Chapter 11:
A Stochastic Model for Predicting the Mortality of Breast Cancer

Sandra Lee, Marvin Zelen

Consider a cohort of women, identified by year of birth, some of whom will eventually be diagnosed with breast cancer. A stochastic model is developed for predicting the U.S. breast cancer mortality that depends on advances in therapy and dissemination of mammographic screening. The predicted mortality can be compared with the same cohort having usual care with no screening program and absence of modern therapy, or a cohort in which only a proportion participate in a screening program and have modern therapy. The model envisions that a woman may be in four health states: i.e., 1) no disease or breast cancer that cannot be diagnosed ($S_0$), 2) preclinical state ($Sp$), 3) clinical state ($Sc$), and 4) disease-specific death ($Sd$). The preclinical disease refers to breast cancer that is asymptomatic but that may be diagnosed with a special exam. The clinical state refers to symptomatic disease diagnosed under usual care. One of the basic assumptions of the model is that the disease is progressive; i.e., the transitions for the first three states are $S_0 \rightarrow Sp \rightarrow Sc$. The other basic assumption is that any reduction in mortality associated with earlier diagnosis is due to a stage shift in diagnosis; i.e., early diagnosis results in a larger proportion of earlier stage patients. The model is used to predict changes in female breast cancer mortality in the U.S. women for 1975–2000. The model is general and may predict mortality for other chronic diseases that satisfy the two basic assumptions. [J Natl Cancer Inst Monogr 2006;36:79–86]

The early detection of chronic diseases presents opportunities for using existing technologies to substantially improve patient benefit. The possibility of diagnosing a disease early, while it is asymptomatic, may result in treating the disease in an earlier stage which may enhance the benefit of treatment. This paper describes a stochastic model for predicting the mortality of breast cancer as a function of both treatment and an early detection screening program. The early detection modalities consist of mammogram exams possibly combined with physical exams. The screening program consists of a series of examinations. The mortality predictions may be for chronological time and/or age for a defined cohort group. The model integrates possible advances in therapy and the changing dissemination of screening by chronological time. Although motivated by breast cancer, the model is general and may be used for other chronic diseases that satisfy the basic assumptions inherent in the model.

MODEL DETAILS

Natural History of Disease

The theoretical model builds on the natural history of the disease. The basic assumption of the natural history is that breast cancer is a progressive disease. Four or possibly five states of health are envisioned, as follows. $S_0$: a woman is disease free or has disease but is asymptomatic and cannot be diagnosed by any modality; $Sp$: a woman has breast cancer but is asymptomatic and may be diagnosed by a special examination; $Sc$: a woman having usual care is diagnosed with invasive breast cancer; and $Sd$: death attributed to breast cancer.

The progressive disease model may be described by the path $S_0 \rightarrow Sp \rightarrow Sc$. Some women may die of their disease, whereas others will die from other causes. The main interest is the reduction in breast cancer–specific mortality. Women diagnosed with breast cancer who eventually die of other causes are regarded as right-censored observations.

The goal of a breast cancer screening program is to diagnose women who are asymptomatic for breast cancer. Hence by definition women diagnosed by a screening exam are in the preclinical state. It is necessary to distinguish among cases that are diagnosed: 1) by a screening exam, 2) after a negative exam when the disease becomes symptomatic, and 3) by usual care. Screen-detected cases are those in which the women are asymptomatic and the disease is diagnosed by an early detection examination. Interval cases are those not detected at a screening examination, but there is a history of at least one negative screening examination. An incident case refers to women who have no history of screening exams but are diagnosed by usual care; i.e., the disease has generated signs/symptoms that makes the women seek medical attention. Interval and incident cases are assumed to be diagnosed in the clinical state. Mammography and/or a physical exam may be used to aid in the diagnosis of breast cancer when there are signs/symptoms as well as being used to detect cases in which there are no signs/symptoms. The latter is referred to as a screening exam, whereas the former is a diagnostic exam even though the same examination modality is used. In addition to the assumption that breast cancer is a progressive disease, the other basic assumption is that the potential reduction in breast cancer specific mortality from screening is due to a favorable stage shift in diagnosis relative to the distribution of stages when diagnosis is by usual care. We have used the AJCC classification for breast cancer staging. However, any system of disease staging may be used in the model.

