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ORIGINAL REPORT

Psychosexual Functioning Among Adult Female Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
Childhood cancer survivors may be at risk for impaired psychosexual functioning as a direct result of their cancer or its treatments, psychosocial difficulties, and/or diminished quality of life.

Patients and Methods
Two thousand one hundred seventy-eight female adult survivors of childhood cancer and 408 female siblings from the Childhood Cancer Survivor Study (CCSS) completed a self-report questionnaire about their psychosexual functioning and quality of life. On average, participants were age 29 years (range, 18 to 51 years) at the time of the survey, had been diagnosed with cancer at a median age of 8.5 years (range, 0 to 20) and were most commonly diagnosed with leukemia (33.2%) and Hodgkin lymphoma (15.4%).

Results
Multivariable analyses suggested that after controlling for sociodemographic differences, survivors reported significantly lower sexual functioning (mean difference [MnD], −0.2; $P = .01$), lower sexual interest (MnD, −0.2; $P < .01$), lower sexual desire (MnD, −0.3; $P < .01$), lower sexual arousal (MnD, −0.3; $P < .01$), lower sexual satisfaction (MnD, −0.2; $P = .01$), and lower sexual activity (MnD, −0.1; $P = .02$) compared with siblings. Risk factors for poorer psychosexual functioning among survivors included older age at assessment, ovarian failure at a younger age, treatment with cranial radiation, and cancer diagnosis during adolescence.

Conclusion
Decreased sexual functioning among female survivors of childhood cancers seems to be unrelated to emotional factors and is likely to be an underaddressed issue. Several risk factors among survivors have been identified that assist in defining high-risk subgroups who may benefit from targeted screening and interventions.

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INTRODUCTION

Given the increases in survival rates for childhood cancer, more attention is being paid to survivors' late effects and long-term psychosocial functioning.[1] One potential long-term consequence for young adult cancer survivors is the risk for impaired psychosexual functioning. Childhood cancer survivors in particular may experience sexual difficulties and/or a delay in achieving sexual milestones as a result of having been diagnosed with cancer during psychosexual development. The psychosocial difficulties childhood cancer survivors experience, including significant changes in peer relationships, disturbed body image, worry about the future, difficulties with intimate relationships, and diminished quality of life (QOL), can influence psychosexual development.[2-4] Additional factors that may influence psychological and sexual functioning include disruptions in normal pubertal development, premature ovarian failure (OF), and the burden of medical comorbidities.[4-6]

Despite data demonstrating that psychosexual functioning can be impaired by medical illness, empirical data on psychosexual functioning in female survivors of childhood cancer are limited.[4,6-10] Although many of the studies suggest that psychosexual development and sexual experiences of survivors are affected negatively by the cancer experience,[4,6,7,9] the data are inconsistent and limited by small sample sizes. Therefore, understanding the prevalence of and risk factors for psychosexual sequelae among female young adult survivors of childhood cancer is essential to provide optimal care and to develop

targeted interventions. We hypothesized that survivors would report poorer sexual functioning and greater psychological symptoms than a comparison group. We also hypothesized that poorer sexual functioning would be reported by survivors with OF compared with those with normal menses but that these differences would be moderated by the use of hormone replacement therapy. To that end, this study sought to address some of the gaps in the current literature by assessing psychosexual outcomes by using standardized measures in a large, diverse, and well-characterized cohort of adult female survivors of childhood cancer compared with a cohort of siblings.

PATIENTS AND METHODS

Childhood Cancer Survivor Study

Participants were females enrolled onto the Childhood Cancer Survivor Study (CCSS), a multicenter cohort study of individuals treated for childhood cancer and a comparison group of siblings. Participating centers are provided in Appendix Table A1 (online only). The CCSS design and cohort have been reported in detail previously.[11,12] Eligibility criteria for participation in the CCSS included the following: diagnosed between 1970 and 1986 with leukemia, CNS tumor, lymphoma, kidney cancer, neuroblastoma, soft tissue sarcoma, or malignant bone tumor; diagnosis and initial therapy at one of 25 CCSS institutions; age less than 21 years at diagnosis; and survival at least 5 years since diagnosis. For the current analysis, survivors and sibling controls had to be at least 18 years of age and without siblings reporting OF. Individuals were considered in OF if they reported that they either never experienced spontaneous menses or experienced spontaneous menses and had cessation of menses before age 40. The study protocol was approved by the institutional review boards at each participating institution.

