Chapter 6:
Modeling the Impact of Treatment and Screening on U.S. Breast Cancer Mortality: A Bayesian Approach

Donald A. Berry, Lurdes Inoue, Yu Shen, John Venier, Debbie Cohen, Melissa Bondy, Richard Theriault, Mark F. Munsell

Background: **Breast cancer mortality (BCM) in the United States declined from 33.1 per 100 000 women in 1990 to 26.6 per 100 000 women in 2000, yielding a 19.6% relative decline in BCM since 1990. Our goal is to apportion this decline between screening and therapy and to be able to state with some certainty that these interventions affected this decline.** ***Methods:*** **We started with an age-appropriate population of 2 000 000 women in 1975 and monitored these women through 2000. On the basis of population data each year, we assigned screening and breast cancer to women. If a woman was diagnosed with breast cancer, we simulated a lifetime for her with death from breast cancer, and we modified this lifetime depending on the use of adjuvant therapy and whether the cancer was screen-detected. A woman's lifetime was taken as the minimum of her lifetime with death from breast cancer and her simulated natural lifetime. We used Bayesian simulation modeling, which allows for associating probability distributions with our estimates.** ***Results:*** **We calculated the probabilities that screening mammography and adjuvant therapy contributed to the observed decline in BCM to be 90% and 99%, respectively. The posterior mean reduction in BCM due to screening is 10.6% ± 5.7% and due to therapy is 19.5% ± 5.4%. The decrease in the hazard of BCM due to tamoxifen use for ER-positive tumors is 37% ± 14% and that due to adjuvant (nontaxane) chemotherapy is 15% ± 14%.** ***Discussion:*** **The spread in our posterior distributions reflect the uncertainty present in the data sources available to us. However, despite this uncertainty we conclude a high probability that both screening and improvements in therapy contributed to the reduction in BCM observed in the United States from 1990 to 2000. [J Natl Cancer Inst Monogr 2006;36:30–6]**

Model Purpose

The decade from 1990 to 2000 saw an overall decrease in breast cancer mortality in the United States *(1)*. This encouraging trend has also been observed in other Western countries including Canada and the United Kingdom *(2,3)*. Although there are a variety of possible explanations for such a decline, such as environmental factors or changing biology of the disease, two of the most likely are earlier detection and improved treatment. Our model considers only these two explanations.

Our principal goal 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. Using our model we may also address the potential impact on future U.S. breast cancer mortality of changes in the prevalence of screening mammography, increased use of tamoxifen, and further improvements in chemotherapy as well as greater dissemination of chemotherapy.

Model Overview

We begin with a cohort of women in 1975. We monitor this cohort until 2000, simulating the various breast cancer events and other relevant events annually for each woman in the cohort. The cohort is dynamic in that each year we allow women to enter (births, immigration) and leave (deaths, emigration) the population.

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 every 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 previous 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 (ER) 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 prior distributions for these effects.

Affiliations of authors: Departments of Biostatistics and Applied Mathematics (DAB, YS, JV, DC, MFM), Epidemiology (MB), and Breast Medical Oncology (RT), The University of Texas M. D. Anderson Cancer Center, Houston, TX; Department of Biostatistics, University of Washington, Seattle, WA (LI).

Correspondence to: Donald A. Berry, PhD, Department of Biostatistics and Applied Mathematics, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 447, Houston, TX 77030-4009 (e-mail: dberry@mdanderson.org).

See "Notes" following "References."

DOI: 10.1093/jncimonographs/lgj006

We use Bayesian updating *(4,5)* 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" *(6,7)*: 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 complicated and cannot be exhibited in closed form. Data sources for the various model inputs are summarized in chapters 2–5 of this monograph *(8–11)*.

Developing the posterior distribution using the rejection method proceeds as follows. In each year we determine which women die of breast cancer and which die of causes other than breast cancer (on the basis of actuarial survival information) and we keep track of both. The consequent estimate of breast cancer mortality from 1975 to 2000 is compared to the observed breast cancer mortality in the United States over that period. If the two agree sufficiently well then the various parameter values are accepted into the joint posterior distribution. Details of this procedure and the meaning of "sufficiently well" are given later.

