Supplementary Online Content

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

eMethods

Computing the Relative Contributions Associated with Screening and Treatment

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

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

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

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

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

eTable 1. Model Parameters

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

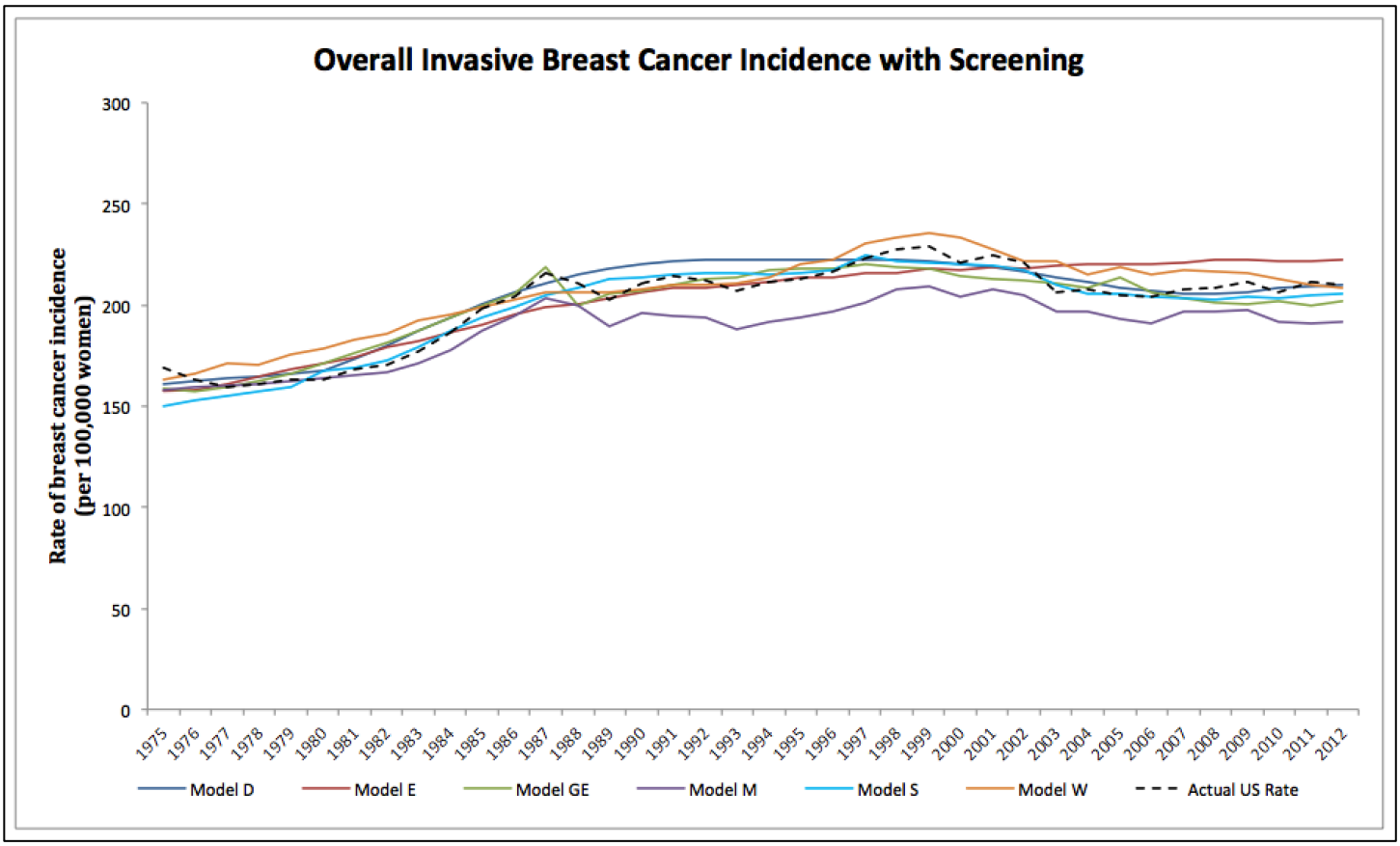
*Row sum is 100%, within rounding error.