Target and Comparison Populations

From among 4,643 adult female survivors age 18 to 50 who were enrolled onto the CCSS, 2,178 survivors (47%) had completed the first follow-up questionnaire as well as a supplemental psychosexual questionnaire (available at http://ccss.stjude.org/docs/ccss/survey-women-health.pdf) and were thus evaluable for this study. To assess the effect that cancer and associated treatments might have on psychosexual functioning, a comparison group representing a noncancer population of siblings of survivors in the full CCSS cohort (CCSS siblings) was assessed. Of the 1,066 eligible adult female siblings who were sent the study survey, 408 females (38.3%) participated.

Nonparticipant survivors were significantly more likely to be younger, never married, have lower educational status, be racial or ethnic minorities, have normal menstrual functioning at the follow-up questionnaire, have been diagnosed with cancer at a younger age (before age 10 years), and have been diagnosed with a CNS cancer. Among siblings, nonparticipants were more likely to have lower educational status.

Measures

The 122-item Women's Sexual Health Questionnaire was administered separately from other CCSS questionnaires by using either a mailed survey or telephone interview. Additional information for this analysis was gathered from the follow-up questionnaire, which contained sociodemographics and ovarian function questions. On completion of the follow-up questionnaire, the psychosexual questionnaire was sent to participants for completion. Both questionnaires were administered within a year of the other. Detailed treatment information has also been collected for the survivor cohort.[12]

The Women's Sexual Health Questionnaire consisted of several validated assessment tools, including the Sexual Functioning Questionnaire (SFQ), Women's Health Questionnaire (WHQ), Sexual Self-Schema (SSS) for women, and the Medical Outcomes Survey Short Form-36 (SF-36).[13-16]

The SFQ is a validated and reliable measure of current female sexual functioning and satisfaction in which higher scores represent better functioning.[15] It consists of an overall score and several subscales. The interest subscale measures having sexual fantasies; desire assesses desire for types of

Table 1. Participants' Sociodemographic and Clinical Characteristics

Characteristic	Survivors (n = 2,178) No.	%	Siblings (n = 408) No.	%	P
Age at last contact, years					< .001
18-30	1,217	55.9	179	43.7	
31-51	961	44.1	229	56.1	
Marital status					< .001
Never married	1,142	53.5	144	35.6	
Formerly married	149	7.0	30	7.4	
Currently married	844	39.5	230	56.9	
Unknown	43		4		
Income, $					< .001
< 20,000	376	18.6	49	12.6	
≥ 20,000	1,646	81.4	341	87.4	
Unknown	156		18		
Education					< .001
≤ High school	762	36.7	87	22.2	
> High school	1,315	63.3	307	77.8	
Unknown	101		16		
Ethnicity/race					< .001
Non-Hispanic white	1,920	88.4	368	92.7	
Other	253	11.6	29	7.3	
Unknown	5		11		
OF					
No	1,943	89.2	NA		
Yes	235	10.8	NA		
Among those with OF, use of OCP/HRT					
No	141	60			
Yes	94	40			
Age at diagnosis, years					
0-10	1,304	59.9	NA		
11-20	874	40.1	NA		
Age at onset of OF, years					
No OF	1,943	89.2	NA		
12-25	164	7.5	NA		
26-48	71	3.3	NA		
Maximum ovarian radiation dose, Gy					
None	708	34.6	NA		
< 5 Gy	1,106	54.1			
≥ 5 Gy	235	11.5	NA		
Unknown	129		NA		
Primary diagnosis					
Hodgkin lymphoma	335	15.4	NA		
CNS tumor	206	9.5	NA		
Non-Hodgkin lymphoma	116	5.3	NA		
Leukemia	723	33.2	NA		
Bone cancer	227	10.4	NA		
Neuroblastoma	138	6.3	NA		
Kidney cancer (Wilms)	241	11.1	NA		
Soft tissue sarcoma	192	8.8	NA		
Brain radiation					
No	1,506	72.7	NA		
Yes	565	27.3	NA		
Unknown	107		NA		
Major medical condition*					
No	1,491	74.9	NA		
Yes	499	25.1	NA		
Unknown	188		NA		

NOTE. Siblings who participated were without OF. Survivors who participated were with or without OF.