Mortality Modeling

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

No Screening History Model

We define the following:

- \( v \) = year of birth cohort;
- \( \tau \) = age of incidence;
- \( T \) = age at death;
- \( S_v(t) \) = probability of normal population surviving to age \( t \) for birth cohort \( v \); the normal population is defined as a population free of disease up to age \( t \).
- \( I_v(t) \) = age-specific disease incidence for birth cohort \( v \);
- \( g(t|v+\tau) \) = probability density function (p.d.f.) of disease-specific survival for subject incident at age \( \tau \) in chronological year \( v+\tau \);
- \( d_v(T) \) = probability of disease-specific death at age \( T \) for birth cohort \( v \);
- \( M_v(T) \) = age-specific mortality rate for birth cohort \( v \).

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

\[
g(t|v+\tau) = \sum_{i=1}^{k} \theta_i g_i(t|v+\tau), \tag{11.1}
\]

where \( \theta_i \) is the probability of being diagnosed in stage \( i \) \((i=1, 2, \ldots, k) \) and \( g_i(t|v+\tau) \) is the survival distribution p.d.f. for stage \( i \) for a subject diagnosed in chronological year \( \tau + v \) for a subject having incidence at age \( \tau \).

In the chronological year of diagnosis \( \tau + v \), there may be several treatment options \((r=1, \ldots, R)\) that may have different survival outcomes. Here \( g_i(t|v+\tau) \) may be written as the mixture

\[
g^*_i(t|v+\tau) = \sum_{r=1}^{R} \phi_i(r|v+\tau)g_{ir}(t|v+\tau), \tag{11.2}
\]

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

\[
g^*(t|\tau + v) = \sum_{i=1}^{k} \theta_i g^*_i(t|\tau + v). \tag{11.3}
\]

The age-specific mortality rate for a subject from birth cohort year \( v \) is defined as

\[
M_v(T) = \frac{d_v(T)}{S_v(T)} \times 100000, \tag{11.4}
\]

where

\[
d_v(T) = \int_{T}^{T+1} \left\{ \int_0^\tau S_v(\tau)I_v(\tau)g^*(y - \tau|v+\tau)d\tau \right\}dy \tag{11.5}
\]

That is, the age-specific mortality rate represents the probability of disease-specific death between ages \((T, T+1]\) for a birth cohort year \( v \). The inner integral in [11.5] is the probability of a disease related death in the age interval \((0, \tau)\). The outer integral restricts the probability of disease-related death to the age interval \((T, T+1]\). The sequence of events in the inner integral, conditional on birth cohort \( v \) is as follows: 1) normal population surviving to age \( \tau \), 2) conditional on being alive at age \( \tau \), to become incident with disease in the age interval \((\tau, \tau + dt)\), and 3) living an additional years of life within the interval \((y - \tau, y + \tau + dy)\).

The range of integration for the inner integral is 0 < \( \tau \leq y \).

One aim of the model is to estimate the age specific mortality by chronological year. If \( t \) refers to chronological year and \( T \) denotes the age of death, then \( t = T + v \). Hence by choosing a birth cohort year, estimates can be made about age specific mortality corresponding to chronological time \( t \).

Overall disease-specific mortality rate for a chronologic year \( t \) may be calculated with reference to some base year. Suppose that \( p_0(T) \) represents the distribution of ages for a chosen base year. Then the age-adjusted disease-specific mortality rate for chronological year \( t \) is

\[
M(t) = \int M_{t-T}(T)p_0(T)dT. \tag{11.6}
\]

The range of integration will be over the values of \( T \) in which \( p_0(T) \) is nonnegligible.

Screening History Model

Subjects undergoing screening require a more complex model than those without a screening history. Furthermore it is necessary to distinguish between cases diagnosed at a screening examination (screen-detected cases) and those diagnosed at other than a screening exam (interval cases). Suppose that a subject from cohort year \( v \) has a history of screening exams \( H_i \) at ages \( t_1 < t_2 < \ldots < t_n \). Screen-detected cases get diagnosed at any exam given at ages \( t_1, t_2, \ldots, t_n \). It is assumed that no further exams are given after a diagnosis. Interval cases get diagnosed in between exams \((t_i, t_{i+1})\) for \( i = 1, \ldots, n-1 \) or after the last exam at \( t_n \).

