ORIGINAL ARTICLE

Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer

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ABSTRACT

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BACKGROUND

We used modeling techniques to assess the relative and absolute contributions of screening mammography and adjuvant treatment to the reduction in breast-cancer mortality in the United States from 1975 to 2000.

METHODS

A consortium of investigators developed seven independent statistical models of breast-cancer incidence and mortality. All seven groups used the same sources to obtain data on the use of screening mammography, adjuvant treatment, and benefits of treatment with respect to the rate of death from breast cancer.

RESULTS

The proportion of the total reduction in the rate of death from breast cancer attributed to screening varied in the seven models from 28 to 65 percent (median, 46 percent), with adjuvant treatment contributing the rest. The variability across models in the absolute contribution of screening was larger than it was for treatment, reflecting the greater uncertainty associated with estimating the benefit of screening.

CONCLUSIONS

Seven statistical models showed that both screening mammography and treatment have helped reduce the rate of death from breast cancer in the United States.

THE CANCER INTERVENTION AND SURveillance Modeling Network (CISNET) is a consortium of investigators sponsored by the National Cancer Institute whose purpose is to measure the effect of cancer-control interventions on the incidence of and risk of death from cancer in the general population. This report of the CISNET Breast Cancer Working Group provides estimates of the contributions of screening mammography and adjuvant treatment to the reduction in the rate of death from breast cancer among U.S. women from 1975 to 2000.

In 1975, the rate of death from breast cancer among women 30 to 79 years of age, adjusted for age to the 2000 population, was 48.3 deaths per 100,000 women. By 1990, the rate had increased slightly to 49.7 per 100,000, but then fell to 38.0 per 100,000 by 2000, a decrease of 24 percent from 1990.[1] Similar reductions have been observed in other countries.[2] Likely explanations for these reductions are early detection by mammographic screening and advances in treatment.

Screening can reduce the rate of death from breast cancer only when followed by treatment. Tumors that are detected by screening before they metastasize can be cured by surgery, and breast cancer detected at an early stage of metastasis can be effectively treated by chemotherapy.[3] Currently, most organizations recommend that women begin to undergo screening mammography in their 40s.[4-6] By the year 2000, about 70 percent of women over the age of 40 years reported undergoing mammography in the previous two years.[7]

Controversies over the value of screening mammography arose from questions regarding the quality of the randomized trials that evaluated the effectiveness of this approach.[6,8-10] Moreover, the most recent estimates of benefits of screening from some of these trials are substantially lower than earlier estimates.[9] Even if screening trials provided undisputed evidence of a reduced rate of death from breast cancer, it is unclear how such a finding would translate to the general population.

The use of adjuvant chemotherapy and tamoxifen for all stages of breast cancer has also increased. Randomized clinical trials have demonstrated survival benefits associated with the use of adjuvant therapies, with estimated reductions in the annual odds of death ranging from 8 percent to 28 percent, depending on the type and duration of therapy, the age of the patients, and the characteristics of the tumor.[11-13] However, the extent to which these benefits translate to the population outside the controlled conditions of clinical trials is unknown. Furthermore, whether advances in adjuvant treatment have diminished or enhanced the value of screening has not, to our knowledge, been analyzed previously.

Knowing whether screening, adjuvant therapy, or both have contributed to the recent reductions in the rate of death from breast cancer is important. Since no single national registry contains all the data needed to evaluate the effect of these interventions at the population level, a way of integrating relevant information from separate population databases is required. The National Institutes of Health selected seven groups to develop models of mortality from breast cancer in the United States. These models made use of the best information available from the period 1975 to 2000 as common sources of data but applied different modeling approaches. The results of these various approaches differed, but there were points of agreement in the overall conclusions.

METHODS

The National Institutes of Health used a competitive peer-review process to choose seven groups to model the effect of screening and treatment on trends in the incidence of and rate of death from breast cancer: the Dana–Farber Cancer Institute, Boston (model D); Erasmus University Medical Center, Rotterdam, the Netherlands (model E); Georgetown University, Washington, D.C. (model G); the M.D. Anderson Cancer Center, Houston (model M); Stanford University, Stanford, California (model S); the University of Rochester, Rochester, New York (model R); and the University of Wisconsin–Madison, Madison (model W).[14] The joint analysis was designed by the CISNET consortium of 43 investigators (listed in the Appendix). The seven groups worked independently to develop their models but interacted as a consortium to investigate shared problems and to facilitate comparisons by developing uniform reporting structures. These comparisons allowed the modelers to identify differences in approaches and underlying assumptions and helped identify errors, but the general modeling approach and model structures were not modified to achieve consistency among the seven groups. The National Cancer Institute prepared databases of the information used in all seven models; individual groups collected data required for their particular models. Data used by all seven groups are

publicly accessible, and additional detail related to the variables can be found on the CISNET Web site (http://cisnet.cancer.gov/).

