Health-Related Quality of Life in Adult Survivors of Childhood Wilms Tumor or Neuroblastoma: A Report From the Childhood Cancer Survivor Study

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Background. Long-term survivors of Wilms tumor and neuroblastoma may experience significant late adverse effects from their disease and its therapy. Little is known, however, about the health-related quality of life experienced by these survivors. **Procedure.** Health-related quality of life, measured by the 36-Item Short Form Health Survey (SF-36), was assessed from self-report in adult survivors of Wilms tumor (N = 654) and neuroblastoma (N = 432) who participated in the Childhood Cancer Survivor Study. **Results.** More than 90% of the study population was 18–34 years old at interview, and 58% were females. There was no significant difference on any SF-36 subscale or summary scale between the two diagnostic groups. On average, survivors reported no decrement on the Physical Component Summary scale of the SF-36 when compared to population norms. However, both groups scored significantly below the population mean score (50) on the Mental Component Summary Scale of the SF-36 (Wilms tumor mean = 41.66, standard error = 2.19, $P < 0.0001$; neuroblastoma mean = 42.41, standard error = 2.23, $P < 0.0001$) reflecting decreased emotional health. Independent risk factors for lower scores on this scale included female gender, Native American race, unemployment, and household income below $20,000. **Conclusions.** Adult survivors of childhood Wilms tumor and neuroblastoma do not differ from population norms on most health-related quality of life (HRQL) measures. These data, however, indicate that the emotional well being of adult survivors may be compromised. Health care providers should be aware of the risk of adverse outcomes in emotional health even many years after treatment and cure. Pediatr Blood Cancer 2007;49:704–715. © 2006 Wiley-Liss, Inc.

Key words: health-related quality of life; neuroblastoma; survivorship; Wilms tumor

INTRODUCTION

Neuroblastoma and Wilms tumor are the two most common extracranial solid tumors in children younger than age 15 years, accounting for approximately 13.6% of malignancies in the pediatric population [1]. Similarities between these tumors include their embryonal origin, a peak incidence in children younger than 5 years of age, and a predominantly abdominal presentation (65% of neuroblastomas and all Wilms tumors) [2]. However, Wilms tumor is associated with a high rate of cure [3], while children with high-risk neuroblastoma fare poorly despite intensive therapy [4]. In Wilms tumor, the evolution of therapy has focused on achieving higher cure rates with a minimization of long-term adverse effects. Although there has been a similar focus in children with low or intermediate risk neuroblastoma, treatment of patients with high-risk disease has become increasingly intensified [5]. In prior treatment eras, children with Wilms tumor and low or intermediate risk neuroblastoma were exposed to more aggressive multimodal therapies, including radical surgery, orthovoltage radiation, and chemotherapy. Consequently, long-term survivors of low or intermediate risk neuroblastoma as well as Wilms tumor may experience significant long-term adverse effects.

Although several publications have described the long-term medical complications from Wilms tumor [6–11] and neuroblastoma [12–19], there are few studies describing the health-related quality of life (HRQL) of these survivors. Barr and colleagues compared HRQL between survivors of Wilms tumor (stages 2–5) and advanced neuroblastoma (stage 4 and inoperable stage 3) using the Health Utilities Index (HUI) in a cohort of 78 patients, 5 years after completion of their therapy [20]. There was no difference in mean overall HRQL utility scores between the two populations, although survivors of Wilms tumor were more likely to be assessed by their parents as having no disabilities. Survivors of neuroblastoma had a higher frequency of deficits in

hearing and speech, which is consistent with the high doses of cisplatin that are typically included in treatment regimens for high-risk disease [21,22]. In another study of 19 patients receiving therapy for high-risk neuroblastoma, decrements in HRQL were noted during the period immediately following diagnosis and in the first few weeks after bone marrow transplantation [23]; however, this study did not assess long-term outcomes. The greatest morbidity was observed in the pain, self-care, mobility, and emotion domains.

The goal of the present study was to assess HRQL in long-term survivors of Wilms tumor and neuroblastoma, and to examine the sociodemographic, disease and treatment variables that influence these outcomes. We examined data from the Childhood Cancer Survivor Study (CCSS), a follow-up study of approximately 14,000

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long-term survivors of pediatric cancer [24]. This cohort includes a considerably larger group of survivors of Wilms tumor and neuroblastoma and a longer period of follow-up than the above-mentioned studies. Our primary a priori hypothesis was that the prevalence of adverse outcomes in HRQL would be higher in survivors of neuroblastoma than in survivors of Wilms tumor.

PATIENTS AND METHODS

Childhood Cancer Survivor Study (CCSS)

The survivors of Wilms tumor and neuroblastoma evaluated in this study are a subset of the 14,370 participants in the CCSS. The methodology of the CCSS and a description of the study participants have been published in detail previously [24]. Briefly, the CCSS is a multi-institutional study aimed at determining the late adverse outcomes following treatment for cancer during childhood or adolescence. The CCSS cohort consists of survivors of childhood cancer who were diagnosed before the age of 21 years between 1970 and 1986, and who were alive at least 5 years from their original diagnosis. At the time of study enrollment (1995–1996 for most participants), a comprehensive baseline questionnaire was completed by the participant (if aged 18 years or older) or his or her parent (if younger than age 18 years), and detailed medical information was abstracted from hospital records. Several subsequent questionnaires have been completed by the study participants, including a questionnaire on quality of life that is the basis for this analysis. The study methodology was approved by the Institutional Review Board of each of the 26 participating institutions and informed consent was obtained from each participant or his or her parent or guardian.