The probability of disease-specific death at age \( T \) for birth cohort \( v \) who follows a screening pattern \( H_i \) has a more complicated expression than the probability expression [11.5] of the nonscreened population. It can be written as

\[
d_v(T|H_i) = \int_0^{T+1} \left\{ D_v(t|H_i) + I_v(t|H_i) \right\}d\tau dy,
\]

where

\[
D_v(t|H_i) = \text{Probability of disease-specific death at age } t \\
\text{for screen detected cases with screening history of } H_i; \tag{11.6}
\]

\[
I_v(t|H_i) = \text{Probability of disease-specific death at age } t \\
\text{for interval cases with a screening history of } H_i.
\]

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

The survival distribution for screen-detected cases is assumed to be a mixture of distributions as described in equation [11.1], except that the probabilities \((\theta_i)\) of being diagnosed in the various disease stages have changed due a possible stage shift. In our model the stage shift is represented by the new values of \( \theta_i \). Generally larger values \((\theta_i)\) are expected for better prognostic stages.
when screening is involved. The lead time, which is defined to be the difference between the age transitioning into the clinical state and the age of earlier diagnosis, is a random variable, which is not observed. It is equivalent to having a random guaranteed survival time; i.e., the subject will live at least to the age at which clinical diagnosis is made. The model accounts for the guaranteed survival time. Otherwise there will be a lead time bias when compared to non-screened cases.

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

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

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

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

where $h_i$ is the probability of screening history $H_i$.

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

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

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

### Mortality Reduction

We have formulated the expressions for the overall disease-specific mortality rate at chronological year $t$. This formulation can be used to estimate the mortality reduction due to treatment, screening, or to both treatment and screening disseminated in the population over years. Using the expressions in equations [11.6] and [11.8], one can estimate the overall disease-specific mortality reduction at chronological year $t$ due to screening as

$$MR_{csc}(t|H) = \left[\left(M_{t-T}(T) - M_{t-T}(T|H)\right)p_0(T)dT/M(t)\right].$$  

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

$$MR_{ct}(t) = \left[\left(M_{t-T}(T) - M^*_{t-T}(T)\right)p_0(T)dT/M(t)\right].$$  

where $M^*_{t-T}(T)$ can be estimated from equation [11.6] using the treatment incorporated survival p.d.f. described in [11.3]. Finally, the mortality reduction due to both screening and treatment disseminated in the population is formulated as

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

## DATA INPUT AND SOURCES

Our model requires input data that may come from various sources. They include the following: survival conditional on stage, sensitivity of mammograms, sojourn time distribution in the preclinical stage, stage distribution with and without screening, dissemination of screening and therapy in the 1975–2000 period, and the estrogen receptor (ER) status. Many of these inputs may be age related. Here we discuss the values of these inputs.

The philosophy of the model is that the input data may be observed or can be estimated from existing data. Examples of the latter are the sensitivity of the screening modality and the transition probabilities into $S_p$. The model does not contain parameters that are estimated to fit existing mortality. Here the sources of the basic input data and applications to our model are described. The notation used in this section was previously defined. We have used the software Mathcad 2001i from Mathsoft Inc. (/1) to carry out the calculations of the breast cancer mortality in the U.S. women in 1975–2000.

### Survival, Sensitivity, Sojourn Time in the Preclinical State, and Stage Distribution

The SEER database provides breast cancer incidence, staging and survival for 1975–1979. We have chosen this period for the input data, as breast cancer screening was not common at that time. Choosing a later period would result in these data sources being influenced by screening. The estimate of the age-specific breast cancer mortality for birth cohort year $v$ without screening history ($d_v(T)$, defined in equation [11.5]) has used the input data $S_v(t)$ and $I_v(t)$ for birth cohort $v$ that was provided by the CISNET NCI group (2,3). In our model, ductal carcinoma in situ (DCIS) cases were not included. The survival of DCIS cases is essentially the same as individuals without breast carcinoma. A small percentage of DCIS cases do convert to invasive carcinoma. They are included in our model as invasive cases. Hence omission of DCIS cases does not affect the breast cancer mortality in our model.

Table 1 summarizes the stage distribution without screening ($0_0$) on the basis of the SEER data. The CISNET NCI group has estimated the AJCC stage distributions using the SEER extent of disease data for 1975–1979 (4). Age-specific breast cancer survival, conditional on the AJCC stage, has also been provided by the CISNET NCI group (4). We estimated the annual hazard rate

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Stage I</th>
<th>Stage II-</th>
<th>Stage II+</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>0.31</td>
<td>0.23</td>
<td>0.31</td>
<td>0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>40–49</td>
<td>0.30</td>
<td>0.23</td>
<td>0.31</td>
<td>0.10</td>
<td>0.06</td>
</tr>
<tr>
<td>50–59</td>
<td>0.29</td>
<td>0.22</td>
<td>0.31</td>
<td>0.10</td>
<td>0.08</td>
</tr>
<tr>
<td>60–69</td>
<td>0.30</td>
<td>0.22</td>
<td>0.27</td>
<td>0.10</td>
<td>0.11</td>
</tr>
<tr>
<td>70–84</td>
<td>0.32</td>
<td>0.27</td>
<td>0.22</td>
<td>0.10</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*SEER = Surveillance, Epidemiology, and End Results.
and cumulative survival conditional on stage and age. By multiplying these two quantities, the p.d.f of age-specific breast cancer survival conditional on stage was estimated. Then the p.d.f of breast cancer specific survival as defined in equation [11.1] was generated using the stage distributions \( \theta(t) \) and the p.d.f. of breast cancer survival conditional on stage.

