Association of Screening and Treatment With Breast Cancer Mortality by Molecular Subtype in US Women

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ABSTRACT

Importance

Given recent advances in screening mammography and adjuvant therapy, quantifying their separate and combined effects on US breast cancer mortality reductions by molecular subtype could guide future decisions to reduce disease burden.

Objective

To evaluate the contributions associated with screening and treatment to breast cancer mortality reductions by molecular subtype based on estrogen-receptor (ER) and human epidermal growth factor receptor 2 (ERBB2, formerly HER2 or HER2/neu).

Design, Setting and Participants

Six Cancer Intervention and Surveillance Network (CISNET) models simulated US breast cancer mortality from 2000 to 2012 using national data on plain-film and digital mammography patterns and performance, dissemination and efficacy of ER/ERBB2-specific treatment, and competing mortality. Multiple US birth cohorts were simulated.

Exposures

Screening mammography and treatment.

Main Outcomes and Measures

The models compared age-adjusted, overall, and ER/ERBB2-specific breast cancer mortality rates between 2000 and 2012 for women aged 30 to 79 years relative to the estimated mortality rate in the absence of screening and treatment (baseline rate); mortality reductions were apportioned to screening and treatment.

Results

In 2000, the estimated reduction in overall breast cancer mortality rate was 37% (model range, 27%-42%) relative to the estimated baseline rate in 2000 of 64 deaths (model range, 56-73) per 100 000 women: 44% (model range, 35%-60%) of this reduction was associated with screening and 56% (model range, 40%-65%) with treatment. In 2012, the estimated reduction in overall breast cancer mortality rate was 49% (model range, 39%-58%) relative to the estimated baseline rate in 2012 of 63 deaths (model range, 54-73) per 100 000 women: 37% (model range, 26%-51%) of this reduction was associated with screening and 63% (model range, 49%-74%) with treatment. Of the 63% associated with treatment, 31% (model range, 22%-37%) was associated with chemotherapy, 27% (model range, 18%-36%) with hormone therapy, and 4% (model range, 1%-6%) with trastuzumab. The estimated relative contributions associated with screening vs treatment

varied by molecular subtype: for ER+/ERBB2−, 36% (model range, 24%-50%) vs 64% (model range, 50%-76%); for ER+/ERBB2+, 31% (model range, 23%-41%) vs 69% (model range, 59%-77%); for ER−/ERBB2+, 40% (model range, 34%-47%) vs 60% (model range, 53%-66%); and for ER−/ERBB2−, 48% (model range, 38%-57%) vs 52% (model range, 44%-62%).

Conclusions and Relevance

In this simulation modeling study that projected trends in breast cancer mortality rates among US women, decreases in overall breast cancer mortality from 2000 to 2012 were associated with advances in screening and in adjuvant therapy, although the associations varied by breast cancer molecular subtype.

INTRODUCTION

Breast cancer mortality rates have been steadily declining over time in the United States (US).[1] Simulation models developed within the Cancer Intervention and Surveillance Network (CISNET) estimated that screening mammography and adjuvant therapy (treatment) contributed approximately equally to the reduction in breast cancer mortality from 1975 to 2000.[2] Since then, mammography has transitioned from plain-film to digital technology optimized for tumor detection.[3,4] At the same time, there have been advances in molecularly-targeted treatments based on expression of estrogen-receptor (ER) and human epidermal growth factor receptor 2 (ERBB2, formerly HER2 or HER2/neu), including aromatase inhibitors for ER+, and trastuzumab for ERBB2+ cancers. In addition, there have been advances in chemotherapy, particularly increasing use of taxanes.[5,6]

It is not known how screening and treatment advances have contributed to recent population-level, molecular subtype-specific breast cancer mortality rates. No single national registry contains sufficient information to assess this progress. Moreover, most clinical trials do not consider both screening and treatment effects, and do not readily translate to population effect. Given these circumstances, simulation modeling can be useful to integrate high-quality data from randomized-controlled trials, large observational studies, and population registries to estimate the relative contributions of advances on population-level mortality.[2]

In this report, six CISNET models compared the separate and combined contribution associated with screening and treatment on US breast cancer mortality rates by molecular subtype from 2000 and 2012.

METHODS

The Institutional Review Board at Georgetown University, the site of the CISNET Breast Cancer Coordinating Center, approved the study as exempt based on the use of de-identified data. The 6 CISNET models were Dana-Farber Cancer Institute (model D)[7], E Erasmus Medical Center (model E)[8], Georgetown University-Albert Einstein College of Medicine (model G-E)[9], MD Anderson Cancer Center (model M),[10] Stanford University (model S),[11,12] and University of Wisconsin-Harvard (model W-H).[13] Compared to earlier analyses[2,14,15] the models portray ER/ERBB2-specific subtypes,[11] include digital screening[3,4] and recent treatment advances,[16] and have updated incidence[17] and competing non-breast cancer mortality.[18] The modeling approach is summarized below; additional details are available in the Supplement and online.[19]

The models incorporated updated estimates of breast cancer incidence[17] and ER/ERBB2-specific survival trends in the *absence* of screening or treatment and then incorpo-

rated information on screening use and molecular subtype-specific treatment patterns to reproduce observed US incidence and mortality trends.[1,20,21] Screen-detection during the preclinical screen-detectable period could result in diagnosis of earlier-stage or smaller tumors than diagnosed via symptomatic detection. This could translate into lower breast cancer mortality. Molecular subtype, age-specific, and stage-specific treatment could reduce the hazards of breast cancer death (models D, GE, M, and S) or result in cure for some cases (models E and W-H).

Model Input Parameters

Each group used a common set of inputs [22] based on their specific model structure, prior research,[15] and assumptions to best reproduce US breast cancer incidence and mortality trends (Supplemental Table 1).[5,6,10-17,22-27] Five models used age-period-cohort (APC) analyses to estimate 1975-2012 breast cancer incidence rates in the absence of screening (baseline incidence rate)[17,25]; model M applied a Bayesian approach to extend 1975-1979 Surveillance Epidemiology and End Results (SEER) rates forward in time with a 4% (SD 0.2%) annual increase. Plain-film and digital mammography sensitivity data from the Breast Cancer Surveillance Consortium (BCSC) for 1994-2012 were used to estimate sensitivity for detection of invasive and DCIS cancers by age group, first vs subsequent screen, and time since last mammogram.

Screening dissemination was derived from national survey data for age at first screen and subsequent screening frequency by birth cohort.[23,24] Plain-film mammography was assumed before 2000. Digital mammography was phased-in starting in 2001 based on data from the BCSC (unpublished data) and the US Food and Drug Administration Mammography Quality Standards Act and Program.[28]

Molecular subtype-specific treatment dissemination was based on SEER patterns-of-care special studies for 1975-1996[26,27] and the National Comprehensive Cancer Network data for 1997 onwards[14,19]. Tamoxifen was used in the 1980s; aromatase inhibitor use began in 1997; taxanes in 1998; and trastuzumab in 2006. Treatment effectiveness was conditioned on stage and ER/ERBB2 status (and age, if applicable), based on clinical trials; all estimates assumed local therapy.[16]

Analyses

Each model simulated mortality rates under four intervention scenarios: 1) no screening or treatment (the baseline mortality rate); 2) screening alone; 3) treatment alone; and 4) combined screening and treatment. Rates were age-adjusted using the 2000 US Standard Population[29] and outcomes were reported for women ages 30-79.

The absolute mortality reductions associated with screening alone, treatment alone, or the combination in a given calendar year were calculated as the difference between the age-adjusted mortality rates predicted with intervention (scenarios 2, 3, or 4) and

the baseline mortality rate in that year (scenario 1). The percent mortality reduction (hereafter referred to as mortality reduction) in a given calendar year was calculated as this difference divided by the baseline mortality rate in that calendar year (scenario 1; Supplemental Table 2).

ER/ERBB2-specific mortality rates were computed by dividing the number of women who died of breast cancer with that subtype by the total breast cancer population at risk. In this manner, rates of all subtypes sum to the overall age-adjusted breast cancer mortality rate.

To estimate the separate contributions associated with screening and treatment to mortality reductions, we considered the modeled effects of screening alone and of treatment alone as a fraction of the combined modeled effect in each calendar year.

The *relative* contribution associated with screening versus treatment to the combination of both was computed as the ratio of the screening alone effect to the sum of the screening alone effect and the treatment alone effect; the relative contribution of treatment was calculated similarly. Alternative approaches for computing these relative contributions were considered, and the main conclusions were unchanged (Supplemental Methods and Supplemental Table 3).

When considering the mortality reductions associated with each treatment intervention (eg, chemotherapy, hormonal therapy, and trastuzumab) to their combination, the relative contribution associated with the various treatments were decomposed by first considering the chemotherapy contribution; then the hormonal therapy contribution for ER+ cases, given chemotherapy contributions; and lastly, the contribution associated with trastuzumab for ERBB2+ cases, given the other therapies.

To estimate relative contributions associated with the most recent advancements, we compared the mortality reduction from 2000 and 2012. We focused on this difference to remove the modeled effect of changes in the baseline rate during this period.

Uncertainty Analysis

All results were reported by model and summarized as the mean and range across models. The range provided a measure of uncertainty because each model has different assumptions and structures to represent unobservable factors such as baseline incidence rate and breast cancer natural history. Results consistent across models were considered robust.

RESULTS

Rates of mammography increased over time (Figure 1A), and plain-film was rapidly replaced by digital mammography starting in 2001 (Figure 1B). Treatment use varied by

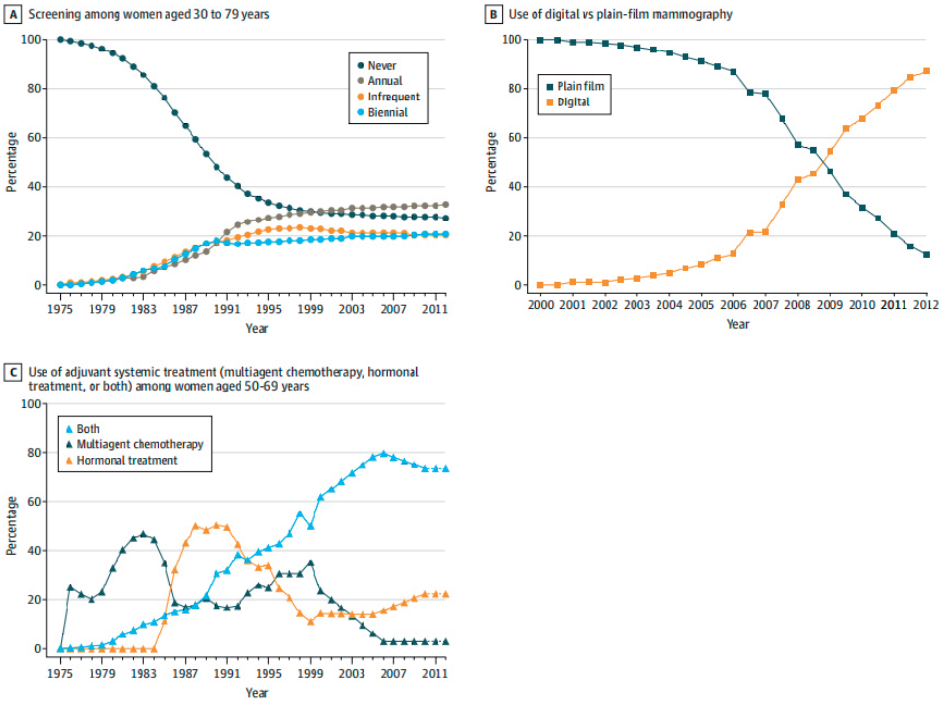

Figure 1 Dissemination of Screening Mammography, Type of Mammography, and Adjuvant Therapy 1975-2012

Panel A shows use of screening among US women ages 30-79 by calendar year based on data from multiple rounds of the National Health Interview Survey over time and Breast Cancer Surveillance Consortium (BCSC) data from 1994-2012. These observed data were used a targets in modeling dissemination of screening and intervals between screens. Note that the rate of never screened includes women ages 30-39.