Abbreviations: NA, not applicable; OCP/HRT, oral contraceptives or hormone replacement therapy; OF, ovarian failure.

*As defined by Zebrack et al.[23]

Table 2. Sexual Functioning, Symptoms, and Quality of Life for Survivors and Siblings: SFQ

Subscale	Survivors (n = 2,178)			Siblings (n = 408)			β Coefficient*	P
	No.	Mean	95% CI	No.	Mean	95% CI		
Interest	2,126	2.18	0.00 to 5.00	400	2.42	0.00 to 5.00	−0.24	< .001
Desire	2,107	2.71	0.00 to 5.00	396	3.01	0.00 to 5.00	−0.30	< .001
Arousal	2,074	1.87	0.00 to 5.00	394	2.13	0.00 to 5.00	−0.26	< .001
Satisfaction	1,774	3.30	−0.50 to 5.00	365	3.52	−0.50 to 5.00	−0.22	.01
Masturbation	2,083	0.96	0.00 to 5.00	392	1.11	0.00 to 5.00	−0.15	.03
Relationship	1,643	2.91	0.21 to 4.50	348	2.95	0.88 to 4.50	−0.04	.4
Activity	1,602	2.32	0.00 to 5.00	340	2.47	0.00 to 5.00	−0.14	.02
Problems	1,596	4.06	0.67 to 5.00	345	4.29	1.83 to 5.00	−0.23	.2
Overall score	1,633	2.72	0.25 to 4.70	345	2.89	1.05 to 4.59	−0.17	.004

Abbreviation: SFQ, Sexual Functioning Questionnaire.
*Mean difference for survivors compared with siblings, adjusted for age at study, marital status, education level, income, and ethnicity/race.

sex activity; arousal measures subjective arousal to sexual stimuli; orgasm subscale includes both orgasm and pleasure from touch; satisfaction measures satisfaction with sex and intimacy; activity subscale includes a variety of couple sexual activities; and relationship includes communication and satisfaction. We examined the problems subscale in greater detail, including problems with vaginal dryness, tightness, painful penetration, vaginal bleeding, sharp pain, and increased sensitivity.

The WHQ is a reliable and validated scale assessing women's perceptions of a range of physical and emotional symptoms including depressed mood, somatic symptoms, memory/concentration difficulties, vasomotor symptoms, anxiety/fear, sexual behavior, sleep problems, menstrual problems, and perception of attractiveness.[14] We dichotomized the raw continuous score, which ranged from 0 to 1, into a zero (no symptoms) versus greater than zero (symptomatic and poorer outcome) binary variable for analysis. In addition to the guidelines in the user's manual, if a participant had fewer than 50% of the required items missing, the mean from the nonmissing items was substituted to impute the score.

The SSS, a reliable and validated measure, contains 26 trait adjectives that assess cognitions about sexual aspects of oneself.[13] The SSS has a total schema score in which lower scores represent a more negative sexual self perception and three factors reflecting the following dimensions: loving-romantic, direct-open, and embarrassment-conservatism. Missing values were imputed similar to the WHQ.