Our model requires further input data to incorporate screening history and advances in treatment over chronological time. Using the age-specific incidence data \( I_v(t) \) for birth cohort \( v \), we have estimated transition probabilities between \( S_0 \) to \( S_5 \) and \( S_5 \) to \( S_6 \). We have further assumed that the preclinical sojourn time follows an exponential distribution with an age dependent mean. The mean sojourn times \( m(t) \) serving as input to the model are as follows:

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

These values are based on data from the early detection randomized clinical trials. The Breast Cancer Surveillance Consortium (BCSC) published the age-dependent sensitivities of screening mammograms in the United States administered in 1996–1998 (5). We used their estimates in the model. (The BCSC project was founded by NCI in 1994 to evaluate mammogram screening practices in the U.S. population.) The BCSC database currently contains mammogram screening data and follow-up for approximately 1 million U.S. women beginning in 1994. Specifically the age-dependent estimated sensitivities \( \beta(t) \) for screening exams from the BCSC data are as follows:

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

For simplicity, the above \( \beta(t) \) values have been rounded. Shen and Zelen (6) estimated sensitivities of screening examinations and mean preclinical sojourn times from the randomized clinical trials evaluating the benefit of mammography. In their calculations, the mammogram sensitivities had an improving trend over time for screening clinical trials conducted in 1963 through the 1990s. Therefore the sensitivities presented above were applied to screening exams conducted in 1995–2000 and the sensitivities for the previous years were lowered. For 1985–1995, the sensitivities were lowered by 0.10 for ages younger than 45 years and by 0.05 for the older age groups. The sensitivities for 1975–1985 were further lowered by 0.10 and 0.05 from the sensitivities of 1985–1995 for younger (<45 years) and older age groups, respectively.

Finally the assumption of exponential sojourn times in the preclinical state can be justified from two sources. Zelen and Feinleib (7) have proved that the necessary and sufficient condition for the sojourn time to follow an exponential distribution is that the mean age of diagnosis for the initial early detection exam be the same age as those diagnosed in a control group. This condition was verified in the HIP randomized trial. The second source is the empirical study carried out by Day and Walter (8) in which they investigated various distributions for the preclinical sojourn time in the HIP trial and found that the exponential distribution gave the best fit.

### Stage Shift

The BCSC has provided data on AJCC stages at diagnosis for screen-detected and interval cases. In the BCSC data, a screen-detected cancer was defined as cancer diagnosed within 4 months of a positive screening mammogram (bilateral mammograms indicated by the radiologist to be done for routine screening). An interval cancer was defined as cancer diagnosed within 4 months of a diagnostic mammogram (mammogram indicated by the radiologist to be done for evaluation of a breast problem). A mammogram was considered positive if it was given a final BI-RADS assessment code of 0 (need additional imaging evaluation), 4 (suspicious abnormality), 5 (highly suggestive of malignancy), or 3 (probably benign finding) with a recommendation for immediate follow-up. Time since prior mammography was determined using dates of prior examinations in the mammography registry or self-reported information. We have categorized the time since prior mammogram as 1 year and longer than 1 year.

We estimated the distribution of AJCC stages for screen-detected cases in age groups of younger than 50, 50–59, 60–69, and 70 years or older by screening intervals (1 year versus longer than 1 year). The results are summarized in Table 2A. Similarly, the AJCC stage distribution for interval cases is displayed in Table 2B. The summaries in Tables 2A and 2B are based on the data received from the BCSC as of December 2003.

The stage distribution in the absence of screening can be compared to the stage distribution estimated from the BCSC data. For example, for women younger than 50 years, 54% were diagnosed with Stage I/II – disease when no screening was conducted. (Stage I/II – disease is essentially node negative or local disease stage.) However, 73% of the same age group were detected at screening with stage I/II– with annual mammograms and 70% with exams having longer than a 1-year interval between exams. This shift of 54% to 73% in finding more cases at an earlier stage (stage I/II–), when women were screened annually, results in a mortality reduction.