Survivors of Wilms Tumor or Neuroblastoma

Eligibility for this analysis of CCSS participants was limited to those diagnosed with Wilms tumor or neuroblastoma who were aged 18 years or older at the time of the CCSS follow-up questionnaire that was administered in 2002 and 2003. Information regarding HRQL and current sociodemographic status (age at interview, household income, health insurance, education, marital status, employment status) were obtained as part of this follow-up questionnaire. Baseline demographics (gender, race), disease variables (diagnosis, age at diagnosis, location of tumor in neuroblastoma patients), and treatment variables (chemotherapy including alkylating agent score and anthracycline score, surgery including history of laminectomy, laparotomy, nephrectomy or thoracotomy, and radiation field and dose) were abstracted from the CCSS database. These data were also used to determine if participants had a major medical condition. This composite measure was defined as the presence of one or more of seizures, congestive heart failure, myocardial infarction, stroke, cirrhosis, pulmonary disease requiring oxygen, solid organ transplant, second malignancy, amputation, or joint replacement [25].

Measures of Health-Related Quality of Life

HRQL was assessed with the 36-Item Short Form Health Survey (SF-36). The SF-36 is a widely used and well-validated global HRQL instrument that contains eight individual subscales representing physical, emotional, and social well being [26]. These subscales are physical function, role function—physical (assessing role limitations caused by physical factors), bodily pain, social function, mental health, role function—emotional (assessing role limitations caused by emotional factors), vitality, and general health. The SF-36 can also be scored as two summary scales, the Physical Component Summary scale (PCS) and the Mental Component Summary scale (MCS). General population norms are available for the subscales and summary scales [27]. Data are normalized and presented as t-scores with a normal population mean score set at 50 with a standard deviation of 10.

Statistical Analysis

Descriptive statistics for the sociodemographic, disease and treatment variables were calculated separately for the Wilms tumor and neuroblastoma survivor groups. Means and standard deviations were calculated for the eight subscales and two summary scales of the SF-36, stratified by diagnosis, sociodemographic variables, and the presence or absence of a major medical condition. Means were compared between the two diagnostic groups and between levels of the sociodemographic variables with two sample t-tests. General linear regression was used to evaluate the association between diagnosis, sociodemographic variables, major medical condition, and each of the HRQL outcomes in adjusted models [28]. Results are reported as means and standard deviations with two-sided P-values.

To determine the diagnostic and treatment characteristics of the survivors who indicated poor HRQL, we dichotomized those patients with complete treatment data into two groups for each SF-36 subscale and summary scale. Individuals who scored lower than 40 (greater than one standard deviation below the mean) on any of the SF-36 subscales or summary scales were considered to have poor HRQL in that domain. Frequencies and percents of poor outcomes on each of the SF-36 subscales and summary scales were calculated separately for Wilms tumor and neuroblastoma survivors by diagnostic and treatment variables, and proportions were compared with Chi-squared tests. Multiple variable unconditional logistic regression was used to evaluate the magnitude of the associations between diagnostic and treatment variables and poor HRQL. Final models were selected using goodness of fit methods and by comparing Chi-squared values between full and reduced models [29]. Results are reported as adjusted odds ratios with 95% confidence intervals. SAS version 9.1 (Cary, N.C.) was used for all analyses.

RESULTS

Characteristics of the Study Cohort

A total of 1,440 patients (843 Wilms tumor, 597 neuroblastoma) were eligible for these analyses. Of these, 654 (77.6%) Wilms tumor survivors and 432 (72.4%) neuroblastoma survivors completed the HRQL follow-up questionnaire. The 1,086 study participants were statistically similar to the 354 eligible non-participants in terms of employment status and current health insurance, but differed significantly for several other sociodemographic characteristics. Non-participants tended to be somewhat younger than participants (48.9% vs. 43.0% age 18–24 years), were more likely to be of Black race (10.7% vs. 3.5%), were less likely to have a college degree (25.7% vs. 40.3%), were more likely to be in the lowest annual

household income category (14.1% vs. 9.7% with <$20,000), and were more likely to have a major medical condition (12.7% vs. 8.9%). The sociodemographic characteristics of the study participants are displayed in Table I. Survivors of neuroblastoma were younger and more likely to describe themselves as "single" than were survivors of Wilms tumor.

Treatment data were available for 1,019 of the 1,086 patients who completed the HRQL follow-up questionnaire. Diagnosis and treatment characteristics of these survivors are shown in Table II. Survivors of Wilms tumor were more likely than survivors of neuroblastoma to have received either chemotherapy or radiation, to have received an anthracycline, or radiation to the abdomen or pelvis, or to have undergone a nephrectomy. In contrast, survivors of neuroblastoma were more likely than survivors of Wilms tumor to have been followed for a longer period of time from diagnosis, to have been treated with either surgery alone or surgery and radiation (compared to treatment with combined modality therapy that includ-

ed chemotherapy), to have received an alkylating agent, or radiation to the head, neck or spine, or to have undergone a laminectomy or thoracotomy.

