component

REFERENCES:

-
- ¹ CISNET. “Modeling impact of mammography and adjuvant treatment on U.S. breast cancer mortality rates: collective results from the Cancer Intervention and Surveillance Modeling Network.” in *Journal of the National Cancer Institute Monograph* 2004;
 - ² Early Breast Cancer Trialists' Collaborative Group. “Polychemotherapy for early breast cancer: an overview of the randomized trials.” in *The Lancet* 1998; 352: 930-942
 - ³ Early Breast Cancer Trialists' Collaborative Group. “Tamoxifen for early breast cancer: An Overview of the randomised trials” in *The Lancet* 1998; 351: 1451-1467
-



-
- ⁴ Shapiro, S, Venet, W, Strax, P, et al. "Periodic Screening for Breast Cancer: The Health Insurance Plan Project and its Sequelae, 1963-1986" 1988;
 - ⁵ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years." in Canadian Medical Association Journal 1992; 147: 1459-1476
 - ⁶ Miller, AB, Baines, CJ, To, T, et al. "Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years." in Canadian Medical Association Journal 1992; 147: 1477-1488
 - ⁷ CISNET. "Modeling impact of mammography and adjuvant treatment on U.S. breast cancer mortality rates: collective results from the Cancer Intervention and Surveillance Modeling Network." in Journal of the National Cancer Institute Monograph 2004;
-



RESULTS COMPONENT

SUMMARY

This document describes how we estimate the parameters for our model. We also describe here how we estimate the benefits of treatment and screening mammography.

OVERVIEW

We simulate a population of women and follow them from 1975 to 2000, assigning breast cancer events, screening, and treatment as appropriate for each year. We then compare the simulated breast cancer mortality to the observed breast cancer mortality for these years.

DETAIL

Updating the Posterior Distributions of Intervention Effects

To compare our simulated breast cancer mortality to the observed breast cancer mortality from 1975–2000 we implement the following strategy. We place an "acceptance window" on each year from 1975–2000. If the simulated mortality falls within this acceptance window for each year, then the parameters from the parameter set that we used in that simulation are candidates for acceptance into the respective posterior distributions.

We also divide the interval 1985–2000 into three five-year intervals (1985–1990, 1990–1995, 1995–2000). Then we calculate the slope of the observed mortality curve in each of these three intervals. For each of these slopes we define tolerance limits. For our simulated mortality curve we calculate the slope in these same three intervals. If the slope in each of the three intervals calculated from the simulated mortality curve falls within the tolerance limits of the slopes of the observed mortality curve, then the parameter values that were used to simulate the particular mortality curve are candidates for acceptance into the respective posterior distributions.

Only parameter sets that pass both tests described above are accepted into the respective posterior distributions. By simulating and following the population thousands of times, we will populate the posterior distributions with parameters accepted jointly in this fashion. *Figure 1* (see [Figures](#)) illustrates the acceptance algorithm, and *Figure 2* (see [Figures](#)) shows the average of our accepted simulations. The prior and posterior distributions of the 4 intervention parameters are illustrated in *Figure 3* (see [Figures](#)).

Estimating Impact of Interventions on Breast Cancer Mortality



Through simulation we can create populations of women where every woman aged 40 or older receives screening mammograms beginning in 1975. We can also simulate populations of women with the actual screening behavior that occurred from 1975 to 2000. Some women from each of these two groups will have developed breast cancer and some will have been treated with tamoxifen or adjuvant chemotherapy. By comparing the breast cancer mortality between these two populations of women we can obtain a posterior estimate of the effectiveness of screening mammography in reducing breast cancer mortality. Similarly, we can obtain posterior estimates of the effectiveness of tamoxifen and of chemotherapy.

We can also estimate the effectiveness of combinations of the various interventions as well as the effectiveness of each intervention in the presence of the others. By changing the proportion of women in each age cohort which use screening mammography in our model, we can estimate the potential impact on breast cancer mortality of future changes in the prevalence of screening mammography for each age cohort. Similarly, we can assess the potential impact of changes in the use of tamoxifen and chemotherapy. And we can estimate the effectiveness of combinations of these three interventions for specific age groups. Refer to the [Results Overview](#) for some results of our modeling.

RELEVANT ASSUMPTIONS

See [Assumption Overview](#) .

RELEVANT PARAMETERS

See [Parameter Overview](#) .

