Supplementary Online Content

Yeh JM, Ward ZJ, Chaudhry A, et al. Life Expectancy of adult survivors of childhood cancer over 3 decades. *JAMA Oncol.* Published online January 2, 2020. doi:10.1001/jamaoncol.2019.5582

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

eMethods. Additional methodological details on model development

Model Inputs

Childhood Cancer Survivor Study (CCSS)

We obtained individual-level data for 22,150 survivors in the Childhood Cancer Survivor Study (CCSS) who completed the baseline questionnaire and were covered by the National Death Index. Each respondent was weighted with inverse probability weights (IPW) based on their probability of participation (p[Sampled]*p[Included in subset]) so that our results for the modeled cohort can be generalized to the larger population of childhood cancer survivors. Treatment exposure groups were sampled based on 10 imputed datasets for those with missing values. Due to small sample size we grouped "None" and "Surgery only" together into one exposure group.

Here we present the reported counts and mean imputed counts across the 10 datasets.

Code	Treatment Group	Reported #	Imputed #
0	No treatment/Missing	1,769	78.4
1	Surgery only	1,721	1,831.4
2	Chemotherapy only (no radiotherapy)	7,144	7,607.4
3	Radiotherapy only (no chemotherapy)	1,916	2,009.8
4	Chemoradiotherapy	9,600	10,623

Mortality Rates

Using data from the CCSS, we estimated late mortality rates for each treatment exposure group and era for the following years since diagnosis intervals: 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, and 35+ years. Specifically, based on International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10) criteria for cause of death, we estimated 1) annual mortality rates due to late recurrence or progression of original cancer, 2) annual excess mortality rates for external causes, including accidents, suicides, and poisonings (ICD-9 codes 800-999 and ICD-10 codes V00-V99, W00-W99, X00-X99, and Y00-Y89), and 3) annual excess mortality rates due to health-related causes, including subsequent (primary) cancers (ICD-9 codes 140-239 and ICD-10 codes C00-C97 and D10-D36), cardiac causes (ICD-9 codes 390-398, 402, 404, and 410-429 and ICD-10 codes I00-I02, I05-I09, I11, I13, I14, I20-I28, and I30-I52), pulmonary causes (ICD-9 codes 460-519 and ICD-10 codes J00-J99), and all other causes.

To inform background mortality rates, we obtained CDC cause-specific rates for the general population stratified by sex, age group, and year (1974-2014) for the following causes.

Cause	Index
All-cause	0
Cardiac	1
External	2
Other	3
Pulmonary	4
Secondary malignant neoplasm (SMN)	5
Late recurrence	6

The following age groups were used: <1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+. Mortality rates were interpolated linearly from the midpoint of each age group. We held future mortality rates in the model equal to the latest observed rates in 2014.

Model Calibration

To ensure that model outcomes were consistent with observed survival and cumulative mortality risks among survivors eligible for the CCSS when competing risks were considered, we used model calibration to identify plausible parameter sets of late recurrence and late effects mortality rates for each treatment subgroup by treatment era.

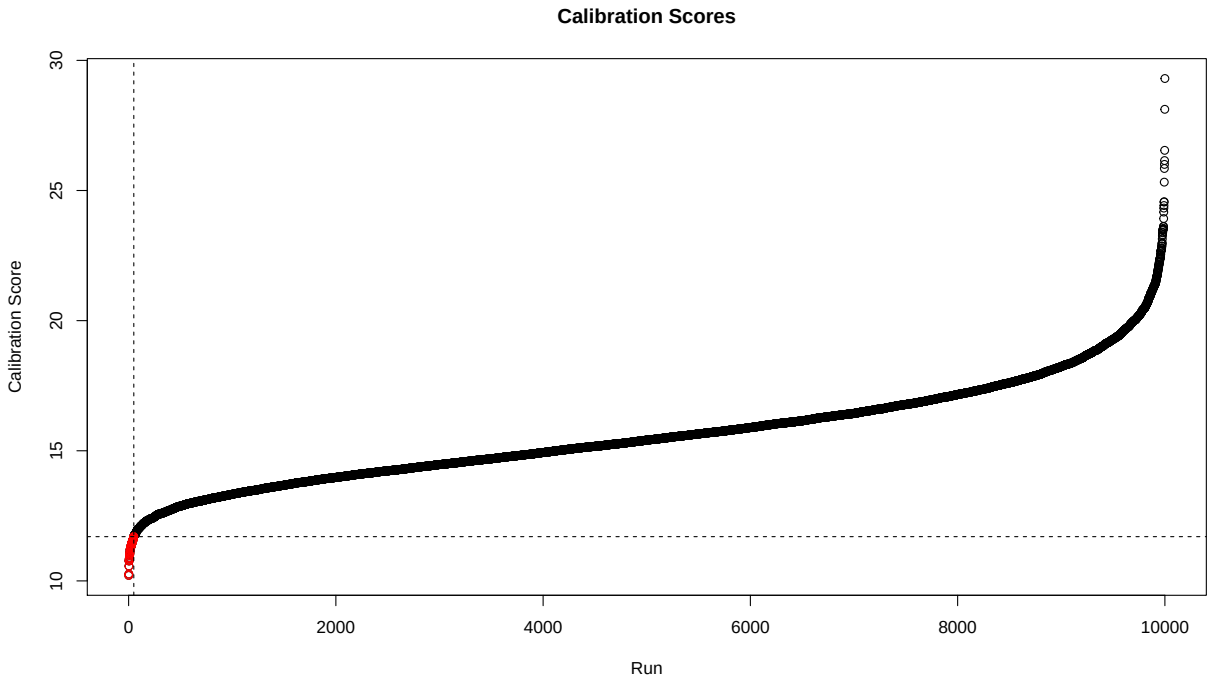
Specifically, for each subgroup, we set prior probability distributions for each model parameter based on the 95% confidence intervals (95% CIs) estimated from CCSS data. We then used searched the parameter space using a simulating annealing algorithm to identify parameter sets that were consistent with observed overall survival and cause-specific cumulative incidence at 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, and 35+ years since diagnosis. Goodness-of-fit for each parameter set was calculated as the sum of squared distances of model predictions from these calibration targets, weighted inversely proportional to widths of their confidence intervals. We identified the 50 best-fitting parameter sets, which were then used as the basis of the analysis. As shown in Section 1.2.3, projected survival for survivors (overall cohort, treatment and ALL subgroups) diagnosed in 1970-79, 1980-89 and 1990-99 were consistent with observed CCSS data by years since diagnosis.

We used common random numbers within each calibration search to reduce stochastic noise (for both treatment imputation and microsimulation).

When sampling parameters we set a floor of 0 for AERs, except for External causes, as cancer treatment is unlikely to be protective for health-related causes of death. We enforced the relative shape of the AER curves when sampling. When parameter estimates had no data we projected the estimates using linear extrapolation from previous years based on the shape of the previous cohort. We also constrained these parameters to be lower than the previous cohort (except External, which were fit overall). We also constrained Late Recurrence mortality rates to be decreasing by years since diagnosis (within era).

Scores

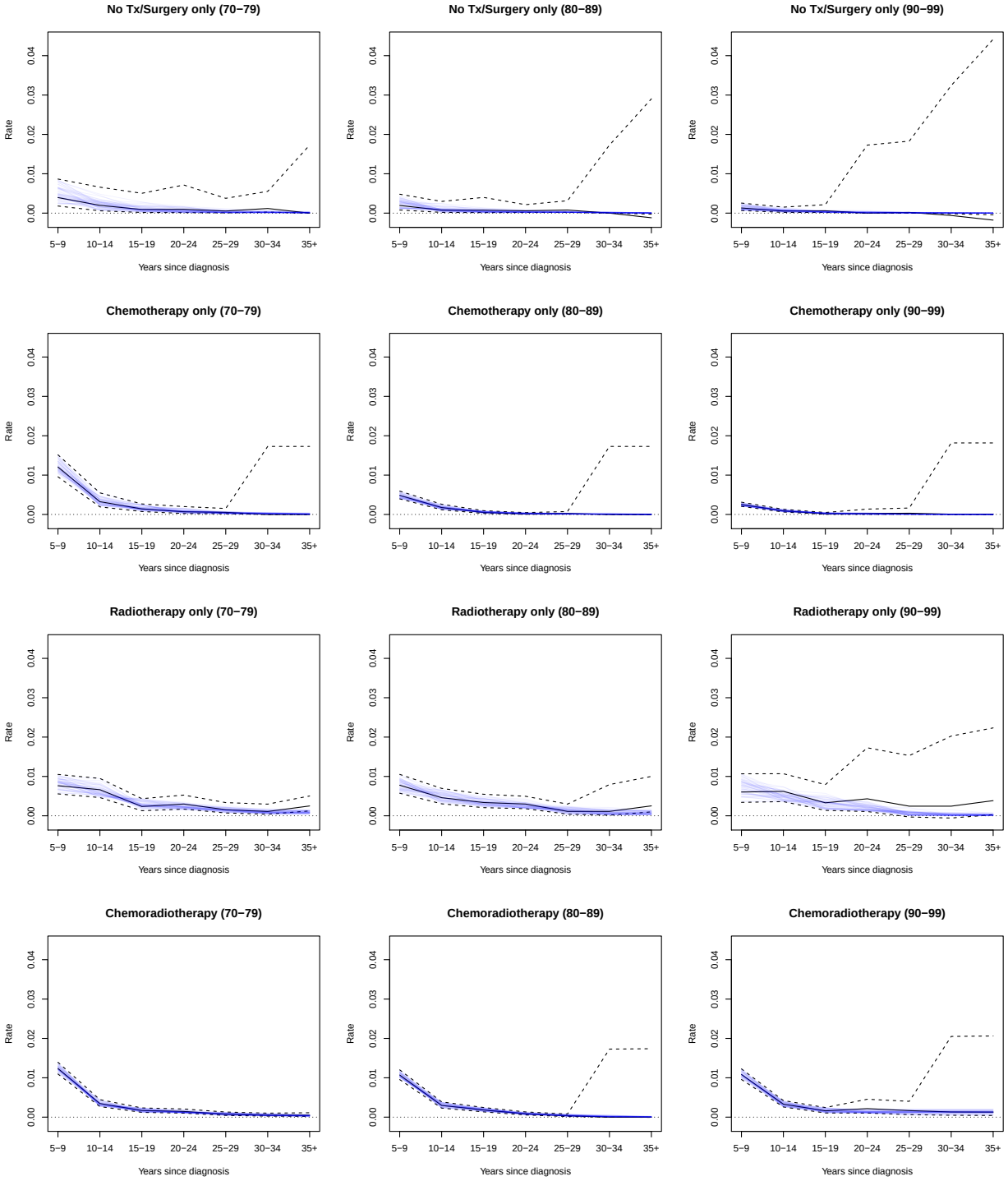
Here we plot the calibration scores and the top 50 sets (highlighted in red).



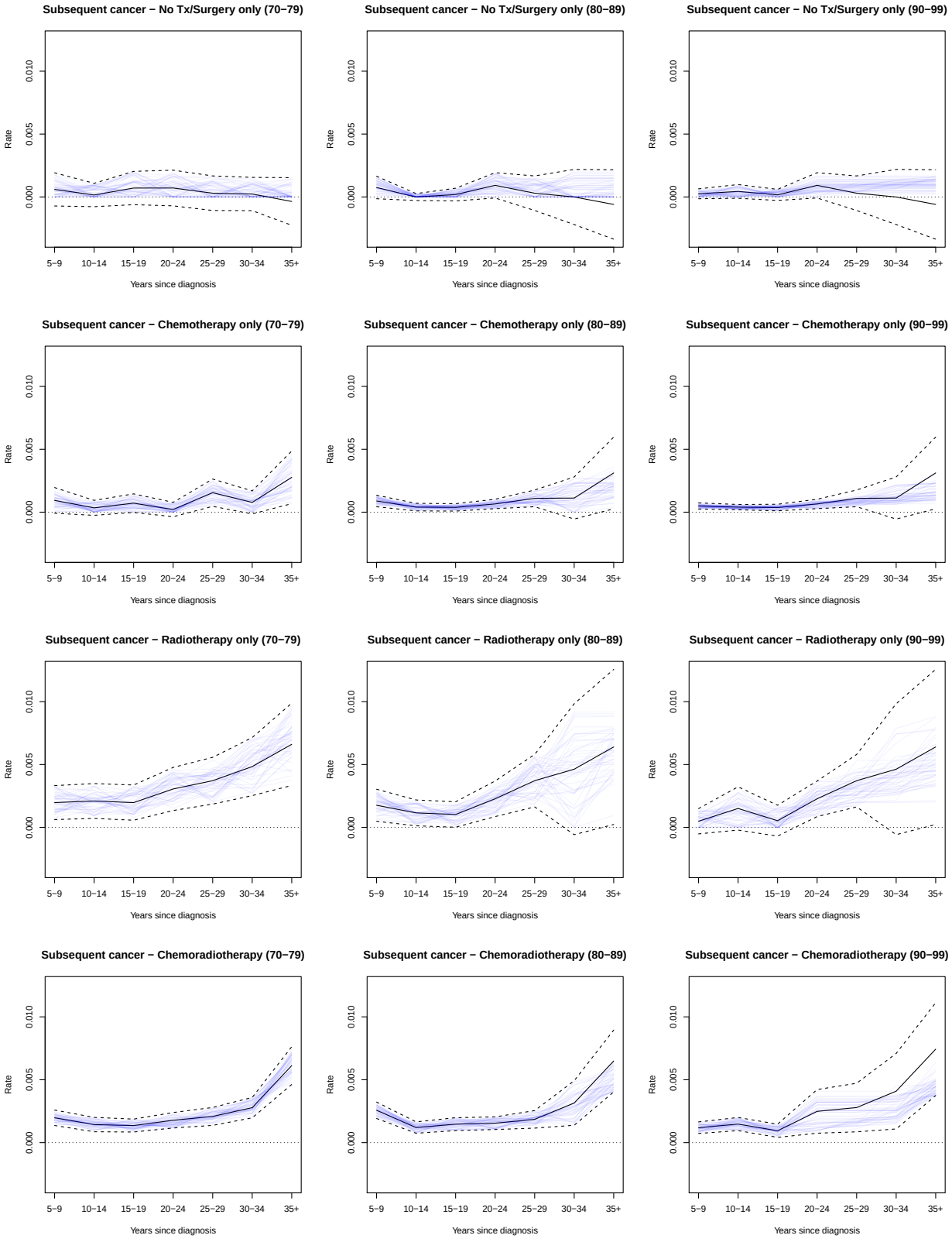
Calibrated Parameters

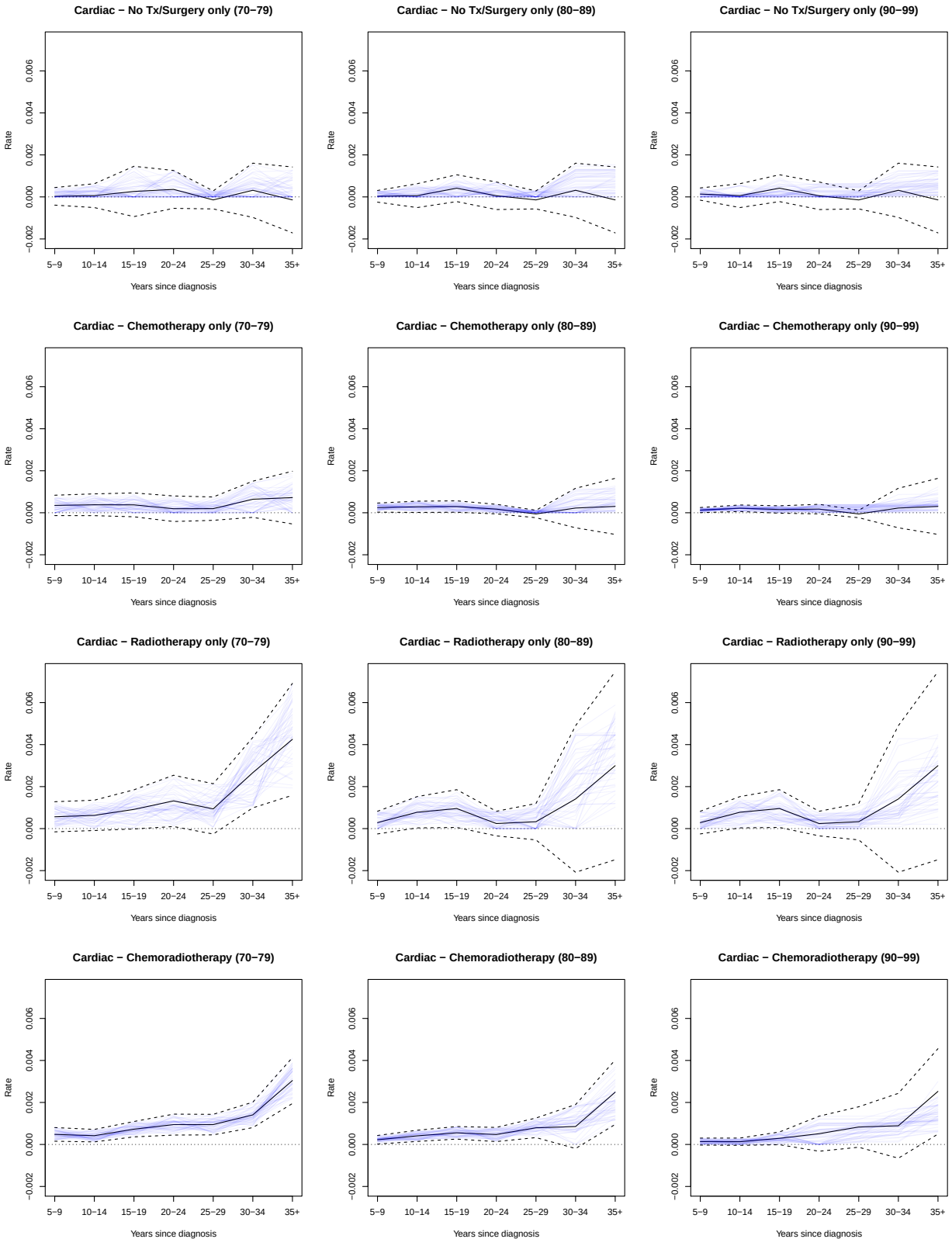
Here we compare our treatment era-specific calibrated parameters to the estimates based on CCSS data. Black lines indicate CCSS estimates (solid = mean, dashed = 95% CI), and blue lines indicate parameter sets identified via calibration.

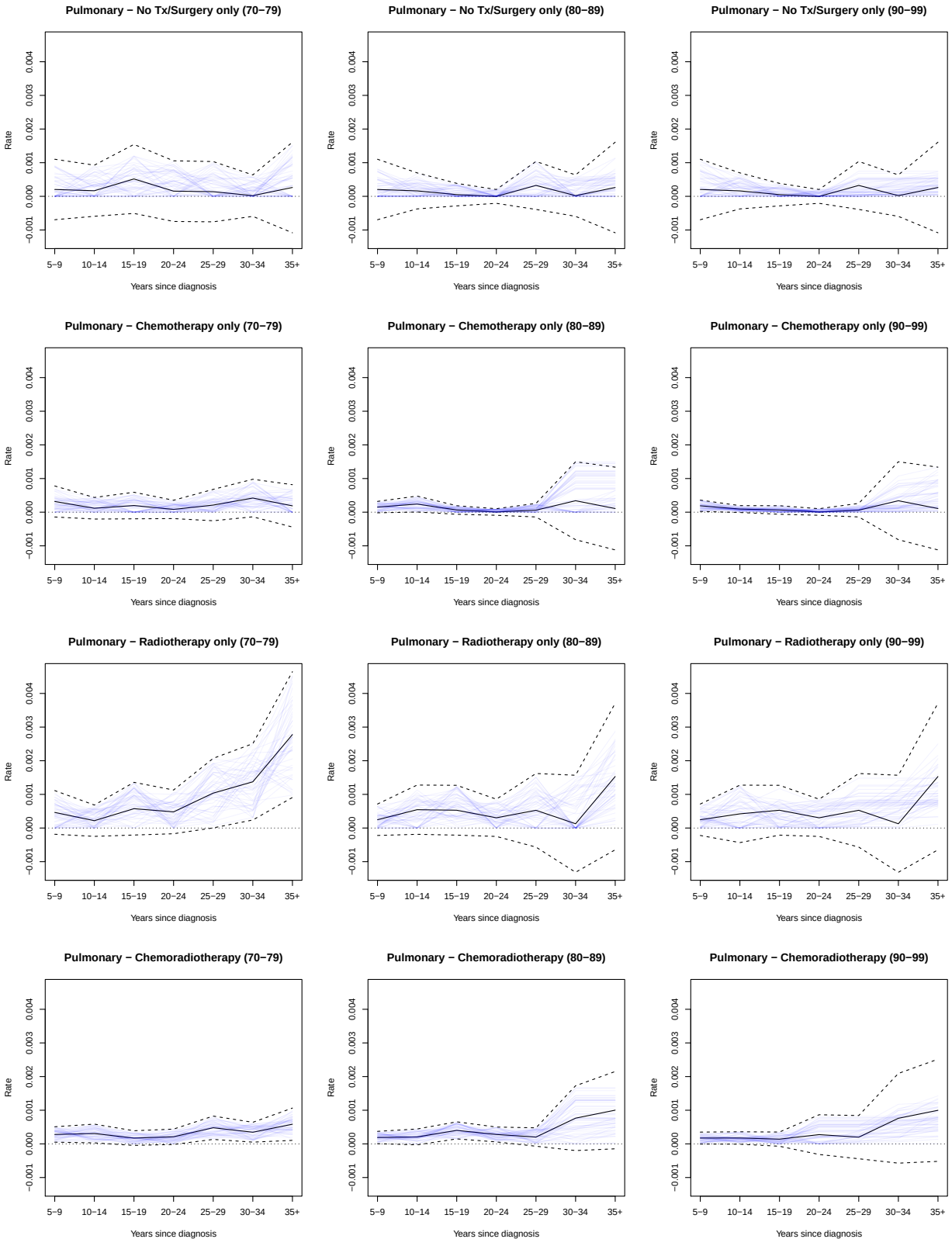
Late recurrence mortality (annual rate)

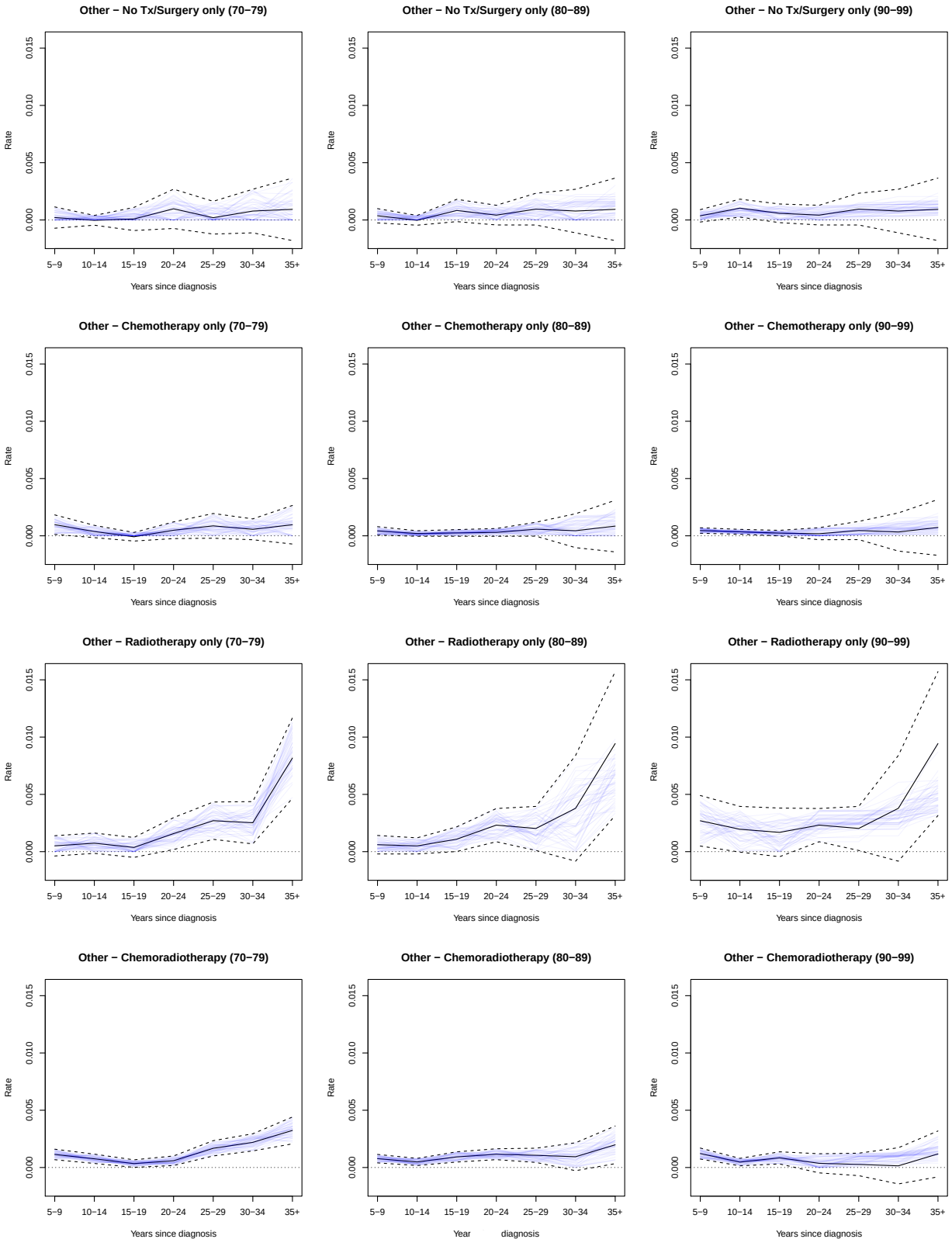


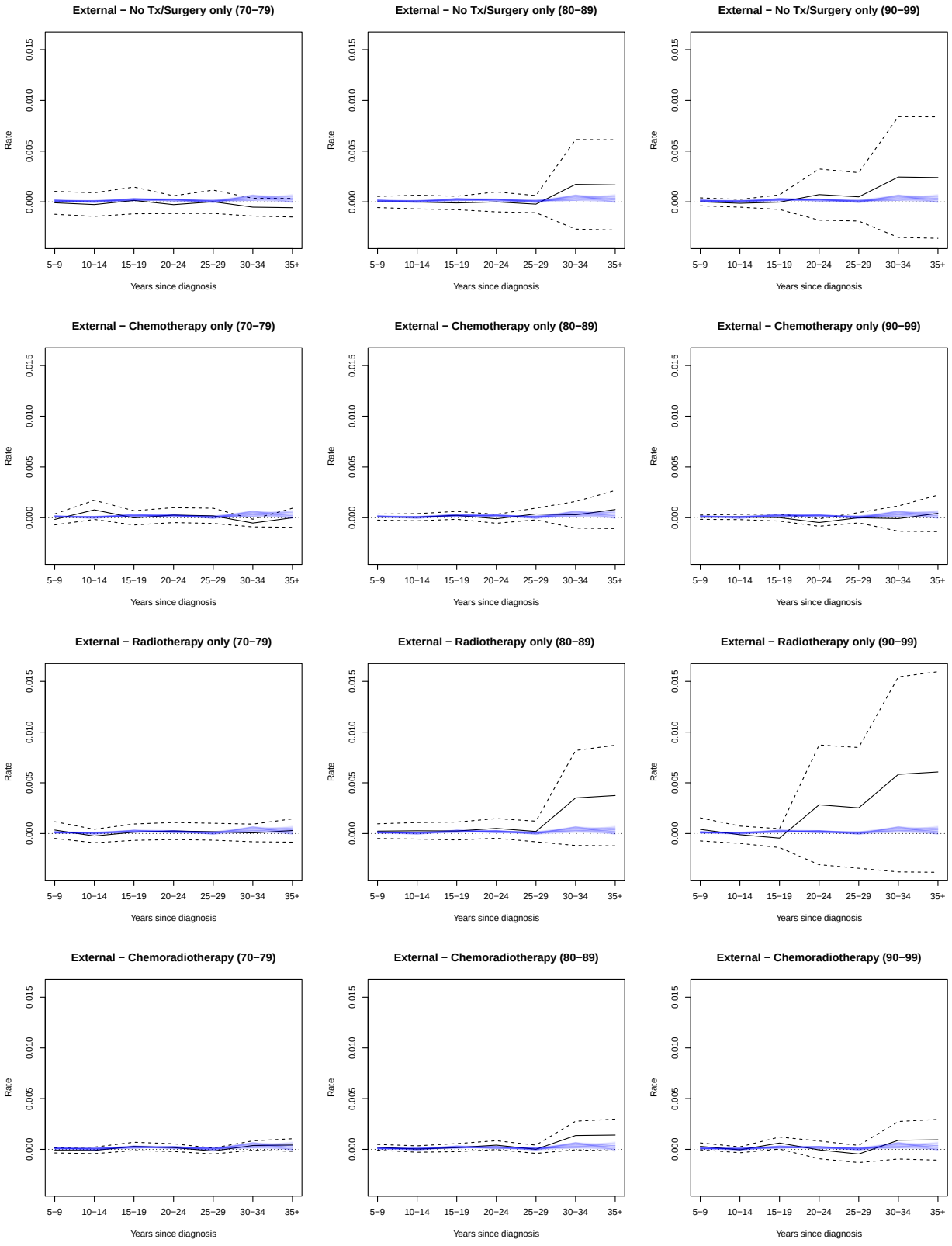
Absolute excess risk (AER) for late effects (annual rate)







