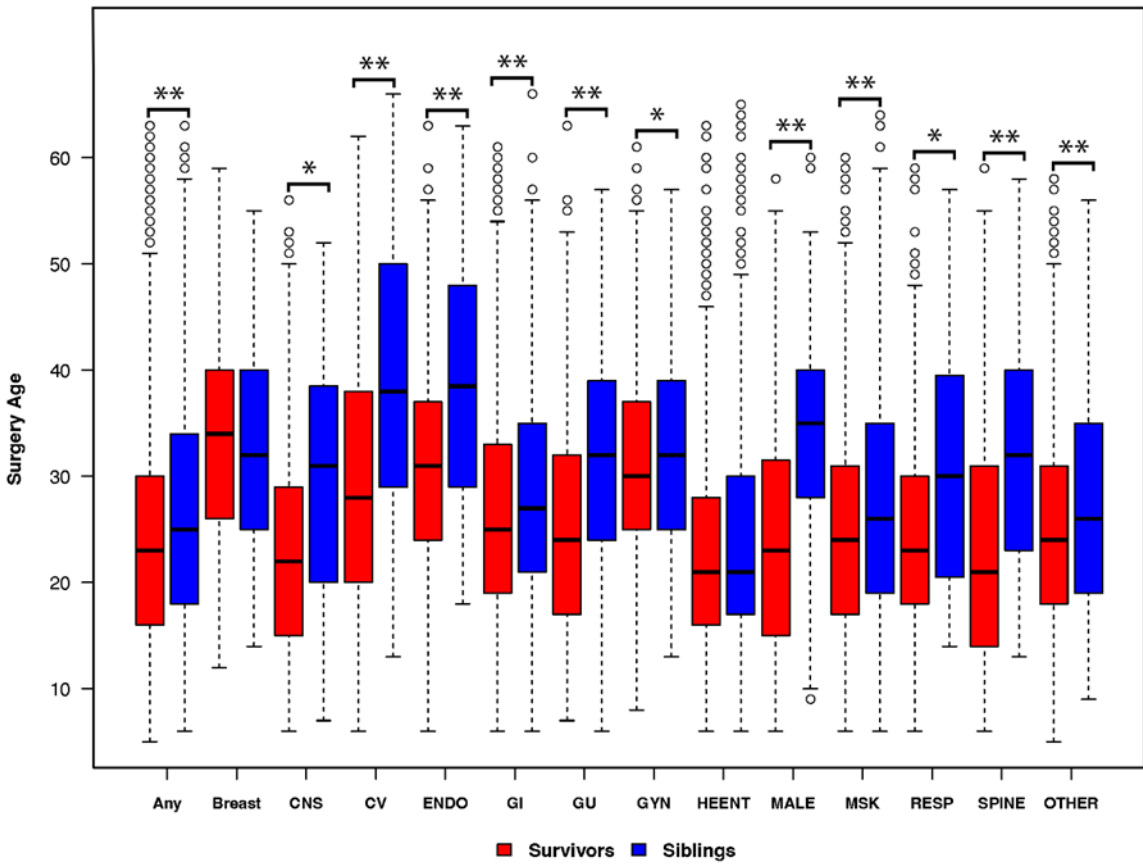


Supplementary Material

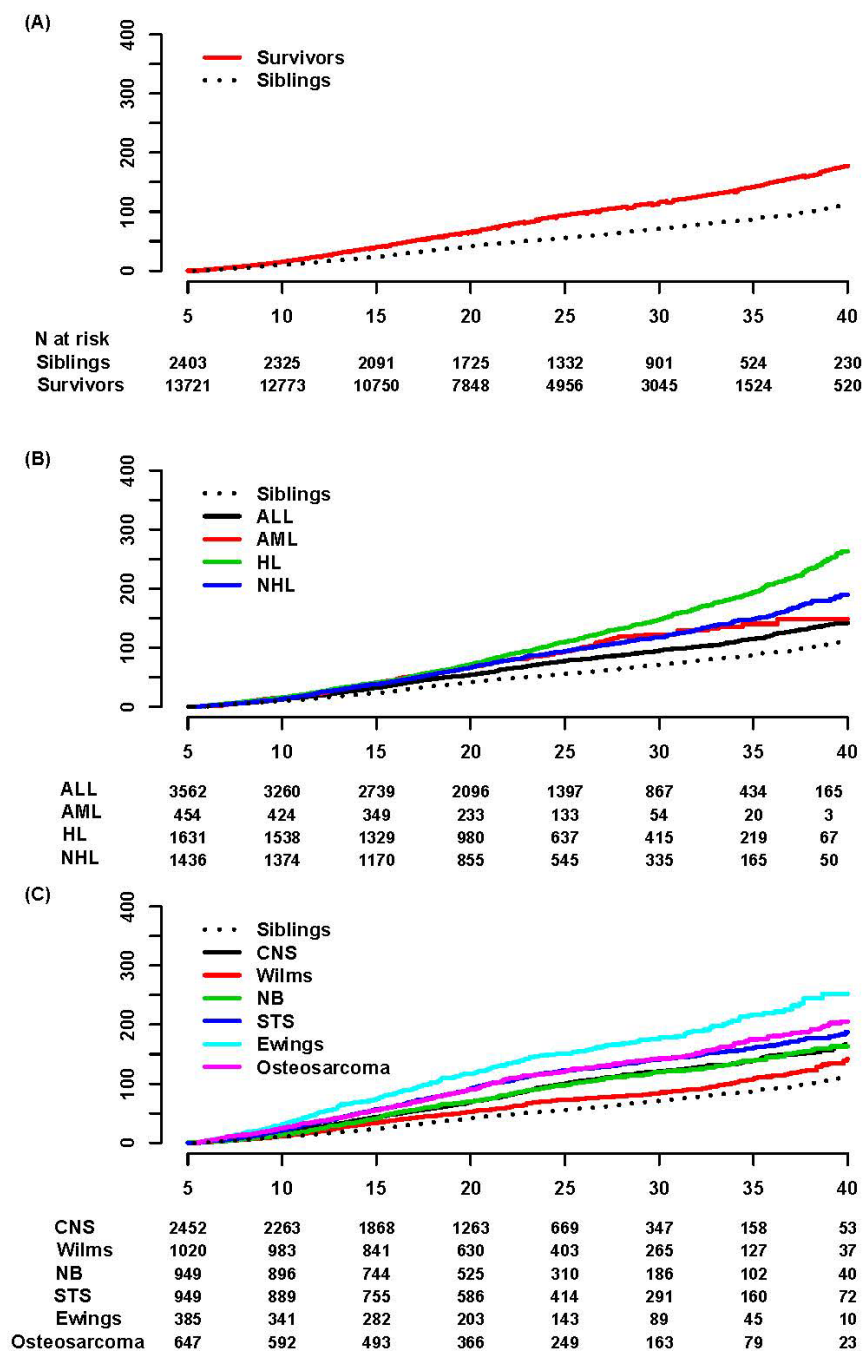
Table of Contents