RELEVANT COMPONENTS

[Cancer Incidence Component](#)

[Treatment Component](#)

[Survival And Mortality Component](#)



COMPONENT LISTING

A more detailed listing of the steps in the simulation follows.

A. Select Parameters

- Sample parameters from their prior distributions or use fixed values for parameters
- Relevant Inputs:
 - prior distribution on the reduction in risk of breast cancer mortality due to tamoxifen use or fixed value
 - prior distribution on the reduction in risk of breast cancer mortality due to improvements in chemotherapy or fixed value
 - prior distribution for reduction in risk of breast cancer due to mammography screening (beyond stage shift) or fixed values
 - prior distribution on hazard for underlying survival distributions by stage and age or fixed value
 - prior distribution on impact of age–period–cohort model or fixed value

B. Simulate Cohort in 1975

- simulate year of birth
 - Relevant Inputs:
 - age distribution of women in the U.S. in 1975
- simulate prevalent breast cancer cases in 1975 and their survival
 - Relevant Inputs:
 - incidence of breast cancer in the U.S. from 1940–1974
 - distribution of stage in clinically detected breast cancer
 - underlying breast cancer survival

C. Follow Cohort Through 2000

- Validation Step:
 - check number of women in the U.S. for each year 1975–2000

D. Allow Migration, Births, and Deaths

- births
 - input:
 - number of female births in the U.S. for each year 1975–2000
- deaths
 - Relevant Inputs:



- number of female deaths in the U.S., by age, due to causes other than breast cancer for each year 1975–2000

E. Simulate Breast Cancer Incidence

- simulate screening mammography dissemination
 - inputs:
 - screening mammogram dissemination generation software provided by NCI¹
- simulate breast cancer incidence
 - inputs:
 - breast cancer incidence for women who have never had a screening mammogram, by age and year²
 - breast cancer incidence at screening mammograms, by age, adjusted for year
 - breast cancer incidence during intervals between screening mammograms, by characteristics of last screening mammogram, years since last screening mammogram, age, and year
 - validation:
 - breast cancer incidence in the U.S., by age, for each year 1975–2000

F. Simulate Breast Cancer Survival

- simulate tumor characteristics
 - input:
 - stage distribution for breast cancer in women who have never had a screening mammogram, by age³
 - stage distribution for breast cancer detected by a screening mammogram, by age and screening mammogram characteristics⁴
 - stage distribution for breast cancer detected during intervals between screening mammograms⁶
 - node status distribution by mode of detection of breast cancer⁶
 - estrogen receptor status distribution by age⁶
- simulate treatment dissemination⁷
 - input:
 - distribution of treatment type by age, stage, node status, year, and estrogen receptor status
 - distribution of tamoxifen duration by year
- simulate breast cancer survival⁸
 - input:



- modified baseline breast cancer survival by age and stage, modified by effect of treatment type, effect of tamoxifen duration, effect of ER status, etc., interactions, etc.
- validation:
 - number of female deaths in the U.S., by age, due to breast cancer for each year 1975–2000

G. Derive Posterior Distributions for the Parameters in Component 0 which Were Drawn from Prior Distributions, as Both a Validation and Inferential/Output Step

REFERENCES:

-
- ¹ Cronin, K., Kraphcho, M. "Cancer Intervention and Surveillance Modeling Network; Base Case" 2002;
 - ² Holford, T. "Cancer Intervention and Surveillance Modeling Network; Base Case" 2003;
 - ³ Centers for Disease Control and Prevention. "National Breast and Cervical Cancer Early Detection Program (NBCCEDP)" 2002;
 - ⁴ National Cancer Institute. "Breast Cancer Surveillance Consortium (BCSC)" 2003;
 - ⁵ Shapiro, S, Venet, W, Strax, P, et al. "Periodic Screening for Breast Cancer: The Health Insurance Plan Project and its Sequelae, 1963-1986" 1988;
 - ⁶ Fracheboud, J, Groenewoud, JH, Boer, R, Broeders, MJM, Baan, CA, Verbeek, ALM, et al. "Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 2000 (VIII)" in Instituut Maatschappelijke Gezondheidszorg. : 35-41
 - ⁷ 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 Journal of Epidemiology and Community Health 2002; 57: 7: 525-6
 - ⁸ CISNET. "Modeling impact of mammography and adjuvant treatment on U.S. breast cancer mortality rates: collective results from the Cancer Intervention and Surveillance Modeling Network." in Journal of the National Cancer Institute Monograph 2004;
-