The consortium's analyses relied on the incidence of breast cancer as reported by the Surveillance, Epidemiology, and End Results (SEER) program and the rate of death from breast cancer as reported by the National Center for Health Statistics (NCHS). Because neither SEER nor NCHS contains information on screening history or mode of detection and SEER underreports the use of adjuvant therapy,[15] we incorporated additional databases concerning uses of screening and treatment and their efficacy in the population. In the first phase of our collaboration, we jointly developed and agreed on a set of common, or "base-case," variables to make possible comparisons of the models. The base-case variables and the data sources that were used to estimate them are listed in Table 1. Base-case variables include the background incidence of breast cancer in the absence of screening; the use of adjuvant treatment according to the patients' age, receptor status, calendar year, and tumor stage; and the risk of death from other causes. The background trend was estimated from the Connecticut Tumor Registry and SEER with the use of an age-period cohort model.[16]

Cohort-specific screening patterns were estimated from data on the percentage of the population that had ever undergone mammography, as reported in the National Health Interview Survey[7,17] and the screening patterns from population-based data on the use of mammography collected by the Breast Cancer Surveillance Consortium for the period 1994 to 2000.[18]

We used breast-cancer–specific survival curves derived from SEER for patients who received a diagnosis of breast cancer from 1975 to 1979 to estimate the rate of death among patients who did not receive chemotherapy or tamoxifen. The birth-cohort–specific rate of death from any cause, obtained from the Human Mortality Database,[19] was adjusted to exclude deaths from breast cancer.

Table 2 summarizes the base-case variables and other distinguishing characteristics of the models. Six of the seven groups estimated the benefit derived from screening and treatment with the use of a model of the natural history of invasive breast cancer, with three groups (models E, G, and W) also modeling progression from ductal carcinoma in situ to invasive disease. These three groups included ductal carcinoma in situ as an early, precursor stage of invasive breast cancer. The other models considered only invasive cancer.

Model M did not use a model of the natural history of the disease but used Bayesian updating of model variables — including the results of treatment trials — to estimate the contributions of the various interventions. Group M simulated screening and breast-cancer histories of women who were alive in 1975. The model allowed for the possibility that patients with tumors detected by screening would survive longer than patients whose cancer was detected on the basis of symptoms, even in the case of tumors at the same stage in both settings.

In all models except model R, patients with breast cancer either received adjuvant treatment (tamoxifen, chemotherapy, or both) or did not receive adjuvant treatment, depending on the year, the age of the patients, tumor stage, and estrogen-receptor status. A survival benefit of tamoxifen was applied only to patients with estrogen-receptor–

Table 1. Base-Case Variables.

Variable	Data Set*						
	NHIS	SEERPOC	BCSC	SEER 9	Connecticut Tumor Registry	Human Mortality Database	NCHS
Background incidence of breast cancer				+	+		
Dissemination of mammography	+		+				
Dissemination of treatment		+		+			
Death from other causes						+	+
Breast-cancer survival in 1975				+			
Breast-cancer prevalence in 1975				+	+		

* NHIS denotes National Health Interview Survey, SEERPOC SEER Patterns of Care, BCSC Breast Cancer Surveillance Consortium, and SEER 9 SEER Nine Registries. A plus sign indicates that the data set was used to estimate the variable in question.