The Medical Outcomes Study SF-36[16] is a standard and widely used reliable and valid measure of QOL that assesses eight areas: limitations in physical activities as a result of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities as a result of physical health or emotional problems, bodily pain, psychological distress and well being, vitality, and general health perceptions.[16] We dichotomized SF-36 *t* scores greater than 40 versus fewer or equal to 40 as has been used in previous publications[17] for survivors and siblings. This cutoff was chosen as it reflects one standard deviation below the population mean, representing a level of functioning that falls below the 16th percentile of the normative sample.[18-19]

Statistical Analyses

Descriptive statistics were calculated for demographic and treatment variables for nonparticipants and participants within survivors and siblings. Measures were compared between survivors and siblings by using multivariable regression models adjusting for age at study, marital status, education level, income, and ethnicity or race. Unconditional logistic regression models were used for the binary psychological outcomes, SF-36, and WHQ. Linear regression models were used for the continuous psychosexual outcomes, SSS and SFQ. Similar models were used to evaluate relationships between risk factors and outcomes among survivors to compare those with OF with those without OF, adjusting for current age, age at cancer diagnosis, marital status, education, income, ethnicity or race, having had cranial radiation, and having a major medical condition. Furthermore, we evaluated the same risk factors, demographic variables, age of onset of OF, and currently taking oral contraceptive pills or hormone replacement therapy (OCP/HRT) among survivors with OF. All analyses involving comparisons between survivors and siblings accounted for intrafamily correlation by using robust sandwich variance estimates.[20] All statistical analyses were performed with SAS Version 9.1 (SAS Institute, Cary, NC), by using two-sided statistical inferences and a significance level of $P \leq .05$.

RESULTS

Compared with siblings, survivors were younger and less likely to be married, non-Hispanic white, have an annual income greater than $20,000, or have graduated high school (Table 1). Approximately two thirds of survivors were diagnosed with cancer before age 11 years (59.9%) with 40% reporting a cancer diagnosis between ages 11 and 20 years. The most common cancer diagnoses included leukemia (33%), Hodgkin lymphoma (15%), kidney cancers (11%), bone cancers (10%), and CNS cancers (10%).

Among survivors, 10.8% had OF, and among this group, 40% were on OCP/HRT. Approximately 20% of women who either developed OF within the year after cancer diagnosis or much later (20 to 29 years) were on OCP/HRT. In contrast, for those women who experienced OF between 1 and 14 years postdiagnosis, 47% were on OCP/HRT. Another difference in use of OCP/HRT was found by age at OF, in which younger women at time of OF (age 12 to 25 years) were more likely to be receiving OCP/HRT than those who were older at OF (age 26 to 40 years; 51% *v* 14%).

Sexual Functioning in Survivors Versus Siblings

Participants who reported that they were not sexually active in the previous month (28% of survivors and 17% of siblings) were excluded in subsequent psychosexual functioning analyses. A small group of survivors (7%) and siblings (2.4%) reported never being sexually active. Among participants who reported no sexual activity in the past month, the most prevalent reasons included no current partner (13% of survivors *v* 9.2% of siblings), lack of interest (6.4% *v* 3.4%), being too tired (4.5% *v* 2.9%), and/or a physical problem (2.4% *v* 0.7%).

Fewer survivors reported having a current sexual partner (77.4%) compared with siblings (86.9%; $P < .001$). We examined the

Table 3. Sexual Functioning, Symptoms, and Quality of Life for Survivors and Siblings: WHQ and SF-36