HRQL Outcomes

Adjusted mean scores on the PCS and MCS are displayed in Table III by sociodemographic variables and diagnostic category. There was no difference between the Wilms tumor and neuroblastoma survivors on either of the two summary scales. Overall, survivors who were looking for work or unable to work (compared to those employed or not seeking paid work) and those without health insurance (compared to those with health insurance) scored significantly lower on the PCS (indicating decreased HRQL due to poor physical function), while patients aged 18–24 years scored significantly higher on the PCS than those older than age 35 years. On the MCS, both the Wilms tumor (mean = 41.66, SE = 2.19)

TABLE I. Characteristics of the Study Population

	Wilms tumor		Neuroblastoma		Total		
	N = 654		N = 432		N = 1,086		
	N	%	N	%	N	%	P-value*
Age group at the time of questionnaire							0.007
18–24 years	261	(39.9)	206	(47.7)	467	(43.0)	
25–34 years	343	(52.4)	203	(47.0)	546	(50.3)	
35+ years	50	(7.6)	23	(5.3)	73	(6.7)	
Gender							0.94
Female	383	(58.6)	252	(58.3)	635	(58.5)	
Male	271	(41.4)	180	(41.7)	451	(41.5)	
Race/ethnicity							0.65
White	589	(90.1)	401	(92.8)	990	(91.2)	
Native American	4	(0.6)	2	(0.5)	6	(0.6)	
Asian	4	(0.6)	6	(1.4)	10	(0.9)	
Black	30	(4.6)	8	(1.9)	38	(3.5)	
Hispanic	25	(3.8)	11	(2.5)	36	(3.3)	
Other	2	(0.3)	4	(0.9)	6	(0.6)	
Household income (annual)							0.57
<$20,000	63	(9.6)	42	(9.7)	105	(9.7)	
$20–59,000	270	(41.3)	185	(42.8)	455	(41.9)	
$60–99,999	163	(24.9)	93	(21.5)	256	(23.6)	
$1,00,000+	82	(12.5)	44	(10.2)	126	(11.6)	
Unknown	76	(11.6)	68	(15.7)	144	(13.3)	
Education							0.88
<High school	26	(4.0)	19	(4.4)	45	(4.1)	
High school graduate	362	(55.4)	235	(54.4)	597	(55.0)	
College graduate	262	(40.1)	176	(40.7)	438	(40.3)	
Unknown	4	(0.6)	2	(0.5)	6	(0.6)	
Marital status							<0.0001
Married or living as married	304	(46.5)	141	(32.6)	445	(41.0)	
Single	323	(49.4)	275	(63.7)	598	(55.1)	
Divorced or separated	20	(3.1)	13	(3.0)	33	(3.0)	
Unknown	7	(1.1)	3	(0.7)	10	(0.9)	
Employment							0.84
Employed or caring for home	445	(68.0)	287	(66.4)	732	(67.4)	
Looking for work or unable to work	64	(9.8)	39	(9.0)	103	(9.5)	
Student	145	(22.2)	106	(24.5)	251	(23.1)	
Current health insurance	573	(87.6)	377	(87.3)	950	(87.5)	0.87
Major medical condition	54	(8.3)	43	(10.0)	97	(8.9)	0.34

*P-value reported for Chi-squared comparison of Wilms tumor versus neuroblastoma.

TABLE II. Diagnosis and Treatment Characteristics*

	Wilms tumor		Neuroblastoma		Total		
	N = 612		N = 407		N = 1,019		
	N	%	N	%	N	%	P-value**
Age at diagnosis (Wilms tumor)							
<2 years	193	(31.5)					
2–5 years	334	(54.6)					
6+ years	85	(13.9)					
Age at diagnosis (neuroblastoma)							
≤ 1 year			219	(53.8)			
1+ years			188	(46.2)			
Survival time							0.006
16–20 years	243	(39.7)	122	(30.0)	365	(35.8)	
21–25 years	193	(31.5)	149	(36.6)	342	(33.6)	
26–30 years	135	(22.1)	96	(23.6)	231	(22.7)	
31–35 years	41	(6.7)	40	(9.8)	81	(7.9)	
Treatment modalities[a]							
Chemotherapy	601	(98.2)	237	(58.2)	838	(82.2)	<0.0001
Radiation	393	(64.2)	203	(49.9)	596	(58.5)	0.0001
Surgery	612	(100.0)	400	(98.3)	1,012	(99.3)	0.001
Treatment regimen							
Surgery alone	9	(1.5)	103	(25.3)	112	(11.0)	<0.0001
Chemotherapy +/− surgery	210	(34.3)	102	(25.1)	312	(30.6)	0.002
Radiation +/− surgery	3	(0.5)	67	(16.5)	70	(6.9)	<0.0001
Chemotherapy and radiation +/− surgery	390	(63.7)	135	(33.2)	525	(51.5)	<0.0001
Anthracyclines received							<0.0001
Yes	224	(36.6)	93	(22.9)	317	(31.1)	
No	388	(63.4)	314	(77.1)	702	(68.9)	
Alkylating agents received							<0.0001
Yes	46	(7.5)	193	(47.4)	239	(23.5)	
No	566	(92.5)	214	(52.6)	780	(76.5)	
Radiation therapy site							
Head or cranial	0	(0.0)	41	(10.1)	41	(10.1)	<0.0001
Neck	4	(0.7)	30	(7.4)	34	(3.3)	<0.0001
Chest	134	(21.9)	79	(19.4)	213	(20.9)	0.15
Abdomen	373	(60.9)	113	(27.8)	486	(47.7)	<0.0001
Spine	0	(0.0)	13	(3.2)	13	(1.3)	<0.0001
Pelvis	188	(30.7)	64	(15.7)	252	(24.7)	<0.001
Limb	0	(0.0)	7	(1.7)	7	(0.7)	0.36
Total body	0	(0.0)	7	(1.7)	7	(0.7)	0.36
Surgical procedures							
Laminectomy	0	(0.0)	22	(5.4)	22	(2.2)	<0.0001
Laparotomy	170	(27.8)	126	(31.0)	296	(29.0)	0.15
Nephrectomy	576	(94.1)	23	(5.7)	599	(58.8)	<0.0001
Thoracotomy	16	(2.6)	55	(13.5)	71	(7.0)	<0.0001
Treatment era							0.91
1970–1979	262	(42.8)	210	(51.6)	472	(46.3)	
1980–1986	350	(57.2)	197	(48.4)	547	(53.7)	