Supplementary Figures 1-5 (Pages 2-6)

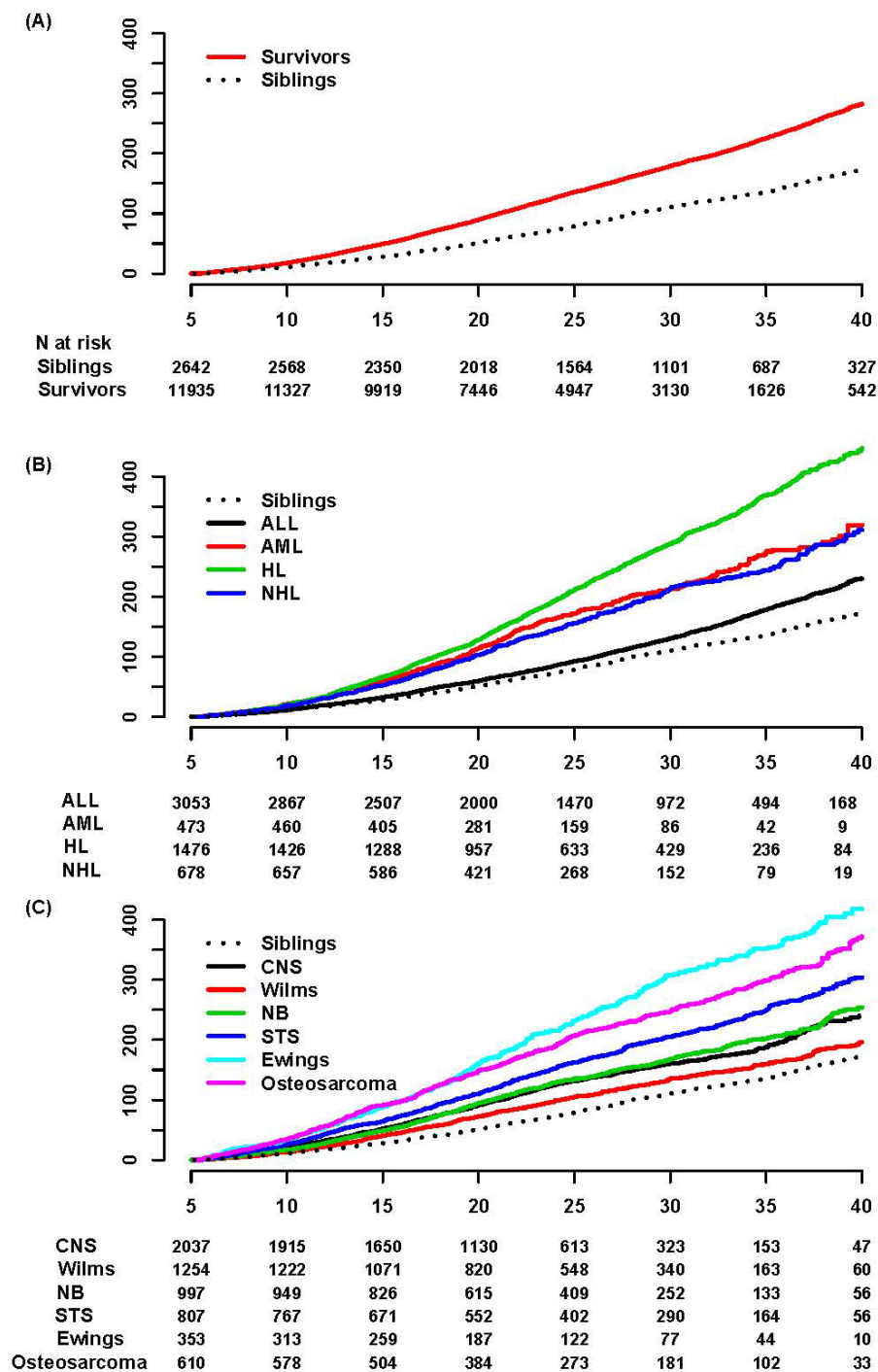
Supplementary Tables 1-7 (Pages 7-13)



