Supplementary Online Content

Caswell-Jin JL, Sun LP, Munoz D, et al. Analysis of breast cancer mortality in the US—1975 to 2019. *JAMA*. Published January 16, 2024. doi:10.1001/jama.2023.25881

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

eMethods. **Model inputs and assumptions**

Modeling the occurrence of metastatic recurrence and subsequent baseline survival

In the original CISNET breast cancer models, we used estimates of a stage- and ER/ERBB2 category-specific baseline breast cancer survival curve, denoted by S_0, which captures breast cancer survival for patients who are symptomatically detected, in the absence of screening, and who are treated with surgery and radiation, per NCCN guidelines. To maintain consistency with this framework and enable modeling distant recurrence, we deconstruct S_0 into two components: (i) baseline survival from initial diagnosis of Stage I-III breast cancer to the detection of distant recurrence, denoted by $S1_0$, and also referred to as baseline distant recurrence-free survival; and (ii) baseline survival from detection of distant recurrence to breast cancer death, denoted by $S2_0$, assumed to be the same as the baseline progression-free survival curve during metastasis.

To estimate $S1_0$ *and* $S2_0$, we leveraged the NCCN breast cancer recurrence data, together with the Model S, and made the following assumptions:

- Treatment benefits follow a proportional hazards model (as assumed in prior work).
- Metastatic patients receive all the available treatments sequentially, per standard of care.
- Baseline survival from detection of distant recurrence to breast cancer death and baseline progression-free survival curve during metastasis are equal.
- *S1* and *S2* are dependent. Assuming independence between S1 and S2 generated *S2* >> S1 for many patients, contradicting real world observations.
- *S2* does not depend on mode of detection. When we compared *S2* curves from the NCCN dataset between clinically diagnosed and screened patients, we found no significant differences.

Step 1 – Initial estimate of $S2_0$: We first simulate a virtual cancer registry using the original Model S in the absence of screening but in the presence of Stage I-III treatment. Sampling from Kaplan-Meier estimates of *S2* from the NCCN dataset, we compute dates of distant recurrence in the virtual registry. We then assign metastatic treatments depending on each patient's date of distant recurrence using our new treatment dissemination inputs (**eTable 3**). Finally, to generate the baseline curve $S2_0$, we remove the estimated metastatic treatments benefits (**eTable 3**) from the observed *S2* curves, assuming proportional hazards.

Step 2 – Initial estimate of $S1_0$: We simulate a virtual registry using the original Model S in the absence of screening and Stage I-III treatment, then subtract survival times from distant recurrence for each patient using initial estimates of $S2_0$ (Step 1). From the simulated events we compute Kaplan-Meier estimates of $S1_0$.

Step 3 – Calibration of $S2_0$: We incorporate the initial estimates of $S1_0$ (Step 2) and $S2_0$ (Step 1) into the revised Model S, which we use to generate $S2_0$ through microsimulation and calibrate $S2_0$ so that simulated results match previously reported *S2* medians in the 1970s where the treatment options were limited and NCCN-observed *S2* curves for the calendar years 1997-2012. These are the final estimates of $S2_0$.

Step 4 – Calibration of $S1_0$: We repeat Step 2, except using the calibrated estimates of $S2_0$ from Step 3.

We validate the final estimates of $S1_0$ and $S2_0$ by comparing the simulated outputs of the revised Model S with various observed real-world data, namely the incidence and mortality rates from SEER overall and by ER subtype, *S2* from the NCCN Outcomes Database (**eFigure 1),** *S1* from the NCCN Outcomes Database (**eFigure 2**), and *S2* in the clinical trials of patients with metastatic breast cancer (**eFigure 3**). For comparison with clinical trials of first-line treatments, we assumed that overall survival from trial enrollment would approximate breast cancer–specific survival after metastasis in the model.

Three models (Models D, M, and S) used these baseline curves $S1_0$ and $S2_0$ as generated through the above inference process. In contrast, Model W uses a nonparametric mixture cure modeling approach to represent post-diagnosis events. Upon diagnosis and initial treatment, Model W assumes a proportion of patients are cured of breast cancer and their tumor natural history and progression are interrupted and these women are destined to die of non-breast cancer causes. For the remaining who are uncured, their tumors continue to progress according to the underlying tumor growth and progression trajectory. In Model W, the tumor natural history model includes individualized

growth model that determine sizes and a progression model that includes spread to lymph nodes and metastases. When a tumor reaches the metastatic state, it is assigned a subtype-specific remaining distant survival time based on the CISNET common-input. Breast cancer death occurs through progression to the metastatic state. In Model W, overall survival times are derived functions of the previously calibrated growth model parameters, new re-calibrated cure model parameters and CISNET common inputs on distant survival, treatment use and effectiveness. In order to incorporate diagnosis and treatment of distant recurrence into Model W, they first re-estimated the proportion of the patients who are cured of breast cancer and the proportion of the patients who are not cured in the absence of neoadjuvant, adjuvant, and metastatic therapy treatment. They then adjusted the proportion of the cured patients depending on the use and effectiveness of treatments. This model was calibrated to match observed mortality in the US from 1975 forward.

Modeling the treatment of Stage I-III breast cancer

Modeling Stage I-III treatment was similar to our previous publications [1], except that benefits were applied to the curve from diagnosis to recurrence instead of from diagnosis to death. All models used the same inputs for Stage I-III treatment efficacy and dissemination.

We used the dissemination patterns for Stage I-III treatments as in our prior publication, using the Surveillance Epidemiology and End Results (SEER) patterns-of-care special studies for 1975-1996 and the National Comprehensive Cancer Network (NCCN) Outcomes Data Base from 1997 onwards [1].

Four treatments entered clinical practice after 2012, later than the scope of our prior publication: ovarian suppression for premenopausal women with ER+ disease, pertuzumab for ERBB2+ disease, capecitabine for triple-negative disease, and neratinib for ERBB2+ disease. In the absence of data available for the usage patterns of these recent drugs, their dissemination was estimated using a combination of expert opinion (authors JLC and AWK) and available data on chemotherapy usage patterns [2-4].

The probability of receiving ovarian suppression was set as 64% of simulated patients with regional ER+/ERBB2- disease; 21% with local ER+/ERBB2- disease; and 64% with ER+/ERBB2+ disease. These numbers were extrapolated from chemotherapy usage patterns, given that, based on results of subgroup analyses from the SOFT/TEXT trials [5], ovarian suppression is typically given to patients with disease at sufficiently high risk to warrant the receipt of chemotherapy. In an analysis of the Georgia and Los Angeles SEER registries in 2015, 64% of patients with regional ER+/ERBB2- disease and 21% of patients with local ER+/ERBB2- disease received chemotherapy [2]. The estimate for ER+/ERBB2+ disease assumed similar chemotherapy usage patterns as for regional ER+/ERBB2- disease.

The probability of receiving pertuzumab was set as 90% of patients with regional ERBB2+ disease, based on expert opinion.

The probability of receiving capecitabine was set as 18% of patients with ER-/ERBB2- disease. This number was extrapolated from data about chemotherapy usage patterns for ER-/ERBB2- disease, assuming that patients with ER-/ERBB2- disease treated with neoadjuvant chemotherapy with residual disease would receive capecitabine. A study used data from the National Cancer Data Base (NCDB) to report that in 2010-2011, 81% of ER-/ERBB2- patients received chemotherapy [3]. We estimated that at time of introduction of adjuvant capecitabine, 50% of ER-/ERBB2- patients would receive neoadjuvant therapy. We assumed a pathogenic complete response (pCR) to neoadjuvant therapy rate of 44%, in between the pCR rate of dose-dense doxorubicin/cyclophosphamide and paclitaxel (AC-T, 41%) and the pCR rate of AC-T with carboplatin (54%) in the CALGB 40603 trial [6], based on data from the Georgia and California statewide SEER registries [4].

The probability of receiving neratinib was set as 10% of patients with regional ER+/ERBB2+ disease, based on expert opinion.

For each Stage I-III treatment, we identified the hazard ratio for recurrence-free survival (if available) or disease-free survival (if recurrence-free survival was not reported) from the most recent report from the randomized phase 3 clinical trial that led to its approval (**eTable 3**). Hazard ratios from the intention-to-treat populations were used with the following exceptions, where the drug appeared to be more efficacious in a subpopulation and then was

recommended to be used generally in that subpopulation: neratinib for ER+/HER2+ tumors, pertuzumab for node-positive tumors, and capecitabine for ER-/HER2- tumors.

Modeling the treatment of metastatic disease

Three models (Models D, S, and W) assumed that patients with metastatic disease were treated with sequential specific treatment regimens (**Figure 1B**), with specific benefits derived as below.

We compiled a list of available drugs from the current National Comprehensive Cancer Network (NCCN) guidelines for the management of metastatic breast cancer [7] and identified their years of approval from publicly available reports of the U.S. Food and Drug Administration [8]. We identified the hazard ratios for overall survival with these drugs from the most recent reports of the randomized phase 3 clinical trials that led to their approval (**eTable 3**); we did not include drugs that had demonstrated a progression-free survival, but not an overall survival, benefit. As no data were available comparing the earliest available chemotherapies (e.g. anthracyclines) or endocrine therapies (e.g. tamoxifen) to no treatment in the metastatic setting, we estimated these hazard ratios based on the range of benefits observed for chemotherapy and endocrine therapy to no treatment in the Stage I-III setting as well as the range of benefits observed for newer chemotherapies and endocrine therapies compared to older in the metastatic setting (**eTable 3**)

Simulated patients with metastatic disease received lines of therapy according to standard of care at the time (**Figure 1B**). Baseline (in the absence of treatment) overall survival from diagnosis of metastatic recurrence was assumed to be equal to baseline progression-free survival after metastasis; that is, we assume that in the absence of available treatment, death typically occurs shortly after progression. Hazard ratios for overall survival for metastatic drugs were assumed to be comparable to their hazard ratios for progression-free survival. When a line of therapy was given, its benefits were applied to the simulated patient's baseline survival curve to the next progression, or death if all lines of therapy were exhausted. "Standard of care" was determined from NCCN guidelines in 2019 and extrapolated to previous years using expert opinion (authors JLC and AWK), with reference to control arms of the pivotal clinical trials of newly approved drugs. Because models applied benefits of only those regimens with demonstrated overall survival benefit, the complexity of treatment selection for later-line therapy was narrowed in the models. For example, no simulated patients with metastatic disease received everolimus, alpelisib, lapatinib, or single-agent cyclophosphamide, as these agents have not demonstrated overall survival benefit. Moreover, in a simplified approximation of real-world practice, all simulated patients received lines of therapy in the same pre-specified order.

In those regimens that include multiple agents (for example, taxane/trastuzumab/pertuzumab for ERBB2+ disease), the benefit received was the product of the benefit for each drug individually, based on reports of clinical trials. Similarly, in those regimens in which at least one drug replaced a prior drug that also had an overall survival benefit, the benefit received was the product of the benefit of the prior drug and the benefit of the new drug: for example, a simulated patient receiving trastuzumab emtansine for metastatic ERBB2+ disease received the overall survival benefit of capecitabine (used in the control arm of the EMILIA trial) multiplied by the overall survival benefit of trastuzumab emtansine (as reported by the EMILIA trial) [9]. In this scenario, the drug whose overall survival benefit was already applied could not be used in a later line of therapy (e.g., after the introduction of trastuzumab emtansine, the benefit of capecitabine was given with trastuzumab emtansine, and not again in a later line of therapy). In the years after a treatment had moved from the metastatic to the Stage I-III setting, we halved its efficacy in the metastatic setting if the patient had already received it in the Stage I-III setting.

The probability that a simulated patient would receive a given number of lines of therapy was estimated for 2010-2019 from IBM MarketScan US insurance claims for 2007-2014 [10]. In these data, of 6,180 women with metastatic breast cancer, 100% received at least one line of therapy, 72% at least two lines of therapy, 44% at least three lines of therapy, and 23% at least four lines of therapy. Adjusting for the fact that this study used receipt of at least one line of therapy for metastatic disease for cohort definition, we used the following parameters in the models: 90% probability of receiving at least one line of therapy, 68% at least two lines of therapy, 51% at least three lines of therapy (if available), and 25% four lines of therapy (if available). We assumed that before 1990, half of eligible simulated patients received each available line of therapy, and between 1990 and 2010, dissemination was interpolated to increase linearly to 2010 levels. These assumptions produced drug usage patterns over time as illustrated in **eFigure 4.**

Model M used different assumptions about the treatment of metastatic disease from those described above. Instead of simulating the receipt of specific treatment regimens, Model M applied subtype-specific benefits to the curve from metastasis to death that captured the effects of metastatic treatments in a given year of diagnosis of metastatic disease. To do so, they introduced four parameters to represent the overall survival benefits of metastatic treatments [1,11]. They denote these four parameters as $\alpha_{--}, \alpha_{-+}, \alpha_{+-}, \alpha_{++}$. They represent the hazard ratios of metastatic treatments for overall survival following distant metastasis in year 2020 for the primary disease subtypes ER-/ERBB2-, ER-/ERBB2+, ER+/ERBB2- and ER+/ERBB2+, respectively. As with all unknown parameters in the Bayesian approach, they have probability distributions. These distributions are updated based on the evidence, which in this case is the fit of the Model M results to observed (from SEER) breast cancer mortality. The baseline distributions (years 1975 to 1990) for the breast-cancer survival following distant metastasis are assumed to be exponentially distributed with a median of 1.35 and 1.70 years for the ER- and ER+ subtypes, respectively. These baseline distributions include any benefits of real-world pre-1990 chemotherapy and, for ER+ subtypes, tamoxifen.

Model M derives the hazard ratios of metastatic treatments for ER/ERBB2 subtypes in years 1975 to 2019 using $\alpha_{--}, \alpha_{-+}, \alpha_{+-},$ and α_{++}, based on the inputs on metastatic treatment dissemination and efficacy as used by the other models. The procedure involves two steps. Step 1 is to construct an approximate "standardized" hazard reduction table by subtype and year for metastatic treatments, based on the calculated raw hazard reductions. Step 2 is to discount the raw hazard reductions proportionally using the standardized hazard reduction table and the four α parameters. The details are given below.

Step 1: For each ER/ERBB2 subtype and in each year from 1975-2019, the raw hazard reduction is calculated as the product of the dissemination probability of the therapy and the hazard reduction (i.e., 1 - hazard ratio) due to the therapy for overall survival. Only first-line therapy benefits were included. For combination therapies, the hazard ratio is the product of the hazard ratios of the component therapies. We then standardize the hazard reduction table by dividing each raw hazard reduction in each year by the raw hazard reduction in year 2020 for each ER/ERBB2 subtype. The hazard reductions in 2020 equal 1.0. The full set of calculated standardized hazard reductions is presented in eTable 4.

