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Association of Screening and Treatment With Breast Cancer Mortality by Molecular Subtype in US Women, 2000-2012

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IMPORTANCE Given recent advances in screening mammography and adjuvant therapy (treatment), 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 from 2000 to 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.

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Supplemental content

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Breast cancer mortality rates have been steadily declining over time in the United States.[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, 6 CISNET models compared the separate and combined contribution associated with screening and treatment on US breast cancer mortality rates by molecular subtype from 2000 to 2012.

Key Points

Question What are the associations of screening and adjuvant treatment with reductions in US breast cancer mortality rates by molecular subtype?

Findings In this study of 6 simulation models that projected US breast cancer mortality trends for women aged 30 to 79 years, advances in treatment, such as use of newer adjuvant therapies, compared with screening advances were associated with greater estimated reductions in overall breast cancer mortality from 2000 to 2012, although the associations varied by breast cancer molecular subtype.

Meaning Simulation modeling estimated that advances in treatment were associated with greater decreases in breast cancer mortality rates than advances in screening, although these associations varied by molecular subtype.

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 deidentified data. The 6 CISNET models were Dana-Farber Cancer Institute (model D),[7] 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 with 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 incorporated 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-specific, age-specific, and stage-specific treatment could reduce the hazards of breast cancer death (models D, G-E, 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 (eTable 1 in the Supplement).[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 ductal carcinoma in situ cancers by age group, first vs subsequent screening, 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 4 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 aged 30 to 79 years.

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 percentage of 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; eTable 2 in the Supplement).

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 vs treatment to the combination associated with both was computed as the ratio of the screening alone modeled effect to the sum of the screening alone modeled effect and the treatment alone modeled effect; the relative contribution associated with treatment was calculated similarly. Alternative approaches for computing these relative contributions were considered, and the main conclusions were unchanged (eMethods and eTable 3 in the Supplement).

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 was 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 to 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 1**A), and plain-film was rapidly replaced by digital mammography starting in 2001 (Figure 1B). Treatment use varied by 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 (eFigure 1 in the Supplement) and breast cancer mortality trends from 1975 to 2012 (**Figure 2**A). 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; eTable 2 in the Supplement). The estimated screening contribution associated with this mortality reduction was 37% (model range, 26%-51%), whereas the contribution associated with treatment was 63% (model range, 49%-74%). The larger contribution associated with treatment vs screening in 2012 was predicted in 5 of 6 models (Table 1, columns 7-8). Note, in 2000, screening was associated with 44% (model range, 35%-60%) of the mortality reduction and treatment was associated with 56% (model range, 40%-65%) (eTable 5 in the Supplement).

The estimated 63% (model range, 49%-74%) relative contribution associated with treatment in 2012 consisted of 31% (model range, 22%-37%) from chemotherapy, 27% (model range, 18%-36%) from hormone therapy, and 4% (model range, 1%-6%) from trastuzumab (**Table 2**).

