

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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# Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer

## SUPPLEMENT

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### Introduction

This supplement describes in greater detail the seven models used to assess relative and absolute contributions of screening and treatment to the reduction in breast cancer mortality in the U.S. over the period from 1975 to 2000. These models represent a five-year effort by interdisciplinary teams, and as such pose challenges in describing them succinctly and in ways that allow direct comparison of the models and their results. The CISNET consortium met this challenge by developing a software tool, referred to as the Model Profiler, to aid in model documentation and comparison. The content in this supplement was derived from the CISNET Model Profiles each group contributed as part of this collaboration. The complete, current profiles and tools for comparing them are provided at: <http://cisnet.cancer.gov/profiles/>. This supplement is a brief summary of the detailed information that is available in the profiles.

## 1.0 Dana-Farber Cancer Institute

### 1.1 Description

The model is a stochastic model of the natural history of the disease. It involves a series of equations that predict the age-specific mortality rate. The introduction of screening in the model makes the mortality rate equations more complex as it is necessary to distinguish among screen-detected and interval cases. The model takes into account both lead-time and length sampling biases. The assumption for the beneficial effect of screening is that the diagnosis of screen-detected cases leads to mortality benefit if it changes the distribution of disease stages beyond what would be expected due to length-

biased sampling. This shift is in the direction of having a higher proportion of favorable prognostic cases. The basic probability model requires the choice of a reference time point in chronological time. The model predicts the cumulative mortality relative to this reference time conditional on being a specific age at the reference time point. If the time point is chosen as a birth cohort year, then the model can predict the age-specific mortality rate for a specific birth cohort year. The age-specific mortality for any point in chronological time may be calculated by choosing a collection of birth cohort years. These may be averaged with respect to a weight function to give the overall mortality rate for a specific chronological year.

This model is based on a natural history component which assumes that breast cancer is progressive and can be summarized as having five states of health:

- Disease free or undetectable disease state
- Detectable disease state (pre-clinical state; i.e., disease is asymptomatic, but can be diagnosed by special examination)
- Clinical disease state
- Death attributed to breast cancer
- Death not attributed to breast cancer (ignored in this analysis since the focus is reduction in mortality attributed to breast cancer)

The transition into these states is dependent on both age and chronological time. Using these states, the model is designed around five basic equations which provide: a) the probability of the unscreened population surviving to year  $t$ ; b) the age-specific disease incidence by cohort; c) the probability density function of disease-specific survival for subjects incident at a certain age and chronological year; d) the probability of disease-specific death at a certain age by birth cohort; and e) age-specific mortality rate by cohort.

## **1.2 Distinguishing Characteristics**

This model is one of two (see section 5.0) strictly analytical models applied to this analysis. While software tools were used to perform the calculations, the model primarily exists as a set of analytical equations. The equations refer to cohorts rather than individuals and are applicable to other chronic diseases which satisfy the basic assumptions that (i) the disease is progressive and (ii) screening benefit occurs if screening results in a stage shift in favor of better prognosis. Also, this model relies solely on observed inputs or parameters directly estimated from existing data. Estimation of parameters is not made to calibrate the model. In particular, the model is not calibrated to match observed mortality.

## **2.0 Erasmus MC, University Medical Center, Rotterdam**

### **2.1 Description**

The MISCAN computer simulation program (1,2) has been developed for building models for cancer screening in a dynamic population, and for subsequently applying these models to analyze and explain the results of cancer screening trials, to predict and compare the (cost-) effectiveness of different screening policies, and to monitor the results of population screening programs. For this effort, the standard MISCAN model was extended to include a more biologically oriented continuous tumor growth component as an alternative for the standard discrete-stage natural history and screening component in MISCAN. This “Fadia” component simulates histories of tumors based on continuous tumor growth and the concept of a fatal diameter: each tumor has a size (the fatal diameter, which differs between tumors) at which diagnosis and treatment will no longer result in cure. At this point the tumor enters the stage of fatal disease, i.e., one or more micrometastases exist for which treatment will not be effective and will cause death from breast cancer. If the tumor is diagnosed (either on the basis of symptoms or by screening) and treated before the tumor reaches the fatal diameter, the woman’s disease will be cured. In Fadia, a distinction is made between tumor biology (tumor growth rate distribution) and model variables that may vary between areas and over time and/or age (diameter at clinical diagnosis, screening threshold diameter, fatal disease diameter, and survival).