Step 2: The hazard ratio in each year from 1975-2019 for each ER/ERBB2 subtype is then calculated as 1.0 – (1.0 – α_{ij})*r where *i* and *j* equal + or – and *r* is the corresponding standardized hazard reduction in eTable 4. For example, the hazard ratio for a patient of ER-/ERBB2- subtype in 2010 is 1.0 – (1.0 – α_{--})*0.80684. Similarly, the hazard ratio for a patient of ER+/ERBB2- subtype in 2010 is 1.0 – (1.0 – α_{+-})*0.7099.

Using the same approximate Bayesian computation method as in references [1,11,12], Model M obtains the posterior distributions of all the parameters in the model. These include the parameters in the earlier versions of Model M as well as the α parameters. However, the treatment efficacy parameters (i.e., hazard ratios) for survival in the previous versions of Model M are now replaced by hazard ratios for time from diagnosis to disease recurrence. The resulting posterior distribution of breast-cancer mortality over time in Model M was based on 172 accepted parameter sets. These formed the basis of their simulations of breast cancer incidence and mortality in the eight counterfactual scenarios.

Computation of the relative contributions to mortality reduction associated with each cancer control intervention

Previous work

In our prior work [1,13], we considered the effect of two cancer control interventions on breast cancer mortality reduction, namely screening and treatment of stage I-III breast cancer. To compute their relative contributions to mortality reduction, we used the following notation:

- *MR*(*scr*): mortality reduction associated with screening only
- *MR*(*tx*): mortality reduction associated with treatment only
- *RC*(*scr*): relative contribution to mortality reduction associated with screening only

- *RC*(*tx*): relative contribution to mortality reduction associated with treatments only

We computed relative contributions as follows:

$$RC(scr) = \frac{MR(scr)}{MR(scr) + MR(tx)} = 1 - RC(tx)$$

We refer to this approach as the "symmetrical approach."

Because $MR(scr) + MR(tx) \neq MR(scr, tx)$, there is an interaction between screening and treatment. Consequently, two other approaches to computing the relative contributions are possible, which we call the "asymmetrical approaches" as their results vary depend on which intervention we consider first. If screening is considered first, then the relative contributions are:

$$RC'(scr) = \frac{MR(scr)}{MR(scr, tx)} = 1 - RC'(tx)$$

If adjuvant treatment is considered first, then the relative contributions are:

$$RC''(tx) = \frac{MR(tx)}{MR(scr, tx)} = 1 - RC''(scr)$$

We previously showed that the symmetrical approach is roughly equal to the average of the two asymmetrical approaches. For this reason, we report the results from the symmetrical approach as our main findings.

Current work

After incorporating metastatic recurrence into the models, there are now three interventions contributing to mortality reduction, namely: screening, Stage I-III adjuvant treatment and metastatic treatment, which we denote as ***scr***, ***tx_early*** and ***tx_met,*** *respectively*. Now there are 127 possible approaches to compute, which are summarized in **eFigure 5**.

The most straightforward approach is the symmetrical one, which is computed as follows:

$$RC(scr) = \frac{MR(scr)}{MR(scr) + MR(tx\_early) + MR(tx\_met)}$$
$$RC(tx\_early) = \frac{MR(tx\_early)}{MR(scr) + MR(tx\_early) + MR(tx\_met)}$$
$$RC(tx\_met) = \frac{MR(tx\_met)}{MR(scr) + MR(tx\_early) + MR(tx\_met)}$$

For the other approaches, we will go through one example to demonstrate how they differ. Of note, the first key distinction is how we choose to compute the total mortality reduction associated with all three interventions. Indeed, one could say it is simply equal to $MR(scr, tx\_early, tx\_met)$ (mortality reduction associated with the counterfactual scenario with all three interventions), however in the world of counterfactuals, we could also say it is equal to $MR(scr) + MR(tx\_early, tx\_met)$.

The difference between these approaches is the way we handle interaction terms between each intervention. In actuality, we are choosing one partition of a set with three elements. For instance, the symmetrical approach is derived from the partition with singleton subsets.

Let's say we choose $MR(tx\_early) + MR(scr, tx\_met)$. Now the order with which we decide to compute relative contributions matters (unlike the symmetrical approach…). If we decide to consider screening first, we can either compute it first, or last, which gives, respectively:

$$RC(scr) = \frac{MR(scr)}{MR(tx\_early) + MR(scr, tx\_met)} = 1 - RC(tx\_early, tx\_met)$$

$$RC(scr) = 1 - \frac{MR(tx\_early, tx\_met)}{MR(tx\_early) + MR(scr, tx\_met)} = 1 - RC(tx\_early, tx\_met)$$

Note that if we consider adjuvant treatment, computing it first or last yields the same results.

Next, to separate the relative contribution associated with adjuvant and metastatic treatments, we can proceed as in the previous work when only two interventions were considered: we can either select one of the two asymmetrical approaches or the symmetrical approach. For example:

$$RC(tx\_early) = RC(tx\_early, tx\_met) \times \frac{MR(tx\_early)}{MR(tx\_early, tx\_met)}$$

However, we could also consider these three computations in the presence of screening. Using the same example as above:

$$RC(tx\_early) = RC(tx\_early, tx\_met) \times \frac{MR(tx\_early, scr)}{MR(tx\_early, tx\_met, scr)}$$

With this final step, we covered all possible approaches to compute the relative contributions.

These approaches yield differing estimates of the component of the mortality reduction attributed to each intervention because of interactions between the three interventions. For example, if we consider *MR(tx_early, tx_met, scr)* as the denominator – that is, the mortality reduction in the presence of all three interventions, or the "real world" scenario counterfactual – we find that, across all models, each of the interventions taken alone represents a higher proportion of this overall mortality reduction than we report in the symmetrical approach. By the symmetrical approach, Model D estimates Stage I-III treatment to account for 35% of the overall mortality reduction, but when the scenario of Stage I-III treatment is considered in the absence of screening or metastatic treatment, it alone achieves 49% of that overall mortality reduction (for Model M it is 60% vs 70%; for Model S 44% vs 57%; and for Model W 47% vs 63%). This is not surprising: without screening, disease is diagnosed at a later stage and therefore associated with a worse baseline survival curve, and so the impact of treatment is greater given that the treatment effect is modeled as a proportional hazard. Similarly, by the symmetrical approach Model D estimates metastatic treatment to account for 33% of the overall mortality reduction, but when the scenario of metastatic treatment is considered in the absence of screening or Stage I-III treatment, it alone achieves 46% of that overall mortality reduction (for Model M it is 19% vs 24%; for Model S 31% vs 40%; and for Model W 32% vs 43%). Here, the absence of Stage I-III treatment means both that more patients develop metastatic disease and that the impact of that treatment is greater, because of the absence of resistance to previously received therapies. In total, the sum of the mortality reductions from the three single interventions exceeds the total mortality reduction in all four models – 141% for Model D, 127% for Model M, 130% for Model S, and 134% for Model W – underscoring the importance of the interactions between the interventions.

In the main paper, we reported the symmetrical approach, because it is relatively close to the average of all approaches (**eFigure 6**) and it maintains consistency with our previous work.

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eTable 1. Breast cancer model input parameters

Input Parameter	Description	Source	Model Differences	References
Breast cancer development				
Breast cancer incidence	Estimated from age-period cohort models (D, S, W) or with annual increase (M).	[11]	D uses age-period cohort model directly M samples from prior distribution based on incidence and mammography use S modifies age-period cohort model to consider HRT W uses age-period cohort model as a calibration target	[11,14,15]
Life history				
Other-cause mortality	Age at death from causes other than breast cancer, per birth cohort	[16]	D, S, and W use directly M uses to construct prior distribution	[17]
Breast cancer natural history				
Stage at diagnosis	Stage by age group (<50, 50-64, 65+), mode of detection, screening round, and screening interval	BCSC	D uses AJCC M uses to construct prior distribution S uses local/regional/distant W uses DCIS/local/regional/distant	[18]
ER/ERBB2 at diagnosis	ER/ERBB2 status by age (<50, 50+) and stage at diagnosis	BCSC	D, S, and W use directly M uses to construct prior distribution	[18]
Occurrence of metastatic recurrence	ER/ERBB2-specific overall survival by decade of age and stage, with survival after metastasis subtracted	SEER, BCSC, NCCN Outcomes Database	D and S use directly M uses to construct prior distribution W uses to estimate cure fraction	[14], eMethods
Survival after metastasis	ER/ERBB2-specific overall survival after diagnosis of metastasis by decade of age	NCCN Outcomes Database	D, S, and W use directly M uses to construct prior distribution	eMethods
Interventions				
Dissemination of mammogram	Frequency of mammogram by decade of age and calendar year	National Health Interview Survey, BCSC	All use directly	[18]
Mammogram performance	Sensitivity of initial and subsequent mammogram by age and screening interval	BCSC	D uses directly M uses to construct prior distribution S and W use as calibration target	[18]
Dissemination of stage I-III treatment	Dissemination of systemic treatment by age, stage, and ER/ERBB2 status	SEER patterns of care, NCCN, expert opinion	D, S, and W use directly M uses to construct prior distribution	[18], eMethods

Input Parameter	Description	Source	Model Differences	References
Benefit of stage I-III treatment	Hazards of reduction in recurrence with stage I-III treatment, from clinical trial results	Clinical trials	D and S use to reduce hazard of recurrence M uses to construct prior distribution for hazard of recurrence W uses to increase chance of cure	eTable 3
Dissemination of metastatic treatment	Dissemination of systemic treatment by ER/ERBB2	Expert opinion, claims data [10]	D, S, and W use directly M does not use	Figure1B, eMethods
Benefit of metastatic treatment	Hazards of reduction in mortality with metastatic treatment, from clinical trial results	Clinical trials, expert opinion	D, S, and W use to reduce hazard of death M uses to construct prior distribution for hazard of death	eTable 3

SEER = Surveillance, Epidemiology, and End Results Registry. AJCC = American Joint Committee on Cancer. BCSC = Breast Cancer Surveillance Consortium. ER = estrogen receptor. NCCN = National Comprehensive Cancer Network.

Italicized parameters are new in these models.

eTable 2. NCCN Outcomes Database cohort characteristics

		Total		Distant recurrence by 2012			
				Yes		No	
		N	(%)	N	%	N	%
All patients		82252	100	7740	100	74512	100
Race							
	White/Caucasian	68812	83.7	6253	80.8	62559	84
	Black/African American	8026	9.8	1120	14.5	6906	9.3
	Asian or Pacific Islander	2604	3.2	183	2.4	2421	3.2
	American Indian, Aleutian or Eskimo	270	0.3	27	0.3	243	0.3
	Other or unknown	2540	3.1	157	2	2383	3.2
Ethnicity							
	Non-Hispanic	57810	70.3	5999	77.5	51811	69.5
	Hispanic	3963	4.8	479	6.2	3484	4.7
	Unknown	20479	24.9	1262	16.3	19217	25.8
Year of diagnosis							
	1997-2001	10827	13.2	1898	24.5	8929	12
	2002-2007	25634	31.2	3089	39.9	22545	30.3
	2008-2012	45791	55.7	2753	35.6	43038	57.8
Age at diagnosis (years)							
	0-39	6624	8.1	1148	14.8	5476	7.3
	40-49	19408	23.6	1833	23.7	17575	23.6
	50-59	23348	28.4	2121	27.4	21227	28.5
	60-69	18472	22.5	1392	18	17080	22.9
	≥70	14400	17.5	1246	16.1	13154	17.7
Tumor size (cm)							
	<1	17077	20.8	396	5.1	16681	22.4
	1 to <2	21697	26.4	1044	13.5	20653	27.7
	2 to <3	9928	12.1	1096	14.2	8832	11.9
	3 to <4	3381	4.1	491	6.3	2890	3.9
	4 to <5	1416	1.7	260	3.4	1156	1.6
	≥5	1944	2.4	452	5.8	1492	2
	Unknown	26809	32.6	4001	51.7	22808	30.6
Lymph node involvement							
	No	42649	51.9	1299	16.8	41350	55.5
	Yes	17629	21.4	2569	33.2	15060	20.2
	Unknown	21974	26.7	3872	50	18102	24.3

		Total		Distant recurrence by 2012			
				Yes		No	
		N	(%)	N	%	N	%
Stage IV at diagnosis							
	No	69780	84.8	4565	59.0	65215	87.5
	Yes	2845	3.5	2834	36.6	11	0
	Unknown	9627	11.7	341	4.4	9286	12.5
Tumor grade							
	I	11766	14.3	332	4.3	11434	15.3
	II	28063	34.1	2241	29	25822	34.7
	III	25817	31.4	4490	58	21327	28.6
	Unknown	16606	20.2	677	8.7	15929	21.4
Estrogen receptor status							
	Positive	61554	74.8	4647	60	56907	76.4
	Negative	16551	20.1	2957	38.2	13594	18.2
	Unknown	4147	5	136	1.8	4011	5.4
ERBB2 status							
	Positive	10673	13	1689	21.8	8984	12.1
	Negative	52378	63.7	5229	67.6	47149	63.3
	Unknown	19201	23.3	822	10.6	18379	24.7
Mode of detection							
	Screening	44258	53.8	1516	19.6	42742	57.4
	Clinical	33580	40.8	5272	68.1	28308	38
	Unknown	4414	5.4	952	12.3	3462	4.6
Vital status at last follow-up							
	Dead	7800	9.5	5123	66.2	2677	3.6
	Alive	74452	90.5	2617	33.8	71835	96.4
Death with breast cancer							
	Yes	5123	6.2	5123	66.2	0	0
	No	77129	93.8	2617	33.8	74512	100
Surgery							
	Mastectomy	34803	42.3	3989	51.5	30814	41.4
	Breast conserving surgery	39865	48.5	1688	21.8	38177	51.2
	No surgery	7584	9.2	2063	26.7	5521	7.4
Adjuvant radiation therapy							
	Yes	48353	58.8	3424	44.2	44929	60.3
	No	33899	41.2	4316	55.8	29583	39.7
Adjuvant chemotherapy							
	Yes	27117	33	2581	33.3	24536	32.9
	No	55135	67	5159	66.7	49976	67.1

		Total		Distant recurrence by 2012			
				Yes		No	
		N	(%)	N	%	N	%
Neoadjuvant chemotherapy							
	Yes	9739	11.8	2004	25.9	7735	10.4
	No	72513	88.2	5736	74.1	66777	89.6
Adjuvant hormone therapy							
	Yes	48435	58.9	2457	31.7	45978	61.7
	No	33817	41.1	5283	68.3	28534	38.3

eTable 3. Breast cancer treatments and their efficacy, 1975-2019.

