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Article

ARTICLE

Survival Differences Between Males and Females Diagnosed With Childhood Cancer

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Abstract

Background: Males have worse survival for childhood cancer, but whether this disparity exists among all childhood cancer types is undescribed.
Methods: We estimated sex differences in survival for 18 cancers among children (0–19 years) in Surveillance, Epidemiology, and End Results 18 (2000–2014). We used Kaplan-Meier survival curves (log-rank *P* values) to characterize sex differences in survival and Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between sex and death for each cancer type. We used an inverse odds weighting method to determine whether the association between sex and death was mediated by stage of disease for solid tumors.
Results: Males had worse overall survival and a higher risk of death for acute lymphoblastic leukemia (HR = 1.24, 95% CI = 1.12 to 1.37), ependymoma (HR = 1.36, 95% CI = 1.05 to 1.77), neuroblastoma (HR = 1.28, 95% CI = 1.09 to 1.51), osteosarcoma (HR = 1.29, 95% CI = 1.08 to 1.53), thyroid carcinoma (HR = 3.25, 95% CI = 1.45 to 7.33), and malignant melanoma (HR = 1.97, 95% CI = 1.33 to 2.92) (all log-rank *P* values < .02). The association between sex and death was mediated by stage of disease for neuroblastoma (indirect HR = 1.12, 95% CI = 1.05 to 1.19), thyroid carcinoma (indirect HR = 1.24, 95% CI = 1.03 to 1.48), and malignant melanoma (indirect HR = 1.28, 95% CI = 1.10 to 1.49). For these six tumors, if male survival had been as good as female survival, 21% of male deaths and 13% of total deaths after these cancer diagnoses could have been avoided.
Conclusions: Consideration of molecular tumor and clinical data may help identify mechanisms underlying the male excess in death after childhood cancer for the aforementioned cancers.

Cancer continues to be a leading cause of death among children and adolescents, particularly those aged 5–14 years (1). Survival differences between childhood cancer types are well-documented with central nervous system and bone tumors resulting in lower survival and acute lymphoblastic leukemia (ALL) and lymphomas having higher survival rates (2–4). In epidemiologic survival analyses, males and females are traditionally grouped together to estimate survival percentages, and sex-adjusted hazard ratios (HRs) for the risk of death from childhood cancer are often presented. However, even though males have worse survival than females for childhood cancer overall, there is little information on sex differences in survival by cancer type, making it unclear whether the sex variation observed for childhood cancer survival overall extends to individual childhood tumor types (2,5,6).

The identification of sex differences in survival after a childhood cancer diagnosis may be helpful in uncovering biological mechanisms responsible for the increased risk of death among males. These findings may also help guide future research to identify treatments that may have greater benefit in male or female children as done among adults, where sex differences in tumor genomics were used to identify clinically actionable therapies with potential sex-specific benefits (7). The survival differences between sexes are likely to be multifactorial depending on features such as sex differences in diagnosis delay (8), pharmacogenetics (9–12), and/or cancer biology. To identify cancer

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types with sex differences in survival and to determine whether these differences depend on stage of disease, we used the Surveillance, Epidemiology, and End Results (SEER) Program 18 registries (2000–2014) to conduct a survival analysis for 18 childhood cancers (13). We characterized sex differences in overall survival and estimated the risk of death for males relative to females for each cancer. We then conducted a mediation analysis for the association between sex and death, treating stage of disease as a mediator.

Methods

Study Population

Cancer cases (n = 57 004) aged 0–19 years were identified using the SEER Program 18 registries. Cases included in SEER 18 (14) (2000–2014) arise from Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, rural Georgia, the Alaska Native Tumor Registry, greater California, greater Georgia, Kentucky, Louisiana, and New Jersey. To be included in this analysis, individuals must have had a microscopically confirmed first primary tumor classified as one of the main International Classification of Childhood Cancer [3rd edition (13)] types that had at least 500 cases (n = 45 229) available for analysis. Additional tumor types excluded were germ cell tumors, because these arise from different cell types in males and females and survival differences have been characterized elsewhere (15), and tumors with "other" classifications (Supplementary Table 1, available online). Of the cases identified in SEER for this analysis, 47 were missing survival time and were not included in the survival analyses.

Cancer Type

The International Classification of Childhood Cancer categories included in the current analysis were I Leukemias (Ia Acute lymphoid leukemia, Ib Acute myeloid leukemia), II Lymphomas (IIa Hodgkin lymphoma, IIb Non-Hodgkin lymphoma, IIc Burkitt lymphoma), III Central Nervous System (IIIa Ependymoma, IIIb Astrocytoma, IIIc.1 Medulloblastoma, IIIc.2 Peripheral Neuroectodermal Tumor [PNET]), IVa Neuroblastoma, V Retinoblastoma, VIa Nephroblastoma, VIIa Hepatoblastoma, VIII Bone (VIIIa Osteosarcoma, VIIIc Ewing tumor and related sarcomas of bone [Ewing sarcoma]), IX Soft Tissue Sarcomas (IXa Rhabdomyosarcoma), and XI Other malignant epithelial neoplasms and malignant melanomas (XIb Thyroid carcinoma, XId Malignant melanoma).

Variables of Interest

From SEER we obtained age at diagnosis (<1, 1–4, 5–9, 10–14, 15–19 years), year of diagnosis (2000–2004, 2005–2009, 2010–2014), race or ethnicity (non-Hispanic, white, black, Asian or Pacific Islander, Hispanic), tumor size (<2 cm, 2 to <5 cm, ≥5 cm; not available for I Leukemias or II Lymphomas), stage of disease (local, regional, distant; not available for I Leukemias), metastases (yes or no; not available for I Leukemias or II Lymphomas), months of survival (defined in SEER using the date of diagnosis to the date of death from any cause or last contact by the study end date of December 31, 2014), and vital status.

Statistical Analysis

Five-year survival percentages stratified by sex for each cancer type were estimated. Kaplan-Meier survival curves and log-rank *P* values to identify statistically significant sex differences in overall survival were generated. We used Cox proportional hazards models to estimate hazard ratios and the corresponding 95% confidence intervals (CIs) for the association between male sex, relative to female sex, and death for each cancer. There was no violation of the proportional hazards assumption when considering an interaction term between sex and time in the models. Age-stratified analyses for the association between sex and death were carried out using age at diagnosis categories: 0–4, 4–9, 10–14, and 15–19 years. A *P* value was calculated for each cancer through use of an age-sex interaction term in each model.

For solid cancers with a statistically significant sex difference in survival, we conducted a mediation analysis to determine if the association between sex and the risk of death after a cancer diagnosis was mediated by stage of disease using an inverse odds weighting method (16–19). Briefly, the inverse odds weighting Cox proportional hazards model allows for estimation of the association between sex and death, independent of stage of disease. The weight for sex was estimated from a logistic regression model for stage of disease in association with sex where the reference category, female, was assigned the weight of 1. Males were assigned a value of the inverse odds of the aforementioned logistic models conducted separately for each cancer. The indirect effect of sex on death operating through stage of disease was calculated by subtracting the direct effect beta from the total effect beta ($\beta_{\text{indirect}} = \beta_{\text{total}} - \beta_{\text{direct}}$). For the total, direct, and indirect effects, the resulting hazard ratios were estimated, and bootstrapped standard errors (1000 replications) were used to estimate the 95% confidence intervals. A statistically significant indirect effect was interpreted as evidence of mediation by stage of disease for the association between sex and death.