The basic assumptions of this model include:

- Age distribution of the tumor initiation rate is the same for all birth cohorts.
- Life-time breast cancer risk is the same for all women in a certain birth cohort.
- Hazards of death from breast cancer and from other causes are independent.
- Tumors grow exponentially with growth rate governed by a lognormal distribution.
- Screen detection of an invasive tumor is determined by a threshold size for screen detection, which depends on age and year of screening.
- The fatal diameter for a particular tumor is governed by a Weibull distribution.
- If a tumor reaches its fatal diameter prior to detection and treatment, the woman will die from the cancer.

### **2.2 Distinguishing Characteristics**

The MISCAN-Fadia model is one of two CISNET models that incorporate a concept of “cure” in the survival model (see section 7.0). It is unique in its diameter-based approach to determining cure status. The survival and mortality benefits of early detection follow from the fatal disease concept which is a special case of the “cure” type of screening model. For each tumor there is a point at which the disease cannot be cured by treatment. The screening benefit (cure) occurs only if the tumor is detected by screening before it has become fatal and would otherwise have been diagnosed after it had become fatal. This model is one of four models that did not calibrate to observed mortality.

## 3.0 Georgetown University

### 3.1 Description

This model is an event-driven continuous-time state transition model. Women from different birth cohorts are simulated, and the times at which relevant events occur are determined by sampling from pre-specified time interval distributions. There are no special assumptions made about the mechanism by which breast cancer progresses or kills. Using U.S. Census data, a population of women born in or after 1890 is generated to simulate the population distribution of adult women alive in 1975. Women who are destined to develop breast cancer may either be screen-detected, present with clinical symptoms, or die of other causes before breast cancer is diagnosed. At presentation, the cancer has a stage assigned, based on whether the tumor is screen-detected or clinically detected. The stage for screen-detected cancers is calculated from what the stage would have been had the tumor presented with symptoms, and the lead time gained from screening is calculated using a formula derived from Bayes' theorem. Cancers are designated as being estrogen-receptor (ER) positive or negative. Survival is conditional on age and stage at diagnosis, ER status, and treatment. For each woman, the model produces a life history that identifies whether or not a diagnosis of breast cancer is made, and if so, in what stage it presents, and what treatment was chosen, as well as a date of death and an indication of whether death is from breast cancer or other causes. These life histories are then summarized to produce annual estimates of breast cancer incidence and mortality grouped by decade of age.

The basic assumptions for this model include:

- The benefit of mammography screening is represented by the effects of shifting diagnosis to an earlier stage of disease. Early detection that is not early enough to result in detection at an earlier stage does not, on average, alter survival. Early detection which does result in an earlier stage at diagnosis is “rewarded” with the full difference in stage-specific survivals.
- In the absence of screening, the distribution of stages of clinically detected tumors would resemble the distribution of stages of clinically detected tumors from the early part of the era from 1975 to 2000.
- Breast cancer progresses from a pre-clinical stage to a clinical presence, and then through stages of local, regional, and distant spread. The dwelling times in each stage are assumed to have exponential distributions.
- All tumors, including all ductal carcinomas *in situ*, have the potential to progress to metastatic disease and cause death.
- Dwelling times in each successive stage are independent of each other and of the sojourn time, and are exponentially distributed.

### 3.2 Distinguishing Characteristics

This model makes very modest assumptions about the natural history of the disease. Actually, there is no explicit model for the natural history of breast cancer; rather all

aspects of breast cancer are modeled in terms of stage dwelling times, ER status and age of the woman. This model considers only complete shifts in stage when assigning early detection benefit. Given this “stage shift only” approach it might be expected that this model would generally attribute less mortality reduction to screening than the others. Also, this model does not calibrate to observed breast cancer mortality.