Table 2. Specifications of the Models.*

Model Characteristic	Model D	Model E	Model G	Model M	Model S	Model R	Model W
Variables							
Total no.	9	21	12	6	10	11	40
No. calibrated according to observed mortality	0	0	0	—†	0	4	2
No. calibrated according to observed incidence of breast cancer	3	5‡	2	—†	2	3§	38
Type of model							
Simulation		+	+	+			+
Analytic	+						
Both					+	+	
Aspects included in natural-history modeling							
Explicit natural-history model	+	+	+		+	+	+
Progression							
From preclinical to clinical disease (unstaged)	+	+	+			+	
From ductal carcinoma in situ to local to regional to distant disease (staged)		+	+		+¶		+
Tumor growth (exponential or Gompertzian)		+			+	+	+
Direction of model							
Forward, from onset	+	+				+	+
Backward, from clinical incidence			+‖		+		
Diameter of tumor when fatal		+					
Stage at diagnosis							
AJCC stage	+	+**		+			
SEER historical stage			+		+	+	+
Covariates for sensitivity of screening mammography							
Age at screening	+	+	+	+			+
Calendar year (or birth cohort)	+	+		+			+
Tumor size		+			+	+	+
Breast density					+		
Preclinical stage at screening	+		+				
Covariates for breast-cancer survival after diagnosis							
Age- and stage-specific survival curves	+		+	+††			+‡‡
Age-, stage-, and size-specific survival curves					+	+	
Cure (or no cure) based on tumor-diameter threshold		+					+
Lead-time guarantee (i.e., death from cancer not allowed during lead time)	+	+	+		+		+
Allowed survival benefit in addition to stage shift		+		+	+	+	
Covariates for treatment benefit after diagnosis (independent of screening)							
Estrogen-receptor status	+		+	+	+		+
Age	+	+		+	+	+	+
Year						+	

* D denotes Dana–Farber Cancer Institute, E Erasmus University Medical Center, G Georgetown University, M M.D. Anderson Cancer Center, S Stanford University, R University of Rochester, W University of Wisconsin–Madison, and AJCC American Joint Committee on Cancer. A plus sign indicates that the model had the characteristic in question.
† Posterior distributions were found with the use of Bayesian rejection sampling.
‡ The natural-history variables were estimated with the use of incidence data from the Two-County Swedish Study,[20] not SEER data.
§ This number was estimated from the Canadian National Breast Screening Studies CNBSS I and II[21,22] and calibrated according to SEER incidence data.
¶ This model did not include in situ breast carcinoma.
‖ Preclinical onset was determined through the selection of sojourn time from an exponential distribution.
** The stage was driven by size alone, estimated with the use of AJCC data through the calibration of nodal status and metastasis status to base-case stage-distribution variable.
†† 1975 Survival estimates were modified by a "drift" term.
‡‡ If not cured, disease was assumed to progress to a late stage, with survival characteristics of SEER distant disease.

positive tumors and depended on the duration of treatment (two or five years). The estimated relative-risk ratios for death from any cause were 0.82 for two years of tamoxifen therapy and 0.72 for five years of therapy.[13] The relative-risk ratio for chemotherapy depended on the age at detection: 0.73 for women younger than 50 years of age, 0.86 for women 50 to 59 years of age, and 0.92 for women 60 years of age or older.[11]

The University of Rochester group (Group R) used SEER data to calibrate their model according to the effect of treatment and the change in survival over time, controlling for age, tumor size, and clinical stage. Thus, the treatment variable in model R included not only adjuvant therapy but also the possibility that surgical and radiation-therapy procedures and patient care more generally resulted in prolonged survival for patients with breast cancer.

All the models measured the contribution or effect of various factors, such as the use of screening and the reduction in the relative-risk ratio for death owing to five years of tamoxifen therapy. The modelers had to estimate the effect of these factors. Three models (models M, R, and W) were calibrated according to the observed rate of death from breast cancer in the United States, in that they gave more weight to data that produced results consistent with the observed rates from 1975 to 2000. The other four groups did not fit variables on the basis of the observed rate of death from breast cancer in the United States but instead relied on a variety of data sources and processes to derive mortality trends. More detailed descriptions of the individual models are available in the Supplementary Appendix (available with the full text of this article at www.nejm.org) and at http://cisnet.cancer.gov/resources/.[23]

