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# Analysis of Breast Cancer Mortality in the US—1975 to 2019

Jennifer L. Caswell-Jin, MD, [1] Liyang P. Sun, MSc, [2] Diego Munoz, PhD, [2] Ying Lu, PhD, [2] Yisheng Li, PhD, [3] Hui Huang, MS, John M. Hampton, MSc, [5] Juhee Song, PhD, [3] Jinani Jayasekera, PhD, [6] Clyde Schechter, MD, MA, [7] Oguzhan Alagoz, PhD, [8] Natasha K. Stout, PhD, [9] Amy Trentham-Dietz, PhD, [5] Sandra J. Lee, ScD, [4,10] Xuelin Huang, PhD, [3] Jeanne S. Mandelblatt, MD, MPH, [11,12] Donald A. Berry, PhD, [3] Allison W. Kurian, MD, MSc, [1,13] and Sylvia K. Plevritis, PhD [2,14]

[1]Department of Medicine, Stanford University School of Medicine, Stanford, California
[2]Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, California
[3]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston
[4]Department of Data Sciences, Dana-Farber Cancer Institute, Boston, Massachusetts
[5]Department of Population Health Sciences and Carbone Cancer Center, University of Wisconsin–Madison School of Medicine and Public Health, Madison
[6]Intramural Research Program, National Institute on Minority Health and Health Disparities, National Institutes of Health, Bethesda, Maryland
[7]Department of Family and Social Medicine, Albert Einstein College of Medicine, Bronx, New York
[8]Department of Industrial and Systems Engineering, University of Wisconsin–Madison, Madison
[9]Department of Population Medicine, Harvard Medical School, Boston, Massachusetts
[10]Department of Data Sciences, Harvard Medical School, Boston, Massachusetts
[11]Department of Oncology, Georgetown University Medical Center, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC
[12]Georgetown-Lombardi Institute for Cancer and Aging, Washington, DC
[13]Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California
[14]Department of Radiology, Stanford University School of Medicine, Stanford, California
Corresponding author.

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**Corresponding Author:** Sylvia K. Plevritis, PhD, Stanford University School of Medicine, 318 Campus Dr, James H. Clark Center, Stanford, CA 94305-5405 (sylvia.plevritis@stanford.edu).

**Author Contributions:** Drs Caswell-Jin and Plevritis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Caswell-Jin and Mr Sun contributed equally to this work. Drs Kurian and Plevritis contributed equally to this work.

*Concept and design:* Caswell-Jin, Sun, Munoz, Schechter, Stout, Lee, Mandelblatt, Berry, Kurian, Plevritis.

*Acquisition, analysis, or interpretation of data:* Caswell-Jin, Sun, Munoz, Lu, Li, H. Huang, Hampton, Song, Jayasekera, Alagoz, Stout, Trentham-Dietz, Lee, X. Huang, Mandelblatt, Berry, Kurian, Plevritis.

*Drafting of the manuscript:* Caswell-Jin, Sun, H. Huang, Hampton, Jayasekera, X. Huang, Mandelblatt, Berry, Kurian, Plevritis.

*Critical review of the manuscript for important intellectual content:* Sun, Munoz, Lu, Li, Song, Jayasekera, Schechter, Alagoz, Stout, Trentham-Dietz, Lee, X. Huang, Mandelblatt, Berry, Kurian, Plevritis.

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## Key Points

### Question

What are the relative associations of breast cancer screening, treatment of stage I to III breast cancer, and treatment of metastatic breast cancer with improved breast cancer mortality in the US between 1975 and 2019?

### Findings

Improvements in treatment and screening after 1975 were associated with a 58% reduction in breast cancer mortality in 2019, from an estimated 64 deaths without intervention to 27 per 100 000 women (age adjusted). Approximately 29% of this reduction was associated with treating metastatic breast cancer, 25% with screening, and 47% with treating stage I to III breast cancer.

### Meaning

Based on 4 simulation models, breast cancer screening, treatment of stage I to III breast cancer, and treatment of metastatic breast cancer were each associated with reduced breast cancer mortality between 1975 and 2019 in the US.

## Abstract

### Importance

Breast cancer mortality in the US declined between 1975 and 2019. The association of changes in metastatic breast cancer treatment with improved breast cancer mortality is unclear.

### Objective

To simulate the relative associations of breast cancer screening, treatment of stage I to III breast cancer, and treatment of metastatic breast cancer with improved breast cancer mortality.

### Design, Setting, and Participants

Using aggregated observational and clinical trial data on the dissemination and effects of screening and treatment, 4 Cancer Intervention and Surveillance Modeling Network (CISNET) models simulated US breast cancer mortality rates. Death due to breast cancer, overall and by estrogen re-

ceptor and *ERBB2* (formerly *HER2*) status, among women aged 30 to 79 years in the US from 1975 to 2019 was simulated.

## Exposures

Screening mammography, treatment of stage I to III breast cancer, and treatment of metastatic breast cancer.

## Main Outcomes and Measures

Model-estimated age-adjusted breast cancer mortality rate associated with screening, stage I to III treatment, and metastatic treatment relative to the absence of these exposures was assessed, as was model-estimated median survival after breast cancer metastatic recurrence.

## Results

The breast cancer mortality rate in the US (age adjusted) was 48/100 000 women in 1975 and 27/100 000 women in 2019. In 2019, the combination of screening, stage I to III treatment, and metastatic treatment was associated with a 58% reduction (model range, 55%-61%) in breast cancer mortality. Of this reduction, 29% (model range, 19%-33%) was associated with treatment of metastatic breast cancer, 47% (model range, 35%-60%) with treatment of stage I to III breast cancer, and 25% (model range, 21%-33%) with mammography screening. Based on simulations, the greatest change in survival after metastatic recurrence occurred between 2000 and 2019, from 1.9 years (model range, 1.0-2.7 years) to 3.2 years (model range, 2.0-4.9 years). Median survival for estrogen receptor (ER)–positive/*ERBB2*-positive breast cancer improved by 2.5 years (model range, 2.0-3.4 years), whereas median survival for ER–/*ERBB2*– breast cancer improved by 0.5 years (model range, 0.3-0.8 years).