	Year of introduction	Population	Hazard ratio[a]	Reference
Treatments for Stage I-III breast cancer				
Cyclophosphamide, methotrexate, 5-FU	1976[b]	All	0.77	[19]
Anthracycline	1983[b]	All	0.89	[19]
Tamoxifen or aromatase inhibitor	1983[b]	ER+	0.69	[19]
Taxane	1998[b]	All	0.84	[20]
Trastuzumab	2005	ERBB2+	0.60	[21]
Ovarian suppression	2014	ER+, age <50 at diagnosis	0.75	[5]
Pertuzumab	2017	ERBB2+, node-positive	0.72	[22]
Capecitabine	2017	TNBC	0.58	[23]
Neratinib	2017	ER+/ERBB2+, node-positive	0.58	[24]
Treatments after metastasis				
Chemotherapy[c]	Prior to 1975	All	0.70	Estimated[d]
Tamoxifen	1976	ER+	0.80	Estimated[d]
Taxane	1991	All	0.70	[25]
Aromatase inhibitor	1995	ER+	0.90	[26]
Capecitabine	1998	All	0.78	[27]
Trastuzumab	2001	ERBB2+	0.80	[28]
Fulvestrant	2002	ER+	0.70	[29]
Eribulin	2011	All	0.81	[30]
Pertuzumab	2012	ERBB2+	0.69	[31]
Trastuzumab emtansine	2012	ERBB2+	0.75	[9]
CDK4/6 inhibitor	2017	ER+/ERBB2-	0.76	[32]

[a] Hazard ratio is for disease-free or recurrence-free survival (as available) for Stage I-III treatments, and for breast cancer–specific survival for treatments after metastasis.

[b] Dissemination of these treatments follows data from Surveillance, Epidemiology, and End Results (SEER) special patterns of care studies and the National Comprehensive Cancer Network database [1].

[c] Chemotherapy prior to 1975 included cyclophosphamide, methotrexate, 5-FU and anthracycline-containing regimens [33].

5-FU = 5-fluorouracil; ER, estrogen receptor; TNBC, triple-negative breast cancer

[d] There were no clinical trials comparing chemotherapy to placebo or tamoxifen to placebo in the metastatic setting. These hazard ratios were selected to fit within the range of benefits observed for chemotherapy and tamoxifen compared to no treatment in stage I-III breast cancer, as well as the range of benefits observed for new chemotherapies and endocrine therapies compared to prior in metastatic breast cancer.

eTable 4. Model M raw hazard reductions for overall survival after metastasis by ER/ERBB2 subtype and year based on first-line metastatic therapy

Year	ER-/ERBB2-	ER-/ERBB2+	ER+/ERBB2-	ER+/ERBB2+
1975	0	0	0	0
1976	0	0	0	0
1977	0	0	0	0
1978	0	0	0	0
1979	0	0	0	0
1980	0	0	0	0
1981	0	0	0	0
1982	0	0	0	0
1983	0	0	0	0
1984	0	0	0	0
1985	0	0	0	0
1986	0	0	0	0
1987	0	0	0	0
1988	0	0	0	0
1989	0	0	0	0
1990	0	0	0	0
1991	0.46618	0.27993	0	0
1992	0.48411	0.2907	0	0
1993	0.50204	0.30146	0	0
1994	0.51996	0.31223	0	0
1995	0.53789	0.323	0.12791	0.10767
1996	0.55582	0.33376	0.13217	0.11125
1997	0.57375	0.34453	0.13644	0.11484
1998	0.59168	0.3553	0.1407	0.11843
1999	0.60961	0.36606	0.14496	0.12202
2000	0.62754	0.37683	0.14923	0.12561
2001	0.64547	0.56848	0.15349	0.56848
2002	0.6634	0.58427	0.5837	0.58427
2003	0.68133	0.60006	0.59947	0.60006
2004	0.69926	0.61585	0.61525	0.61585
2005	0.71719	0.63164	0.63102	0.63164
2006	0.73512	0.64743	0.6468	0.64743
2007	0.75305	0.66322	0.66257	0.66322
2008	0.77098	0.67901	0.67835	0.67901
2009	0.78891	0.6948	0.69412	0.6948
2010	0.80684	0.71059	0.7099	0.71059
2011	0.80684	0.71059	0.7099	0.71059

Year	ER-/ERBB2-	ER-/ERBB2+	ER+/ERBB2-	ER+/ERBB2+
2012	0.80684	1	0.7099	1
2013	0.80684	1	0.7099	1
2014	0.80684	1	0.7099	1
2015	0.80684	1	0.7099	1
2016	0.80684	1	0.7099	1
2017	0.80684	1	1	1
2018	0.80684	1	1	1
2019	0.80684	1	1	1
2020	1	1	1	1

eTable 5. Estimated absolute breast cancer age-adjusted mortality rate and its reduction relative to no intervention by subtype across eight scenarios in 2019, by CISNET model

	None	Screen		Stage I-III therapy		Met therapy		Stage I-III and met therapy		Screen and Stage I-III therapy		Screen and met therapy		All three interventions	
	Abs *	Abs	Rel †	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel	Abs	Rel
Overall															
Model D	63.1	46.1	27%	45.0	29%	45.9	27%	32.9	48%	32.0	49%	36.9	42%	25.9	59%
Model M	61.9	53.0	14%	36.2	42%	53.8	13%	31.9	49%	32.0	48%	46.2	25%	28.1	55%
Model S	65.2	52.9	19%	43.8	33%	50.4	23%	35.0	46%	34.2	48%	41.7	36%	27.8	57%
Model W	66.7	55.2	17%	40.8	39%	49.3	26%	31.4	53%	33.2	50%	41.1	38%	25.9	61%
Average	64.2	51.8	19%	41.5	35%	49.8	22%	32.8	49%	32.8	49%	41.5	35%	26.9	58%
ER+ERBB2-															
Model D	41.8	30.0	28%	30.3	27%	29.4	30%	21.1	50%	21.1	50%	23.6	44%	16.6	60%
Model M	37.0	31.7	15%	21.0	43%	32.3	13%	18.4	50%	18.7	50%	27.8	25%	16.3	56%
Model S	40.4	32.6	19%	27.1	33%	30.4	25%	20.9	48%	21.1	48%	25.2	38%	16.5	59%
Model W	40.4	34.0	16%	24.9	38%	29.2	28%	18.4	55%	20.5	49%	24.8	39%	15.4	62%
Average	39.9	32.1	19%	25.9	35%	30.3	24%	19.7	51%	20.3	49%	25.3	36%	16.2	59%
ER+ERBB2+															
Model D	8.0	6.1	24%	4.3	46%	5.5	31%	3.0	62%	3.1	61%	4.6	43%	2.5	69%
Model M	8.4	7.1	16%	3.9	54%	6.2	26%	3.0	64%	3.4	59%	5.4	36%	2.7	68%
Model S	9.7	7.8	19%	4.9	49%	7.1	27%	3.8	61%	3.7	62%	5.8	40%	2.7	72%
Model W	9.8	8.0	18%	3.9	60%	6.7	31%	2.9	70%	3.1	68%	5.6	43%	2.3	76%
Average	9.0	7.2	19%	4.2	52%	6.4	29%	3.2	64%	3.3	63%	5.3	40%	2.6	71%
ER-ERBB2+															
Model D	4.4	3.3	23%	2.8	35%	3.0	31%	2.0	55%	2.1	51%	2.4	45%	1.5	65%
Model M	7.3	6.3	14%	4.5	39%	6.4	13%	3.9	47%	3.9	46%	5.5	25%	3.5	53%
Model S	5.6	4.5	20%	3.7	34%	4.2	25%	2.9	48%	2.9	49%	3.5	37%	2.4	57%
Model W	6.2	4.9	21%	3.7	41%	4.5	28%	2.7	56%	2.8	54%	3.5	43%	2.1	66%
Average	5.9	4.8	20%	3.7	37%	4.5	24%	2.9	52%	3.0	50%	3.7	37%	2.4	60%
ER-ERBB2-															
Model D	8.9	6.7	25%	7.6	15%	8.0	10%	6.8	24%	5.7	37%	6.3	29%	5.3	40%
Model M	9.2	7.9	14%	6.8	26%	8.9	3%	6.5	29%	5.9	35%	7.6	17%	5.7	38%
Model S	9.5	7.9	17%	8.0	16%	8.7	9%	7.5	22%	6.6	31%	7.2	24%	6.2	35%
Model W	10.3	8.3	19%	8.4	19%	8.9	13%	7.4	28%	6.8	34%	7.2	30%	6.0	42%
Average	9.5	7.7	18%	7.7	19%	8.6	9%	7.0	26%	6.2	34%	7.1	25%	5.8	39%

* "Abs" (absolute) refers to the predicted age-adjusted breast cancer mortality rate per 100,000 women under each scenario. † "Rel" (relative) refers to the percentage reduction in that mortality rate as compared to predicted mortality with no interventions ("none"). ER = estrogen receptor, met = metastatic.

eTable 6. Estimated median breast cancer–specific survival after distant recurrence over time by estrogen receptor/ERBB2 subtype, by CISNET model

Subtype	Year *	Median Breast Cancer–Specific Survival After Recurrence (Years)				
		Model D	Model M	Model S	Model W	Mean
ER+/ERBB2-	1975	1.37	1.78	1.04	1.00	1.30
	1976	1.65	1.78	1.13	1.00	1.39
	1977	1.65	1.78	1.15	1.00	1.39
	1978	1.65	1.78	1.15	1.00	1.39
	1979	1.64	1.78	1.16	1.00	1.40
	1980	1.64	1.78	1.15	1.00	1.39
	1981	1.63	1.78	1.14	1.00	1.39
	1982	1.63	1.78	1.15	1.00	1.39
	1983	1.63	1.78	1.16	1.00	1.39
	1984	1.62	1.78	1.15	1.00	1.39
	1985	1.62	1.78	1.15	1.00	1.39
	1986	1.61	1.78	1.15	1.00	1.39
	1987	1.61	1.78	1.16	1.00	1.39
	1988	1.60	1.78	1.15	1.00	1.38
	1989	1.60	1.78	1.18	1.00	1.39
	1990	1.59	1.78	1.18	1.00	1.39
	1991	1.68	2.02	1.26	1.00	1.49
	1992	1.72	2.26	1.29	1.00	1.57
	1993	1.76	2.50	1.30	1.00	1.64
	1994	1.80	2.58	1.35	1.00	1.68
	1995	1.93	2.67	1.41	1.00	1.75
	1996	1.99	2.75	1.46	1.00	1.80
	1997	2.05	2.75	1.45	1.00	1.81
	1998	2.34	2.75	1.59	1.00	1.92
	1999	2.44	2.83	1.63	1.00	1.98
	2000	2.54	2.92	1.67	1.50	2.16
	2001	2.66	3.00	1.74	1.50	2.22
	2002	3.26	3.00	2.15	1.50	2.48
	2003	3.41	3.00	2.29	1.50	2.55
	2004	3.56	3.00	2.47	1.50	2.63
	2005	3.72	3.08	2.62	1.50	2.73
	2006	3.87	3.17	2.74	2.00	2.95
	2007	4.03	3.25	2.89	2.00	3.04
	2008	4.20	3.25	3.05	2.00	3.12
	2009	4.36	3.33	3.09	2.00	3.19
	2010	4.53	3.42	3.12	2.00	3.27
	2011	4.95	3.50	3.29	2.00	3.43
	2012	4.94	3.50	3.15	2.00	3.40
	2013	4.93	3.50	3.17	2.00	3.40
	2014	4.92	3.50	3.07	2.00	3.37
	2015	4.91	3.52	3.08	2.00	3.38
	2016	4.90	3.53	3.05	2.50	3.50
	2017	5.55	3.55	3.44	2.50	3.76
	2018	5.54	3.55	3.36	2.50	3.74
	2019	5.53	3.55	3.27	2.50	3.71

Subtype	Year *	Median Breast Cancer–Specific Survival After Recurrence (Years)				
		Model D	Model M	Model S	Model W	Mean
ER+/ERBB2+	1975	1.41	1.79	1.06	1.00	1.32
	1976	1.69	1.79	1.23	1.00	1.43
	1977	1.69	1.79	1.19	1.00	1.42
	1978	1.68	1.79	1.21	1.00	1.42
	1979	1.68	1.79	1.22	1.00	1.42
	1980	1.68	1.79	1.19	1.00	1.41
	1981	1.67	1.80	1.23	1.00	1.43
	1982	1.67	1.81	1.21	1.00	1.42
	1983	1.68	1.82	1.20	1.00	1.42
	1984	1.66	1.82	1.19	1.00	1.42
	1985	1.66	1.82	1.25	1.00	1.43
	1986	1.66	1.82	1.16	1.00	1.41
	1987	1.65	1.82	1.19	1.00	1.42
	1988	1.65	1.82	1.21	1.00	1.42
	1989	1.64	1.82	1.20	1.00	1.42
	1990	1.64	1.82	1.19	1.00	1.41
	1991	1.72	2.21	1.26	1.00	1.55
	1992	1.75	2.61	1.28	1.00	1.66
	1993	1.79	3.00	1.33	1.00	1.78
	1994	1.83	3.00	1.29	1.00	1.78
	1995	1.95	3.08	1.41	1.00	1.86
	1996	2.00	3.17	1.39	1.00	1.89
	1997	2.06	3.33	1.40	1.00	1.95
	1998	2.32	3.46	1.56	1.50	2.21
	1999	2.41	3.58	1.60	1.00	2.15
	2000	2.51	3.75	1.72	1.50	2.37
	2001	3.11	3.87	2.02	1.50	2.63
	2002	3.43	4.00	2.31	1.50	2.81
	2003	3.58	4.08	2.39	2.00	3.01
	2004	3.73	4.25	2.46	2.00	3.11
	2005	3.89	4.50	2.76	2.00	3.29
	2006	4.05	4.75	3.24	2.00	3.51
	2007	4.18	4.92	3.31	2.50	3.73
	2008	4.31	5.08	3.64	2.50	3.88
	2009	4.45	5.25	3.70	2.50	3.97
	2010	4.58	5.42	3.88	3.00	4.22
	2011	4.97	5.58	3.79	3.00	4.33
	2012	6.15	5.67	4.74	3.50	5.01
	2013	6.12	5.75	4.40	3.50	4.94
	2014	6.10	5.75	4.19	3.50	4.88
	2015	6.08	5.75	4.09	3.50	4.85
	2016	6.06	5.75	4.07	3.50	4.85
	2017	6.05	5.75	4.19	3.50	4.87
	2018	5.98	5.75	4.15	3.50	4.84
	2019	5.93	5.83	4.24	3.50	4.88
ER-/ERBB2+	1975	1.34	1.44	1.05	1.00	1.21
	1976	1.33	1.44	1.00	1.00	1.19
	1977	1.32	1.44	1.08	1.00	1.21
	1978	1.32	1.44	1.03	1.00	1.20
	1979	1.31	1.46	1.02	1.00	1.20
	1980	1.31	1.48	1.06	1.00	1.21