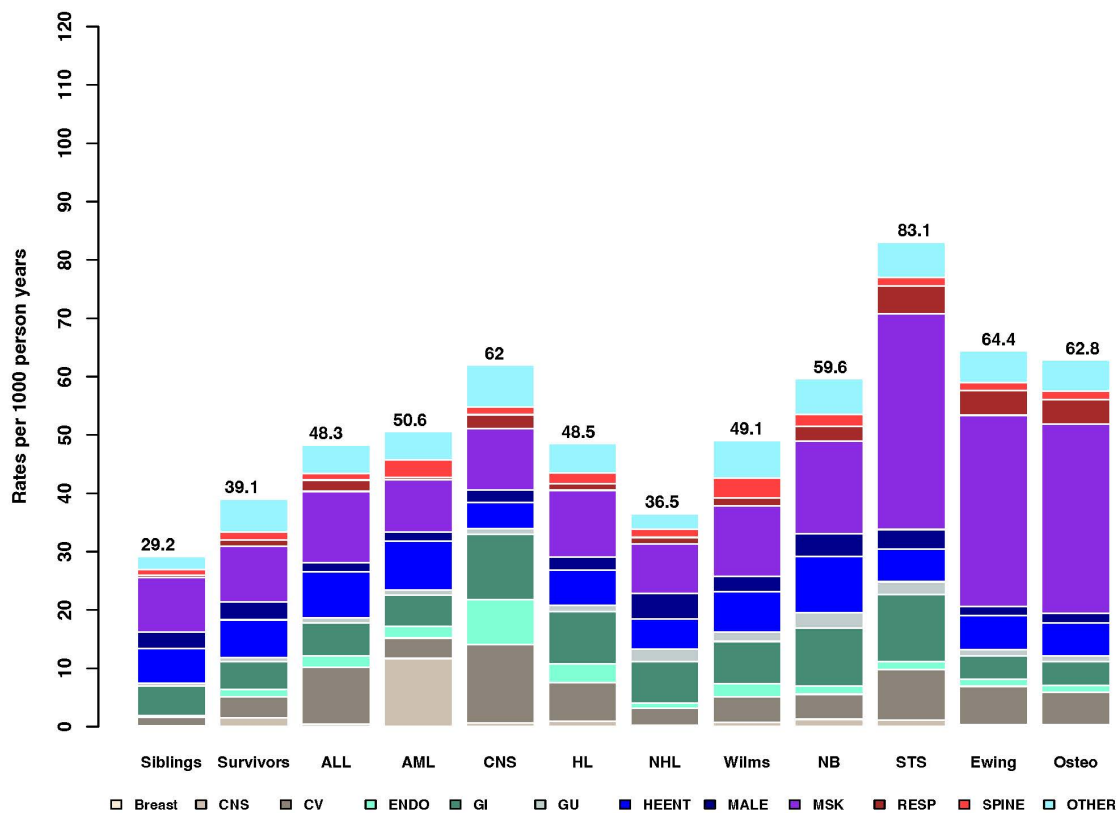
Supplementary Figure 1. Median age at the first late, major surgical intervention (any, and by organ system) in survivors of childhood cancer versus siblings. Boxplots show median (horizontal black line) with interquartile range (red or blue shaded boxes). *p<0.05, **p<0.001