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

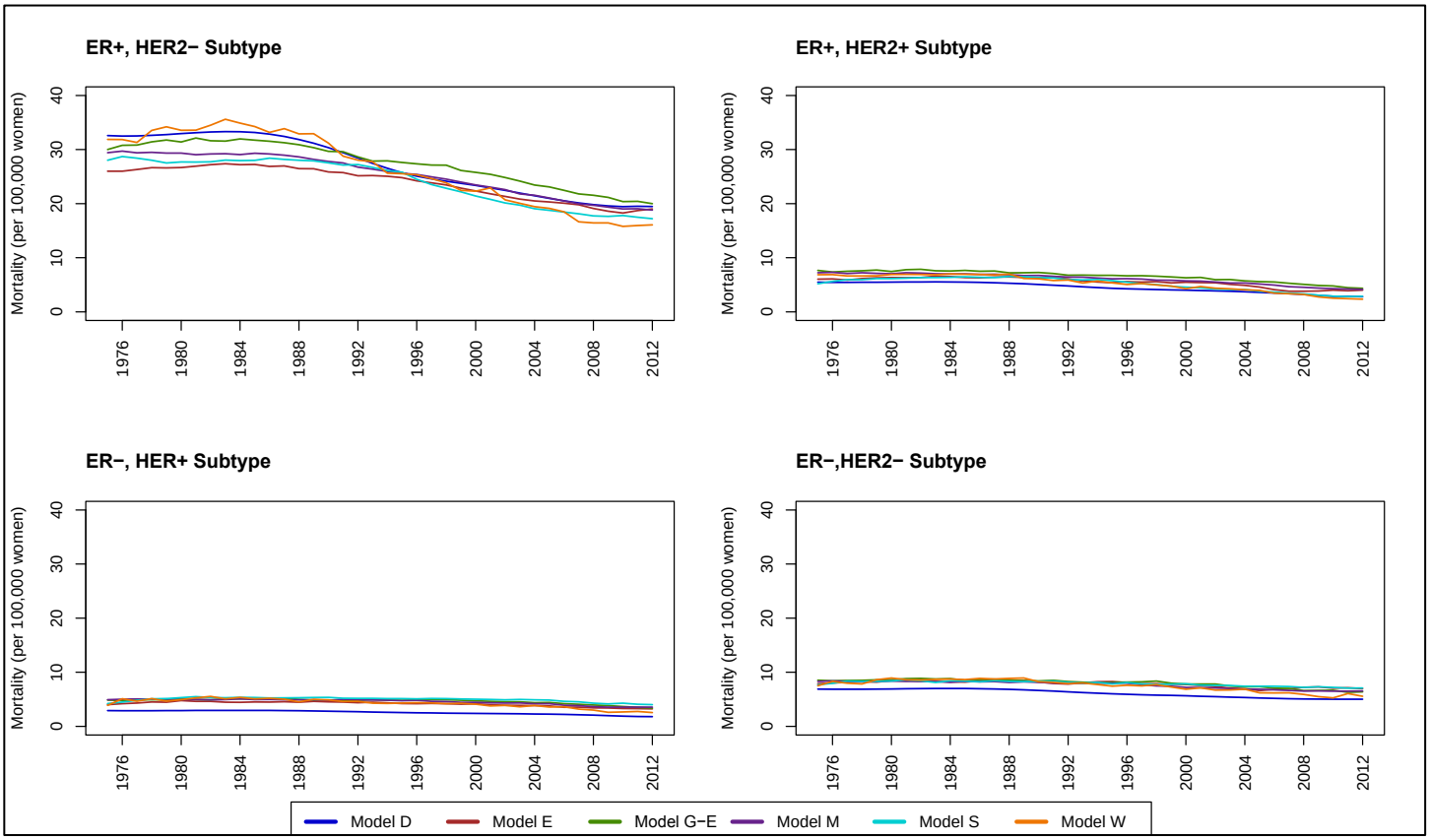
Model	ER+/ERBB2- Subtype	ER+/ERBB2+ Subtype	ER-/ERBB2+ Subtype	ER-/ERBB2- Subtype
Dana-Farber	70	13	6	11
Erasmus	62	17	10	12
Georgetown-Einstein	62	15	9	14
MD Anderson	61	17	9	13
Stanford	65	16	8	11
Wisconsin-Harvard	66	15	8	11
Mean	**64**	**16**	**8**	**12**

*Row sum is 100%.