To produce estimates of the effects of screening and adjuvant therapy from 1975 to 2000, the models were used to simulate trends in the incidence of and rate of death from breast cancer under four scenarios: no screening and no adjuvant therapy; use of base-case screening, but no adjuvant therapy; no screening, but base-case use of adjuvant therapy; and base-case screening and base-case use of adjuvant therapy ("base-case" corresponds to the estimated actual use of screening and adjuvant therapy from 1975 to 2000). The models estimated the contribution of screening in the absence of treatment by comparing the first and second scenarios, the effect of treatment in the absence of screening by comparing the first and third scenarios, and the effect of both screening and treatment by comparing the es-
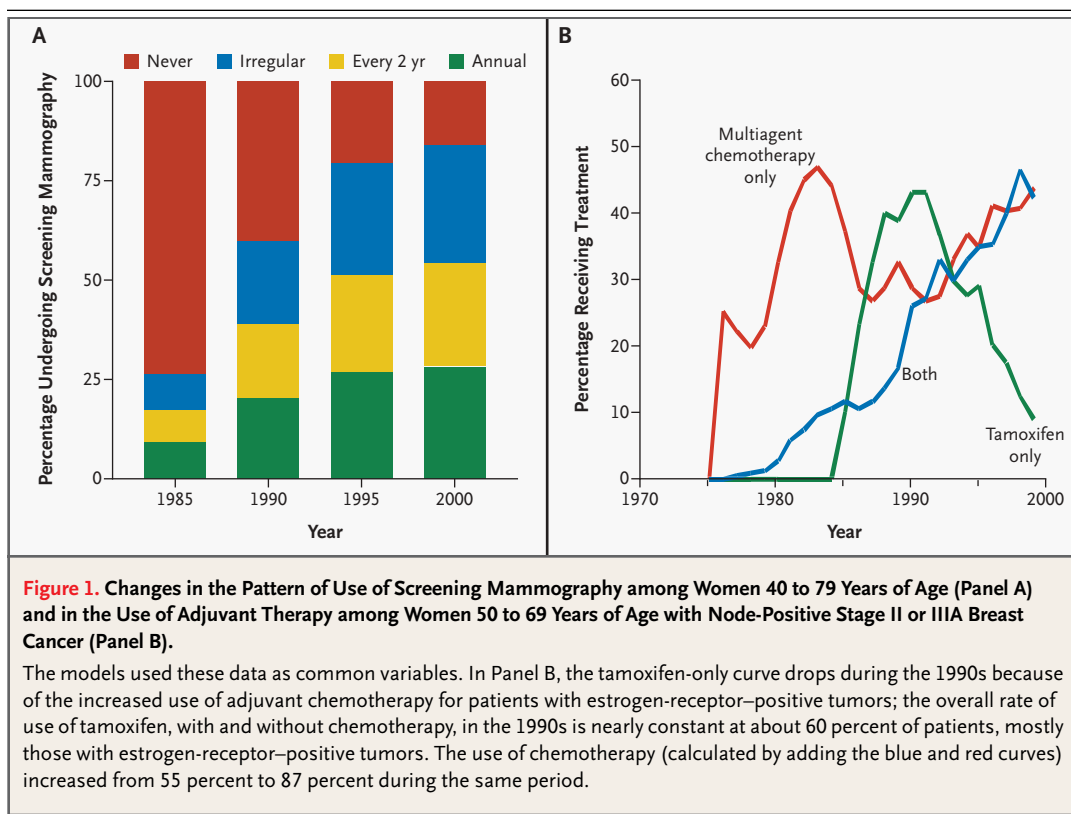
timated individual contributions with the combined contribution as estimated by comparing the base-case (fourth) scenario with the first scenario.

The models provide estimates of absolute reductions in the rate of death in 2000 owing to the use of tamoxifen, chemotherapy, these two treatments combined, screening, and all these factors combined. We present and plot the seven pairs of estimates (declines in the rate of death from breast cancer due to screening and adjuvant therapy) that were produced by the models. For the purposes of representing the uncertainty in these estimates, we regarded these seven pairs to be a sample from a larger population of possible model results. Using a statistical method called kernel estimation,[24] we estimated the distribution of this larger population. We used a bivariate normal kernel with a standard deviation and correlation taken from the data plot of the seven estimates.

RESULTS

Figure 1A shows the use of screening (annual, every two years, irregular, and never) among women who were at least 40 years of age in calendar years 1985, 1990, 1995, and 2000.[25] The use of screening increased dramatically during this period. The use of adjuvant treatment depended on the calendar year, the age of the patients, the tumor stage, and estrogen-receptor status.[26] These data were derived from SEER treatment information adjusted for underreporting as assessed from SEER patterns-of-care studies.[15] Figure 1B shows representative curves describing the use of treatment for node-positive stage II or stage IIIA disease among women 50 to 69 years of age. The percentage of women who received chemotherapy increased from essentially 0 percent in 1975 to about 80 percent in 2000. Similarly, the use of tamoxifen increased from essentially 0 percent in 1975 to about 50 percent in 2000; this drug was used mainly in patients with estrogen-receptor–positive tumors.