## Conclusions and Relevance

According to 4 simulation models, breast cancer screening and treatment in 2019 were associated with a 58% reduction in US breast cancer mortality compared with interventions in 1975. Simulations suggested that treatment for stage I to III breast cancer was associated with approximately 47% of the mortality reduction, whereas treatment for metastatic breast cancer was associated with 29% of the reduction and screening with 25% of the reduction.

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This simulation study estimates the association of breast cancer screening, treatment of stage I-III breast cancer, and treatment of metastatic breast cancer on changes in mortality due to breast cancer in US women for the period 1975-2019.

## Introduction

Breast cancer mortality in the US declined between 1975 and 2019 from an age-adjusted rate of 48 deaths per 100 000 women to 27 deaths per 100 000 women.[1,2] Advances in breast cancer treatment contributed to this decline.[3,4] More than 2000 phase 3 trials in breast cancer are registered in ClinicalTrials.gov, with approximately 1 new clinical trial added each day.[5] The US Food and Drug Administration approved 30 drugs for the treatment of breast cancer between 2010 and 2020. Of these, 26 were for metastatic disease and 4 were for stage I to III breast cancer.[6]

The Cancer Intervention and Surveillance Modeling Network (CISNET) developed simulation models to quantify the associations of screening mammography and stage I to III therapy with reductions in breast cancer mortality.[3,4] Since 2000, results of new randomized clinical trials for metastatic breast cancer demonstrated further improved patient outcomes,[7,8,9,10] yet the consequences of these changes have not been quantified. Therefore, the CISNET models were revised to specifically evaluate how recent treatments of metastatic breast cancer may have been associated with reduced breast cancer mortality in the US.

The revised CISNET models provided estimates of the relative magnitude of associations of treatment of stage I to III breast cancer, treatment of metastatic breast cancer, and screening mammography with the reduction in US breast cancer mortality rates between 1975 and 2019.

## Methods

We used 4 breast cancer simulation models developed within CISNET for this study: model D (Dana-Farber Cancer Institute), model M (MD Anderson Cancer Center), model S (Stanford University), and model W (University of Wisconsin–Harvard). Each model used a distinct approach, formulated through microsimulation or analytic framework or a combination of the two. Model D defined a set of disease states and implemented analytic formulations to estimate the association of interventions on transitions between these states, as well as on breast cancer incidence and mortality.[11,12] Model S was a microsimulation model that used an analytic formulation of a natural history model of tumor size and stage progression to model detection; treatments benefits were applied to baseline survival curves based on stage, age, and estrogen receptor (ER)/*ERBB2* (formerly *HER2*) status at detection.[13] Model W used a tumor growth model, calibrated to breast cancer incidence[14] and mortality[2] observed in the Surveillance, Epidemiology, and End Results Program (SEER) registry, as well as a cure fraction, distinct from the proportional hazards assumptions of models D and S.[15] Model M used a bayesian approach, assessing the probability distributions for unknown parameters, including treatment benefits, and fitting to observed breast cancer mortality.[2,16] The models used shared inputs (eTable 1 in Supplement 1). The range of results produced by the models served as a measure of uncertainty in modeling assumptions. The study was determined to not be human subjects research by the University of Wisconsin institutional review board, the site of the CISNET Breast Cancer Coordinating Center, so no participant consent was required.

### Incorporation of Metastasis Into the Models

Previous versions of the CISNET models simulated the events of breast cancer diagnosis and death from breast cancer; in the present study, diagnosis of metastatic recurrence and post-metastatic survival were simulated (Figure 1A). Categories of breast cancer by ER/*ERBB2* status (ER+/*ERBB2*–, ER+/*ERBB2*+, ER–/*ERBB2*+, and ER–/*ERBB2*–) were modeled separately.

To evaluate treatment of metastatic breast cancer, the models required a distribution of baseline survival curves after metastasis by ER/*ERBB2* status and age. These baseline survival curves represented survival in the absence of the modeled exposures of screening and systemic treatment after 1975; that is, they would include typical local therapy (surgery and in some cases radiation) for stage I to III disease and no therapy for metastatic disease. The associations of screening and treatment with survival could then be superimposed on these baseline survival curves. To infer the baseline distribution of time from diagnosis of breast cancer to diagnosis of metastatic recurrence and from diagnosis of metastasis to breast cancer death, we used the National Comprehensive Cancer Network Outcomes Database,[17] which included 82 252 patients with breast cancer, of whom 7740 had metastatic recurrence (eTable 2 and eFigure 1 in Supplement 1). To translate these actual outcomes from diagnosis of metastatic recurrence to death into baseline survival, we removed the treatment benefits (estimated from clinical trials), assuming proportional hazards. The distribution of time from diagnosis of metastatic recurrence to death of these patients was then subtracted from the overall breast cancer–specific survival used in previous versions of the models (eMethods and eFigure 2 in Supplement 1), generating baseline survival curves from diagnosis of breast cancer to diagnosis of metastatic recurrence. To assess the external validity of the model results produced by this approach on independent data, the survival results from model S were compared with the survival of patients treated in the control group of 5 phase 3 clinical trials of first-line therapies for metastatic breast cancer[9,10,18,19,20] (eFigure 3 in Supplement 1). Model W used the same distribution of survival from diagnosis of metastasis to breast cancer death as the other models, but a different approach to estimating time from diagnosis to metastatic recurrence. Specifically, model W used survival curves from diagnosis of breast cancer to diagnosis of metastatic recurrence to estimate the proportion of patients who were cured and then applied their tumor growth model to estimate the time of recurrence for simulated patients who were not cured (eMethods in Supplement 1).