*Limited to those with complete treatment data; **P-value reported for Chi-squared or Fisher exact test comparison of Wilms tumor versus neuroblastoma; [a]Patients may have been treated with more than one modality.

and neuroblastoma (mean = 42.41, SE = 2.23) groups scored almost one standard deviation below the population mean of 50 (P < 0.0001 for both comparisons). Females (compared to males), Native Americans (compared to those who identified themselves as white), and those with an annual household income less than $20,000 (compared to a household income greater than $100,000) scored significantly lower on the MCS.

Table IV demonstrates the adjusted mean SF-36 subscale scores by diagnostic group and sociodemographic variables. As with the two summary scales, there were no differences between the Wilms tumor and neuroblastoma survivors on any of the eight subscales. Females scored significantly lower than males on all of the subscales except for bodily pain. Physical function scores were lower in those survivors who had not graduated from college, were looking for work or unable

TABLE III. Adjusted Mean Scores on SF-36 Summary Scales

	PCS			MCS		
	Mean[b]	SE	P-value	Mean[b]	SE	P-value
Diagnosis						
Wilms[a]	54.17	1.43		41.66	2.19	
Neuroblastoma	53.42	1.45	0.15	42.41	2.23	0.36
Age group						
18–24 years	55.92	1.44	<0.001	41.74	2.21	0.36
25–34 years	53.62	1.42	0.09	40.99	2.18	0.14
35+ years[a]	51.83	1.70		43.37	2.60	
Gender						
Male[a]	54.31	1.43		43.79	2.20	
Female	53.28	1.45	0.05	40.28	2.22	<0.001
Race/ethnicity						
White[a]	51.53	1.18		46.24	1.81	
Native American	55.01	3.60	0.31	31.34	5.52	<0.001
Asian	55.00	2.89	0.19	37.66	4.43	0.03
Black	52.08	1.74	0.69	48.91	2.67	0.21
Hispanic	51.48	1.76	0.97	48.69	2.70	0.26
Other	57.66	3.45	0.08	39.38	5.29	0.20
Household income (annual)						
<$20,000	52.13	1.57	0.02	38.02	2.41	<0.001
$20–59,999	53.21	1.44	0.05	43.14	2.20	0.84
$60–99,000	55.16	1.51	0.77	43.76	2.31	0.80
$100,000+[a]	54.89	1.60		43.40	2.45	
Education						
<High school	51.95	1.84	0.05	40.15	2.81	0.09
High school graduate	54.69	1.45	<0.001	43.79	2.22	0.07
College graduate[a]	52.93	1.38		42.20	2.11	
Marital status						
Married or living as married[a]	52.43	1.49		43.23	2.28	
Single	51.93	1.52	0.42	43.72	2.32	0.61
Divorced or separated	54.14	2.05	0.15	39.01	3.15	0.04
Employment						
Employed or caring for home[a]	56.10	1.47		42.92	2.25	
Looking for work or unable to work	48.95	1.52	<0.001	40.50	2.32	0.09
Student	56.33	1.55	0.74	42.69	2.37	0.83
Health insurance						
Yes[a]	54.87	1.54		42.01	2.35	
No	52.72	1.41	0.01	42.06	2.16	0.97
Major medical condition						
No[a]	54.53	1.39		42.93	2.13	
Yes	53.06	1.58	0.11	41.14	2.42	0.20

PCS, physical component summary scale; MCS, mental component summary scale; SE, standard error; [a]Reference category; [b]Adjusted for all of the other variables in the model.

to work, had an annual household income less than $20,000, did not have health insurance, or reported a major medical condition.

The results of the multiple variable models evaluating the association between diagnostic and treatment variables and poor outcome (score < 40) on the summary scales or subscales of the SF-36 are shown in Tables V and VI, stratified for the two diagnostic categories. In survivors of Wilms tumor (Table V), the final model included gender, age group at questionnaire, chest radiation, abdominal radiation, and pelvic radiation. After adjusting for the other variables in the model, no variable was associated significantly with a poor PCS score. However, females were more likely to have a poor MCS score than males (OR = 1.67, 95% CI = 1.1–2.5, $P < 0.05$). Female gender was also associated with a significantly increased risk of a poor outcome on the general health (OR = 2.13,

95% CI = 1.3–3.4, $P < 0.05$), vitality (OR = 1.89, 95% CI = 1.3–2.7, $P < 0.05$), and role function—emotional (OR = 1.90, 95% CI = 1.3–2.8, $P < 0.05$) subscales. Pelvic radiation was associated with poor outcome on the role function—physical subscale (OR = 1.80, 95% CI = 1.0–3.3, $P < 0.05$).