## **4.0 M. D. Anderson Cancer Center**

### **4.1 Description**

This model utilizes Bayesian updating (3, 4) to estimate the contributions of screening mammography, chemotherapy, and tamoxifen use to the observed decline in breast cancer mortality in the United States since 1990. Computations of posterior distributions are made using a likelihood-based “rejection method” (5, 6). The model begins with the population of women prevalent in 1975. This population, along with subsequent newborns and immigrants, is followed until the year 2000. Breast cancer events depend on each woman’s age, screening mammography use, and treatment, all of which depend on time. Screening behavior is determined at the level of the individual woman and depends on the patterns of screening by age in that year and on her previous screening history. When detected, breast cancer is assigned an AJCC (American Joint Committee on Cancer) stage, nodal status, and estrogen-receptor status according to the woman’s age and the means by which the cancer was detected. Detection itself depends on the woman’s age, mode of detection, and time since her last screening. The natural history of the disease is not modeled explicitly. Therapy is assigned based on the characteristics of the cancer and on chronological dissemination patterns. The efficacy of therapy is regarded as unknown with the prior distribution based on results from the international overview (7, 8). Covariates include AJCC stage, ER status, the woman’s age, and the duration of treatment if the woman receives tamoxifen.

Assumptions in this model include:

- Screening and treatment have independent effects.
- The observed decrease in mortality is due to some combination of screening and treatment.
- Women with stage IV disease receive no survival benefit from chemotherapy or hormonal therapy.
- Some women with stage I-III disease who received chemotherapy in later years were also treated with taxanes and received an additional survival benefit.
- Tumors detected more than 3 years after a screening mammogram have the same characteristics as clinically detected tumors.
- Tumors detected by screening are allowed to have better prognosis than those detected clinically even if the characteristics of the tumors are the same in both cases.
- ER status is dependent on mode of detection.

### **4.2 Distinguishing Characteristics**

This model has no explicit modeling of the natural history of breast cancer. Also, it contains almost no explicit natural history assumptions with the exception of the characteristics of interval cancers mentioned above. Survival benefits from screening depend on stage shift and mode of detection based on data from earlier trials (9, 10). This model is one of two (see section 7.0) that employs Bayesian rejection techniques to

determine posterior distributions for quantities of interest. As such, this model replicates (within fixed rejection bounds) the observed breast cancer mortality in the U.S. population. So this model is one of the three that calibrates to observed mortality trends (see sections 5.0 and 7.0).

## **5.0 University of Rochester**

### **5.1 Description**

This model includes both analytical and simulation components. Analytical models of natural history and cancer mortality are implemented as a simulation-based model to allow more flexible exploration of the basic model under theoretical scenarios. The authors estimate the natural history of breast cancer from bivariate data on the tumor size and age of the patient at diagnosis using the joint distribution of these variables. The natural history model is used to estimate the effects of screening on the age-specific cancer incidence and the distribution of major covariates at the time of diagnosis. The modelers use a bounded cumulative hazard model to incorporate the short- and long-term effects of covariates (age, tumor size, and stage) on the post-detection survival of breast cancer patients. This regression model allows for nonzero cure rates, thereby providing an adequate description of nonproportional covariate effects in breast cancer survival. (11)

Key assumptions of this model include:

- A two-stage model of carcinogenesis (12)
- A monotone increasing tumor growth model (no regression)
- Clinical and screen detection of disease depends on tumor size (with different coefficients).

### **5.2 Distinguishing Characteristics**

This model is one of two (see section 1.0) primarily analytical models. While simulation is used to generate results, the model is primarily expressed in terms of equations that can be evaluated analytically. This model is one of three (see sections 4.0 and 7.0) that calibrate model inputs to replicate observed mortality. This model involves fewer parameters in the calibration than do the other two, focusing only on the parameters responsible for systematic differences in data sets. This group does not model chemotherapy and tamoxifen benefits separately. Moreover, “treatment” for Group R includes not only adjuvant therapy but also better surgical and radiation procedures and improved patient care more generally.