Panel B illustrates the transition to use of digital vs. plain-film mammography over time using MQSA data on digital mammography facilities from the FDA and the BCSC, which includes over 2.3 million women, aged 30-79, with over 9.5 million mammograms, 95,000 breast cancer cases and 180,000 breast biopsies.

Panel C depicts use of adjuvant systemic treatment dissemination from 1975-2012 for an exemplar stage and set of molecular markers (node positive AJCC 6 stage 2b, ER+/ERBB2-) among women 50 to 69 years of age at diagnosis based on data from SEER special patterns of care studies and the National Comprehenisve Cancer Network. These data were used for all other combinations of ages, stages, and molecular subtypes.

Models used 2010 treatment dissemination data for subsequent years (indicated by dashed segments).

In general, in the 1980's and early 1990's multi-agent chemotherapy included primarily cytoxan, methotrexate, and 5-flourouricil (CMF) regimens; starting in the mid-1990's anthracycline-based regimens were included and increased in use, and in 1997 taxanes could be added to those regimens. Hormonal therapy began with tamoxifen in the 1980's and starting in 1997 also included aromatase inhibitors. Hormonal therapy could be used alone or in combination with multi-agent chemotherapy. Over time, there was an increasing use of both multi-agent chemotherapy and hormonal therapy. For women diagnosed with ERBB2+ tumors (not shown in this example), trastuzumab was disseminated independently of other treatments and, based on its immediate rapid uptake, all ERBB2+ patients were modeled as receiving trastuzumab beginning in year 2006.

molecular subtype, age, and stage, with high rates of dissemination of recent advances (Figure 1C). Incorporating these observed screening and treatment patterns, the models reproduced observed age-adjusted incidence (Supplemental Figure 1) and breast cancer mortality trends from 1975 to 2012 (Figure 2A). Predicted mortality trends for a representative model (Model G-E) illustrate that the mortality reduction associated with treatment alone increased faster than that associated with screening alone over time (Figure 2B).

Overall Breast Cancer Mortality in 2012

With the observed changes in screening technology and treatment regimens, we estimated a 49% (model range: 39%-58%) decrease in overall breast cancer mortality in 2012 relative to the estimated baseline rate in 2012 of 63 deaths (model range, 54-73) per 100,000 women (Table 1, Column 4; Supplemental Table 2). The estimated screening contribution to this mortality reduction was 37% (model range, 26%-51%), while treatment was 63% (model range, 49%-74%). The larger contribution associated with treatment vs. screening in 2012 was predicted in five of six models (Table 1, Columns 7-8).

The estimated 63% (model range, 49%-74%) relative contribution associated with treatment in 2012 consisted of 31% (model range, 23%-37%) from chemotherapy, 27% (model range, 18%-36%) from hormone therapy, and 4% (model range, 1%-6%) from trastuzumab (Table 2).

Molecular Subtype-Specific Breast Cancer Mortality in 2012

The ER+/ERBB2- subtype was estimated to be associated with 64% (model range, 61%-70%) of the overall mortality reduction in 2012 because it was the most common subtype (Supplemental Table 7).

Within-subtype analyses demonstrated significant variations in breast cancer mortality reduction in 2012 (vs estimated subtype-specific baseline rates; Table 1, Column 4). The estimated mortality reduction was largest for the ER+/ERBB2+ subtype at 58% (model range, 46%-71%), followed by the ER+/ERBB2- subtype at 51% (model range, 42%-55%), and the ER-/ERBB2+ subtype at 44% (model range, 33%-55%). The lowest mortality reduction was estimated for the ER-/ERBB2- subtype at 37% (model range, 27%-46%).

The estimated relative contributions associated with screening vs treatment also varied by molecular subtype, ranging from 31% (model range, 23%-41%) versus 69% (model range, 59%-77%) for the ER+/ERBB2+ subtype to 48% (model range, 38%-57%) versus 52% (model range, 43%-62%) for the ER-/ERBB2- subtypes, respectively (Table 1, Columns 7-8). The estimated relative contributions associated with specific treatments varied by subtype (Table 2). For example, for the ER+/ERBB2+ subtype, of the 69% (model range, 59%-77%) relative contribution associated with treatment, 26% (model range, 15%-32%) was associated with chemotherapy, 29% (model range, 23%-36%) with hormone therapy, and 14% (model range, 9%-18%) with trastuzumab (Table 2). For the

ER-/ERBB2- subtype, the 52% (model range, 43%-62%) relative contribution associated with treatment was associated with chemotherapy alone.

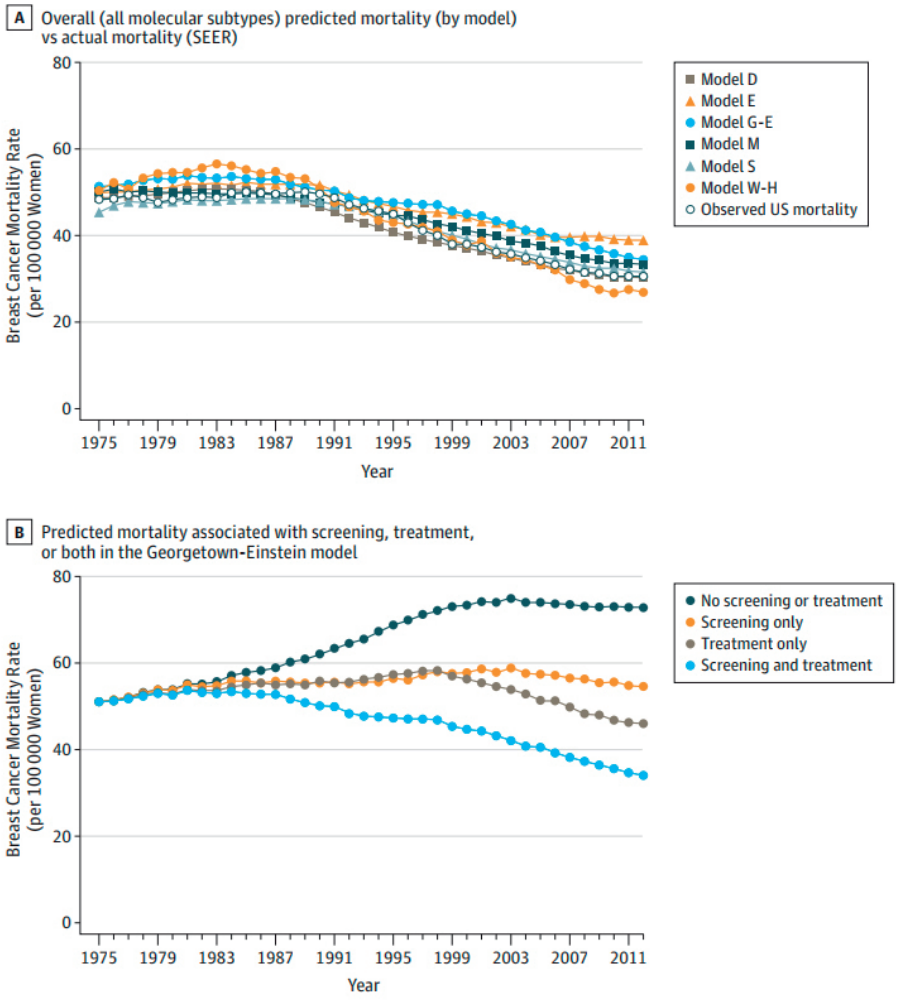

Figure 2 Age-Adjusted Breast Cancer Mortality From 1975-2012 by Model

Panel A compares the predictions the six models for rates of overall breast cancer mortality (all molecular subtypes) to actual US breast cancer mortality among the US population ages 30-79 from 1975 to 2012.

Panel B illustrates predicted breast cancer mortality rates in the US population ages 30-79 from 1975 to 2012 in the absence of screening and adjuvant treatment, presence of screening alone, presence of adjuvant treatment alone, and combination of screening and adjuvant treatment for a representative model (Model Georgetown-Einstein).

Contribution of Screening and Treatment Advances Between 2000 and 2012

The estimated overall breast cancer mortality reduction in 2000 was 37% (model range, 27%-42%) relative to the estimated baseline rate in 2000 of 64 deaths (model range, 56-73) per 100,000 women (Table 3, Column 2; Supplemental Table 2). The estimated overall breast cancer mortality reduction in 2000 was 49% (model range, 39%-58%) relative to the estimated baseline rate in 2012 of 63 deaths (model range, 54-73) per 100,000 women (Table 3, Column 3; Supplemental Table 2). Hence, the estimated difference in the overall breast cancer mortality reduction in 2012 vs. 2000 was 12% (model range, 10%-16%) (Table 3, Column 4; Supplemental Table 5). The estimated relative contribution associated with screening advances to this difference was 17% (2%-31%) (Table 2, Column 5); treatment advances were 83% (69%-98%) (Table 3, sum of Columns 6-8). Of the 83% (69%-98%) treatment-related advances, 38% (model range, 21%-54%) was associated with advances in chemotherapy, largely taxanes; 29% (model range, 9%-44%) was associated with advances in hormone therapy, largely the addition of aromatase inhibitors, and 15% (model range, 4%-25%) with the introduction of trastuzumab (Table 3, Columns 6-8).