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

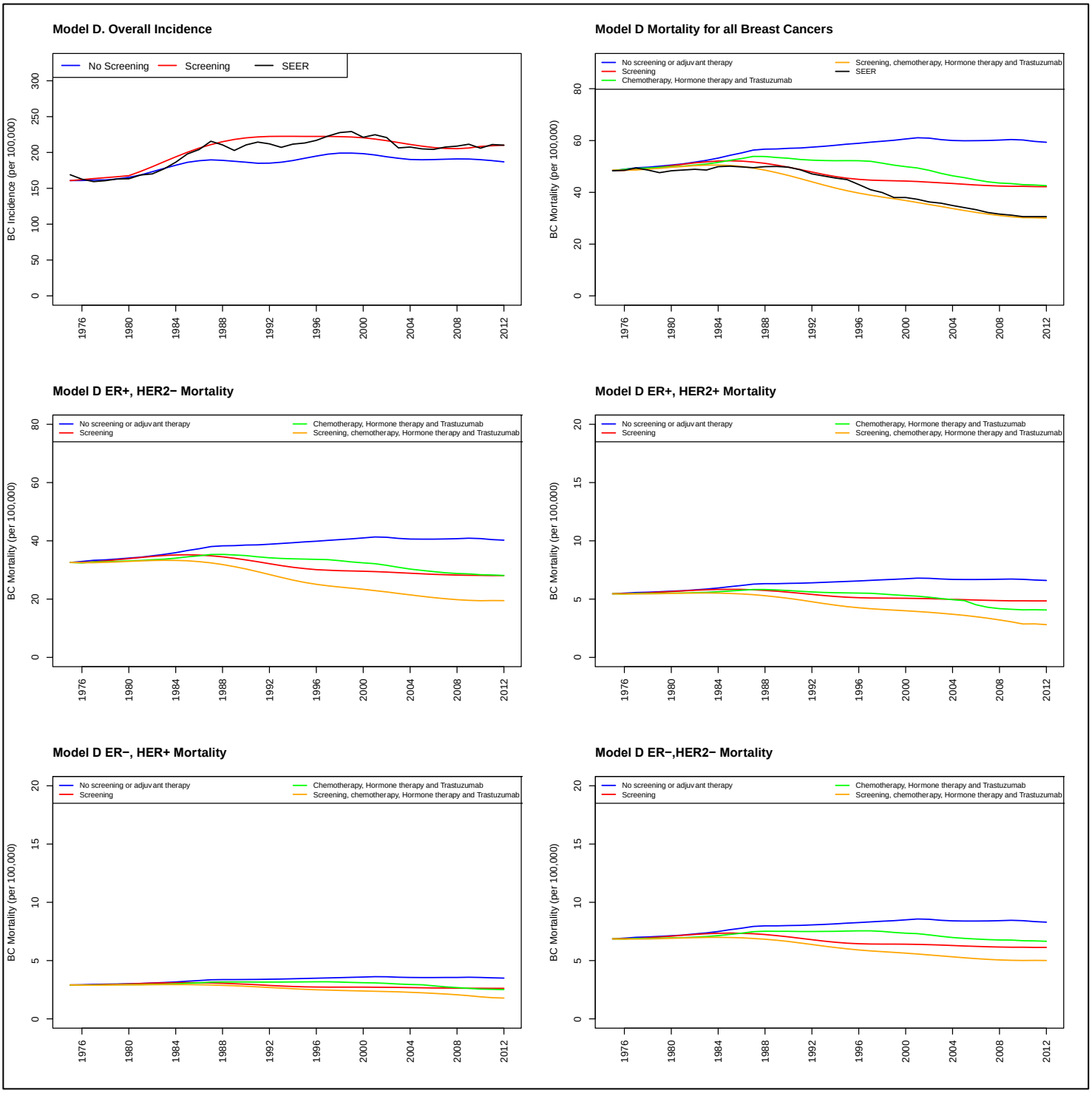


eFigure 2. Comparison of model projections for ER-/ ERBB2-specific breast cancer mortality trends between 1975-2012, for women ages 30-79, by molecular subtype. (Upper left) ER+/ERBB2-, (upper right) ER+/ERBB2+, (lower left) ER-/ERBB2+, (lower right) ER-/ERBB2- subtypes**.**