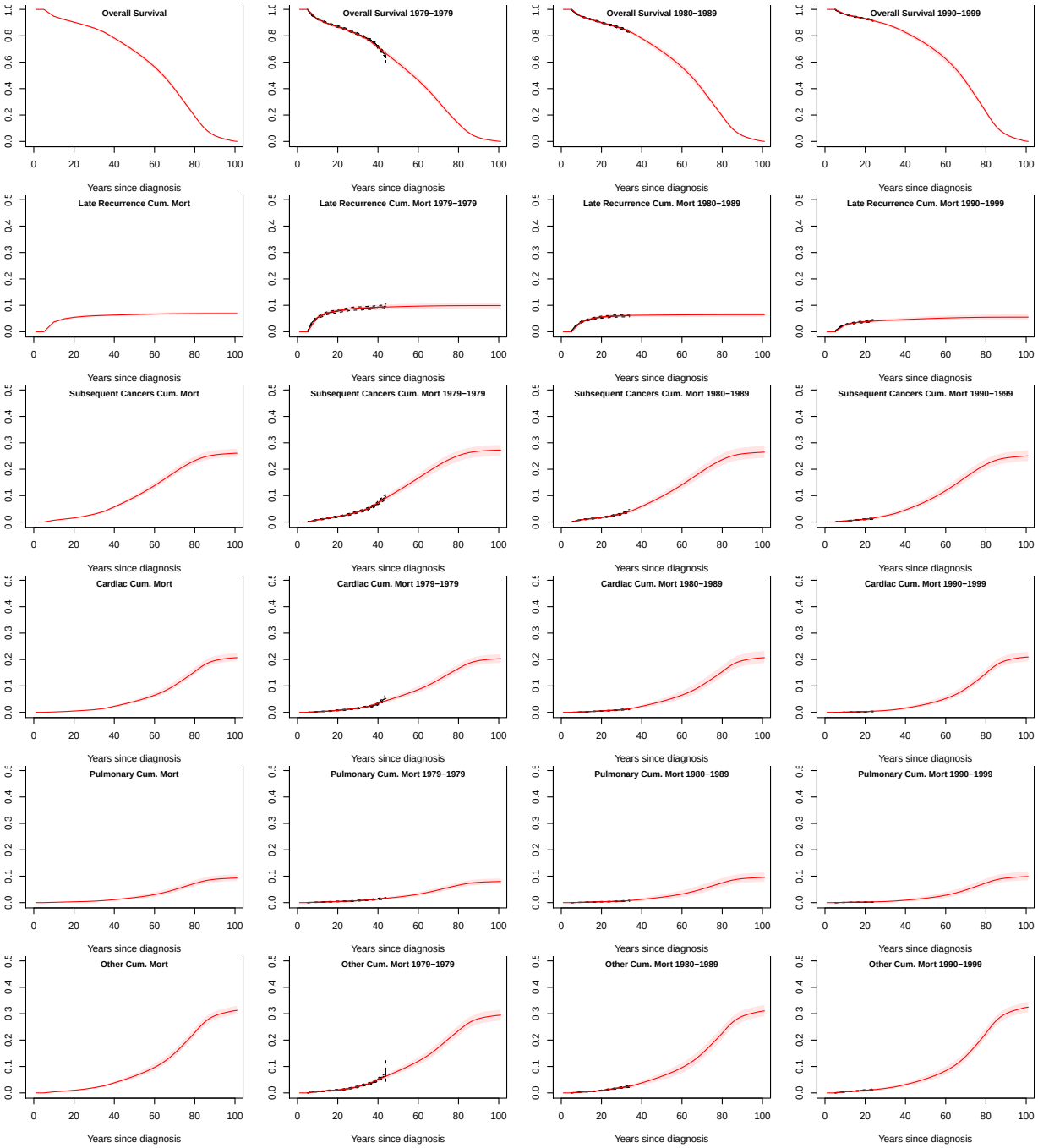


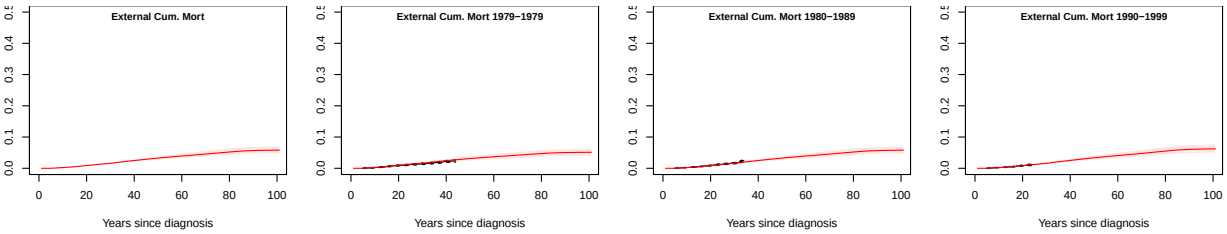


Calibration Targets

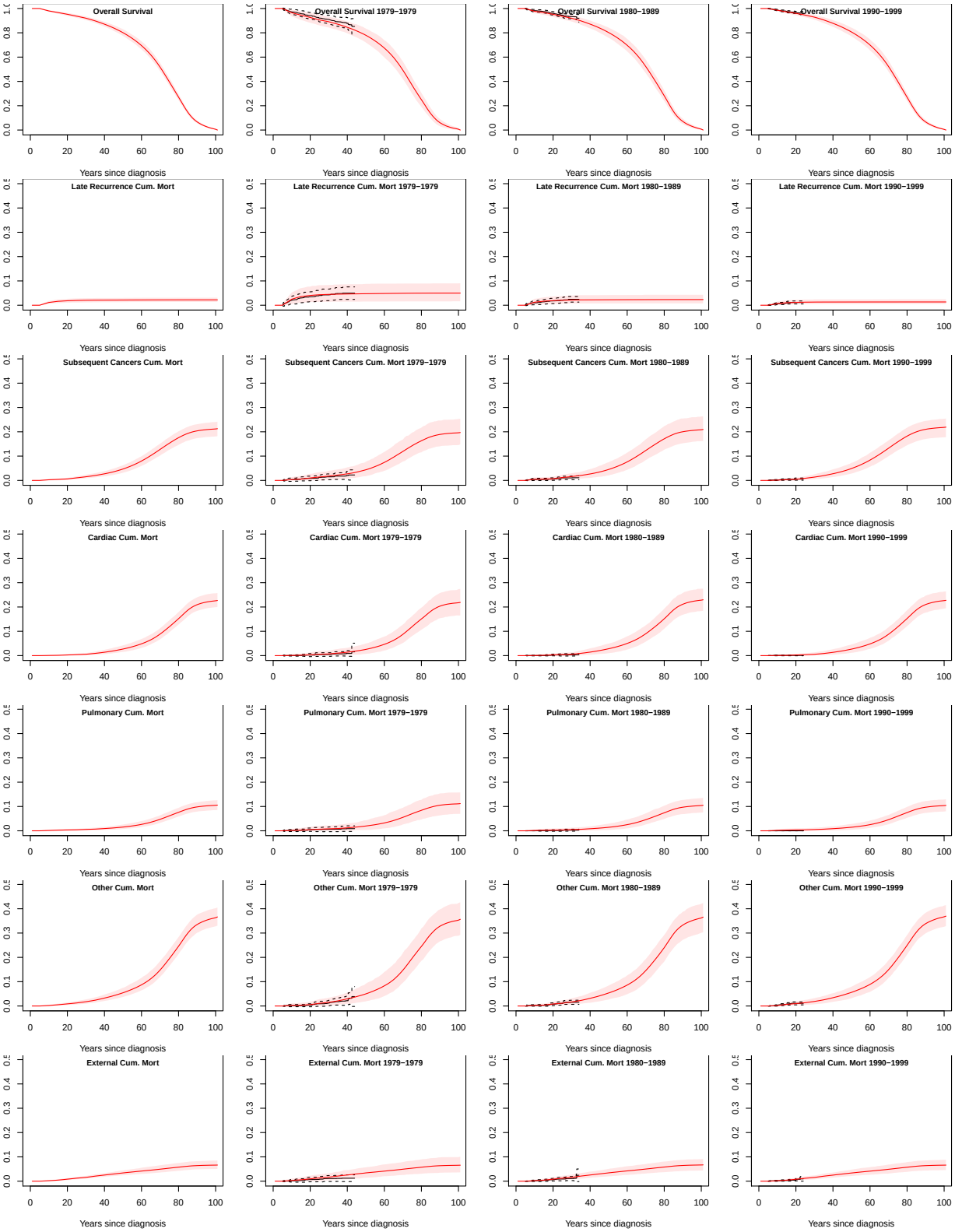
Here we plot our calibrated model estimates of survival (overall) and cumulative mortality (cause-specific) by years since diagnosis compared to the observed CCSS estimates (shown in black). Red = modeled survivors. Shaded regions = 95% uncertainty intervals (UI) among 1000 iterations.

Overall

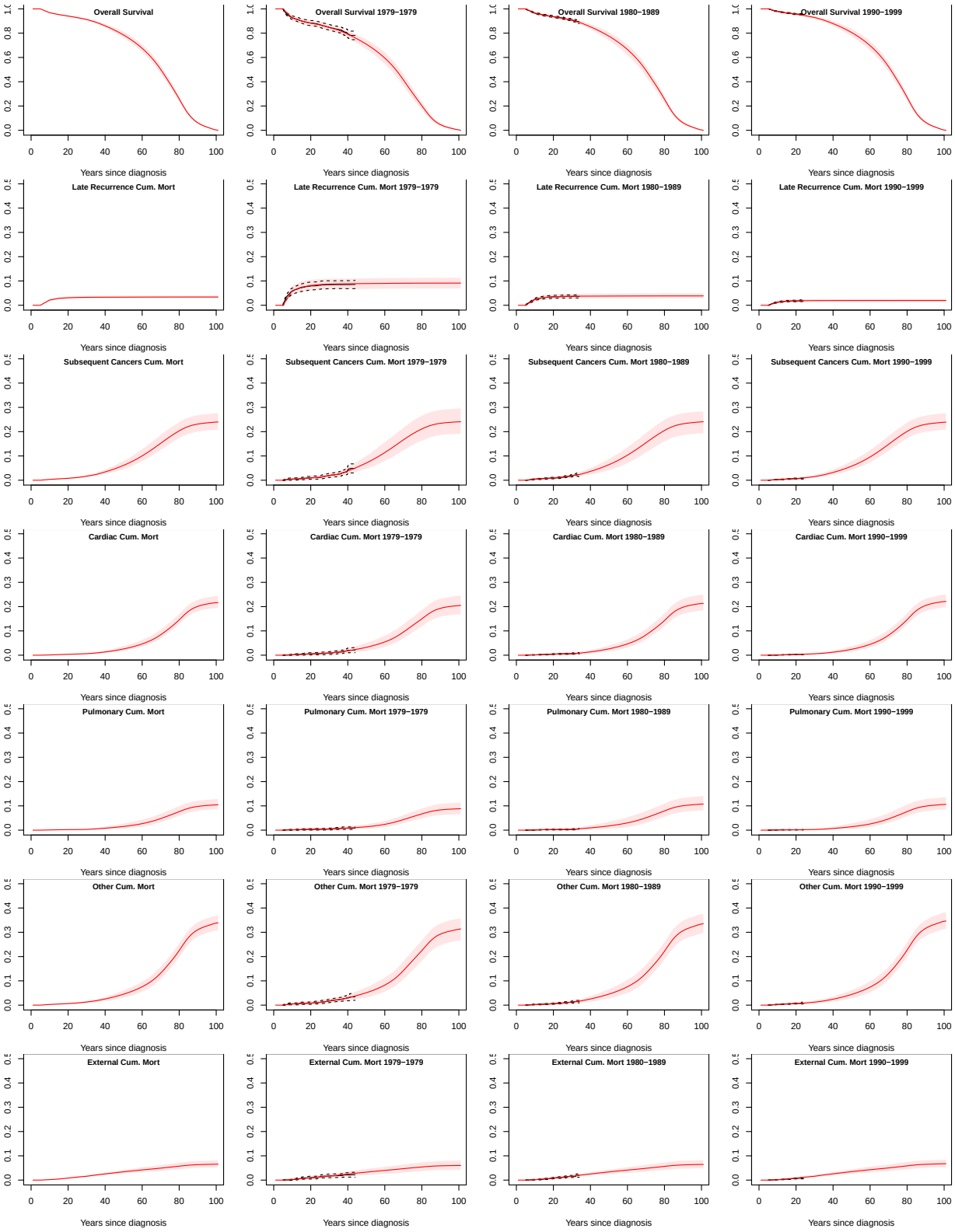




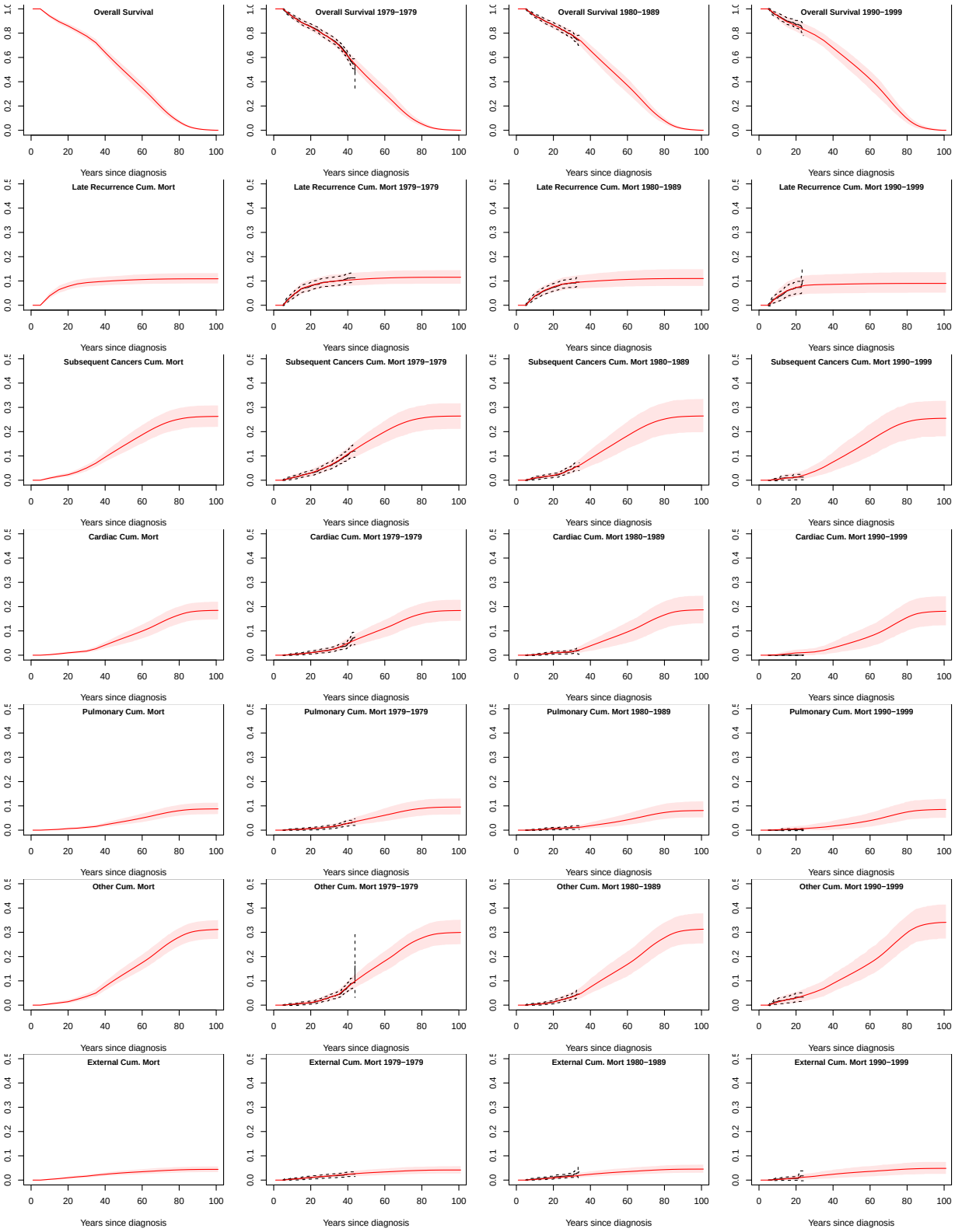
No Treatment/Surgery Only



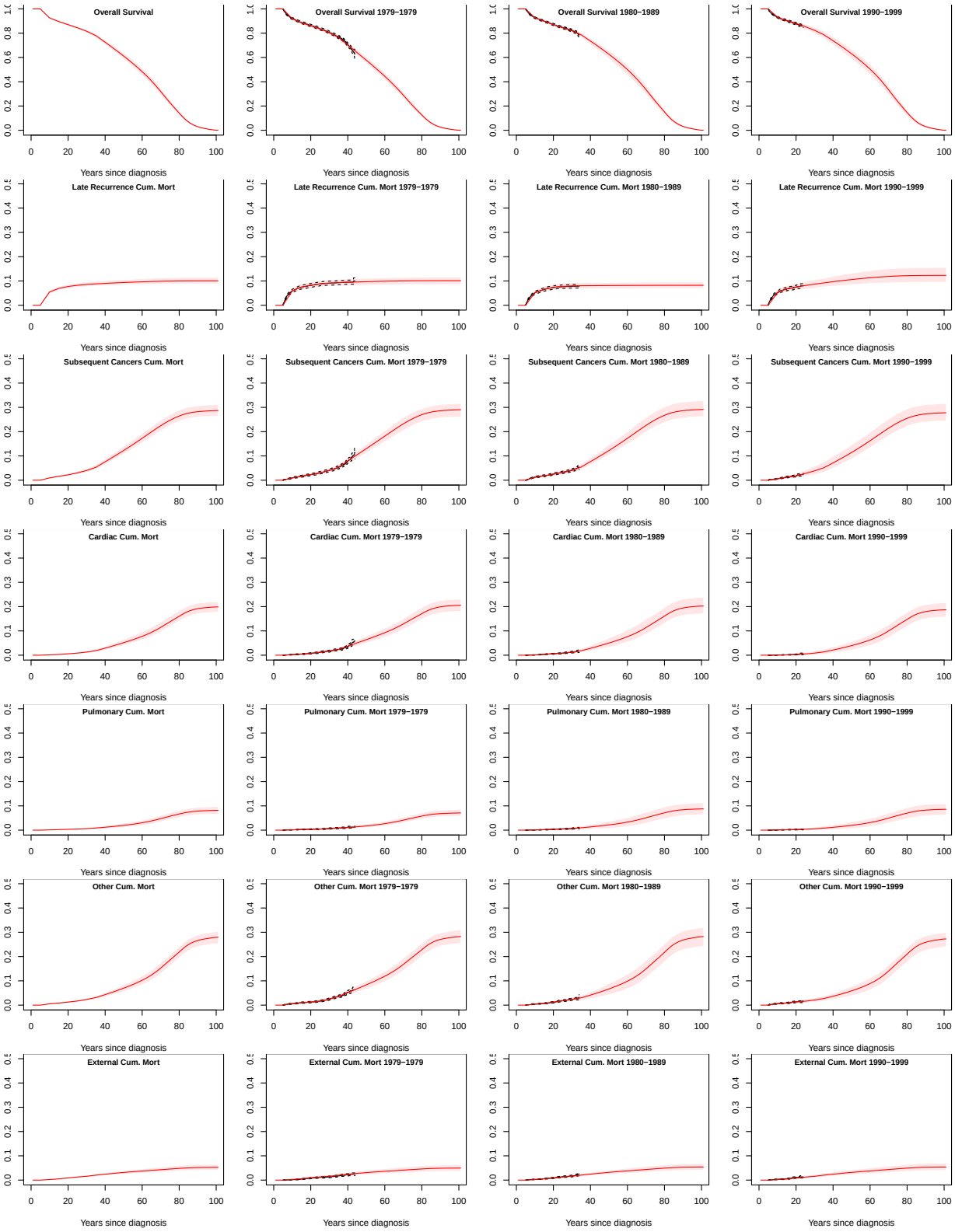
Chemotherapy Only



Radiotherapy Only



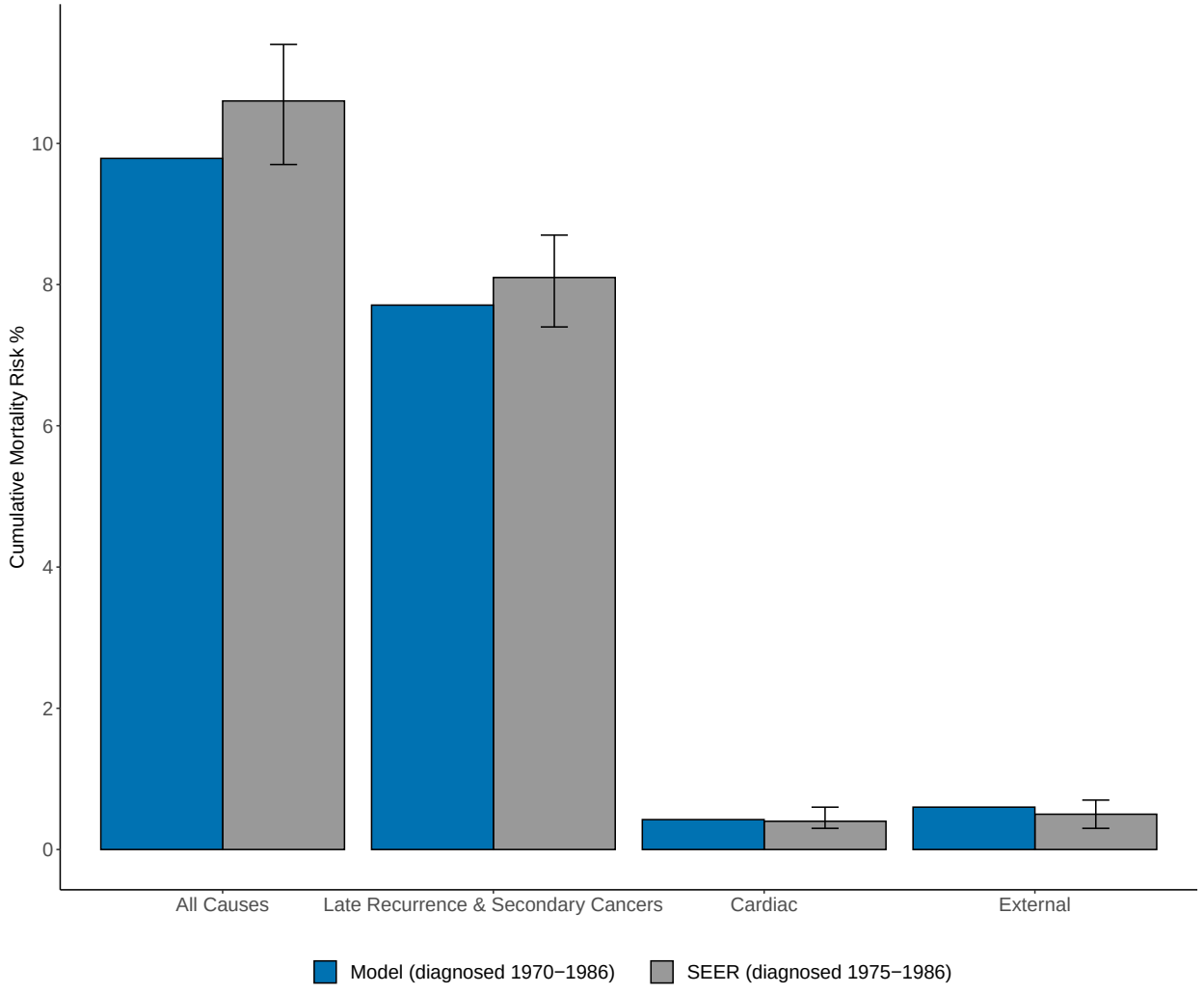
Chemoradiotherapy



Model Validation

To assess the validity of our model predictions, we compared predicted survival at 15-years after diagnosis with empirical data from the Surveillance, Epidemiology and End Results (SEER) program (Mertens et al. Cancer 2015;121(7):1108-17), and general population conditional life expectancy estimates from the US National Center for Health Statistics (NCHS) (Arias et al. Natl Vital Stat Rep 2017;66(4):1-64). At 15 years after diagnosis, modeled overall survival for survivors diagnosed with cancer between 1970 and 1989 approximated estimates for SEER patients diagnosed between 1975 and 1986 (90.2% vs. 89.4%, respectively). Modeled cause-specific mortality estimates fell within the 95% CI of cause of death estimates available in SEER, as shown in Supplemental Figure 2. Additionally, projected conditional life expectancy for individuals without a history of childhood cancer (65.9 years at 12.3 years of age (mean age of overall cohort) for a life expectancy of 73.2 years) was similar to US National Center for Health Statistics estimates for individuals born in 1979-81 (65.1 years at 10 years of age for a life expectancy of 75.1 years).