FIGURES

THE UNIVERSITY OF TEXAS
MDANDERSON
CANCER CENTER
Making Cancer History™

- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Key References

FIGURE 1. Acceptance Criteria for Simulated Mortality

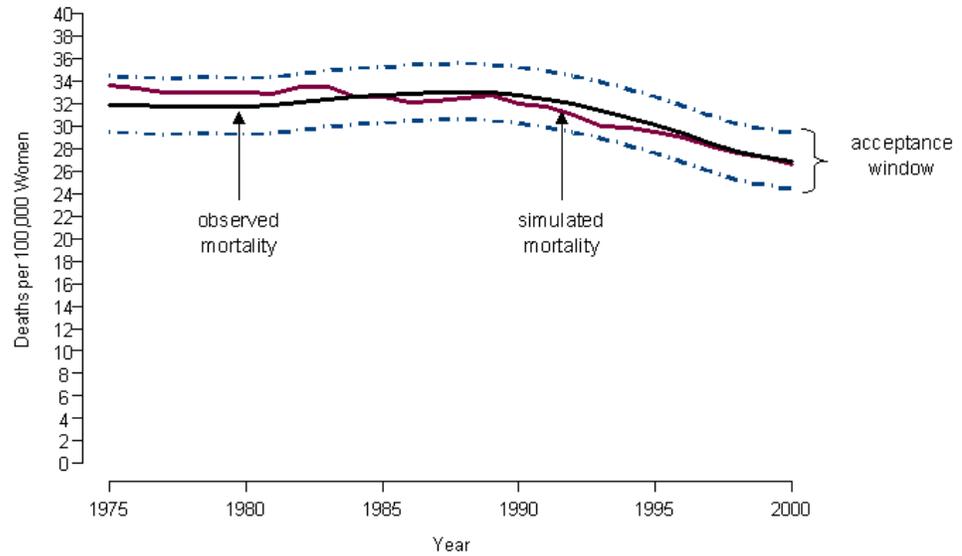


FIGURE 2. Simulated Mortality (Average)