Analyses were done using SAS v9.4 (SAS Institute, Cary, NC) and Stata v15.0 (StataCorp, College Station, Texas). Figures were generated in GraphPad Prism v8.0.1 (GraphPad Software, La Jolla, CA). Statistical significance was determined using two-sided hypothesis tests (alpha = .05). Because this is observational research, no adjustment for multiple comparisons was made in our analysis (20).

Results

The distribution of age, race, tumor size, stage of diseases, metastases at diagnosis, vital status, and year of diagnosis by sex for each cancer is in Table 1. Males comprised 53% of the study sample (results not shown). Tumors with a female predominance included nephroblastoma (48% male, 52% female), thyroid carcinoma (19% male, 81% female), and malignant melanoma (43% male, 57% female). The race or ethnicity distribution of cases was similar between sexes for each cancer. Among children with solid cancers and tumor size available, there were few sex differences except Ewing sarcoma, where males more frequently had tumors larger than 5 cm (79% male, 70% female) and PNETs where males less frequently had tumors larger than 5 cm (48% male, 57% female). For stage of disease, differences in the distribution by sex emerged among some cancers. Males were more frequently diagnosed with distant stage of disease for Hodgkin lymphoma (40% male, 33% female), neuroblastoma (56% male, 49% female), and osteosarcoma (24% male, 20% female). Conversely, males were less frequently

Table 1. Demographic, tumor, and clinical characteristics of males and females diagnosed with childhood cancer by cancer type, SEER 18 (2000–2014)

	Ia Acute lymphoblastic leukemia		Ib Acute myeloid leukemia		IIa Hodgkin lymphoma		IIb Non-Hodgkin lymphoma		IIc Burkitt lymphoma		IIIa Ependymomas	
	n = 12 050		n = 2770		n = 4201		n = 3126		n = 860		n = 905	
Characteristic	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)
	5235 (43.4)	6815 (56.6)	1311 (47.3)	1459 (52.7)	1929 (45.9)	2272 (54.1)	1149 (36.8)	1977 (63.2)	161 (18.7)	699 (81.3)	419 (46.3)	486 (53.7)
Age at diagnosis, y												
Average (SD)	6.4 (4.9)	7.3 (5.4)	9.0 (6.8)	9.0 (6.6)	15.5 (3.3)	14.5 (4.1)	12.4 (5.3)	12.4 (5.0)	10.1 (5.2)	10.3 (5.0)	6.5 (5.8)	6.6 (5.9)
<1	183 (3.5)	161 (2.4)	158 (12.1)	166 (11.4)	0 (0.0)	0 (0.0)	11 (1.0)	10 (0.5)	0 (0.0)	3 (0.4)	41 (9.8)	51 (10.5)
1–4	2412 (46.1)	2855 (41.9)	321 (24.5)	358 (24.5)	19 (1.0)	52 (2.3)	118 (10.3)	189 (9.6)	29 (18.0)	95 (13.6)	164 (39.1)	189 (38.9)
5–9	1321 (25.2)	1643 (24.1)	163 (12.4)	196 (13.4)	107 (5.6)	274 (12.1)	196 (17.1)	370 (18.7)	50 (31.1)	229 (32.8)	93 (22.2)	93 (19.1)
10–14	817 (15.6)	1098 (16.1)	269 (20.5)	336 (23.0)	444 (23.0)	592 (26.1)	332 (28.9)	547 (27.7)	40 (24.8)	198 (28.3)	60 (14.3)	78 (16.1)
15–19	502 (9.6)	1058 (15.5)	400 (30.5)	403 (27.6)	1359 (70.5)	1354 (59.6)	492 (42.8)	861 (43.6)	42 (26.1)	174 (24.9)	61 (14.6)	75 (15.4)
Race or ethnicity												
Non-Hispanic white	2393 (46.4)	3118 (46.5)	602 (47.0)	673 (47.0)	1170 (61.4)	1261 (56.3)	553 (48.9)	998 (51.6)	86 (53.8)	450 (65.5)	200 (48.7)	246 (51.3)
Black	347 (6.7)	475 (7.1)	157 (12.3)	180 (12.6)	229 (12.0)	266 (11.9)	185 (16.4)	279 (14.4)	23 (14.4)	58 (8.4)	50 (12.2)	56 (11.7)
Asian or Pacific Islander	405 (7.9)	510 (7.6)	124 (9.7)	133 (9.3)	99 (5.2)	153 (6.8)	112 (9.9)	164 (8.5)	9 (5.6)	57 (8.3)	27 (6.6)	35 (7.3)
Hispanic	2017 (39.1)	2600 (38.8)	397 (31.0)	446 (31.2)	408 (21.4)	559 (25.0)	281 (24.9)	493 (25.5)	42 (26.3)	122 (17.8)	134 (32.6)	143 (29.8)
Missing	73	112	31	27	23	33	18	43	1	12	8	6
Tumor size, cm*												
≤2											22 (9.2)	25 (8.9)
>2 to ≤5											113 (47.3)	127 (45.4)
>5											104 (43.5)	128 (45.7)
Missing											180	206
Stage of disease†												
Local					218 (11.6)	370 (16.8)	378 (34.8)	599 (32.0)	47 (29.8)	176 (25.8)	307 (75.4)	364 (78.6)
Regional					1039 (55.4)	955 (43.4)	224 (20.6)	365 (19.5)	26 (16.5)	160 (23.5)	71 (17.4)	71 (15.3)
Distant					620 (33.0)	874 (39.8)	484 (44.6)	908 (48.5)	85 (53.8)	345 (50.7)	29 (7.1)	28 (6.1)
Unknown					52	73	63	105	3	18	12	23
Metastases at diagnosis‡												
No											273 (93.8)	326 (95.3)
Yes											18 (6.2)	16 (4.7)
Missing or unknown											128	144
Vital status												
Alive	4626 (88.4)	5837 (85.7)	839 (64.0)	940 (64.4)	1814 (94.0)	2163 (95.2)	972 (84.6)	1687 (85.3)	143 (88.8)	623 (89.1)	325 (77.6)	343 (70.6)
Dead	609 (11.6)	978 (14.4)	472 (36.0)	519 (35.6)	115 (6.0)	109 (4.8)	177 (15.4)	290 (14.7)	18 (11.2)	76 (10.9)	94 (22.4)	143 (29.4)
Year of diagnosis												
2000–2004	1664 (31.8)	2200 (32.3)	410 (31.3)	483 (33.1)	618 (32.0)	698 (30.7)	356 (31.0)	605 (30.6)	52 (32.3)	233 (33.3)	139 (33.2)	157 (32.3)
2005–2009	1746 (33.4)	2332 (34.2)	447 (34.1)	488 (33.5)	698 (36.2)	810 (35.6)	370 (32.2)	635 (32.1)	59 (36.7)	231 (33.1)	132 (31.5)	157 (32.3)
2010–2014	1825 (34.9)	2283 (33.5)	454 (34.6)	488 (33.5)	613 (31.8)	764 (33.6)	423 (36.8)	737 (37.3)	50 (31.1)	235 (33.6)	148 (35.3)	172 (35.4)

*Tumor size not applicable for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and Burkitt lymphoma (BL). PNET = peripheral neuroectodermal tumor; SEER = Surveillance, Epidemiology, and End Results.