As previously reported, the 4 models used a set of common inputs for competing mortality, breast cancer incidence, screening dissemination, stage I to III treatment benefits, and stage I to III treatment dissemination (eTable 1 in Supplement 1).[3] Instead of using overall survival benefits of treatments for stage I to III cancer, as in prior work,[3,4] we used the effects of stage I to III treatments on the risk of metastatic recurrence and the effects of metastatic treatments on survival after metastatic recurrence, both based on clinical trial reports (eTable 3 in Supplement 1). We included only metastatic treatments that had overall survival benefits demonstrated in clinical trials. Models S and W simulated the receipt of specific treatment regimens available during the simulated year and model D derived probability expressions that incorporated metastatic treatments (Figure 1B; eFigure 4 and eMethods in Supplement 1); model M instead applied mean benefits across available treatments in a given year, inferring these benefits through approximate bayesian computation. In models D, S, and W, when a patient received a line of therapy, the multiplicative benefits of the drugs included in that line of therapy were applied to that patient's baseline survival curve from diagnosis of metastatic recurrence to progression or death, assuming that breast cancer–

specific survival and progression-free survival curves were similar in the absence of treatment (eMethods in Supplement 1). Model M started by assuming a single hazard ratio representing the benefit from all metastatic therapy that was the standard of care in 2019 for each of the 4 categories of breast cancer by ER/*ERBB2* status, with that hazard ratio reduced proportionally before 2019, based on inputs used by the other models in each year (eMethods and eTable 4 in Supplement 1). The posterior distributions of the 4 ER/*ERBB2* specific hazard ratios in 2019 and other parameters in the model were determined with approximate bayesian computation,[16,21] comparing simulated breast cancer incidence and mortality for 1975-2019 with those from the SEER registry.[2,14]

## Estimates of Mortality Reduction and Its Association With Screening and Treatment

Consistent with prior work,[3,4] all models simulated breast cancer mortality for women aged 30 to 79 years from 1975-2019 based on the actual US population and reported estimated annual mortality age adjusted to the 2000 population. These results were compared with actual breast cancer mortality rates, age adjusted to the 2000 population, reported from death record data in the SEER registry.[2] The models reported breast cancer mortality under 8 intervention scenarios: (1) the absence of modeled interventions, (2) screening alone, (3) stage I to III therapy alone, (4) metastatic therapy alone, (5) screening and stage I to III therapy, (6) screening and metastatic therapy, (7) stage I to III therapy and metastatic therapy, and (8) all 3 interventions of screening, stage I to III therapy, and metastatic therapy. Because in these scenarios simulated patients with both de novo stage IV and recurrent metastatic disease could receive metastatic treatments, the benefit of metastatic therapy included both patients with de novo metastasis and metastasis developing after initial stage I to III diagnosis (recurrence). Mortality reduction was reported as the difference between the estimated age-adjusted mortality rate under an intervention scenario and the estimated age-adjusted mortality rate in the absence of any intervention, divided by the mortality rate in the absence of any intervention. The relative proportion of the mortality reduction attributed to each intervention was reported as the mortality reduction from the intervention divided by the mortality reduction from the sum of the first 3 intervention scenarios (eMethods in Supplement 1); this approach was approximately equal to the mean of the other possible approaches (eFigures 5 and 6 in Supplement 1) and maintained consistency with prior work,[3,4] which assessed the effect of 2, rather than 3, possible interventions. Estimates of mortality reduction were provided as means of the 4 models, weighted equally, followed by the range across models.

## Survival Estimates

Incorporating the event of metastatic recurrence into the models allowed them to assess measures of survival from metastatic recurrence to death, as well as from diagnosis to metastatic recurrence. These survival measures cannot be observed directly in SEER, which does not capture metastatic recurrence.[22] For survival from metastatic recurrence to death by calendar year of diagnosis of metastatic recurrence, we reported breast cancer–specific survival. For survival from diagnosis to metastatic recurrence by calendar year of initial diagnosis, we reported 5- and 10-year distant (metastatic) recurrence-free survival. To generate estimates for median breast cancer–specific survival after a diagnosis of metastatic recurrence over time, each model simulated the outcomes of a cohort of patients with ER+/*ERBB2*−, ER+/*ERBB2*+, ER−/*ERBB2*+, and

ER−/*ERBB2*− breast cancer conditional on diagnosis of metastatic recurrence in each calendar year. Similarly, to generate estimates for 5- and 10-year distant recurrence-free survival over time, each model simulated the outcomes of a cohort of patients with ER+/*ERBB2*−, ER+/*ERBB2*+, ER−/*ERBB2*+, and ER−/*ERBB2*− breast cancer conditional on diagnosis of stage I to III breast cancer in each calendar year. Simulated patients with de novo stage IV breast cancer were not included in these survival cohorts because survival after stage IV diagnosis is directly observable in SEER and therefore model-produced outputs were not needed to estimate it. Survival estimates were provided as means of the 4 models, weighted equally, followed by the range across models.

## Results

### Breast Cancer Mortality Reduction

Age-adjusted breast cancer mortality rates in the US were 48 per 100 000 women in 1975 and 27 per 100 000 in 2019.[2] The simulation models reproduced breast cancer mortality trends (Figure 2 A; eFigure 7 in Supplement 1). On average, the models calculated an age-adjusted breast cancer mortality rate of 49 deaths (model range, 45-52 deaths) per 100 000 women in 1975 and 27 deaths (model range, 26-28 deaths) per 100 000 women in 2019. The models also reproduced observed breast cancer incidence from SEER[14] (eFigure 8 in Supplement 1) and estimated that, with the increase in breast cancer incidence from 1975 to 2019, the age-adjusted breast cancer mortality rate in 2019 in the absence of new interventions since 1975 would have been 64 deaths (model range, 62-67 deaths) per 100 000 women. The models' relative estimates for the reduction in breast cancer mortality—associated with the combination of screening, stage I to III treatment, and metastatic treatment, and relative to breast cancer interventions available in 1975—were similar: across all models, in 2019 the overall absolute reduction in breast cancer mortality was 58% (model range, 55%-61%) (Table; eTable 5 in Supplement 1). Breast cancer mortality reduction varied by ER/*ERBB2* status (eTable 5 in Supplement 1). Age-adjusted breast cancer mortality reduction in 2019 was greatest for ER+/*ERBB2*+ disease (71%; model range, 68%-76%), reducing from 9.0 (model range, 8.0-9.8) per 100 000 women in the absence of intervention to 2.6 (model range, 2.3-2.7) per 100 000 women with screening, stage I to III therapy, and metastatic therapy. Age-adjusted breast cancer mortality reduction in 2019 was the smallest for ER−/*ERBB2*− disease (39%; range, 35%-42%), reducing from 9.5 (model range, 8.9-10.3) per 100 000 women in the absence of intervention to 5.8 (model range, 5.3-6.2) per 100 000 women with screening, stage I to III therapy, and metastatic therapy.