Figure 2A shows the rates of death from breast cancer from 1975 to 2000 as estimated by the seven models, in comparison with the actual rate in the United States. Models that were calibrated according to the actual mortality rate (models M, R, and W) tend to fit better than those that were not calibrated in this manner. However, the shapes of the seven curves are similar. Moreover, Figure 2A shows that all models predict similar proportional reductions in mortality from the combination of screening and adjuvant therapy. Figure 2B shows the age-adjusted

Figure 1. Changes in the Pattern of Use of Screening Mammography among Women 40 to 79 Years of Age (Panel A) and in the Use of Adjuvant Therapy among Women 50 to 69 Years of Age with Node-Positive Stage II or IIIA Breast Cancer (Panel B).

The models used these data as common variables. In Panel B, the tamoxifen-only curve drops during the 1990s because of the increased use of adjuvant chemotherapy for patients with estrogen-receptor–positive tumors; the overall rate of use of tamoxifen, with and without chemotherapy, in the 1990s is nearly constant at about 60 percent of patients, mostly those with estrogen-receptor–positive tumors. The use of chemotherapy (calculated by adding the blue and red curves) increased from 55 percent to 87 percent during the same period.

rate of death from breast cancer in the absence of screening or adjuvant treatment or both for a single model. We selected Model W for this demonstration because its results were typical. This figure shows that the estimated rate of death from breast cancer in the absence of screening and adjuvant therapy would have increased by about 30 percent from 1975 to 2000. This increase derives from the modeled background trend in the incidence of breast cancer in the absence of screening.

Table 3 gives the estimated reductions in the rate of death in 2000 owing to the use of tamoxifen therapy, chemotherapy, both therapies combined, screening, and the overall combination. The decline in the rate of death from breast cancer in 2000 attributable to the combination of screening and adjuvant therapy ranges from 24.9 percent to 38.3 percent, which because of the increasing background trend (that is, with no screening) is larger than the actual decline of 21.3 percent from 1975 to 2000. However, in these models, the relative contributions of screening and treatment to the reduction in the rate of death from breast cancer are insensitive to variations in the background trend of the incidence of breast cancer. We estimated that screening as practiced in the United States reduced

the rate of death from breast cancer in the range of 7 to 23 percent across the seven models, with a median of 15 percent. The percentage of the reduction attributable to adjuvant therapy was in the range of 12 to 21 percent, with a median of 19 percent. The combination of screening and adjuvant therapy reduced the rate of death by an estimated 25 to 38 percent, with a median of 30 percent. For each of the seven models, the combination of screening and adjuvant therapy reduced the rate of death by slightly less than the sum of the contributions from screening and adjuvant therapy alone. As indicated in Table 3, the proportion of the decrease in the rate of death from breast cancer that was attributable to screening ranged from 28 percent to 65 percent, with a median of 46 percent.