Model Component Overview

Simulating prevalent cases. To determine which women are the prevalent cases in 1975 we begin by considering an initial cohort of 2 000 000 women who were alive in 1940. We monitor this cohort to 1975, diagnosing women with breast cancer over 1940–1975 on the basis of the incidence by age and stage in each year. We assign each woman in this initial cohort a length of life assuming cause of death other than breast cancer *(9)*. Call this the woman's "natural lifetime." If she is found to have breast cancer then we simulate a lifetime assuming that breast cancer is the cause of death, and we assign the actual cause of death on the basis of the shorter of these two lifetimes.

Women do not enter this cohort until 1975, and women exit this initial cohort only by dying (of any cause). The women in this cohort who have breast cancer and are alive in 1975 are prevalent cases when we construct a new cohort of women in 1975. We repeat this procedure for each simulation of the model.

Simulating population of women. Once we have identified women to serve as 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. *(12)*, including the prevalent cases. For each woman who is not a prevalent case we simulate a natural lifetime, where cause of death is anything other than breast cancer. As we monitor the population in discrete yearly intervals, each woman gets 1 year older. For each woman we determine whether she is diagnosed with breast cancer depending on the incidence of the disease for women her age in that year, on whether she had a screening mammogram in that year, and her history of mammography.

Each year we allow for births, deaths, and migration. Those women born into the population after 1975 are not likely to develop breast cancer in their first 26 years, but they contribute to the size and age distribution of the population. We use the data from Woods & Poole Economics *(12)* to define migration patterns by comparing the U.S. female age distributions in consecutive years. For example, we know the population size in 1987. We also know the number of births and deaths in that year. To get the population size in 1988 we add the births and subtract the deaths for that year to the population size in 1987. If the result is smaller than the known population size in 1988 then we add immigrants to achieve the correct population size and if the result is larger than the known population size in 1988 then we subtract emigrants. We assign a natural lifetime to each woman who immigrates into the population. We also assign her breast cancer events by following the same procedure as for women who were initially in the population in 1975, as described below.

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. 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. A woman who dies of other causes or emigrates is removed from the at-risk population.

Simulating intervention effects from prior distributions. We impose separate and independent prior distributions on the reduction in the risk of breast cancer mortality due to adjuvant tamoxifen and adjuvant chemotherapy. We take the mean for the prior distribution of the tamoxifen effect from the 1998 report by the Early Breast Cancer Trialists' Collaborative Group *(13)*. We also used the standard error of the tamoxifen effect given in this report. However, the report is based on the results of randomized clinical trials. These results may not apply in actual clinical practice. Therefore, we incorporated additional uncertainty into the prior distribution and used a standard deviation that was three times the standard error in this report. We used the effect of chemotherapy reported by the Early Breast Cancer Trialists' Collaborative Group *(14)* as the mean of our prior distribution on the effect of chemotherapy. Again, we inflated the standard error of the effect of chemotherapy in determining the standard deviation of the prior distribution.

For those tumors that are detected via screening mammograms, we recognize the stage shift through the assignment of tumor stage on the basis of data from the Breast Cancer Surveillance Consortium (National Cancer Institute [2003] and Breast Cancer Surveillance Consortium [BCSC]; unpublished data). We also recognize that the degree of this stage shift depends on the time since the woman's previous screening mammogram.

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 screening. We include separate prior distributions for the reduction in the risk of breast cancer mortality beyond stage shift for AJCC stages 1–2 and for AJCC stages 3–4. We estimate the effect on survival beyond stage shift from the Health Insurance Plan Project (HIP) *(15)* and the Canadian National Breast Screening Study (CNBSS) *(16,17)*, and we use these data to derive the means and standard deviations of the prior distributions for the two beyond-stage-shift parameters—see Shen et al. *(18)*.

We select one sample from each prior distribution and run the full simulation by using the parameters selected. This sample of