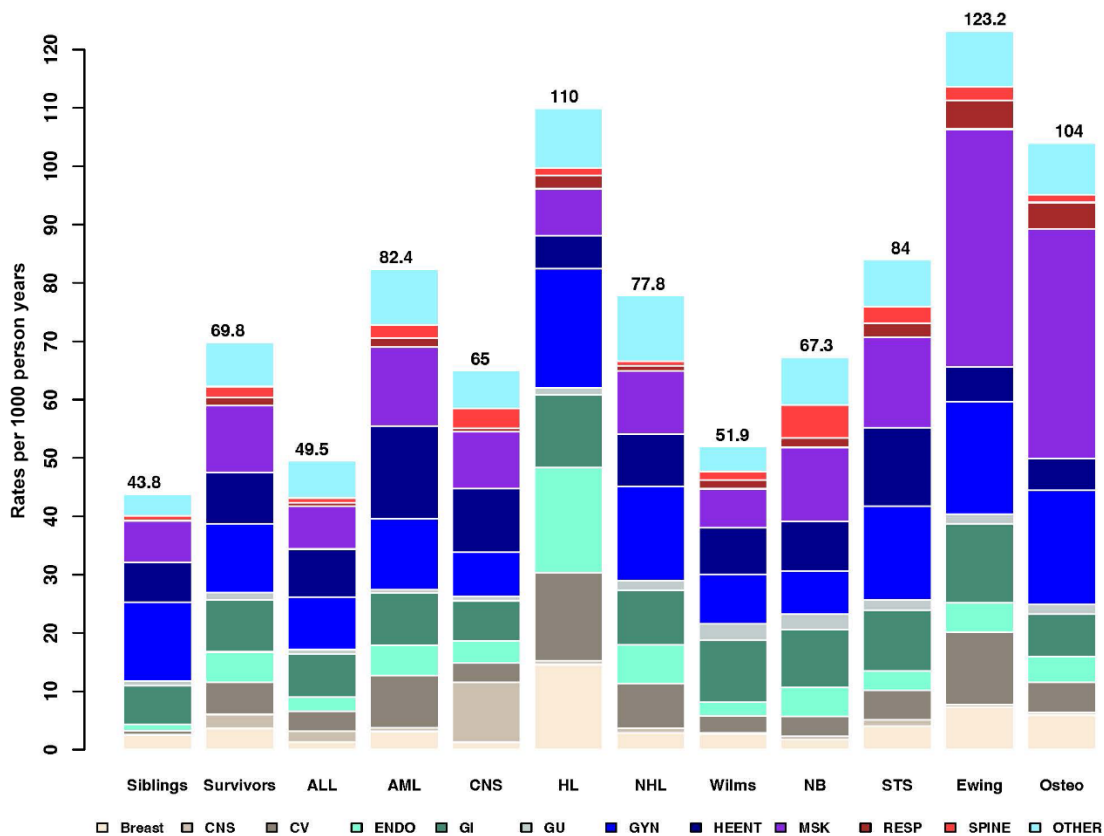
Supplementary Figure 2. (A) Mean cumulative counts of major late surgical interventions in male childhood cancer survivors compared to nearest-age sibling controls. (B) Mean cumulative counts of major late surgical procedures undergone by childhood cancer survivors of hematologic malignancies and (C) solid tumors compared to nearest-age sibling controls. ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, HL – Hodgkin lymphoma, NHL – non-Hodgkin lymphoma, CNS – central nervous system tumors, Wilms – Wilms tumor, NB – neuroblastoma, STS – soft tissue sarcoma, Ewings – Ewing sarcoma, N – number. Y-axis shows mean cumulative counts per 100 individuals; X-axis shows years from cancer diagnosis for A-C.