Figure 3A shows a contour plot of the estimated distribution of a larger population of model results from which our seven models represent a sample. When considering the results of all seven models, the most likely conclusion is that the contributions of screening and adjuvant treatment are similar. The spread of the distribution shown in Figure 3B reflects the uncertainty that is present in the available data and the differences in the modeling approaches.
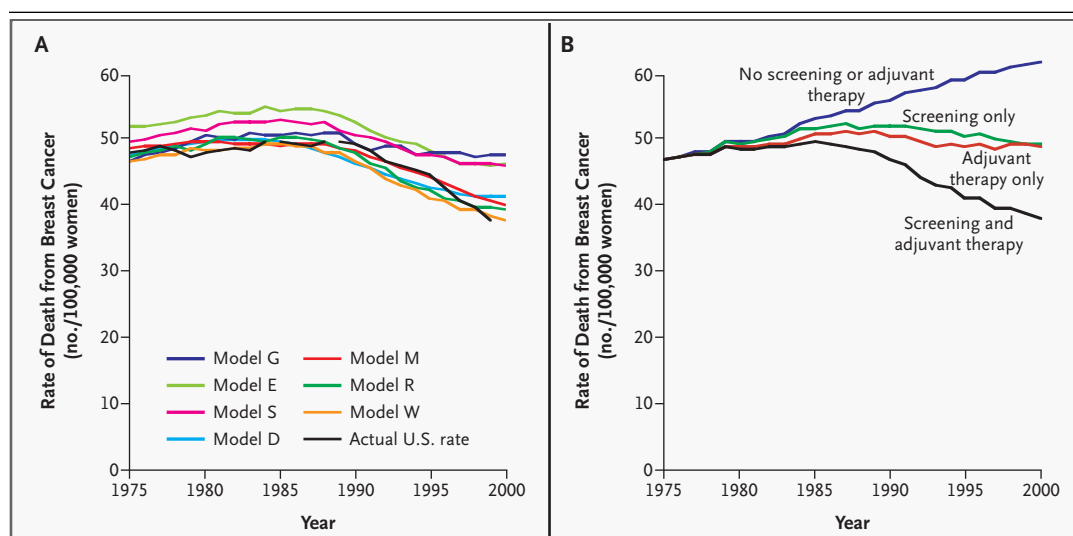
Figure 2. Estimated and Actual Rates of Death from Breast Cancer among Women 30 to 79 Years of Age from 1975 to 2000 (Panel A) and under Hypothetical Assumptions about the Use of Screening Mammography and Adjuvant Treatment (Panel B).

Panel A, which compares the model-based results with the actual rates in the United States from 1975 to 2000, shows the variability across the model estimates. Some of the models were calibrated according to the observed rate of death from breast cancer in the United States, and some were not. Panel B shows the results from model W (the University of Wisconsin–Madison) of estimated mortality trends for the four scenarios considered: no screening and no adjuvant treatment; base-case screening, but no adjuvant treatment; no screening, but base-case adjuvant treatment; base-case screening and adjuvant treatment. Rates in both panels are age-adjusted to the 2000 U.S. standard.

Table 3. Estimated Reductions in the Rate of Death from Breast Cancer in 2000 Attributed to Adjuvant Treatments and Screening.*

Model	Tamoxifen	Chemotherapy	Both Therapies	Screening	Overall
		percent (percent of reduction)			
D (Dana–Farber Cancer Institute)	6.1	6.1	12.0 (35)	22.7 (65)	32.9
E (Erasmus University Medical Center)	12.0	9.6	20.9 (58)	15.3 (42)	30.9
G (Georgetown University)	7.7	7.0	14.6 (54)	12.4 (46)	24.9
M (M.D. Anderson Cancer Center)	10.7	9.5	19.5 (65)	10.6 (35)	27.5
R (University of Rochester)	NA	NA	19.0 (72)	7.5 (28)	25.6
S (Stanford University)	8.9	6.9	14.9 (47)	16.9 (53)	29.9
W (University of Wisconsin–Madison)	12.5	8.9	20.8 (51)	20.3 (49)	38.3

* Values are point estimates from each model; percentages in parentheses are the percentages of the overall reduction that are attributable to treatment or screening. NA denotes not applicable.