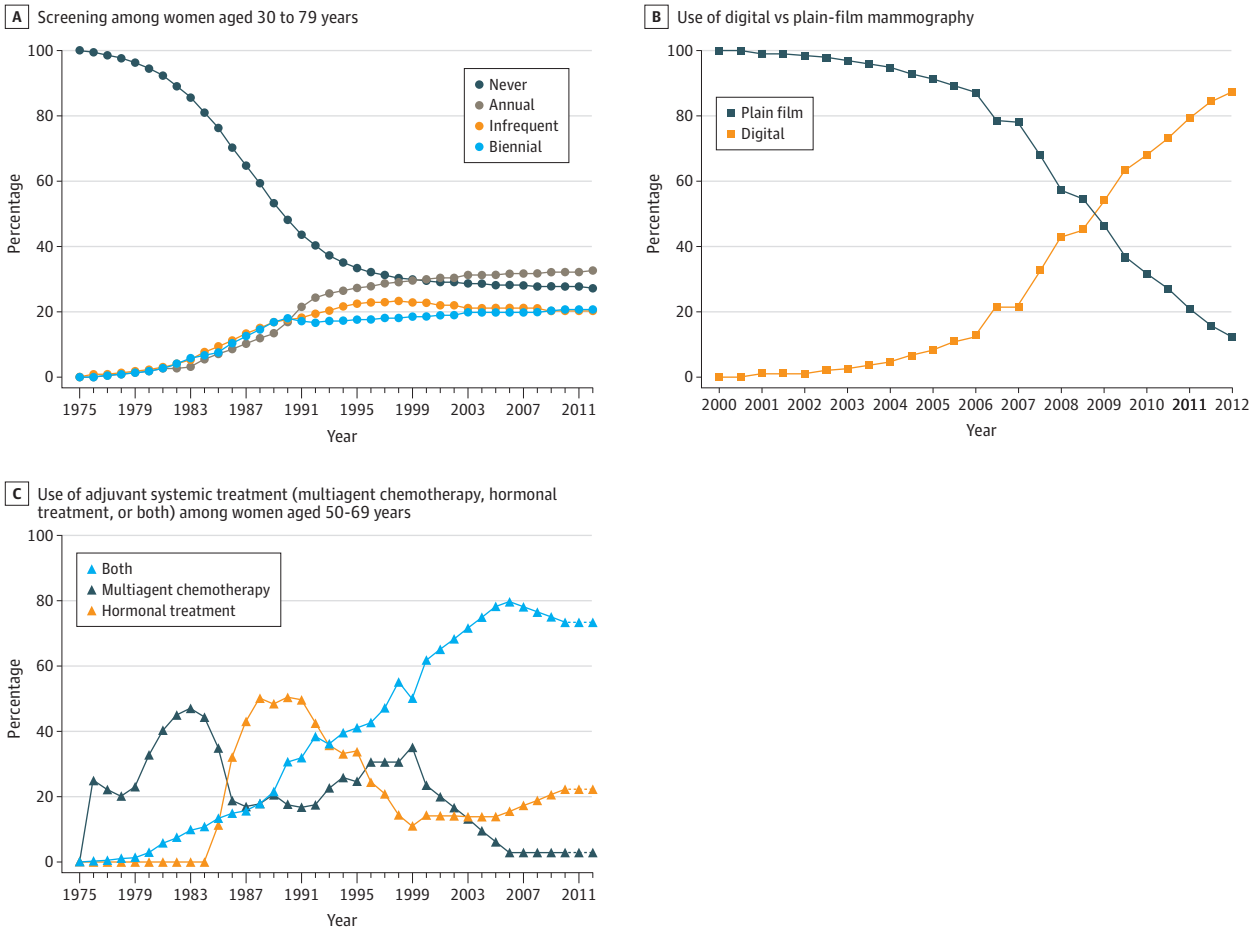
Molecular Subtype–Specific Breast Cancer Mortality in 2012

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 (eTable 7 in the Supplement).

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 ER+/*ERBB2*− at 51% (model range, 42%-59%), and ER−/*ERBB2*+ at 45% (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%) with screening vs 69% (model range, 59%-77%) with treatment for the *ER+/ERBB2*+ subtype to 48% (model range, 38%-57%) with screening vs 52% (model range, 43%-62%) with treatment for

Figure 1. Dissemination of Screening Mammography, Type of Mammography, and Adjuvant Therapy Among US Women, 1975-2012