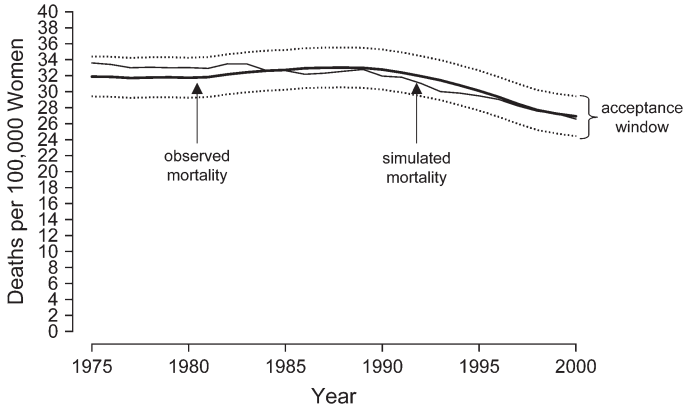

Fig. 1. Acceptance criteria for simulated breast cancer mortality. Observed U.S. mortality from 1975 through 2000 is shown as the **smooth heavy solid line**. The acceptance window is shown as the **two dashed lines** above and below observed mortality. One example of a simulated mortality curve is shown as a **light solid line**.

parameter values is used in simulating the population from 1975 through 2000. Each woman who is detected with breast cancer has a risk of dying of the disease that depends on the parameters selected as well as on her tumor's characteristics, whether her tumor was detected by a screening mammogram, and the treatment she received. Each time a population cohort is simulated, we sample again from the prior distributions to obtain a different sample of parameter values.

Updating the posterior distribution of intervention effects. To compare each simulated breast cancer mortality from 1975 to 2000 with that actually observed, we implement the following strategy. Each year over this period has an "acceptance window." In addition to these annual windows, we calculate the slopes in simulated and in actual breast cancer mortality over three 5-year intervals: 1985–1990, 1990–1995, and 1995–2000. If each of these slopes falls within preassigned acceptance limits, and if the simulated mortality falls within the annual acceptance windows, the parameter values used in that particular simulation are accepted as a sample from the posterior distribution.

By simulating and following the population many thousands of times, we populate the joint posterior distributions with parameters accepted in this fashion. Fig. 1 illustrates the acceptance algorithm.

Estimating impact of interventions on breast cancer mortality. Once we have the joint posterior distributions for the various parameters, we can explore the impact of different interventions. For example, we can estimate breast cancer mortality in the absence of screening or adjuvant therapy by rerunning the simulation while assuming no use of the corresponding intervention.

We can also estimate the effectiveness of combinations of 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 who use screening mammography, we can estimate the potential impact on breast cancer mortality of future changes in the use 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.

Model Details

Modeling Breast Cancer Incidence

Breast cancer detected clinically. In each year starting in 1975, we consider each woman who is at least 20 years old and determine whether 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 possibility of a secular trend in incidence estimated from the age–period–cohort (APC) model *(10)*. However, this model is an estimate. Like all estimates it is subject to uncertainty. We consider this uncertainty explicitly by allowing for the possibility that the incidence is more nearly constant over time than that of the APC model. In particular, we generate a value from a uniform(0, 1) (prior) distribution and weigh APC incidence by this value with the complementary probability associated with constant incidence. Using a uniform(0, 1) prior distribution for this parameter assumes that little is known about its value a priori, and so all values between 0 and 1 are equally likely to be used in our model. A value of 1 implies the breast cancer incidence estimated by the APC model, whereas a value of 0 implies constant incidence over time. This method allows for the possibility that the APC model overestimates the background incidence and lets the actual observed data determine the weight attributed to the APC model.

Breast cancer detected by screening mammography. For a woman who has a screening mammogram in a particular 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 (Centers for Disease Control and Prevention [2002] and National Breast and Cervical Cancer Early Detection Program [NBCCEDP]; unpublished data). This probability also depends on whether it was her first mammogram. If it was not her first mammogram then this probability depends on the length 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 allow for breast cancer to be diagnosed clinically between screening mammograms (interval cases). For women who have had previous screening mammograms, the probability of an interval case of breast cancer depends on whether her previous mammogram was her first mammogram, the time since her last screening mammogram, her age and the current year *(19)*.

Modeling Survival

Baseline survival. For cancers detected in the absence of screening and not treated with either chemotherapy or tamoxifen, breast cancer survival to time t is $S_{ij}(t)$, for i = 1, 2, 3, 4, and age group j *(11)*. In view of uncertainty in this underlying survival distribution, we allow for the data to modify them. We do this by imposing a uniform(0.80, 1) prior distribution on the hazard of $S_{ij}(t)$ so that each value between 0.80 and 1 has an equal chance of being selected. That is, for the simulation we sample a value, say λ, from a uniform(0.80, 1) distribution and adjust each underlying survival distribution by the transformation $S^*_{ij}(t) = S_{ij}(t)^{\lambda}$. Thus, parameter λ enters multiplicatively in the hazard of death.