DISCUSSION

We present results from seven models that were developed to estimate the effect of screening mammography and adjuvant therapy on the rates of death from breast cancer from 1975 to 2000 in the United States. The models used common sources of data, but their approaches and assumptions differed. Despite these differences, all seven groups concluded that screening and treatment have contributed to the observed decline in the rate of death from breast cancer and that the decline can be explained by a combination of screening and therapy and not by either one alone.
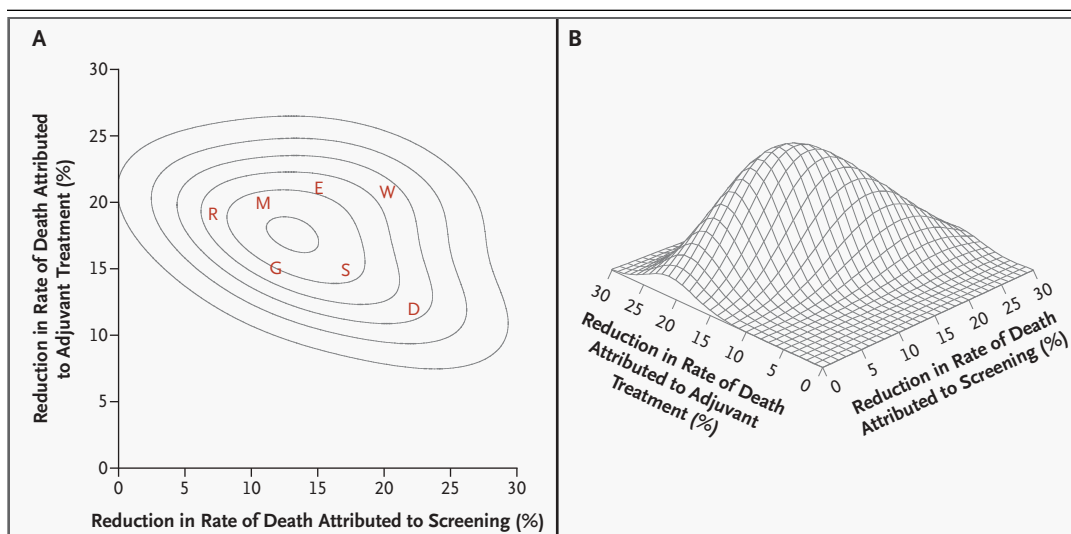
Figure 3. Estimated Joint Distribution of the Reduction in the Rate of Death from Breast Cancer among U.S. Women 30 to 79 Years of Age Attributed to Adjuvant Treatment and to Screening Mammography.

Values are compared with the rate of death in 2000 in the absence of both screening and treatment. Panel A shows the point estimates from the individual models (designated by their letters) provided in Table 3. The distribution contours for the combined model results are derived by kernel-density estimation; each contour shows the locus of points having a constant density. Each model's point estimate is assumed to be at the mean of its own bivariate normal density whose covariance structure was estimated from that of the seven model estimates. These seven densities were then averaged with equal weights to obtain an estimated posterior joint distribution. The "hill" in Panel B is a three-dimensional rendering of the contour plot. The height of the hill shows the likelihood of the corresponding reductions due to screening and treatment. For example, a point near the top of the hill (from 10 to 15 percent for screening and from 15 to 20 percent for treatment) is about twice as likely to be the actual state than is a point on the third largest contour in Panel A.

Although the conclusions of these models are qualitatively similar, their estimates vary. This variability is not surprising, given the diversity of the modeling approaches and assumptions. Although we strove for some consistency in modeling by using common sources of data concerning the use of mammography and adjuvant therapy over time, rates of death from causes other than breast cancer, and trends in background incidence that were not due to screening, some groups involved in our consortium used equivalent "input" variables suiting their models' structure. In addition, the groups used different data sets (surveillance information, results of meta-analyses of treatment trials, and data from screening trials) to estimate variables specific to their models. Some models focused on invasive breast cancer, and others accounted for ductal carcinoma in situ in the natural history of and screening for the disease. The differences in conclusions reflect uncertainties in the interpretation of available information, rather than contradictions among the models.

The variability in the quantitative conclusions across the models (Fig. 3 and Table 3) demonstrates an interplay between screening and treatment. Screening would have no benefit if not followed by treatment (including surgery), and treatment is likely to be more effective if cancer is detected at earlier stages by screening. Because the increasing use of adjuvant therapies and screening occurred over nearly the same periods, distinguishing between the two effects is not easy. A consequence of the concurrent introduction of the two interventions is that slight variations in modeling assumptions can result in marked changes in estimated effects. It is reassuring that the qualitative conclusions agree in the face of this sensitivity to assumptions.

The slight negative statistical correlation between the models' estimates of the relative contributions of the two interventions (Fig. 3) reflects the intuitive notion that either screening or therapy can provide some of the benefit not offered by the other intervention. For example, if adjuvant therapy explains more of the observed reduction in mortality, then less is left for screening to explain. One of the models (model M) specifically addressed within-

model uncertainty. The variability among models shown in Figure 3A is similar to the variability within the results of model M (not shown), suggesting that the variation among models is similar in magnitude to the variability within a single model's estimate after the uncertainties related to various aspects of the analysis are accounted for.

Addressing a complex public health question through the collaboration of seven modeling groups is unusual in health and medical-decision sciences.

The challenges of model comparisons were mitigated by this collaborative effort.

APPENDIX

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