Within each molecular subtype, the estimated difference in the breast cancer mortality reductions between 2012 and 2000 was largest for the ER+/ERBB2+ subtype at 19% (model range, 17%-25%) and the smallest for the ER-/ERBB2- subtype at 8% (model range, 5%-11%) (Table 3, Column 4). The estimated relative contribution of screening and treatment to these differences also varied by subtype: the relative contribution of trastuzumab was 41% (model range, 27%-58%) in the ER+/ERBB2+ subtype and 57% (model range, 35%-78%) in the ER-/ERBB2+ subtype (Table 3, Column 8).

To complement the above analysis, we decomposed the overall mortality reduction in 2012 in terms of the contributions associated with advances before 2000 and after 2000 (Supplemental Table 6). Of the 37% (model range, 27%-42%) mortality reduction associated with screening in 2012, 33% (model range, 29%-48%) was associated with screening advances before 2000 and 4% (model range, 1%-8%) after 2000, largely digital mammography. The introduction of trastuzumab was associated with 15% of overall mortality reduction between 2000 and 2012. Of the 31% (model range, 23%-37%) associated with chemotherapy, 22% (model range, 15%-30%) was associated with chemotherapy advances before 2000 and 9% (model range, 7%-14%) after 2000, largely taxanes. Of the 27% mortality reduction (model range, 18%-36%) associated with hormone therapy, 20% (model range, 15%-27%) was associated with advances in hormone therapy before 2000 and 7% (model range, 2%-12%) after 2000, largely from aromatase inhibitors. Supplemental Table 6 provides subtype-specific results.

Table 1 Overall And Subtype-Specific Breast Cancer Mortality Reductions in 2012 Associated with Screening, Treatment, Or Both by Model*

	(A) From Screening Alone	(B) From Treatment Alone	(C) From Combined Screening and Treatment	(D) Percentage of Mortality Reduction Associated with Screening Alone	(E) Percentage of Mortality Reduction Associated with Treatment Alone	(F) Relative Contribution Associated with Screening to Combined Screening and Treatment, %	(G) Relative Contribution Associated with Treatment to Combined Screening and Treatment, %
Operation**	A	B	C	A/C	B/C	A/(A+B)	B/(A+B)
Model				**Overall**			
Dana-Farber	29	28	49	59	57	51	49
Erasmus	18	30	43	41	70	37	63
Georgetown-Einstein	25	37	53	47	69	40	60
MD Anderson	17	29	39	44	73	38	62
Stanford	18	37	50	36	74	33	67
Wisconsin-Harvard	17	49	58	30	84	26	74
Mean	21	35	49	43	71	37	63
				ER+, ERBB2- Subtype			
Dana-Farber	30	30	52	59	58	50	50
Erasmus	18	34	46	39	73	35	65
Georgetown-Einstein	26	39	54	48	71	40	60
MD Anderson	17	31	42	42	75	36	64
Stanford	19	41	53	35	77	31	69
Wisconsin-Harvard	16	51	59	27	86	24	76
Mean	21	38	51	42	73	36	64
				ER+, ERBB2+ Subtype			
Dana-Farber	27	38	57	46	67	41	59
Erasmus	20	42	52	39	82	32	68
Georgetown-Einstein	24	43	58	41	74	36	64
MD Anderson	18	38	46	38	82	32	68
Stanford	17	58	66	26	88	23	77
Wisconsin-Harvard	19	62	71	26	87	23	77
Mean	21	47	58	36	80	31	69

Table 1 Overall And Subtype-Specific Breast Cancer Mortality Reductions in 2012 Associated with Screening, Treatment, Or Both by Model* (continued)

	(A) From Screening Alone	(B) From Treatment Alone	(C) From Combined Screening and Treatment	(D) Percentage of Mortality Reduction Associated with Screening Alone	(E) Percentage of Mortality Reduction Associated with Treatment Alone	(F) Relative Contribution Associated with Screening to Combined Screening and Treatment, %	(G) Relative Contribution Associated with Treatment to Combined Screening and Treatment, %
ER-, ERBB2+ Subtype							
Dana-Farber	25	28	49	52	58	47	53
Erasmus	17	28	41	40	68	37	63
Georgetown-Einstein	25	32	52	48	62	43	57
MD Anderson	15	23	33	45	70	39	61
Stanford	17	25	40	42	63	40	60
Wisconsin-Harvard	23	43	55	41	79	34	66
Mean	20	30	45	45	67	40	60
ER-, ERBB2- Subtype							
Dana-Farber	26	20	40	66	50	57	43
Erasmus	17	22	35	47	64	43	57
Georgetown-Einstein	24	29	46	53	63	45	55
MD Anderson	18	14	27	65	52	56	44
Stanford	18	17	33	53	50	52	48
Wisconsin-Harvard	18	30	42	43	70	38	62
Mean	20	22	37	55	58	48	52

* The column labels are defined as follows: (A) mortality reduction associated with screening alone, relative to the estimated baseline mortality in 2012; (B) mortality reduction associated with treatment alone relative to the estimated baseline mortality in 2012; (C) mortality reduction associated with combined screening and treatment alone, relative to the estimated baseline mortality in 2012 ("combined mortality reduction"); (D) percentage of combined mortality reduced captured by screening alone; (E) percentage of combined mortality reduction captured by treatment alone; (F) relative contribution of screening to combined mortality reduction; (G) relative contribution of treatment to combined mortality reduction. Note: Columns F and G sum to 100%.

** Operation refers to the calculation of the result in the table. For example, column D (Percentage of Mortality Reduction Captured by Screening Alone) is calculated as the result in column A for screening alone divided by the result in column C for the combined mortality reduction with both screening and treatment.

Table 2 Relative Contributions of Treatments to Mortality Reduction in 2012

	Relative Contribution Associated with Chemotherapy, %	Relative Contribution Associated with Hormone Therapy, %	Relative Contribution Associated with Trastuzumab, %
Model		**Overall**	
Dana-Farber	23	24	2
Erasmus	37	25	1
Georgetown-Einstein	37	18	4
MD Anderson	22	34	6
Stanford	34	28	5
Wisconsin-Harvard	33	36	5
Mean	31	27	4
		ER+, ERBB2- Subtype	
Dana-Farber	25	25	0
Erasmus	30	35	0
Georgetown-Einstein	34	24	0
MD Anderson	21	42	0
Stanford	33	36	0
Wisconsin-Harvard	29	47	0
Mean	29	35	0
		ER+, ERBB2+ Subtype	
Dana-Farber	24	23	12
Erasmus	28	30	10
Georgetown-Einstein	32	23	9
MD Anderson	15	36	18
Stanford	30	30	17
Wisconsin-Harvard	25	34	18
Mean	26	29	14
		ER-, ERBB2+ Subtype	
Dana-Farber	36	0	16
Erasmus	45	0	18
Georgetown-Einstein	43	0	11
MD Anderson	24	0	29
Stanford	35	0	25
Wisconsin-Harvard	42	0	23
Mean	37	0	21
		ER-, ERBB2- Subtype	
Dana-Farber	43	0	0
Erasmus	57	0	0
Georgetown-Einstein	53	0	0
MD Anderson	42	0	0
Stanford	48	0	0
Wisconsin-Harvard	62	0	0
Mean	51	0	0

Table 3 Relative Contributions Associated with Advances In Screening and Treatment to The Difference In The Mortality Reduction Between 2000 and 2012

	(A) Mortality Reduction in 2000 (Relative to the estimated baseline mortality rate in 2000), %	(B) Mortality Reduction in 2012 (Relative to the estimated baseline mortality rate in 2012), %	(C) Difference in the Mortality Reduction Between 2000 and 2012, %	Relative Contributions to the Difference in the Mortality Reduction Between 2000 and 2012, % *			
				(D) Relative Contribution Associated with Screening Advances Between 2000 and 2012, %	(E) Relative Contribution Associated with Chemo-therapy Advances Between 2000 and 2012, %	(F) Relative Contribution Associated with Hormone Therapy Advances Between 2000 and 2012, %	(G) Relative Contribution Associated with Trastuzumab, %
Operation*			B-A	D+E+F+G = 100%			
Model			**Overall**				
Dana-Farber	39	49	10	13	34	44	10
Erasmus	32	43	10	31	32	33	4
Georgetown-Einstein	39	53	14	21	54	9	15
MD Anderson	27	39	13	23	21	37	18
Stanford	40	50	10	14	41	20	25
Wisconsin-Harvard	42	58	16	2	48	31	18
Mean	**37**	49	12	17	38	29	15
			ER+, ERBB2- Subtype				
Dana-Farber	43	52	9	14	39	47	0
Erasmus	34	46	13	21	14	64	0
Georgetown-Einstein	41	54	13	29	62	9	0
MD Anderson	29	42	13	24	25	50	0
Stanford	45	53	8	19	46	35	0
Wisconsin-Harvard	45	59	14	3	49	48	0
Mean	39	51	12	19	39	42	0
			ER+, ERBB2+ Subtype				
Dana-Farber	41	57	17	10	19	29	42
Erasmus	33	52	19	24	8	41	27
Georgetown-Einstein	41	58	17	14	46	16	24
MD Anderson	28	46	18	17	6	32	45
Stanford	47	66	19	4	23	14	58
Wisconsin-Harvard	46	71	25	0	29	20	51
Mean	**39**	**58**	**19**	12	22	25	41
			ER-, ERBB2+ Subtype				
Dana-Farber	33	49	16	11	37	0	52
Erasmus	26	41	15	13	37	0	50
Georgetown-Einstein	33	52	19	21	44	0	35
MD Anderson	20	33	13	20	3	0	78
Stanford	26	40	14	0	30	0	70

Table 3 Relative Contributions Associated with Advances In Screening and Treatment to The Difference In The Mortality Reduction Between 2000 and 2012 (continued)

	(A) Mortality Reduction in 2000 (Relative to the estimated baseline mortality rate in 2000), %	(B) Mortality Reduction in 2012 (Relative to the estimated baseline mortality rate in 2012), %	(C) Difference in the Mortality Reduction Between 2000 and 2012, %	Relative Contributions to the Difference in the Mortality Reduction Between 2000 and 2012, % *			
				(D) Relative Contribution Associated with Screening Advances Between 2000 and 2012, %	(E) Relative Contribution Associated with Chemo-therapy Advances Between 2000 and 2012, %	(F) Relative Contribution Associated with Hormone Therapy Advances Between 2000 and 2012, %	(G) Relative Contribution Associated with Trastuzumab, %
Wisconsin-Harvard	33	55	22	0	42	0	58
Mean	**29**	**45**	15	11	32	0	57
ER-, ERBB2- Subtype							
Dana-Farber	34	40	6	13	87	0	0
Erasmus	26	35	10	34	66	0	0
Georgetown-Einstein	35	46	11	14	86	0	0
MD Anderson	22	27	5	41	59	0	0
Stanford	27	33	7	23	77	0	0
Wisconsin-Harvard	32	42	10	9	91	0	0
Mean	**29**	**37**	8	22	78	0	0

* Operation refers to the calculation of the results in the table for each column. The column labels (A through G) are included with each column title.