In 2019, with modeled interventions introduced since 1975 compared with their absence, 29% (model range, 19%-33%) of the reduction in overall breast cancer mortality was associated with metastatic treatment, 47% (model range, 35%-60%) with stage I to III treatment, and 25% (model range, 21%-33%) with screening (Table; eFigure 9 in Supplement 1). Breast cancer screening was associated with the greatest relative component of the mortality reduction for ER−/*ERBB2*− breast cancer, representing 40% of the mortality reduction (model range, 33%-49%), and with the smallest relative component for ER+/*ERBB2*+ breast cancer, representing 19% of the mortality reduction (model range, 16%-24%). In contrast to screening, metastatic treatment was associated with the smallest relative component of the mortality reduction for ER−/*ERBB2*− breast cancer at 19% of the total mortality reduction (model range, 6%-26%), with higher relative components for the

other ER/*ERBB2* categories: 30% of the mortality reduction (model range, 18%-35%) for ER+/*ERBB2*− breast cancer, 29% of the mortality reduction (model range, 20%-35%) for ER−/*ERBB2*+ breast cancer, and 29% of the mortality reduction (model range, 27%-31%) for ER+/*ERBB2*+ breast cancer. The relative associations of screening and metastatic treatment with overall breast cancer mortality reduction were comparable and both largely stable, whereas the relative component of stage I to III treatment was associated with increased mortality reduction from 2000 to 2019 (Figure 2B; eFigure 10 in Supplement 1).

## Temporal Change in Survival

First, survival from metastatic recurrence to death by calendar year of diagnosis of metastatic recurrence was evaluated. For 2019, median breast cancer–specific survival after a metastatic recurrence of breast cancer was estimated to be 3.2 years (model range, 2.0-4.9 years) regardless of ER/*ERBB2* status. Median breast cancer–specific survival after metastatic recurrence was 3.7 years (model range, 2.5-5.5 years) for ER+/*ERBB2*− breast cancer, 4.9 years (model range, 3.5-5.9 years) for ER+/*ERBB2*+ breast cancer, 3.5 years (model range, 2.5-5.1 years) for ER−/*ERBB2*+ breast cancer, and 1.6 years (model range, 1.0-2.1 years) for ER−/*ERBB2*− breast cancer (Figure 3A; eTable 6 in Supplement 1). Between 2000 and 2019, the period during which estimated median breast cancer–specific survival after metastatic recurrence changed the most in the simulation models (eTable 6 in Supplement 1), median breast cancer–specific survival after a metastatic recurrence across the 4 models improved from a mean of 1.9 years (model range, 1.0-2.7 years) to a mean of 3.2 years (model range, 2.0-4.9 years). The greatest improvement was observed for patients with ER+/*ERBB2*+ disease (mean improvement of 2.5 years; model range, 2.0-3.4 years), followed by patients with ER+/*ERBB2*− disease (1.6 years; model range, 0.6-3.0 years) and patients with ER−/*ERBB2*+ disease (1.6 years; model range, 0.8-2.8 years). The smallest improvement in survival was observed for patients with ER−/*ERBB2*− metastatic recurrent breast cancer (0.5 years; model range, 0.3-0.8 years).

Survival from diagnosis to distant metastatic recurrence was evaluated by calendar year of initial diagnosis. In 2019, the simulation models calculated that 5-year distant (metastatic) recurrence-free survival rates were 90% (model range, 86%-92%) for ER+/*ERBB2*− breast cancer, 92% (model range, 91%-94%) for ER+/*ERBB2*+ breast cancer, 84% (model range, 83%-86%) for ER−/*ERBB2*+ breast cancer, and 82% (model range, 76%-86%) for ER−/*ERBB2*− breast cancer. Five- and 10-year distant recurrence-free survival rates improved from 2000 to 2019 across ER+/*ERBB2*−, ER+/*ERBB2*+, ER−/*ERBB2*+, and ER−/*ERBB2*− disease (Figure 3B; eTable 7 in Supplement 1). The simulation models suggested that greatest improvements occurred in *ERBB2*+ breast cancers, with an absolute improvement in 5-year distant recurrence-free survival from 2000 to 2019 of 10.0% (range, 6.5%-13.5%) for ER+/*ERBB2*+ breast cancer and 11.3% (model range, 6.6%-14.7%) for ER/*ERBB2*+ breast cancer compared with 2.4% (model range, 1.2%-4.5%) for ER+/*ERBB2*− breast cancer and 2.8% (model range, −0.6% to 6.7%) for ER−/*ERBB2*− breast cancer.

## Discussion

CISNET modeling has previously reported, based on simulation models, that improvements in breast cancer screening and therapy for stage I to III breast cancer between 1975 and 2012 were associated with a reduction in breast cancer mortality in the US.[3,4] The updated CISNET models reported here describe the association of treatments for metastatic breast cancer with population-level mortality for the period 1975-2019. The results suggest that advances in the treatment of metastatic breast cancer were associated with lower rates of breast cancer mortality in the US. As of 2019, based on the simulation models, treatment for metastatic breast cancer was associated with about 25% of the approximately 58% reduction in breast cancer mortality, whereas mammogram screening was associated with approximately 25% of the reduction and stage I to III treatment was associated with approximately 50% of the reduction. The models also provide estimates of survival after metastatic recurrence, demonstrating improvements starting in approximately 2000 across ER+/*ERBB2*−, ER+/*ERBB2*+, ER−/*ERBB2*+, and ER−*ERBB2*− breast cancer. The degree of improvement from 2000 to 2019 varied, with survival improving by 2.5 years for ER+/*ERBB2*+ breast cancer and by 0.5 years for ER−/*ERBB2*− breast cancer.