Table 1. Prior distributions for intervention effects

Parameter	Distribution	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 1–2	Uniform(0, 0.80)	0.40	0.23
Beyond Stage Shift 3–4	Uniform(0, 0.50)	0.25	0.14

Parameter λ is handled in the same way as other unknown model parameters: It is accepted as part of the posterior distribution if the simulated breast cancer mortality that results from using the particular parameter vector is accepted as being close to the actual breast cancer mortality.

Impact of interventions on survival. The prior distributions for the intervention effects are listed in Table 1. We sample a value from each of these prior distributions to yield a parameter vector, $\gamma = (\gamma_{TMX}, \gamma_{CMT}, \gamma_{BSS1}, \gamma_{BSS3})$, that we use throughout the simulation of a population. We assume that the beyond stage shift parameters for stage 1 and stage 2 are equal (to γ_{BSS1}) and for stage 3 and stage 4 are equal (to γ_{BSS3}). If a woman's cancer is ER positive and of stage 1, 2, or 3 and is treated with tamoxifen for 5 years, then $S^*_{ij}(t)$ is raised to the power $1-\gamma_{TMX}$, where γ_{TMX} is the reduction in hazard due to tamoxifen. The benefit of 2 years of tamoxifen is assumed to be 64% of the benefit of tamoxifen for 5 years [Early Breast Cancer Trialists Collaborative Group *(13)*]. If the cancer is stage 1, 2, or 3 and the woman is treated with chemotherapy, then $S^*_{ij}(t)$ is raised to the power $1-\gamma_{CMT}$, where γ_{CMT} is the reduction in hazard due to chemotherapy. Based on the overview results *(11)*, if the woman is aged 50 years or younger, we impose an additional 10% reduction in the hazard due to chemotherapy. If the cancer is screen-detected, then the survival distribution $S^*_{ij}(t)$ is raised to the power $1-\gamma_{BSSi}$, for i = 1, 2, 3, 4. Here $\gamma_{BSS1} = \gamma_{BSS2}$ is the reduction in hazard beyond stage shift for stage 1 (and 2) disease, and $\gamma_{BSS3} = \gamma_{BSS4}$ is the reduction in hazard beyond stage shift for stage 3 (and 4) disease. We assume that women with stage 4 disease receive no survival benefit from chemotherapy or hormonal therapy. This assumption is not exactly correct, but improvements in survival of the magnitude seen in clinical trials of metastatic breast cancer have a minimal effect on population mortality rates.

Once we have a full sample of parameters from the prior distributions, we simulate a population of women in 1975 and monitor them through the years, attributing the corresponding benefits to the women who use the interventions. If a woman is diagnosed with breast cancer, we determine her survival from breast cancer each year by using the model described above.

Screening Dissemination

We use the screening mammogram dissemination model *(20)* to determine whether a woman will have screening mammograms. If so then we use this screening mammography dissemination model to determine her screening schedule. We assume that all women age in discrete increments of one year.

Our model allows for immigration and emigration. For immigrants it is possible that the screening dissemination model assigns screening mammograms before the woman enters the U.S. population. Any such mammograms are ignored.

Tumor Characteristics

Screen-Detected Tumors

If a woman is diagnosed with breast cancer, the tumor is assigned American Joint Committee on Cancer (AJCC) stage (I–IV), nodal status (positive or negative), and estrogen receptor status (positive or negative) with the appropriate joint distribution. For a tumor detected by a screening mammogram, these characteristics are assigned based on the woman's age and her screening history using data from the BCSC (National Cancer Institute [2003] and Breast Cancer Surveillance Consortium [BCSC]; unpublished data).

Interval Tumors

We simulate breast cancer incidence 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 on the basis of 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) *(21)*, HIP *(15)*, CNBSS *(16,17)*, and results of two Scandinavian studies *(22,23)* to estimate the probability that an interval cancer is of a given stage. Nodal status and estrogen receptor status were assigned based on data from the BCSC (National Cancer Institute [2003] and Breast Cancer Surveillance Consortium [BCSC]; unpublished data). For those tumors detected more than 3 years after a screening mammogram, we assign the same tumor characteristics as for clinically detected tumors.