Details on the computations are included in the Supplemental methods. Briefly, the estimated mean overall mortality reduction associated with combined screening and treatment in 2012 relative to the estimated baseline mortality rate in 2012 (Table 3, Column B) was 49% and in 2000 (Table 3, Column A) it was 37%. Thus, there was an additional 12% mortality reduction in 2012 compared to 2000 (Table 3, Column C).

In 2000, the estimated relative contribution of screening to the mortality reduction associated with combined screening and treatment was 44% (Supplemental Table 4, Row D), hence the mortality reduction associated with screening is 44% of 37% = 16%.

In 2012, the estimated relative contribution of screening to the mortality reduction associated with combined screening and treatment was 37% (Table 1 and Supplemental Table 4, Row M), hence the mortality reduction associated with screening is 37% of 49% = 18%.

The difference in the mortality reduction associated with screening between 2012 and 2000 is 18%-16% = 2%. Hence, the relative contribution of screening advances to the difference in the mortality reduction associated with combined screening and treatment was 2% divided by 12% (Table 3, Column C), giving 17% (Column D). The remainder (83%) is associated with treatment advances. This 83% is distributed by treatment type in columns E-G. Columns D to G total 100%.

DISCUSSION

This model-based analysis provides clinically relevant insights about the separate and combined population contributions associated with screening and treatment advances on reducing breast cancer mortality by molecular subtype. Six independent models found that both screening and treatment were associated with overall and subtype-specific breast cancer mortality declines over time. Between 2000 and 2012, advances in treatment were associated with a larger contribution than screening to overall US breast cancer mortality decreases and for all molecular subtypes except ER-/ERBB2-, the subtype that also had the lowest modeled mortality reduction.

These results build upon past CISNET analyses and other studies that have examined the period before 2000[2,30-32] or considered the role of ER-status.[15,33] The current analysis considered the study period from 2000 to 2012. In this period, digital mammography increased screening sensitivity compared with plain-film mammography, especially for women younger than 50 years and women with dense breasts,[34] and has increased somewhat the number of breast cancer deaths averted with screening.[35] The current results support findings that advances in mammography continue to contribute to reducing breast cancer mortality. It will be important to update the analysis when there is sufficient evidence about the benefits of tomosynthesis or other emerging screening approaches.[36,37]

Even with the recent screening advances, findings from this model-based analysis demonstrate a shift in the relative contributions associated with screening and treatment to breast cancer mortality, with greater contributions associated with treatment in 2012. Recent observational analyses have also found stage-specific survival improvements related to current treatment.[33] The results from this model analysis confirm the benefits at the population level from the discovery and rapid dissemination over this past decade of several new classes of molecularly-targeted therapies, improvements in delivery of standard regimens, and refinements in therapy based on molecular subtype based by ER and ERBB2 status.

A unique contribution of this population-level analysis is how the relative contributions associated with screening and treatment varied by molecular subtype. In 2012, when gains from treatment alone were estimated, treatment alone could have provided roughly 70% of the predicted mortality reduction achieved with both screening and treatment for the all the subtypes expressing the ER and/or ERBB2 receptors. However, screening is likely to remain important even if future treatments could cure all breast cancers, because screening can detect disease at earlier stages where there is less surgical and treatment-related morbidity compared to that with therapy for more advanced stages.

Among the advances in recent adjuvant treatments, advances in chemotherapy with the addition of taxanes were associated with roughly 37% of the difference in overall

breast cancer mortality reduction from 2000 to 2012. Advances in hormone therapy with the addition of aromatase inhibitors had comparable contribution associated with mortality reduction. The contribution associated with trastuzumab was smaller on overall breast cancer mortality (13%), because ERBB2+ cases only account for approximately 20% of all newly diagnosed breast cancers.[38] However, trastuzumab was associated with more than 40% of the difference in mortality reduction between 2000 and 2012 among the ERBB2+ subtypes.

All of the models concluded that the ER-/ERBB2- subtype had the lowest overall modeled mortality reduction over time, although the relative contributions associated with screening and treatment varied somewhat by model, with three of the six models estimating a modestly higher contribution associated with treatment compared to screening in 2012. Prior analysis of SEER data have similar results, with greater mortality declines for those with ER+ vs. ER-tumors.[15,39] Given that treatment advancements are lagging for ER-/ERBB2- cancers, more intensive screening approaches, or screening with different modalities, might be considered for groups at highest risk for this subtype, including African American women. Continued investments to discover molecularly-targeted treatments for the ER-/ERBB2- subgroup remain important to continue to lower breast cancer death rates.

Overall, the models projected that screening and treatment each were associated with continued reductions in breast cancer mortality, but in 2012 treatment was associated with a larger relative proportion than screening of the mortality reductions overall and for all subtypes, except the ER-/ERBB2-. Because ER+ cancers are most prevalent and this group is expected to increase with time,[40] additional advances for this subtype could have the largest impact on reducing the overall population burden of breast cancer. Looking ahead, model-based approaches may continue to be important to evaluate continued population-level progress in reducing the burden of breast cancer through a combination of continued discovery and dissemination of effective molecularly-targeted therapies, invention of novel screening technologies to optimize early detection of aggressive cancer subtypes, and greater ability to identify risk of developing specific molecular subtypes to permit tailored prevention and early detection.

This study has several strengths. First, by synthesizing national and clinical trial data, the results fill an important knowledge gap, especially because current surveillance data systems do not contain information on both screening and treatment. Second, the main findings were robust across six independent models, despite differences in model structures and assumptions. Third, the validity of this comparative modeling approach is supported by the consistency of conclusions across models, and the ability of each model to closely replicate the patterns of observed trends in incidence and mortality.

This research also has several limitations. First, the accuracy of model results depends on the availability of good quality data for input parameters and reasonable assumptions

about unobservable events. For instance, because there are limited long-term clinical trial or registry data on survival by ERBB2 status, the models extrapolated long-term survival. Second, modeled treatment effects were based on efficacy in trials included in the Oxford Overview,[16] so could have slightly over-estimated actual population treatment effects, and the relative contribution of treatment to mortality reductions. Third, each model also made different assumptions about the baseline incidence and natural history of breast cancer, leading to variability in the magnitude of results. Fourth, the models considered only five years of hormonal therapy since recommendations to consider 10-years among women at high-risk of late recurrence were just recently introduced and have not yet been uniformly applied. Future modeling could incorporate the population-level dissemination and effectiveness of longer-term hormonal therapy. Fifth, progesterone-receptor status was not explicitly modeled since it is missing from many data sources. Sixth, subtype results for various racial/ethnic subgroups were not modeled. Understanding interactions between race, ethnicity, and subtype-specific outcomes represents an important future direction.[41] Seventh, the effect of screening and subtype-specific treatment on morbidity and all-cause mortality was not evaluated. Eighth, modeling was based on estimates until 2012, and it is uncertain whether or how well these estimates reflect current breast cancer screening, treatment, or outcomes after 2012.

CONCLUSIONS

In this simulation modeling study that projected trends in breast cancer mortality rates among US women, decreases in overall breast cancer mortality from 2000 to 2012 were associated with advances in screening and in adjuvant therapy, although the associations varied by breast cancer molecular subtypes.

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Supplementary Online Content

Plevritis SK, Munoz D, Kurian A, et al. Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000-2012. *JAMA*. doi:10.1001/jama.2017.19130

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

eMethods

Computing the Relative Contributions Associated with Screening and Treatment

In the main text, the relative contribution associated with screening versus treatment to the combination was computed as the ratio of the screening alone mortality reduction divided by the sum of the screening alone mortality reduction and treatment alone mortality reduction; similarly for the relative contribution associated with treatment. Herein, we refer to this approach as "Method A." Two alternative approaches for computing the relative contributions associated with screening and treatment were also considered. In "Method B," we evaluated the relative contributions associated with screening and treatment by first quantifying the contributions associated with screening alone and assigning the remainder of the combined effect to treatment. In "Method C", we evaluated the relative contributions associated with screening and treatment by first quantifying the contributions associated with treatment alone and assigning the remainder of the combined effect to screening. A comparison of all three approaches to compute the relative contributions associated with screening and treatment on overall breast cancer mortality is provided in Supplemental eTable 3. All three approaches provide the same ranking of relative contributions, but results differ because the combination associated with screening and treatment is less than the sum of the contributions associated with screening alone and treatment alone. If the combination was equal to the sum of screening alone and treatment alone, all three methods would give the same result. Because Method A provided a result that was "in-between" Methods B and C, we choose it for the primary analysis.

Computing the Relative Contributions Associated with Screening and Treatment to the Difference in the Reduction Between 2000 and 2012

In Table 3 of the main text, the relative contribution associated with screening and treatment advances to the different in the mortality reduction between 2000 and 2012 are provided. The results in Table 3 are based on the difference in breast cancer mortality reduction in 2012 and breast cancer mortality reduction 2000. Note that the mortality reduction in 2012 is computed relative to the estimated baseline breast cancer mortality in 2012, where the estimate baseline mortality rate in a given calendar year is defined as the estimate mortality rate in that calendar year had there never been screening or adjuvant therapy. Similarly, the mortality reduction in 2000 is computed relative to the estimated baseline breast cancer mortality in 2000. By computing the difference between 2000 and 2012, the baseline effect is removed and the difference estimates the effect of screening and treatment only (not the baseline effect) over this time period. If we did not remove the effect of baseline then the difference in the mortality rate between 2012 and 2000 could be associated with changes in the baseline as well as changes in screening and treatment. Removing the estimated baseline trend provides more robust results for the relative contributions associated with screening and treatment.