It is unclear whether the benefits of metastatic breast cancer treatment are best measured by reduction in the population-level mortality rate or by change in survival, both of which are reported here. Survival estimates may vary according to time of diagnosis of disease or recurrence, whereas mortality rates are unaffected by these patterns. However, the reduction in population-level mortality may be uniquely associated with new treatments. For example, when a new treatment for metastatic disease is introduced, it may postpone the deaths of a cohort of individuals, leading to an acute decrease in mortality that rebounds in subsequent years. Thus, continual introduction of new treatments may be necessary to sustain a strong association of metastatic treatment with mortality reduction over time.

The largest mortality reduction from screening and treatment collectively was estimated in ER+/*ERBB2*+ breast cancer; and the smallest, in ER−/*ERBB2*− breast cancer. Similarly, the largest improvement in survival after metastasis was estimated in ER+/*ERBB2*+ disease; and the smallest, in ER−/*ERBB2*− disease. These differences may reflect the efficacy of targeted treatments of ER+ and *ERBB2*+ cancers.

Breast cancer screening accounts for an increasingly smaller proportion of breast cancer mortality reduction as improvements in stage I to III therapy continue.[1,3] Accordingly, screening accounts for the largest proportion of breast cancer mortality reduction in ER−/*ERBB2*− breast cancer, where treatment has least advanced. However, the absolute contribution of screening to mortality reduction remained consistent in the models, emphasizing that cancers diagnosed in the absence of screening were associated with poorer outcomes that cannot be overcome with modern treatments.

## Limitations

This study has several limitations. First, the model accuracy depends on the assumptions made, for which accurate data were not always available. Second, the models did not incorporate potential disparities, for example, by age, race, and ethnicity, in dissemination or efficacy of screening and treatments. Disparities in breast cancer screening, as well as timeliness and quality of treatment, may contribute to differential breast cancer mortality rates.[23] Third, treatment costs and their associations with outcomes were not included in the models.

## Conclusions

According to 4 simulation models, breast cancer screening and treatment in 2019 were associated with a 58% reduction in US breast cancer mortality compared with interventions in 1975. Simulations suggested that treatment for stage I to III breast cancer was associated with approximately 47% of the mortality reduction, whereas treatment for metastatic breast cancer was associated with 29% and screening with 25% of the reduction.

## Educational Objective: To identify the key insights or developments described in this article.

1. Between 1975 and 2019, age-adjusted mortality from breast cancer dropped from 48 to 27 deaths per 100 000. What does the Cancer Intervention and Surveillance Modeling Network hope to add to the understanding of improvements in breast cancer mortality?

    A. The network tracks breast cancer mortality and overall mortality to better clarify how breast cancer surveillance and intervention relates to mortality from all causes.
    B. The network tracks specific interventions across a broad span of facilities to develop deeper understanding of the relative efficacy of disparate therapies.
    C. Through simulation models, the network seeks to quantify the associations of screening mammography and therapy with reductions in breast cancer mortality.

2. What were the contributions of screening and treatment to breast cancer mortality reduction based on modeling for 2019?

    A. Almost all the reduction in breast cancer mortality was the result of improved detection through screening.
    B. Screening was associated with approximately 25% of the mortality reduction while treatment was associated with 3 times as much.
    C. Successful treatment of metastatic disease, reflecting improvements in operative and chemotherapeutic approaches, accounted for most of the mortality reduction.

3. How do the authors suggest the findings might be interpreted?

A. Although screening may account for smaller proportions of breast cancer mortality reduction, cancers diagnosed in the absence of screening were associated with poorer outcomes that cannot be overcome with modern treatments.
B. Because breast cancer screening is associated with a steadily smaller proportion of breast cancer mortality reduction, screening programs can be de-emphasized and greater attention turned to new treatment development.
C. Newly developed breast cancer therapies so markedly reduce breast cancer mortality that attention and funding can now be shifted to treatment related and more general causes of death.

## Notes

### Supplement 1.

**eMethods.** Model Inputs and Assumptions

eReferences.

**eTable 1.** Breast Cancer Model Input Parameters

**eTable 2.** NCCN Outcomes Database Cohort Characteristics

**eTable 3.** Breast Cancer Treatments and Their Efficacy, 1975-2019

**eTable 4.** Model M Raw Hazard Reductions for Overall Survival After Metastasis by ER/*ERBB2* Subtype and Year Based on First-Line Metastatic Therapy

**eTable 5.** Estimated Absolute Breast Cancer Age-Adjusted Mortality Rate and Its Reduction Relative to No Intervention by Subtype Across Eight Scenarios in 2019, by CISNET Model

**eTable 6.** Estimated Median Breast Cancer–Specific Survival After Distant Recurrence Over Time by Estrogen Receptor/ERBB2 Subtype, by CISNET Model

**eTable 7.** Estimated Five and Ten-Year Distant Recurrence-Free Survival Over Time by Estrogen Receptor/ERBB2 Subtype

**eFigure 1.** Breast Cancer–Specific Survival After Distant Recurrence by Subtype in the NCCN Outcomes Database as Compared to Model S

**eFigure 2.** Distant Recurrence-Free Survival by Subtype in the NCCN Outcomes Database as Compared to Model S

**eFigure 3.** Survival After Metastasis as Observed in Clinical Trials Versus Predicted From Model S

**eFigure 4.** Metastatic Therapy Usage by Year of Diagnosis of Metastatic Recurrence

**eFigure 5.** Summary of 127 Approaches to Calculate Contributions of Interventions to Breast Cancer Mortality Reduction

**eFigure 6.** Comparison of Symmetrical to Asymmetrical Approaches to Calculate Contributions of Interventions to Breast Cancer Mortality Reduction

**eFigure 7.** Estimated Age-Adjusted Breast Cancer Mortality Over Time Across Eight Scenarios Compared to Observed Mortality, by CISNET Model

**eFigure 8.** Estimated Breast Incidence, Average Across All Models and by Model, as Compared to SEER Breast Cancer Incidence