Comparison of model results with published SEER estimates

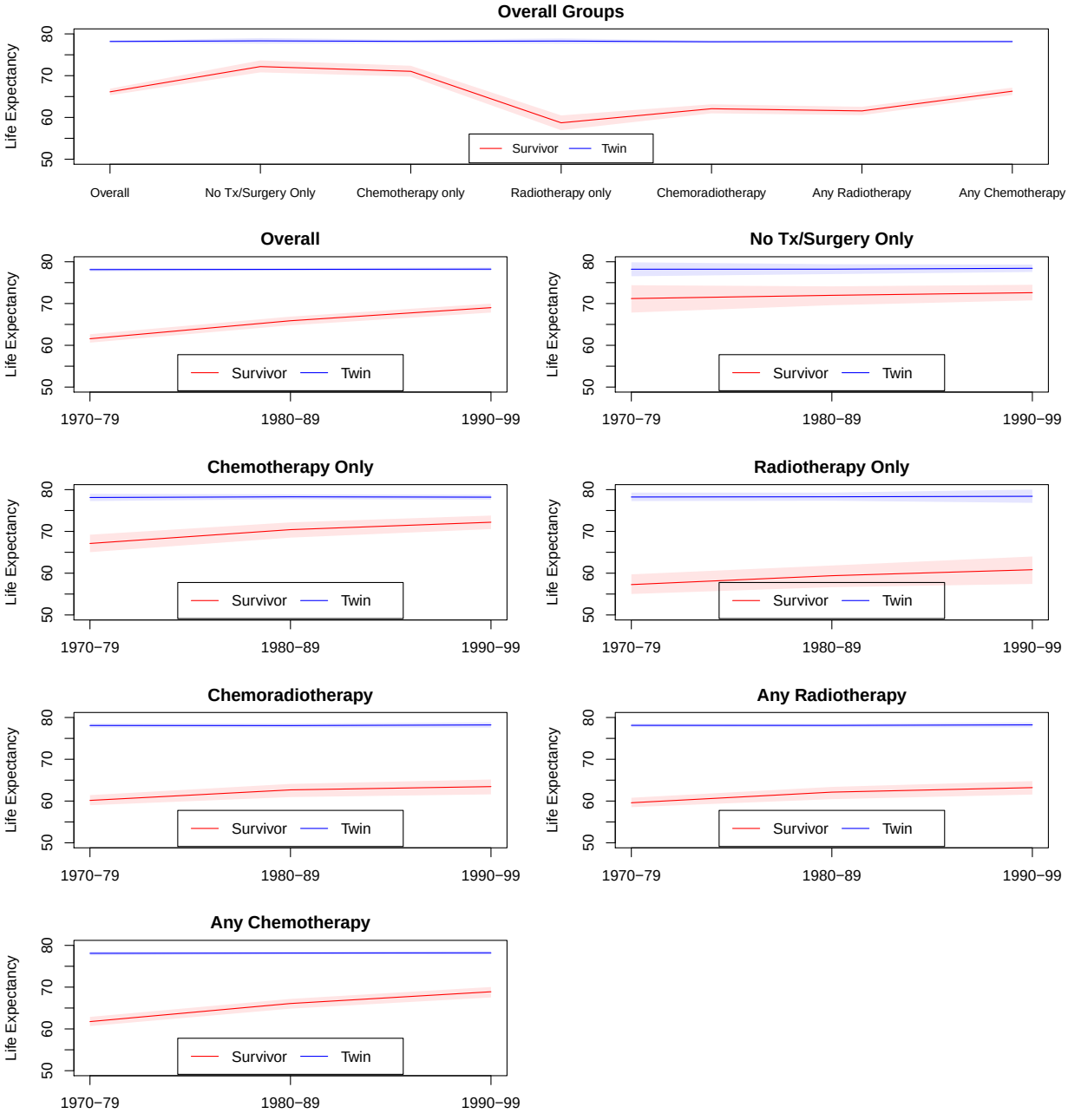


Model Outcomes

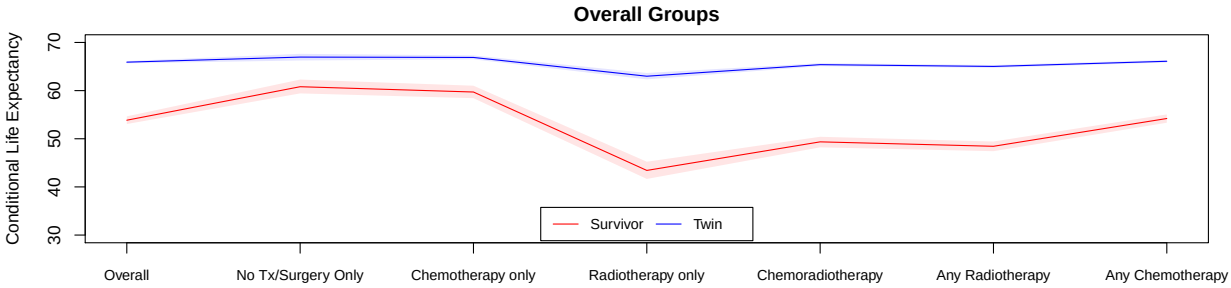
We ran 1,000 iterations of the model to account for first-order (stochastic) and second-order (parameter) uncertainty. To account for first-order uncertainty we bootstrapped the CCSS cohort using the original cohort size with a random bootstrap in each iteration. To account for second-order uncertainty we sampled a parameter set (from the top 50) uniformly at random. We compared each respondent to a synthetic 'twin' created at the individual-level by removing survivor-related late recurrence mortality and AERs. Shaded areas indicate 95% UI.