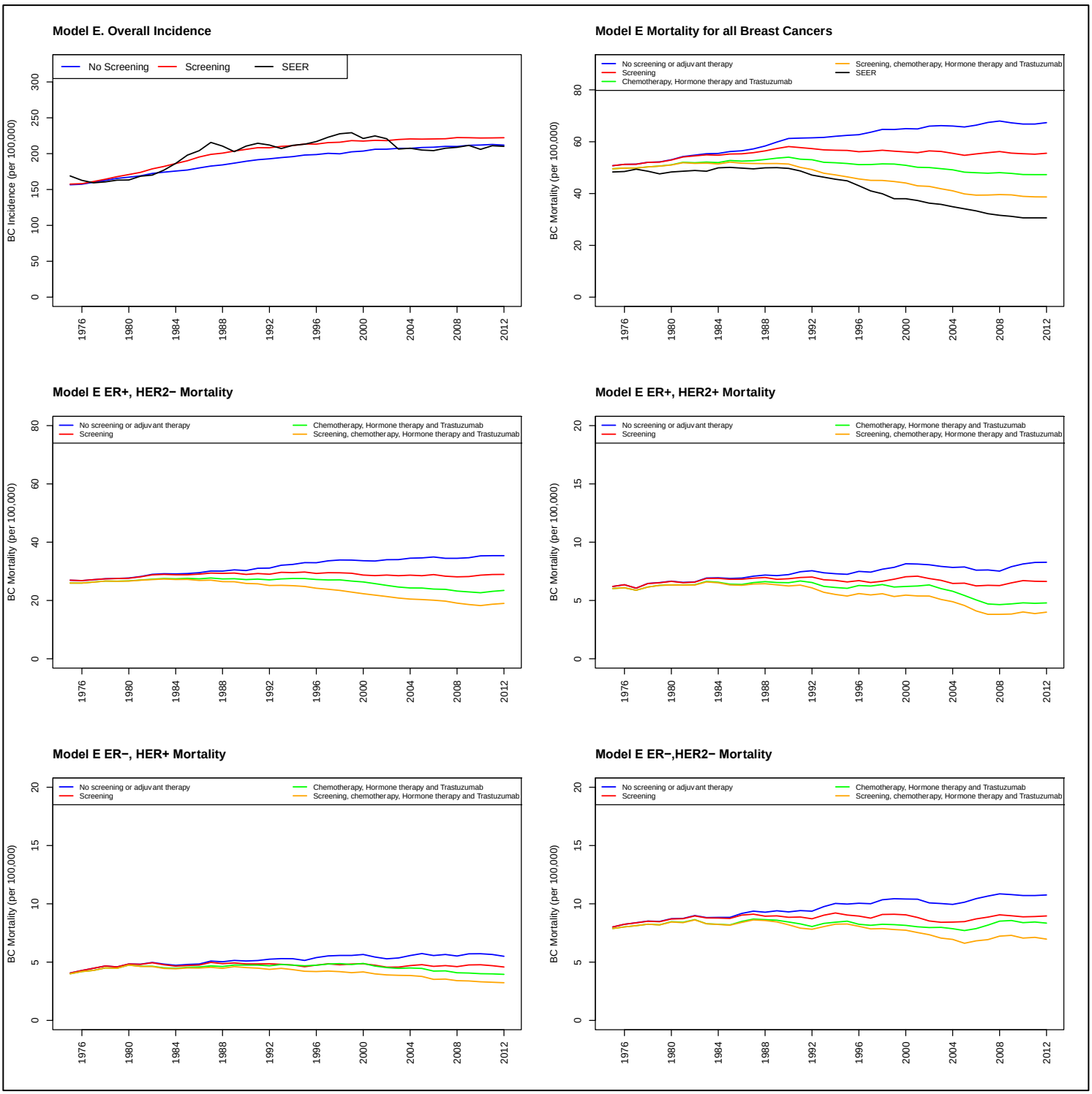


eFigure 3. Individual model projections for overall US breast cancer incidence and mortality (vs. SEER) and ER/ERBB2-subtype-specific mortality from 1975-2012, for women ages 30-79*