**eFigure 9.** Associations With Overall Breast Cancer Mortality Reduction of Screening, Stage I-III Treatments, and Metastatic Treatments in 2019, by CISNET Model and Within Model M

**eFigure 10.** Associations With Overall Breast Cancer Mortality Reduction of Screening, Stage I-III Treatments, and Metastatic Treatments Over Time, by CISNET Model

## Supplement 2.

Data Sharing Statement

## References


1. Cancer stat facts: female breast cancer. National Cancer Institute. Accessed September 20, 2022. https://seer.cancer.gov/statfacts/html/breast.html

2. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Mortality all COD, aggregated with state, total U.S. (1969-2019) <Katrina/Rita Population Adjustment>. Accessed January 31, 2023. https://seer.cancer.gov/data/

3. Plevritis SK, Munoz D, Kurian AW, et al.. Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000-2012. *JAMA*. 2018;319(2):154-164. doi: 10.1001/jama.2017.19130 [PMCID: PMC5833658] [PubMed: 29318276] [CrossRef: 10.1001/jama.2017.19130]

4. Berry DA, Cronin KA, Plevritis SK, et al.; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators . Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784-1792. doi: 10.1056/NEJMoa050518 [PubMed: 16251534] [CrossRef: 10.1056/NEJMoa050518]

5. Clinical trial search page. National Library of Medicine. Accessed July 7, 2023. https://clinicaltrials.gov/search?cond=breast%20cancer&term=phase%203

6. Arora S, Narayan P, Osgood CL, et al.. US FDA drug approvals for breast cancer: a decade in review. *Clin Cancer Res*. 2022;28(6):1072-1086. doi: 10.1158/1078-0432.CCR-21-2600 [PMCID: PMC8923912] [PubMed: 34711632] [CrossRef: 10.1158/1078-0432.CCR-21-2600]

7. Cortes J, O'Shaughnessy J, Loesch D, et al.; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) Investigators . Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet*. 2011;377(9769):914-923. doi: 10.1016/S0140-6736(11)60070-6 [PubMed: 21376385] [CrossRef: 10.1016/S0140-6736(11)60070-6]

8. Diéras V, Miles D, Verma S, et al.. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated *HER2*-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732-742. doi: 10.1016/S1470-2045(17)30312-1 [PMCID: PMC5531181] [PubMed: 28526536] [CrossRef: 10.1016/S1470-2045(17)30312-1]

9. Swain SM, Miles D, Kim SB, et al.; CLEOPATRA Study Group . Pertuzumab, trastuzumab, and docetaxel for *HER2*-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020;21(4):519-530. doi: 10.1016/S1470-2045(19)30863-0 [PubMed: 32171426] [CrossRef: 10.1016/S1470-2045(19)30863-0]

10. Hortobagyi GN, Stemmer SM, Burris HA, et al.. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. 2022;386(10):942-950. doi: 10.1056/NEJMoa2114663 [PubMed: 35263519] [CrossRef: 10.1056/NEJMoa2114663]

11. Lee SJ, Li X, Huang H, Zelen M. The Dana-Farber CISNET model for breast cancer screening strategies: an update. *Med Decis Making*. 2018;38(1 suppl):44S-53S. doi: 10.1177/0272989X17741634 [PMCID: PMC5929104] [PubMed: 29554465] [CrossRef: 10.1177/0272989X17741634]

12. Lee S, Zelen M. A stochastic model for predicting the mortality of breast cancer. *J Natl Cancer Inst Monogr*. 2006;(36):79-86. doi: 10.1093/jncimonographs/lgj011 [PubMed: 17032897] [CrossRef: 10.1093/jncimonographs/lgj011]

13. Munoz DF, Xu C, Plevritis SK. A molecular subtype-specific stochastic simulation model of US breast cancer incidence, survival, and mortality trends from 1975 to 2010. *Med Decis Making*. 2018;38(1 suppl):89S-98S. doi: 10.1177/0272989X17737508 [PMCID: PMC6538507] [PubMed: 29554473] [CrossRef: 10.1177/0272989X17737508]

14. SEER*Stat Database: Incidence - SEER Research Data. Accessed January 31, 2023. http://www.seer.cancer.gov

15. Alagoz O, Ergun MA, Cevik M, et al.. The University of Wisconsin breast cancer epidemiology simulation model: an update. *Med Decis Making*. 2018;38(1 suppl):99S-111S. doi: 10.1177/0272989X17711927 [PMCID: PMC5862066] [PubMed: 29554470] [CrossRef: 10.1177/0272989X17711927]

16. Huang X, Li Y, Song J, Berry DA. A Bayesian simulation model for breast cancer screening, incidence, treatment, and mortality. *Med Decis Making*. 2018;38(1 suppl):78S-88S. doi: 10.1177/0272989X17714473 [PMCID: PMC5711634] [PubMed: 28627297] [CrossRef: 10.1177/0272989X17714473]

17. Weeks J; National Comprehensive Cancer Network . Outcomes assessment in the NCCN: 1998 update. *Oncology (Williston Park)*. 1999;13(5A):69-71. [PubMed: 10370922]

18. Mehta RS, Barlow WE, Albain KS, et al.. Overall survival with fulvestrant plus anastrozole in metastatic breast cancer. *N Engl J Med*. 2019;380(13):1226-1234. doi: 10.1056/NEJMoa1811714 [PMCID: PMC6885383] [PubMed: 30917258] [CrossRef: 10.1056/NEJMoa1811714]

19. Lu YS, Im SA, Colleoni M, et al.. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/*HER2*- advanced breast cancer in MONALEESA-7: a phase III randomized clinical trial. *Clin Cancer Res*. 2022;28(5):851-859. doi: 10.1158/1078-0432.CCR-21-3032 [PMCID: PMC9377723] [PubMed: 34965945] [CrossRef: 10.1158/1078-0432.CCR-21-3032]

20. Emens LA, Adams S, Barrios CH, et al.. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. *Ann Oncol*. 2021;32(8):983-993. doi: 10.1016/j.annonc.2021.05.355 [PubMed: 34272041] [CrossRef: 10.1016/j.annonc.2021.05.355]