†Stage of disease not applicable for ALL and AML.

‡Metastases at diagnosis not available from 2000 to 2003 for all tumors or for ALL, AML, HL, NHL, BL.

Table 1. (continued)

Characteristic	IIIb Astrocytomas		IIIc.1 Medulloblastoma		IIIc.2 PNET		IVa Neuroblastoma		V Retinoblastoma		VIa Nephroblastoma	
	n = 4538		n = 1323		n = 533		n = 2683		n = 885		n = 2056	
	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)
	2179 (48.0)	2359 (52.0)	485 (36.7)	838 (63.3)	236 (44.3)	297 (55.7)	1297 (48.3)	1386 (51.7)	421 (47.6)	464 (52.4)	1074 (52.2)	982 (47.8)
Age at diagnosis, y												
Average (SD)	8.9 (5.5)	9.4 (5.7)	7.2 (5.1)	7.2 (5.0)	7.3 (5.9)	7.6 (5.7)	2.5 (3.3)	2.5 (3.3)	1.4 (1.8)	1.5 (1.7)	3.5 (3.0)	3.1 (3.0)
<1	97 (4.5)	88 (3.7)	20 (4.1)	38 (4.5)	15 (6.4)	24 (8.1)	405 (31.2)	443 (32.0)	154 (36.6)	148 (31.9)	116 (10.8)	131 (13.3)
1–4	493 (22.6)	527 (22.3)	150 (30.9)	247 (29.5)	91 (38.6)	97 (32.7)	667 (51.4)	714 (51.5)	250 (59.4)	291 (62.7)	657 (61.2)	638 (65.0)
5–9	599 (27.5)	585 (24.8)	175 (36.1)	303 (36.2)	47 (19.9)	69 (23.2)	154 (11.9)	159 (11.5)	13 (3.1)	23 (5.0)	255 (23.7)	176 (17.9)
10–14	554 (25.4)	604 (25.6)	76 (15.7)	159 (19.0)	42 (17.8)	56 (18.9)	57 (4.4)	46 (3.3)	4 (1.0)	2 (0.4)	29 (2.7)	26 (2.7)
15–19	436 (20.0)	555 (23.5)	64 (13.2)	91 (10.9)	41 (17.4)	51 (17.2)	14 (1.1)	24 (1.7)	0 (0.0)	0 (0.0)	17 (1.6)	11 (1.1)
Race or ethnicity												
Non-Hispanic white	1265 (59.2)	1410 (61.0)	262 (54.8)	504 (60.7)	122 (52.1)	166 (56.3)	732 (57.9)	813 (59.4)	169 (40.5)	182 (40.4)	533 (50.6)	522 (54.3)
Black	254 (11.9)	239 (10.3)	51 (10.7)	51 (6.1)	30 (12.8)	30 (10.2)	176 (13.9)	170 (12.4)	71 (17.0)	67 (14.9)	185 (17.6)	156 (16.2)
Asian or Pacific Islander	123 (5.8)	138 (6.0)	38 (8.0)	60 (7.2)	21 (9.0)	17 (5.8)	96 (7.6)	89 (6.5)	39 (9.4)	43 (9.6)	45 (4.3)	44 (4.6)
Hispanic	495 (23.2)	524 (22.7)	127 (26.6)	215 (25.9)	61 (26.1)	82 (27.8)	261 (20.6)	296 (21.6)	138 (33.1)	158 (35.1)	290 (27.5)	239 (24.9)
Missing	42	48	7	8	2	2	32	18	4	14	21	21
Tumor size, cm*												
≤2	175 (15.1)	212 (16.9)	10 (3.3)	20 (3.9)	3 (2.7)	11 (8.4)	34 (4.7)	53 (6.5)	167 (83.1)	160 (86.0)	28 (3.7)	26 (3.9)
>2 to ≤5	637 (54.9)	657 (52.3)	242 (78.6)	387 (75.2)	44 (40.0)	57 (43.5)	227 (31.4)	243 (29.6)	18 (9.0)	13 (7.0)	56 (7.4)	54 (8.0)
>5	349 (30.1)	387 (30.8)	56 (18.2)	108 (21.0)	63 (57.3)	63 (48.1)	463 (64.0)	525 (64.0)	16 (8.0)	13 (7.0)	678 (89.0)	593 (88.1)
Missing	1018	1103	177	323	126	166	573	565	220	278	312	309
Stage of disease†												
Local	1774 (84.8)	1958 (86.0)	334 (70.0)	602 (73.5)	135 (59.2)	167 (59.0)	294 (24.3)	287 (21.7)	294 (76.6)	329 (75.1)	440 (42.4)	430 (45.2)
Regional	264 (12.6)	265 (11.6)	54 (11.3)	75 (9.2)	48 (21.1)	57 (20.1)	322 (26.6)	300 (22.7)	74 (19.3)	83 (19.0)	329 (31.7)	291 (30.6)
Distant	53 (2.5)	55 (2.4)	89 (18.7)	142 (17.3)	45 (19.7)	59 (20.9)	595 (49.1)	737 (55.7)	16 (4.2)	26 (5.9)	268 (25.8)	231 (24.3)
Unknown	88	81	8	19	8	14	86	62	37	26	37	30
Metastases at diagnosis‡												
No	1482 (98.1)	1600 (98.0)	293 (84.4)	491 (83.1)	108 (79.4)	138 (82.1)	461 (51.4)	468 (47.1)	302 (97.7)	296 (99.0)	607 (76.9)	541 (77.5)
Yes	29 (1.9)	32 (2.0)	54 (15.6)	100 (16.9)	28 (20.6)	30 (17.9)	436 (48.6)	525 (52.9)	7 (2.3)	3 (1.0)	182 (23.1)	157 (22.5)
Missing or unknown	668	727	138	247	100	129	400	393	112	165	285	284
Vital status												
Alive	1797 (82.5)	1912 (81.1)	347 (71.6)	589 (70.3)	136 (57.6)	165 (55.6)	1042 (80.3)	1044 (75.3)	411 (97.6)	450 (97.0)	976 (90.9)	895 (91.1)
Dead	382 (17.5)	447 (19.0)	138 (28.5)	249 (29.7)	100 (42.4)	132 (44.4)	255 (19.7)	342 (24.7)	10 (2.4)	14 (3.0)	98 (9.1)	87 (8.9)
Year of diagnosis												
2000–2004	719 (33.0)	810 (34.3)	159 (32.8)	263 (31.4)	112 (47.5)	139 (46.8)	421 (32.5)	440 (31.8)	131 (31.1)	189 (40.7)	326 (30.4)	330 (33.6)
2005–2009	709 (32.5)	757 (32.1)	166 (34.2)	284 (33.9)	68 (28.8)	96 (32.3)	435 (33.5)	493 (35.6)	146 (34.7)	154 (33.2)	370 (34.5)	329 (33.5)
2010–2014	751 (34.5)	792 (33.6)	160 (33.0)	291 (34.7)	56 (23.7)	62 (20.9)	441 (34.0)	453 (32.7)	144 (34.2)	121 (26.1)	378 (35.2)	323 (32.9)

*Tumor size not applicable for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and Burkitt lymphoma (BL).
†Stage of disease not applicable for ALL and AML.
‡Metastases at diagnosis not available from 2000 to 2003 for all tumors or for ALL, AML, HL, NHL, BL.