This staging information compared to the SEER stage distribution presented in Table 1 allows comparison of stage shift data for screening versus usual care. There is a larger proportion of women detected at earlier stages when diagnosed by screening. Furthermore, the stage shift is slightly more pronounced with a shorter screening interval. Similar stage shift data are available from the eight randomized early detection clinical trials and are in close agreement (see “Discussion”). Finally, the p.d.f. of disease-specific survival for screening exam diagnosed groups

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**Table 2A. Summary of stage distribution for screen-detected cases**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Stage I</th>
<th>Stage II–</th>
<th>Stage II+</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.62</td>
<td>0.11</td>
<td>0.21</td>
<td>0.04</td>
</tr>
<tr>
<td>50–59</td>
<td>0.67</td>
<td>0.11</td>
<td>0.19</td>
<td>0.03</td>
</tr>
<tr>
<td>60–69</td>
<td>0.76</td>
<td>0.07</td>
<td>0.14</td>
<td>0.02</td>
</tr>
<tr>
<td>≥70</td>
<td>0.78</td>
<td>0.09</td>
<td>0.11</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**AJCC stage distribution with annual screening (from BCSC)**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Stage I</th>
<th>Stage II–</th>
<th>Stage II+</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.58</td>
<td>0.12</td>
<td>0.24</td>
<td>0.04</td>
</tr>
<tr>
<td>50–59</td>
<td>0.62</td>
<td>0.15</td>
<td>0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>60–69</td>
<td>0.66</td>
<td>0.13</td>
<td>0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>≥70</td>
<td>0.73</td>
<td>0.13</td>
<td>0.11</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**AJCC stage distribution with screening interval > 1 y (from BCSC)**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Stage I</th>
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<th>Stage II+</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
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<tr>
<td>60–69</td>
<td>0.66</td>
<td>0.13</td>
<td>0.18</td>
<td>0.03</td>
</tr>
<tr>
<td>≥70</td>
<td>0.73</td>
<td>0.13</td>
<td>0.11</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*AJCC = American Joint Committee on Cancer; BCSC = Breast Cancer Surveillance Consortium.*
Table 2B. Summary of stage distribution for interval cases*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage II+</th>
<th>Stage III</th>
<th>Stage IV</th>
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<tbody>
<tr>
<td>&lt;50</td>
<td>0.46</td>
<td>0.19</td>
<td>0.26</td>
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<td>0.02</td>
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<tr>
<td>50–59</td>
<td>0.45</td>
<td>0.17</td>
<td>0.30</td>
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<td>0.01</td>
</tr>
<tr>
<td>60–69</td>
<td>0.54</td>
<td>0.15</td>
<td>0.23</td>
<td>0.06</td>
<td>0.01</td>
</tr>
<tr>
<td>≥70</td>
<td>0.54</td>
<td>0.23</td>
<td>0.16</td>
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</table>

AJCC stage distribution with annual screening (from BCSC)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage II+</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.37</td>
<td>0.22</td>
<td>0.31</td>
<td>0.08</td>
<td>0.02</td>
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<tr>
<td>50–59</td>
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<td>0.26</td>
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<tr>
<td>60–69</td>
<td>0.41</td>
<td>0.22</td>
<td>0.27</td>
<td>0.07</td>
<td>0.03</td>
</tr>
<tr>
<td>≥70</td>
<td>0.43</td>
<td>0.29</td>
<td>0.18</td>
<td>0.07</td>
<td>0.03</td>
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</table>

AJCC stage distribution with interval > 1 y (from BCSC)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage II+</th>
<th>Stage III</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.37</td>
<td>0.22</td>
<td>0.31</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td>50–59</td>
<td>0.29</td>
<td>0.26</td>
<td>0.26</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>60–69</td>
<td>0.41</td>
<td>0.22</td>
<td>0.27</td>
<td>0.07</td>
<td>0.03</td>
</tr>
<tr>
<td>≥70</td>
<td>0.43</td>
<td>0.29</td>
<td>0.18</td>
<td>0.07</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*AJCC = American Joint Committee on Cancer; BCSC = Breast Cancer Surveillance Consortium.

Screening Dissemination

Screening patterns for each birth cohort year have been modeled by the CISNET NCI group by using the data from the National Health Interview Survey (NHIS) and BCSC (4). This effort provides information on the probability of the first screening examination for birth cohorts 1891–1970 at chronological years 1975–2000. This information is directly incorporated into our model. Also, the information on screening patterns, conditional on the age at the first screening examination, was available. The screening pattern was incorporated into our model using the age intervals 18–39, 40–49, 50–59, 60–69, and 70–79 years. In addition, the screening patterns are summarized using three idealized screening intervals, i.e., short (1 year), medium (2 years), and long (5 years). For women starting the first screening examination at ages 50–59 years, the possible screening patterns and probabilities of observing specific patterns are summarized in Table 3. If women die of breast cancer before age 70, screening patterns up to age 69 and the corresponding probabilities are used.