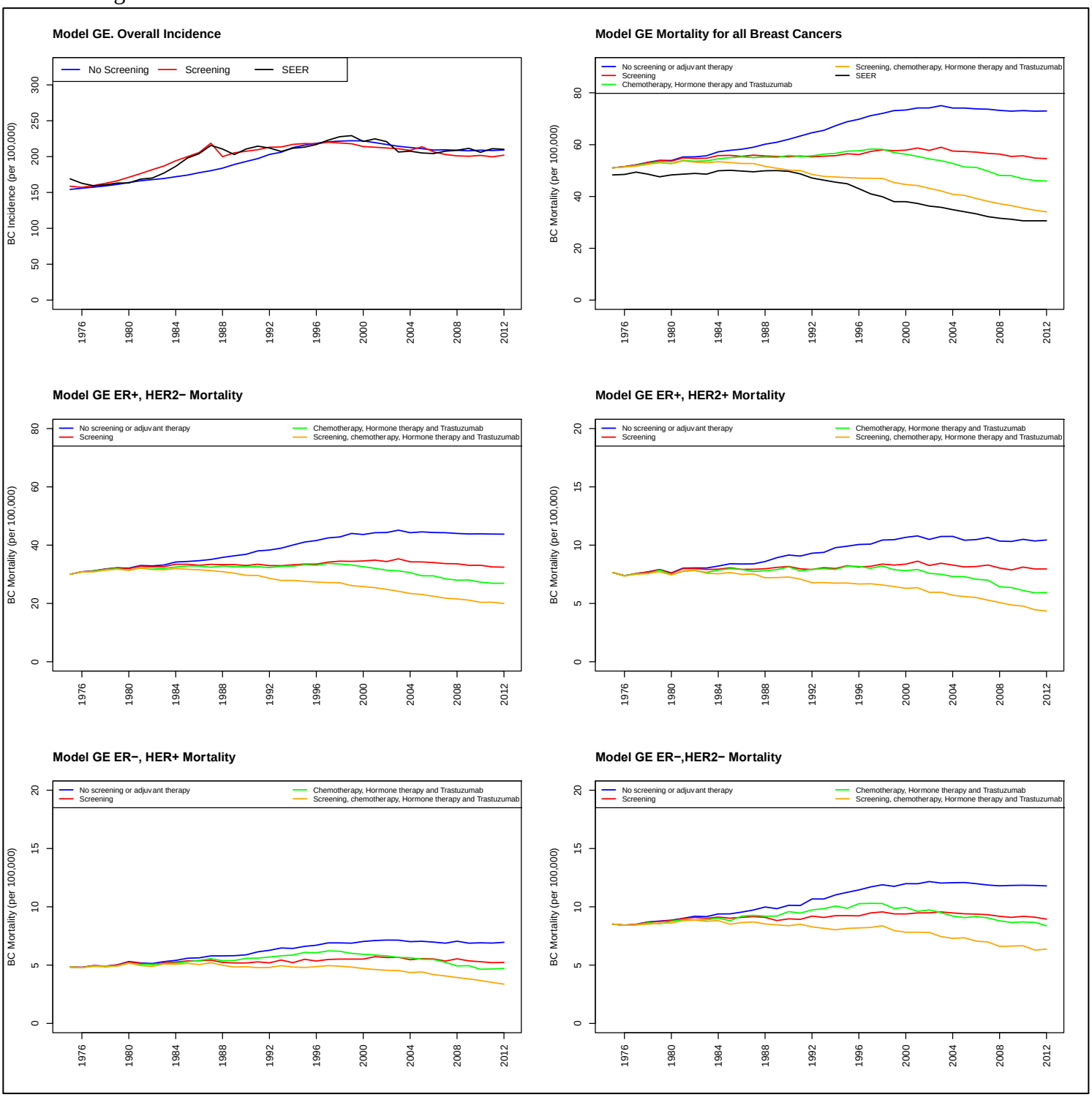
Model Dana-Farber



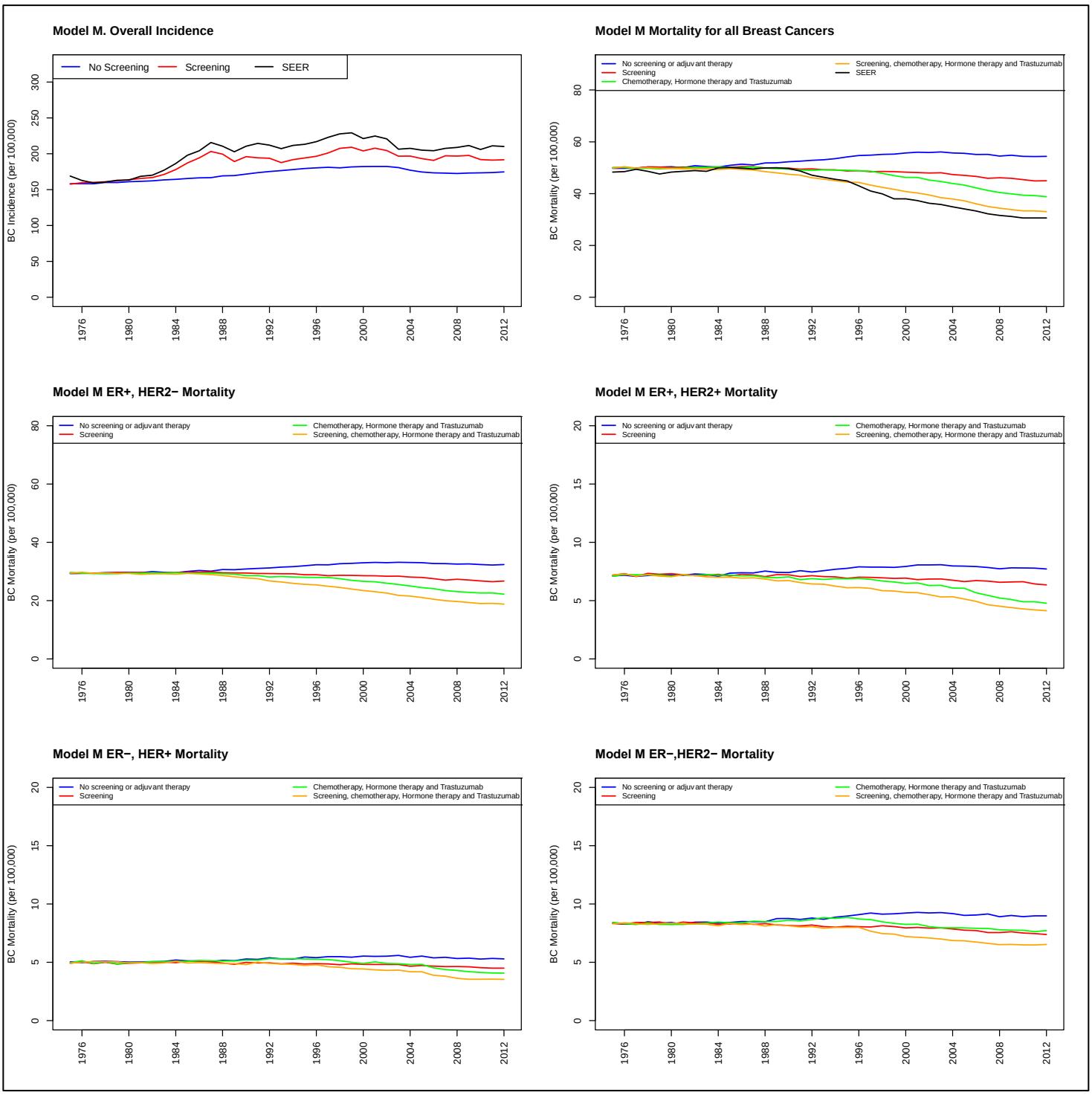