	Survivors (n = 2,178)		Siblings (n = 408)				
Subscale	No.	%	No.	%	OR*	95% CI	*P*
			WHQ				
Depressed mood					1.13	0.90 to 1.43	.3
> 0-1	1,304	60.2	226	55.5			
0	863	39.8	181	44.5			
Somatic symptoms					1.24	0.90 to 1.70	.2
> 0-1	1,895	87.2	339	83.3			
0	279	12.8	68	16.7			
Memory/concentration					1.29	1.03 to 1.63	.03
> 0-1	1,272	58.6	206	50.5			
0	900	41.4	202	49.5			
Vasomotor symptoms					1.27	0.98 to 1.64	.07
> 0-1	694	31.9	112	27.5			
0	1,480	68.1	296	72.5			
Anxiety/fears					1.33	1.06 to 1.68	.01
> 0-1	1,316	60.7	208	51.1			
0	852	39.3	199	48.9			
Sexual behavior					1.17	0.92 to 1.50	.2
> 0-1	927	49.8	182	49.2			
0	933	50.2	188	50.8			
Sleep problems					1.02	0.81 to 1.29	.9
> 0-1	1,335	61.6	242	59.5			
0	833	38.4	165	40.5			
Menstrual problems					0.90	0.69 to 1.17	.4
> 0-1	1,589	73.1	297	72.8			
0	585	26.9	111	27.2			
Attractiveness					1.11	0.89 to 1.40	.4
> 0-1	1,097	50.5	192	47.1			
0	1,077	49.5	216	52.9			
			SF-36				
Physical functioning					0.39	0.19 to 0.78	.008
0 to < 40	126	5.8	9	2.2			
≥ 40 to 100	2,045	94.2	398	97.8			
Role—physical					0.68	0.47 to 1.00	.05
0 to < 40	302	13.9	36	8.9			
≥ 40 to 100	1,867	86.1	370	91.1			
Bodily pain					0.65	0.39 to 1.06	.09
0 to < 40	173	8.0	21	5.2			
≥ 40 to 100	1,996	92.0	386	94.8			
General health perceptions					0.41	0.27 to 0.61	< .001
0 to < 40	369	17.0	33	8.1			
≥ 40 to 100	1,802	83.0	374	91.9			
Vitality					0.91	0.72 to 1.14	.4
0 to < 40	1,073	49.5	183	45			
≥ 40 to 100	1,095	50.5	224	55			
Social functioning					0.64	0.38 to 1.07	.09
0 to < 40	180	8.3	19	4.7			
≥ 40 to 100	1,978	91.7	383	95.3			
Role—emotional					0.98	0.74 to 1.31	.9
0 to < 40	497	22.9	81	20			
≥ 40 to 100	1,669	77.1	323	80			
Mental health					1.51	0.91 to 2.51	.1
0 to < 40	97	4.5	23	5.7			
≥ 40 to 100	2,072	95.5	384	94.3			
Physical summary scale					0.42	0.027 to 0.63	< .001
0 to < 40	342	15.9	29	7.3			
≥ 40 to 100	1,809	84.1	371	92.7			
Mental summary scale					1.04	0.79 to 1.35	.8
0 to < 40	559	26.0	96	24.0			
≥ 40 to 100	1,592	74.0	304	76.0			

Abbreviations: OR, odds ratio; SF-36, Medical Outcomes Study Short Form-36; WHQ, Women's Health Questionnaire.
*Siblings used as referent to compare proportion of score 0 over score 0 to 1 with survivors for WHQ and to compare proportion of *t* score ≥ 40 to 100 over *t* score 0 to < 40 with survivors for SF-36.

Table 4. Psychosexual Functioning Among Survivors With or Without OF: SFQ

Subscale	With OF (n = 235)			Without OF (n = 1,943)			Mean Difference*	*P*
	No.†	Mean	95% CI	No.†	Mean	95% CI		
Interest	222	1.61	1.40 to 1.82	1,904	2.17	2.05 to 2.30	−0.57	< .001
Desire	217	2.07	1.84 to 2.29	1,890	2.69	2.55 to 2.82	−0.62	< .001
Arousal	214	1.39	1.17 to 1.61	1,860	1.88	1.75 to 2.01	−0.49	< .001
Satisfaction	180	2.81	2.04 to 3.57	1,594	2.92	2.22 to 3.63	−0.11	.75
Masturbation	216	0.70	0.48 to 0.91	1,867	1.03	0.91 to 1.16	−0.34	< .001
Relationship	167	2.81	2.66 to 2.96	1,476	2.94	2.85 to 3.03	−0.13	.05
Activity	163	2.16	1.95 to 2.36	1,439	2.33	2.21 to 2.46	−0.18	.06
Problems	159	3.78	3.62 to 3.94	1,437	4.20	4.11 to 4.30	−0.42	< 0.01
Vaginal dryness	157	2.75	2.50 to 3.00	1,442	1.91	1.75 to 2.06	0.84	< .001
Vaginal tightness	155	2.66	2.41 to 2.92	1,422	2.07	1.92 to 2.23	0.59	< .001
Painful penetration	160	2.33	2.10 to 2.56	1,429	1.81	1.67 to 1.95	0.52	< .001
Vaginal bleeding	159	1.86	1.67 to 2.05	1,428	1.57	1.45 to 1.68	0.30	< .001
Sharp pain	158	1.63	1.46 to 1.79	1,439	1.44	1.34 to 1.54	0.18	.01
Increased sensitivity	157	1.87	1.63 to 2.10	1,424	1.81	1.66 to 1.95	0.06	.57
Overall score	166	2.44	2.30 to 2.58	1,467	2.80	2.71 to 2.88	−0.36	< .001