Table 1. (continued)

Characteristic	VIIa Hepatoblastoma		VIIIa Osteosarcoma		VIIIc Ewing sarcoma		IXa Rhabdomyosarcoma		XIb Thyroid carcinoma		XIb Malignant melanoma	
	n = 603		n = 1743		n = 968		n = 1649		n = 2657		n = 1749	
	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)	Female No. (%)	Male No. (%)
	226 (37.5)	377 (62.5)	782 (44.9)	961 (55.1)	375 (38.7)	593 (61.3)	690 (41.8)	959 (58.2)	2160 (81.3)	497 (18.7)	1001 (57.2)	748 (42.8)
Age at diagnosis, y												
Average (SD)	1.7 (2.5)	1.8 (2.5)	12.6 (3.7)	13.6 (3.7)	11.7 (4.6)	12.5 (4.7)	7.8 (5.7)	8.0 (5.7)	16.0 (3.0)	15.3 (3.7)	15.2 (4.4)	14.9 (4.3)
<1	80 (35.4)	111 (29.4)	1 (0.1)	0 (0.0)	4 (1.1)	3 (0.5)	35 (5.1)	54 (5.6)	1 (0.1)	1 (0.2)	8 (0.8)	4 (0.5)
1–4	126 (55.8)	239 (63.4)	17 (2.2)	16 (1.7)	31 (8.3)	44 (7.4)	239 (34.6)	295 (30.8)	9 (0.4)	5 (1.0)	31 (3.1)	33 (4.4)
5–9	14 (6.2)	16 (4.2)	130 (16.6)	131 (13.6)	78 (20.8)	97 (16.4)	151 (21.9)	232 (24.2)	78 (3.6)	37 (7.4)	83 (8.3)	54 (7.2)
10–14	4 (1.8)	10 (2.7)	375 (48.0)	344 (35.8)	144 (38.4)	211 (35.6)	144 (20.9)	202 (21.1)	430 (19.9)	124 (25.0)	166 (16.6)	150 (20.1)
15–19	2 (0.9)	1 (0.3)	259 (33.1)	470 (48.9)	118 (31.5)	238 (40.1)	121 (17.5)	176 (18.4)	1642 (76.0)	330 (66.4)	713 (71.2)	507 (67.8)
Race or ethnicity												
Non-Hispanic white	108 (48.2)	165 (45.3)	354 (45.8)	436 (45.9)	241 (65.1)	398 (67.8)	345 (50.8)	475 (50.4)	1275 (60.5)	304 (62.8)	836 (87.5)	632 (87.9)
Black	15 (6.7)	29 (8.0)	133 (17.2)	152 (16.0)	10 (2.7)	18 (3.1)	103 (15.2)	151 (16.0)	99 (4.7)	27 (5.6)	14 (1.5)	7 (1.0)
Asian or Pacific Islander	24 (10.7)	47 (12.9)	55 (7.1)	77 (8.1)	24 (6.5)	34 (5.8)	37 (5.5)	72 (7.6)	193 (9.2)	34 (7.0)	19 (2.0)	18 (2.5)
Hispanic	77 (34.4)	123 (33.8)	231 (29.9)	284 (29.9)	95 (25.7)	137 (23.3)	194 (28.6)	244 (25.9)	539 (25.6)	119 (24.6)	87 (9.1)	62 (8.6)
Missing	2	13	9	12	5	6	11	17	54	13	45	29
Tumor size, cm*												
≤ 2	3 (2.0)	8 (3.2)	13 (2.7)	19 (3.3)	11 (5.6)	18 (5.9)	36 (9.1)	32 (5.7)	811 (50.3)	162 (43.0)	176 (81.9)	141 (83.9)
>2 to ≤5	20 (13.3)	27 (10.6)	55 (11.6)	59 (10.2)	49 (24.9)	47 (15.4)	127 (32.0)	203 (36.4)	690 (42.8)	180 (47.8)	24 (11.2)	14 (8.3)
>5	127 (84.7)	219 (86.2)	407 (85.7)	503 (86.6)	137 (69.5)	241 (78.8)	234 (58.9)	323 (57.9)	113 (7.0)	35 (9.3)	15 (7.0)	13 (7.7)
Missing	76	123	307	380	178	287	293	401	546	120	786	580
Stage of disease†												
Local	104 (47.5)	170 (46.8)	274 (36.2)	300 (32.4)	107 (29.7)	168 (30.1)	222 (33.8)	314 (34.0)	1089 (51.1)	221 (45.3)	787 (83.1)	562 (78.0)
Regional	67 (30.6)	109 (30.0)	332 (43.9)	407 (43.9)	138 (38.3)	214 (38.4)	224 (34.2)	313 (33.9)	958 (45.0)	239 (49.0)	142 (15.0)	133 (18.5)
Distant	48 (21.9)	84 (23.1)	150 (19.8)	220 (23.7)	115 (31.9)	176 (31.5)	209 (31.9)	296 (32.1)	83 (3.9)	28 (5.7)	18 (1.9)	26 (3.6)
Unknown	7	14	26	34	15	35	35	36	30	9	54	27
Metastases at diagnosis‡												
No	131 (79.9)	224 (78.6)	454 (80.9)	538 (78.0)	203 (73.0)	296 (70.0)	355 (72.9)	480 (71.5)	1644 (97.5)	376 (95.9)	647 (98.3)	483 (96.4)
Yes	33 (20.1)	61 (21.4)	107 (19.1)	152 (22.0)	75 (27.0)	127 (30.0)	132 (27.1)	191 (28.5)	42 (2.5)	16 (4.1)	11 (1.7)	18 (3.6)
Missing or unknown	62	92	221	271	97	170	203	288	474	105	343	247
Vital status												
Alive	187 (82.7)	296 (78.5)	570 (72.9)	639 (66.5)	276 (73.6)	398 (67.1)	459 (66.5)	642 (66.9)	2146 (99.4)	486 (97.8)	959 (95.8)	688 (92.0)
Dead	39 (17.3)	81 (21.5)	212 (27.1)	322 (33.5)	99 (26.4)	195 (32.9)	231 (33.5)	317 (33.1)	14 (0.7)	11 (2.2)	42 (4.2)	60 (8.0)
Year of diagnosis												
2000–2004	73 (32.3)	111 (29.4)	260 (33.3)	314 (32.7)	119 (31.7)	186 (31.4)	232 (33.6)	322 (33.6)	558 (25.8)	116 (23.3)	396 (39.6)	314 (42.0)
2005–2009	67 (29.7)	117 (31.0)	269 (34.4)	329 (34.4)	118 (31.5)	214 (36.1)	226 (32.8)	331 (34.5)	673 (31.2)	167 (33.6)	350 (35.0)	230 (30.8)
2010–2014	86 (38.0)	149 (39.5)	253 (32.4)	318 (33.1)	138 (36.8)	193 (32.6)	232 (33.6)	306 (31.9)	929 (43.0)	214 (43.1)	255 (25.5)	204 (27.3)

*Tumor size not applicable for acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and Burkitt lymphoma (BL).
†Stage of disease not applicable for ALL and AML.
‡Metastases at diagnosis not available from 2000 to 2003 for all tumors or for ALL, AML, HL, NHL, BL.