In survivors of neuroblastoma (Table VI), the final model included gender, age at questionnaire, survival time, abdominal radiation, spinal radiation, pelvic radiation, and laminectomy. As with Wilms tumor, no variable was associated with a poor PCS score. Again, females were more likely to have a poor MCS score than males (OR = 1.66, 95% CI = 1.0–2.8, $P < 0.05$). Female gender was also associated with a significantly increased risk of a poor outcome on the role function—physical (OR = 2.07, 95% CI = 1.1–4.0, $P < 0.05$), general health (OR = 2.10, 95% CI = 1.2–

TABLE IV. Adjusted Mean Scores on SF-36 Subscales

	Physical function			Role physical			Bodily pain			General health		
	Mean[b]	SE	P-value	Mean[b]	SE	P-value	Mean[b]	SE	P-value	Mean[b]	SE	P-value
Diagnosis												
Wilms tumor[a]	52.52	1.15		52.39	1.87		53.27	1.53		48.81	1.73	
Neuroblastoma	52.02	1.16	0.24	52.09	1.90	0.65	52.84	1.56	0.44	48.99	1.76	0.77
Age group at the time of questionnaire												
18–24 years	53.61	1.15	0.01	53.58	1.88	0.14	55.06	1.54	0.00	50.71	1.74	0.05
25–34 years	52.09	1.14	0.25	51.80	1.86	0.74	52.92	1.52	0.12	48.07	1.72	0.91
35+ years[a]	51.11	1.36		51.34	2.22		51.18	1.82		47.92	2.06	
Gender												
Male[a]	52.87	1.15		53.09	1.87		53.35	1.54		50.59	1.73	
Female	51.67	1.16	0.004	51.40	1.89	0.01	52.76	1.55	0.30	47.22	1.75	<0.001
Race/ethnicity												
White[a]	51.13	0.95		51.91	1.54		51.77	1.27		48.54	1.43	
Native American	54.86	2.89	0.18	49.26	4.71	0.56	50.26	3.86	0.68	42.08	4.36	0.12
Asian	53.40	2.32	0.29	53.22	3.78	0.70	52.43	3.10	0.82	50.19	3.50	0.61
Black	51.65	1.40	0.64	52.80	2.28	0.63	53.20	1.87	0.34	50.24	2.11	0.31
Hispanic	51.95	1.41	0.47	50.76	2.30	0.54	52.90	1.89	0.46	51.22	2.13	0.12
Other	50.62	2.77	0.85	55.51	4.51	0.43	57.75	3.70	0.11	51.12	4.18	0.54
Household income (annual)												
<$20,000	49.68	1.26	<0.001	49.63	2.06	0.01	51.63	1.68	0.09	46.85	1.90	0.02
$20–59,999	52.26	1.15	0.08	52.28	1.87	0.18	52.59	1.54	0.22	48.59	1.74	0.14
$60–99,000	53.11	1.21	0.63	54.33	1.97	0.65	54.22	1.61	0.60	50.99	1.82	0.43
$100,000+[a]	53.46	1.28		53.79	2.09		53.71	1.71		50.13	1.94	
Education												
< High school	50.36	1.47	0.01	50.64	2.40	0.89	49.69	1.97	<0.001	47.58	2.22	0.02
High school graduate	53.12	1.16	0.001	50.89	1.90	0.29	55.43	1.55	<0.001	51.42	1.76	<0.001
College graduate[a]	51.62	1.10		50.09	1.80		52.59	1.47		49.09	1.66	
Marital status												
Married or living as married[a]	51.69	1.19		51.82	1.94		52.15	1.59		47.42	1.80	
Single	52.11	1.21	0.40	51.68	1.98	0.86	51.39	1.62	0.25	47.37	1.83	0.95
Divorced or separated	52.43	1.65	0.80	51.34	2.68	0.87	52.51	2.20	0.49	48.34	2.48	0.60
Employment												
Employed or caring for home[a]	54.97	1.18		55.30	1.92		54.59	1.57		49.84	1.77	
Looking for work or unable to work	47.27	1.21	<0.001	46.40	1.98	<0.001	49.53	1.62	<0.001	46.15	1.83	0.00
Student	54.57	1.24	0.47	55.02	2.02	0.76	55.04	1.66	0.54	50.71	1.87	0.30
Health insurance												
Yes	53.16	1.23	0.01	53.30	2.01	0.04	54.11	1.65	0.01	48.95	1.86	0.91
No	51.38	1.13		51.18	1.84		51.99	1.51		48.85	1.70	
Major medical condition												
No	53.25	1.11		52.80	1.82		53.53	1.49		50.27	1.68	
Yes	51.29	1.27	0.01	51.69	2.06	0.35	52.57	1.69	0.32	47.53	1.91	0.01

(Continued)

TABLE IV. (Continued)