Clinically Detected Tumors

Characteristics of tumors that are detected by means other than screening mammography are determined from the 1975 data in SEER *(1)* as adjusted and described in chapter 5 of CISNET *(11)*. These data provide a mechanism for assigning AJCC disease stage. We determine nodal status based on data from HIP *(15)*, and we determine ER status from data from SEER *(1)*.

Treatment Dissemination

We use the treatment dissemination model developed by Mariotto et al. *(8,24)* 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 opinion (Theriault R, Carlson R, Stockdale F; personal communication [2003]). We assign an additional 14% survival benefit for women receiving taxanes *(25)*.

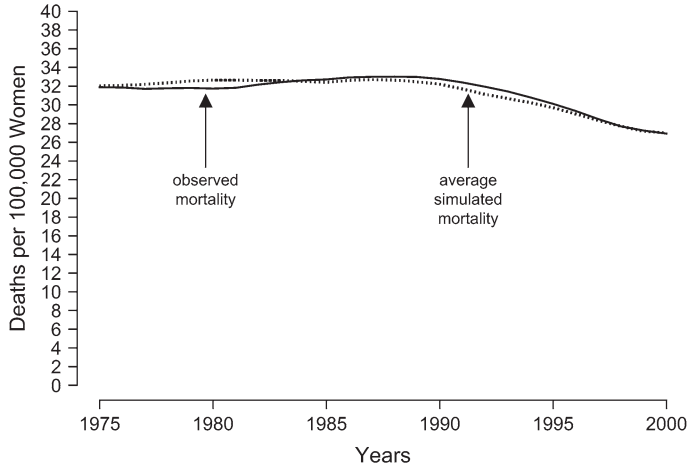

Fig. 2. Simulated breast cancer mortality (average). Observed U.S. mortality from 1975 through 2000 is shown as the **smooth heavy solid line**. The average of the 176 accepted simulations of mortality from 1975 through 2000 is shown as the **smooth dashed line**.

Results

We simulated approximately 80 000 populations, monitoring them from 1975 to 2000. Each of these simulations gave rise to a candidate set of parameters from the posterior distributions, as described earlier (see Fig. 1). Of these 80 000 simulations we accepted 176 using an acceptance window on each year of ±2.5 per 100 000 women and a window on the slope of ±0.17 per year. The corresponding parameters represent a sample of size 176 from the posterior distribution. The average breast cancer mortality from these 176 accepted simulations is compared with observed mortality in Fig. 2.

Posterior Distributions of Intervention Effects

The prior and posterior distributions for the four intervention parameters are shown in Figure 3. The means and standard deviations

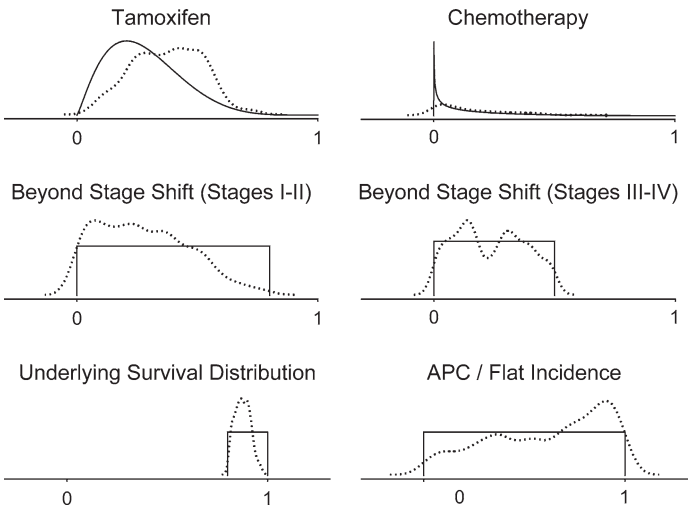

Fig. 3. Prior and posterior distributions of model parameters. Prior distributions are shown as **solid lines**. Posterior distributions are estimated from the 176 accepted simulations using kernel density estimation and are shown as **dashed lines**.

Table 2. Posterior estimates of model parameters

Parameter	Mean	Std Dev
Tamoxifen	0.37	0.14
Chemotherapy	0.15	0.14
Beyond Stage Shift 1–2	0.28	0.19
Beyond Stage Shift 3–4	0.23	0.14
Underlying Survival Dist	0.87	0.04
APC Incidence	0.61	0.29

of the posterior distributions of these four intervention parameters are shown in Table 2. As described above, we also place prior distributions 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. The means and standard deviations of these two parameters are also shown in Table 2.