Supplementary Figure 3. (A) Mean cumulative counts of major late surgical interventions in female childhood cancer survivors compared to nearest-age sibling controls. (B) Mean cumulative counts of major late surgical procedures undergone by childhood cancer survivors of hematologic malignancies and (C) solid tumors compared to nearest-age sibling controls. ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, HL – Hodgkin lymphoma, NHL – non-Hodgkin lymphoma, CNS – central nervous system tumors, Wilms – Wilms tumor, NB – neuroblastoma, STS – soft tissue sarcoma, Ewings – Ewing sarcoma, N – number. Y-axis shows mean cumulative counts per 100 individuals; X-axis shows years from cancer diagnosis for A-C.



Supplementary Figure 4. Rates of late, major surgical intervention among male childhood cancer survivors, per 1000-person years of follow-up. Rates of intervention are stratified by cancer diagnosis and compared with age-matched sibling controls. Cancer types: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, CNS – central nervous system tumors, HL – Hodgkin lymphoma, NHL – non-Hodgkin lymphoma, Wilms – Wilms tumor, NB – neuroblastoma, STS – soft tissue sarcoma, Ewing – Ewing sarcoma. Organ systems: CNS – central nervous system, CV – cardiovascular, ENDO – endocrine, GI – gastrointestinal, GU – genitourinary, HEENT – head, eye, ears, nose and throat, Male – male reproductive surgery, MSK – musculoskeletal, RESP – respiratory



Supplementary Figure 5. Rates of late, major surgical intervention among female childhood cancer survivors, per 1000-person years of follow-up. Rates of intervention are stratified by cancer diagnosis and compared with age-matched sibling controls. Cancer types: ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, CNS – central nervous system tumors, HL – Hodgkin lymphoma, NHL – non-Hodgkin lymphoma, Wilms – Wilms tumor, NB – neuroblastoma, STS – soft tissue sarcoma, Ewing – Ewing sarcoma. Organ systems: CNS – central nervous system, CV – cardiovascular, ENDO – endocrine, GI – gastrointestinal, GU – genitourinary, GYN – gynecologic, HEENT – head, eye, ears, nose and throat, MSK – musculoskeletal, RESP – respiratory

Supplementary Table 1. Adjusted rate ratios for undergoing any late, major surgical intervention for childhood cancer survivors, overall and by primary cancer diagnosis, compared to siblings

	Rate Ratio* (95% confidence interval)
Siblings	1.0 (ref.)
All Survivors	1.8 (1.7-1.9)
<i>Primary Cancer Diagnosis (relative to siblings)</i>	
Acute Lymphoblastic Leukemia	1.5 (1.4 - 1.6)
Acute Myeloid Leukemia	2.1 (1.9 - 2.3)
Central nervous system	1.8 (1.6 - 1.9)
Astrocytomas	1.7 (1.5 - 1.8)
Medulloblastoma, PNET	2.0 (1.8 - 2.2)
Other CNS tumors	1.8 (1.6 - 2.1)
Hodgkin Lymphoma	2.1 (1.9 - 2.2)
Non-Hodgkin Lymphoma	1.7 (1.6 - 1.9)
Wilms Tumor	1.6 (1.4 - 1.7)
Neuroblastoma	2.2 (2.0 - 2.4)
Soft Tissue Sarcoma	2.0 (1.8 - 2.1)
Ewing Sarcoma	2.6 (2.4 - 2.9)
Osteosarcoma	2.1 (1.9 - 2.3)

*Adjusted for attained age as cubic splines, sex, race/ethnicity, and health insurance status; CNS – central nervous system; PNET – primitive neuroectodermal tumor

Supplementary Table 2. Mean Cumulative Counts of Late, Major Surgical Interventions in Childhood Cancer Survivors and Siblings According to Time and Diagnosis