Subtype	Year *	Median Breast Cancer–Specific Survival After Recurrence (Years)				
		Model D	Model M	Model S	Model W	Mean
	1981	1.30	1.50	1.03	0.50	1.08
	1982	1.30	1.50	1.05	1.00	1.21
	1983	1.29	1.50	1.03	0.50	1.08
	1984	1.29	1.50	1.02	0.50	1.08
	1985	1.29	1.50	0.98	0.50	1.07
	1986	1.28	1.50	0.96	0.50	1.06
	1987	1.28	1.50	1.00	0.50	1.07
	1988	1.28	1.50	0.97	0.50	1.06
	1989	1.27	1.50	0.97	1.00	1.18
	1990	1.27	1.50	1.00	1.00	1.19
	1991	1.49	1.67	1.13	1.00	1.32
	1992	1.50	1.83	1.15	1.00	1.37
	1993	1.52	2.00	1.13	1.00	1.41
	1994	1.53	2.00	1.23	1.00	1.44
	1995	1.55	2.00	1.18	1.00	1.43
	1996	1.56	2.08	1.19	1.00	1.46
	1997	1.58	2.17	1.19	1.00	1.58
	1998	2.20	2.25	1.52	1.00	1.74
	1999	2.24	2.25	1.45	1.00	1.73
	2000	2.29	2.29	1.53	1.50	1.90
	2001	2.60	2.34	1.76	1.50	2.05
	2002	2.67	2.46	1.67	1.50	2.08
	2003	2.74	2.54	1.81	1.50	2.15
	2004	2.81	2.62	1.90	1.50	2.21
	2005	2.88	2.62	1.99	1.50	2.25
	2006	2.95	2.66	2.45	1.50	2.39
	2007	2.98	2.76	2.34	1.50	2.40
	2008	3.02	2.86	2.30	1.50	2.42
	2009	3.06	2.92	2.32	1.50	2.45
	2010	3.10	2.95	2.43	2.00	2.62
	2011	4.01	2.97	2.73	2.00	2.93
	2012	5.29	3.00	3.58	3.00	3.72
	2013	5.27	3.02	3.35	3.00	3.66
	2014	5.25	3.03	3.34	3.00	3.66
	2015	5.24	3.05	3.16	3.00	3.61
	2016	5.23	3.05	3.26	3.00	3.63
	2017	5.22	3.05	3.19	3.00	3.62
	2018	5.15	3.07	3.40	2.50	3.53
	2019	5.10	3.10	3.09	2.50	3.45
ER-/ERBB2-	1975	0.73	1.50	0.54	0.50	0.82
	1976	0.73	1.50	0.57	0.50	0.83
	1977	0.73	1.50	0.57	0.50	0.83
	1978	0.73	1.50	0.59	0.50	0.83
	1979	0.73	1.50	0.56	0.50	0.82
	1980	0.72	1.50	0.58	0.50	0.83
	1981	0.72	1.50	0.55	0.50	0.82
	1982	0.72	1.50	0.56	0.50	0.82
	1983	0.72	1.50	0.56	0.50	0.82
	1984	0.72	1.50	0.55	0.50	0.82
	1985	0.71	1.50	0.55	0.50	0.82
	1986	0.71	1.50	0.55	0.50	0.82

Subtype	Year *	Median Breast Cancer–Specific Survival After Recurrence (Years)				
		Model D	Model M	Model S	Model W	Mean
	1987	0.71	1.50	0.56	0.50	0.82
	1988	0.71	1.50	0.56	0.50	0.82
	1989	0.71	1.50	0.57	0.50	0.82
	1990	0.71	1.50	0.55	0.50	0.81
	1991	0.84	1.58	0.66	0.50	0.90
	1992	0.85	1.67	0.65	0.50	0.92
	1993	0.86	1.75	0.64	0.50	0.94
	1994	0.86	1.75	0.67	0.50	0.95
	1995	0.87	1.75	0.68	0.50	0.95
	1996	0.88	1.75	0.67	0.50	0.95
	1997	0.89	1.75	0.68	0.50	0.96
	1998	1.26	1.75	0.85	0.50	1.09
	1999	1.28	1.75	0.87	0.50	1.10
	2000	1.31	1.75	0.91	0.50	1.12
	2001	1.34	1.75	0.91	0.50	1.12
	2002	1.37	1.76	0.94	0.50	1.14
	2003	1.40	1.78	0.96	0.50	1.16
	2004	1.44	1.79	1.00	0.50	1.18
	2005	1.47	1.79	1.00	1.00	1.31
	2006	1.50	1.79	1.00	1.00	1.32
	2007	1.54	1.79	1.05	1.00	1.34
	2008	1.57	1.82	1.04	1.00	1.36
	2009	1.60	1.86	1.08	1.00	1.39
	2010	1.64	1.89	1.11	1.00	1.41
	2011	2.16	1.89	1.33	1.00	1.60
	2012	2.15	1.89	1.24	1.00	1.57
	2013	2.15	1.89	1.32	1.00	1.59
	2014	2.14	1.89	1.30	1.00	1.58
	2015	2.14	1.93	1.29	1.00	1.59
	2016	2.14	1.96	1.27	1.00	1.59
	2017	2.13	2.00	1.27	1.00	1.60
	2018	2.13	2.00	1.31	1.00	1.61
	2019	2.12	2.00	1.35	1.00	1.62
All	1975	1.28	1.75	0.94	1.00	1.24
	1976	1.50	1.75	1.00	1.00	1.31
	1977	1.50	1.75	1.02	1.00	1.32
	1978	1.50	1.75	1.02	1.00	1.32
	1979	1.49	1.75	1.03	1.00	1.32
	1980	1.49	1.75	1.02	1.00	1.32
	1981	1.49	1.75	1.02	1.00	1.31
	1982	1.48	1.75	1.02	1.00	1.31
	1983	1.48	1.75	1.02	1.00	1.31
	1984	1.47	1.75	1.01	1.00	1.31
	1985	1.47	1.75	1.02	1.00	1.31
	1986	1.47	1.75	1.00	1.00	1.30
	1987	1.46	1.75	1.01	1.00	1.31
	1988	1.46	1.75	1.01	1.00	1.30
	1989	1.45	1.75	1.02	1.00	1.30
	1990	1.44	1.75	1.02	1.00	1.30
	1991	1.55	1.92	1.12	1.00	1.40
	1992	1.58	2.08	1.14	1.00	1.45

Subtype	Year *	Median Breast Cancer–Specific Survival After Recurrence (Years)				
		Model D	Model M	Model S	Model W	Mean
	1993	1.61	2.33	1.14	1.00	1.52
	1994	1.65	2.42	1.17	1.00	1.56
	1995	1.75	2.50	1.21	1.00	1.61
	1996	1.79	2.50	1.24	1.00	1.63
	1997	1.83	2.50	1.41	1.00	1.64
	1998	2.16	2.50	1.41	1.00	1.77
	1999	2.24	2.67	1.44	1.00	1.81
	2000	2.33	2.67	1.49	1.00	1.87
	2001	2.50	2.75	1.60	1.00	1.96
	2002	2.93	2.75	1.81	1.50	2.25
	2003	3.05	2.83	1.91	1.50	2.32
	2004	3.18	2.92	2.03	1.50	2.41
	2005	3.30	3.00	2.14	1.50	2.49
	2006	3.43	3.00	2.29	1.50	2.56
	2007	3.55	3.00	2.34	1.50	2.60
	2008	3.67	3.00	2.44	1.50	2.65
	2009	3.80	3.08	2.46	1.50	2.71
	2010	3.93	3.17	2.49	2.00	2.90
	2011	4.39	3.25	2.70	2.00	3.09
	2012	4.59	3.25	2.74	2.00	3.15
	2013	4.57	3.25	2.72	2.00	3.14
	2014	4.56	3.25	2.63	2.00	3.11
	2015	4.54	3.25	2.62	2.00	3.10
	2016	4.53	3.25	2.56	2.00	3.09
	2017	4.95	3.25	2.76	2.00	3.24
	2018	4.93	3.25	2.79	2.00	3.24
	2019	4.91	3.25	2.73	2.00	3.22

* Year is the year of diagnosis of metastatic recurrence. ER = estrogen receptor. Figure 3A of the main paper is a graphical display of the model mean results from 2000 to 2019.

eTable 7. Estimated five and ten-year distant recurrence-free survival over time by estrogen receptor/ERBB2 subtype

Subtype	Year*	5-Year DRFS (%)					10-Year DRFS (%)				
		D	M	S	W	Mean	D	M	S	W	Mean
ER+ ERBB2-	1975	78.8	79.8	83.1	65.7	76.8	71.6	73.4	76.2	64.6	71.5
	1976	79.2	80.0	83.6	65.8	77.1	72.1	73.5	76.6	64.7	71.7
	1977	79.2	80.4	83.6	66.7	77.5	72.1	73.9	76.9	65.6	72.1
	1978	79.4	80.3	83.8	66.2	77.4	72.3	74.1	77.1	65.1	72.2
	1979	79.6	80.6	84.0	67.0	77.8	72.6	74.3	77.2	66.0	72.5
	1980	80.1	80.9	84.2	66.2	77.9	73.2	74.4	77.6	65.2	72.6
	1981	80.6	81.2	84.4	67.0	78.3	73.8	75.0	78.1	66.0	73.2
	1982	81.1	81.1	85.0	67.1	78.6	74.4	75.1	78.6	65.9	73.5
	1983	81.5	82.2	85.2	68.3	79.3	74.8	76.3	78.8	67.2	74.3
	1984	81.8	82.8	85.7	69.0	79.8	75.2	76.6	79.5	67.9	74.8
	1985	82.3	83.4	86.3	69.4	80.3	75.8	77.7	80.2	68.2	75.5
	1986	82.8	84.2	86.9	70.4	81.1	76.5	78.5	81.1	69.1	76.3
	1987	83.4	85.1	87.7	71.3	81.9	77.2	79.8	82.0	69.9	77.2
	1988	84.5	85.9	88.2	73.7	83.1	87.8	80.9	83.0	72.6	78.8
	1989	85.2	85.9	88.7	75.7	83.9	79.5	81.0	83.5	74.4	79.6
	1990	86.0	87.0	89.4	77.4	84.9	80.5	82.2	84.4	76.4	80.9
	1991	86.4	86.9	89.6	78.3	85.3	81.0	82.2	84.7	77.3	81.3
	1992	86.6	87.3	90.0	79.2	85.8	81.4	82.8	85.3	78.1	81.9
	1993	86.7	86.9	90.1	80.1	85.9	81.4	82.4	85.4	79.1	82.1
	1994	86.9	87.5	90.0	80.4	86.2	81.7	83.1	85.5	79.3	82.4
	1995	87.0	87.4	90.2	81.0	86.3	81.8	82.9	85.4	79.4	82.4
	1996	87.0	87.3	90.3	81.0	86.4	81.9	82.6	85.7	80.1	82.6
	1997	87.0	90.1	89.8	79.0	86.5	81.9	86.4	85.0	78.0	82.8
	1998	87.8	90.4	90.3	81.0	87.4	82.9	86.8	85.6	80.1	83.9
	1999	88.0	90.6	90.3	81.7	87.6	83.1	87.1	85.7	80.8	84.2
	2000	88.1	90.9	90.4	81.5	87.7	83.4	87.5	85.8	80.6	84.3
	2001	88.3	91.0	90.6	82.4	88.1	83.6	87.5	86.1	81.6	84.7
	2002	88.5	91.7	91.6	83.1	88.7	83.8	89.7	87.6	82.2	85.8
	2003	88.7	91.8	91.7	83.8	89.0	84.1	89.9	87.8	82.9	86.2
	2004	88.8	92.0	91.9	84.1	89.2	84.3	90.2	88.0	83.3	86.5
	2005	89.0	92.1	92.1	85.1	89.6	84.6	90.3	88.2	84.4	86.9
	2006	89.2	92.3	92.3	85.2	89.8	84.8	90.6	88.6	84.4	87.1
	2007	89.2	92.2	92.3	85.4	89.8	84.8	90.6	88.6	84.8	87.2
	2008	89.3	92.2	92.3	85.7	89.9	84.9	90.5	88.5	85.0	87.2
	2009	89.3	92.5	92.4	85.8	90.0	84.9	90.8	88.7	85.1	87.4
	2010	89.3	92.1	92.5	85.9	90.0	84.9	90.3	88.9	85.3	87.3
	2011	89.3	92.2	92.3	85.9	89.9	84.9	90.5	88.6	85.3	87.4
	2012	89.3	92.2	92.4	85.8	89.9	84.9	90.5	88.7	85.3	87.4
	2013	89.3	92.3	92.5	86.1	90.1	85.0	90.5	88.8	85.5	87.4
	2014	89.7	92.3	92.7	86.4	90.3	85.4	90.6	89.1	85.8	87.7
	2015	89.7	92.4	92.8	86.1	90.3	85.4	90.6	89.3	85.4	87.7
	2016	89.7	92.2	92.9	86.0	90.2	85.4	90.4	89.3	85.3	87.6
	2017	89.7	92.2	92.8	86.2	90.2	85.4	90.4	89.2	85.5	87.6
	2018	89.7	92.3	92.7	86.1	90.2	85.4	90.4	89.2	85.5	87.6
	2019	89.7	92.1	92.8	86.0	90.1	85.4	90.4	89.2	85.4	87.6