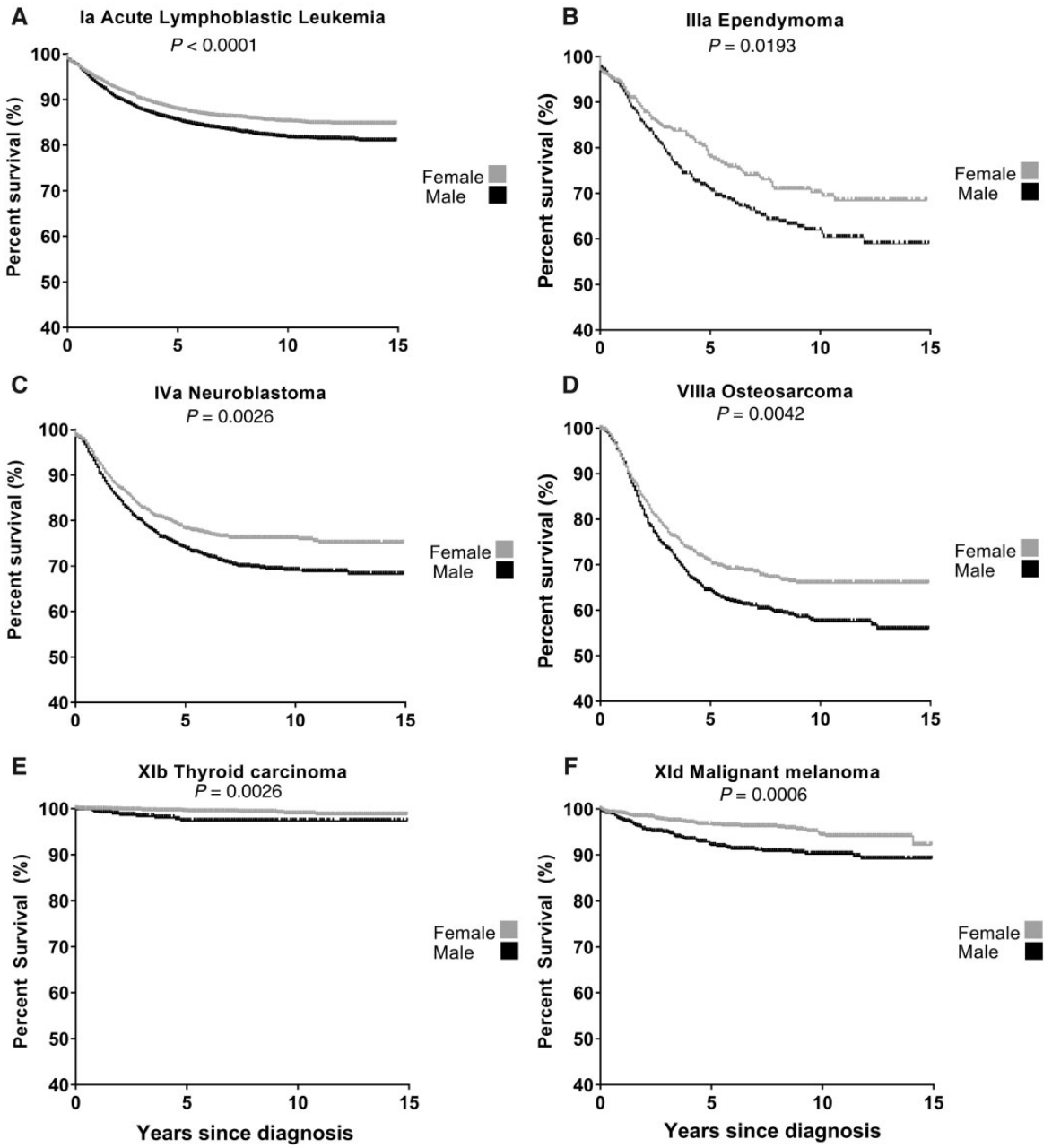

Figure 1. Kaplan-Meier survival curves for cancers with sex differences in overall survival. **A**) Acute lymphoblastic leukemia. **B**) Ependymoma. **C**) Neuroblastoma. **D**) Osteosarcoma. **E**) Thyroid carcinoma. **F**) Malignant melanoma. Surveillance, Epidemiology, and End Results 18 (2000–2014). Two-sided *P* values were calculated using a log-rank test.

diagnosed with local disease for thyroid carcinoma (45% male, 51% female) and malignant melanoma (78% male, 83% female).

Five-year survival differed by sex with males having worse survival proportions (≥3% difference) for ALL (85% male, 88% female), ependymoma (71% male, 78% female), PNET (56% male, 60% female), neuroblastoma (74% male, 78% female), hepatoblastoma (77% male, 82% female), osteosarcoma (64% male, 71% female), Ewing sarcoma (67% male, 71% female), and malignant melanoma (92% male, 97% female) (survival proportions and 95% confidence intervals are in Supplementary Table 2 (available online), event and censor counts are in Supplementary Table 3 (available online)). Males had statistically significantly worse overall survival during the 15-year study period for ALL (log-rank $P < .001$), ependymoma (log rank $P = .02$), neuroblastoma (log rank $P = .003$), osteosarcoma (log rank $P = .004$), thyroid carcinoma (log rank $P = .003$), and malignant melanoma (log rank $P < .001$) (Figure 1A–F). Kaplan-Meier curves and log-rank *P* values for the remaining cancers can be found in Supplementary Figure 1 (available online).