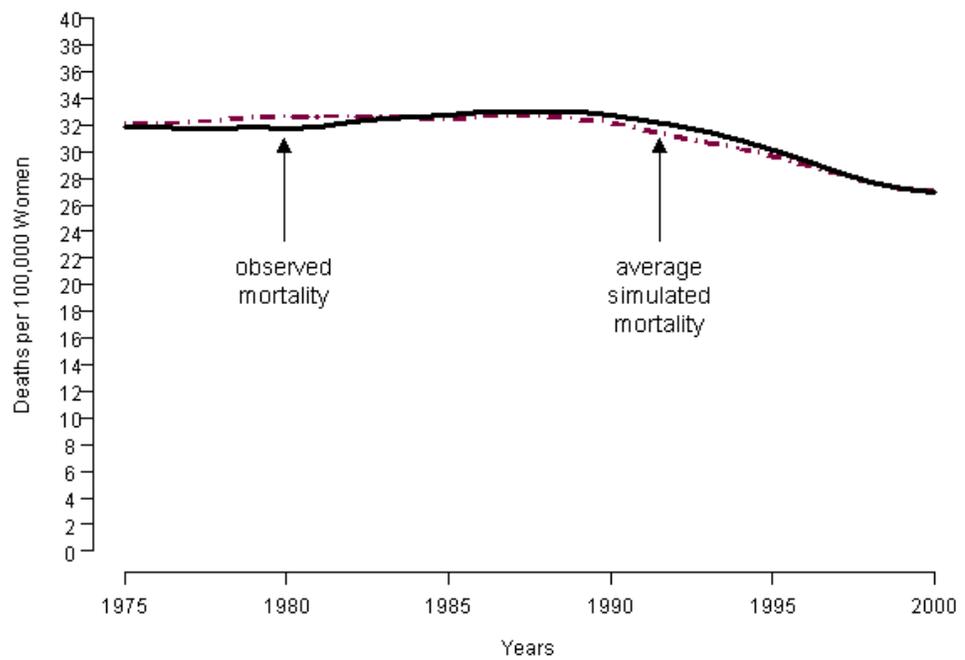


FIGURE 3. Prior and Posterior Distributions of Intervention Effects

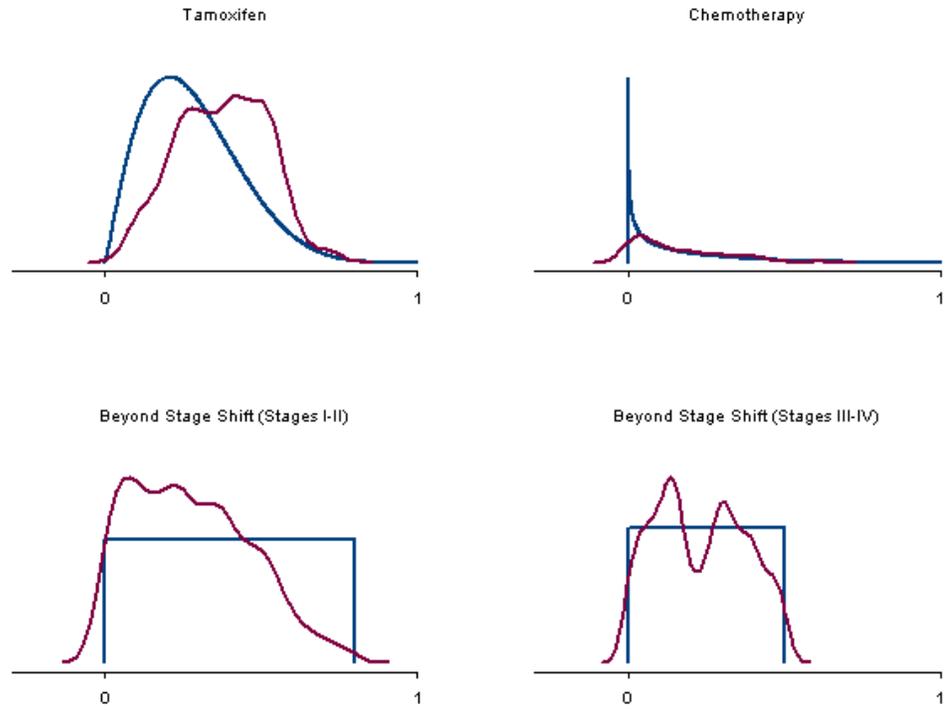
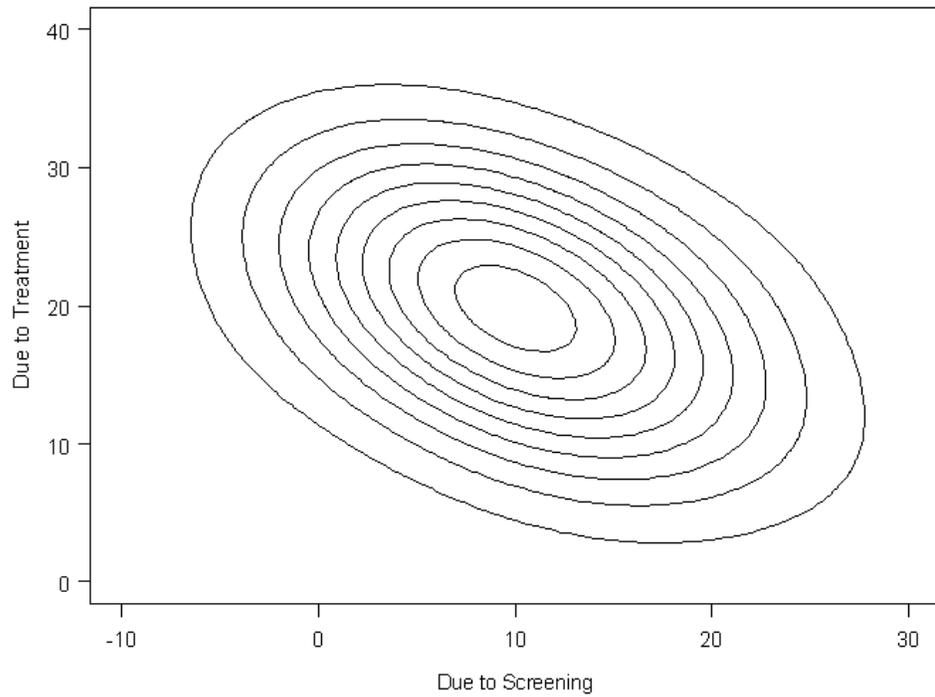