To understand how the relative contributions associated with screening and treatment to the difference in the mortality reduction between 2000 and 2012 is computed, we describe the calculations based on overall mortality using the mean results in Table 3. The overall mortality reduction associated with combined screening and treatment was estimated as 37% in 2000 and 49% in 2012, yielding a difference of 12% between 2000 and 2012. In 2000, the relative contribution associated with screening to

the overall mortality reduction was 44% (based on Method A in Supplemental eTable 3), so the mortality reduction associated with screening (vs. baseline) was 44% of 37% = 16% in 2000. In 2012, the relative contribution associated with screening to the overall mortality reduction was 37% (based on Method A in Supplemental Table 3), so the mortality reduction associated with screening (vs. baseline) was 37% of 49% = 18%. The difference in the mortality reduction associated with screening between 2012 and 2000 was 18%- 16% = 2%. This was associated with screening advances (in this case the conversion to digital mammography because the dissemination of screening had not significantly changed). Hence the relative contribution of screening advances to the difference in the mortality reduction associated with combined screening and treatment was estimated as 2% divided by 12%, giving 17%. This leaves 83% associated with treatment advances. **Supplemental eTable 5** provides the results of these calculations for each model, and the mean across the models.

eTable 1. Model Parameters

Parameters	Data	Data Source*
Common Model Parameters		
Incidence in the absence of screening	An age-period-cohort model is used as a starting point for most models (except Model M)	Ref. [1,2]
Mammography dissemination	Screening dissemination is based on the age at first screening and frequency by birth cohort derived from BCSC and NHIS data through 2012	Ref.[3,4]
Proportion of plain film vs. digital mammograms by year	Estimated percent of mammograms in the US that are digital by year from FDA MQSA and BCSC data	Ref.[5,6] BCSC (unpublished data)
Mammography performance	By age, type of screen (initial vs. subsequent), screen interval, and plain film vs. digital	BCSC (unpublished data)
Distribution of ER/ERBB2-status by age and stage	The probability of ER/ERBB2 conditional on age and stage at diagnosis	BCSC (unpublished data)
Survival in the absence of screening and treatment, Overall and by ER/ERBB2	26-year breast cancer survival before adjuvant treatment by joint ER/ERBB2 status, age group, and AJCC/SEER stage or tumor size	Ref.[18]
ER/ERBB2 specific treatment dissemination by year	Based on observed dissemination in the population over time from SEER and the NCCN Outcomes Database (1997-2012)	Ref. [5,7,8] NCCN Outcomes Database (unpublished data)
ER/ERBB2-specific treatment efficacy	Meta-analyses of clinical trial results	Ref.[9]
Non-cancer competing causes of death	Age- and cohort-specific all-cause mortality rates by year	Ref. [10]
Model-specific Parameters		
Tumor sojourn time (or mean tumor doubling time)	Sojourn time by joint ER/ERBB2 status and age group	Ref.[18]
Proportion of DCIS that progresses to invasive cancer	Varies by model	Ref.[5,11-16]
Mean stage dwell time** or tumor growth rates or both	Varies by models based on model structure; can vary by age and/or ER/ERBB2 status	Ref.[11-17]
Screening effects	Stage-shift or change in tumor size between screened and unscreened populations	Ref.[11-16]

* All reference citations refer to those in the main text.
** The mean stage well time is defined as the average time a tumor spends in each stage before progressing to the next.

eTable 2. Computation of the Percent Mortality Reduction, Relative to the Baseline Rate

	Mortality Rate, per 100,000 Women				Mortality Reduction, Relative to Baseline Rate, %		
	No Screening, No Treatment ("Baseline")	Screening Alone	Treatment Alone	Combined Screening and Treatment	Screening Alone	Treatment Alone	Combined Screening and Treatment
Column ID	A	B	C	D	E	F	G
Operation	A	B	C	D	(A-B)/A	(A-C)/A	(A-D)/A
Model	Calendar Year 2000						
Dana Farber	61	44	50	37	27	18	39
Erasmus	65	56	51	44	14	22	32
Georgetown-Einstein	73	58	56	45	21	23	39
MD Anderson	56	48	46	41	13	17	27
Stanford	65	54	47	39	17	28	40
Wisconsin	65	54	45	38	17	30	42
Mean	64	52	49	40	**18**	**23**	**37**
	Calendar Year 2012						
Dana Farber	59	42	43	30	29	28	49
Erasmus	67	56	47	39	18	30	43
Georgetown-Einstein	73	55	46	34	25	37	53
MD Anderson	54	45	39	33	17	29	39
Stanford	63	51	39	31	18	37	50
Wisconsin	63	52	32	27	17	49	58
Mean	63	50	41	32	**21**	**35**	**49**

eTable 3. Comparison of three alternative methods to compute the relative contributions associated with screening and treatment on overall breast cancer mortality reduction in 2012*

				Method A (Main text)		Method B		Method C	
	Mortality reduction in 2012 relative to the estimated baseline mortality rate in 2012, %			Relative contribution associated with screening, %	Relative contribution associated with treatment, %	Relative contribution associated with screening, %	Relative contribution associated with treatment, %	Relative contribution associated with screening, %	Relative contribution associated with treatment, %
	Screening alone	Treatment alone	Combined screening and treatment						
Column ID	A	B	C	D	E	F	G	H	I
Operation	A	B	C	A/(A+B)	B/(A+B)	A/C	1-A/C	1-B/C	B/C
Model	**Overall Breast Cancer Mortality**								
Dana-Farber	29	28	49	51	49	59	41	43	57
Erasmus	18	30	43	37	63	41	59	30	70
Georgetown -Einstein	25	37	53	40	60	47	53	31	69
MD Anderson	17	29	39	38	62	44	56	27	73
Stanford	18	37	50	33	67	36	64	26	74
Wisconsin-Harvard	17	49	58	26	74	30	70	16	84
Mean	**21**	**35**	**49**	**37**	**63**	**43**	**57**	**29**	**71**

* See Supplemental Methods subsection "*Computing the Relative Contributions Associated with Screening and Treatment*" for description of these calculations.

eTable 4. Comparison of breast cancer mortality reduction, overall and by ER/ERBB2-subtype, across models, in 2000 vs 2012

	Mortality reduction in 2000 relative to the estimated baseline mortality rate in 2000, %			Mortality reduction in 2012 relative to the estimated baseline mortality rate in 2012, %			Difference in the mortality reduction between 2012 and 2000, %			Relative contribution associated with screening in 2000, %	Relative contribution associated with treatment in 2000, %	Relative contribution associated with screening in 2012, %	Relative contribution associated with treatment in 2012, %
	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Treatment alone	Combined screening and treatment				
Column ID	A	B	C	D	E	F	G	H	I	J	K	L	M
Operation	A	B	C	D	E	F	D-A	E-B	F-C	A/(A+B)	B/(A+B)	D/(D+E)	E/(D+E)
Model	**Overall**												
Dana-Farber	27	18	39	29	28	49	2	11	10	60	40	51	49
Erasmus	14	22	32	18	30	43	4	8	10	39	61	37	63
Georgetown-Einstein	21	23	39	25	37	53	4	14	14	48	52	40	60
MD Anderson	13	17	27	17	29	39	4	12	13	44	56	38	62
Stanford	17	28	40	18	37	50	1	9	10	38	62	33	67
Wisconsin-Harvard	17	30	42	17	49	58	1	18	16	35	65	26	74
Mean	**18**	**23**	**37**	**21**	**35**	**49**	**3**	**12**	**12**	**44**	**56**	**37**	**63**

eTable 4 (Continued). Comparison of breast cancer mortality reduction, overall and by ER/ERBB2-subtype, across models, in 2000 vs 2012

	Mortality reduction in 2000 relative to the estimated baseline mortality rate in 2000, %			Mortality reduction in 2012 relative to the estimated baseline mortality rate in 2012, %			Difference in the mortality reduction between 2012 and 2000, %			Relative contribution associated with screening in 2000, %	Relative contribution associated with treatment in 2000, %	Relative contribution associated with screening in 2012, %	Relative contribution associated with treatment in 2012, %
	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Screening alone	Treatment alone				
Column ID	A	B	C	D	E	F	G	H	I	J	K	L	M
Operation	A	B	C	D	E	F	D-A	E-B	F-C	A/(A+B)	B/(A+B)	D/(D+E)	E/(D+E)
Model	**ER+, ERBB2- Subtype**												
Dana-Farber	28	21	43	30	30	52	2	9	9	57	43	50	50
Erasmus	15	22	34	18	34	46	4	12	13	40	60	35	65
Georgetown-Einstein	21	25	41	26	39	54	5	13	13	45	55	40	60
MD Anderson	13	19	29	17	31	42	4	12	13	41	59	36	64
Stanford	17	34	45	19	41	53	1	7	8	34	66	31	69
Wisconsin-Harvard	15	35	45	16	51	59	1	16	14	30	70	24	76
Mean	**18**	**26**	**39**	**21**	**38**	**51**	**3**	**11**	**12**	**41**	**59**	**36**	**64**

eTable 4 (Continued). Comparison of breast cancer mortality reduction, overall and by ER/ERBB2-subtype, across models, in 2000 vs 2012

	Mortality reduction in 2000 relative to the estimated baseline mortality rate in 2000, %			Mortality reduction in 2012 relative to the estimated baseline mortality rate in 2012, %			Difference in the mortality reduction between 2012 and 2000, %			Relative contribution associated with screening in 2000, %	Relative contribution associated with treatment in 2000, %	Relative contribution associated with screening in 2012, %	Relative contribution associated with treatment in 2012, %
	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Screening alone	Treatment alone				
Column ID	A	B	C	D	E	F	G	H	I	J	K	L	M
Operation	A	B	C	D	E	F	D-A	E-B	F-C	A/(A+B)	B/(A+B)	D/(D+E)	E/(D+E)
Model	**ER+, ERBB2+ Subtype**												
Dana-Farber	25	21	41	27	38	57	2	17	17	54	46	41	59
Erasmus	14	24	33	20	42	52	6	18	19	36	64	32	68
Georgetown-Einstein	22	27	41	24	43	58	2	16	17	45	55	36	64
MD Anderson	13	18	28	18	38	46	5	20	18	41	59	32	68
Stanford	16	37	47	17	58	66	1	21	19	31	69	23	77
Wisconsin-Harvard	18	31	46	19	62	71	0	31	25	37	63	23	77
Mean	**18**	**26**	**39**	**21**	**47**	**58**	**3**	**21**	**19**	**41**	**59**	**31**	**69**

eTable 4 (Continued)**.** Comparison of breast cancer mortality reduction, overall and by ER/ERBB2-subtype, across models, in 2000 versus 2012

	Mortality reduction in 2000 relative to the estimated baseline mortality rate in 2000, %			Mortality reduction in 2012 relative to the estimated baseline mortality rate in 2012, %			Difference in the mortality reduction between 2012 and 2000, %			Relative contribution associated with screening in 2000, %	Relative contribution associated with treatment in 2000, %	Relative contribution associated with screening in 2012, %	Relative contribution associated with treatment in 2012, %
	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Screening alone	Treatment alone				
Column ID	A	B	C	D	E	F	G	H	I	J	K	L	M
Operation	A	B	C	D	E	F	D-A	E-B	F-C	A/(A+B)	B/(A+B)	D/(D+E)	E/(D+E)
Model	**ER-, ERBB2+ Subtype**												
Dana-Farber	24	14	33	25	28	49	1	15	16	64	36	47	53
Erasmus	14	14	26	17	28	41	3	15	15	51	49	37	63
Georgetown-Einstein	21	16	33	25	32	52	3	17	19	58	42	43	57
MD Anderson	13	11	20	15	23	33	2	12	13	53	47	39	61
Stanford	17	10	26	17	25	40	0	15	14	63	37	40	60
Wisconsin-Harvard	22	16	33	23	43	55	1	27	22	58	42	34	66
Mean	**19**	**13**	**29**	**20**	**30**	**45**	**2**	**17**	**16**	**58**	**42**	**40**	**60**

eTable 4 (Continued)**.** Comparison of breast cancer mortality reduction, overall and by ER/ERBB2-subtype, across models, in 2000 versus 2012