The hazard ratios and 95% confidence intervals for male sex, relative to female sex, and the risk of death were elevated for ALL (HR = 1.24, 95% CI = 1.12 to 1.37), ependymoma (HR = 1.36, 95% CI = 1.05 to 1.77), neuroblastoma (HR = 1.28, 95% CI = 1.09 to 1.51), osteosarcoma (HR = 1.29, 95% CI = 1.08 to 1.53), thyroid carcinoma (HR = 3.25, 95% CI = 1.45 to 7.33), and malignant melanoma (HR = 1.97, 95% CI = 1.33 to 2.92) (Table 2). These results

Table 2. Hazard ratios and 95% confidence intervals for the association between male sex and childhood cancer by cancer type, Surveillance, Epidemiology, and End Results 18 (2000–2014)

	Unadjusted model			Model A*			Model B†		
Cancer type	Female No. (%)	Male No. (%)	HR (95% CI)	Female No. (%)	Male No. (%)	HR (95% CI)	Female No. (%)	Male No. (%)	HR (95% CI)
Ia Acute lymphoblastic leukemia	5235 (43.4)	6814 (56.6)	1.24 (1.12 to 1.37)	5162 (43.5)	6702 (56.5)	1.14 (1.03 to 1.27)			
Ib Acute myeloid leukemia	1311 (47.3)	1459 (52.7)	0.98 (0.87 to 1.11)	1280 (47.2)	1432 (52.8)	0.97 (0.85 to 1.10)			
IIa Hodgkin lymphoma	1928 (45.9)	2271 (54.1)	0.82 (0.63 to 1.06)	1905 (46.0)	2238 (54.0)	0.91 (0.70 to 1.19)	1856 (46.1)	2169 (53.9)	0.92 (0.70 to 1.21)
IIb Non-Hodgkin lymphoma	1146 (36.7)	1975 (63.3)	0.97 (0.80 to 1.17)	1128 (36.9)	1932 (63.1)	0.97 (0.81 to 1.18)	1070 (36.8)	1834 (63.2)	0.92 (0.76 to 1.11)
IIc Burkitt lymphoma	161 (18.7)	699 (81.3)	0.98 (0.59 to 1.64)	160 (18.9)	687 (81.1)	1.01 (0.60 to 1.71)	157 (19.0)	670 (81.0)	1.02 (0.60 to 1.73)
IIIa Ependymomas	418 (46.3)	485 (53.7)	1.36 (1.05 to 1.77)	410 (46.1)	479 (53.9)	1.49 (1.14 to 1.94)	398 (46.5)	457 (53.5)	1.52 (1.15 to 2.00)
IIIb Astrocytomas	2176 (48.0)	2358 (52.0)	1.10 (0.96 to 1.26)	2134 (48.0)	2310 (52.0)	1.09 (0.95 to 1.26)	2051 (47.9)	2232 (52.1)	1.11 (0.96 to 1.28)
IIIc.1 Medulloblastoma	483 (36.6)	837 (63.4)	1.04 (0.84 to 1.28)	476 (36.5)	829 (63.5)	1.05 (0.85 to 1.30)	468 (36.6)	810 (63.4)	1.08 (0.87 to 1.33)
IIIc.2 Peripheral neuroectodermal tumor	235 (44.2)	297 (55.8)	1.09 (0.84 to 1.42)	233 (44.1)	295 (55.9)	1.17 (0.90 to 1.53)	225 (44.5)	281 (55.5)	1.12 (0.85 to 1.47)
IVa Neuroblastoma	1293 (48.4)	1381 (51.6)	1.28 (1.09 to 1.51)	1261 (48.0)	1364 (52.0)	1.33 (1.12 to 1.56)	1182 (47.5)	1305 (52.5)	1.06 (0.90 to 1.26)
V Retinoblastoma	421 (47.6)	464 (52.4)	1.14 (0.51 to 2.58)	417 (48.1)	450 (51.9)	1.37 (0.60 to 3.16)	380 (47.1)	427 (52.9)	1.45 (0.57 to 3.66)
VIa Nephroblastoma	1074 (52.2)	982 (47.8)	0.94 (0.70 to 1.25)	1053 (52.3)	961 (47.7)	0.98 (0.73 to 1.32)	1017 (52.2)	933 (47.8)	0.94 (0.70 to 1.26)
VIIa Hepatoblastoma	225 (37.5)	375 (62.5)	1.29 (0.87 to 1.90)	223 (38.1)	362 (61.9)	1.34 (0.90 to 1.99)	217 (38.3)	349 (61.7)	1.31 (0.87 to 1.98)
VIIIa Osteosarcoma	782 (44.9)	961 (55.1)	1.29 (1.08 to 1.53)	773 (44.9)	949 (55.1)	1.21 (1.02 to 1.45)	749 (45.0)	917 (55.0)	1.16 (0.97 to 1.39)
VIIIc Ewing sarcoma	375 (38.7)	593 (61.3)	1.23 (0.97 to 1.57)	370 (38.7)	587 (61.3)	1.16 (0.90 to 1.48)	355 (39.1)	553 (60.9)	1.17 (0.91 to 1.52)
IXa Rhabdomyosarcoma	690 (41.9)	957 (58.1)	0.98 (0.82 to 1.16)	679 (41.9)	940 (58.1)	0.92 (0.77 to 1.09)	645 (41.6)	907 (58.4)	0.92 (0.77 to 1.10)
XIb Thyroid carcinoma	2160 (81.3)	496 (18.7)	3.25 (1.45 to 7.33)	2106 (81.3)	483 (18.7)	2.53 (1.08 to 5.91)	2079 (81.4)	474 (18.6)	2.20 (0.91 to 5.35)
XId Malignant melanoma	1001 (57.2)	748 (42.8)	1.97 (1.33 to 2.92)	956 (57.1)	719 (42.9)	2.18 (1.45 to 3.28)	907 (56.7)	693 (43.3)	1.83 (1.19 to 2.80)

*Model A adjusted for race, age, and year at diagnosis. CI = confidence interval; HR = hazard ratio.

†Model B adjusted for race, age, and year at diagnosis and stage of disease; stage of disease not available for acute lymphoblastic leukemia, acute myeloid leukemia, and CMD.

Table 3. Hazard ratios and 95% confidence intervals for the association between male sex and the risk of death by cancer type stratified by age at diagnosis category, Surveillance, Epidemiology, and End Results 18 (2000–2014)