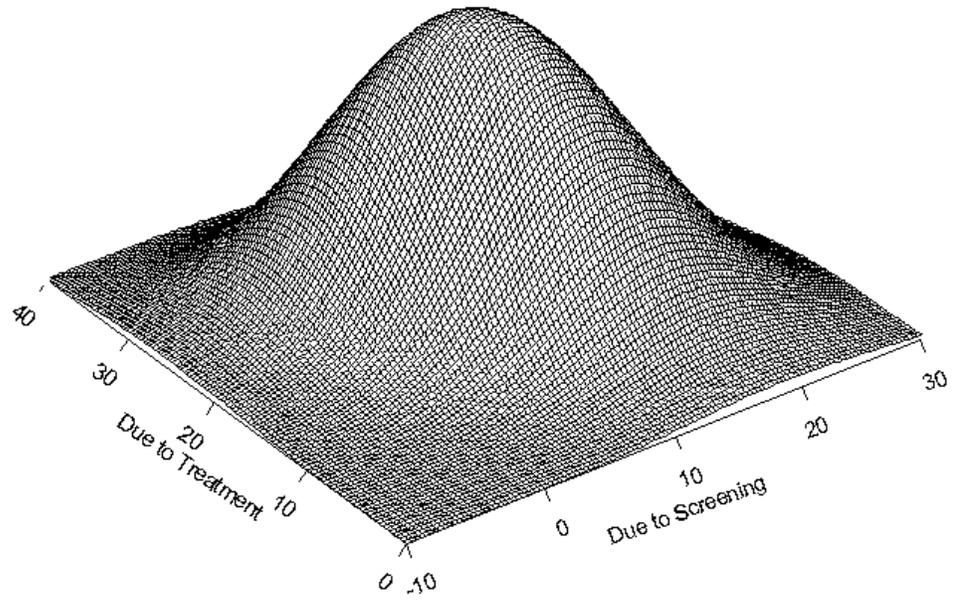
FIGURE 4A. % Reduction in Breast Cancer Mortality





U. of Texas MDACC
Figures

FIGURE 4B. % Reduction in Breast Cancer Mortality





KEY REFERENCES

- (1996) Trends in Cancer Screening – United States, 1987 and 1992 in *Morbidity and Mortality Weekly* 45:3, p 57–61
- BCSC** (2003) Breast Cancer Surveillance Consortium (BCSC) in *National Cancer Institute*,
- Berry, DA & Parmigianni, G** (1998) Assessing the Benefits of Testing for Breast Cancer Susceptibility Genes: A Decision Analysis in *Breast Disease* 10:(1,2), p 115–125
- Berry, DA & Stangl, DK.** (1996) Bayesian Biostatistics,
- Berry, DA.** (1996) Statistics: A Bayesian Perspective,
- CISNET.** (2004) Modeling impact of mammography and adjuvant treatment on U.S. breast cancer mortality rates: collective results from the Cancer Intervention and Surveillance Modeling Network. in *Journal of the National Cancer Institute Monograph*,
- Cancer Surveillance Research Program, National Cancer Institute.** (1998) The Surveillance, Epidemiology, and End Results (SEER) Program,
- Centers for Disease Control and Prevention.** (2002) National Breast and Cervical Cancer Early Detection Program (NBCCEDP),
- Cronin, K, Krapcho, M.** (2003) Cancer Intervention and Surveillance Modeling Network; Base Case; unpublished data.
- ,
- Cronin, K., Kraphcho, M.** (2002) Cancer Intervention and Surveillance Modeling Network; Base Case,
- Early Breast Cancer Trialists' Collaborative Group.** (1992) Systemic Treatment of Early Breast Cancer by Hormonal, Cytotoxic, or Immune Therapy: 133 Randomised Trial Involving 31,000 Recurrences and 24,000 Deaths Among 75,000 Women – Part 2 in *The Lancet* 339:8785,
- Early Breast Cancer Trialists' Collaborative Group.** (1992) Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women in *The Lancet*:339, p 1–15,71–85
- Early Breast Cancer Trialists' Collaborative Group.** (1998) Tamoxifen for early breast cancer: An Overview of the randomised trials in *The Lancet*:351, p 1451–1467
- Early Breast Cancer Trialists' Collaborative Group.** (1998) Polychemotherapy for early breast cancer: an overview of the randomized trials. in *The Lancet*:352, p 930–942
- Fletcher, S. Black W, Harris, R, et al.** (1993) Report of the international workshop on screening for breast cancer in *Journal of the National Cancer Institute* 85:20, p 1643–165
- Fracheboud, J, Groenewoud, JH, Boer, R, Broeders, MJM, Baan, CA, Verbeek, ALM, et al.** Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 2000 (VIII) in *Instituut Maatschappelijke Gezondheidszorg.*, p 35–41
- Frisell, J Eklund, G, Hellstrom, L, Somell, A** (1987) Analysis of interval breast carcinomas in a randomized screening trial in Stockholm in *Breast Cancer Research and Treatment* 9:3, p 219–225
- Hakkama, M, Holli, K, Isola, J, et al.** (1995) Aggressiveness of screen-detected breast cancers in *The Lancet*:345, p 221–224