	Mortality reduction in 2000 relative to the estimated baseline mortality rate in 2000, %			Mortality reduction in 2012 relative to the estimated baseline mortality rate in 2012, %			Difference in the mortality reduction between 2012 and 2000, %			Relative contribution associated with screening in 2000, %	Relative contribution associated with treatment in 2000, %	Relative contribution associated with screening in 2012, %	Relative contribution associated with treatment in 2012, %
	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Treatment alone	Combined screening and treatment	Screening alone	Screening alone	Treatment alone				
Column ID	A	B	C	D	E	F	G	H	I	J	K	L	M
Operation	A	B	C	D	E	F	D-A	E-B	F-C	A/(A+B)	B/(A+B)	D/(D+E)	E/(D+E)
Model	**ER-, ERBB2- Subtype**												
Dana-Farber	25	13	34	26	20	40	1	6	6	65	35	57	43
Erasmus	13	15	26	17	22	35	4	7	10	46	54	43	57
Georgetown-Einstein	22	17	35	24	29	46	2	12	11	56	44	45	55
MD Anderson	14	11	22	18	14	27	4	3	5	57	43	56	44
Stanford	17	12	27	18	17	33	1	5	7	59	41	52	48
Wisconsin-Harvard	16	18	32	18	30	42	2	12	8	48	52	38	62
Mean	**18**	**14**	**29**	**20**	**22**	**37**	**2**	**8**	**8**	**55**	**45**	**48**	**52**

eTable 5. Relative contributions associated with screening and treatment advances on the difference in the breast cancer mortality reduction between 2000 and 2012*

				Model**						
Year	Metric	Row ID	Operation	D	E	G-E	M	S	W-H	Mean
2000	Mortality Reduction in 2000 Relative to Baseline in 2000, Screening Alone, %	A	A	27	14	21	13	17	17	**17**
	Mortality Reduction in 2000 Relative to Baseline in 2000, Treatment Alone, %	B	B	18	22	23	17	28	30	**23**
	Mortality Reduction in 2000 Relative to Baseline in 2000, Combined Screening and Treatment, %	C	C	39	32	39	27	40	42	**37**
	Relative Contribution Associated with Screening, %	D	A/(A+B)	60	39	48	44	38	35	**44**
	Relative Contribution Associated with Treatment, %	E	B/(A+B)	40	61	52	56	62	65	**56**
	Mortality Reduction Associated with Screening given Combination, %	F	D*C	24	13	19	12	15	15	**16**
	Mortality Reduction Associated with treatment given combination, %	G	E*C	16	20	21	15	25	27	**21**
2012	Mortality Reduction Relative to Baseline, Screening Alone, %	H	H	29	18	25	17	18	17	**21**
	Mortality Reduction Relative to Baseline, Treatment Alone, %	I	I	28	30	37	29	37	49	**35**
	Mortality Reduction Baseline, Combined Screening and Treatment, %	J	J	49	43	53	39	50	58	**49**
	Relative Contribution Associated with Screening, %	K	H/(H+I)	51	37	40	38	33	26	**37**
	Relative Contribution Associated Treatment, %	L	I/(H+I)	49	63	60	62	67	74	**63**
	Mortality Reduction Associated with Screening given Combination, %	M	K*J	25	16	22	15	16	15	**18**
	Mortality Reduction associated with Treatment given Combination, %	N	L*J	24	27	32	24	34	43	**31**
2000 vs 2012	Difference in Mortality Reduction Between 2000 and 2012, %	Q	J-C	10	10	14	13	10	16	**12**
	Difference in the Mortality Reduction Associated with Screening Advances Between 2000 and 2012, %	O	M-F	1	3	3	3	1	0	**2**
	Difference in the Mortality Reduction Associated with Treatment Advances Between 2000 and 2012, %	P	N-G	9	7	11	10	9	15	**10**
	Relative Contribution Associated with Screening Advances Between 2000 and 2012, %	R	O/Q	13	31	21	24	14	2	**17**
	Relative Contribution Associated with Treatment Advances Between 2000 and 2012, %	S	P/Q	87	69	79	76	86	98	**83**

* See Supplemental Methods subsection "*Computing the Relative Contributions of Screening and Treatment to the Difference in the Reduction Between Two Calendar Years*" for description of these calculations.
** *Abbreviations*: Model D is Dana Farber; Model E is Erasmus; Model G-E is Georgetown-Einstein; Model M is MD Anderson; Model S is Stanford; Model W-H is Wisconsin-Harvard.

eTable 6. Relative contributions associated with screening, chemotherapy, hormone therapy and trastuzumab to breast cancer mortality reduction in 2012, broken down by advances before and after 2000*

Relative Contributions Associated with Mortality Reduction in 2012, Percent							
	Screening Advances before 2000	Screening Advances after 2000	Chemo-therapy Advances before 2000	Chemo-therapy Advances after 2000	Hormone Therapy Advances before 2000	Hormone Therapy Advances after 2000	Trast-uzumab
Model	**Overall**						
Dana-Farber	48	3	16	7	15	9	2
Erasmus	29	8	30	8	17	8	1
Georgetown-Einstein	35	5	23	14	16	2	4
MD Anderson	30	8	15	7	22	12	6
Stanford	30	3	26	8	24	4	5
Wisconsin-Harvard	26	1	20	13	27	9	5
Mean	33	4	22	9	20	7	4
	ER+, ERBB2- Subtype						
Dana-Farber	48	2	19	6	17	8	0
Erasmus	29	6	26	4	17	18	0
Georgetown-Einstein	35	6	21	13	22	2	0
MD Anderson	29	8	13	8	27	16	0
Stanford	28	3	26	7	30	5	0
Wisconsin-Harvard	23	1	17	12	35	11	0
Mean	32	4	20	8	25	10	0
	ER+, ERBB2+ Subtype						
Dana-Farber	38	3	18	6	15	8	12
Erasmus	23	9	25	3	15	15	10
Georgetown-Einstein	32	4	19	14	19	5	7
MD Anderson	25	7	12	2	23	13	18
Stanford	22	1	24	7	26	4	17
Wisconsin-Harvard	23	0	14	10	27	7	18
Mean	27	4	19	7	21	9	14
	ER-, ERBB2+ Subtype						
Dana-Farber	44	4	25	12	0	0	16
Erasmus	32	5	31	13	0	0	18
Georgetown-Einstein	38	7	30	14	0	0	11
MD Anderson	34	8	25	1	0	0	32
Stanford	40	0	24	11	0	0	25
Wisconsin-Harvard	34	0	25	17	0	0	24
Mean	37	4	27	11	0	0	21

eTable 6 (Continued)**.** Relative contributions associated with screening, chemotherapy, hormone therapy and trastuzumab to breast cancer mortality reduction in 2012, broken down by advances before and after 2000*

Relative Contributions Associated with Mortality Reduction in 2012, Percent							
	Screening Advances before 2000	Screening Advances after 2000	Chemo-therapy Advances before 2000	Chemo-therapy Advances after 2000	Hormone Therapy Advances before 2000	Hormone Therapy Advances after 2000	Trast-uzumab
	ER-, ERBB2- Subtype						
Dana-Farber	55	2	30	13	0	0	0
Erasmus	34	9	40	18	0	0	0
Georgetown-Einstein	43	3	35	19	0	0	0
MD Anderson	46	10	28	15	0	0	0
Stanford	47	5	33	15	0	0	0
Wisconsin-Harvard	36	2	39	23	0	0	0
Mean	44	5	34	17	0	0	0

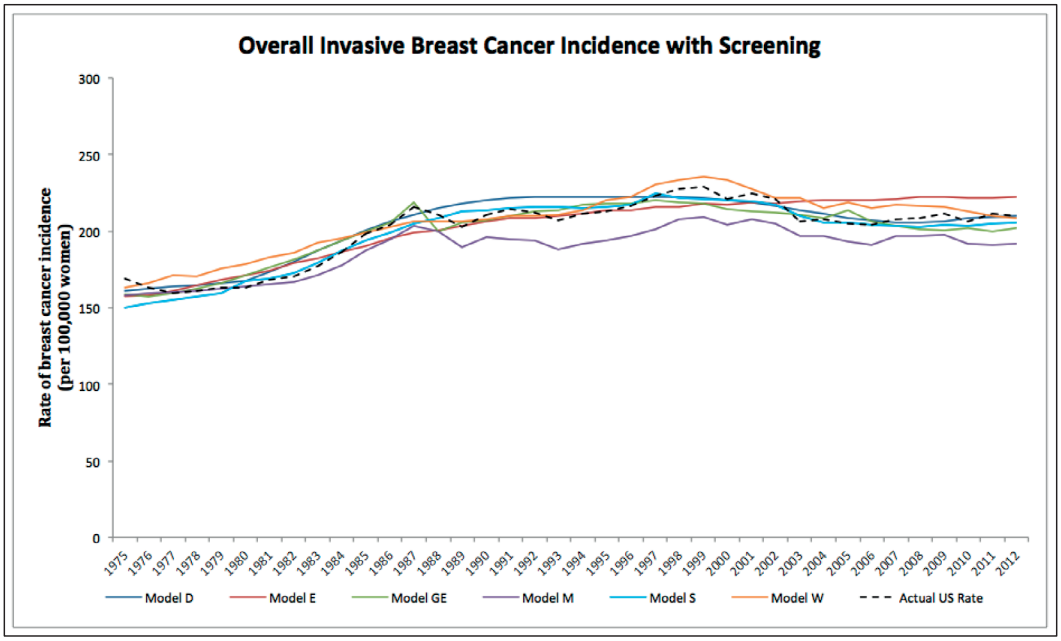
*Row sum is 100%, within rounding error.

eTable 7. Breakdown of overall breast cancer mortality reduction in 2012 by molecular subtype*