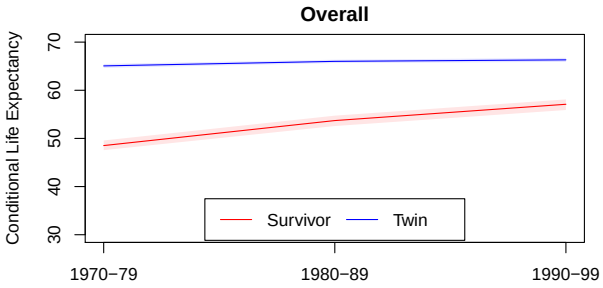
Life Expectancy

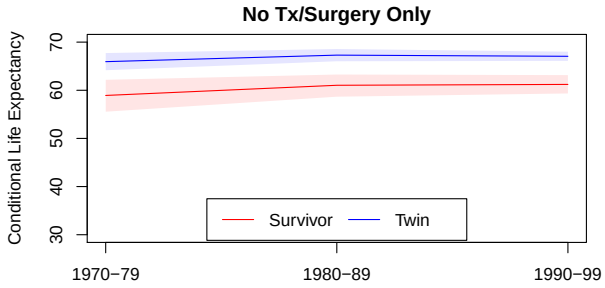
Total

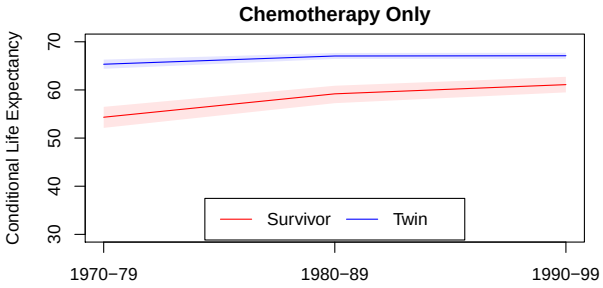


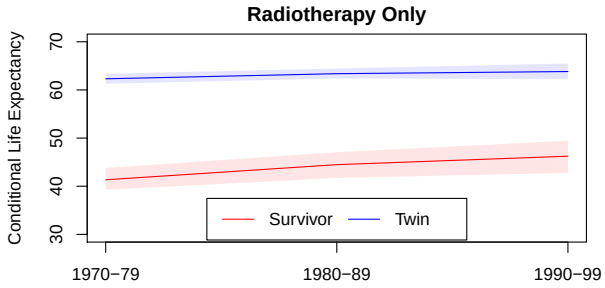
Conditional

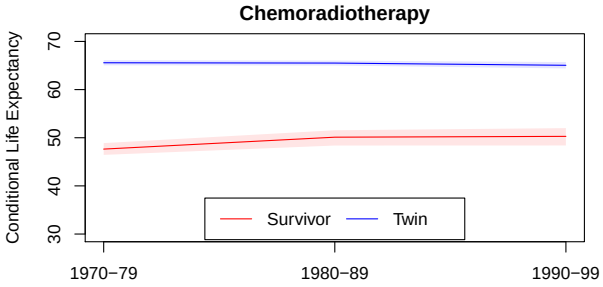


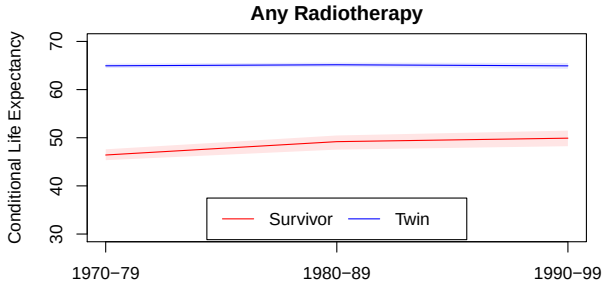


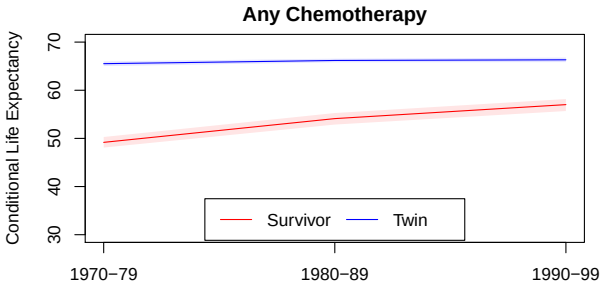




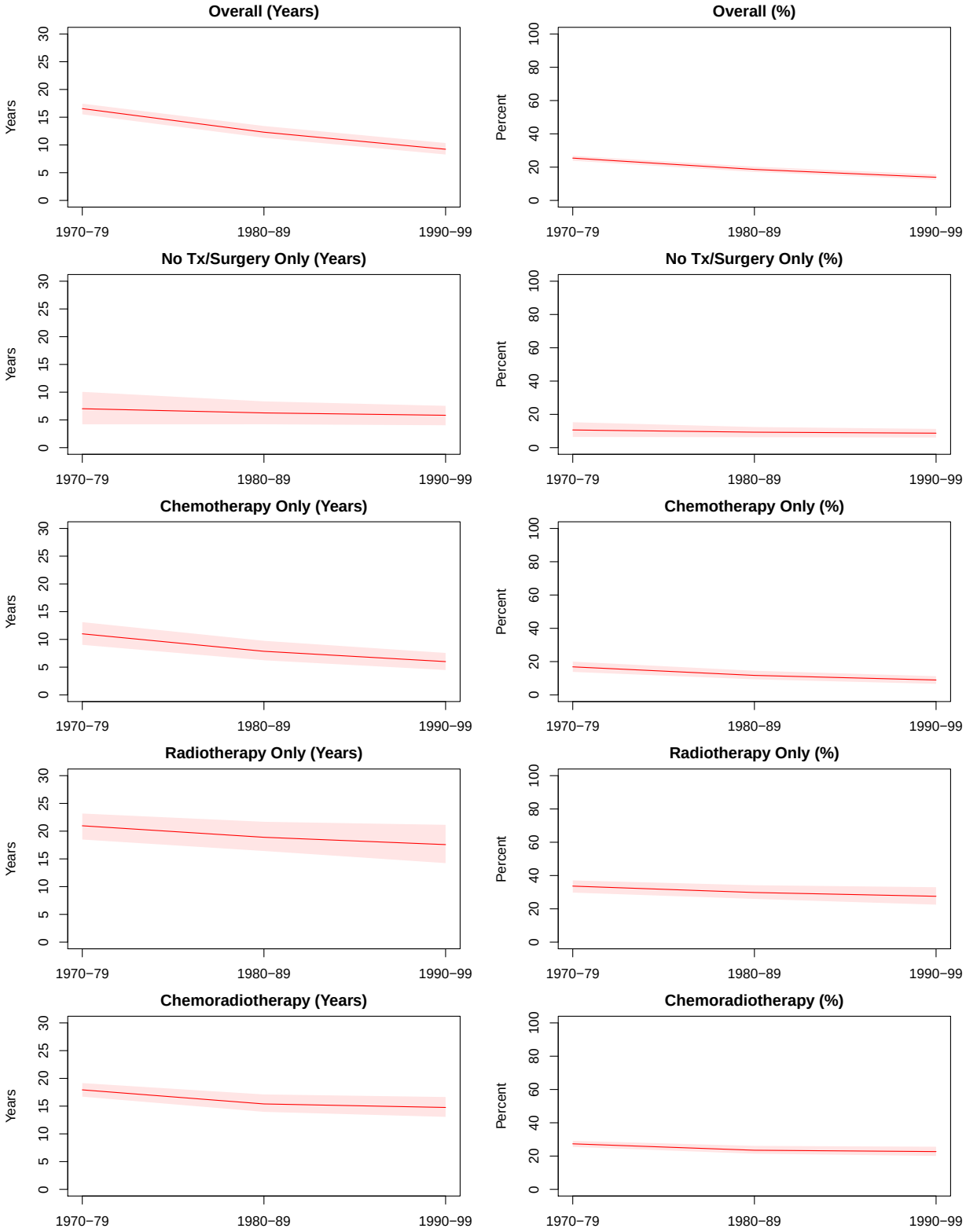


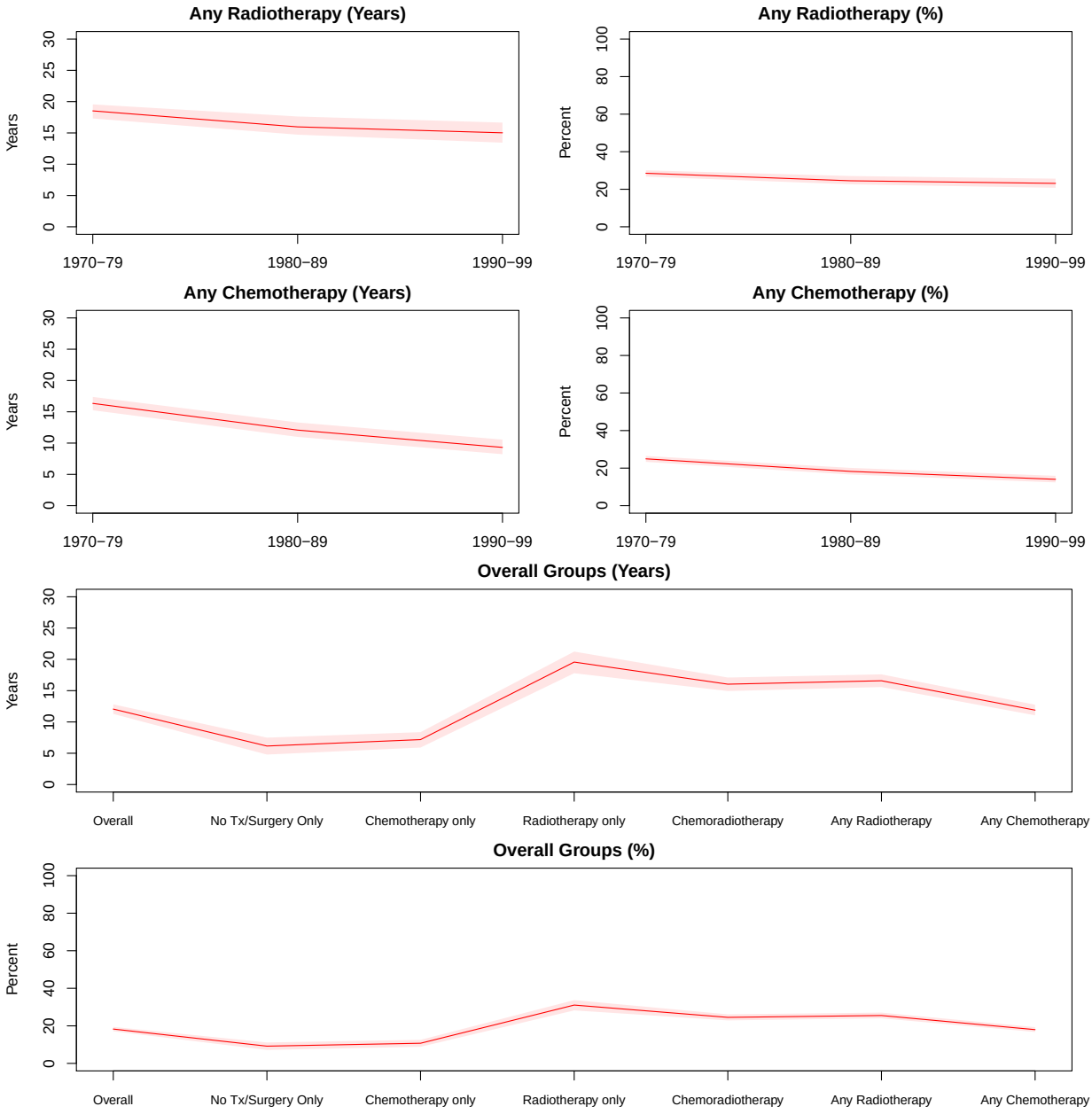






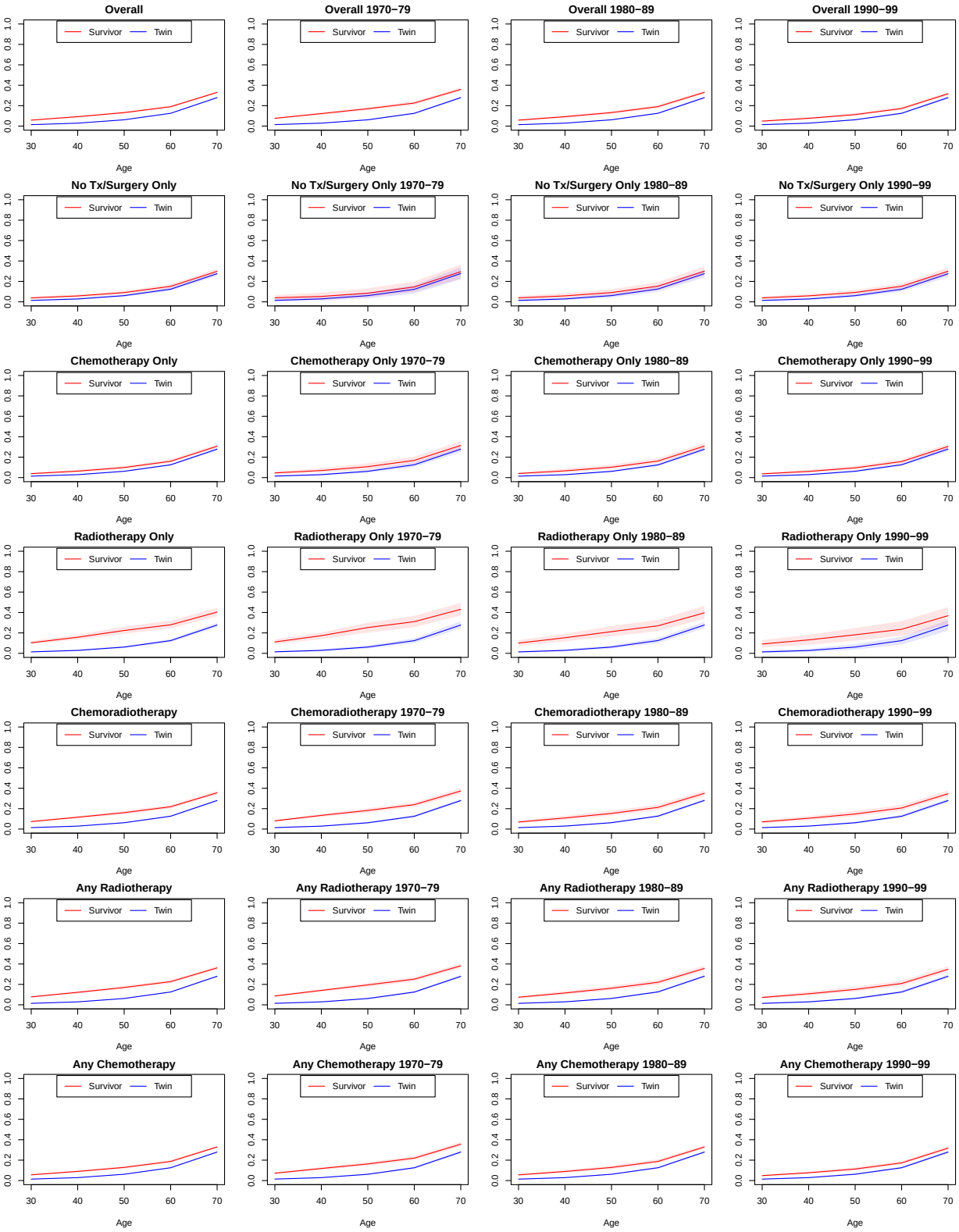
Loss of Conditional LE



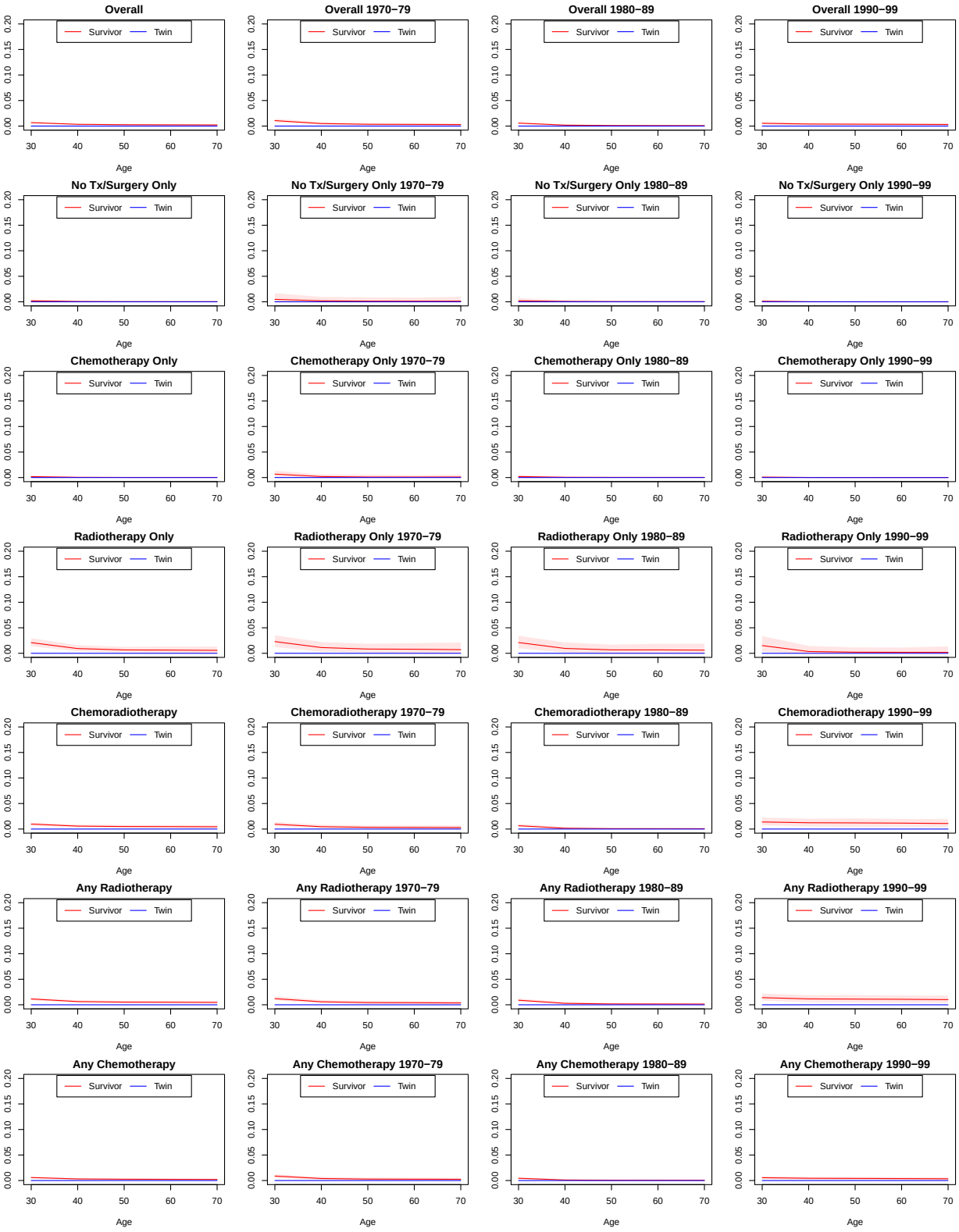


Ten-Year Mortality Risk

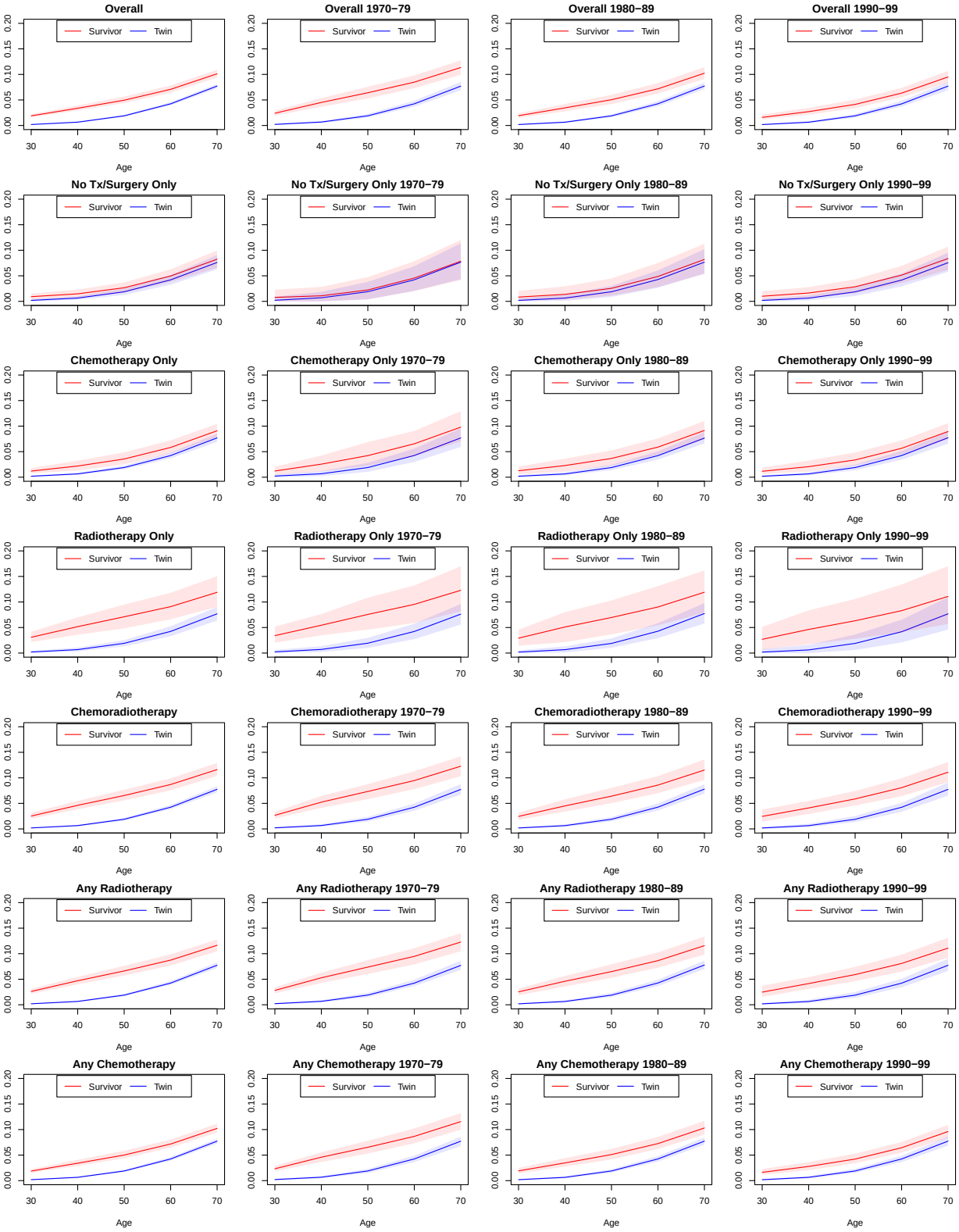
Overall



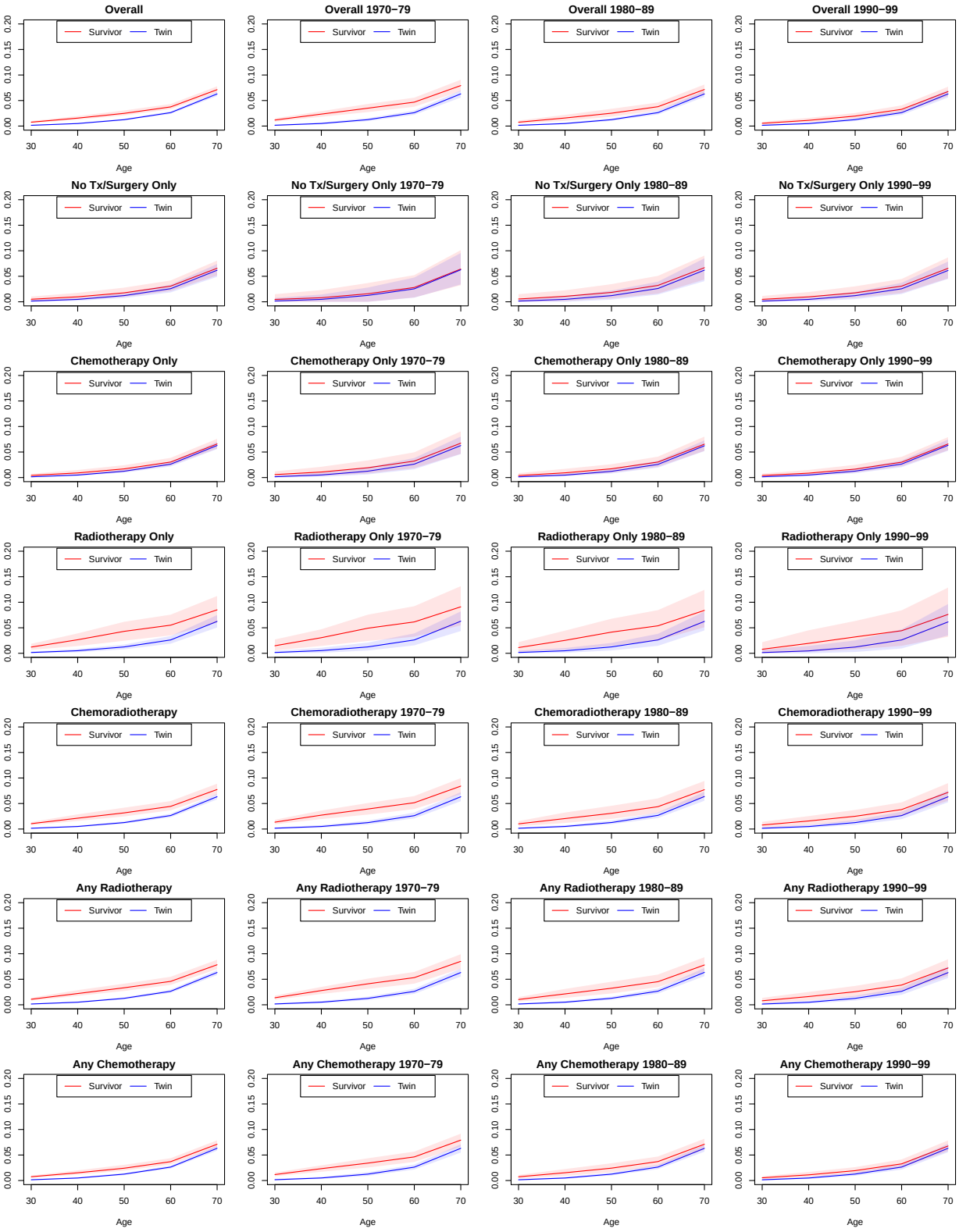
Late Recurrence



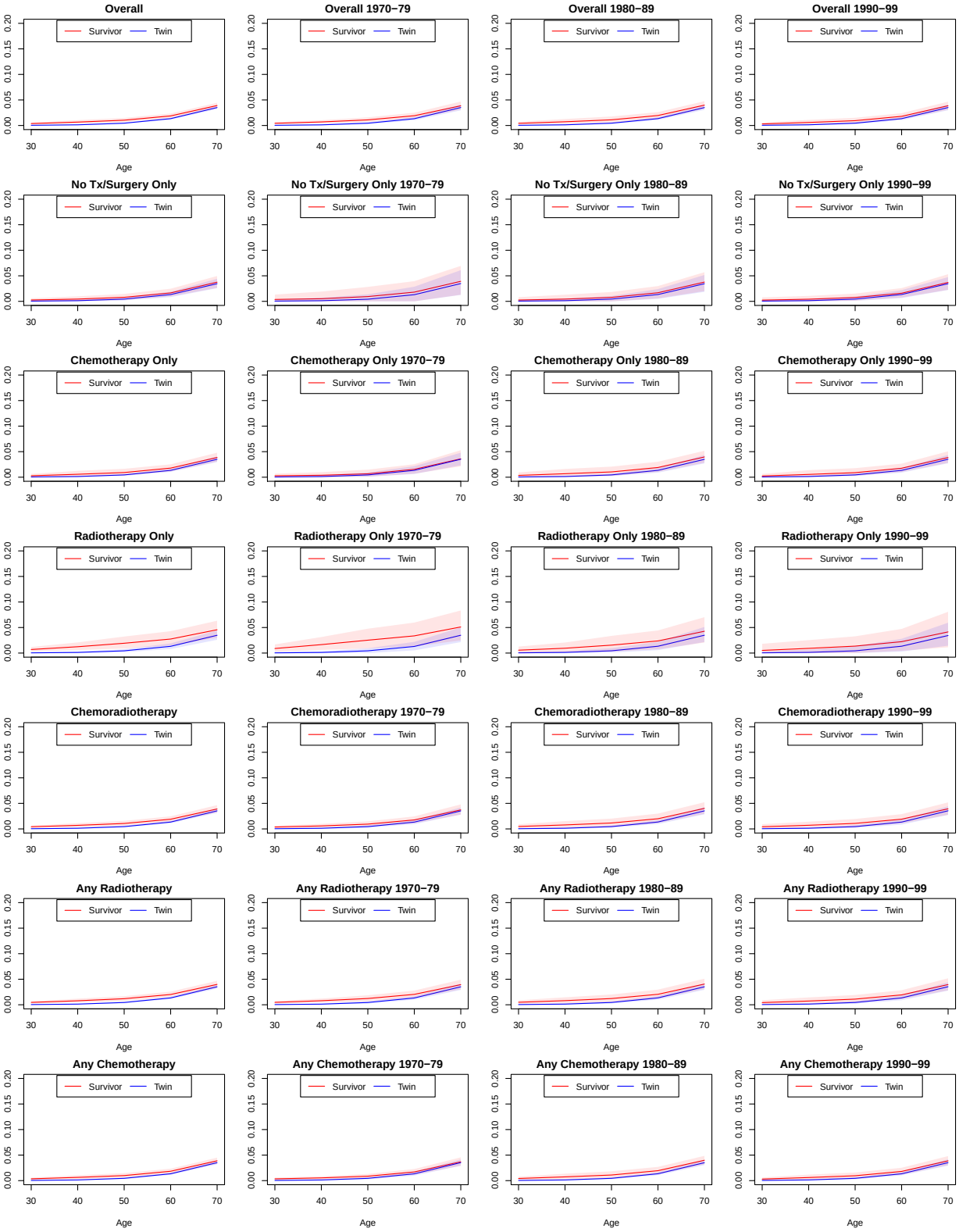
Subsequent Cancers



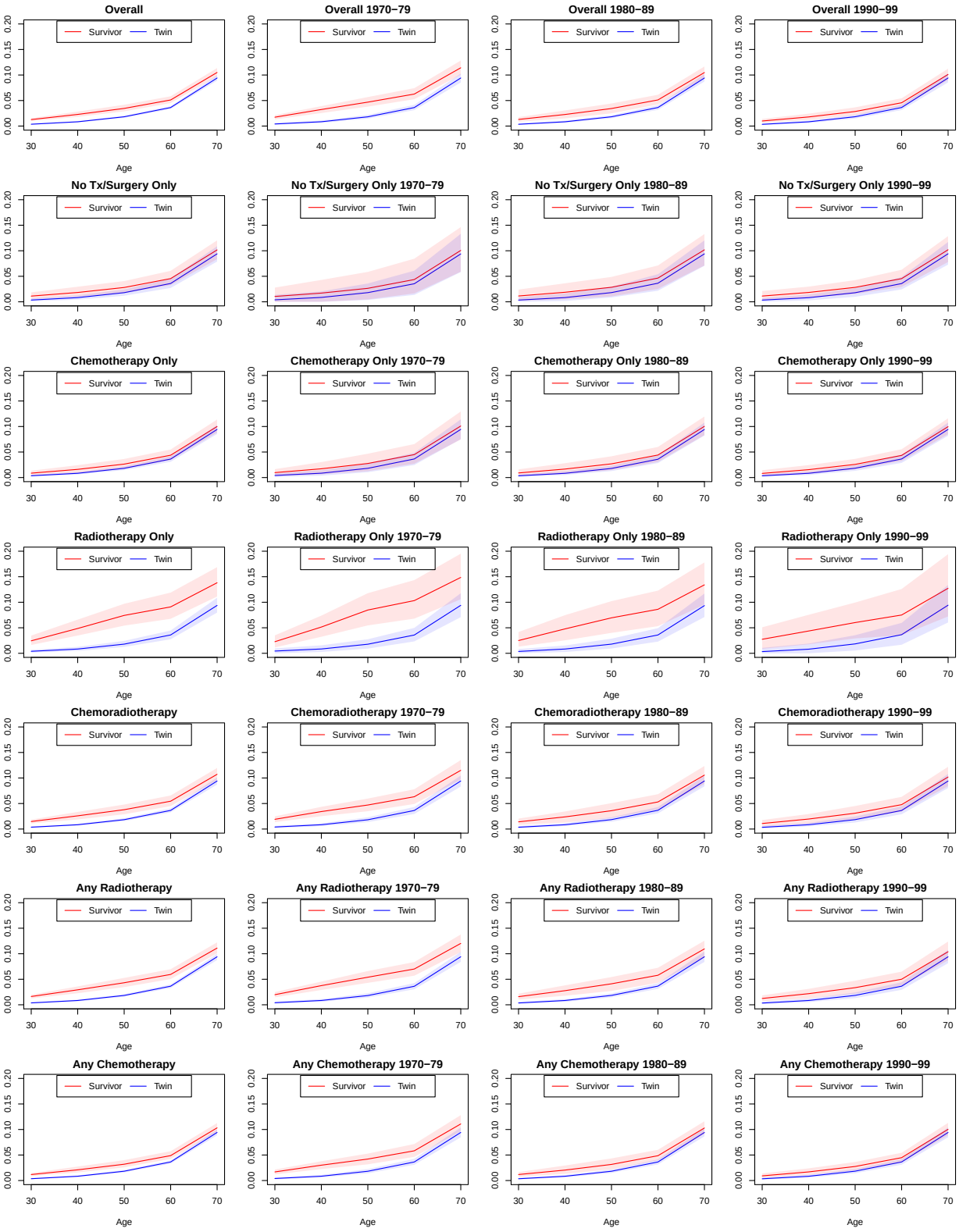
Cardiac



Pulmonary



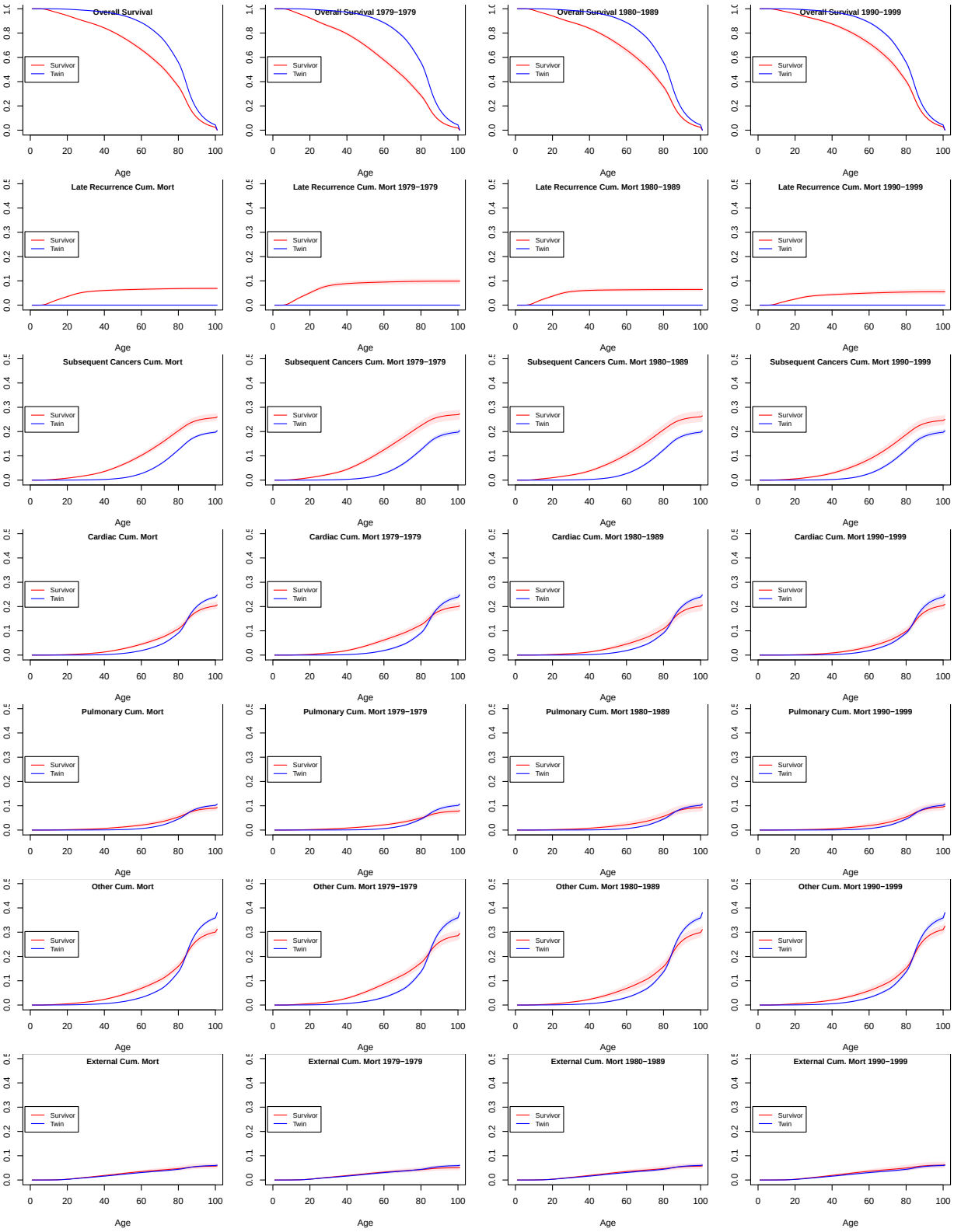
Other



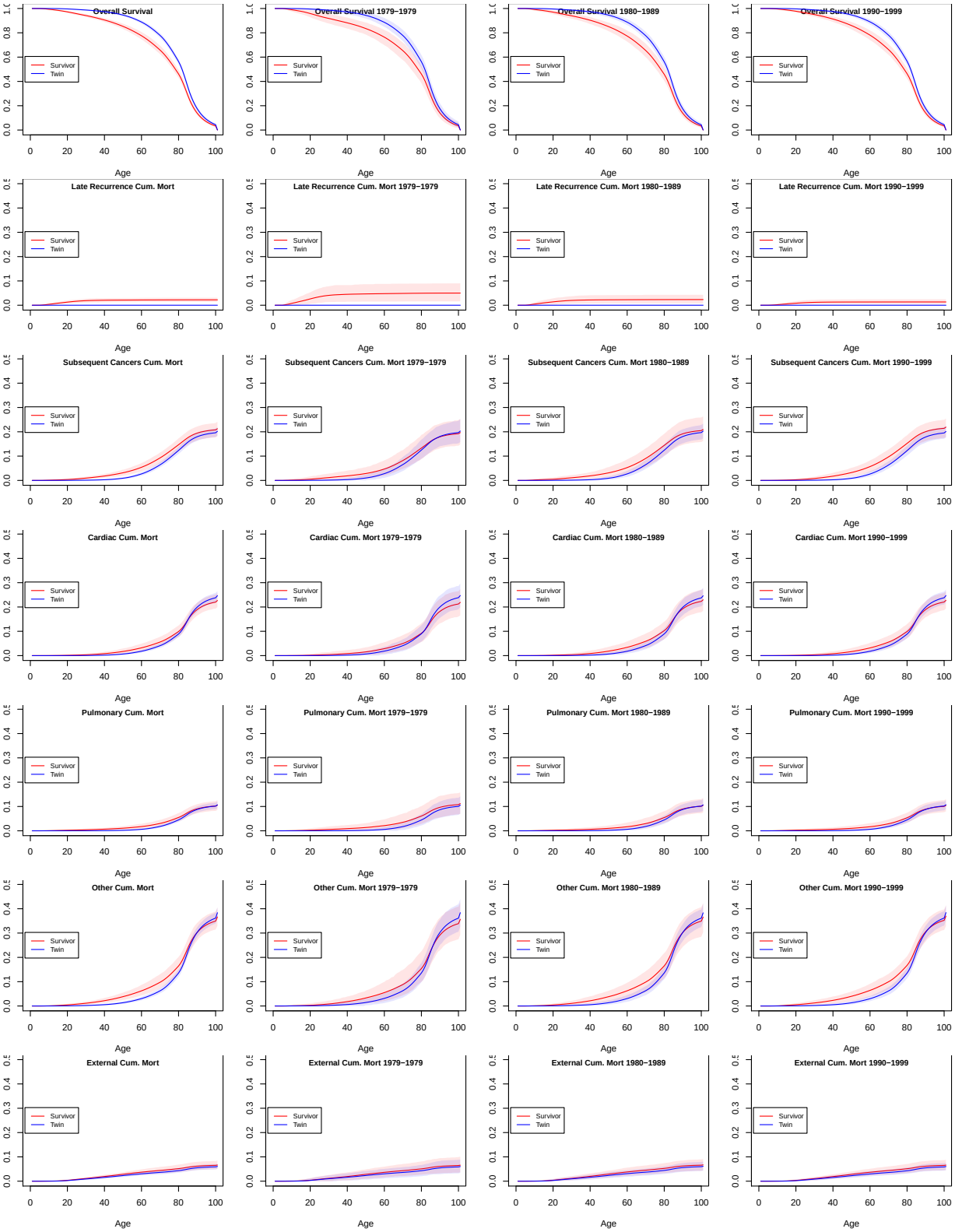
External

Survival Curves/Cumulative Mortality by Age

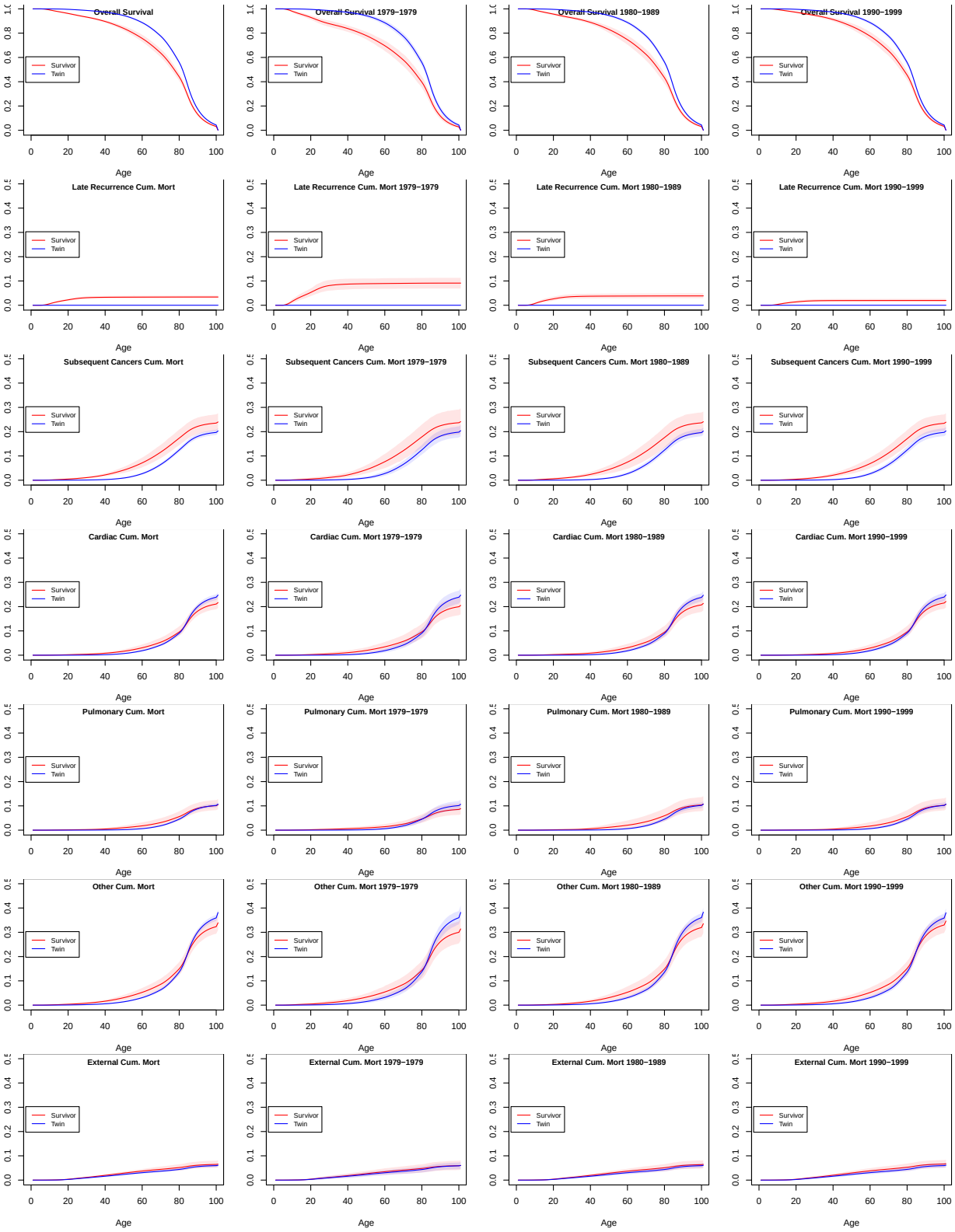
Overall



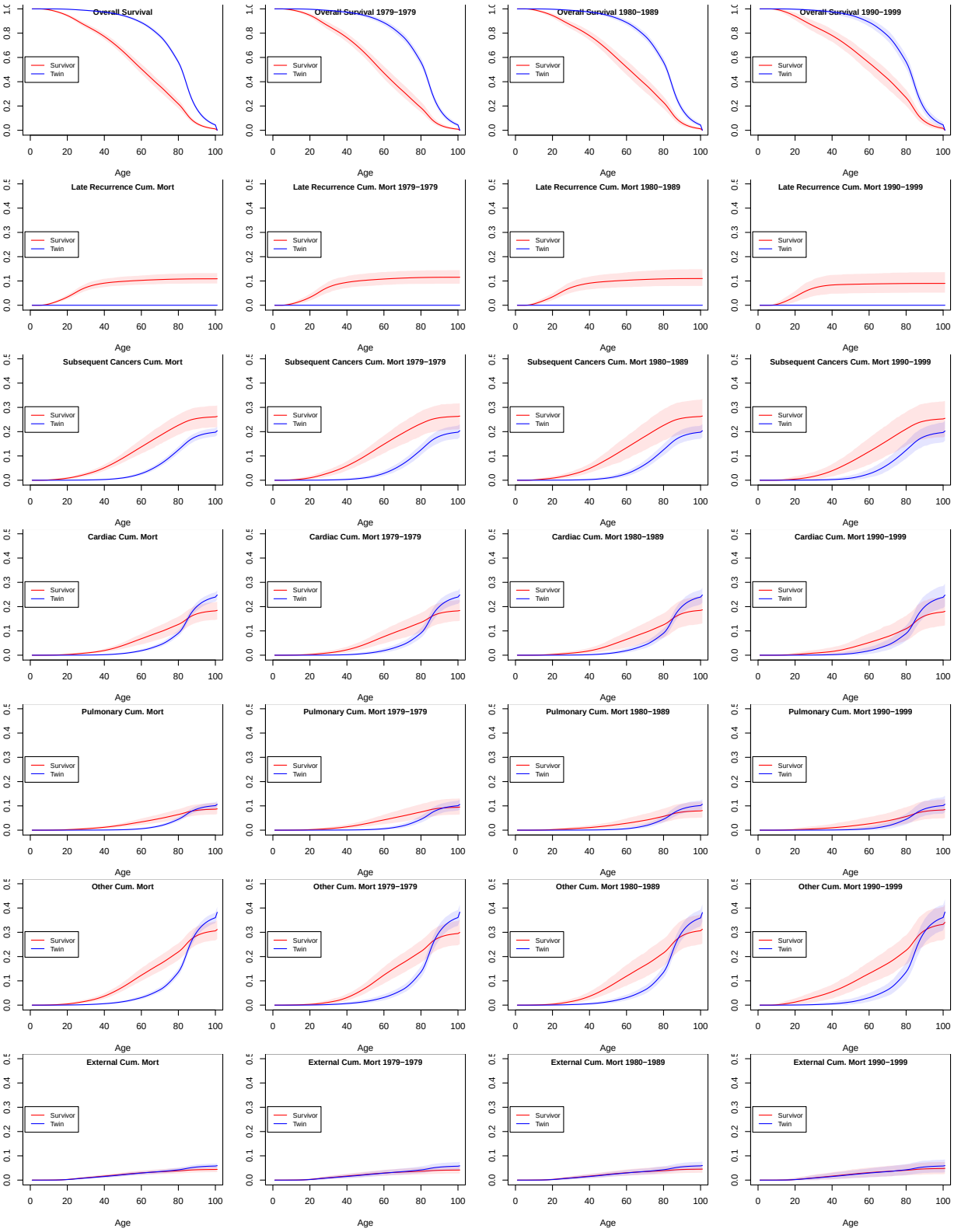
No Treatment/Surgery Only



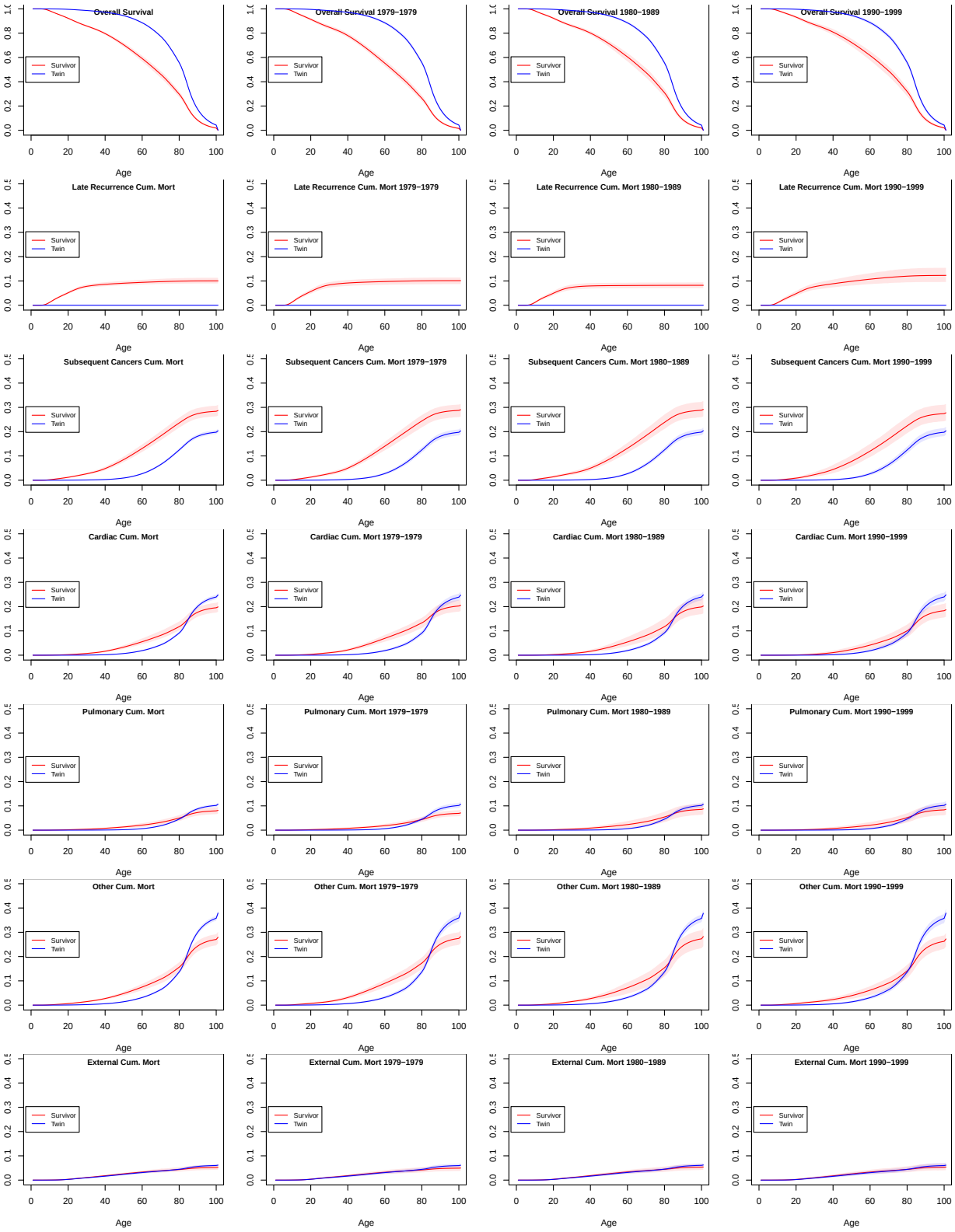
Chemotherapy Only



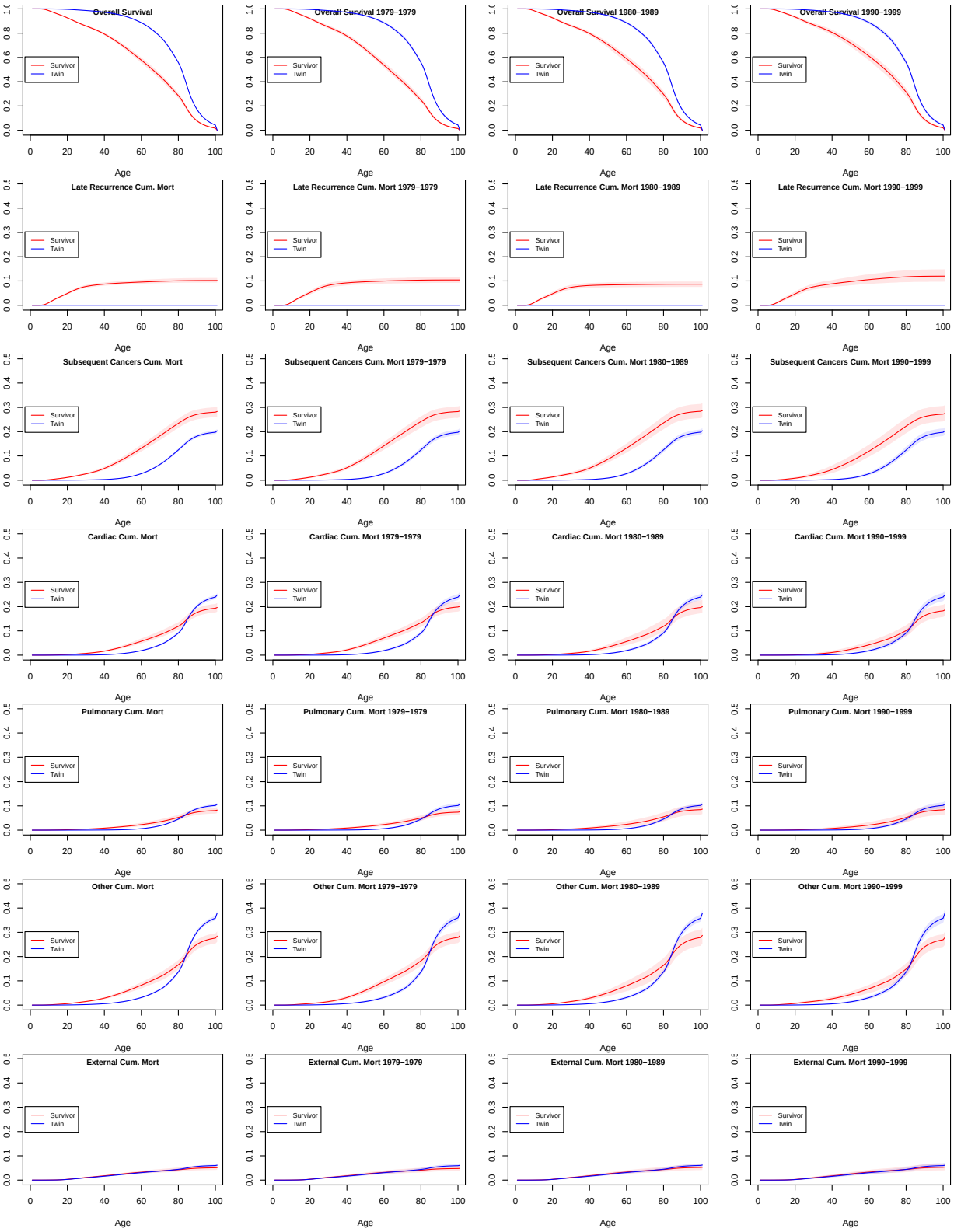
Radiotherapy Only



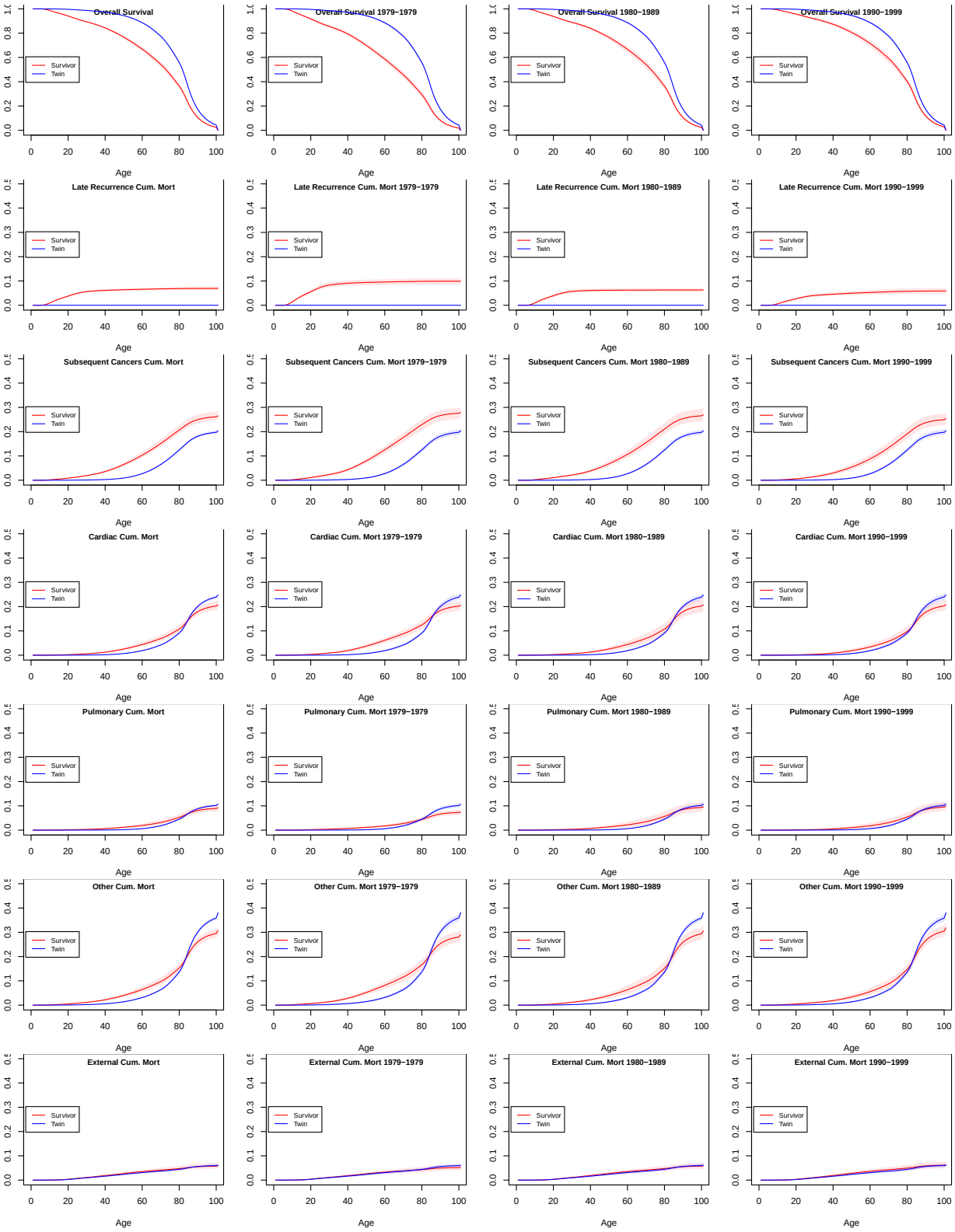
Chemoradiotherapy



Any Radiotherapy



Any Chemotherapy



Subgroup Analysis - Acute Lymphoblastic Leukemia

CCSS Cohort

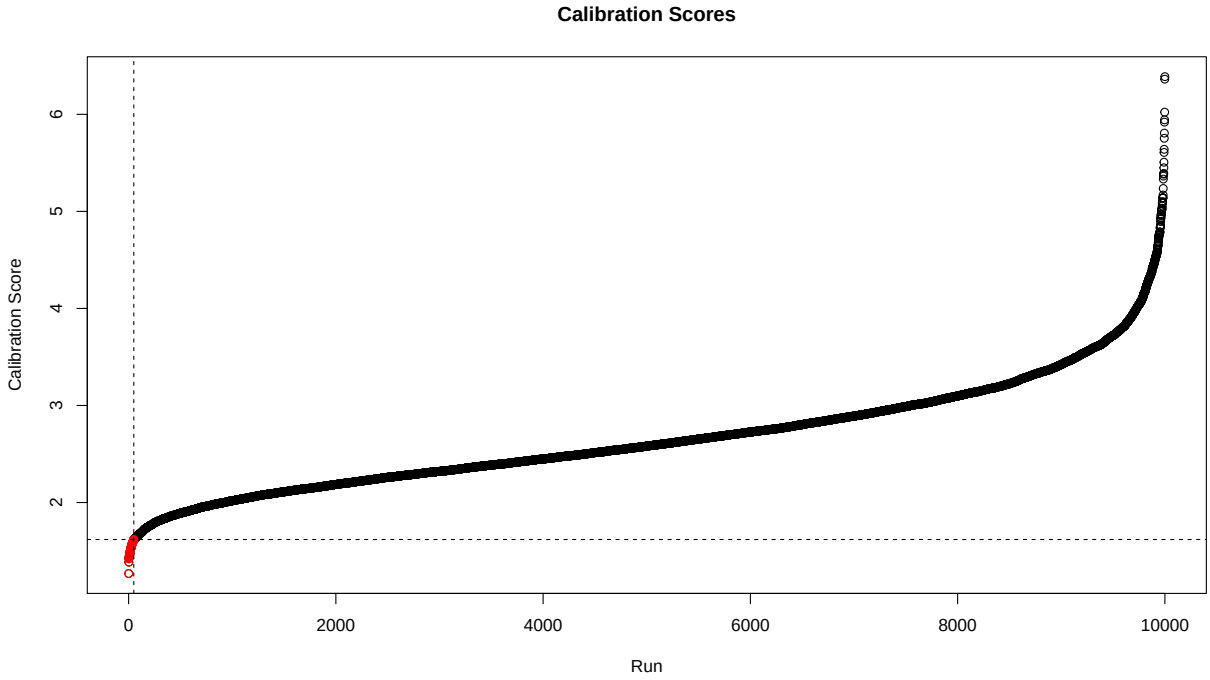