From Table 2 we see that the posterior mean effect of tamoxifen is 0.37, corresponding to a 37% decrease in the hazard of breast cancer mortality due to the use of 5 years of tamoxifen for ER-positive tumors in actual clinical practice. The posterior mean effect of screening mammography beyond stage shift for stages I–II is 0.28. So screening mammography provides an estimated additional reduction in hazard of 28% for those women who are diagnosed with stage I–II disease through screening. This latter reduction is also in addition to any benefit that would be achieved due to the cancer's being detected at an earlier stage than it might have been if detected clinically.

The posterior means of the effect of chemotherapy and the benefit of screening mammography beyond stage shift for stage III–IV disease are similar to the prior means. For example, the posterior estimate of the reduction in hazard of breast cancer mortality the actual clinical use of (nontaxane) chemotherapy is 15%, and the reduction in the hazard due to mammography beyond stage shift for stage III–IV disease is 23%.

Posterior Estimates of Background Survival and Incidence

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 effects of screening and treatment are in addition to this initial adjustment.

The age–period–cohort model estimates a secular trend in incidence of breast cancer in the absence of screening and adjuvant therapy. On the basis of the observed mortality and other inputs, our model allows for discounting the impact of the age–period–cohort (APC) model on estimating incidence of breast cancer. The posterior mean of the corresponding parameter is 0.61 (standard deviation = 0.29). So, on average our model uses only 61% of the increase in 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

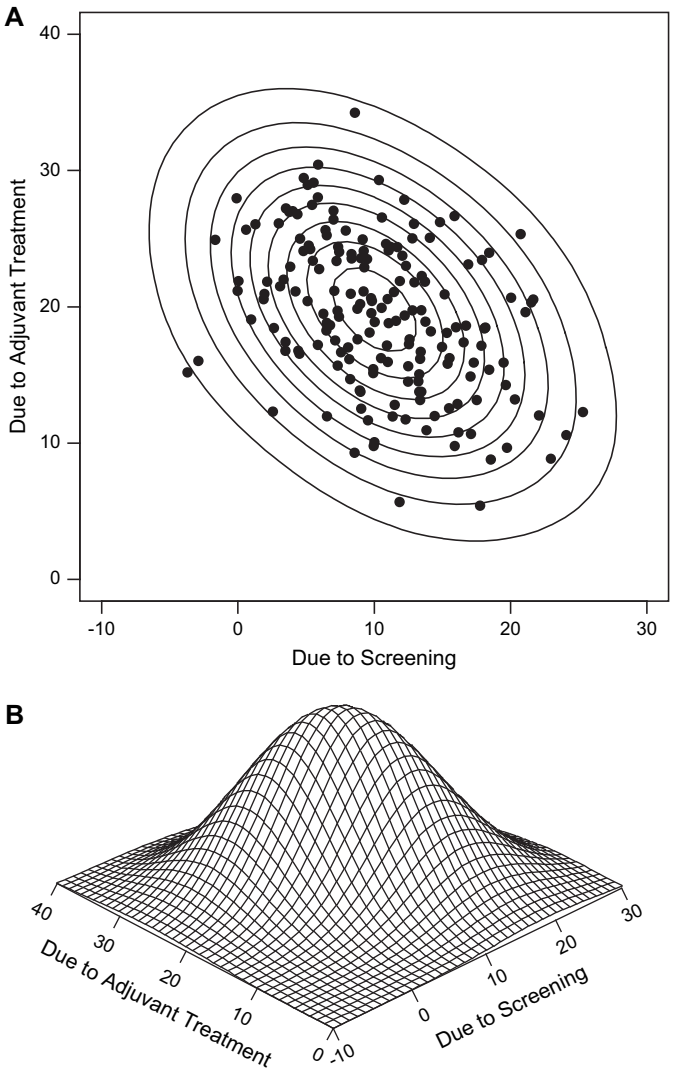

Fig. 4. A) Percent reduction in breast cancer mortality. Posterior joint distribution of percent reduction in breast cancer mortality for U.S. women aged 30–79 due to screening and treatment. The points are the results from the 176 accepted simulations. The contour plot is for the joint posterior probability distribution estimated from the 176 accepted simulations. The contours are derived by kernel density estimation, and contours are shown for equal intervals of height, that is, density. The concentric curves show the locus of percent reduction in breast cancer mortality due to screening and adjuvant therapy that have equal posterior probability density. The center of the figure has the highest posterior probability and corresponds to the top of the hill that is shown in panel B. **B**) Percent reduction in breast cancer mortality: three-dimensional rendering of the contour plot shown in panel A.