Subtype	Year*	5-Year DRFS (%)					10-Year DRFS (%)				
		D	M	S	W	Mean	D	M	S	W	Mean
ER+ ERBB2+	1975	68.1	67.5	70.6	64.7	67.7	60.6	60.1	62.5	63.4	61.6
	1976	68.6	68.9	70.6	66.2	68.6	61.1	61.5	62.6	65.4	62.7
	1977	68.6	67.8	71.1	66.1	68.4	61.1	61.5	63.4	65.0	62.8
	1978	68.9	69.1	72.0	63.1	68.3	61.4	62.3	64.1	61.9	62.4
	1979	69.2	69.0	71.8	66.6	69.2	61.8	62.4	64.3	65.2	63.4
	1980	69.9	69.8	72.7	64.9	69.3	62.5	63.6	65.1	63.7	63.7
	1981	70.6	69.7	73.7	65.4	69.9	63.4	62.7	66.1	64.4	64.2
	1982	71.3	69.1	74.2	68.4	70.7	64.1	62.0	66.5	66.7	64.8
	1983	71.8	71.5	74.5	67.4	71.3	64.6	65.6	67.2	66.5	66.0
	1984	72.2	70.4	75.4	69.3	71.8	65.1	64.0	68.8	68.0	66.5
	1985	72.8	72.6	76.1	68.5	72.5	65.8	65.3	68.6	67.5	66.8
	1986	73.4	73.3	77.0	69.3	73.3	66.5	66.6	70.2	68.1	67.8
	1987	74.1	73.9	78.4	71.7	74.5	67.3	67.8	71.6	70.6	69.3
	1988	75.8	74.8	79.5	74.8	76.2	69.3	68.5	73.0	73.3	71.0
	1989	76.7	75.8	80.9	74.6	77.0	70.4	69.5	75.1	73.9	72.2
	1990	77.8	77.6	81.6	76.1	78.3	71.7	71.6	75.7	75.2	73.6
	1991	78.4	77.4	82.4	77.5	78.9	72.4	72.0	76.5	76.6	74.4
	1992	78.8	78.1	82.4	79.1	79.6	72.9	72.3	76.8	78.4	75.1
	1993	78.8	76.7	82.7	76.8	78.8	72.9	71.6	77.0	76.0	74.4
	1994	79.1	77.4	83.0	77.7	79.3	73.3	71.7	77.3	76.7	74.7
	1995	79.2	77.8	82.9	78.3	79.6	73.4	72.0	77.3	77.5	75.0
	1996	79.3	77.3	82.7	79.7	79.7	73.5	71.9	77.3	79.2	75.5
	1997	79.1	83.7	82.4	79.3	81.1	73.3	79.0	76.8	78.4	76.9
	1998	80.3	84.0	83.3	80.9	82.1	74.7	79.1	77.8	80.2	77.9
	1999	80.6	83.7	83.1	79.9	81.8	75.1	79.5	77.5	78.9	77.7
	2000	80.9	84.1	83.6	79.6	82.0	75.4	79.7	78.1	78.7	78.0
	2001	81.1	83.9	83.4	81.3	82.4	75.7	79.6	78.2	80.4	78.5
	2002	81.4	85.8	85.4	82.2	83.7	76.0	83.4	80.7	81.4	80.4
	2003	81.7	85.2	85.5	83.1	83.9	76.4	83.0	80.7	82.0	80.5
	2004	81.9	85.7	86.2	83.5	84.3	76.7	83.6	81.5	82.6	81.1
	2005	82.2	86.4	91.3	83.9	86.0	77.0	84.6	88.2	83.3	83.3
	2006	88.4	90.8	91.7	90.2	90.3	84.9	89.6	88.5	89.9	88.2
	2007	88.5	90.4	91.2	91.3	90.3	84.9	89.1	88.1	90.6	88.2
	2008	88.5	90.3	91.9	89.4	90.0	84.9	89.2	89.0	88.9	88.0
	2009	88.5	90.3	91.5	90.7	90.2	84.9	89.2	88.5	90.1	88.2
	2010	88.5	90.7	91.7	89.9	90.2	85.0	89.4	88.7	89.5	88.1
	2011	88.5	91.1	91.8	90.7	90.5	85.0	89.7	88.8	90.2	88.4
	2012	88.5	90.6	91.3	91.7	90.6	85.0	89.4	88.3	91.3	88.5
	2013	88.5	90.6	91.9	89.3	90.1	85.0	89.3	88.9	88.6	87.9
	2014	89.3	91.0	92.2	91.9	91.1	86.0	89.8	89.5	91.6	89.2
	2015	89.3	90.6	92.1	90.2	90.5	86.0	89.5	89.3	89.8	88.6
	2016	89.3	90.0	92.0	91.0	90.6	86.0	88.9	89.0	90.7	88.6
	2017	90.6	90.3	93.4	93.6	92.0	87.4	88.9	91.0	93.2	90.1
	2018	90.6	90.9	93.5	92.3	91.8	87.4	89.6	91.0	92.1	90.0
	2019	90.6	90.6	93.9	93.1	92.0	87.4	89.4	91.5	92.8	90.3
ER- ERBB+	1975	61.3	59.8	62.9	54.2	59.6	54.5	53.3	56.2	52.7	54.2
	1976	61.5	59.6	63.2	52.6	59.2	54.8	52.8	56.2	51.5	53.8
	1977	61.6	60.2	64.6	56.2	60.7	54.8	53.1	58.0	54.5	55.1
	1978	61.8	61.0	64.0	55.9	60.7	55.0	54.3	56.9	54.9	55.3
	1979	62.1	60.3	64.7	54.5	60.4	55.4	54.2	57.9	53.7	55.3

Subtype	Year*	5-Year DRFS (%)					10-Year DRFS (%)				
		D	M	S	W	Mean	D	M	S	W	Mean
	1980	62.7	60.2	64.6	55.6	60.8	56.0	52.9	58.1	54.3	55.3
	1981	63.3	61.6	65.8	56.3	61.8	56.7	54.9	59.1	55.5	56.5
	1982	63.9	60.9	66.4	58.7	62.5	57.3	54.0	59.9	56.6	56.9
	1983	64.4	63.1	66.8	58.5	63.2	57.7	55.7	60.0	57.6	57.8
	1984	64.7	63.7	67.4	56.7	63.1	58.1	57.4	60.8	54.9	57.8
	1985	65.1	64.1	68.1	59.6	64.2	58.5	57.7	61.2	58.3	58.9
	1986	65.5	66.0	68.7	60.3	65.1	59.0	60.1	61.9	57.9	59.7
	1987	66.1	66.4	69.8	61.1	65.8	59.5	60.4	63.5	59.8	60.8
	1988	67.0	65.7	70.2	61.8	66.2	60.6	58.9	63.8	59.9	60.8
	1989	67.7	66.3	71.4	62.1	66.9	61.4	60.5	65.1	60.9	62.0
	1990	68.3	67.1	72.6	61.7	67.4	62.1	60.8	66.7	59.9	62.4
	1991	68.8	66.5	73.2	64.8	68.3	62.5	59.9	67.5	63.5	63.4
	1992	69.1	66.5	73.6	62.4	67.9	62.9	60.6	67.6	60.2	62.8
	1993	69.4	66.1	73.2	65.6	68.6	63.2	60.1	67.1	63.8	63.5
	1994	69.6	67.0	74.0	65.8	69.1	63.5	60.9	68.3	64.3	64.2
	1995	69.8	66.8	72.9	67.5	69.3	63.7	61.1	67.4	65.9	64.5
	1996	70.0	67.4	73.7	65.9	69.2	63.9	61.3	68.1	64.5	64.4
	1997	69.2	77.3	71.6	65.1	70.8	63.0	72.9	66.1	63.4	66.3
	1998	70.5	78.2	72.7	67.6	72.5	64.5	73.4	67.7	65.9	67.9
	1999	70.7	77.9	73.7	66.9	72.3	64.6	73.1	67.5	65.0	67.6
	2000	70.8	78.2	74.4	68.1	72.9	64.8	73.8	68.6	66.8	68.5
	2001	70.9	79.0	73.7	70.0	73.4	65.0	74.2	67.9	68.7	68.9
	2002	71.1	77.7	74.0	68.6	72.8	65.2	73.5	68.2	67.5	68.6
	2003	71.2	77.2	74.0	69.0	72.9	65.3	73.1	68.0	67.6	68.5
	2004	71.4	77.8	75.2	70.6	73.7	65.5	73.3	69.3	69.1	69.3
	2005	71.6	77.8	83.0	70.0	75.6	65.7	73.8	79.0	67.8	71.6
	2006	80.8	84.7	83.4	82.8	82.9	76.5	81.5	79.2	81.9	79.8
	2007	81.0	85.2	83.3	77.7	81.8	76.7	82.1	79.5	76.6	78.7
	2008	81.1	85.4	83.3	77.9	81.9	76.9	82.1	79.0	76.9	78.7
	2009	81.3	84.9	83.4	79.0	82.1	77.1	81.6	79.3	78.1	79.0
	2010	81.5	84.7	82.6	78.8	81.9	77.3	81.6	78.8	77.6	78.8
	2011	81.5	84.3	83.8	79.2	82.2	77.3	81.3	79.9	77.9	79.1
	2012	81.5	84.6	82.8	77.5	81.6	77.3	81.4	78.7	76.5	78.5
	2013	81.5	84.4	83.4	81.1	82.6	77.3	80.8	79.7	80.1	79.5
	2014	81.5	85.2	83.7	79.1	82.4	77.4	82.0	79.9	77.9	79.3
	2015	81.5	85.2	83.6	80.3	82.7	77.4	82.0	79.8	79.4	79.6
	2016	81.5	84.9	82.9	79.5	82.2	77.4	82.2	78.8	78.6	79.2
	2017	83.3	84.2	85.9	83.8	84.3	79.4	81.1	82.3	82.7	81.4
	2018	83.3	84.0	85.4	82.8	83.9	79.4	80.5	81.5	81.9	80.8
	2019	83.3	84.8	85.9	82.8	84.2	79.4	81.4	82.4	82.5	81.4
ER-ERBB2-	1975	72.5	72.2	72.9	56.3	68.5	65.2	65.1	65.1	55.0	62.6
	1976	73.1	73.2	73.9	57.1	69.3	65.8	66.4	66.0	56.5	63.7
	1977	73.1	72.6	74.8	59.1	69.9	65.8	65.3	67.0	58.0	64.0
	1978	73.3	73.3	74.3	59.5	70.1	66.0	66.2	66.5	58.4	64.3
	1979	73.5	73.7	75.3	58.9	70.4	66.3	66.7	67.5	57.6	64.5
	1980	74.0	73.5	75.8	59.1	70.6	66.8	66.8	68.0	57.5	64.8
	1981	74.5	73.7	75.5	58.0	70.4	67.4	66.1	67.9	56.6	64.5
	1982	74.9	74.4	76.1	58.9	71.1	67.9	67.9	68.5	57.3	65.4
	1983	75.2	74.5	76.7	60.8	71.8	68.2	67.6	69.1	59.2	66.0
	1984	75.5	74.9	77.3	62.8	72.6	68.5	67.9	69.9	61.3	66.9

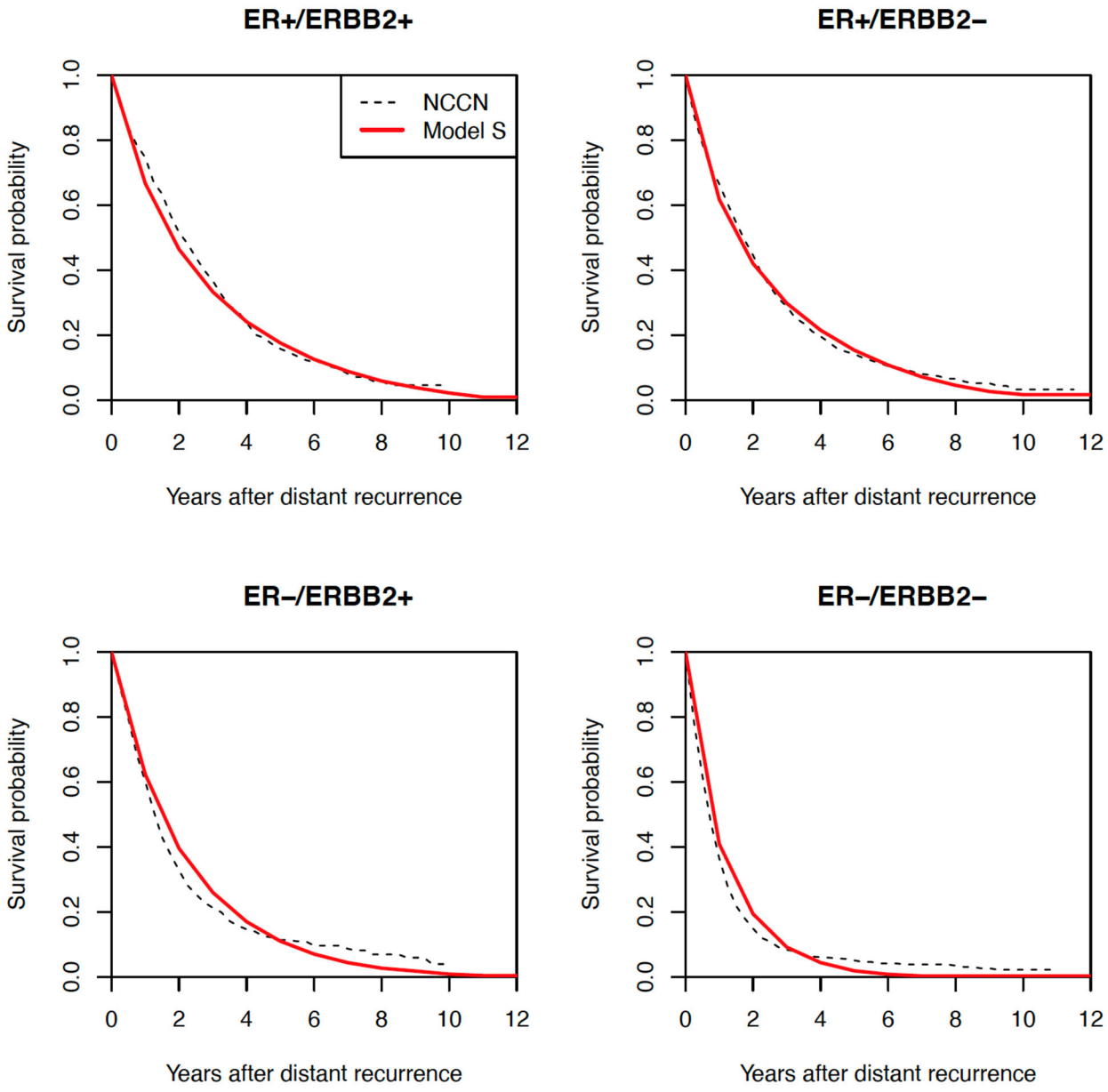
Subtype	Year*	5-Year DRFS (%)					10-Year DRFS (%)				
		D	M	S	W	Mean	D	M	S	W	Mean
	1985	75.7	76.9	77.7	61.6	73.0	68.8	70.4	70.4	60.0	67.4
	1986	76.0	77.7	78.8	60.8	73.3	69.1	70.7	71.5	59.1	67.6
	1987	76.4	77.2	78.8	62.6	73.8	69.5	70.8	71.7	60.6	68.2
	1988	77.1	76.7	80.2	64.6	74.7	70.4	70.1	73.5	63.3	69.3
	1989	77.6	77.5	80.5	64.5	75.0	71.0	70.9	73.4	62.8	69.5
	1990	78.1	76.7	80.8	67.6	75.8	71.5	70.9	74.3	65.8	70.6
	1991	78.4	76.8	81.3	68.2	76.2	71.8	70.8	74.8	66.8	71.1
	1992	78.6	77.9	81.5	67.0	76.3	72.1	71.4	75.0	65.6	71.0
	1993	78.8	76.8	81.7	70.0	76.8	72.3	70.2	75.0	68.3	71.5
	1994	79.1	77.4	82.3	68.5	76.8	72.6	71.4	75.4	67.2	71.7
	1995	79.2	77.8	81.9	70.9	77.5	72.7	71.8	75.5	69.4	72.4
	1996	79.3	77.8	81.5	68.7	76.8	72.9	71.5	75.4	67.3	71.8
	1997	78.7	85.4	80.5	69.0	78.4	72.2	81.3	73.4	67.2	73.5
	1998	79.8	85.3	82.2	69.3	79.1	73.4	80.7	75.5	67.8	74.4
	1999	79.9	85.5	82.3	69.5	79.3	73.6	81.1	75.5	67.7	74.5
	2000	80.0	86.1	82.1	69.5	79.4	73.7	81.8	75.5	68.1	74.8
	2001	80.1	85.6	82.1	70.6	79.6	73.9	81.0	75.7	69.1	74.9
	2002	80.2	85.6	82.7	70.9	79.9	74.0	81.2	76.2	69.5	75.2
	2003	80.3	85.2	82.4	69.7	79.4	74.2	81.2	76.1	68.5	75.0
	2004	80.5	85.7	82.3	71.3	79.9	74.3	81.5	75.6	69.9	75.3
	2005	80.6	85.5	82.6	71.8	80.1	74.5	81.1	76.3	70.6	75.6
	2006	80.8	85.4	83.0	72.5	80.4	74.8	81.0	76.7	71.4	76.0
	2007	81.0	85.6	82.8	73.9	80.8	75.0	81.3	76.3	72.7	76.3
	2008	81.2	85.6	83.2	73.7	80.9	75.2	81.7	76.6	72.8	76.6
	2009	81.3	85.1	83.2	73.8	80.8	75.4	80.9	77.1	72.7	76.5
	2010	81.5	85.7	83.4	74.5	81.2	75.6	81.3	77.1	73.4	76.9
	2011	81.5	85.7	82.9	74.9	81.3	75.6	81.3	76.8	74.1	77.0
	2012	81.5	85.2	83.2	74.3	81.1	75.6	81.0	77.2	73.1	76.7
	2013	81.5	85.3	83.6	75.1	81.4	75.6	81.0	77.4	74.0	77.0
	2014	81.5	85.7	83.1	73.6	81.0	75.7	81.5	76.9	72.5	76.6
	2015	81.5	86.0	83.3	74.0	81.2	75.7	81.3	77.0	72.7	76.7
	2016	81.5	86.1	83.5	74.3	81.4	75.7	81.6	77.3	72.8	76.8
	2017	82.8	86.2	84.4	76.2	82.4	77.3	81.8	78.9	75.1	78.3
	2018	82.8	86.0	84.2	74.7	81.9	77.3	81.8	78.3	73.4	77.7
	2019	82.8	85.5	84.3	76.2	82.2	77.3	81.3	78.6	75.0	78.0
All	1975	76.0	76.0	79.0	63.7	73.7	68.8	69.4	71.9	62.6	68.2
	1976	76.5	76.4	79.6	64.0	74.1	69.3	69.8	72.4	63.0	68.6
	1977	76.5	76.7	79.8	65.0	74.5	69.3	70.0	72.9	63.9	69.0
	1978	76.6	76.8	80.0	64.4	74.5	69.5	70.4	73.0	63.2	69.0
	1979	76.9	77.0	80.3	65.2	74.9	69.9	70.6	73.3	64.1	69.5
	1980	77.4	77.3	80.6	64.5	75.0	70.4	70.8	73.7	63.4	69.6
	1981	78.0	77.6	80.9	65.0	75.4	71.1	71.1	74.3	64.0	70.1
	1982	78.5	77.6	81.5	65.7	75.8	71.7	71.4	74.8	64.4	70.6
	1983	78.9	78.9	81.8	66.7	76.6	72.1	72.7	75.1	65.5	71.4
	1984	79.2	79.3	82.4	67.5	77.1	72.5	73.0	75.9	66.3	71.9
	1985	79.7	80.2	82.9	67.7	77.6	73.1	74.2	76.5	66.5	72.6
	1986	80.2	81.2	83.6	68.5	78.4	73.8	75.2	77.5	67.1	73.4
	1987	80.8	81.9	84.4	69.7	79.2	74.4	76.3	78.4	68.3	74.3
	1988	81.9	82.4	85.1	72.1	80.4	75.9	77.0	79.4	70.9	75.8
	1989	82.6	82.6	85.7	73.5	81.1	76.8	77.3	80.1	72.2	76.6