Model Erasmus



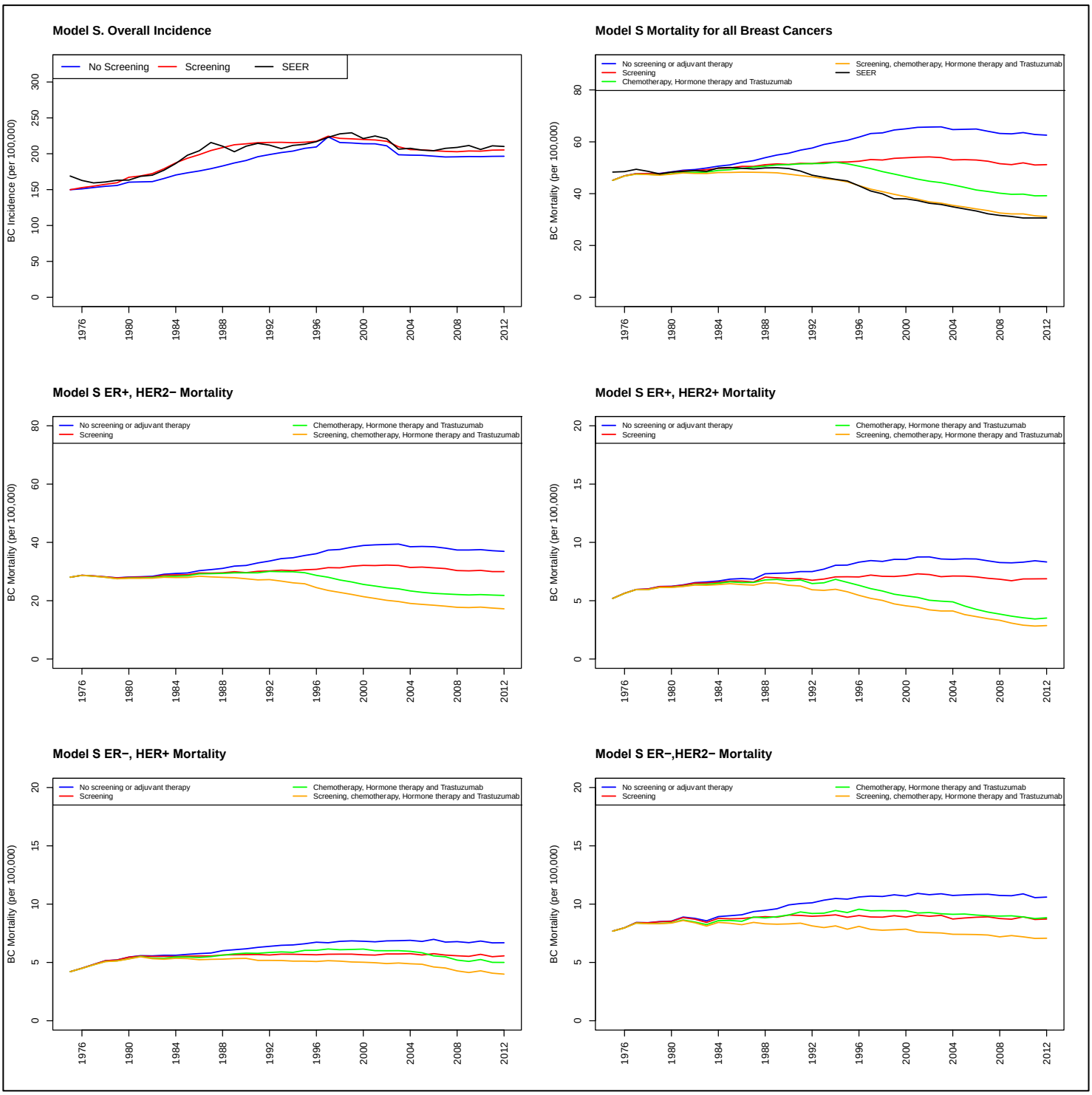
Model Georgetown-Einstein