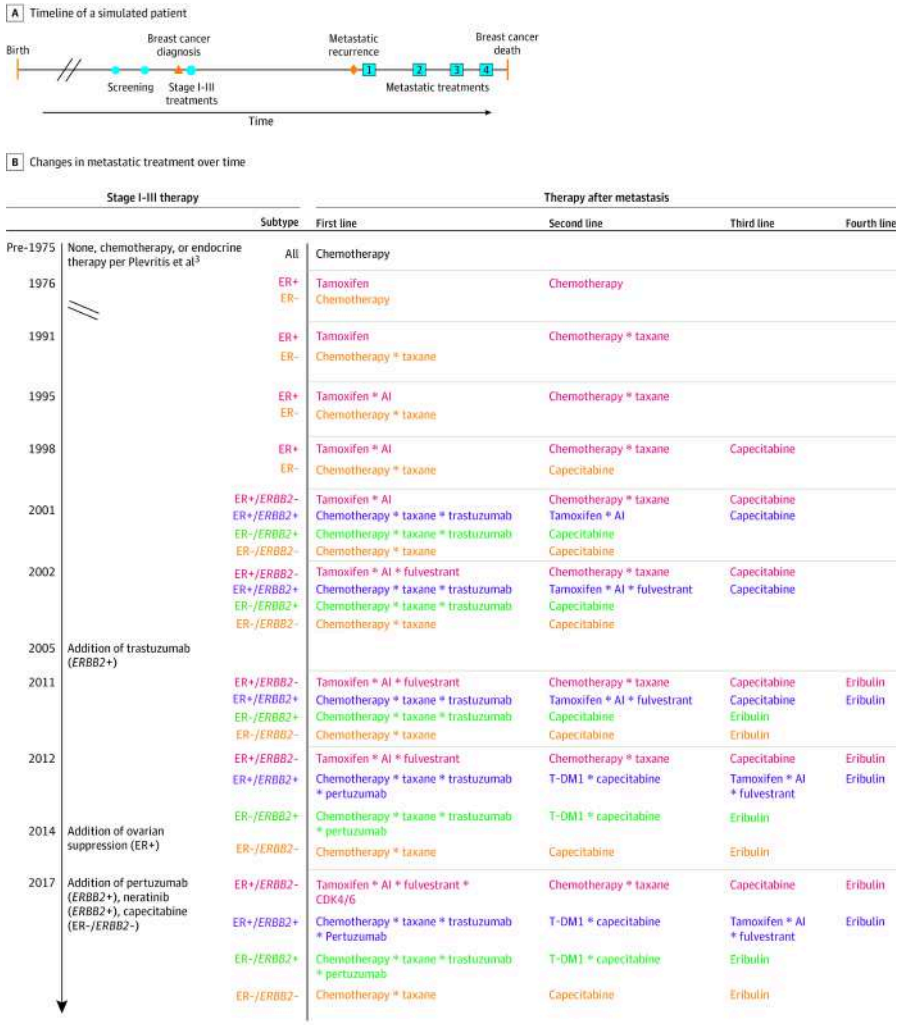
21. Berry DA, Inoue L, Shen Y, et al.. Modeling the impact of treatment and screening on US breast cancer mortality: a Bayesian approach. *J Natl Cancer Inst Monogr*. 2006;(36):30-36. doi: 10.1093/jncimonographs/lgj006 [PubMed: 17032892] [CrossRef: 10.1093/jncimonographs/lgj006]

22. Warren JL, Yabroff KR. Challenges and opportunities in measuring cancer recurrence in the United States. *J Natl Cancer Inst*. 2015;107(8):djv134. doi: 10.1093/jnci/djv134 [PMCID: PMC4580558] [PubMed: 25971299] [CrossRef: 10.1093/jnci/djv134]

23. Jatoi I, Sung H, Jemal A. The emergence of the racial disparity in US breast-cancer mortality. *N Engl J Med*. 2022;386(25):2349-2352. doi: 10.1056/NEJMp2200244 [PubMed: 35713541] [CrossRef: 10.1056/NEJMp2200244]

# Figures and Tables

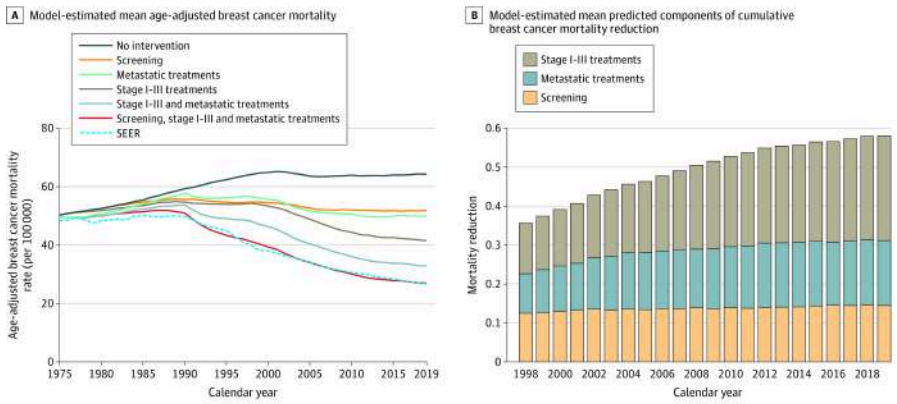
## Figure 1.




**Modeling Overview of Breast Cancer Diagnosis and Metastatic Recurrence**

A, Simulated events and interventions over time of a representative patient with breast cancer and metastatic recurrence. Triangle represents breast cancer diagnosis and diamond, metastatic recurrence. Interventions in blue: circles indicate screening; hexagon, stage I to III treatments; and squares, 4 representative metastatic treatments. B, Illustration of changes in metastatic treatment across multiple lines of therapy by calendar year (eTable 3 in Supplement 1). In 3 of the models (D, S, and W), benefits from multiple lines of metastatic treatments are applied sequentially based on time to progression from prior treatment and treatment options available at progression. When a clinical trial demonstrated an overall survival benefit of one therapy over a control therapy (rather than over placebo), the benefits (hazard ratios of overall survival) of each of those therapies were multiplied to determine the benefit of the new therapy. Model M instead applies a single hazard ratio intended to capture the benefit of all sequential lines of therapy at diagnosis of metastatic disease. AI indicates aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ER, estrogen receptor; and T-DM1, trastuzumab emtansine. Asterisks indicate that the benefits of these treatments are multiplied to determine the benefit of that line of therapy. See the Methods section for an explanation of each of the methods (D, M, S, and W).