Subtype	Year*	5-Year DRFS (%)					10-Year DRFS (%)				
		D	M	S	W	Mean	D	M	S	W	Mean
	1990	83.4	83.5	86.3	75.2	82.1	77.7	78.4	81.0	74.0	77.8
	1991	83.8	83.4	86.7	76.3	82.5	78.2	78.4	81.4	75.2	78.3
	1992	84.1	83.9	87.0	76.7	82.9	78.6	79.0	81.8	75.6	78.8
	1993	84.1	83.4	87.1	77.6	83.1	78.7	78.4	81.9	76.5	78.9
	1994	84.0	84.0	87.2	77.8	83.4	79.0	79.1	82.1	76.7	79.2
	1995	84.5	84.0	87.2	78.4	83.5	79.1	79.1	82.1	77.2	79.4
	1996	84.5	83.9	87.2	78.6	83.6	79.1	78.9	82.2	77.6	79,5
	1997	84.4	88.1	86.6	77.0	84.0	79.0	84.2	81.4	75.9	80.1
	1998	85.3	88.4	87.4	78.8	85.0	80.1	84.5	82.3	77.8	81.2
	1999	85.4	88.5	87.4	79.2	85.1	80.3	84.8	82.3	78.1	81.4
	2000	85.6	88.9	87.5	79.1	85.3	80.5	85.2	82.5	78.1	81.6
	2001	85.8	88.9	87.6	80.2	85.6	80.8	85.1	82.7	79.2	81.9
	2002	86.0	89.5	88.6	80.8	86.2	81.0	87.0	84.1	79.8	83.0
	2003	86.1	89.4	88.6	81.2	86.3	81.2	87.1	84.1	80.2	83.2
	2004	86.3	89.7	88.8	81.7	86.6	81.4	87.4	84.3	80.8	83.5
	2005	86.5	89.8	90.1	82.6	87.2	81.7	87.6	86.0	81.7	84.2
	2006	87.7	90.8	90.4	84.1	88.2	83.2	88.8	86.3	83.3	85.4
	2007	87.8	90.8	90.3	84.2	88.3	83.3	88.8	86.3	83.6	85.5
	2008	87.8	90.8	90.4	84.3	88.3	83.3	88.8	86.3	83.5	85.5
	2009	87.8	91.0	90.4	84.5	88.5	83.4	88.9	86.4	83.8	85.6
	2010	87.9	90.7	90.5	84.6	88.4	83.4	88.6	86.6	83.9	85.6
	2011	87.9	90.9	90.4	84.8	88.5	83.4	88.8	86.5	84.1	85.7
	2012	87.9	90.7	90.4	84.6	88.4	83.5	88.7	86.5	83.9	85.6
	2013	87.9	90.8	90.6	84.9	88.6	83.5	88.7	86.7	84.1	85.7
	2014	88.3	91.0	90.8	85.1	88.8	83.9	88.9	86.9	84.4	86.0
	2015	88.3	91.0	90.8	84.8	88.7	83.9	88.9	87.0	84.1	86.0
	2016	88.3	90.8	90.9	84.8	88.7	83.9	88.7	87.0	84.1	85.9
	2017	88.6	90.8	91.3	85.6	89.1	84.3	88.7	87.6	84.9	86.4
	2018	88.6	90.9	91.2	85.3	89.0	84.3	88.7	87.4	84.6	86.3
	2019	88.6	90.8	91.3	85.5	89.1	84.3	88.7	87.6	84.8	86.4

* Year is the year of diagnosis of stage I-III breast cancer. ER = estrogen receptor. Figure 3B of the main paper is a graphical display of the average results from 2000-2019.

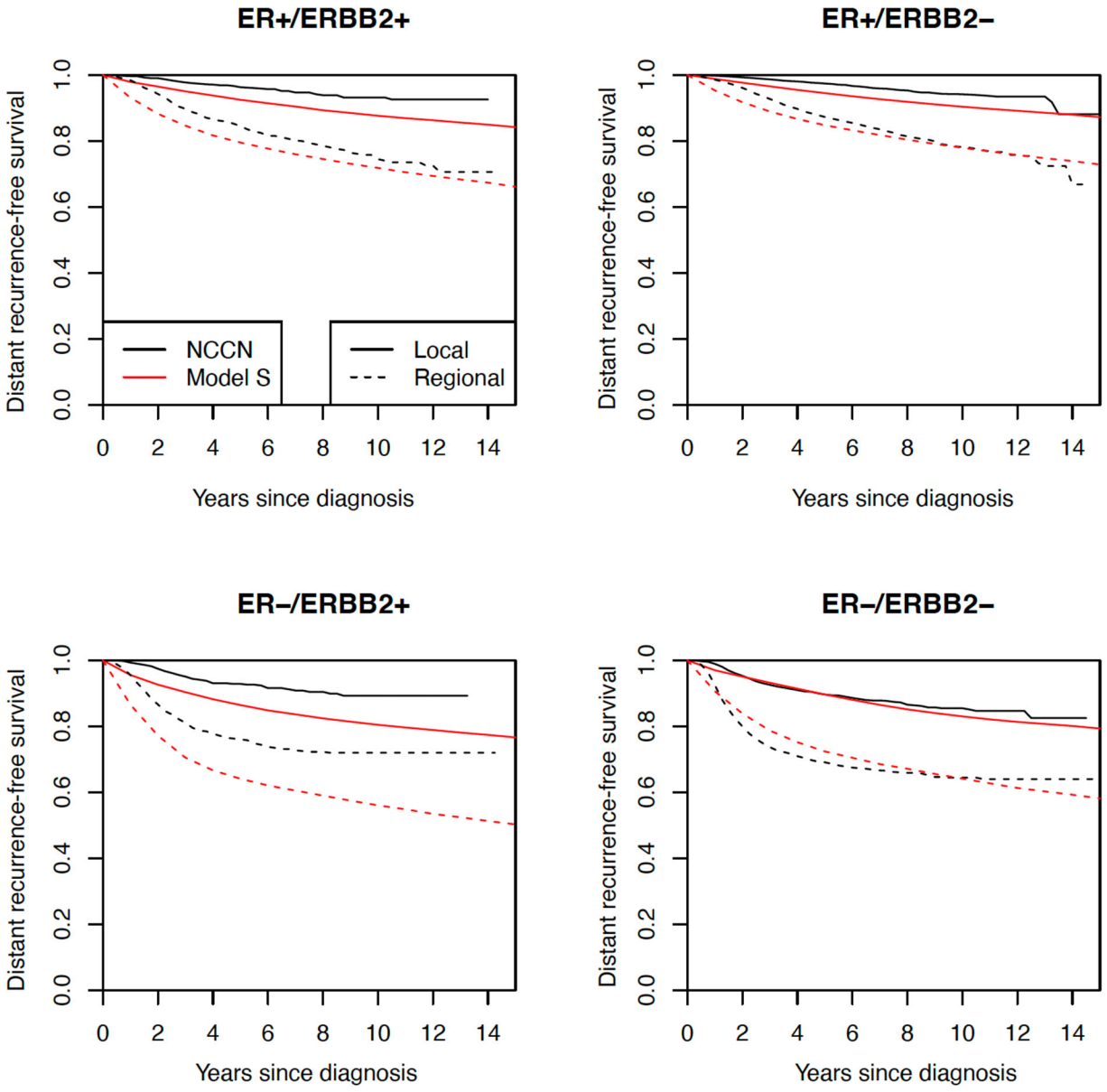
eFigures

eFigure 1. Breast cancer–specific survival after distant recurrence by subtype in the NCCN Outcomes Database as compared to Model S



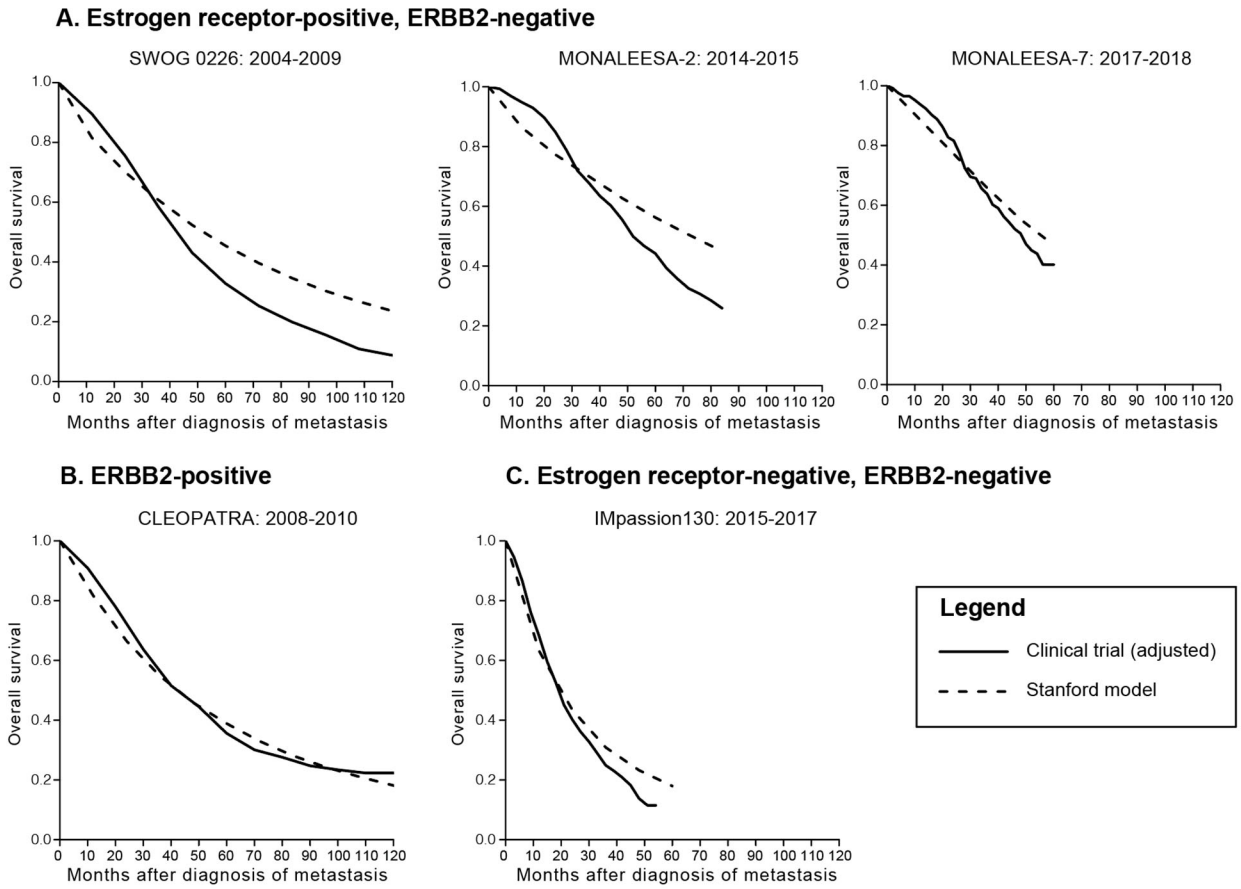
ER = estrogen receptor.