For illustration, we have displayed only a summary of screening patterns for women who had their first screening examinations between ages 50 and 59 years. However, we have created similar tables for all of the age categories described above. The combinations of various screening patterns \((H_i)\) for \(i = 1, \ldots, k\) together with disease-specific survival data and stage shift information have been incorporated into equation [11.8] to assess the disease-specific mortality for the screened population. These screening patterns are based on a simulation model developed by the CISNET NCI group (4).

The stage distributions used in the model correspond to the screening patterns summarized in Tables 2A and 2B. For women following screening exams with mixed intervals (1, 2, and 5 years), the stage distribution associated with screening interval greater than 1 year was used. When all the screening exams are 5 years apart, the stage shift associated with screening interval greater than 1-year interval was lowered by combining it with the stage distribution of the control group in Table 1. In particular, we combined \((1/3 \times \text{entries in Table 1})\) and \((2/3 \times \text{entries in Table 2A or 2B})\) matched by age and stage categories to generate the stage distribution of screen-detected or interval cases following the screening schedule of every 5 years. These adjustments were made to take into account the empirical observation that the magnitude of the stage shift is associated with actual screening intervals.

Treatment Dissemination

The dissemination of adjuvant therapies for breast cancer has also been modeled by the NCI CISNET group. The patterns of care data have been used to model the dissemination of breast cancer treatments in the United States between the years 1975 and 2000 (9,10). The CISNET NCI group has provided the data on the proportion of women receiving tamoxifen, multichemotherapy, or both by age groups (<50, 50–69, >69) and the AJCC stages for the years 1975–2000. For each treatment option, a median smoothing technique \((l)\) was applied to model the proportion of women receiving therapy as a function of chronological years 1975–2000. The smoothed function of the dissemination pattern for each treatment option has been directly incorporated into our model.

We have used the survival benefit of multichemotherapies reported by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (11). The EBCTCG reported the proportional reduction in the annual odds of death for multichemotherapies by age groups younger than 50, 50–59, 60–69, and older than 69 years. This proportional reduction was used to modify the disease-specific survival from the SEER 1975–1979 database. The adjustment was made conditional on the age groups.

A similar adjustment was made for the survival benefit attributed to tamoxifen. The EBCTCG (12) reported the proportional reduction in the annual odds of death ratio for tamoxifen use of 2 years and 5 years of continuous use. Again the disease specific survival from the SEER 1975–1979 database has been appropriately adjusted using the reported annual odds of death for 2-year or 5-year course of tamoxifen therapy. We have estimated the age specific ER positivity using the 1988–1993 SEER data (ER status data became available in the SEER database beginning in 1988). Table 4 summarizes the age-specific ER status data used in our model. The benefit of tamoxifen was applied only to ER+ women.

Table 3. Screening patterns for women with first screening exam at ages 50–59 years*

<table>
<thead>
<tr>
<th>Screening during ages, y</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>s</td>
<td>s</td>
<td>s</td>
<td></td>
<td>.369</td>
</tr>
<tr>
<td>s</td>
<td>s</td>
<td>m</td>
<td></td>
<td>.033</td>
</tr>
<tr>
<td>m</td>
<td>s</td>
<td>m</td>
<td></td>
<td>.012</td>
</tr>
<tr>
<td>m</td>
<td>m</td>
<td>m</td>
<td></td>
<td>.259</td>
</tr>
<tr>
<td>m</td>
<td>m</td>
<td>l</td>
<td></td>
<td>.034</td>
</tr>
<tr>
<td>m</td>
<td>l</td>
<td>l</td>
<td></td>
<td>.001</td>
</tr>
<tr>
<td>m</td>
<td>l</td>
<td>l</td>
<td></td>
<td>.292</td>
</tr>
</tbody>
</table>

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

Table 4. Distribution of ER status by age group in SEER 1988–1993*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>ER+, %</th>
<th>ER-, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>63</td>
<td>37</td>
</tr>
<tr>
<td>50–69</td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td>≥70</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

*ER = estrogen receptor; SEER = Surveillance, Epidemiology, and End Results.
Also, the dissemination and benefit of tamoxifen have been modeled separately for the 2-year versus 5-year use of tamoxifen.