NOTE. Adjusted for age at study, age at primary diagnosis, marital status, education level, income, ethnicity/race, cranial irradiation, and major medical condition.
Abbreviations: OF, ovarian failure; SFQ, Sexual Functioning Questionnaire.
*Mean difference from beta coefficient in adjusted models for OF compared with no OF.
†Missing No. for row not shown.

presence of a sexual partner among survivors and siblings by age quartiles and found that there were no differences, with the exception of the 24-to-30-year-old age group (75.7% of survivors *v* 90% of siblings; $P < .001$).

Survivors reported significantly poorer overall sexual functioning on the SFQ compared with siblings ($P = .004$), adjusted for demographic variables (Tables 2 and 3). Survivors also reported significantly lower sexual interest, desire, arousal, satisfaction, and activity compared with siblings (all *P* values $< .01$). Multivariable analyses suggested no significant differences between survivors and siblings regarding their sexual self schema, and therefore, the SSS questionnaire was not used in any other subsequent analyses.

Sexual Functioning of Survivors With OF Versus Those With Normal Menses

Multivariable linear regression demonstrated that survivors with OF reported lower sexual interest, desire, arousal, satisfaction, lower masturbation scores, greater sexual problems, and lower overall sexual functioning scores compared with those survivors without OF (Tables 4 and 5). Specifically, the women with OF reported more sexual problems, including vaginal dryness, tightness, painful sexual intercourse, and vaginal bleeding.

To further examine risk factors for poorer psychosexual functioning among the subgroup of survivors with OF, multivariable models were constructed (Tables 6 to 8). Among survivors with OF, sexual desire and arousal were lowest for those who were unmarried, had cranial radiation, were older (currently age 31 to 53 *v* 18 to 30 years), and reported a lower income (< $20,000).

Sexual Functioning: OCP/HRT Versus No OCP/HRT Among Survivors With OF

Among women with OF, there were no significant differences on any of the sexual functioning subscales or sexual problems reported (Appendix Tables A2 and A3, online only) by OCP/HRT status.

WHQ

Multivariable logistic regression was used to determine the odds ratio for having a poor outcome on the WHQ for survivors versus siblings (Table 3). After adjusting for sociodemographic variables, there were no significant differences on multivariable analyses regarding depressed mood, somatic symptoms, sexual behavior, vasomotor symptoms, sleep problems, menstrual problems, or attractiveness. The odds of survivors reporting memory or concentration problems (odds ratio, 1.3; $P = .03$) and anxieties or fears (odds ratio, 1.3; $P = .01$) were significantly higher for survivors than for siblings.

WHQ: Survivors With OF Versus Those With Normal Menses

Significant differences between survivors with OF compared with those without were found by multivariable logistic regression on subscales measuring vasomotor symptoms, problems with sexual behavior, sleep problems, and menstrual problems (Tables 4 and 5). Survivors with OF did not differ significantly from those without for depression, somatic symptoms, memory or concentration problems, anxiety or fear, and feelings of attractiveness. In addition, in multivariable models among survivors with OF, those who reported major medical conditions were significantly more likely to report somatic symptoms, vasomotor problems, or anxiety or fear compared with those without any major medical conditions (Tables 6 to 8).

WHQ: OCP/HRT Versus No OCP/HRT Among Survivors With OF

There were no differences in sexual functioning, somatic symptoms, vasomotor problems, and/or anxiety/fear among survivors with OF by OCP/HRT status. Survivors taking OCP/HRT did have significantly higher odds of reporting sleep problems (Tables 4 and 5; Appendix Tables A2 and A3, online only).