	10-year MCC	15-year MCC	20-year MCC	25-year MCC	30-year MCC	35-year MCC
All survivors	17.0 (16.4 - 17.6)	46.5 (45.3 - 47.7)	82.1 (80.3 - 83.8)	123.5 (121.0 - 125.9)	162.9 (159.7 - 166.0)	206.7 (202.7 - 210.8)
Siblings	10.9 (9.8 - 12.1)	27.3 (25.4 - 29.2)	50.3 (47.6 - 53.0)	74.4 (70.8 - 78.0)	103.1 (98.3 - 107.8)	128.9 (123.0 - 134.7)
Acute lymphoblastic leukemia	12.5 (11.4 - 13.6)	33.7 (31.6 - 35.8)	59.1 (56.0 - 62.1)	89.8 (85.3 - 94.2)	122.9 (117.3 - 128.6)	164.6 (157.2 - 172.0)
Acute myeloid leukemia	18.9 (15.4 - 22.5)	52.0 (45.4 - 58.6)	95.9 (85.6 - 106.1)	145.7 (131.3 - 160.2)	184.5 (166.2 - 202.9)	236.7 (208.8 - 264.6)
Central Nervous System	19.4 (17.8 - 21.0)	48.6 (45.8 - 51.4)	81.8 (77.7 - 85.9)	120.1 (114.4 - 125.8)	147.6 (140.4 - 154.9)	173.9 (163.6 - 184.2)
Hodgkin lymphoma	19.5 (17.4 - 21.6)	59.7 (55.7 - 63.7)	112.6 (106.9 - 118.4)	184.7 (176.7 - 192.6)	256.6 (246.2 - 267.0)	333.3 (320.1 - 346.6)
Non-Hodgkin lymphoma	16.1 (13.7 - 18.4)	45.9 (41.6 - 50.1)	84.6 (78.4 - 90.9)	127.7 (119.2 - 136.2)	178.1 (165.0 - 191.2)	216.3 (200.8 - 231.7)
Wilms tumor	12.4 (10.5 - 14.2)	38.0 (34.7 - 41.4)	66.1 (61.3 - 70.9)	94.7 (88.3 - 101.2)	120.4 (112.2 - 128.6)	149.2 (138.5 - 160.0)
Neuroblastoma	15.5 (13.4 - 17.6)	45.0 (41.2 - 48.9)	84.9 (78.6 - 91.3)	120.9 (112.3 - 129.5)	152.1 (141.0 - 163.3)	185.1 (170.9 - 199.3)
Soft tissue sarcoma	24.3 (21.3 - 27.4)	65.0 (59.8 - 70.2)	107.9 (101.0 - 114.8)	156.1 (146.5 - 165.7)	194.7 (182.9 - 206.6)	233.8 (219.4 - 248.2)
Ewing sarcoma	33.7 (28.6 - 38.8)	83.5 (74.5 - 92.4)	148.8 (135.5 - 162.2)	206.7 (189.5 - 223.8)	270.4 (247.1 - 293.7)	322.9 (294.5 - 351.3)
Osteosarcoma	30.9 (27.1 - 34.6)	77.1 (70.4 - 83.8)	127.8 (118.5 - 137.1)	180.5 (167.1 - 193.9)	219.1 (202.9 - 235.4)	269.6 (250.1 - 289.2)

MCC – Mean cumulative count per 100 individuals

Supplementary Table 3. Rates of Death (Competing Event) in Siblings, Survivors, and Survivors According to Primary Cancer Diagnosis

	Number of deaths	Death Rate per 1000 person years (95% confidence interval)
Siblings	8	0.1 (0.0 - 0.1)
All Survivors	1823	3.7 (3.6 - 3.9)
<i>Primary Cancer Diagnosis</i>		
Acute Lymphoblastic Leukemia	440	3.2 (2.9 - 3.4)
Acute Myeloid Leukemia	53	3.4 (2.6 - 4.5)
Central nervous system	413	5.6 (5.1 - 6.2)
Hodgkin Lymphoma	247	4.2 (3.7 - 4.7)
Non-Hodgkin Lymphoma	94	2.4 (2.0 - 3.0)
Wilms Tumor	67	1.6 (1.2 - 2.0)
Neuroblastoma	99	2.8 (2.3 - 3.4)
Soft Tissue Sarcoma	131	3.8 (3.2 - 4.5)
Ewing Sarcoma	112	9.1 (7.5 - 10.9)
Osteosarcoma	109	4.7 (3.9 - 5.7)

Supplementary Table 4. Sex-Specific Rates of Late, Major Surgical Intervention Displayed as Females Compared to Males (Reference)

	All late, major surgical interventions		All late, major surgical interventions, excluding sex-specific surgeries*	
	Rate Ratio** (95% confidence interval)	P-value	Rate Ratio** (95% confidence interval)	P-value
All Survivors	1.4 (1.4 - 1.5)	<.0001	1.2 (1.1 - 1.2)	<.0001
<i>Primary Cancer Diagnosis</i>				
Acute Lymphoblastic Leukemia	1.3 (1.1 - 1.4)	<.0001	1.1 (1.0 - 1.2)	0.16
Acute Myeloid Leukemia	1.5 (1.2 - 1.9)	<.0001	1.3 (1.0 - 1.6)	0.019
Central nervous system	1.3 (1.2 - 1.5)	<.0001	1.2 (1.1 - 1.3)	0.0023
Hodgkin Lymphoma	1.6 (1.5 - 1.8)	<.0001	1.2 (1.1 - 1.3)	0.0012
Non-Hodgkin Lymphoma	1.7 (1.5 - 1.9)	<.0001	1.3 (1.1 - 1.5)	0.00032
Wilms Tumor	1.4 (1.2 - 1.6)	<.0001	1.3 (1.1 - 1.5)	0.0015
Neuroblastoma	1.3 (1.1 - 1.5)	0.00064	1.2 (1.0 - 1.4)	0.022
Soft Tissue Sarcoma	1.4 (1.2 - 1.6)	<.0001	1.1 (1.0 - 1.3)	0.060
Ewing Sarcoma	1.5 (1.2 - 1.8)	<.0001	1.2 (1.0 - 1.5)	0.064
Osteosarcoma	1.6 (1.4 - 1.9)	<.0001	1.3 (1.1 - 1.5)	0.0043