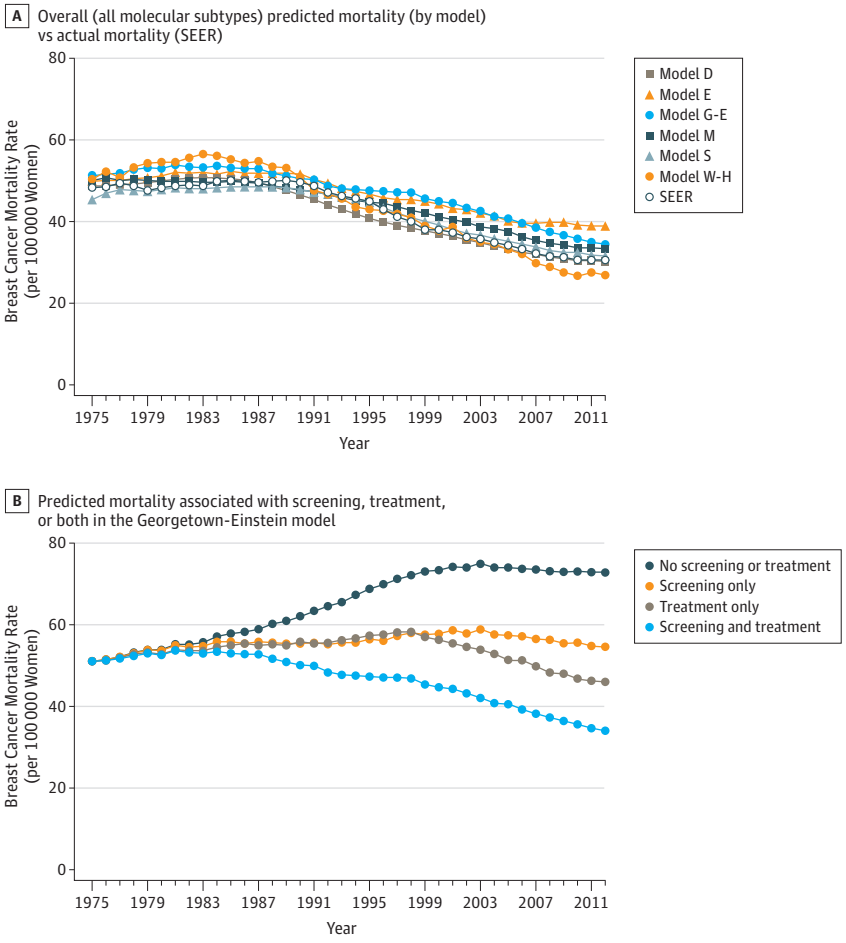
A, Based on data from multiple rounds of the National Health Interview Survey over time and Breast Cancer Surveillance Consortium (BCSC) data from 1994 to 2012. B, Based on Mammography Quality Standards Act of 1992 data on digital mammography facilities from the US Food and Drug Administration and the BCSC. C, An exemplar stage and set of molecular markers (node-positive AJCC 6 stage 2b, ER+/*ERBB2*−) at diagnosis based on data from Surveillance, Epidemiology, and End Results (SEER) special patterns of care studies and the National Comprehensive Cancer Network. These data were used for all other combinations of ages, stages, and molecular subtypes. In general, starting in the mid-1990s anthracycline-based, multiagent chemotherapy regimens were in use, and, in 1997, taxanes could be added to those regimens. Hormonal therapy began with tamoxifen in the 1980s and, starting in 1997, also included aromatase inhibitors. 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. Models used 2010 treatment dissemination data for subsequent years (indicated by the dashed lines).

ER−/*ERBB2*− (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.

Contribution Associated With Screening and Treatment Advances From 2000 To 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; eTable 2 in the Supplement). The estimated overall breast cancer mortality reduction in 2012 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; eTable 2 in the Supplement). 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; eTable 5 in the Supplement). The estimated relative contribution associated with screening advances to this difference was 17% (model range, 2%-31%) (Table 3, column 5); treatment advances were 83% (model range, 69%-98%) (Table 3, sum of columns 6-8, with rounding; eTable 5 in the Supplement). Of the 83% (model range, 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

Figure 2. Age-Adjusted Predicted Breast Cancer Mortality Rate Among US Women Aged 30 to 79 Years From 1975-2012



SEER indicates Surveillance, Epidemiology, and End Results. For model abbreviations, see Methods.

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 from 2000 to 2012 was largest for the *ER+/ERBB2+* subtype at 19% (model range, 17%-25%) and the smallest for *ER−/ERBB2−* at 8% (model range, 5%-11%) (Table 3, column 4). The estimated relative contribution associated with screening and treatment to these differences also varied by subtype: the relative contribution associated with trastuzumab was 41% (model range, 27%-58%) in the *ER+/ERBB2+* subtype and 57% (model range, 35%-78%) in *ER−/ERBB2+* (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 (eTable 6 in the Supplement). Of the 37% mortality reduction (model range, 27%-42%) 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% mortality reduction (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). eTable 6 in the Supplement provides subtype-specific results.

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 decreases over time. Between 2000 and 2012, advances in treatment were associated with a larger contribution

Table 1. Overall and Subtype-Specific Breast Cancer Mortality Reductions in 2012 Associated With Screening, Treatment, or Both by Model[a]

Model	Mortality Reduction, %[b]			Fraction of Combined Mortality Reduction, %		Relative Contribution to Combined Mortality Reduction, %[c]	
	Associated With Screening Alone	Associated With Treatment Alone	Associated With Screening and Treatment[d]	Associated With Screening Alone[e]	Associated With Treatment Alone[f]	Associated With Screening[g]	Associated With Treatment[h]
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
By Molecular Subtype							
ER+/*ERBB2*−							
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*+							
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
ER−/*ERBB2*+							
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*−							
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

Abbreviations: ER, estrogen-receptor; *ERBB2*; human epidermal growth factor receptor 2.