## **6.0 Stanford University**

### **6.1 Description**

The model is a microsimulation build-up from individual models. The individual models are analytic descriptions of distinct processes such as tumor growth, tumor detection by screening and survival outcomes as a function of the mode of detection. The model provides estimates for population-level breast cancer mortality trends by simulating the life history of individual patients from 130 birth cohorts (starting in the year 1890) then aggregating the breast cancer related outcomes at the population level. Via the Monte Carlo method, events that characterize the life history of each woman include: the date of

her birth, the age of her death of causes other than breast cancer, and the ages at which she undergoes screening examinations. For women who develop cancer, additional characteristics include: the age at which she would be detected with invasive breast cancer in the absence of screening, the age at which she would be detected with invasive breast cancer in the presence of screening, 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, the adjuvant treatment she receives in the presence and absence of screening, her breast cancer survival time given her disease stage, size, age at detection and mode of detection, and her cause of death (determined by comparing the minimum of age at death from other causes and age at death from cancer). The model includes an explicit natural history component that starts with a prior knowledge of the tumor size and stage at clinical detection in the absence of screening and reconstructs the tumor size and stage backwards in time to the moment the tumor is 2mm in diameter to inception.

Key assumptions include:

- Exponential tumor growth with gamma distribution of doubling time
- The probability of clinical detection is proportional to the volume of the tumor.
- Clinical detection and onset of regional stage are independent of each other given volume doubling time.
- The detection threshold of screening mammography is size-based and independent of the year the mammography is performed.

## **6.2 Distinguishing Characteristics**

Two of the model parameters are not identifiable from clinical trial data and are instead chosen by calibrating to observed clinical incidence. No model parameters are chosen on the basis of calibrating to mortality. The model's ability to come close to reproducing mortality is used to demonstrate its validity. The model is not expected to exactly match mortality because all of the factors that influence mortality are not likely to be known or at least cannot be quantified from available data.

## **7.0 University of Wisconsin-Madison**

### **7.1 Description**

This model is a discrete-event simulation with a cycle time of six months beginning in calendar year 1950. The model is populated with birth cohorts making up the female population aged 20-100 years of age living between 1950 and 2000. The model consists of five primary processes acting in this population: cancer onset, cancer natural history (growth and progression of breast cancer subsequent to occult onset), cancer incidence by screening or other means (collectively termed "clinical detection"), treatment, and non-breast cancer mortality. Each of these processes is stochastic and together they act in the simulation to produce a data set similar to the observed cancer registry incidence data as well as mortality data. The natural history model is based on an original model proposed by Shwartz, (13) but modified to account for improvements in mammography and also to use a Gompertz-type growth model for tumors.

Key assumptions in this model include:

- The model must account for incidence and consequences of *in situ* as well as invasive breast cancer.
- The probability of breast cancer onset at any given time interval depends on risk factors and a background secular trend.
- Some tumors have limited malignant potential (LMP) and will never result in death from cancer.
- The natural history model is one of progressive growth (i.e. no regression, with the exception of LMP tumors; see below).
- The annual probability of clinical detection depends on tumor size and calendar year.
- The probability of screen detection at mammography depends on tumor size, the woman's age, and calendar year.
- Treatment effectiveness is modeled as cure/no-cure with cure rates conditioned on characteristics of the cancer, and treatment standards in the calendar year being simulated.

Model parameters are determined using massively parallel computing to implement rejection sampling with a goal of matching SEER historical stage-specific incidence data 1975-2000 and NCHS breast cancer mortality rates over the same period.

## 7.2 Distinguishing Characteristics

A unique aspect of this model is the explicit modeling of indolent tumors with limited malignant potential. These LMP tumors grow according to the same Gompertz growth function and growth rate distribution as non-LMP tumors, but cease growth at a maximum diameter of 1 cm. The characteristics of the LMP tumors are determined via calibration to observed incidence data. LMP tumors are assumed to never spread metastatically and thus do not lead to breast cancer death. The model is one of two (see section 2.0) that uses a cure/no-cure approach to treatment efficacy; cure rates are conditional on tumor characteristics. This model is one of three (see sections 4.0 and 5.0) that calibrate certain model parameters using observed mortality.

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