	Vitality			Social function			Role emotional			Mental health		
	Mean[b]	SE	P-value	Mean[b]	SE	P-value	Mean[b]	SE	P-value	Mean[b]	SE	P-value
Diagnosis												
Wilms tumor[a]	40.23	2.00		46.81	1.59		41.28	2.64		49.55	1.67	
Neuroblastoma	39.97	2.03	0.72	46.30	1.62	0.38	42.41	2.68	0.24	50.08	1.69	0.38
Age group												
18–24 years	40.75	2.01	0.76	47.37	1.60	0.56	41.97	2.66	0.81	49.76	1.68	0.49
25–34 years	39.29	1.98	0.51	45.65	1.58	0.41	41.06	2.62	0.46	49.01	1.66	0.18
35+ years[a]	40.26	2.38		46.63	1.89		42.49	3.14		50.68	1.98	
Gender												
Male[a]	42.07	2.00		47.46	1.60		43.84	2.65		50.79	1.67	
Female	38.13	2.02	<0.001	45.65	1.61	0.002	39.84	2.68	<0.001	48.84	1.69	0.001
Race/ethnicity												
White[a]	41.77	1.65		49.18	1.31		45.62	2.18		51.94	1.38	
Native American	36.57	5.03	0.28	41.07	4.01	0.03	29.79	6.66	0.01	43.00	4.20	0.03
Asian	32.57	4.04	0.01	41.73	3.22	0.01	41.56	5.35	0.41	48.08	3.37	0.21
Black	44.49	2.44	0.17	50.46	1.94	0.41	48.30	3.22	0.30	53.83	2.03	0.25
Hispanic	42.23	2.46	0.82	50.02	1.96	0.60	48.54	3.25	0.27	54.09	2.05	0.20
Other	42.97	4.82	0.80	46.85	3.84	0.55	37.24	6.38	0.19	47.96	4.03	0.33
Household income (annual)												
<$20,000	35.94	2.20	0.26	42.91	1.75	0.36	38.17	2.91	0.01	46.62	1.83	0.00
$20–59,999	40.46	2.00	0.81	47.10	1.60	0.51	42.86	2.65	0.66	50.60	1.67	0.99
$60–99,000	41.48	2.10	<0.001	48.64	1.68	<0.001	43.68	2.78	0.94	51.12	1.76	0.64
$100,000+[a]	41.80	2.24		47.97	1.78		43.55	2.96		50.62	1.87	
Education												
< High school	39.23	2.57	0.01	44.40	2.04	0.13	38.82	3.39	0.11	48.22	2.14	0.07
High school graduate	44.03	2.03	0.05	46.73	1.61	0.01	42.87	2.68	0.06	51.12	1.69	0.05
College graduate[a]	42.45	1.92		45.00	1.53		40.86	2.54		49.82	1.60	
Marital status												
Married or living as married[a]	40.60	2.08		46.74	1.65		42.09	2.75		51.10	1.73	
Single	39.01	2.12	0.06	47.36	1.68	0.36	42.87	2.80	0.49	51.84	1.77	0.30
Divorced or separated	37.50	2.87	0.48	45.09	2.28	0.18	39.35	3.79	0.21	47.60	2.39	0.02
Employment												
Employed or caring for home[a]	40.56	2.05		48.52	1.63		43.99	2.71		50.80	1.71	
Looking for work or unable to work	38.89	2.12	0.21	42.94	1.69	<0.001	38.91	2.80	<0.001	47.21	1.77	0.001
Student	40.85	2.16	0.76	48.21	1.72	0.69	42.63	2.86	0.29	51.43	1.80	0.44
Health insurance												
Yes	40.69	2.15	0.29	47.25	1.71	0.12	42.19	2.84	0.64	49.68	1.79	0.78
No	39.51	1.97		45.86	1.57		41.49	2.60		49.95	1.64	
Major medical condition												
No	40.92	1.94		47.28	1.55		42.84	2.57		50.70	1.62	
Yes	39.28	2.21	0.19	45.83	1.76	0.15	40.85	2.92	0.23	48.93	1.84	0.09

[a]Reference category, SE, standard error; [b]Adjusted for all of the other variables in the model.

TABLE V. Odds Ratios* and 95% Confidence Intervals for Scoring More Than one Standard Deviation Below the Mean on the SF-36 Summary Scales or Subscales by Diagnosis and Treatment Variables in Wilms Tumor Survivors

	Physical function		Role physical		Bodily pain		General health		Vitality		Social function		Role emotional		Mental health		PCS		MCS	
N (%)[c]	45 (7.4)		86 (14.1)		57 (9.3)		101 (16.5)		224 (36.6)		108 (17.7)		158 (25.8)		62 (10.1)		58 (9.5)		132 (21.6)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Gender																				
Male[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	1.39	0.7–2.7	1.20	0.7–1.9	1.39	0.8–2.5	2.13[b]	1.3–3.4	1.89[b]	1.3–2.7	1.46	0.9–2.2	1.90[b]	1.3–2.8	1.45	0.8–2.5	1.22	0.7–2.1	1.67[b]	1.1–2.5
Age group at the time of questionnaire																				
18–24 years[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
25–34 years	1.34	0.5–3.7	1.52	0.7–3.5	0.55	0.2–1.9	1.17	0.5–2.7	1.11	0.6–2.1	0.69	0.3–1.7	0.75	0.3–1.6	0.67	0.2–2.3	0.83	0.3–2.5	0.67	0.3–1.6
35 + years	1.80	0.6–5.5	1.18	0.5–2.8	0.83	0.2–3.0	1.04	0.4–2.5	1.17	0.6–2.3	0.79	0.3–2.0	0.57	0.2–1.3	0.64	0.2–2.3	0.98	0.3–3.1	0.60	0.3–1.4
Chest radiation																				
No[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.14	0.5–2.3	1.15	0.6–2.1	0.94	0.5–1.8	0.60	0.2–1.1	0.89	0.6–1.4	1.64[b]	1.0–2.8	1.74[b]	1.1–2.8	1.44	0.7–2.9	1.00	0.5–1.9	1.26	0.8–2.1
Abdominal radiation																				
No[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.64	0.7–3.9	0.78	0.4–1.5	1.27	0.6–2.7	1.32	0.7–2.3	0.85	0.5–1.3	0.54	0.3–1.0	0.87	0.5–1.4	0.51	0.2–1.2	1.19	0.5–2.5	0.93	0.5–1.5
Pelvic radiation																				
No[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.11	0.5–2.3	1.80[b]	1.0–3.3	1.45	0.7–2.8	1.08	0.6–1.8	1.19	0.8–1.8	1.61	0.9–1.8	1.34	0.8–2.1	1.65	0.8–3.4	1.38	0.7–2.7	1.28	0.8–2.1

PCS, physical component summary scale; MCS, mental component summary scale; [a]Reference category; [b]Odds ratio significant at $P < 0.05$ level; [c]Number of patients scoring more than one standard deviation below the mean; *All variables adjusted for the other variables in the model.