## Figure 2.




**Association of Cancer Control Interventions With US Breast Cancer Mortality Reduction Over Time**

A, Model-estimated mean age-adjusted breast cancer mortality among women aged 30 to 79 years under various scenarios compared with observed breast cancer mortality from SEER from 1975 to 2019. The dashed line represents observed mortality (SEER data); solid lines represent model results. Model means are computed across all 4 models, equally weighted; individual model results are shown in eFigure 7 in Supplement 1. B, Model-estimated mean predicted components of cumulative breast cancer mortality reduction associated with screening, metastatic treatments, and stage I to III treatments from 1998 to 2019. All interventions are in addition to standard treatments available in 1975. Because local therapy was part of standard-of-care treatment for stage I to III disease in 1975, the benefit of screening occurs in the presence of standard local therapy. Model means are computed across all 4 models, equally weighted; individual model results are shown in eFigure 10 in Supplement 1. SEER indicates Surveillance, Epidemiology, and End Results Program.

## Table.

**Breast Cancer Mortality Reduction and Relative Contributions in 2019 by ER/*ERBB2* Status and Model**

| | Combined mortality reduction, % | Relative contribution to combined mortality reduction, %[a] | | |
|---|---|---|---|---|
| | | Screening | Stage I-III treatment | Metastatic treatment |
| **Overall** | | | | |
| Model D[b] | 59.0 | 32.5 | 34.6 | 32.9 |
| Model M[c] | 54.6 | 20.9 | 60.1 | 19.0 |
| Model S[d] | 57.3 | 25.4 | 44.1 | 30.5 |
| Model W[e] | 61.2 | 20.9 | 47.2 | 31.8 |
| Mean | 58.0 | 24.9 | 46.5 | 28.6 |
| **ER+/*ERBB2*−** | | | | |
| Model D | 60.4 | 33.1 | 32.1 | 34.8 |
| Model M | 56.1 | 20.6 | 61.2 | 18.2 |
| Model S | 59.2 | 25.0 | 42.7 | 32.2 |
| Model W | 61.9 | 19.4 | 46.7 | 33.9 |
| Mean | 59.4 | 24.5 | 45.7 | 29.8 |
| **ER+/*ERBB2*+** | | | | |
| Model D | 69.0 | 23.9 | 45.4 | 30.7 |
| Model M | 67.9 | 16.5 | 56.3 | 27.2 |
| Model S | 71.6 | 20.0 | 51.9 | 28.1 |
| Model W | 76.1 | 16.3 | 55.1 | 28.6 |
| Mean | 71.2 | 19.2 | 52.2 | 28.6 |
| **ER−/*ERBB2*+** | | | | |
| Model D | 64.9 | 26.0 | 39.1 | 34.9 |
| Model M | 52.7 | 21.0 | 59.4 | 19.6 |
| Model S | 57.3 | 25.6 | 43.1 | 31.3 |
| Model W | 65.7 | 23.4 | 45.5 | 31.1 |
| Mean | 60.1 | 24.0 | 46.8 | 29.2 |
| **ER−/*ERBB2*−** | | | | |
| Model D | 40.3 | 48.8 | 30.5 | 20.7 |
| Model M | 38.3 | 32.5 | 61.1 | 6.4 |
| Model S | 34.8 | 40.6 | 38.0 | 21.5 |

Abbreviation: ER, estrogen receptor.

[a] Relative to estimated baseline mortality in 2019 with no modeled intervention.

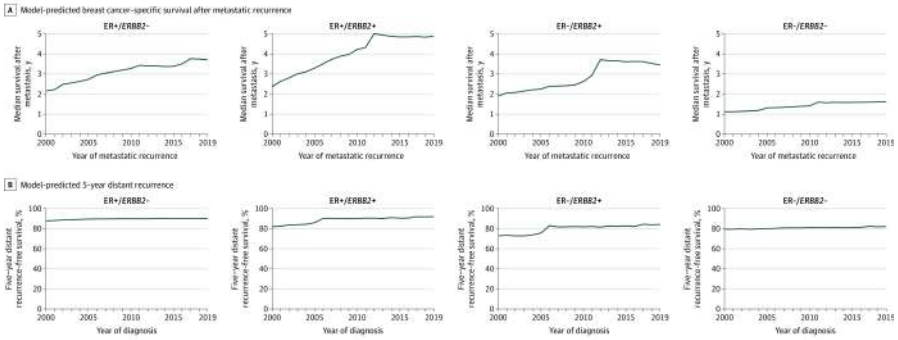
[b] Dana-Farber Cancer Institute (analytic formulations).

[c] MD Anderson Cancer Center (bayesian uncertainty of parameter inputs).

[d] Stanford University (microsimulations with proportional hazards).

[e] University of Wisconsin–Harvard (microsimulations with cure fraction).

## Figure 3.




**Estimated Breast Cancer–Specific Survival After Metastatic Recurrence and 5-Year Distant Recurrence-Free Survival by ER/*ERBB2* Status**

A, Model-estimated median breast cancer–specific survival after metastatic recurrence. Pertuzumab and trastuzumab emtansine were introduced for *ERBB2*+ subtypes in 2012. Model means are computed across all 4 models, equally weighted; individual model results are shown in eTable 6 in Supplement 1. B, Model-estimated mean 5-year distant recurrence-free survival. Trastuzumab was introduced for *ERBB2*+ subtypes in 2005. Model means are computed across all 4 models, equally weighted; individual model results are shown in eTable 7 in Supplement 1.