eFigure 2. Distant recurrence-free survival by subtype in the NCCN Outcomes Database as compared to Model S



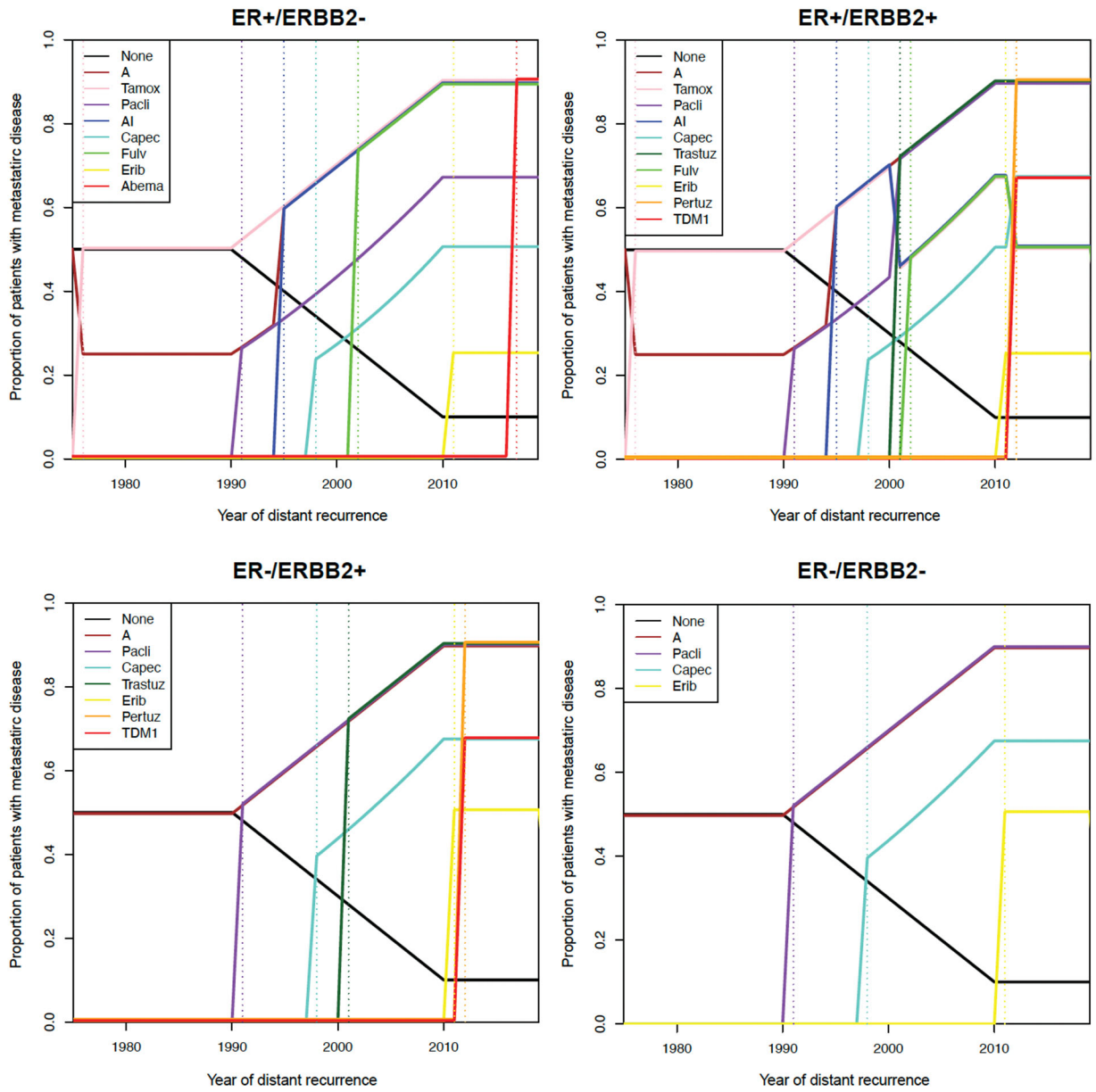
To allow comparability of distant recurrence-free survival between the model and the NCCN Outcomes Database, model outputs were censored in accordance with the pattern of time of last follow-up for patients in the NCCN Outcomes Database. ER = estrogen receptor.

eFigure 3. Survival after metastasis as observed in clinical trials vs predicted from Model S



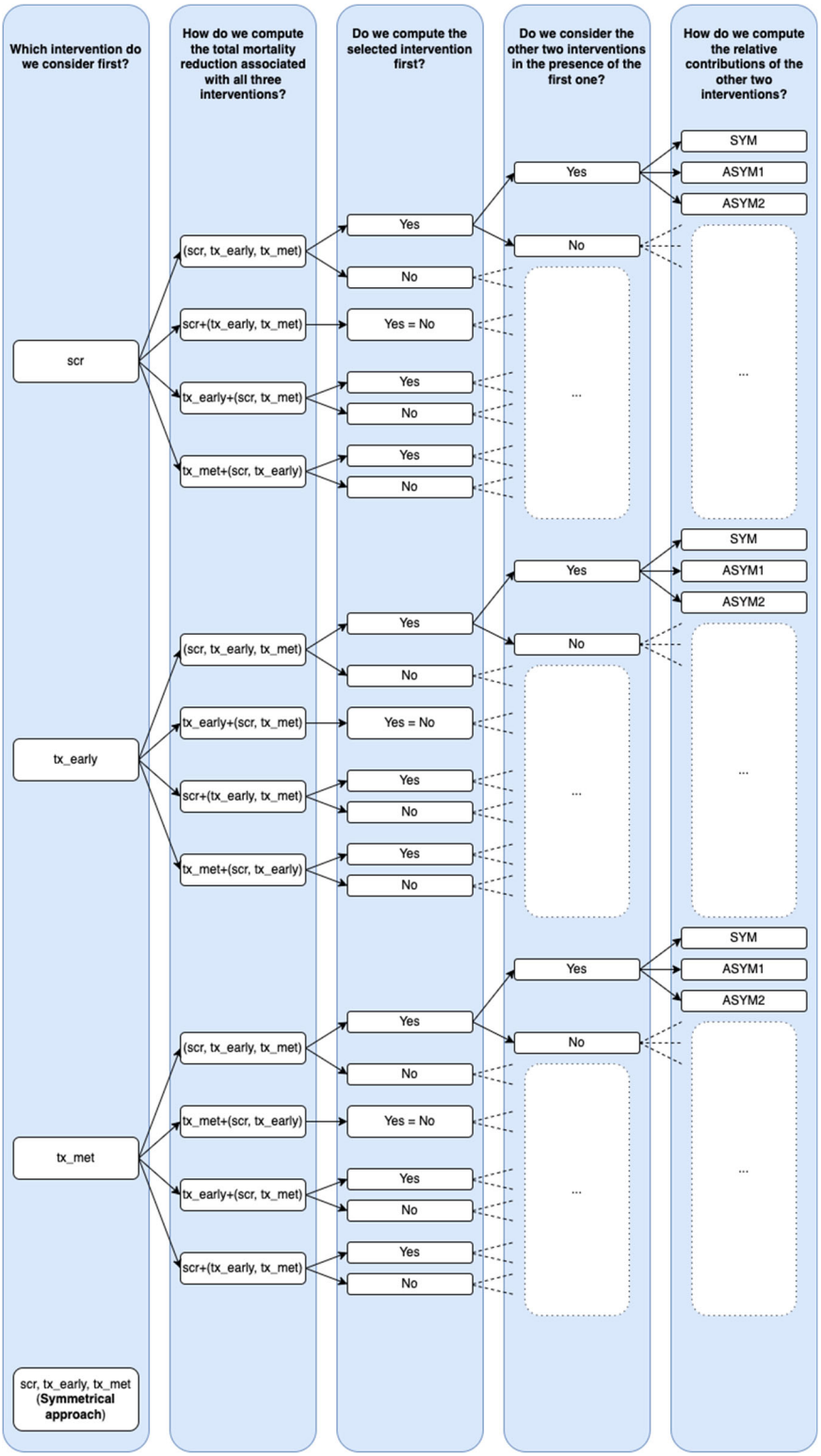
Survival curves from five first-line clinical trials for metastatic breast cancer (solid lines) and the outputs of Model S (Stanford) (dotted lines) are shown across three ER/ERBB2 subtypes (A-C). Overall survival from trial enrollment is compared to model-estimated breast cancer-specific survival after metastasis. Trial control arms, reflecting standard-of-care therapy at the time of trial conduct, are shown. The simulated patients included in the model outputs were diagnosed with metastatic disease during the years the trial was conducted, received first-line therapy, and were sampled based on age at diagnosis of metastatic disease (all trials), receipt of endocrine and/or chemotherapy for Stage I-III disease (all trials), recurrence-free interval (SWOG 0026, MONALEESA-2, MONALEESA-7), and estrogen receptor status (CLEOPATRA) to correspond to the trial population.

eFigure 4. Metastatic therapy usage by year of diagnosis of metastatic recurrence



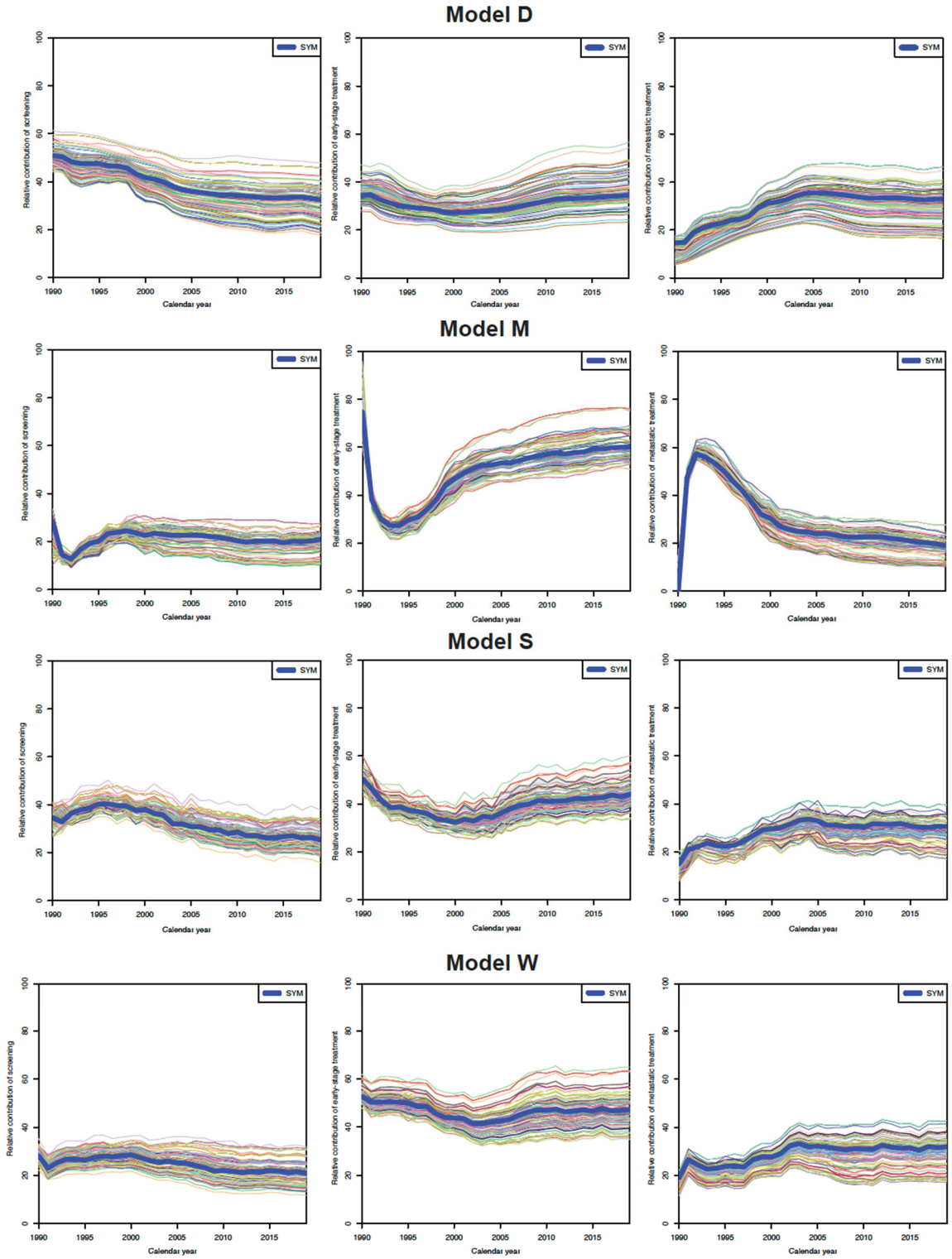
The probability of a simulated patient with metastatic recurrence receiving the benefit of each drug available for the treatment of metastatic disease is plotted against the year of diagnosis of metastatic recurrence. These results are produced by the assumptions about metastatic therapy uptake outlined in the **eMethods**. Because simulated patients may receive multiple (or no) lines of treatment, the proportions do not add up to 1.0. Notably, some of these benefits are given to simulated patients in the absence of them receiving that drug, if the drug they do receive demonstrated its benefit over another drug; for example, the benefit of tamoxifen is given to any simulated patient who receives aromatase inhibitor, as aromatase inhibitors demonstrated their benefit over tamoxifen. These results apply to Models D, S, and W. A = anthracycline, Tamox = tamoxifen, Pacli = Paclitaxel (or any taxane), AI = aromatase inhibitor, Capec = capecitabine, Fulv = fulvestrant, Erib = eribulin, Abema = abemaciclib (or any CDK4/6 inhibitor), Trastuz = trastuzumab, Pertuz = pertuzumab, TDM1 = trastuzumab emtansine.

eFigure 5. Summary of 127 approaches to calculate contributions of interventions to breast cancer mortality reduction