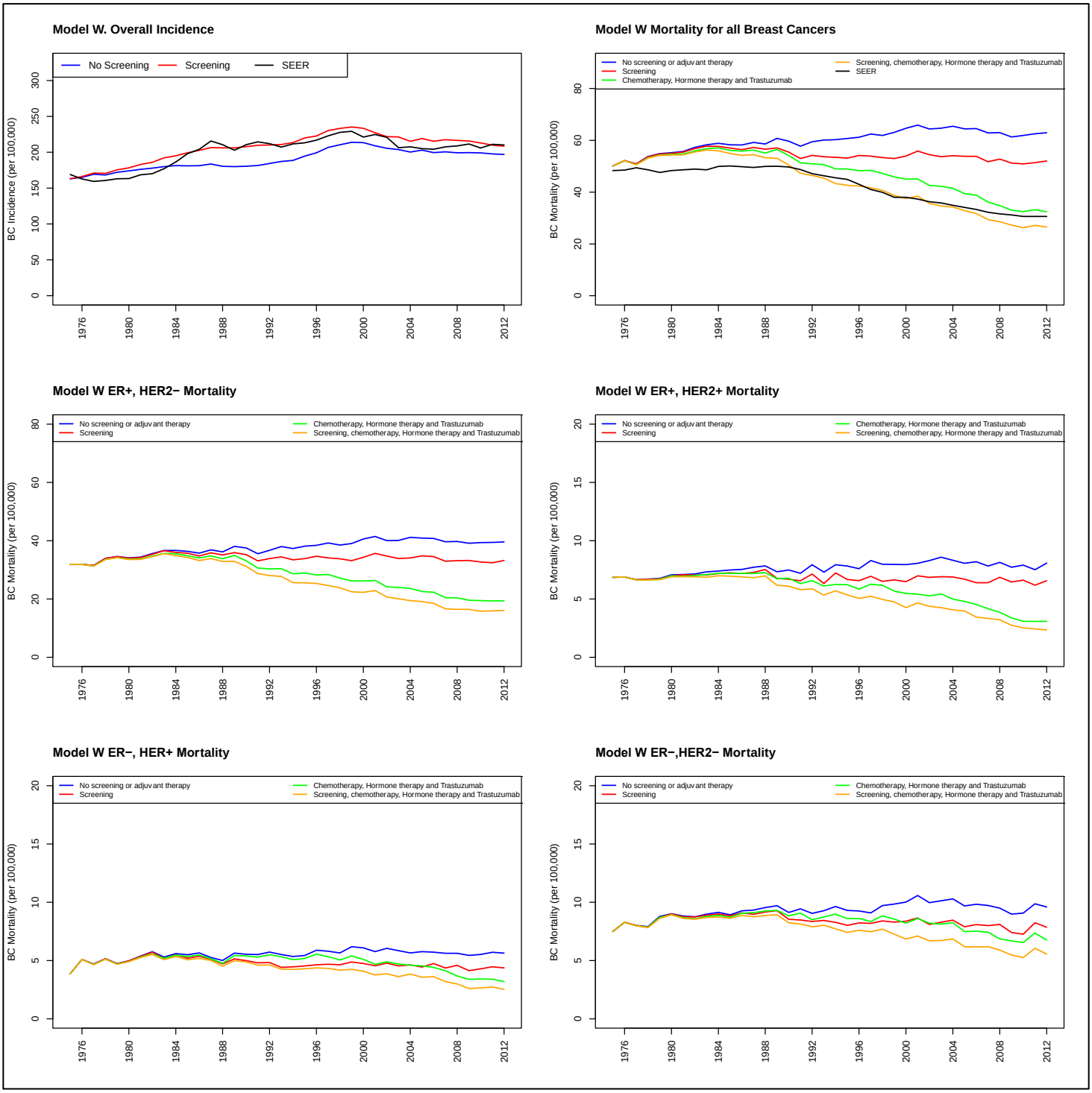
Model MD Anderson



Model Stanford



Model Wisconsin-Harvard



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

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