[a] The column labels are defined as follows:

[b] Relative to the estimated baseline mortality in 2012.

[c] These columns sum to 100%.

[d] Combined mortality reduction.

[e] Column 2 divided by column 4.

[f] Column 3 divided by column 4.

[g] Column 2 divided by the sum of columns 2 and 3.

[h] Column 3 divided by the sum of columns 2 and 3.

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

Table 2. Relative Contributions of Treatments to Mortality Reduction in 2012

Model	Relative Contribution, %[a]		
	Associated With Chemotherapy	Associated With Hormone Therapy	Associated With Trastuzumab
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
By Molecular Subtype			
ER+/*ERBB2*−			
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*+			
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*+			
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*−			
Dana-Farber	43	0	0
Erasmus	57	0	0
Georgetown-Einstein	55	0	0
MD Anderson	44	0	0
Stanford	48	0	0
Wisconsin-Harvard	62	0	0
Mean	52	0	0

Abbreviations: ER, estrogen-receptor; *ERBB2*; human epidermal growth factor receptor 2.

[a] The row sum of columns 2 through 4 equals the value in the corresponding row in column 8 of Table 1, within rounding error.

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

Table 3. Relative Contributions Associated with Advances in Screening and Treatment to the Difference in the Mortality Reduction Between 2000 and 2012[a]

Model	Mortality Reduction, %			Relative Contributions to the Difference in the Mortality Reduction Between 2000 and 2012, %			
	In 2000[b]	In 2012[c]	Difference Between 2000 and 2012[d]	Associated With Screening Advances	Associated With Chemotherapy Advances	Associated With Hormone Therapy Advances	Associated With Trastuzumab
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
By Molecular Subtype							
ER+/*ERBB2*−							
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*+							
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*+							
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
Wisconsin-Harvard	33	55	22	0	42	0	58
Mean	29	45	15	11	32	0	57
ER−/*ERBB2*−							
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

Abbreviations: ER, estrogen-receptor; *ERBB2*; human epidermal growth factor receptor 2.

[a] Details on the computations are included in eMethods and eTable 5 in the Supplement. Briefly, in terms of means only, the overall mortality reduction between 2000 and 2012 associated with combined screening and treatment advances is estimated to be 12% (column 4). In 2012, the estimated relative contribution of screening to the mortality reduction associated with combined screening and treatment is 37% (Table 1, column 7). Hence, in 2012, the mortality reduction associated with screening is 37% of 49% = 18%. Similarly, in 2000, the mortality reduction associated with screening is 16% (eTable 5, row F). The difference in the mortality reduction associated with screening advances between 2012 and 2000 is 2% (= 18% in 2012 minus 16% in 2000). The relative contribution of screening advances to the mortality reduction associated with combined screening and treatment advances is 2% divided by 12% (column 4), giving 17% (column 5). The remainder (83% = 100% − 17%) is associated with treatment advances between 2000 and 2012; 83% is distributed by treatment type in columns 6 through 8. Columns 5 to 8 total 100%, within rounding error.

[b] Relative to the estimated baseline mortality rate in 2000.

[c] Relative to the estimated baseline mortality rate in 2012.

[d] Difference of columns 3 and 2.

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 according to 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 been associated with roughly 70% of the predicted mortality reduction achieved with both screening and treatment for the all the subtypes expressing the ER, *ERBB2* receptors, or both. However, screening is likely to remain important even if future treatments could cure all breast cancers because screening can detect disease at earlier stages, which has less surgical and treatment-related morbidity compared with more advanced stages.

Among the advances in recent adjuvant therapies, 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 mortality reduction (15%), because *ERBB2*+ cases account for approximately 20% of all newly diagnosed breast cancer cases, with variations based on age and race.[38] However, trastuzumab was associated with more than 40% of the difference in mortality reduction from 2000 to 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 3 of the 6 models estimating a modestly higher contribution associated with treatment compared with 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 the most prevalent and this group is expected to increase with time,[40] additional advances for this subtype could have the largest effect 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 6 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.

Limitations

This research 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 there could be a slight overestimation of 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 5 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 because 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 subtype.

ARTICLE INFORMATION

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