**Model Validation and Sensitivity Analysis**

The stochastic model we proposed has two basic assumptions: 1) natural history is progressive and 2) gains from screening are attributed to a stage shift. To validate our model, we applied it to the eight randomized trials investigating the benefits of mammography. The application used input parameters from the trials, e.g., stage shift distribution, exam sensitivities, frequency and spacing of examinations, age distributions, and mean sojourn time in the preclinical state. These parameters would generally be available during the first few years of the trial. The survival, conditional on stage, was obtained from the 1975–1979 SEER database. The follow-up period for the trials ranged from 7 to 19 years. The follow-up times coincided with the last published database.

A sensitivity analysis for the model has also been carried out. We have varied two of the input parameters specific to our model (mammogram sensitivities and stage distributions) to evaluate the impact on disease-specific mortality. In particular we have 1) increased the sensitivity of mammograms to $\beta(t) = 1$ for all ages in 1975–2000, 2) lowered the age-dependent sensitivities to 0.35–0.70 in 1975–2000, 3) changed the stage shift for women following a 5-year screening pattern to the stage distribution from the BCSC for screening with more than 1-year, and 4) lowered the stage shift of women following a 5-year screening pattern to the stage distribution of the control group. The results are displayed in Fig. 1 and 2.

The curve labeled “Model” in Figures 1 and 2 represents our final model prediction equation [11.11]. The other curves represent the changes by varying the input parameters. The curve labeled “Worse Comb” represents a combination of 2) and 4); and the curve labeled “Better Comb” represents a combination of 1) and 3). The magnitude of the reduction depends on the dissemination patterns. Generally, the mortality reduction (MR) increases over time as screening and modern treatment become more widely disseminated in the population. The MR ranged from 0% to 34% in the 25-year period 1975–2000 in the CISNET model.

![Fig. 2. Sensitivity analysis for stage shift.](image)

As displayed in Figure 1, if the sensitivity of the screening examination was increased to 1, the MR increased. In 2000, it increased to 34% compared to 33% from the lower sensitivities in the base case model. When the mammogram sensitivities were lowered, the MR in 2000 was lowered to 32%. Fig. 1 also displays the better and worse combinations of mammogram sensitivities and stage shifts. In 2000, the maximum MR with a better combination of mammogram sensitivities and stage shift was 36% and the minimum MR was 30% with a poorer prognosis combination. Our sensitivity analysis indicates that the deviation from the model predictions was always less than 3%.

The mammogram dissemination patterns modeled by the NCI that indicated approximately 30% of U.S. women, who have started screening, followed a screening schedule of exams 5 years apart. In calculations, a combination of stage distributions from the BCSC estimate for screening with more than a 1-year scheduling interval and SEER (1975–1979, no screening exams) was used for this group. The stage shift for this group has been changed to assess the impact of the stage distribution on MR. Fig. 2 displays the results. A more favorable stage distribution was used by using the BCSC estimate of screening with a more than 1-year screening interval; a less favorable stage distribution was used by using the stage distribution of SEER. The better stage shift improved the MR in 2000 to 35% and the control stage distribution lowered the MR in 2000 to 31%. Thus these sensitivity calculations show that there are small deviations between the model predictions and the predictions based on alternative stage shift distributions. Also the output results are sensitive to the stage shift distributions.

**Discussion and Summary**

We have presented a stochastic model for estimating breast cancer mortality. The major assumptions are that the disease is progressive and that any reduction in mortality associated with screening is due to a stage shift in exam diagnosed cases. Although the model is presented as a breast cancer model, the developments in “Model Details” are general and may be applied to other chronic diseases that satisfy the two basic assumptions. Inherent in our model is that survival is conditional on stage at diagnosis and not necessarily on the mode of diagnosis. If survival also depended on the mode of diagnosis, this feature may also be incorporated in the model. We have not used this more general condition in the breast cancer model described here, as there are no reliable data showing that if all things are
equal, there is a different conditional survival depending on mode of detection. As noted in our paper, the philosophy of the model is not to incorporate parameters with unknown values in which numerical estimates are found by curve fitting the model to observed mortality. Curve fitting will result in a close fit of the model to observed mortality with a closer fit as the number of fitted parameters increases. The parameters in our model are elements of the natural history and detection process, i.e., exam sensitivity, transitions into various disease states, survival condition on stage, stage distribution, and sojourn time with preclinical state. Predicting future changes in mortality in our model would entail only changing the dissemination parameters. All other aspects of the model would remain the same.