*Excludes female gynecologic and male reproductive late, major surgical interventions.

**Adjusted for attained age as cubic splines, sex, race/ethnicity, and health insurance status.

Supplementary Table 5. Identification of Individual ICD-9 Procedures Less Common in Survivors than Siblings

ICD-9 Code	Organ system category	Description of Procedure	# of interventions per 1000 person-years of follow-up, survivors	# of interventions per 1000 person-years of follow-up, siblings	Adjusted rate ratio* (95% confidence interval)	P
11.X	HEENT	Operations on cornea	0.14 (0.11 - 0.18)	0.32 (0.22 - 0.44)	0.5 (0.3 - 0.8)	0.0016
14.X	HEENT	Operations on retina, choroid, vitreous, and posterior chamber	0.05 (0.03 - 0.07)	0.10 (0.05 - 0.18)	0.7 (0.3 - 1.8)	0.43
21.X	HEENT	Operations on nose	0.40 (0.34 - 0.46)	0.53 (0.41 - 0.69)	0.8 (0.6 - 1.2)	0.34
23.X	HEENT	Removal and restoration of teeth	1.60 (1.49 - 1.71)	2.01 (1.76 - 2.29)	0.8 (0.7 - 0.9)	0.0032
28.X	HEENT	Operations on tonsils and adenoids	1.64 (1.53 - 1.75)	1.85 (1.61 - 2.12)	0.8 (0.7 - 1.0)	0.052
41.9X	GI	Other operations on spleen and bone marrow	0.08 (0.06 - 0.11)	0.14 (0.08 - 0.22)	0.5 (0.2 - 0.9)	0.035
47.X	GI	Operations on appendix	1.17 (1.08 - 1.26)	1.39 (1.18 - 1.63)	0.9 (0.7 - 1.0)	0.12
49.X	GI	Operations on anus	0.08 (0.06 - 0.11)	0.24 (0.16 - 0.35)	0.4 (0.2 - 0.7)	0.0018
53.X	GI	Repair of hernia	0.81 (0.73 - 0.89)	1.04 (0.86 - 1.25)	0.8 (0.6 - 1.0)	0.077
59.X	GU	Other operations on urinary tract	0.07 (0.05 - 0.10)	0.12 (0.06 - 0.20)	0.8 (0.4 - 1.5)	0.50
63.X	MALE	Operations on spermatic cord, epididymis, and vas deferens	0.82 (0.71 - 0.93)	2.00 (1.63 - 2.42)	0.5 (0.4 - 0.6)	<.0001
65.X ¹ ,	GYN	Operations on ovary	0.62 (0.52 - 0.72)	0.76 (0.55 - 1.02)	0.9 (0.6 - 1.4)	0.63
66.X	GYN	Operations on fallopian tubes	1.47 (1.32 - 1.63)	2.58 (2.19 - 3.03)	0.6 (0.5 - 0.8)	<.0001
67.X	GYN	Operations on cervix	0.66 (0.56 - 0.77)	1.15 (0.89 - 1.46)	0.6 (0.4 - 0.8)	0.0011
68.X ² ,	GYN	Other incision and excision of uterus	0.76 (0.65 - 0.87)	0.78 (0.57 - 1.04)	1.2 (0.8 - 1.7)	0.34
69.X	GYN	Other operations on uterus and supporting structures	0.97 (0.85 - 1.10)	1.32 (1.04 - 1.64)	0.8 (0.6 - 1.1)	0.20
81.4X	MSK	Other repair of joint of lower extremity	1.31 (1.21 - 1.41)	1.39 (1.18 - 1.63)	1.0 (0.8 - 1.3)	0.85
81.7X	MSK	Arthroplasty and repair of hand, fingers, and wrist	0.09 (0.07 - 0.13)	0.10 (0.05 - 0.18)	1.0 (0.5 - 2.2)	0.92
82.X	MSK	Operations on muscle, tendon, and fascia of hand	0.24 (0.20 - 0.29)	0.39 (0.28 - 0.52)	0.7 (0.5 - 1.1)	0.11
83.X	MSK	Operations on muscle, tendon, fascia, and bursa, except hand	1.21 (1.11 - 1.31)	1.21 (1.02 - 1.43)	1.1 (0.9 - 1.4)	0.40