TABLE VI. Odds Ratios* and 95% Confidence Intervals for Scoring More Than one Standard Deviation Below the Mean on the SF-36 Summary Scales or Subscales by Diagnosis and Treatment Variables in Neuroblastoma Survivors

	Physical function		Role physical		Bodily pain		General health		Vitality		Social function		Role emotional		Mental health		PCS		MCS	
N (%)[c]	30 (7.4)		53 (13.0)		45 (11.0)		68 (16.7)		159 (39.1)		87 (21.4)		98 (24.1)		35 (8.6)		52 (12.8)		83 (20.4)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Gender																				
Male[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Female	1.28	0.6–2.9	2.07[b]	1.1–4.0	1.42	0.7–2.8	2.10[b]	1.2–3.8	2.12[b]	1.4–3.2	1.54	0.9–2.6	1.56[b]	1.0–2.5	1.71[b]	0.8–3.7	1.80	0.9–3.4	1.66[b]	1.0–2.8
Age group at the time of questionnaire																				
18–24 years[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
25–34 years	0.76	0.1–6.8	0.41	0.1–2.0	2.02	0.6–7.1	0.17	0.1–1.4	1.03	0.4–2.7	0.57	0.2–2.1	0.82	0.2–2.6	0.55	0.1–4.6	1.14	0.3–3.9	0.76	0.2–2.8
35 + years	0.41	0.1–4.6	0.83	0.1–4.9	3.43	0.8–15.3	0.40	0.1–3.7	1.71	0.6–5.1	0.87	0.2–3.6	1.21	0.3–4.5	0.74	0.1–7.4	2.14	0.5–9.3	1.06	0.2–4.5
Survival time																				
16–20 years[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
21–25 years	1.40	0.5–3.9	2.36	0.8–6.6	1.81	0.7–4.9	0.93	0.4–2.1	1.43	0.8–2.5	1.78	0.9–3.6	0.81	0.4–1.5	0.98	0.4–2.6	1.25	0.5–3.2	1.25	0.6–2.5
26–30 years	1.68	0.3–8.4	1.40	0.4–5.1	1.47	0.4–5.4	0.49	0.2–1.5	0.74	0.3–1.7	1.16	0.4–3.1	0.56	0.2–1.4	0.50	0.1–2.1	0.99	0.3–3.4	0.87	0.3–2.3
31–35 years	0.41	0.1–5.2	1.90	0.4–8.0	0.27	0.1–1.9	0.67	0.2–2.4	0.44	0.2–1.2	0.54	0.2–2.0	0.34	0.1–1.1	0.57	0.1–3.1	1.03	0.2–4.3	0.35	0.1–1.3
Abdominal radiation																				
No[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.42	0.5–3.9	1.97	0.9–4.2	1.08	0.5–2.5	0.97	0.4–2.1	1.44	0.8–2.5	1.46	0.8–2.8	1.47	0.8–2.8	0.74	0.3–2.1	1.51	0.7–3.3	1.21	0.6–2.4
Spinal radiation																				
No[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	3.10	0.7–14.1	1.12	0.2–6.0	1.09	0.2–5.8	0.55	0.1–2.8	0.50	0.1–1.8	2.23	0.6–7.7	0.87	0.2–3.4	0.56	0.1–4.8	2.68	0.7–10.3	0.62	0.1–3.5
Pelvic radiation																				
No[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	1.60	0.5–5.1	1.20	0.5–2.8	2.00	0.8–5.2	2.32[b]	1.0–5.4	1.02	0.5–2.0	0.94	0.4–2.1	0.49	0.2–1.1	2.29	0.7–7.2	1.35	0.6–3.2	0.86	0.4–2.0
Laminectomy																				
No[a]	1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00		1.00	
Yes	5.48[b]	1.9–16.0	2.41	0.8–6.9	4.38[b]	1.6–12.0	2.30	0.9–6.2	0.95	0.4–2.3	1.02	0.3–2.9	1.15	0.4–3.1	2.36	0.7–7.6	2.38	0.8–3.9	0.57	0.2–2.0

PCS, physical component summary scale; MCS, mental component summary scale; [a]Reference category; [b]Odds ratio significant at $P < 0.05$ level; [c]Number of patients scoring more than one standard deviation below the mean; *All variables adjusted for the other variables in the model.

3.8, $P < 0.05$), vitality (OR $= 2.12$, 95% CI $= 1.4$–3.2, $P < 0.05$), and role function—emotional (OR $= 1.56$, 95% CI $= 1.0$–2.5, $P < 0.05$) subscales. Patients who received pelvic radiation demonstrated an increased risk of poor outcome on the general health subscale (OR $= 2.32$, 95% CI $= 1.0$–5.4, $P < 0.05$). Patients who underwent a laminectomy had an increased risk of a poor outcome on the physical function (OR $= 5.48$, 95% CI $= 1.9$–16.0, $P < 0.05$) and bodily pain (OR $= 4.38$, 95% CI $= 1.6$–12.0, $P < 0.05$) subscales.