Since some of the post-1975 breast cancer deaths would have been diagnosed pre-1975, it is necessary to use incidence and survival data for the period before 1975 in our model. If the pre-1975 data are unreliable, it may cast some doubt on the mortality estimates for post-1975. However the effect on mortality of the pre-1975 cases diminishes in the later years of the 1975–2000 period. Consequently, the contributions of the pre-1975 diagnosis cases is likely to be minimal for (say) the post-1990 years or for predictions past the year 2000.

In this paper we have stressed mortality reduction that compares the relative background mortality from the age-period–cohort (APC) model (2) against the changing dissemination of modern treatment and screening (4,5). We believe that the mortality reduction is a robust measure for evaluating mortality reductions with changing interventions. Both groups have the same disease incidence and survival conditional on stage. The only difference is that one group has changing interventions. The APC model estimates the mortality in the absence of screening and improvements in therapy. It also incorporates the increasing incidence trend. Comparisons with these predictions form a basis for describing reductions in mortality associated with changes in screening dissemination and improvements in therapy.

The observed breast cancer mortality has been steadily dropping since the early 1990s. The combination of disseminations of both screening and modern drug therapy (multichemotherapy and tamoxifen) is widely attributed for the reduction in mortality. An important issue is that the differential reduction which can be attributed to each interventions. For 2000, the mortality reduction relative to the APC is 34%. According to our model, 23% of this reduction is attributed to screening and 11% to chemotherapy.

We have carried out a sensitivity analysis to explore how changes in the input parameter affect reduction in mortality reduction. The sensitivity analysis focused on changing the examination sensitivities and stage distributions. Our analysis indicated that maximum differences between the model prediction of mortality reductions for the worst and best combinations of sensitives and stage shift distributions was limited to about 3%. The 3% discrepancy was for 2000, in which the mortality reduction was 33%. Hence a conservative uncertainty in the model-based mortality reduction is ±10%. Another sensitivity analysis, not discussed here, was made by changing the mean of the sojourn time in the preclinical state by ±20%. The deviations between the outputs and the model were negligible. There are other sources that can also contribute to variations in the mortality reduction estimations. For example, variations associated with our common input data (such as screening patterns, treatment dissemination patterns, treatment benefit) can change the mortality reduction estimation. These variations were not addressed here.

The most important of the input parameters is the stage shift information. The information on stage shift presented in Tables 1 and 2 are in close agreement with the results of the early detection clinical trials. Adding stages I and II– depicts the proportion of patients diagnosed with node-negative disease. It is slightly age related. If we ignore the age dependence, the overall SEER node-negative proportion is 54% compared with 81% with screening. This difference of 27% compares to 28% (screened versus control) for five of the randomized screening trials. (The Stockholm trials did not publish the relevant data and the two Canadian trials had somewhat different experimental designs.)

Our model for breast cancer can be used in other ways to investigate other problems in breast cancer screening. One application addresses the mortality benefit of screening for women in the 40–49 age group. The benefit of screening women in this age group is controversial. Our conclusion was that with annual screening beginning at age 40, the mortality reduction associated with screening women in their 40s would be about 5.3%. Fewer screening examinations would further lower the mortality benefit. It would take a very large clinical trial, enrolling this age group, to show such a small reduction in benefit. Our conclusion is that benefit exists, but it is so small that none of the clinical trials have enough power to show such a benefit. Another application of the model is the investigation of the benefit of periodic screening schedules. This application has been carried out in the paper by Lee, Huang, and Zelen (14) in which annual, biennial, and triennial schedules are evaluated for benefit.

In summary, our model has been partially validated by comparing our predictions with the randomized early detection breast cancer trials. The model appears to be reasonably robust with regard to the input parameters and is flexible in that it can accommodate complex natural histories and interventions. The model may also be used to determine optimal screening schedules and for the early prediction of an early detection clinical trial without long-term follow-up. Although we have only applied to the model to breast cancer, it is a general model and could be useful for other chronic diseases that satisfy our basic assumptions.

References


Notes

Supported by the National Cancer Institute CISNET project funded under grant CA88270.

We gratefully acknowledge the collaboration with Dr. Diana Miglioretti of the Breast Cancer Surveillance Consortium for making the stage shift data (Table 2) available. The NCI CISNET group (Drs. Rocky Feuer, Kathy Cronin, and Angela Mariotto) provided key input data without which the model calculations could not be done. Also, we have had many discussions with Drs. Rebecca Gelmen and Kathy Cronin about our model, which led to many improvements. Finally, we are very much indebted to Ms. Hui Huang for carrying out the difficult calculations required by the model to obtain numerical results.