For this subgroup analysis we included individual-level data for 5,794 Acute Lymphoblastic Leukemia (ALL) survivors from our CCSS dataset. Each respondent was weighted with inverse probability weights (IPW) as described above.

Model Calibration

We re-calibrated the model to ALL-specific estimated survival curves (overall) and cumulative mortality (cause-specific), using the same calibration approach as described above.

Scores

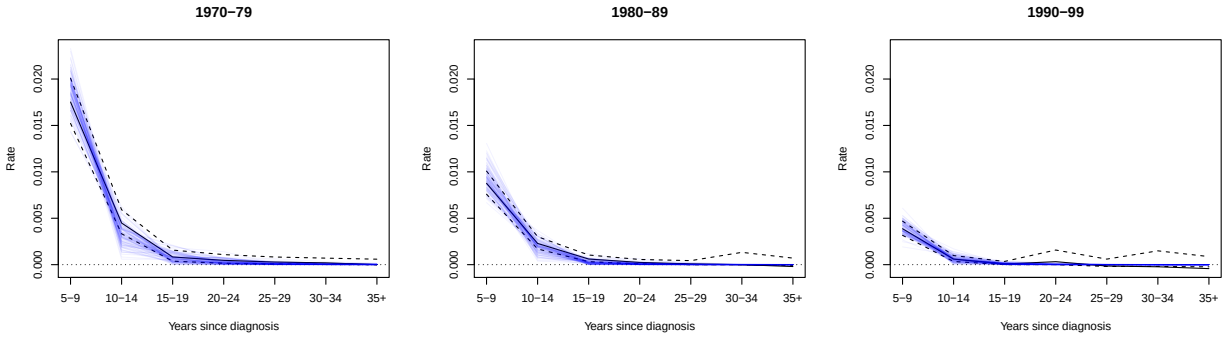
Here we plot the calibration scores and the top 50 sets (highlighted in red).



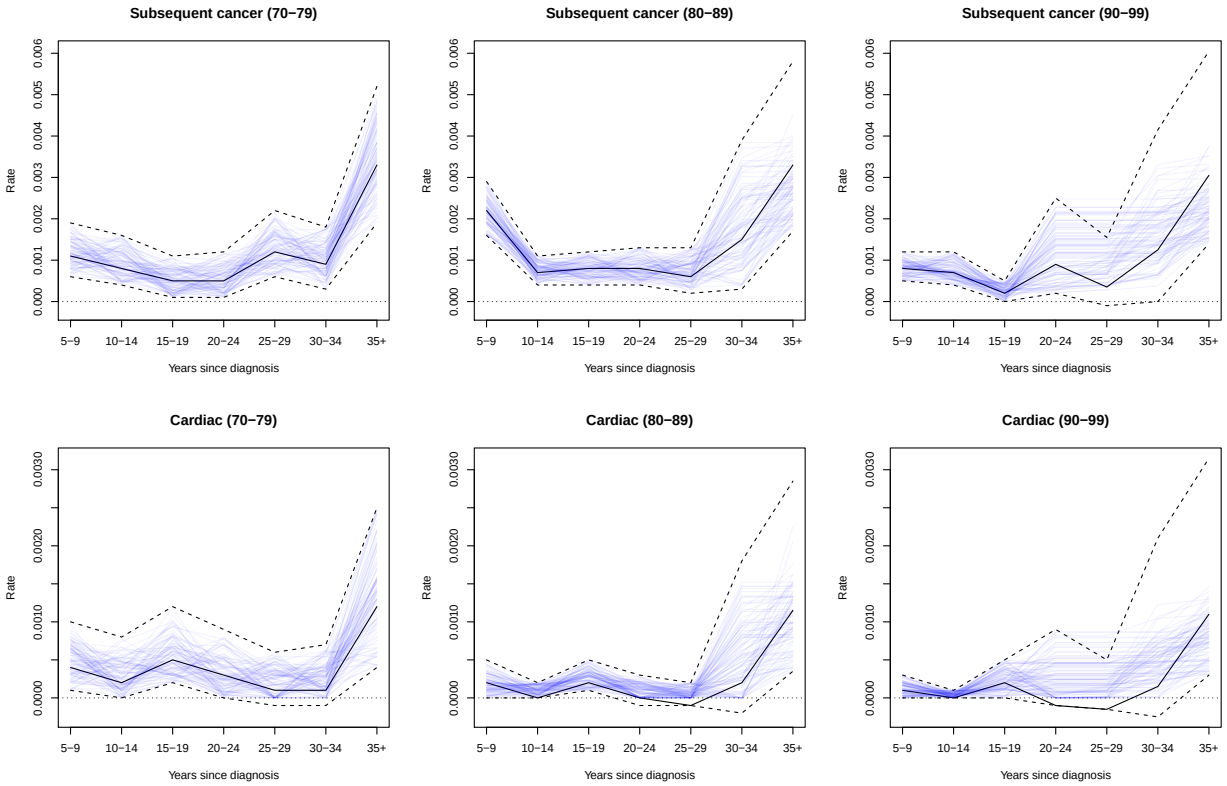
Calibrated Parameters

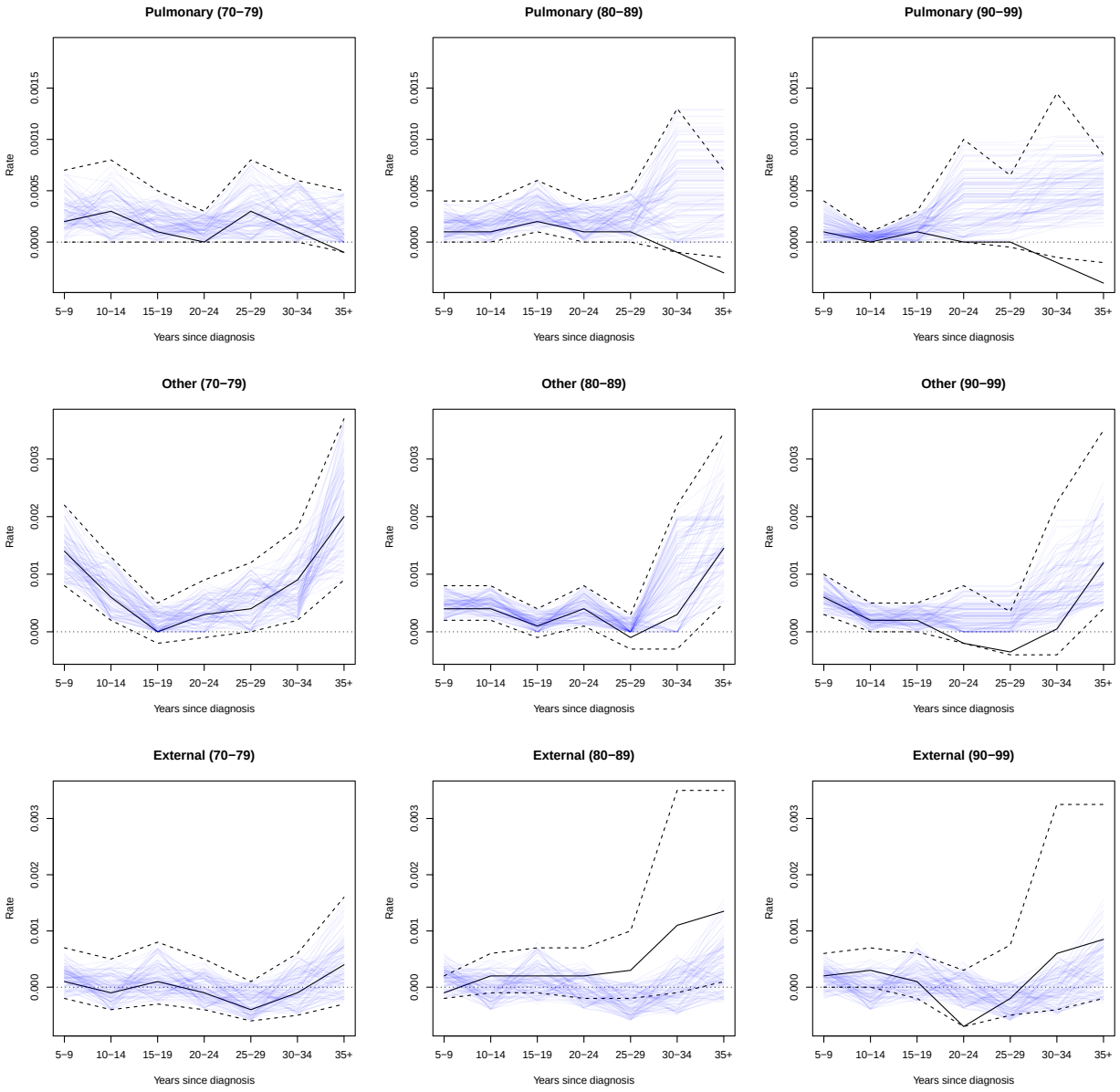
Here we compare our treatment era-specific calibrated parameters to the estimates based on CCSS data. Black lines indicate CCSS estimates (solid = mean, dashed = 95% CI), and blue lines indicate parameter sets identified via calibration.

Late recurrence mortality (annual rate)



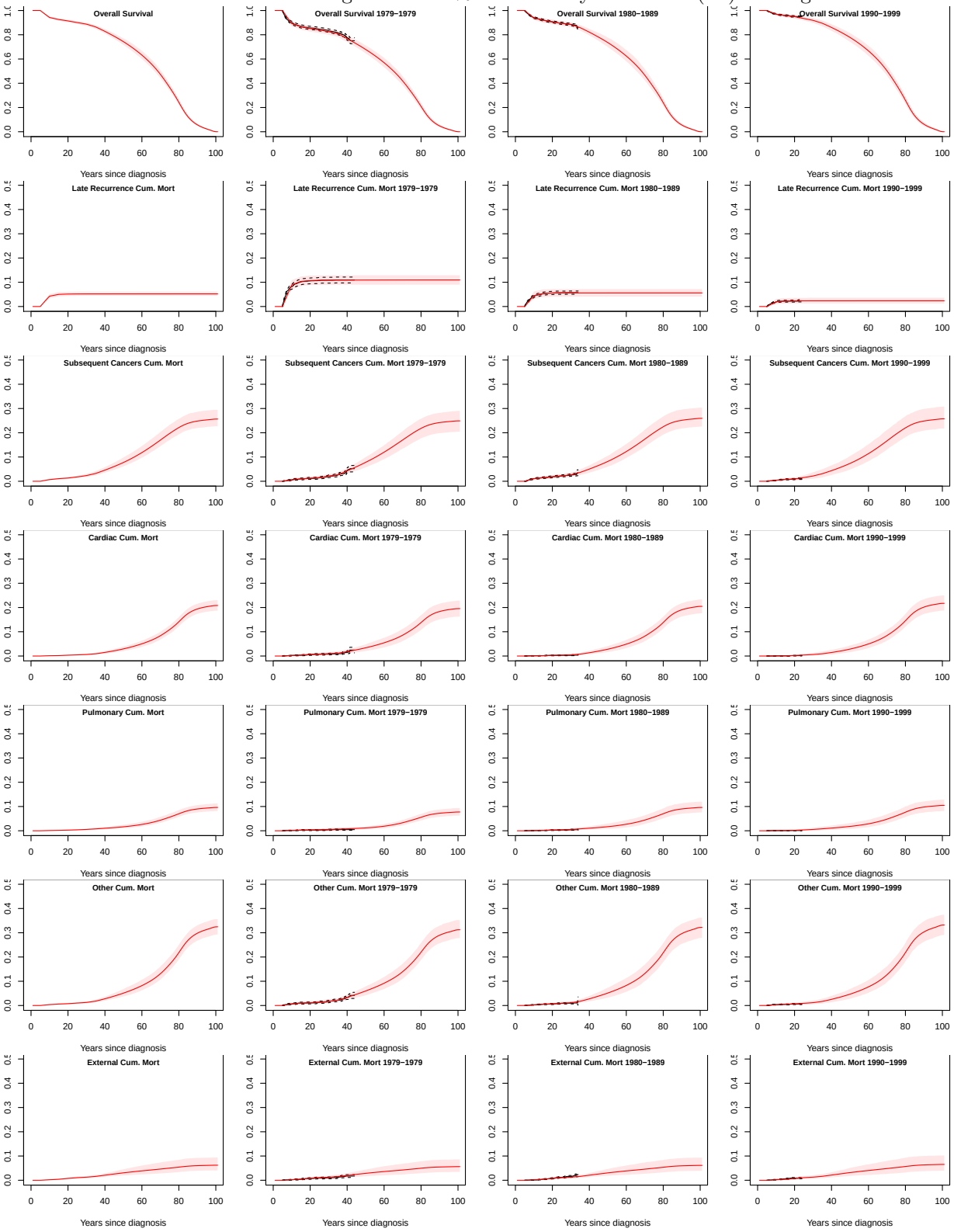
Absolute excess risk (AER) for late effects (annual rate)





Calibration Targets

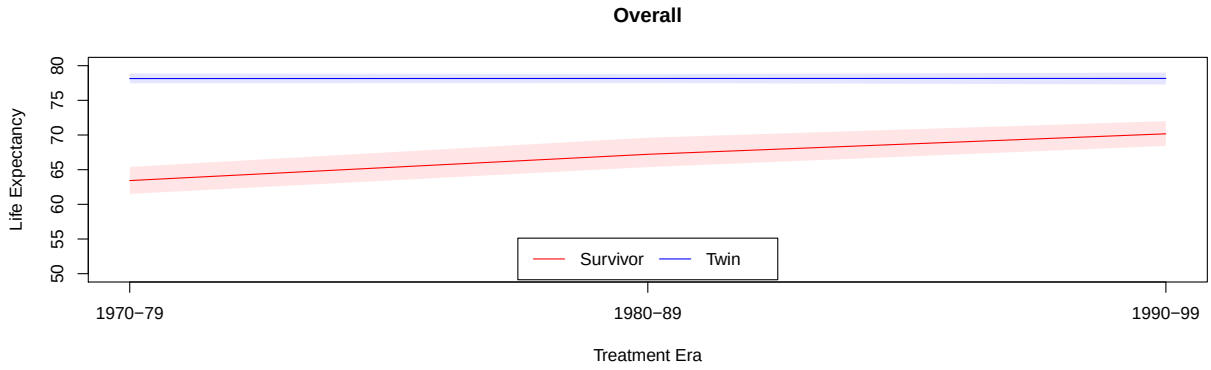
Here we plot our calibrated model estimates of survival (overall) and cumulative mortality (cause-specific) by years since diagnosis compared to the observed CCSS estimates (shown in black). Red = modeled survivors. Shaded regions = 95% uncertainty intervals (UI) among 1000 iterations.