DISCUSSION

This follow-up study adds to the literature on health outcomes among long-term survivors of Wilms tumor and neuroblastoma by evaluating HRQL. In this population of young adults who were treated for cancer at a very young age, we found no evidence for significant deficits in HRQL measures representing physical well being or functioning. However, there is a clear pattern of poor emotional health evident in both diagnostic groups. Survivors scored considerably below population norms on the MCS scale of the SF-36, a composite measure reflecting performance on the vitality, social function, role-emotional, and mental health subscales. This is of particular concern because scores below 42 on this summary scale have been shown to have high sensitivity and specificity for diagnoses of depression in other studies [30]. Although women consistently scored lower than men on these measures, the pattern of lower scores was evident for both sexes. Poorer HRQL outcomes amongst females have been reported in many studies of both acute and chronic illness [31–33], and female survivors of childhood cancer have been demonstrated previously to have a higher likelihood of adverse health status [25] and poorer HRQL than males [34]. In addition to female gender, several other sociodemographic factors correlated with overall worse outcome on one or more measures of HRQL. These included patients who were unemployed or looking for work, those with lower annual incomes, and those who had not graduated from college. Importantly, no specific disease characteristics or treatment exposures were predictive of poorer performance on the MCS subscale for either diagnosis. Thus, treatment intensity is not predictive of poorer emotional health and all survivors should be evaluated for this adverse outcome regardless of the severity of their initial cancer. These findings may be important to primary care physicians, who are the most likely health care providers to have regular contact with this population and may be most able to screen for depression or anxiety during routine care visits.

We observed no difference on any measure of HRQL between diagnostic groups. This might be attributable to two factors. First, the survival of patients with high-risk neuroblastoma is poor [35], resulting in a relative absence of survivors of high-stage disease. Most survivors of high-risk neuroblastoma experience one or more long-term complications of their disease or therapy, with almost one third reporting severe or life-threatening complications [19]. The most common of these are hearing loss, hypothyroidism and acute ovarian failure. Although stage information was not captured in the CCSS database, over 40% of the neuroblastoma survivors in the current cohort did not receive any chemotherapy, suggesting a high proportion of patients with lower stage disease who are less likely to develop long-term adverse effects. Alternatively, the absence of a difference in HRQL between the two groups in this study may be explained by the historical use of more aggressive

multi-modal therapies in many patients with Wilms tumor treated in prior eras. This might serve to increase their risk of long-term morbidity compared to contemporary cohorts. Almost two-thirds of Wilms tumor survivors in this cohort received radiotherapy and over one-third received anthracycline chemotherapy. These treatment modalities may increase the risk of the long-term sequelae of Wilms tumor therapy, including chronic renal failure [36], congestive heart failure [37], and second malignant neoplasms [7], all of which would have impact on HRQL.

As expected, both radiation and surgery for local control of the primary tumor impacted on HRQL. Survivors of Wilms tumor who had received pelvic radiation were more likely to perform poorly on the role function—physical subscale of the SF-36. Pelvic radiation in patients with Wilms tumor has been linked to premature ovarian failure, infertility, adverse pregnancy outcomes [38], and second malignant neoplasms [7]. Survivors of Wilms tumor who had received chest radiation were more likely to perform poorly on the social function and role function—emotional subscales of the SF-36. The use of chest radiation in Wilms tumor is usually reserved for patients with metastatic disease and this may reflect a group of survivors of higher risk disease. In survivors of neuroblastoma, a history of laminectomy was associated with an increased risk of poor performance on the role function—physical and bodily pain subscales of the SF-36. This might reflect the long-term consequences of this surgery which include scoliosis [19,39]. However, children requiring laminectomy are more likely to have presented with spinal cord compression and thus, their poor performance might reflect residual neurologic compromise [40]. In addition, pelvic radiation was linked to poor general health in this group of patients.

This study has some methodological limitations that should be considered when interpreting the results. First, although the SF-36 has been validated as a self-report instrument, data regarding current socioeconomic status and medical complications were generated similarly from self report, and were not validated externally. Second, incomplete participation in the CCSS by eligible patients may have biased our results if survivors with poorer HRQL were less (or more) likely to join the CCSS cohort and to continue to contribute information to the study. Although the response rate for the HRQL questionnaire was good amongst those survivors enrolled in the CCSS (75.4%), non-respondents tended to be of lower socioeconomic status than participants and were somewhat more likely to have reported a major medical condition. These differences, not uncommon in health outcome studies, suggest caution be exercised when generalizing our findings to low social and economic strata. Third, the CCSS did not collect disease stage information because of a lack of consistency between staging systems used at different institutions. As a result, we cannot categorize survivors by disease stage, nor can we show the relationship between stage and HRQL outcomes. Finally, all members of this cohort were treated in the period between 1970 and 1986 and readers must be cautious in generalizing these results to patients treated on more contemporary protocols. Changes in the intensity of therapy, particularly in patients with Wilms tumor and those with low or intermediate risk neuroblastoma may result in different HRQL outcomes. Contemporary protocols often use lower doses of radiation and there have been improvements in the techniques and equipment used to deliver radiotherapy. There have been concomitant improvements in surgical techniques. Thus, patients treated on more recent protocols warrant separate investigation.

Despite differences in therapy, long-term survivors of Wilms tumor and neuroblastoma do not differ in their assessment of HRQL. Their physical well being and functioning is comparable to population norms, but they score significantly below these norms on measures of emotional health. Women and survivors in lower sociodemographic strata demonstrate the greatest risk of adverse outcomes. Health care providers must be sensitive to the risk for adverse outcomes in these vulnerable groups and institute appropriate screening and intervention.

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