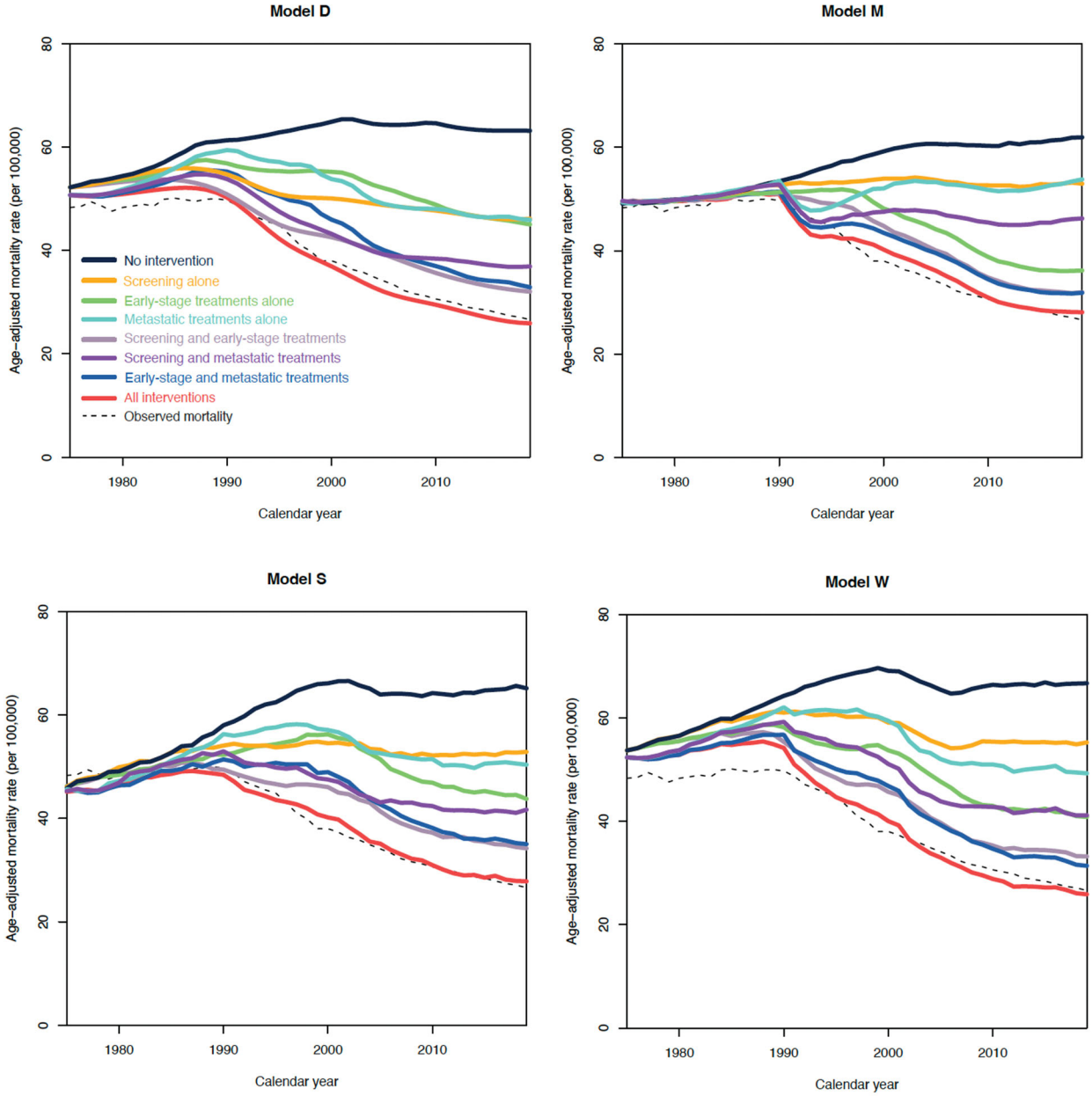
The three interventions are screening (scr), Stage I-III treatment (tx_early), and metastatic treatment (tx_met). For more details, please see eMethods.

eFigure 6. Comparison of symmetrical to asymmetrical approaches to calculate contributions of interventions to breast cancer mortality reduction

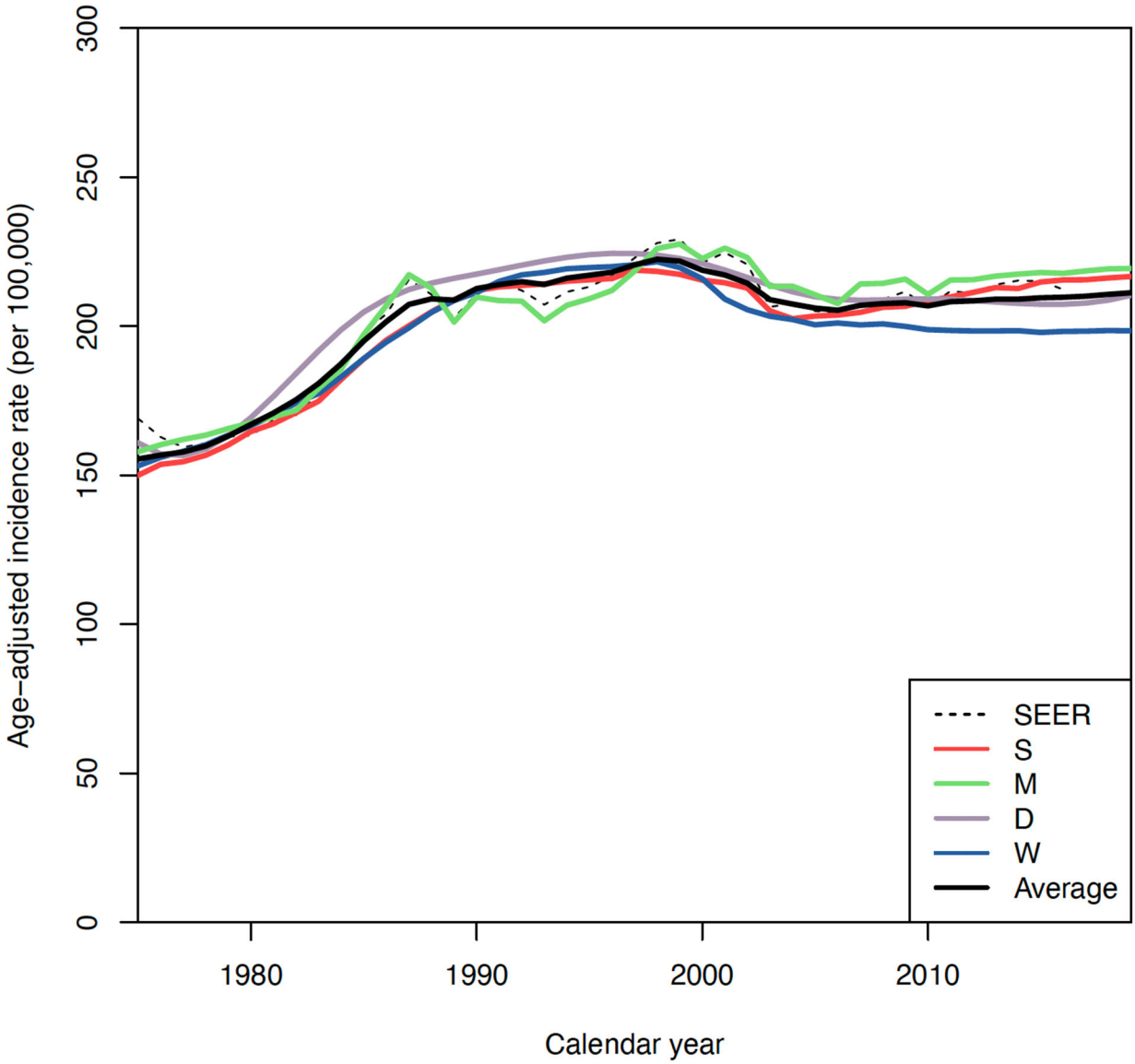


Screening is on the left, Stage I-III treatment in the middle, and metastatic treatment on the right for each of the four models. Calculated relative contributions are shown over time for all 127 approaches, with the symmetrical approach shown in thick blue. For more details, please see eMethods.

eFigure 7. Estimated age-adjusted breast cancer mortality over time across eight scenarios compared to observed mortality, by CISNET model

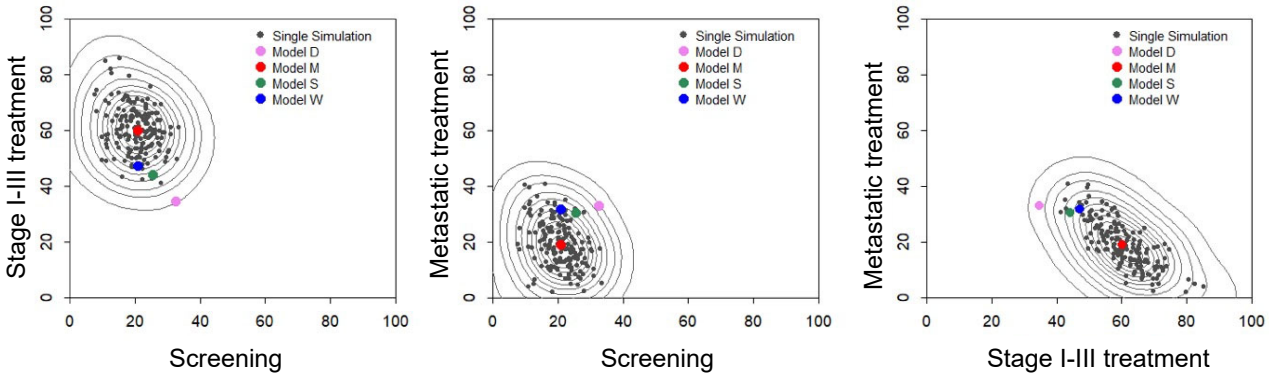


eFigure 8. Estimated breast incidence, average across all models and by model, as compared to SEER breast cancer incidence



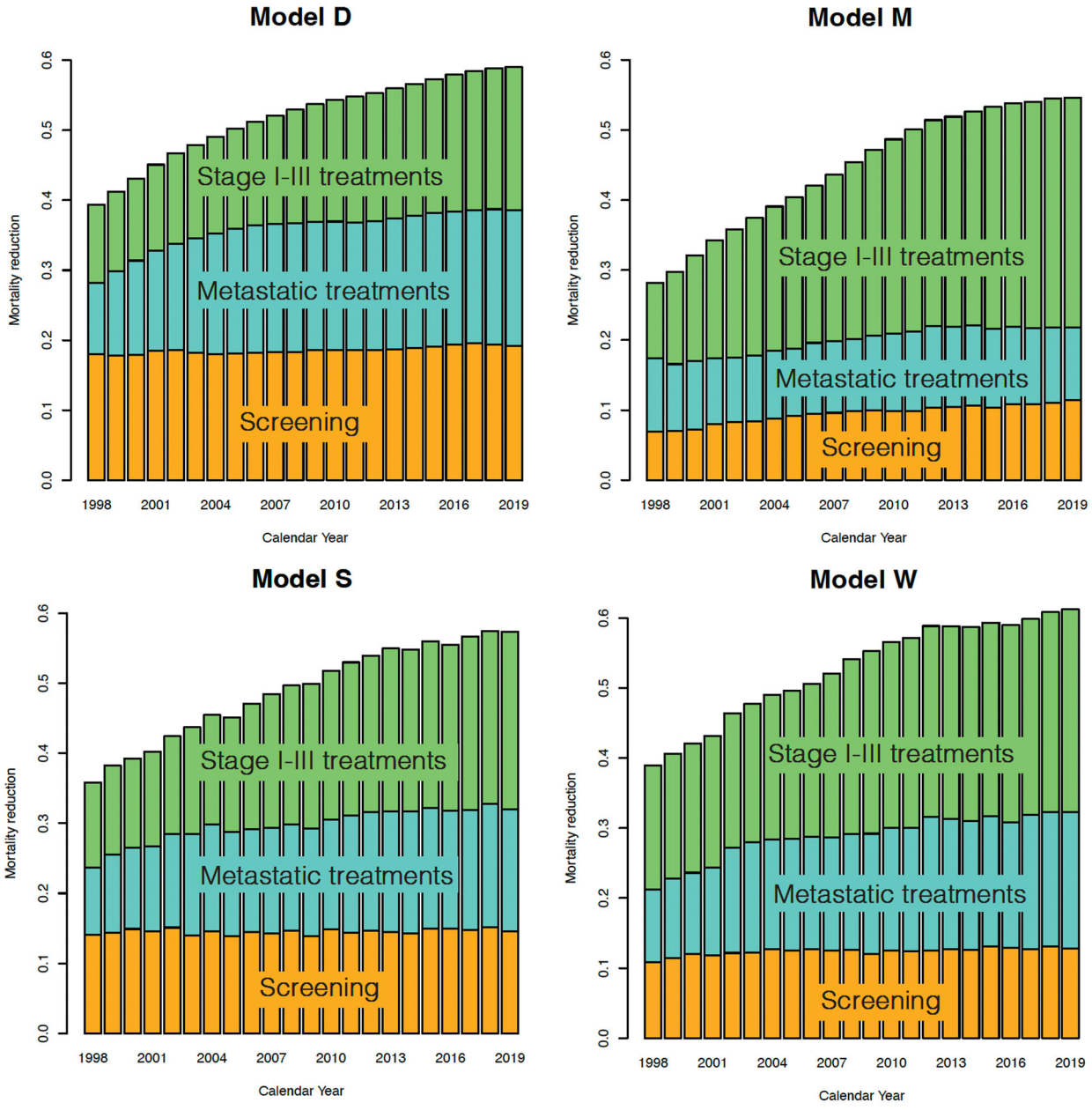
Models D, S, and W use a shared age-period-cohort model [1] to estimate breast cancer incidence in the absence of screening. Model M uses a linear model of increasing annual incidence starting in 1975, whose parameters were selected from Bayesian inference to match observed incidence (SEER = Surveillance, Epidemiology, and End Results). Observed incidence is in the presence of screening.

eFigure 9. Associations with overall breast cancer mortality reduction of screening, Stage I-III treatments, and metastatic treatments in 2019, by CISNET model and within Model M



The percentage of the estimated overall mortality reduction in 2019 attributable to each of the three categories of intervention from the four models is plotted. The point estimates from the four models are shown in large colored dots. The smaller gray dots represent pairs of estimates based on the 172 simulations of Model M; gray contours represent the contour lines of two-dimensional kernel estimation (n=100, h=25) for the contour levels of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 0.95, and 0.99. Model M uses a Bayesian approach to incorporate parameter uncertainty, including in treatment efficacy, that is reflected in this distribution of estimates. Of note, the within-model variability from model M is comparable to the between-model variability.

eFigure 10. Associations with overall breast cancer mortality reduction of screening, Stage I-III treatments, and metastatic treatments over time, by CISNET model



All interventions (Stage I-III treatment, metastatic treatments, and screening) are in addition to standard treatments available in 1975. Because local therapy was part of standard-of-care treatment for Stage I-III disease in 1975, the benefit of screening occurs in the presence of standard local therapy.