Cancer type	Age at diagnosis category				Age-sex *P* interaction
	0–4 years HR* (95% CI)	5–9 years HR* (95% CI)	10–14 years HR* (95% CI)	15–19 years HR* (95% CI)	
Ia Acute lymphoblastic leukemia	1.11 (0.93 to 1.34)	1.28 (1.01 to 1.62)	1.11 (0.90 to 1.37)	1.06 (0.86 to 1.29)	.7
Ib Acute myeloid leukemia	0.92 (0.74 to 1.14)	1.09 (0.75 to 1.57)	1.00 (0.77 to 1.31)	1.03 (0.83 to 1.28)	.8
IIa Hodgkin lymphoma	0.36 (0.02 to 5.71)	2.76 (0.63 to 12.15)	0.84 (0.47 to 1.50)	0.79 (0.58 to 1.08)	.4
IIb Non-Hodgkin lymphoma	0.88 (0.47 to 1.65)	0.69 (0.40 to 1.20)	0.71 (0.50 to 1.00)	1.28 (0.97 to 1.68)	.04
IIc Burkitt lymphoma	†	0.88 (0.30 to 2.64)	0.84 (0.34 to 2.06)	0.88 (0.40 to 1.92)	.9
IIIa Ependymoma	1.44 (1.02 to 2.02)	1.06 (0.59 to 1.88)	1.89 (0.87 to 4.13)	1.24 (0.51 to 3.03)	.7
IIIb Astrocytoma	0.75 (0.54 to 1.03)	1.23 (0.94 to 1.59)	1.15 (0.88 to 1.50)	1.22 (0.94 to 1.59)	.07
IIIc.1 Medulloblastoma	1.27 (0.91 to 1.77)	0.71 (0.50 to 1.02)	1.45 (0.77 to 2.73)	1.15 (0.63 to 2.07)	.09
IIIc.2 Peripheral neuroectodermal tumor	1.34 (0.91 to 1.97)	0.91 (0.50 to 1.65)	0.80 (0.43 to 1.47)	1.18 (0.64 to 2.19)	.5
IVa Neuroblastoma	1.25 (1.03 to 1.50)	1.29 (0.88 to 1.89)	2.39 (1.18 to 4.81)	1.81 (0.56 to 5.82)	.4
V Retinoblastoma	1.15 (0.51 to 2.60)	†	†	†	†
VIa Nephroblastoma	0.99 (0.70 to 1.39)	0.73 (0.37 to 1.42)	1.82 (0.44 to 7.62)	0.97 (0.18 to 5.29)	.7
VIIa Hepatoblastoma	1.28 (0.85 to 1.94)	5.17 (0.63 to 42.11)	0.34 (0.06 to 2.09)	1.41 (0.09 to 23.57)	.2
VIIIa Osteosarcoma	1.45 (0.44 to 4.76)	1.26 (0.77 to 2.05)	1.23 (0.94 to 1.62)	1.24 (0.95 to 1.62)	.9
VIIIc Ewing sarcoma	0.59 (0.20 to 1.75)	1.22 (0.60 to 2.49)	0.91 (0.61 to 1.35)	1.53 (1.05 to 2.21)	.2
IXa Rhabdomyosarcoma	1.21 (0.89 to 1.63)	0.86 (0.57 to 1.30)	0.92 (0.65 to 1.28)	0.83 (0.60 to 1.16)	.3
XIb Thyroid carcinoma	†	†	1.90 (0.37 to 9.89)	5.03 (1.89 to 13.40)	.7
XId Malignant melanoma	0.68 (0.16 to 2.84)	1.52 (0.21 to 10.79)	0.98 (0.40 to 2.41)	2.72 (1.67 to 4.43)	.1

*Unadjusted model. CI = confidence interval; HR = hazard ratio.
†HR, *P* value for an interaction between age category and sex not applicable due to low sample size.

Table 4. Hazard ratios and 95% confidence intervals from the mediation analysis for the association between sex and the risk of death for males, compared with females, diagnosed with ependymoma, neuroblastoma, osteosarcoma, thyroid carcinoma, and malignant melanoma, with stage of disease as the mediator, Surveillance, Epidemiology, and End Results 18 (2000–2014)

Model and cancer type	Indirect		Direct		Total		Change from total to direct effect, %*
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	
Unadjusted model							
IIIa Ependymoma	1.01 (0.97 to 1.05)	.60	1.35 (1.03 to 1.76)	.03	1.36 (1.05 to 1.77)	.02	3
IVa Neuroblastoma	1.12 (1.05 to 1.19)	<.01	1.15 (0.99 to 1.34)	.07	1.28 (1.09 to 1.51)	<.01	44
VIIIa Osteosarcoma	1.06 (1.00 to 1.12)	.05	1.22 (1.03 to 1.43)	.02	1.29 (1.08 to 1.53)	<.01	22
XIb Thyroid carcinoma	1.24 (1.03 to 1.48)	.02	2.63 (1.02 to 6.75)	.04	3.25 (1.27 to 8.35)	.01	18
XId Malignant melanoma	1.28 (1.10 to 1.49)	<.01	1.53 (1.05 to 2.24)	.03	1.97 (1.33 to 2.91)	<.01	37
Model adjusted for race, age at diagnosis, and year of diagnosis							
IIIa Ependymoma	1.03 (0.95 to 1.13)	.44	1.44 (1.07 to 1.92)	.02	1.49 (1.12 to 1.97)	.01	8
IVa Neuroblastoma	1.09 (1.02 to 1.17)	.01	1.22 (1.04 to 1.44)	.01	1.34 (1.13 to 1.59)	<.01	31
VIIIa Osteosarcoma	1.07 (0.99 to 1.15)	.08	1.14 (0.95 to 1.35)	.15	1.21 (1.01 to 1.45)	.04	33
XIb Thyroid carcinoma	1.01 (0.61 to 1.66)	.98	2.59 (0.91 to 7.38)	.08	2.61 (0.95 to 7.19)	.06	1
XId Malignant melanoma	1.23 (1.00 to 1.52)	.05	1.89 (1.19 to 3.03)	.01	2.33 (1.46 to 3.72)	<.01	25

*Percent change from total to direct effect (βtotal − βdirect)/βtotal)*100. CI = confidence interval; HR = hazard ratio.

were generally consistent in direction and magnitude of association in models adjusted for age at diagnosis, race or ethnicity, year of diagnosis, and stage of disease, where applicable.

Because age at diagnosis may modify the association between sex and death for some childhood cancers, we conducted age-stratified analyses. There was heterogeneity in the association between sex and death by age at diagnosis for some cancers (Table 3). Elevated hazard ratios that excluded the null were observed for males aged 0–4 years for ependymoma (HR = 1.44, 95% CI = 1.02 to 2.02) and neuroblastoma (HR = 1.25, 95% CI = 1.03 to 1.50). Among children aged 5–9 years at diagnosis, there was an elevated risk of death among males for ALL (HR = 1.28, 95% CI = 1.01 to 1.62). In adolescents aged 10–14 years at diagnosis, male sex was associated with an increased risk of death for neuroblastoma (HR = 2.39, 95% CI = 1.18 to 4.81). For teens aged 15–19 years, male sex was associated with an increased risk of death for Ewing sarcoma (HR = 1.53, 95% CI = 1.05 to 2.21), thyroid carcinoma (HR = 5.03, 95% CI = 1.89 to 13.40), and malignant melanoma (HR = 2.72, 95% CI = 1.67 to 4.43). Estimates were similar in magnitude and direction when all models were adjusted for race and year at diagnosis (results not shown).

As stage of disease lies on the temporal path between sex and death following a childhood cancer diagnosis, we conducted a mediation analysis treating stage of disease as a mediator for ependymoma, neuroblastoma, osteosarcoma, thyroid

carcinoma, and malignant melanoma (Table 4), which comprised the solid tumors that displayed statistically significant total associations between sex and death. In the first-leg analyses (Supplementary Table 4, available online), male sex was strongly associated with distant stage of disease for neuroblastoma, osteosarcoma, and malignant melanoma. The mediation results (Table 4) revealed a statistically significant direct, but not indirect, effect for male sex and death for ependymoma (direct HR = 1.35, 95% CI = 1.03 to 1.76). In contrast, for neuroblastoma there was a statistically significant indirect, but not direct effect, for sex, operating through stage of disease and death (indirect HR = 1.12, 95% CI = 1.05 to 1.19). Statistically significant indirect and direct effects for sex and death were observed for thyroid carcinoma (indirect HR = 1.24, 95% CI = 1.03 to 1.48; direct HR = 2.63, 95% CI = 1.02 to 6.75) and malignant melanoma (indirect HR = 1.28, 95% CI = 1.10 to 1.49; direct HR = 1.53, 95% CI = 1.05 to 2.24). For osteosarcoma, there was a borderline statistically significant indirect effect for sex and death (indirect HR = 1.06, 95% CI = 1.00 to 1.12) and a statistically significant direct effect for sex and death (direct HR = 1.22, 95% CI = 1.03 to 1.43). Effect estimates were similar in magnitude and direction, though precision was lost, when the mediation analyses were adjusted for age at diagnosis, race or ethnicity, and year of diagnosis.