Table 5. Psychosexual Functioning Among Survivors With or Without OF: WHQ and SF-36

Subscale	With OF (n = 235) No.	%	Without OF (n = 1,943) No.	%	OR*	P
WHQ						
Depressed mood					1.32	.09
> 0 to 1	152	64.7	1,152	59.3		
0	83	35.3	780	40.1		
Somatic symptoms					1.14	.6
> 0 to 1	208	88.5	1,687	86.8		
0	27	11.5	252	13		
Memory/concentration					1.07	.7
> 0 to 1	141	60	1,131	58.2		
0	93	39.6	807	41.5		
Vasomotor symptoms					1.59	.005
> 0 to 1	103	43.8	591	30.4		
0	132	56.2	1,348	69.4		
Anxiety/fears					0.92	.6
> 0 to 1	138	58.7	1,178	60.6		
0	97	41.3	755	38.9		
Sexual behavior					2.36	< .001
> 0 to 1	130	55.6	797	41.7		
0	65	27.8	868	45.4		
Sleep problems					1.53	.01
> 0 to 1	169	71.9	1,166	60		
0	66	28.1	767	39.5		
Menstrual problems					0.58	.001
> 0 to 1	149	63.4	1,440	74.1		
0	86	36.6	499	25.7		
Attractiveness					1.13	.5
> 0 to 1	130	55.3	967	49.8		
0	105	44.7	972	50		
SF-36						
Physical functioning					0.67	.2
0 to < 40	19	8.1	107	5.5		
≥ 40 to 100	216	91.9	1,829	94.1		
Role—physical					0.61	.02
0 to < 40	50	21.3	252	13		
≥ 40 to 100	184	78.3	1,683	86.6		
Bodily pain					0.64	.08
0 to < 40	27	11.5	146	7.5		
≥ 40 to 100	208	88.5	1,788	92		
General health perceptions					0.42	< .001
0 to < 40	69	29.4	300	15.4		
≥ 40 to 100	166	70.6	1,636	84.2		
Vitality					0.78	.1
0 to < 40	129	54.9	944	48.6		
≥ 40 to 100	106	45.1	989	50.9		
Social functioning					0.93	.8
0 to < 40	24	10.2	156	8		
≥ 40 to 100	209	88.9	1,769	91		
Role—emotional					0.89	.6
0 to < 40	55	23.4	442	22.7		
≥ 40 to 100	178	75.7	1,491	76.7		
Mental health					0.74	.4
0 to < 40	12	5.1	85	4.4		
≥ 40 to 100	223	94.9	1,849	95.2		
Physical summary scale					0.64	.03
0 to < 40	56	23.8	286	14.7		
≥ 40 to 100	175	74.5	1,634	84.1		
Mental summary scale					1.09	.7
0 to < 40	56	23.8	503	25.9		
≥ 40 to 100	175	74.5	1,417	72.9		

NOTE. Adjusted for age at study, age at primary diagnosis, marital status, education level, income, ethnicity/race, cranial irradiation, and major medical condition.

Abbreviations: OF, ovarian failure; OR, odds ratio; SF-36, Medical Outcomes Study Short Form-36; WHQ, Women's Health Questionnaire.

*Without OF as referent.

QOL

In analyses adjusted for sociodemographic variables, survivors were significantly less likely to report good physical functioning, physical role functioning, and/or overall physical summary scores compared with siblings (Tables 2 and 3). Poor physical functioning (t score < 40) was reported by 5.8% of survivors (v 2.2% of siblings; P = .008), poor physical role function was reported by 13.9% of survivors (v 8.8% of siblings; P = .05) and overall physical difficulties were endorsed by 15.9% of survivors (compared with 7.3% of siblings; P < .001), suggesting a clinically important difference in physical functioning between groups. Survivors were also significantly less likely to report good health perceptions compared with siblings.

QOL for Survivors With OF Versus Those With Normal Menses

Survivors with OF were not significantly different from those without OF on all QOL subscales with the exceptions of physical role function and general health perception (Tables 4 and 5). In multivariable analyses, survivors with OF (Tables 6 to 8), a major medical condition, and lower income had worse physical functioning. Survivors who were not married, had lower income, and a major medical condition were more likely to report difficulties in their role-emotional functioning. Because survivors with OF did not significantly differ from those without on most subscales of QOL, we did not examine QOL differences by OCP/HRT status.