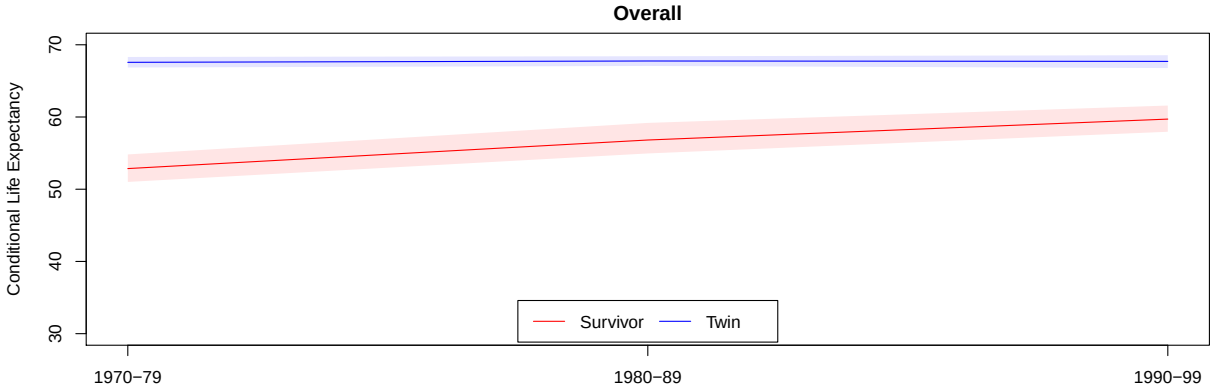
Model Outcomes

Life Expectancy

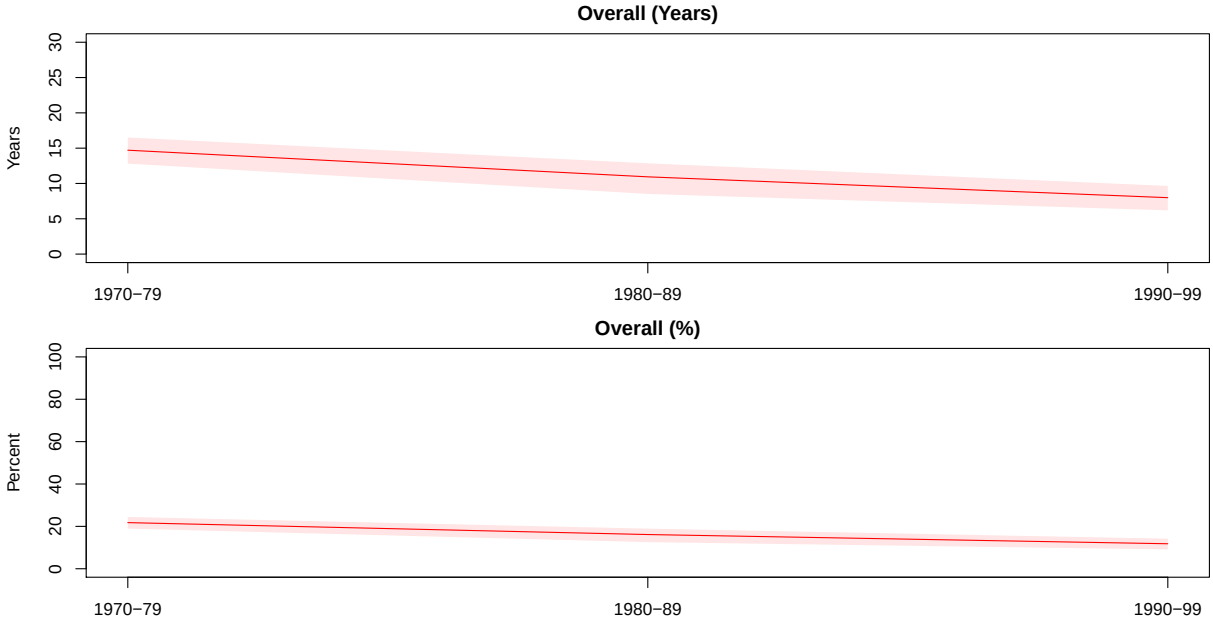
Total



Conditional

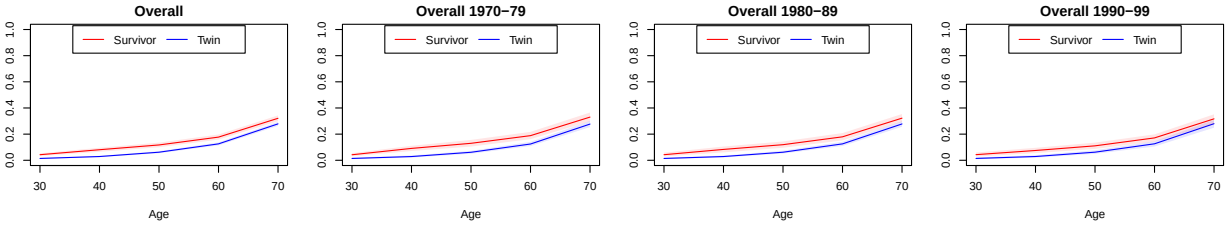


Loss of Conditional LE

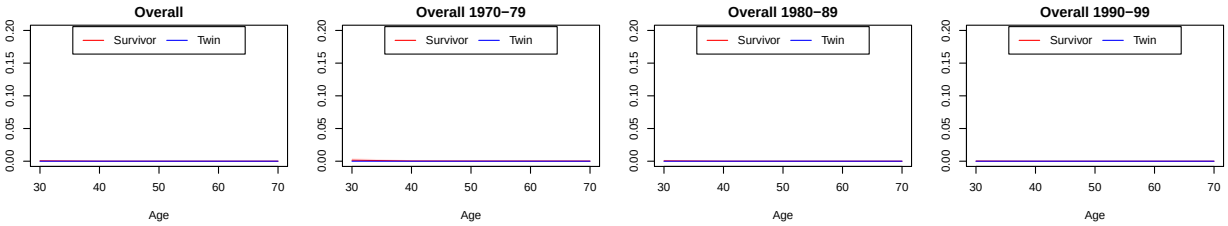


Ten-Year Mortality Risk

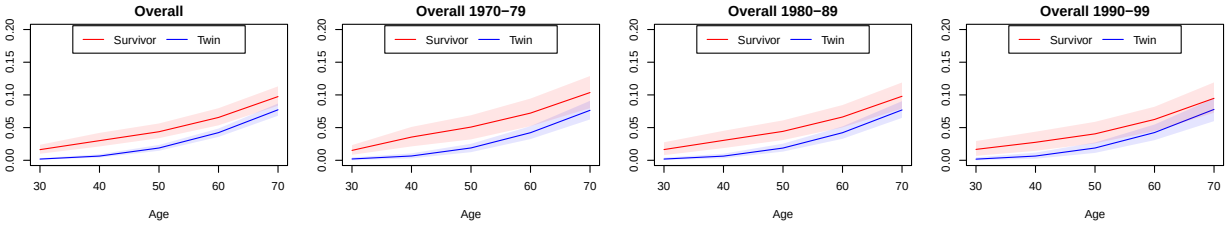
Overall



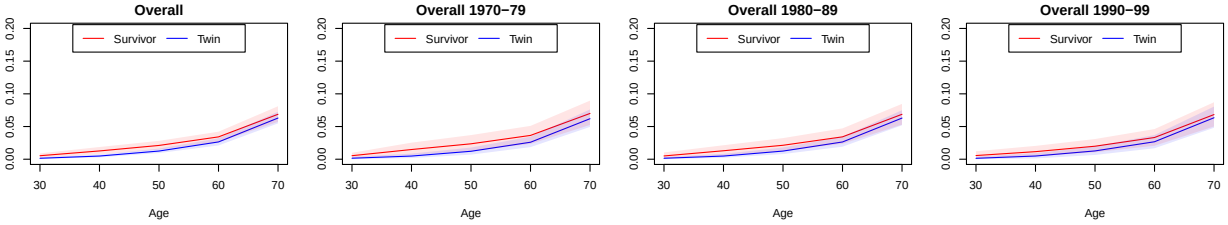
Late Recurrence



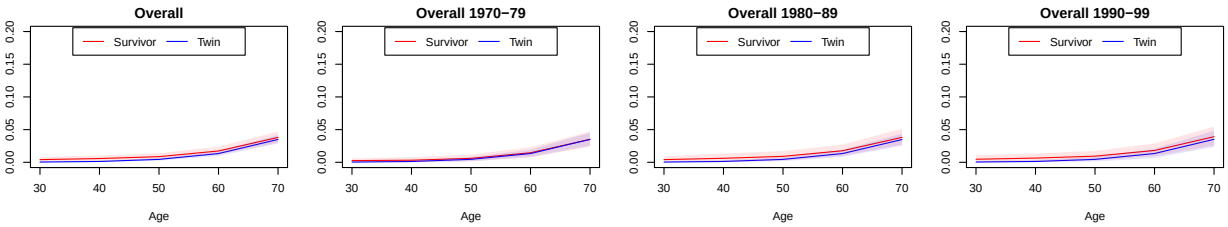
Subsequent Cancers



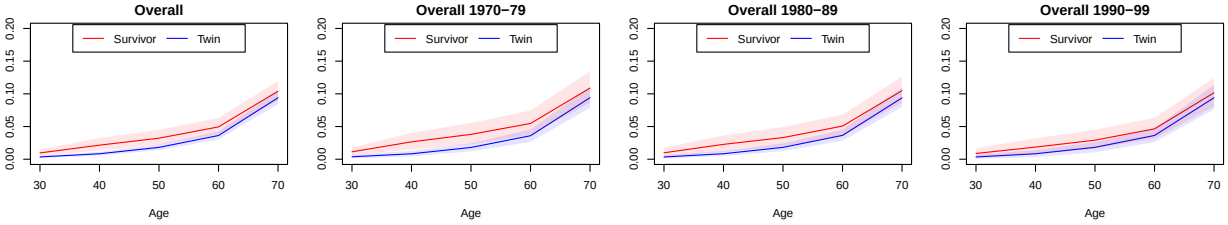
Cardiac



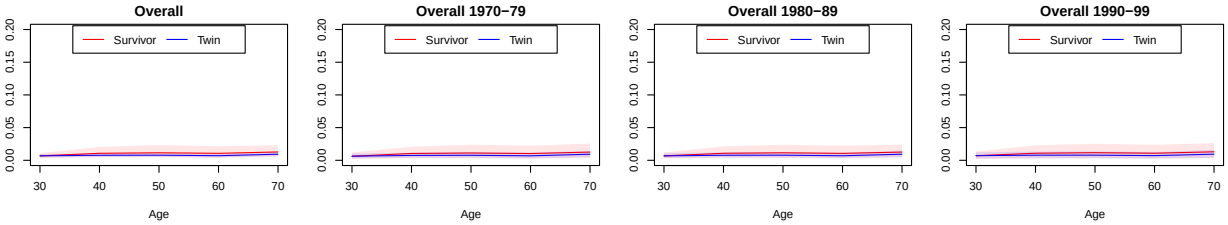
Pulmonary



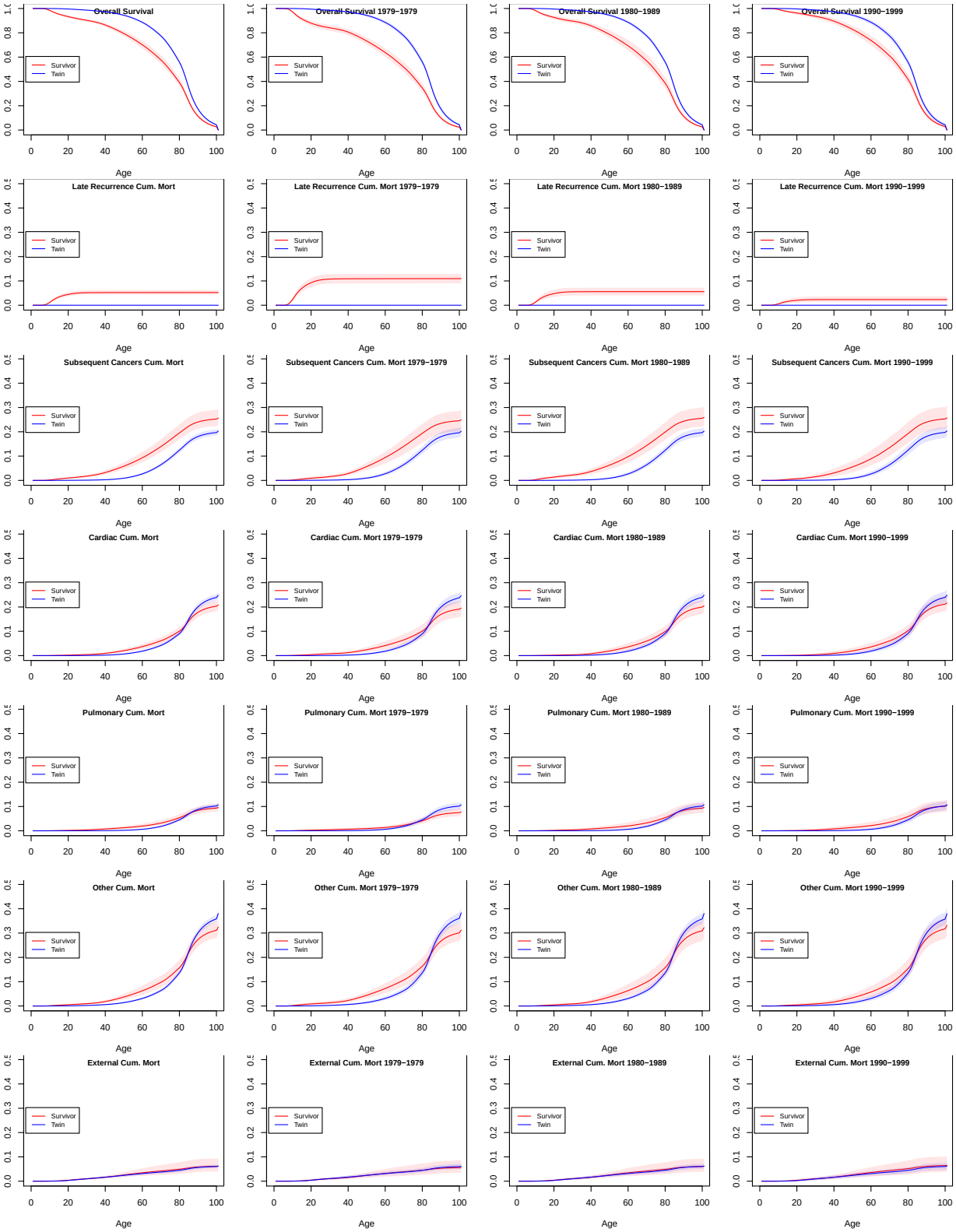
Other



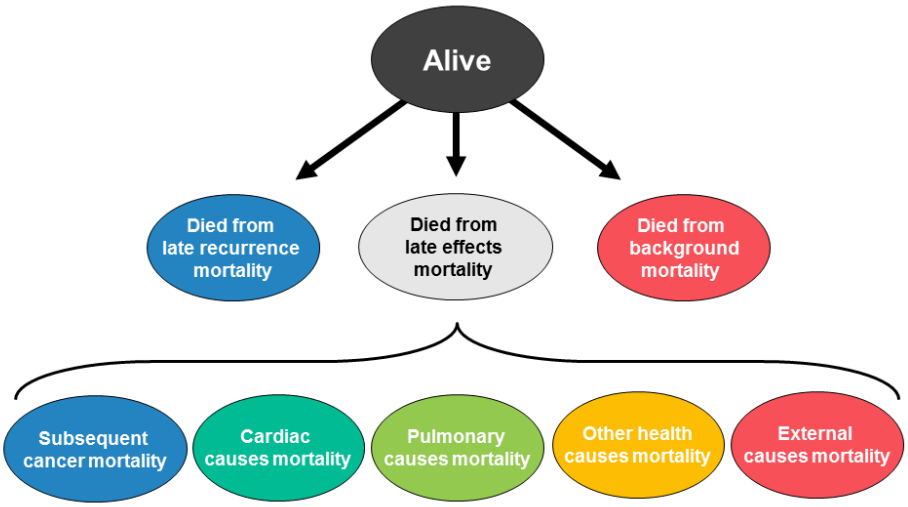
External



Survival Curves/Cumulative Mortality by Age

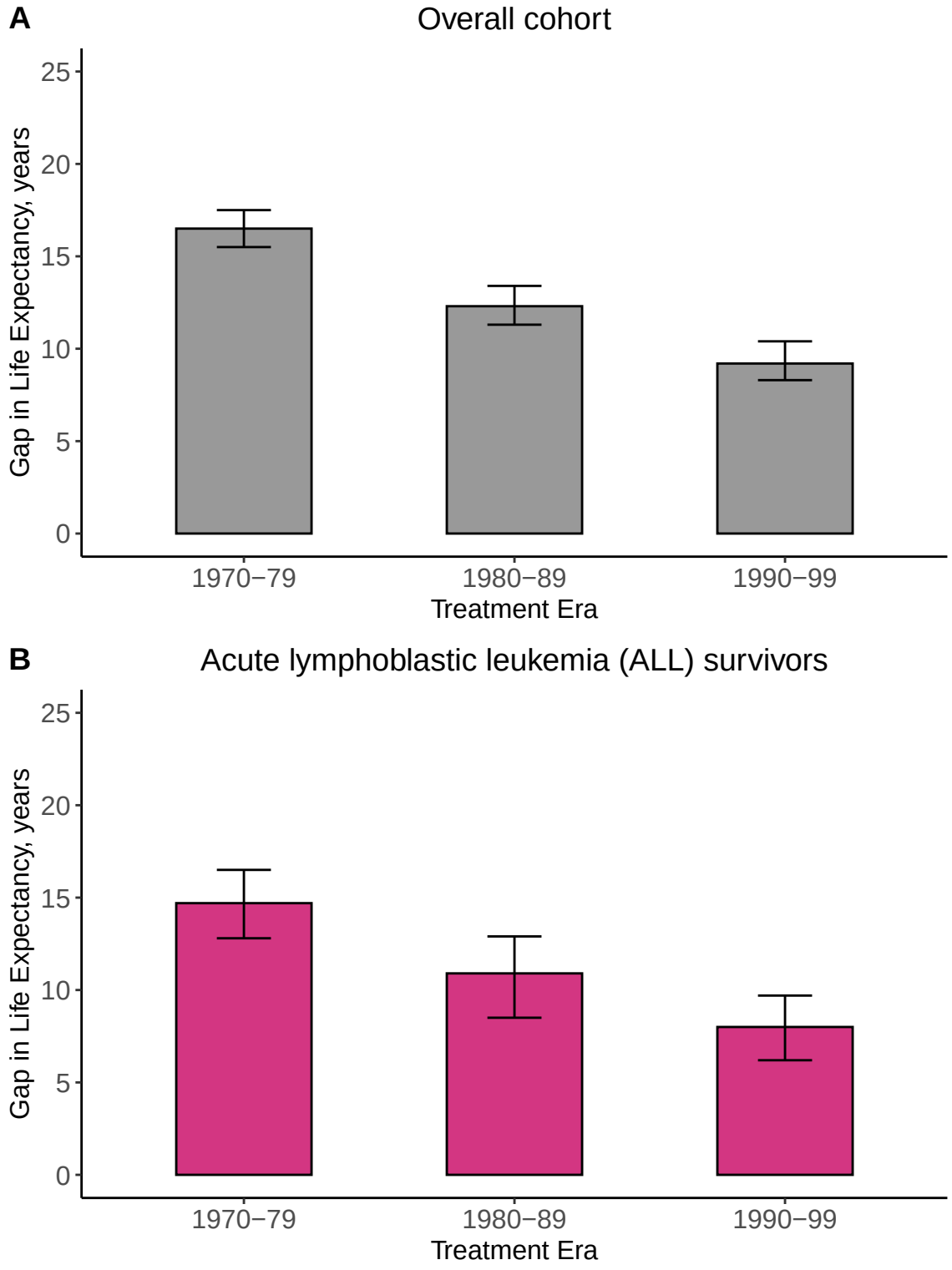


eFigure 1. Model diagram



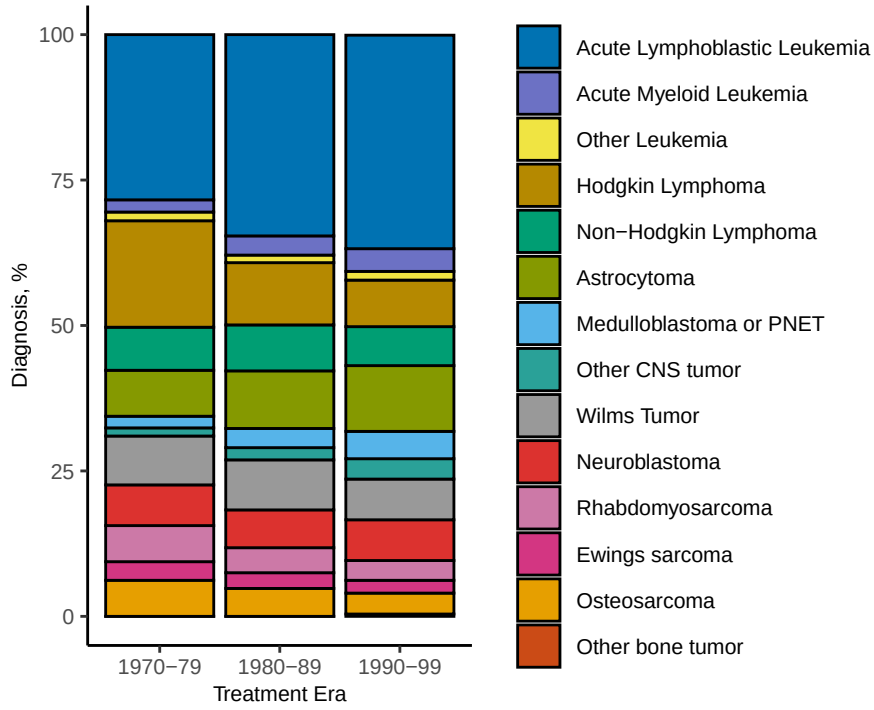
At the start of the simulation, a cohort of five-year cancer survivors enters the model. Each year, individuals face competing risks of dying from background mortality, late recurrence of their original cancer and late effects. Late effects include including health-related (subsequent (primary) cancers, cardiac events, pulmonary conditions, other health causes) and external causes (accidents, suicides, and poisonings). Individuals are followed throughout their lifetime (or until age 100).

eFigure 2. Projected gap in life expectancy among survivors diagnosed in 1970s, 1980s and 1990s: Overall cohort and acute lymphoblastic leukemia (ALL) subgroup

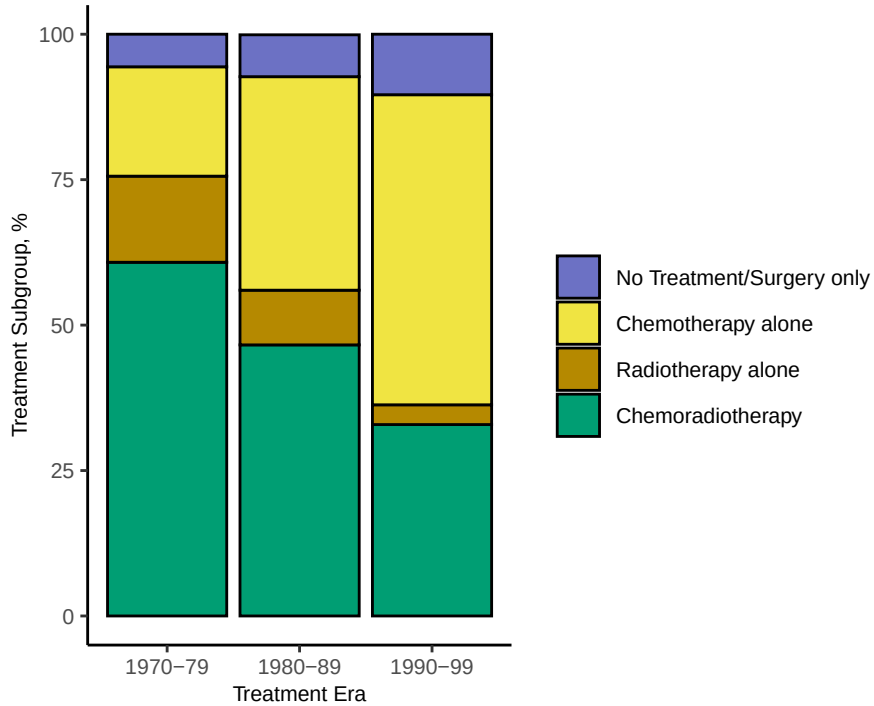


eFigure 3. Cohort composition by treatment era

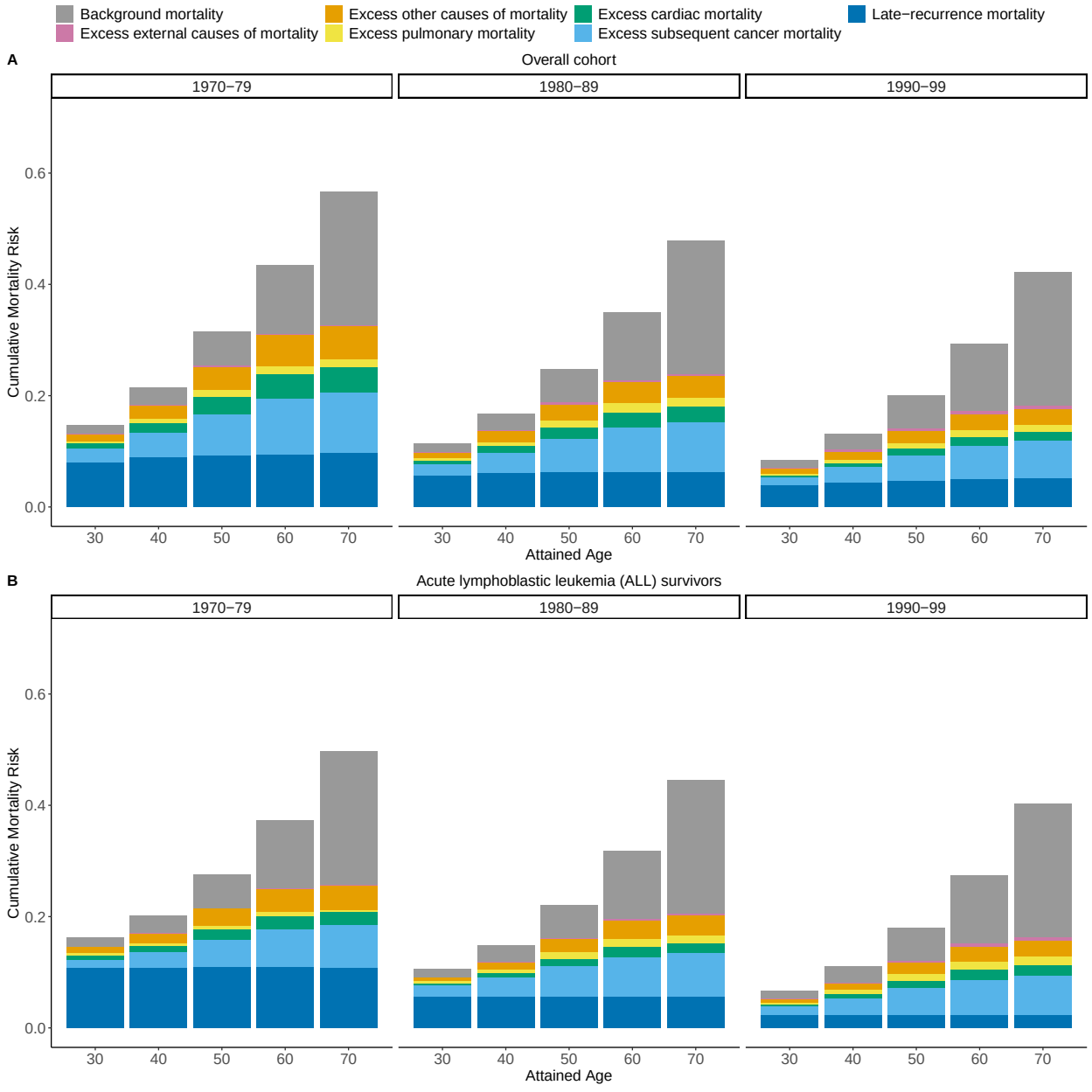
Panel A: Distribution by cancer diagnoses