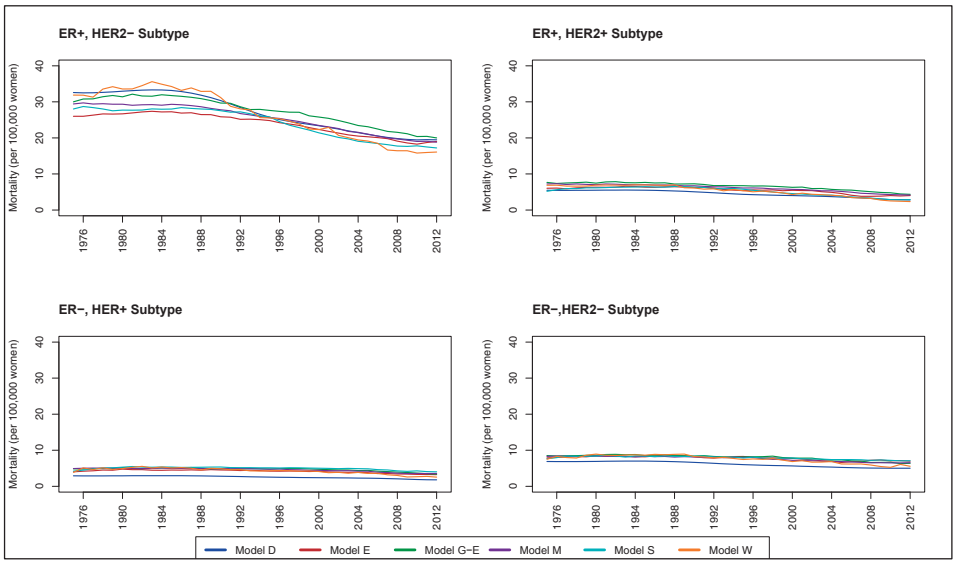
Model	ER+/ERBB2- Subtype	ER+/ERBB2+ Subtype	ER-/ERBB2+ Subtype	ER-/ERBB2- Subtype
Dana-Farber	70	13	6	11
Erasmus	62	17	10	12
Georgetown-Einstein	62	15	9	14
MD Anderson	61	17	9	13
Stanford	65	16	8	11
Wisconsin-Harvard	66	15	8	11
Mean	**64**	**16**	**8**	**12**

*Row sum is 100%.

eFigure 1. Comparison of model projections to actual US breast cancer incidence, for women ages 30-79, invasive cancer only

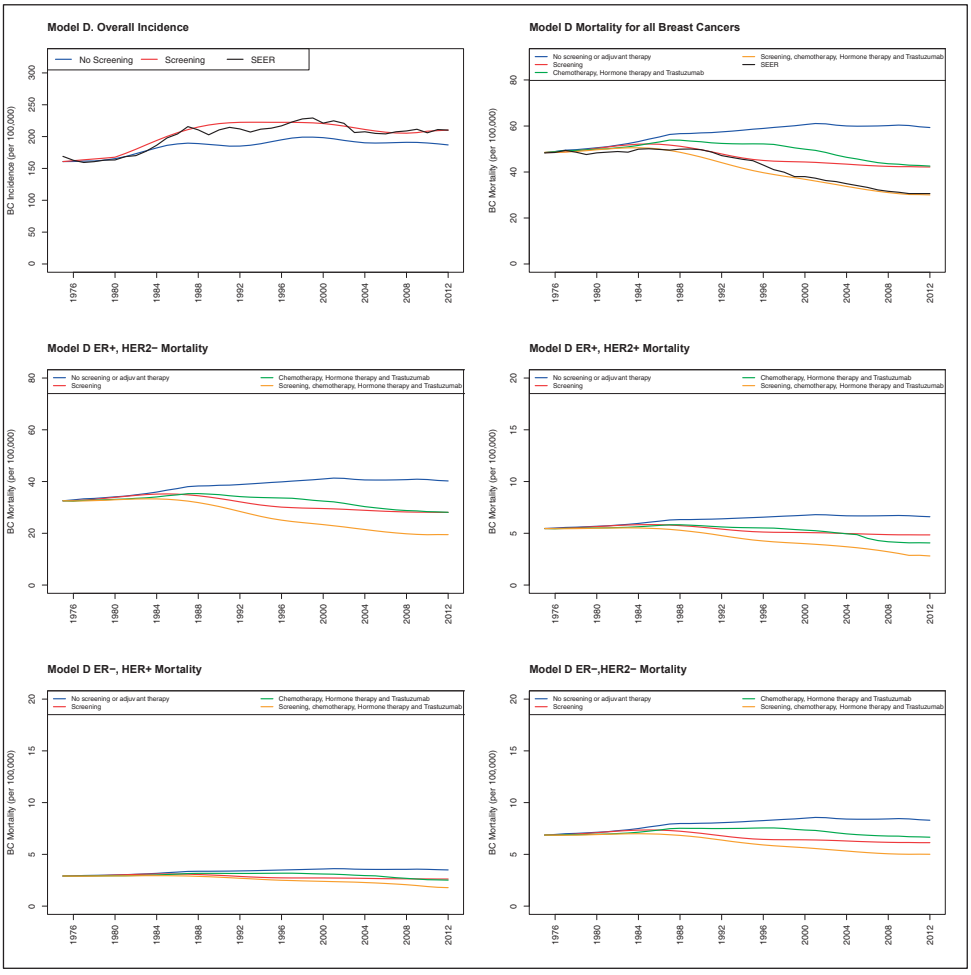


eFigure 2. Comparison of model projections for ER-/ ERBB2-specific breast cancer mortality trends between 1975-2012, for women ages 30-79, by molecular subtype. (Upper left) ER+/ERBB2-, (upper right) ER+/ERBB2+, (lower left) ER-/ERBB2+, (lower right) ER-/ERBB2- subtypes.

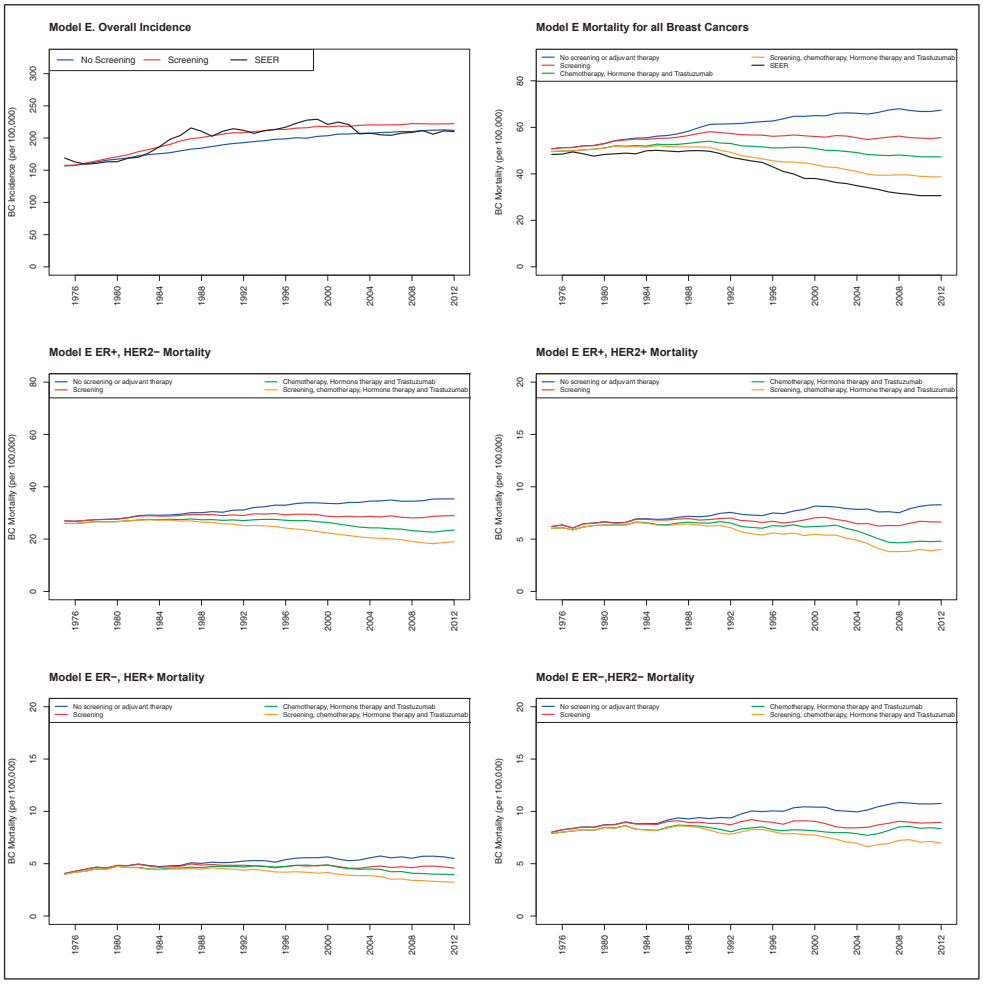


eFigure 3. Individual model projections for overall US breast cancer incidence and mortality (vs. SEER) and ER/ERBB2-subtype-specific mortality from 1975-2012, for women ages 30-79*