Finally, we estimated the percentage of male deaths and total deaths that could have been avoided if males experienced the same survival proportions as females for ALL, neuroblastoma, ependymoma, osteosarcoma, thyroid carcinoma, and malignant melanoma during the study period. First, we obtained the number of male deaths for each of these six cancers (n = 1856; Table 1). Then, we calculated the number of males that would have died if males had the same percentage of deaths as females for each of the six tumors (estimated male deaths = 1467). We then calculated the difference between the observed male deaths and the estimated male deaths (n = 388). Finally, we estimated that approximately 13% of total deaths ([388/3082]*100 = 12.6%) and 21% of male deaths ([388/1856]*100 = 20.9%) for these six cancers could have been avoided if males experienced the same survival as females during the 15-year study period.

Discussion

We observed sex differences in survival for a number of pediatric malignancies using the SEER 18 registries. Males had worse overall survival than females, as others have observed (2,5,6). We and others have reported worse survival and an increased risk of death for males diagnosed with ALL (21–23), ependymoma, neuroblastoma, osteosarcoma (24), thyroid carcinoma (25), and malignant melanoma (26,27). We note that the thyroid carcinoma results arise from a very small number of events (n = 25); thus, these results should be interpreted with caution. We observed slight variation in the association between sex and death by age at diagnosis for ALL, ependymoma, neuroblastoma, osteosarcoma, thyroid carcinoma, and malignant melanoma. Importantly, we estimated that one in five male deaths after a diagnosis with ALL, ependymoma, neuroblastoma, osteosarcoma, thyroid carcinoma, or malignant melanoma could have been avoided if males experienced survival as good as females in this population during the study period.

For neuroblastoma, thyroid carcinoma, and malignant melanoma, we found evidence of mediation by stage of disease for the association between sex and death. Notably, 44%, 18%, and 37% of the observed sex differences in the risk of death for neuroblastoma, thyroid carcinoma, and malignant melanoma, respectively, operated through stage of disease in our study. Our findings suggest that factors other than stage of disease at diagnosis may also contribute to the sex differences in survival and risk of death after a childhood cancer diagnosis.

Although the purpose of this study was to identify survival differences between males and females diagnosed with childhood cancer when considering individual tumor types, there are a number of possible mechanisms underlying the male excess in death that may be relevant across cancer types and warrant further study in more appropriate datasets. The identification of sex differences in diagnosis delay, treatment response, tumor biology, or even treatment received may provide insight into the biological and/or social mechanisms underlying the observed male excess in death. In a review article characterizing diagnosis delay for childhood cancer, there was some evidence of a delay in diagnosis for males compared with females, particularly for Ewing sarcoma (28), which we found to differ by sex in tumor size, 5-year survival, and the risk of death among older children (8). However, the scarcity of literature examining the delay in diagnosis for all cancer types using modern cancer classifications and adequate sample sizes highlights the necessity for further investigation into this factor as a potential mechanism for the male excess in death following childhood cancer.

Sex differences in pharmacogenetics may also affect the pharmacokinetics of therapies in male and female children as observed in adults where pharmacokinetic sex differences of up to 40% have been reported (9–11). Although drug development generally focuses on overall therapeutic efficacy, it may be beneficial to also consider sex differences in the response to current and new therapies. In past, present, and future clinical trials, this could be done by comparing and contrasting the therapeutic responses between boys and girls through sex-stratified analyses.

Sex differences in tumor biology may be an important factor in the observed sex differences in survival after a childhood cancer diagnosis. Concerning ALL, where we observed the strongest increased risk of death among males for children aged 5–9 years at diagnosis, there are known differences the distribution of cytogenomic subtypes by age at diagnosis (29), which also have differing prognoses (30,31). However, there is little information available on sex differences in ALL subtypes, particularly the cytogenomic subtypes. With regard to ALL immunophenotype, T-cell ALL, diagnosed in up to 15% of ALL cases, is twice as common among males and is associated with worse outcomes than B-cell ALL (31–33). This sex difference may contribute to the observed increased risk of death among males.

Although ALL has the most well-characterized subtypes of the pediatric tumors with an increased risk of death in males, molecular subtypes with prognostic differences have been identified in neuroblastoma (34), namely, ploidy and *MYCN* status, and ependymoma, which displays sex differences in subtype (3,35); however, subtypes for osteosarcoma have failed to replicate across studies (36). Molecular subtypes for thyroid carcinoma and malignant melanoma are less often characterized. As such, research on sex differences in childhood cancer subtypes may shed light on the contribution of sex differences in tumor biology to the observed survival differences between males and females.

Even though our findings for the association between sex and the risk of death after cancer diagnosis arise from a large, population-based dataset for the main childhood cancers using modern definitions, our study should be interpreted with the

following limitations in mind. SEER does not have complete or detailed treatment data (37) for cases; therefore, we considered stage of disease to be a potential mediator of the association between sex and the risk of death. Because stage is routinely collected by cancer registries contributing to SEER (38), we hypothesized that stage of disease may serve as a surrogate for treatment received. Treatment received is usually determined by risk stratification for pediatric cancers, which generally depends on age, tumor characteristics (ie, size or molecular subtype), and stage of disease but not sex (3,4,34,36). Clinical studies with detailed treatment and stage data are well-suited to study sex differences in treatment received and should consider treatment as a mediator between sex and death in the future. Characterizing sex differences in survival by tumor subtypes or risk groups is beyond the scope of this analysis, but studies with detailed subtype data, such as the *MLL*-rearranged or *ETV6-RUNX1* subtypes of ALL or the *MYCN* status and risk group information for neuroblastoma, would be well-suited to examine these associations (30,39). Finally, consideration of insurance status, which may affect access to care and care utilization, should be evaluated in studies with adequate insurance information to determine the role of insurance status in the observed sex differences in pediatric cancer survival. Because this information is not available in SEER for cases diagnosed before 2007, this was not considered in our analyses.

In conclusion, we observed sex differences in survival for ALL, neuroblastoma, ependymoma, osteosarcoma, thyroid carcinoma, and malignant melanoma using the SEER 18 registries. These six tumor types combined account for approximately one-third of cancer diagnoses among children and adolescents (5) and almost 40% of deaths in SEER data. Approximately 21% of male deaths and 13% of total deaths due to ALL, neuroblastoma, ependymoma, osteosarcoma, thyroid carcinoma, and malignant melanoma could have been avoided if males experienced survival rates equal to those observed among females during the study period. The observed sex differences in survival may depend to some degree on stage of disease but may also depend on factors such as sex differences in diagnosis delay, tumor biology, and receipt and response to treatment, which should be investigated in epidemiologic or clinical studies with detailed molecular tumor and clinical data.

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Notes

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