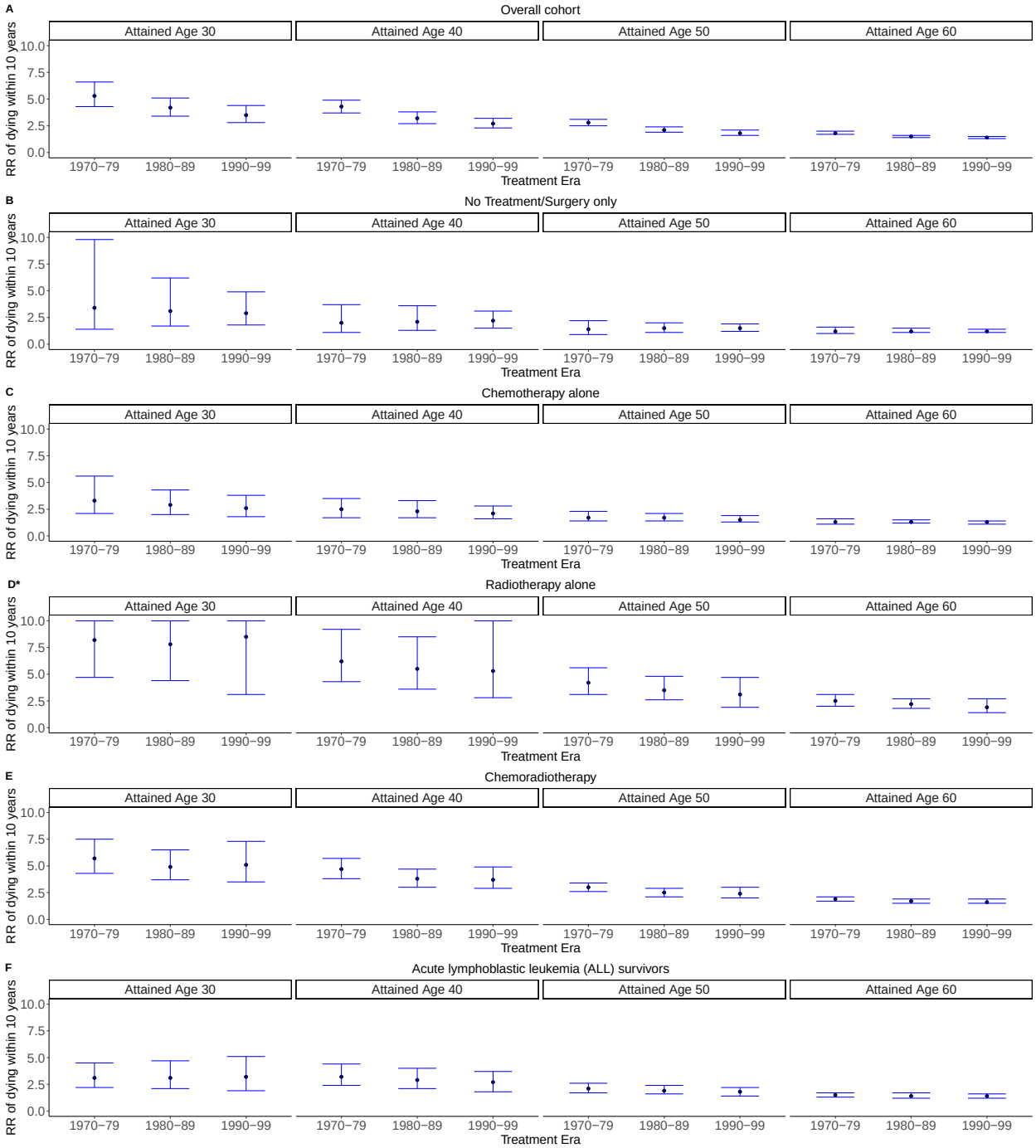
Panel B: Distribution by broad treatment subgroups



eFigure 4. Projected cumulative mortality risks among survivors diagnosed in the 1970s, 1980s and 1990s: Overall cohort and acute lymphoblastic leukemia (ALL) subgroup



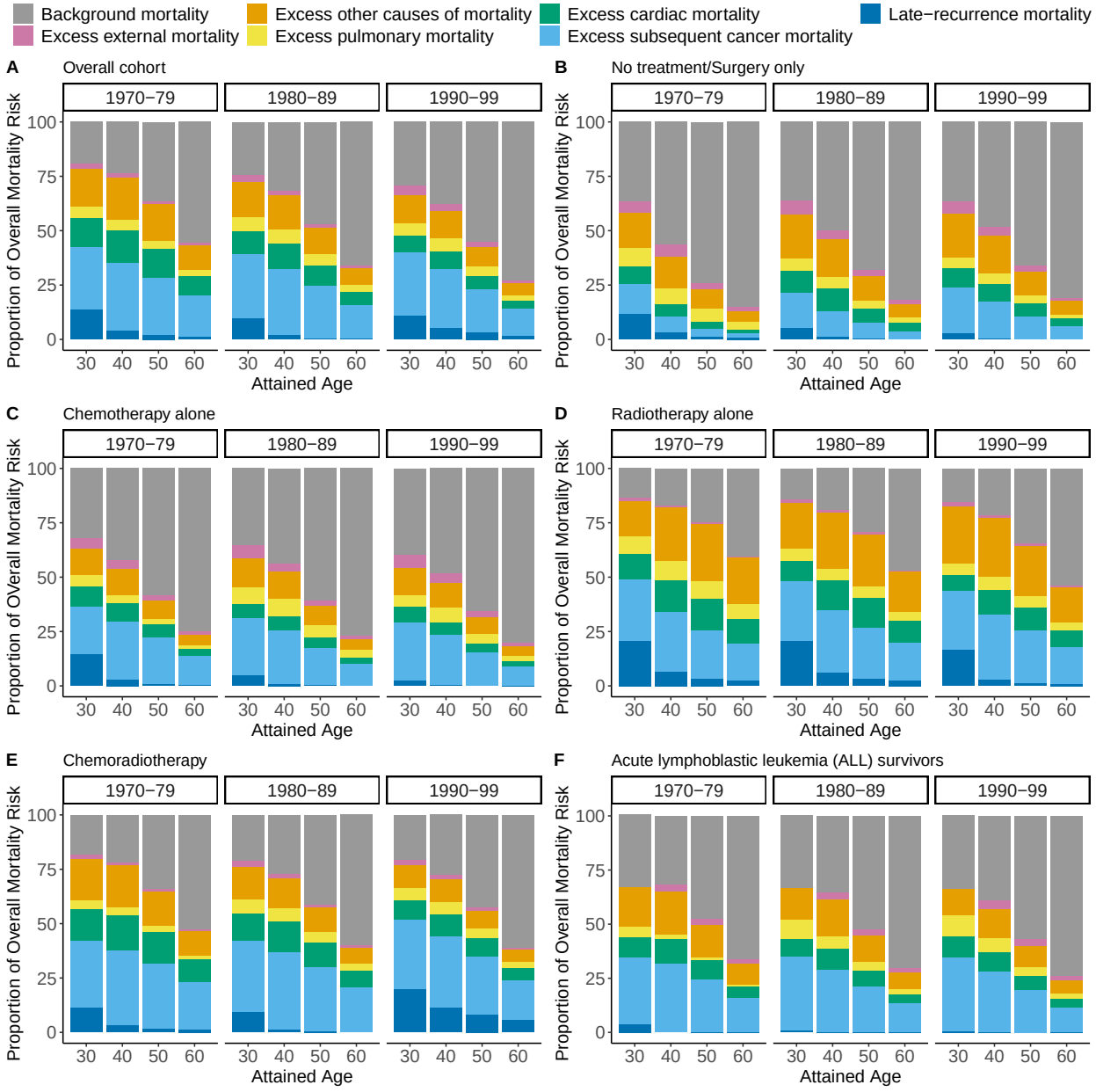
eFigure 5. Projected relative 10-year mortality risk among survivors diagnosed in 1970-79, 1980-89 and 1990-99 by attained age (compared to general population)



Overall cohort (Panel A), no treatment/surgery only (Panel B), chemotherapy alone (Panel C), radiotherapy only (Panel D), chemoradiotherapy (Panel E), and ALL survivors (Panel F). Note: same relative risk (RR) scale for all subgroups, except radiotherapy alone (Panel D) as denoted by the asterisk, for which the upper bound of the 95% uncertainty interval exceeded RR = 10 at age 30 for all treatment eras.

eFigure 6. Cause-specific attributable proportion of projected 10-year mortality risk conditional upon surviving to age 30, 40, 50 and 60 among survivors diagnosed in 1970-79, 1980-89, 1990-99

Panels: A = Overall Cohort, B = No treatment/Surgery only, C= Chemotherapy alone, D = Radiotherapy alone, E = Chemoradiotherapy, and F = Acute lymphoblastic lymphoma survivors



eTable 1. Patient Characteristics and Treatment Subgroup: Overall cohort of survivors of childhood and adolescent cancer

Characteristic[a]	Overall 1970-1999		Treatment Era 1970-1979		1980-1989		1990-1999	
	N	%	N	%	N	%	N	%
Participants	22150	100	5806	23.6	8760	36	7584	40.4
Sex								
Male	11866	55.9	3089	55.6	4746	56.1	4031	55.8
Female	10284	44.1	2717	44.4	4014	43.9	3553	44.2
Age at diagnosis, years								
0 to 4	8841	42.5	2201	37.7	3722	43.9	2918	43.9
5 to 9	4991	23.7	1331	23	1930	22.8	1730	25.1
10 to 14	4660	19.1	1204	20.7	1747	18.8	1709	18.4
15 to 19	3658	14.7	1070	18.6	1361	14.5	1227	12.5
Mean (Range)	7.3 (0-20)		8.1 (0-20)		7.2 (0-20)		6.9 (0-20)	
Follow-up (years since diagnosis)[b]								
Mean (Range)	20.5 (5-39)		27.6 (5-39)		21.2 (5-30)		15.7 (5-24)	
Attained age[b]								
Mean (Range)	27.8 (5-58)		35.7 (5-58)		28.4 (5-49)		22.6 (6-42)	
Diagnosis								
Leukemia	6916	38.7	1922	32.1	3091	39.1	1903	42.1
Acute Lymphoblastic Leukemia	5794	34	1726	28.4	2674	34.6	1394	36.7
Acute Myeloid Leukemia	833	3.3	128	2.1	318	3.3	387	3.9
Other Leukemia	289	1.4	68	1.5	99	1.3	122	1.5
Hodgkin Lymphoma	2872	11.4	1054	18.3	1009	10.7	809	8
Non-Hodgkin Lymphoma	1835	7.3	428	7.4	740	7.9	667	6.7
Central nervous system tumor	3848	16.1	618	11.3	1368	15.3	1862	19.5
Astrocytoma	2349	10	429	7.9	863	9.9	1057	11.3
Medulloblastoma or PNET	904	3.5	115	2	316	3.3	473	4.7
Other	595	2.5	74	1.4	189	2.1	332	3.5
Wilms Tumor	2031	7.9	492	8.4	823	8.6	716	7
Neuroblastoma	1706	6.8	408	7	615	6.5	683	7
Rhabdomyosarcoma	1087	4.4	349	6.2	405	4.3	333	3.4
Bone Tumor	1855	7.5	535	9.4	709	7.6	611	6.3
Ewing sarcoma	673	2.6	189	3.2	262	2.7	222	2.2
Osteosarcoma	1135	4.7	343	6.2	443	4.8	349	3.6
Other	47	0.2	3	0	4	0	40	0.4
Treatment Subgroup (Range)[c]								
None	78.4 (76-81)	0.3 (0.3-0.3)	13.4 (12-15)	0.2 (0.2-0.3)	20.5 (19-22)	0.2 (0.2-0.3)	44.5 (43-46)	0.5 (0.5-0.5)
Surgery only	1831.4 (1821-1840)	7.6 (7.6-7.7)	275.8 (267-283)	4.9 (4.8-5.1)	617.9 (610-625)	6.8 (6.7-6.9)	937.7 (927-944)	10 (9.8-10.0)
Chemotherapy alone	7607.4 (7584-7627)	39.3 (39.2-39.3)	1048.2 (1036-1066)	18.4 (18.1-18.6)	3095.3 (3064-3108)	36.8 (36.5-37.0)	3463.9 (3452-3470)	53.6 (53.5-53.7)
Radiotherapy alone	2009.8 (1994-2027)	8.2 (8.1-8.3)	839.5 (829-856)	14.9 (14.7-15.2)	840.9 (831-855)	9.2 (9.1-9.4)	329.4 (323-332)	3.3 (3.3-3.4)
Chemoradiotherapy	10623 (10594-10648)	44.6 (44.4-44.7)	3629.1 (3610-3650)	61.6 (61.3-61.9)	4185.4 (4167-4216)	46.9 (46.7-47.2)	2808.5 (2798-2817)	32.6 (32.5-32.7)

[a] Unweighted counts (N). Weighted percentages (%) using inverse probability weighting. Numbers may not add up to 100% due to rounding.

[b] Weighted.

[c] Numbers represent an average among 10 imputed treatment datasets and therefore may not add up to 100%. Weighted using inverse probability weighting.

eTable 2. Model results: Cause-specific cumulative risks by age 30, 40, 50, 60 and 70

Era	Attained Age	Cause-specific risk, %													
		Late Recurrence	95% UI	Excess Subsequent Cancers	95% UI	Excess Cardiac	95% UI	Excess Pulmonary	95% UI	Excess Other	95% UI	Excess External	95% UI	Background Mortality	95% UI
By treatment era															
	30	8.1	7.2-9.0	2.4	1.9-2.9	0.9	0.6-1.2	0.5	0.2-0.7	1.2	0.8-1.6	0.1	-0.2-0.5**	1.5	1.2-1.9
	40	8.9	8.0-9.9	4.4	3.8-5.1	1.8	1.4-2.3	0.8	0.5-1.1	2.3	1.7-3.0	0.2	-0.2-0.7**	3	2.6-3.5
1970-79	50	9.3	8.3-10.3	7.3	6.4-8.4	3.2	2.5-3.8	1.2	0.8-1.7	4.1	3.2-4.9	0.2	-0.4-0.9**	6.1	5.4-6.7
	60	9.5	8.5-10.5	9.9	8.4-11.4	4.4	3.4-5.4	1.6	1.0-2.2	5.6	4.3-6.8	0.2	-0.6-1.0**	12.3	11.4-13.2
	70	9.7	8.6-10.7	10.9	8.9-12.8	4.7	3.4-6.0	1.4	0.6-2.3	5.8	4.1-7.5	0.1	-0.9-1.1**	24	22.8-25.1
	30	5.7	5.0-6.3	2.1	1.7-2.5	0.6	0.4-0.8	0.4	0.2-0.6	1	0.7-1.4	0.2	-0.1-0.4**	1.4	1.2-1.7
	40	6.1	5.5-6.8	3.7	3.1-4.3	1.2	0.8-1.6	0.7	0.4-1.1	1.9	1.2-2.5	0.3	-0.1-0.7*	2.9	2.5-3.3
1980-89	50	6.2	5.6-7.0	6	5.0-7.1	2	1.3-2.8	1.2	0.6-2.0	3	1.8-4.0	0.4	-0.2-0.9*	5.9	5.4-6.4
	60	6.3	5.6-7.0	8	6.6-9.4	2.7	1.5-4.2	1.6	0.6-2.8	3.8	2.2-5.5	0.4	-0.4-1.2**	12.2	11.4-12.9
	70	6.4	5.7-7.1	8.8	7.0-10.7	2.8	1.2-4.7	1.7	0.3-3.2	3.9	1.8-5.9	0.4	-0.6-1.4**	24	22.9-24.9
	30	3.9	3.4-4.4	1.4	1.0-1.9	0.4	0.2-0.6	0.3	0.1-0.5	1	0.6-1.4	0.2	-0.1-0.5*	1.3	1.0-1.7
	40	4.4	3.8-5.0	2.8	2.2-3.6	0.7	0.4-1.1	0.5	0.2-0.9	1.6	1.0-2.2	0.3	0.0-0.7*	2.8	2.4-3.3
1990-99	50	4.7	4.0-5.4	4.5	3.6-5.7	1.2	0.7-1.9	0.9	0.3-1.6	2.3	1.4-3.3	0.5	-0.1-1.0*	5.8	5.2-6.5
	60	5	4.2-5.9	6	4.6-7.5	1.6	0.9-2.6	1.2	0.3-2.3	2.9	1.6-4.2	0.6	-0.2-1.4*	12.1	11.2-13.0
	70	5.2	4.4-6.2	6.7	5.0-8.6	1.6	0.7-3.0	1.3	0.1-2.7	2.8	1.2-4.5	0.6	-0.4-1.6**	23.9	22.8-25.1
No Treatment/Surgery only															
	30	4.1	1.3-8.0	1.1	-0.1-2.8**	0.4	0.0-1.5	0.6	0.0-1.9	0.6	-0.4-2.1**	0.2	-1.0-1.3**	1.5	0.3-3.1
	40	4.5	1.4-8.3	1.6	-0.1-3.9**	0.7	0.0-2.1	0.9	-0.3-2.4*	1.3	-0.5-3.6*	0.3	-1.1-1.8**	3	1.1-5.0
1970-79	50	4.7	1.5-8.7	1.9	-0.6-4.7**	0.9	-0.1-2.6*	1.2	-0.3-3.1*	1.9	-0.7-5.3*	0.5	-1.2-2.4**	6	3.3-8.8
	60	4.8	1.5-8.8	1.9	-1.6-5.7**	1	-0.4-3.4*	1.6	-0.6-4.2*	2.4	-1.1-7.3*	0.6	-1.5-3.0**	12.2	8.5-16.0
	70	4.9	1.5-8.9	1.6	-2.5-6.1**	0.9	-1.1-3.6**	1.8	-1.1-5.6**	2.5	-1.8-8.7**	0.7	-1.7-3.4**	23.7	18.9-28.5
	30	2	0.6-3.8	1.1	0.1-2.3*	0.3	0.0-1.0	0.4	-0.1-1.0*	0.9	0.0-2.2*	0.2	-0.5-1.0**	1.4	0.6-2.6
	40	2.2	0.7-4.1	1.7	0.3-3.4**	0.7	0.0-1.9	0.6	-0.1-1.5*	1.7	0.2-3.6	0.4	-0.6-1.6**	2.9	1.6-4.3
1980-89	50	2.2	0.7-4.2	2.3	0.1-5.0**	1.2	0.0-3.0	0.8	-0.2-2.1*	2.6	0.1-5.2	0.6	-0.8-2.0**	5.9	4.1-7.8
	60	2.3	0.7-4.2	2.6	-0.4-6.3**	1.6	-0.2-3.9*	1.1	-0.4-2.9*	3.3	-0.1-6.7*	0.7	-1.1-2.5**	12.1	9.5-14.5
	70	2.3	0.8-4.3	2.6	-1.5-6.7**	1.8	-0.6-4.7**	1.2	-1.0-3.6**	3.6	-0.8-8.0*	0.8	-1.2-2.9**	23.9	20.7-27.3
	30	1.2	0.4-2.3	0.8	0.1-1.7	0.3	0.0-0.9	0.4	0.0-1.1*	1.1	0.2-2.3	0.2	-0.3-0.8**	1.3	0.6-2.1
	40	1.3	0.4-2.4	1.6	0.4-3.0	0.6	0.0-1.6	0.6	-0.1-1.5*	1.9	0.4-3.5	0.4	-0.4-1.3**	2.7	1.8-3.8
1990-99	50	1.3	0.5-2.4	2.4	0.6-4.5	1.1	0.0-2.5	0.8	-0.1-2.1*	2.8	0.6-4.9	0.6	-0.6-1.7**	5.7	4.4-7.3
	60	1.3	0.5-2.4	3.1	0.5-5.8	1.4	-0.1-3.5*	1.1	-0.3-2.7*	3.5	0.7-6.1	0.7	-0.7-2.2**	11.8	9.9-13.9
	70	1.3	0.5-2.4	3.4	0.0-6.7	1.5	-0.4-3.9*	1.1	-0.8-3.1*	3.8	0.5-7.1	0.8	-0.8-2.6**	23.4	20.8-26.2
Chemotherapy only															
	30	8.2	6.1-10.5	1.1	0.3-2.0	0.5	0.1-1.2	0.3	0.0-0.8	0.8	0.0-1.6	0.1	-0.5-0.8**	1.5	0.8-2.3
	40	8.7	6.5-11.0	2	1.0-3.2	0.9	0.2-1.8	0.5	0.0-1.2	1.3	0.2-2.4	0.3	-0.6-1.1**	3	2.1-4.1
1970-79	50	8.9	6.7-11.0	3.5	1.8-5.5	1.3	0.3-2.6	0.7	0.0-1.6	1.9	0.3-3.5	0.4	-0.7-1.5**	6	4.7-7.5
	60	9	6.8-11.2	5	2.0-8.4	1.6	0.2-3.5	0.8	-0.2-2.1*	2.3	-0.1-5.0*	0.4	-0.9-1.9**	12.3	10.4-14.3
	70	9	6.8-11.2	5.7	1.5-10.0	1.5	-0.4-4.2*	0.7	-0.8-2.4*	2.1	-1.0-5.5**	0.5	-1.2-2.3**	24.1	21.5-26.6
	30	3.6	2.7-4.6	1.2	0.7-1.8	0.4	0.2-0.8	0.2	0.0-0.6	0.6	0.2-1.1	0.2	-0.2-0.6**	1.4	1.0-1.9
	40	3.7	2.8-4.8	2.2	1.4-3.3	0.7	0.3-1.2	0.6	0.1-1.3	1.1	0.3-2.0	0.4	-0.2-0.9*	2.9	2.1-3.6
1980-89	50	3.8	2.8-4.8	3.7	1.9-5.5	1	0.3-2.1	1	0.1-2.5	1.8	0.3-3.4	0.5	-0.3-1.3*	5.8	4.8-6.8
	60	3.8	2.9-4.9	4.9	2.1-7.7	1.3	0.2-2.9	1.5	-0.1-3.5*	2.3	0.1-4.7	0.6	-0.4-1.7**	12	10.7-13.3
	70	3.8	2.9-4.9	5.4	1.6-9.2	1.2	-0.3-3.3*	1.7	-0.3-4.2*	2.3	-0.5-5.4*	0.7	-0.5-2.1**	23.7	22.0-25.4
	30	1.9	1.3-2.5	1	0.5-1.5	0.3	0.1-0.7	0.2	0.0-0.4*	0.6	0.1-1.2	0.2	-0.2-0.6**	1.4	0.9-1.9
	40	1.9	1.3-2.6	1.9	1.2-2.9	0.6	0.2-1.1	0.4	0.0-0.9	1.1	0.2-2.1	0.4	-0.1-1.0*	2.8	2.2-3.6
1990-99	50	1.9	1.3-2.6	3.2	1.8-4.9	0.9	0.2-1.8	0.8	0.0-1.9	1.7	0.3-3.2	0.6	-0.1-1.4*	5.9	4.9-6.8
	60	2	1.3-2.6	4.3	2.2-6.8	1.1	0.1-2.5	1.1	-0.1-2.8*	2.2	0.2-4.3	0.7	-0.3-1.8*	12.1	10.8-13.5
	70	2	1.4-2.6	4.8	2.2-8.1	1.1	-0.2-2.9*	1.2	-0.4-3.6*	2.2	-0.2-4.8*	0.8	-0.4-2.2*	24	22.3-25.8
Radiotherapy only															
	30	7.7	5.4-10.1	3.1	1.7-4.5	1	0.3-1.8	0.6	0.1-1.4	1	0.1-2.2	0.1	-0.7-0.9**	1.4	0.7-2.3
	40	9.5	7.2-12.3	5.9	3.8-7.9	2.2	1.0-3.5	1.4	0.6-2.4	2.7	1.1-4.3	0.2	-0.9-1.3**	2.9	1.8-4.2
1970-79	50	10.3	7.9-13.2	9.4	6.4-12.3	4	2.2-5.9	2.6	1.4-4.2	5.9	3.5-8.4	0.2	-1.2-1.4**	6	4.5-7.6
	60	10.8	8.4-13.7	12.2	8.3-16.0	5.9	2.9-8.6	3.7	1.8-6.0	9.5	5.8-13.3	0	-1.6-1.6**	12.2	10.0-14.2
	70	11.2	8.7-14.1	12.7	7.8-17.6	6.3	2.5-9.9	4.1	1.4-7.0	10.9	6.2-15.6	-0.2	-2.0-1.5**	23.8	20.9-26.7
	30	7.5	5.3-9.9	2.4	1.1-3.7	0.8	0.2-1.6	0.6	0.1-1.3	1.4	0.4-2.6	0.1	-0.7-0.9**	1.3	0.6-2.1
	40	9.2	6.6-12.0	4.9	2.9-6.9	1.7	0.7-3.0	1.1	0.3-2.0	3.3	1.7-5.3	0.2	-0.9-1.2**	2.7	1.7-3.9