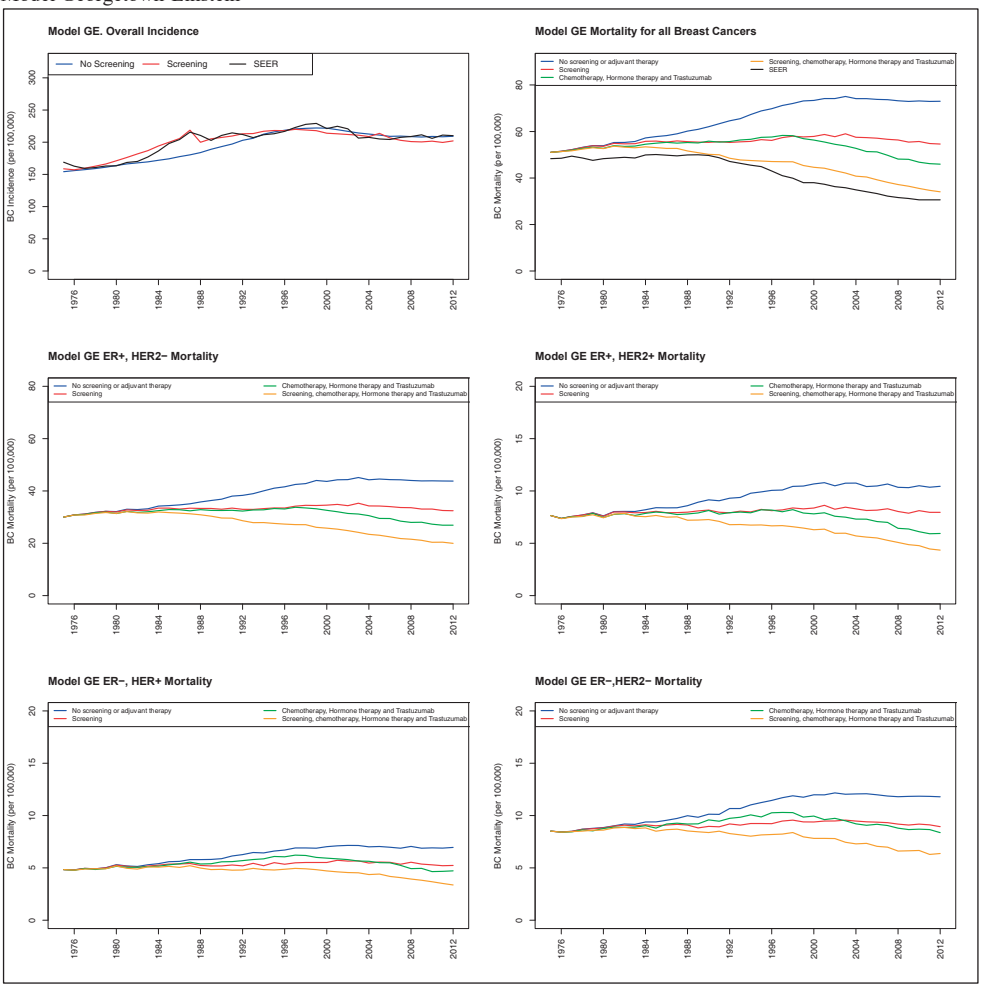
Model Dana-Farber



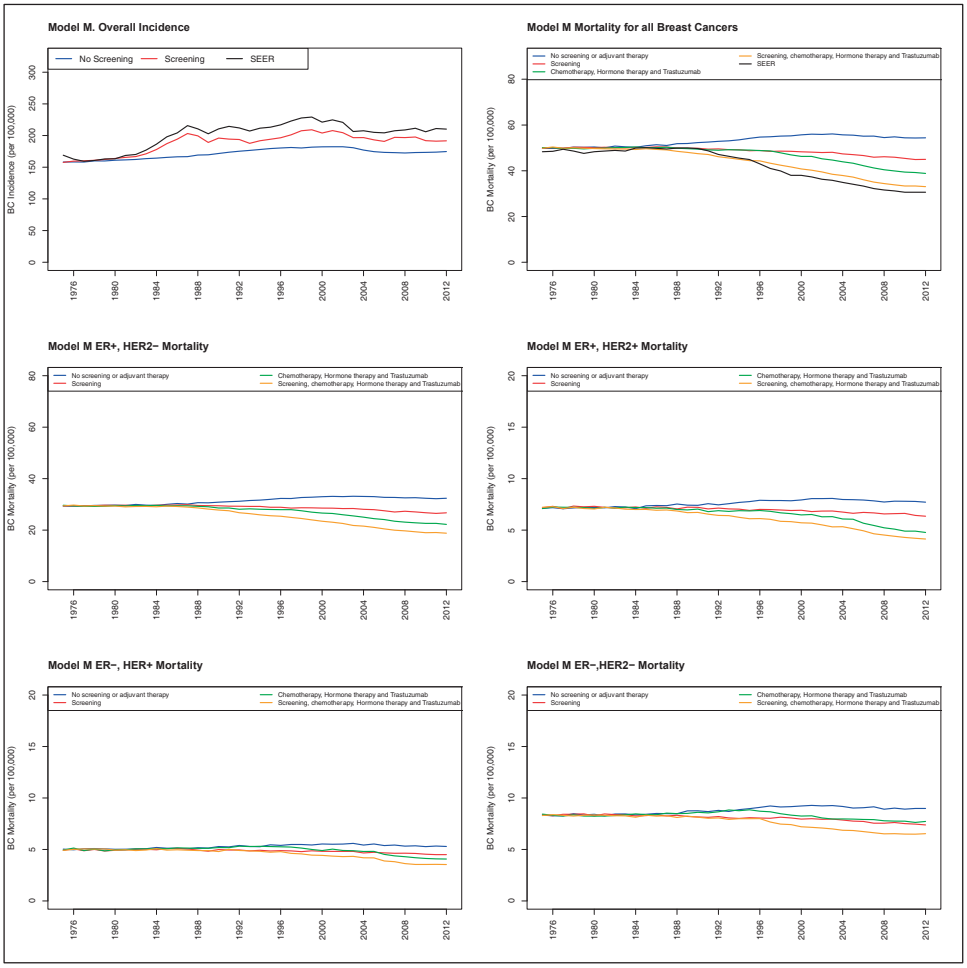
Model Erasmus



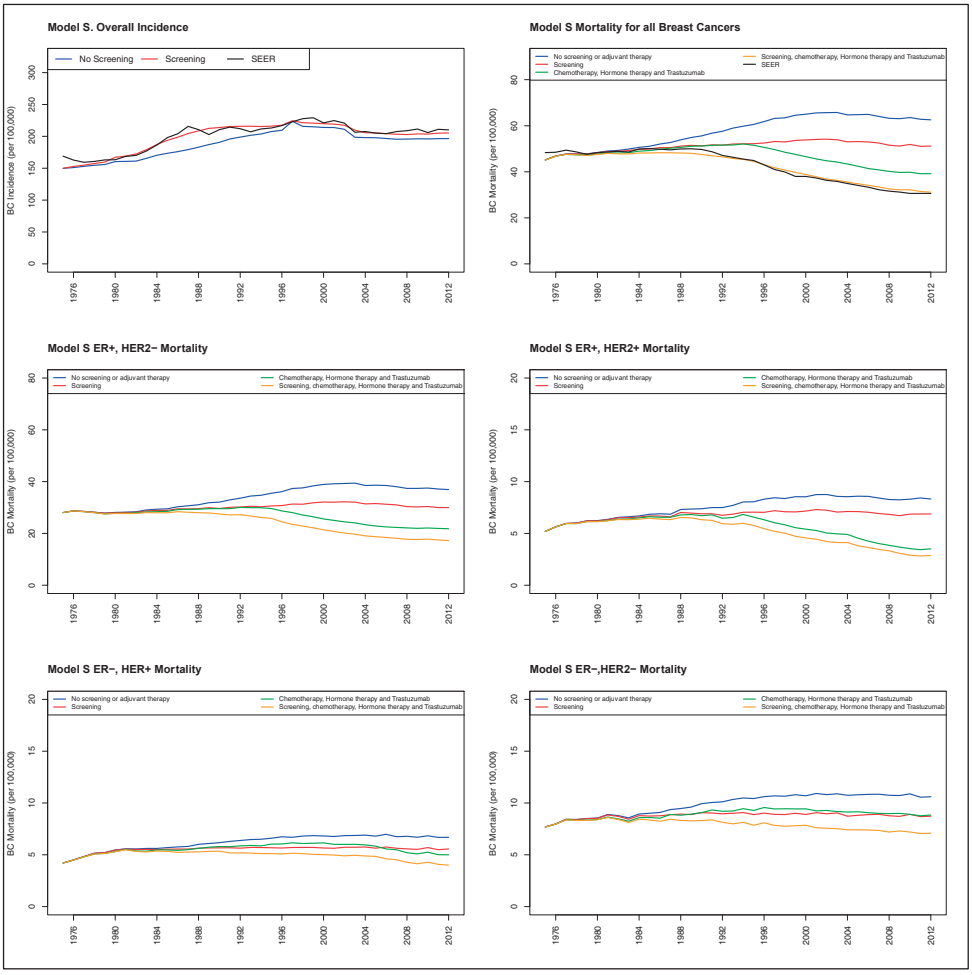
Model Georgetown-Einstein



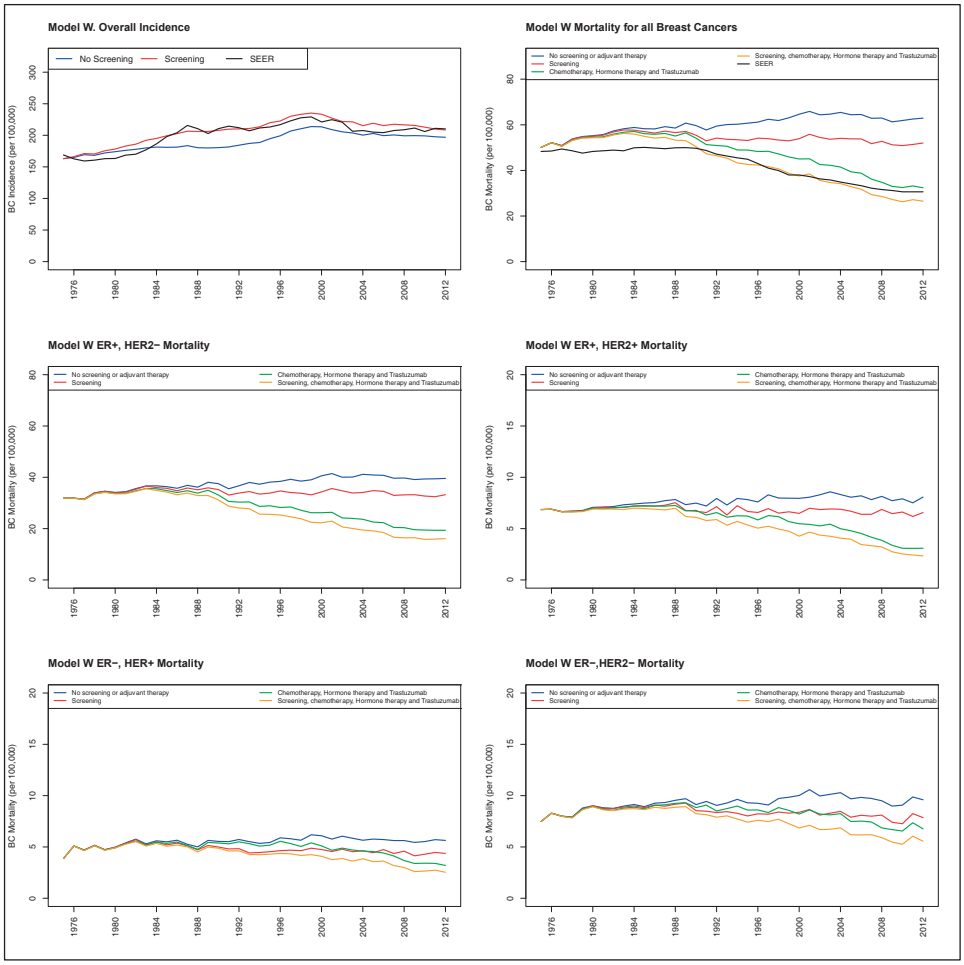
Model MD Anderson



Model Stanford



Model Wisconsin-Harvard



*** Legend for Supplemental Figure 3**: (upper two panels) Individual model projections of breast cancer incidence and mortality rates vs. SEER rates to 2012, with modeled incidence reported in the presence and absence of screening; (lower four panels) Individual model projections by ER/ERBB2 under 4 scenarios: (i) no screening and treatment, (ii) screening alone, (iii) treatment alone, (iv) screening and treatment combined. Subtype-specific comparison to SEER is not possible because ER and ERBB2 status were not jointly reported over this period.

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