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.

Each of the 176 acceptances implies a reduction due to screening and a reduction due to therapy. The average of the 176 reductions due to screening is 10.6% ± 5.7% and of that due to therapy is 19.5% ± 5.4%, or an estimated 65% of the total reduction. Both estimates are subject to the variability shown in Fig. 4, which represents the kernel density estimate of the joint posterior distribution of the contribution of screening and treatment. Fig. 4, A, is a contour plot; each contour shows the locus of points having constant density and are placed at equidistant heights. The "hill" in Fig. 4, B, is a 3-dimensional rendering of the contour plot. There is an evident negative correlation (–0.40) between the two contributions.

By integrating the posterior density in Fig. 4 we conclude that the probability of a screening benefit is 90%. Similarly, we conclude a 99% posterior probability that treatment has a benefit and a 90% posterior probability that the reduction due to treatment is at least 10%.

Discussion

An ideal way to model the benefits of screening and therapy is to have a large database of women monitored for their whole lives. We would then know when individual women got mammograms, when—if ever—breast cancer was detected, the characteristics of the tumor, the treatment received, the progression (or not) of the disease, and the women's survival durations and causes of death. Unfortunately, we do not have such information for individual women. We have different data sources that address these different issues. The lack of woman-specific information leads to greater uncertainty in conclusions. We model such uncertainty explicitly using the Bayesian approach.

One source of information that we use is randomized treatment trials. Whether observations from such trials (or from randomized screening trials) apply to actual practice is open to question. Compliance is usually less clear in practice. And the patient population outside clinical trials is usually more heterogeneous and may differ from trial populations in a variety of ways. Moreover, historical trial results may not apply in actual practice because of technology changes and differences in training of mammographers and oncologists. We allow for uncertainty in applying the benefits of adjuvant therapy to clinical practice by inflating (threefold) the standard deviations of the estimates from randomized treatment trials.

Of particular importance as regards modeling the benefits of screening and therapy is that all trials of these two types of interventions have been conducted separately. In screening trials, the proportions of breast cancers treated with adjuvant therapy varied from one trial to another, and treatment received is not usually known for individual women. On the other hand, individual treatment is known in clinical trials, but method of detection of the individual cancers is not known. Perhaps there is a synergism between screening and treatment in that earlier detection allows for adjuvant therapy to be more effective. Or there may be a negative interaction in that the availability of effective systemic therapies lessens the benefit of early detection.

We make no assumptions about the benefits of screening, from randomized trials or otherwise. Instead, the benefits of screening are outputs of our model. We do use information from the HIP and CNBSS screening trials to form prior distributions for the differential survival of patients whose cancers were detected mammographically as opposed to other means. However, just as in the case of treatment benefits, the prior distributions of "beyond stage shift" parameters have inflated standard deviations compared with trial results.

The net result of explicitly considering the various sources of uncertainty is that our conclusions are uncertain in that our posterior distributions have moderately large standard deviations.

However, we can say with high probability that both screening and adjuvant therapy have contributed to the reductions in U.S. breast cancer mortality observed from 1975 (and especially from 1990) to 2000. Our best estimate is that about two-thirds of the reduction is due to therapy and one-third to screening. Fig. 4 shows the uncertainty associated with these estimates.

Figure 4 also shows the posterior relationship between the benefits of screening and therapy. It is difficult to discriminate between the two types of benefits because both screening and the use of adjuvant therapy were introduced into practice about the same time. Without a detailed analysis of dissemination and other aspects of these interventions, either would seem to explain the observed reduction in breast cancer mortality. Indeed, the negative correlation in Fig. 4 shows this effect: If screening explains less then therapy explains more, and vice versa. However, the standard deviations in Fig. 4 are not so large as to suggest that either intervention could explain all the observed reduction.