1980-89	50	9.9	7.1-13.0	8.2	4.6-11.8	3.3	1.2-5.5	1.7	0.5-3.1	6.3	3.4-9.6	0.2	-1.2-1.5**	5.8	4.3-7.4
	60	10.3	7.4-13.7	10.9	5.7-16.0	4.8	1.3-8.0	2.3	0.5-4.5	9.1	4.6-13.6	0.1	-1.5-1.7**	12	9.9-14.2
	70	10.7	7.8-14.2	11.5	4.7-17.7	5.1	0.5-9.2	2.2	-0.1-5.1*	10.1	4.9-15.5	-0.1	-2.0-1.8**	23.8	20.7-26.7
	30	7.3	3.9-11.1	1.7	0.2-3.6	0.8	0.0-2.1	0.5	0.0-1.7	3.2	1.0-5.6	0.1	-1.1-1.4**	1.2	0.3-2.6
	40	8.4	4.8-12.5	3.9	1.4-6.9	1.4	0.0-3.2	1	0.0-2.7	5.3	2.2-8.4	0.2	-1.5-2.0**	2.7	1.1-4.6
1990-99	50	8.6	4.9-12.9	6.9	2.9-11.4	2.5	0.3-5.0	1.6	0.0-3.9	7.9	4.1-12.0	0.2	-2.0-2.4**	5.6	3.1-8.2
	60	8.8	5.0-13.1	9.3	3.3-15.3	3.5	0.2-6.9	2	-0.2-5.0*	10.1	5.7-1.4	0.2	-2.4-2.8**	11.8	8.3-15.5
	70	8.9	5.1-13.3	10	2.7-17.7	3.5	-0.6-7.9*	2	-0.9-5.6*	10.9	5.0-17.2	0.1	-2.7-3.1**	23.6	18.9-28.0
Chemoradiotherapy															
	30	8.5	7.4-9.7	2.7	2.1-3.4	1	0.7-1.5	0.4	0.1-0.8	1.4	0.8-1.9	0.1	-0.3-0.5**	1.6	1.1-2.0
	40	9.2	8.0-10.4	5	4.1-5.8	2.1	1.5-2.7	0.7	0.3-1.1	2.7	1.8-3.5	0.2	-0.4-0.8**	3.1	2.6-3.6
1970-79	50	9.6	8.2-10.8	8.4	7.2-9.8	3.8	2.8-4.7	1.1	0.5-1.6	4.5	3.1-5.6	0.2	-0.6-1.0**	6.1	5.3-6.8
	60	9.8	8.4-11.0	11.5	9.7-13.5	5.2	3.7-6.6	1.2	0.5-2.0	5.9	4.0-7.6	0.1	-0.8-1.1**	12.3	11.2-13.4
	70	10	8.6-11.2	12.8	10.2-15.5	5.6	3.7-7.3	1	0.0-2.0*	6	3.8-8.1	0	-1.1-1.2**	24.1	22.6-25.5
	30	7.5	6.4-8.6	2.9	2.2-3.7	0.7	0.4-1.1	0.4	0.2-0.8	1.3	0.8-1.9	0.1	-0.3-0.5**	1.5	1.1-1.9
	40	8	6.9-9.1	5	4.0-6.0	1.5	0.9-2.2	0.8	0.4-1.4	2.2	1.3-3.1	0.2	-0.4-0.7**	2.9	2.4-3.5
1980-89	50	8.1	7.0-9.2	8	6.6-9.7	2.7	1.6-4.0	1.3	0.4-2.4	3.3	1.6-4.7	0.2	-0.5-1.0**	6	5.3-6.8
	60	8.1	7.0-9.3	10.7	8.7-13.1	3.6	1.9-5.9	1.7	0.2-3.2	4.1	1.5-6.4	0.2	-0.7-1.1**	12.3	11.3-13.4
	70	8.2	7.0-9.4	11.9	9.3-14.9	3.8	1.5-6.8	1.7	-3.9	3.9	0.6-6.8	0.1	-1.0-1.2**	24.2	22.9-25.6
	30	7.8	6.5-9.3	2.4	1.4-3.5	0.4	0.0-0.9	0.3	0.0-0.7	1.2	0.6-1.9	0.1	-0.3-0.6**	1.3	0.8-1.8
	40	9	7.4-10.7	4.4	2.8-6.5	1	0.2-1.8	0.7	0.1-1.3	1.9	1.0-2.8	0.2	-0.4-0.8**	2.8	2.1-3.5
1990-99	50	10	8.1-12.2	7.1	5.0-9.8	1.8	0.6-2.9	1.1	0.2-2.1	2.6	1.2-3.9	0.2	-0.6-1.0**	5.8	4.8-6.9
	60	10.8	8.8-13.4	9.5	6.8-12.7	2.3	0.6-4.0	1.4	0.1-2.8	3.1	1.0-5.0	0.2	-0.8-1.4**	12.1	10.8-13.6
	70	11.5	9.1-14.4	10.6	7.4-14.1	2.3	0.0-4.4	1.4	-0.3-3.1*	2.7	0.0-5.1	0.2	-1.0-1.4**	23.9	22.1-25.7
Acute Lymphoblastic Leukemia															
	30	10.8	8.9-12.8	1.5	0.8-2.3	0.7	0.3-1.3	0.4	0.1-0.9	1.1	0.5-1.9	-0.1	-0.7-0.6**	1.6	1.0-2.2
	40	10.9	9.0-12.8	2.7	1.8-3.7	1.1	0.5-1.8	0.6	0.1-1.2	1.8	1.0-2.8	-0.1	-0.9-0.7**	3.1	2.3-4.0
1970-79	50	10.9	9.0-12.9	5	3.2-6.7	1.8	0.8-3.0	0.7	0.1-1.4	3.1	1.7-4.8	0	-1.1-1.2**	6.1	5.0-7.3
	60	10.9	9.0-12.9	6.8	4.2-9.5	2.3	0.8-4.0	0.7	-0.1-1.6**	4.1	2.0-6.5	0.1	-1.4-2.6**	12.2	10.7-13.8
	70	10.9	9.0-12.9	7.6	4.1-11.0	2.3	0.3-4.6	0.4	-0.7-1.6**	4.3	1.7-7.3	0.1	-1.7-0.6**	23.9	22.0-25.9
	30	5.5	4.0-7.2	2.2	1.4-3.1	0.3	0.1-0.7	0.4	0.1-0.8	0.7	0.2-1.3	0	-0.4-0.7**	1.5	1.0-2.1
	40	5.6	4.1-7.2	3.6	2.4-4.8	0.7	0.2-1.3	0.7	0.3-1.4	1.3	0.5-2.2	0	-0.7-0.7**	3	2.2-3.7
1980-89	50	5.6	4.1-7.2	5.6	3.6-7.6	1.3	0.4-2.3	1.1	0.3-2.2	2.4	0.8-4.3	0.1	-0.9-1.5**	6	5.0-7.0
	60	5.6	4.1-7.2	7.2	4.6-10.3	1.8	0.5-3.3	1.4	0.2-3.0	3.3	0.8-6.1	0.3	-1.2-2.3**	12.2	10.7-13.6
	70	5.6	4.1-7.2	8	4.8-11.7	1.7	0.1-3.6	1.4	-0.3-3.4*	3.5	0.4-7.1	0.4	-1.5-3.1**	24	22.0-25.9
	30	2.3	1.3-3.6	1.5	0.6-2.6	0.4	0.0-0.9	0.4	0.0-0.9	0.7	0.1-1.4	0.1	-0.5-0.6**	1.4	0.7-2.2
	40	2.3	1.3-3.7	3	1.4-4.9	0.8	0.1-1.7	0.8	0.1-1.7	1.2	0.2-2.4	0	-0.8-0.9**	2.9	2.0-3.9
1990-99	50	2.3	1.3-3.7	4.8	2.5-7.4	1.3	0.3-2.5	1.2	0.3-2.5	2.1	0.3-3.9	0.3	-1.1-1.8**	5.9	4.6-7.3
	60	2.3	1.3-3.7	6.3	3.4-10.0	1.8	0.4-3.3	1.6	0.2-3.2	2.7	0.3-5.5	0.5	-1.3-2.8**	12.2	10.4-14.1
	70	2.3	1.3-3.7	7.1	3.2-11.5	1.8	0.2-3.7	1.7	0.0-3.7	2.8	-0.1-6.2*	0.6	-1.5-3.7**	24	21.6-26.5

* Value was negative in <100 of 950 simulations that comprised the 95% UI.

** Value was negative in 100 to 550 of 950 simulations that comprised the 95% UI.

Observed changes in median therapeutic exposures among the treatment and ALL subgroups

Projected changes in life expectancy gap among treatment subgroups were generally consistent with observed changes in therapeutic exposures within subgroups. For the chemotherapy alone subgroup, the median cumulative anthracycline dosage (400 to 173 mg/m2) and cyclophosphamide equivalent dose (CED) (8,422 to 6217 mg/m2) declined by approximately 30-60% between 1970-79 and 1990-99 (eTable 3). In contrast, median doses for chest (40 to 36 Gy), brain (50 to 54 Gy) and abdominal radiation (37 to 36 Gy) remained largely unchanged for the radiation alone subgroup (eTable 4). For the radiation with chemotherapy subgroup, median cumulative anthracycline dose (294 to 193 mg/m2) and chest (30 to 23 Gy) and abdominal radiation doses (30 to 20 Gy) declined, yet brain radiation dose increased (24 to 38 Gy) (eTable 5). For the ALL subgroup, cumulative anthracycline (281 to 108 mg/m2), CED dose (6,653 to 3,860 mg/m2) and radiation dose (22 to 13 Gy chest, 24 to 18 Gy brain, 22 to 13 Gy abdominal) also declined (eTable 6).

eTable 3. Patient Characteristics and Therapeutic Exposures: Chemotherapy Alone Subgroup

Characteristic[a]	Overall 1970-1999		Treatment Era 1970-1979		1980-1989		1990-1999	
	N	%	N	%	N	%	N	%
Participants	7607	100	1048	11	3095	33.8	3464	55.2
Sex								
Male	4028	55.1	555	55.2	1595	53.5	1878	56.1
Female	3580	44.9	493	44.8	1500	46.5	1586	43.9
Age at diagnosis, years								
0 to 4	3499	49.9	437	41.6	1551	51.6	1512	50.6
5 to 9	1566	23.3	197	18.8	635	22	733	24.9
10 to 14	1481	15.8	216	20.5	522	15.2	743	15.3
15 to 19	1061	11	198	19	387	11.3	476	9.2
Mean (Range)	6.3 (0-20)		7.8 (0-20)		6.2 (0-20)		6.1 (0-20)	
Follow-up (years since diagnosis)[b]								
Mean (Range)	19.0 (5-39)		28.1 (5-39)		21.5 (5-29)		15.7 (5-24)	
Attained age[b]								
Mean (Range)	25.4 (5-57)		35.8 (5-57)		27.7 (6-49)		21.8 (6-41)	
Diagnosis								
Leukemia	3143	54.3	379	37.6	1416	51.6	1348	59.7
Acute Lymphoblastic Leukemia	2496	47.5	287	28.4	1198	45.1	1011	53.2
Acute Myeloid Leukemia	533	5.4	67	5.9	184	5.3	282	5.3
Other Leukemia	114	1.4	26	3.3	34	1.1	55	1.3
Hodgkin Lymphoma	343	3.5	54	4.2	110	3.2	179	3.4
Non-Hodgkin Lymphoma	986	10	78	6.7	347	9.9	562	10.5
Central nervous system tumor	325	3.6	5	0.9	63	1.9	257	5.2
Astrocytoma	239	2.7	5	0.6	43	1.3	191	3.9
Medulloblastoma or PNET	48	0.5	0	0.2	12	0.3	36	0.7
Other	38	0.4	0	0.1	8	0.3	30	0.6
Wilms Tumor	856	8.5	114	10.9	394	11.1	348	6.4
Neuroblastoma	555	5.6	84	8	228	6.5	243	4.6
Rhabdomyosarcoma	237	2.5	57	5.4	87	2.6	93	1.8
Bone Tumor	1162	12.1	277	26.2	451	13.2	434	8.4
Ewing sarcoma	203	2.1	23	2.2	79	2.3	101	1.9
Osteosarcoma	943	9.8	253	23.8	371	10.9	319	6.2
Other	16	0.2	1	0.2	1	0	14	0.3
Treatment Exposures[c]								
Anthracycline Dose, mg/m^2								
None	2903	35	538	51	1441	45.5	925	25.3
0 to <150	1544	27.7	42	4.1	424	16.6	1078	39.3
150 to <300	1472	19.3	100	9.6	485	15.1	887	23.8
300 to <450	1218	13	185	17.8	577	17.8	456	9.1
450 to <600	385	4.1	159	15	131	3.9	95	2
600+	72	0.8	25	2.5	34	1.1	12	0.3
Median dose[d]	218		400		277		173	
Cyclophosphamide Equivalent Dose, mg/m^2								
None	2968	40.5	451	42.6	1270	42.9	1247	38.5
0 to <4,000	1519	23.9	120	11.7	664	21.8	735	27.7
4,000 to <8,000	1418	15.8	171	16.2	576	17.4	671	14.8
8,000 to <12,000	850	10.7	98	9.4	316	9.7	436	11.7
12,000 to <16,000	336	3.6	64	6	132	4.1	139	2.7
16,000 to <20,000	200	2.1	49	4.7	84	2.5	68	1.4
20,000+	317	3.4	96	9.5	53	1.6	167	3.2
Median dose[d]	6153		8422		5745		6217	

[a] Unweighted counts (N). Weighted percentages (%) using inverse probability weighting. Numbers may not add up to 100% due to rounding.

[b] Weighted.

[c] Numbers represent an average among 10 imputed treatment datasets and therefore may not add up to 100%.

[d] Median dose is weighted and calculated among those with dose >0.

eTable 4. Patient Characteristics and Therapeutic Exposures: Radiotherapy Alone Subgroup

Characteristic[a]	Overall 1970-1999		Treatment Era 1970-1979		1980-1989		1990-1999	
	N	%	N	%	N	%	N	%
Participants	2010	100	840	42.9	841	40.7	329	16.5
Sex								
Male	1059	54.8	441	54.8	448	55.3	170	53.4
Female	951	45.2	399	45.2	393	44.7	160	46.6
Age at diagnosis, years								
0 to 4	457	23	173	20.5	217	26.6	67	20.5
5 to 9	431	21.6	154	18.6	177	21.2	100	30.3
10 to 14	505	25	209	24.9	204	23.8	92	28.3
15 to 19	617	30.4	303	35.9	244	28.4	70	20.9
Mean (Range)	10.3 (0-20)		10.9 (0-20)		9.9 (0-20)		9.6 (0-20)	
Follow-up (years since diagnosis)[b]								
Mean (Range)	23.5 (5-39)		28.4 (5-39)		21.4 (5-29)		16 (5-23)	
Attained age[b]								
Mean (Range)	33.8 (5-58)		39.3 (5-58)		31.3 (7-47)		25.6 (8-40)	
Diagnosis								
Leukemia	4	0.3	1	0.1	3	0.6	0	0
Acute Lymphoblastic Leukemia	4	0.3	1	0.1	3	0.6	0	0
Acute Myeloid Leukemia	0	0	0	0	0	0	0	0
Other Leukemia	0	0	0	0	0	0	0	0
Hodgkin Lymphoma	725	35.2	401	47	285	32.6	40	11.2
Non-Hodgkin Lymphoma	33	1.7	25	3	8	0.9	0	0
Central nervous system tumor	1105	55.9	324	39.8	495	60.1	286	87.6
Astrocytoma	721	37.3	235	29.2	322	39.9	164	51.8
Medulloblastoma or PNET	194	9.1	52	6.1	98	11.1	43	12
Other	190	9.6	37	4.5	75	9.1	79	23.8
Wilms Tumor	3	0.2	2	0.3	0	0	1	0.3
Neuroblastoma	120	5.7	74	8.3	45	5.2	1	0.4
Rhabdomyosarcoma	6	0.3	5	0.5	1	0.1	0	0.1
Bone Tumor	13	0.7	8	1	4	0.4	1	0.4
Ewing sarcoma	2	0.1	1	0.1	1	0.1	0	0
Osteosarcoma	11	0.6	7	0.9	3	0.3	1	0.4
Other	0	0	0	0	0	0	0	0
Treatment Exposures[c]								
Chest Radiation								
Yes	957	46.3	467	54.7	396	45.3	94	26.8
No	901	45.7	308	37.2	370	45.5	223	68.6
Missing	151	8	64	8.1	74	9.2	13	4.6
Chest Radiation Dose, Gy[e]								
None	901	45.7	308	37.2	370	45.5	223	68.6
0 to <20	42	2.1	24	2.7	19	2.2	0	0
20 to <30	76	3.6	32	3.8	39	4.4	4	1.2
30+	839	40.7	411	48.2	338	38.8	90	25.6
Median dose[d]	39		40		38		36	
Brain Radiation								
Yes	1074	54.3	323	39.6	482	58.6	269	82.1
No	828	40.4	451	52.8	317	36.6	59	17.7
Missing	107	5.3	65	7.6	42	4.8	1	0.2
Brain Radiation Dose, Gy[e]								
None	828	40.4	451	52.8	317	36.6	59	17.7
0 to <20	20	1.1	8	0.9	6	1	6	1.8
20 to <30	12	0.6	4	0.4	3	0.3	6	1.8
30 to <40	24	1.1	11	1.2	4	0.4	9	2.7
40 to <50	136	6.8	68	8.1	58	6.9	10	3.2
50+	883	44.7	232	29	411	49.9	239	72.6
Median dose[d]	54		50		54		54	
Abdominal Radiation								
Yes	789	38.1	370	43.3	323	37.1	96	27.4
No	1070	53.9	405	48.6	444	53.7	221	68
Missing	151	8	64	8.1	74	9.2	13	4.6
Abdominal Radiation Dose, Gy[e]								
None	1070	53.9	405	48.6	444	53.7	221	68
0 to <20	44	2.2	27	3.2	15	1.8	2	0.6
20 to <30	65	3.1	26	2.9	36	4.1	3	1
30+	679	32.9	317	37.3	272	31.2	90	25.8
Median dose[d]	36		37		36		36	

[a] Unweighted counts (N). Weighted percentages (%) using inverse probability weighting. Numbers may not add up to 100% due to rounding.

[b] Weighted.

[c] Numbers represent an average among 10 imputed treatment datasets and therefore may not add up to 100%.

[d] Median dose is weighted and calculated among those with dose >0.

[e] Chest, brain, and abdominal doses are the maximum tumor dose to the respective regions, taken as the sum of the prescribed dose to all overlapping fields within each region.

eTable 5. Patient Characteristics and Therapeutic Exposures: Chemoradiotherapy Subgroup

Characteristic[a]	Overall 1970-1999		Treatment Era 1970-1979		1980-1989		1990-1999	
	N	%	N	%	N	%	N	%
Participants	10623	100	3629	32.6	4185	37.9	2809	29.5
Sex								
Male	5825	57.3	1949	56.1	2373	58.7	1503	57
Female	4798	42.7	1680	43.9	1812	41.3	1306	43
Age at diagnosis, years								
0 to 4	3993	38.7	1470	40.4	1622	40.2	901	35
5 to 9	2552	24.6	921	25.4	982	23.8	649	24.8
10 to 14	2311	20.9	709	19.4	928	21.1	674	22.1
15 to 19	1768	15.7	529	14.8	654	14.8	584	18.1
Mean (Range)	7.7 (0-20)		7.5 (0-20)		7.6 (0-20)		8.2 (0-20)	
Follow-up (years since diagnosis)[b]								
Mean (Range)	21.3 (5-39)		27.2 (5-39)		20.9 (5-30)		15.5 (5-24)	
Attained age[b]								
Mean (Range)	29.1 (5-57)		34.7 (5-57)		28.4 (5-48)		23.6 (6-42)	
Diagnosis								
Leukemia	3753	38.7	1537	41.2	1668	42.8	549	30.6
Acute Lymphoblastic Leukemia	3290	34.3	1437	38.2	1471	38.1	382	25.2
Acute Myeloid Leukemia	294	2.5	61	1.6	133	2.9	101	3
Other Leukemia	169	1.8	39	1.4	64	1.7	66	2.4
Hodgkin Lymphoma	1803	16	598	16.9	615	13.9	591	17.7
Non-Hodgkin Lymphoma	800	7.1	322	9	377	8.6	102	3.1
Central nervous system tumor	1210	11.1	135	3.9	443	10.4	632	19.8
Astrocytoma	379	3.7	60	1.8	172	4.3	148	4.9
Medulloblastoma or PNET	653	5.8	59	1.6	205	4.6	389	11.9
Other	178	1.7	17	0.5	67	1.6	95	3.1
Wilms Tumor	1139	10	369	10.2	418	9.3	351	10.6
Neuroblastoma	494	4.5	171	4.8	137	3.2	186	5.8
Rhabdomyosarcoma	840	7.6	285	8.1	315	7.1	240	7.5
Bone Tumor	583	5.2	212	5.9	213	4.8	158	4.9
Ewing sarcoma	466	4	163	4.4	182	4	121	3.7
Osteosarcoma	91	0.9	49	1.5	29	0.7	14	0.4
Other	27	0.3	1	0	3	0.1	23	0.8
Treatment Exposures[c]								
Chest Radiation								
Yes	4518	41.8	1365	38	1639	38.4	1514	50.4
No	5545	52.8	2020	55.1	2283	55.3	1242	47.1
Missing	560	5.4	245	6.9	264	6.3	52	2.5
Chest Radiation Dose, Gy[e]								
None	5545	52.8	2020	55.1	2283	55.3	1242	47.1
0 to <20	1452	14.6	288	8	634	15.7	530	20.6
20 to <30	1373	12	382	10.4	425	9.5	566	16.9
30+	1693	15.2	695	19.5	580	13.3	418	12.9
Median dose[d]	24		30		21		23	
Brain Radiation								
Yes	5614	54.9	1892	51.2	2353	58.1	1370	55.2
No	4582	41.2	1538	43.1	1641	37.5	1404	43.7
Missing	426	3.9	200	5.7	192	4.4	35	1.1
Brain Radiation Dose, Gy[e]								
None	4582	41.2	1538	43.1	1641	37.5	1404	43.7
0 to <20	2055	22	358	9.9	1175	30	522	25.2
20 to <30	1790	16.7	1158	30.8	513	12.5	119	6.6
30 to <40	207	2	76	2	86	2.1	46	2
40 to <50	307	2.7	121	3.2	130	3	56	1.8
50+	1255	11.5	179	5.2	450	10.5	627	19.6
Median dose[d]	24		24		20		38	
Abdominal Radiation								
Yes	4352	40.2	1425	39.5	1538	35.8	1388	46.8
No	5712	54.4	1959	53.6	2385	58	1368	50.7
Missing	559	5.4	245	6.9	263	6.2	52	2.5
Abdominal Radiation Dose, Gy[e]								
None	5712	54.4	1959	53.6	2385	58	1368	50.7
0 to <20	1591	15.7	271	7.5	631	15.4	688	25.2
20 to <30	1251	10.9	432	11.7	475	10.5	344	10.6
30+	1511	13.6	723	20.2	432	9.9	356	11
Median dose[d]	22		30		20		20	
Anthracycline Dose, mg/m^2								
None	4767	42.9	2322	64.1	1547	35.7	899	28.7
0 to <150	1474	15.7	225	5.7	639	17.6	610	24.1
150 to <300	2291	21.8	434	11.9	974	22.7	883	31.6
300 to <450	1566	14.7	446	12.5	770	17.9	350	13.2
450 to <600	372	3.4	154	4.3	187	4.4	31	1.1
600+	71	0.7	27	0.8	33	0.8	10	0.4
Median dose[d]	227		294		240		193	

Cyclophosphamide Equivalent Dose, mg/m^2								
None	3237	29.7	1469	40.1	1101	26.2	667	22.6
0 to <4,000	1401	14.1	364	9.8	678	16.7	360	15.5
4,000 to <8,000	1692	16.1	411	11.5	688	15.9	593	21.6
8,000 to <12,000	1618	15.7	457	12.9	724	18	437	15.7
12,000 to <16,000	1099	10.1	358	9.9	503	11.6	238	8.2
16,000 to <20,000	589	5.4	222	6.1	225	5.4	142	4.7
20,000+	986	9	348	9.7	267	6.2	371	11.7
Median dose[d]	9416		10813		9062		8936	

[a] Unweighted counts (N). Weighted percentages (%) using inverse probability weighting. Numbers may not add up to 100% due to rounding.

[b] Weighted.

[c] Numbers represent an average among 10 imputed treatment datasets and therefore may not add up to 100%.

[d] Median dose is weighted and calculated among those with dose >0.

[e] Chest, brain, and abdominal doses are the maximum tumor dose to the respective regions, taken as the sum of the prescribed dose to all overlapping fields within each region.

eTable 6. Patient Characteristics and Therapeutic Exposures: Acute Lymphoblastic Leukemia Subgroup

Characteristic[a]	Overall 1970-1999		Treatment Era 1970-1979		1980-1989		1990-1999	
	N	%	N	%	N	%	N	%
Participants	5794	100	1726	19.7	2674	36.6	1394	43.7
Sex								
Male	3116	56.1	891	53.9	1448	56	777	57.1
Female	2678	43.9	835	46.1	1226	44	617	42.9
Age at diagnosis, years								
0 to 4	2978	54.9	924	53.9	1441	55.8	613	54.7
5 to 9	1494	28	498	28.9	691	27.2	305	28.3
10 to 14	898	11.9	215	12.2	374	11.9	309	11.8
15 to 19	424	5.1	89	5	168	5.1	167	5.2
Mean (Range)	5.5 (0-20)		5.6 (0-20)		5.4 (0-20)		5.5 (0-20)	
Follow-up (years since diagnosis)[b]								
Mean (Range)	20.1 (5-39)		27.4 (5-39)		21.3 (5-30)		15.7 (5-24)	
Attained age[b]								
Mean (Range)	25.5 (5-55)		33.0 (5-55)		26.7 (6-48)		21.2 (7-41)	
Treatment Subgroup[c]								
None	4	0.1	1	0.1	1	0	1	0.1
Surgery only	0	0	0	0	0	0	0	0
Chemotherapy alone	2496	54.9	287	17.2	1198	48.1	1011	77.6
Radiotherapy alone	4	0.1	1	0	3	0.2	0	0
Chemoradiotherapy	3290	45	1437	82.7	1471	51.7	382	22.3
Treatment Exposures[c]								
Chest Radiation								
Yes	603	9.1	259	14.7	226	8.6	118	7.1
No	4585	82.9	1210	69.8	2141	81.5	1234	90
Missing	606	8	257	15.5	307	9.9	42	2.9
Chest Radiation Dose, Gy[e]								
None	4585	82.9	1210	69.8	2141	81.5	1234	90
0 to <20	414	7	94	5.4	206	7.9	114	6.9
20 to <30	173	1.9	154	8.6	16	0.5	3	0.2
30+	16	0.2	11	0.6	4	0.2	1	0
Median dose[d]	15		22		13		13	
Brain Radiation								
Yes	3194	43.2	1421	81.7	1414	49.2	359	20.7
No	2600	56.8	306	18.3	1260	50.8	1035	79.3
Missing	0	0	0	0	0	0	0	0
Brain Radiation Dose, Gy[e]								
None	2600	56.8	306	18.3	1260	50.8	1035	79.3
0 to <20	1536	22.7	308	18.3	957	33.8	270	15.3
20 to <30	1483	18.3	1018	58	392	13.2	74	4.6
30 to <40	93	1.3	36	2.1	42	1.5	14	0.9
40 to <50	76	0.9	54	3	22	0.7	1	0
50+	6	0.1	5	0.3	1	0	0	0
Median dose[d]	21		24		18		18	
Abdominal Radiation								
Yes	581	8.8	260	14.8	207	7.8	114	6.8
No	4608	83.3	1209	69.7	2161	82.4	1238	90.2
Missing	605	7.9	257	15.5	306	9.8	42	3
Abdominal Radiation Dose, Gy[e]								
None	4608	83.3	1209	69.7	2161	82.4	1238	90.2
0 to <20	406	6.8	103	5.9	193	7.4	110	6.7
20 to <30	161	1.8	146	8.1	11	0.3	4	0.2
30+	14	0.2	11	0.7	3	0.1	0	0
Median dose[d]	15		22		12		13	
Anthracycline Dose, mg/m^2								
None	2546	35.6	1134	66.1	1227	41.8	185	16.6
0 to <150	1421	33.8	155	8.3	572	26.7	694	51.4
150 to <300	991	18.7	158	9	425	15.5	409	25.8
300 to <450	591	8.7	167	9.9	327	11.7	97	5.6
450 to <600	196	2.5	94	5.6	97	3.3	5	0.4
600+	50	0.7	19	1.2	27	1	4	0.3
Median dose[d]	170		281		175		108	
Cyclophosphamide Equivalent Dose, mg/m^2								
None	2628	43.6	1109	64.5	1055	40.8	463	36.4
0 to <4,000	1481	29	220	12.8	771	28.2	491	37
4,000 to <8,000	662	10.7	134	7.9	326	11.3	202	11.6
8,000 to <12,000	602	11	92	5.4	314	12.4	195	12.4
12,000 to <16,000	168	2.5	37	2	103	3.6	28	1.8
16,000 to <20,000	107	1.4	48	2.6	52	1.9	7	0.4
20,000+	147	1.8	86	4.8	53	1.8	8	0.4
Median dose[d]	4222		6653		4198		3860	

[a] Unweighted counts (N). Weighted percentages (%) using inverse probability weighting. Numbers may not add up to 100% due to rounding.

[b] Weighted.

[c] Numbers represent an average among 10 imputed treatment datasets and therefore may not add up to 100%.

[d] Median dose is weighted and calculated among those with dose >0.

[e] Chest, brain, and abdominal doses are the maximum tumor dose to the respective regions, taken as the sum of the prescribed dose to all overlapping fields within each region.