- Holford, T.** (2003) Cancer Intervention and Surveillance Modeling Network; Base Case,
- Hortobagyi GN, Hung M, and Buzdar AU** (1999) Recent Developments in Breast Cancer Therapy in *Seminars in Oncology* 26(4):12, p 11–20
- Hortobagyi, GN, Hung, M, Buzdar, AU** (1999) Recent developments in breast cancer therapy in *Seminars in Oncology* 26:4, p Suppl 12:1
- Hortobagyi, GN, Hung, M, Buzdar, AU** (1999) Recent developments in breast cancer therapy in *Seminars in Oncology* 26:4:Suppl 12, p 11–20
- IARC** (1999) The CANCER–Mondial website in *International Agency for Research on Cancer*,
- International Agency for Research on Cancer, IARC** (1999) CANCER–Mondial,
- Jatoi, I** (1999) Breast Cancer Screening in *The American Journal of Surgery* 177, p 518–524
- Kerlikowske K, et al.** (1995) Efficacy of Screening Mammography in *Journal of the American Medical Association* 273:2,
- Kerlikowske, K, Grady, D, Rubin, SM, Sandrock, C, Ernster, VL** (1995) Efficacy of screening mammography. A meta-analysis in *Journal of the American Medical Association* 273:2, p 149–54
- Kricker, A, Farac, K, Smith, D, Sweeny, A, McCredie, M, Armstrong, BK** (1999) Breast cancer in New South Wales in 1972–1995: Tumor size and the impact of mammographic screening. in *International Journal of Cancer* 81:6, p 877–80
- Mariotto, A, Feuer, EJ, Harlan, LC, Wun, LM, Johnson, KA, Abrams, J.** (2002) Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975–1999 in *Journal of Epidemiology and Community Health* 57:7, p 525–6
- Miller, AB, Baines, CJ, To, T, et al.** (1992) Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. in *Canadian Medical Association Journal*:147, p 1477–1488
- Miller, AB, Baines, CJ, To, T, et al.** (1992) Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. in *Canadian Medical Association Journal*:147, p 1459–1476
- NBCCEDP** (2002) National Breast and Cervical Cancer Early Detection Program (NBCCEDP) in *Centers for Disease Control and Prevention*,
- National Cancer Institute.** (2003) Breast Cancer Surveillance Consortium (BCSC),
- National Center for Health Statistics** (1999) Health, United States, 1999 with Health and Aging Chartbook,
- Rosenberg, M.** (2002) Annual probabilities of death from causes other than breast cancer; Base Case,
- Shapiro, S, Venet, W, Strax, P, et al.** (1988) Periodic Screening for Breast Cancer: The Health Insurance Plan Project and its Sequelae, 1963–1986,
- Smart, CR, Byrne, C, Smith, RA, et al.** (1997) Twenty-year follow-up of the breast cancers diagnosed during the breast cancer detection demonstration project in *A Cancer Journal for Clinicians*:47, p 134–149
- Spiegelhalter, DJ, Abrams KR, Myles JP.** (2004) Bayesian Approaches to Clinical Trials and Health–Care Evaluation.,
- Tanner, MA.** (1996) Tools for Statistical Inference: Methods for the Exploration of Posterior Distributions and Likelihood Functions,
- Tengs, TO, et al.** (1999) Testing for BRCA1 Breast–Ovarian Cancer Susceptibility Gene: A Decision Analysis in *Medical Decision Making*,



U. of Texas MDACC
Key References

Therault R, Carlson R, Stockdale F. (2003) (Personal communication),

U.S. Department of Health and Human Services, National Center for Vital Statistics (1992) Vital Statistics of the United States,

Woods & Poole Economics Inc. (2001) 2001 Regional Database: Estimated July 1 population by race, sex and single year and 5-year age groups based on 1990 Census and post-censal Census Bureau estimates.,