References

(1) SEER cancer statistics review, 1975–2001. Ries LA, Eisner MP, Kosary CL, Hankey BF, Miller BA, Clegg L, et al., editors. Bethesda (MD): National Cancer Institute; 2004.

(2) International Agency for Research on Cancer (IARC) (1999). The CANCER-Mondial Web site. Available at: http://www-dep.iarc.fr.

(3) Blanks G, Moss SM, McGahan CE, Quinn MJ, Babb PJ. Effect of NHS breast screening programme on mortality from breast cancer in England and Wales, 1990–8: comparison of observed with predicted mortality. BMJ 2000;321;665–9.

(4) Berry DA. Statistics: a Bayesian perspective. Belmont (CA): Duxbury Press; 1996.

(5) Berry DA, Stangl DK. Bayesian biostatistics. New York (NY): Marcel Dekker; 1996.

(6) Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian approaches to clinical trials and health-care evaluation. London (UK): John Wiley & Sons; 2004.

(7) Tanner MA (1996). Tools for statistical inference: methods for the exploration of posterior distributions and likelihood functions. 3rd ed. New York (NY): Springer; 1996.

(8) Mariotto AB, Feuer EJ, Harlan LC, Abrams J. Dissemination of adjuvant multiagent chemotheraphy and tamoxifen for breast cancer in the United States using estrogen receptor information: 1975–1999. J Natl Cancer Inst Monogr 2006;36:7–15.

(9) Rosenberg MA. Competing risks to breast cancer mortality. J Natl Cancer Inst Monogr 2006;36:15–9.

(10) Holford TR, Cronin KA, Mariotto AB, Feuer EJ. Changing patterns in breast cancer incidence trends. J Natl Cancer Inst Monogr 2006;36:19–25.

(11) Cronin KA, Mariotto AB, Clarke LD, Feuer EJ. Additional common inputs for analyzing impact of adjuvant therapy and mammography on U.S. mortality. J Natl Cancer Inst Monogr 2006;36:26–9.

(12) 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. Washington (DC); 2001.

(13) Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 1998;351:1451–67.

(14) Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 1998; 352:930–42.

(15) Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer: the health insurance plan project and its sequelae, 1963–1986. Baltimore (MD): Johns Hopkins University Press; 1988.

(16) Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. Can Med Assoc J 1992;147:1459–76.

(17) Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study 2: Breast cancer detection and death rates among women aged 50 to 59 years. Can Med Assoc J 1992;147:1477–88.

(18) Shen Y, Yang Y, Inoue LY, Munsell MF, Miller AB, Berry DA. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. J Natl Cancer Inst 2005;97:1195–203.

(19) Fracheboud J, Groenewoud JH, Boer R, Broeders MJ, Baan CA, Verbeek AL, et al. Landelijke evaluatie van bevolkingsonderzoek naar borstkanker in Nederland 2000 (VIII). Rotterdam: Instituut Maatschappelijke Gezondheidszorg; 2000. pp. 35–41.

(20) Cronin KA, Yu B, Kraphcho M, Miglioretti DL, Fay MP, Izmirlian G, et al. Modeling the dissemination of mammography in the United States. Cancer Causes Control 2005;16:701–12.

(21) Smart CR, Byrne C, Smith RA, Garfinkel L, Letton AH, Dodd GD, et al. Twenty-year follow-up of the breast cancers diagnosed during the breast cancer detection demonstration project. CA Cancer J Clin 1997;47:134–49.

(22) Hakkama M, Holli K, Isola J, Olli-Pekka K, Karkkainen A, Visakorpi T, et al. Aggressiveness of screen-detected breast cancers. Lancet 1995;345: 221–4.

(23) Frisell J, Eklund G, Hellstrom L, Somell A. Analysis of interval breast carcinomas in a randomized screening trial in Stockholm. Breast Cancer Research and Treatment 1987;9:219–25.

(24) 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. J Natl Cancer Inst 2002;94:1626–34.

(25) Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976–83.

Notes

Supported by NCI Cooperative Agreement U01-CA88278.

We gratefully acknowledge the National Cancer Institute–funded Breast Cancer Surveillance Consortium for providing information on breast cancer screening practices and characteristics of screen-detected tumors. (Grant numbers included the following: U01CA63740, U01CA86076, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, and U01CA70040.)

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.