*Adjusted for attained age as cubic splines, sex, race/ethnicity, and health insurance status. ¹ Female, excluding 65.3-65.6 “remove ovaries”; ² Female, “excluding 68.3-68.9 Removal of uterus”

Supplementary Table 6. Adjusted rate ratios of Late Surgical Intervention According to Decade of Diagnosis*

<i>Decade of diagnosis</i>	Total survivors		Siblings**		ALL		AML		HL		NHL	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
1970-1979	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
1980-1989	1.0 (0.9 - 1.1)	0.93	1.1 (0.9 - 1.2)	0.41	0.9 (0.8 - 1.0)	0.028	1.0 (0.7 - 1.5)	0.79	1.0 (0.8 - 1.1)	0.50	1.2 (1.0 - 1.5)	0.061
1990-1999	1.4 (1.3 - 1.5)	<.000 1	1.1 (0.9 - 1.3)	0.25	1.4 (1.2 - 1.6)	<.000 1	1.1 (0.8 - 1.5)	0.71	1.2 (1.0 - 1.4)	0.020	1.6 (1.3 - 1.9)	<.000 1

<i>Decade of diagnosis</i>	CNS		Wilms tumor		Neuroblastoma		STS		Ewing sarcoma		Osteosarcoma	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
1970-1979	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
1980-1989	1.2 (1.0 - 1.4)	0.052	0.9 (0.7 - 1.1)	0.20	1.1 (0.9 - 1.3)	0.51	0.9 (0.8 - 1.2)	0.54	1.0 (0.8 - 1.3)	0.79	1.6 (1.2 - 2.0)	0.001 4
1990-1999	1.8 (1.5 - 2.2)	<.000 1	1.1 (0.9 - 1.4)	0.35	1.6 (1.3 - 2.0)	<.000 1	1.4 (1.2 - 1.8)	0.001 1	1.3 (1.0 - 1.6)	0.051	2.8 (2.3 - 3.5)	<.000 1

*Analysis adjusted to include only late, major surgical intervention occurring ≤ 20 years from diagnosis to control for inherent differential follow-up among survivors diagnosed during different decades.**Pseudo-diagnosis date used for age-matched sibling controls. ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, HL – Hodgkin lymphoma, NHL – non-Hodgkin lymphoma, CNS – central nervous system tumors, STS – soft tissue sarcoma

Supplementary Table 7. Adjusted rate ratios of Late Surgical Intervention According to Organ System of Intervention and Decade of Diagnosis*

<i>Decade of diagnosis</i>	Breast		Cardiovascular		Central nervous system		Endocrine		Female gynecologic		Gastrointestinal	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
1970-1979	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
1980-1989	0.5 (0.4 - 0.7)	<.0001	1.2 (0.9 - 1.5)	0.21	1.3 (1.0 - 1.6)	0.095	0.7 (0.6 - 0.9)	0.00050	0.8 (0.6 - 0.9)	0.0032	0.9 (0.8 - 1.1)	0.24
1990-1999	0.4 (0.3 - 0.5)	<.0001	3.3 (2.7 - 4.1)	<.0001	1.9 (1.5 - 2.4)	<.0001	0.7 (0.6 - 0.9)	0.00073	0.7 (0.6 - 0.9)	0.00037	1.1 (0.9 - 1.2)	0.36

<i>Decade of diagnosis</i>	Head and neck		Male reproductive		Musculoskeletal		Renal/urinary		Respiratory		Spine	
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
1970-1979	1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)		1.0 (ref)	
1980-1989	1.0 (0.9 - 1.2)	0.48	1.2 (0.9 - 1.6)	0.27	1.1 (1.0 - 1.2)	0.16	1.1 (0.8 - 1.5)	0.72	0.9 (0.7 - 1.2)	0.50	0.9 (0.7 - 1.2)	0.42
1990-1999	1.3 (1.1 - 1.5)	0.00019	1.1 (0.8 - 1.4)	0.71	1.7 (1.5 - 2.0)	<.0001	1.2 (0.9 - 1.7)	0.25	1.2 (0.9 - 1.7)	0.22	1.1 (0.8 - 1.4)	0.72

*Analysis adjusted to include only late, major surgical intervention occurring ≤ 20 years from diagnosis to control for inherent differential follow-up among survivors diagnosed during different decades.