DISCUSSION

In our study, among a large cohort of female adult survivors of childhood cancer, we found that survivors had significantly poorer psychosexual functioning compared with siblings, even after controlling for sociodemographic variables, including age, marital status, education level, income, and ethnicity or race. Despite the fact that most of our survivors were many years post-treatment, survivors reported significantly impaired sexual functioning, including lower sexual interest, desire, arousal, and satisfaction compared with our comparison group of siblings. Our study demonstrates that sexual functioning continues to be impaired in the long term. Women in our cohort reported similar or slightly more sexual difficulties than what has been reported for a diverse sample of female survivors in the literature,[15] suggesting

Table 6. Psychosexual Function Among Survivors With OF (n = 235): SFQ

Factor	Desire			Arousal			Masturbation			Activity			Problems			Overall Score		
	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*
Age at follow-up, years																		
31-53 *v* 18-30†										−0.71	−1.24 to −0.19	.008						
Marital status																		
Currently *v* never†	0.59	0.08 to 1.10	.024	0.57	0.15 to 0.99	.008	−0.39	−0.76 to −0.02	.039									
Formerly *v* never†	0.82	−0.01 to 1.64	.054	0.55	−0.12 to 1.22	.11	0.03	−0.57 to 0.63	.92									
Education																		
> High school *v* ≤ high school†							0.37	0.04 to 0.71	.03									
Income, $																		
≥ 20,000 *v* < 20,000†													7.71	3.29 to 12.13	< .001	1.89	0.72 to 3.05	.002
Cranial irradiation																		
Yes *v* no†	−0.52	−0.99 to −0.05	.031															

NOTE. Only results for significant factors are shown. SFQ interest, satisfaction, and relationship subscales had no significant relationship with any factor: age at onset of OF, age at follow-up, age at cancer diagnosis, marital status, education, income, ethnicity/race, currently receiving OCP/HRT, cranial irradiation, and major medical condition.

Abbreviations: HRT, hormone replacement therapy; OCP, oral contraceptive pill; OF, ovarian failure; SFQ, Sexual Functioning Questionnaire.

†Adjusted mean difference between level and referent.

*Referent.

Table 7. Psychosexual Function Among Survivors With OF (n = 235): WHQ

Factor	Somatic Symptoms			Memory/Concentration			Vasomotor Symptoms			Anxiety/Fears			Sleep Problems		
	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*	Mean Difference*	95% CI	*P*
Age at follow-up, years															
31-53 *v* 18-30†				2.63	1.01 to 6.83	.048									
Cranial irradiation															
Yes *v* no†							0.34	0.15 to 0.79	.012						
OCP/HRT															
Yes *v* no†													2.7	1.13 to 6.46	.026
Major medical condition															
Yes *v* no†	11.13	1.37 to 90.72	.024				2.05	1.00 to 4.19	.05	3.46	1.61 to 7.40	.001			

NOTE. Only results for significant factors are shown. WHQ depressed mood, sexual behavior, menstrual problems, and attractiveness subscales had no significant relationship with any factor: age at onset of OF, age at follow-up, age at cancer diagnosis, marital status, education, income, ethnicity/race, currently receiving OCP/HRT, cranial irradiation, and major medical condition.

Abbreviations: HRT, hormone replacement therapy; OCP, oral contraceptive pill; OF, ovarian failure; WHQ, Women's Health Questionnaire.

*Adjusted mean difference between level and referent.

†Referent.

Table 8. Psychosexual Function Among Survivors With OF (n = 235): SF-36

	Physical Functioning			Role—Physical			General Health Perception			Vitality			Role—Emotional			Mental Health			Physical Summary Scale		
Factor	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Age at onset of OF, years																					
26-48 *v* 12-25*																0.09	0.01 to 0.77	.028			
Marital status																					
Formerly *v* never*													12.26	1.08 to 139.7	.044						
Education																					
> High school *v* ≤ high school*	5.20	1.55 to 17.47	.008																		
Income, $																					
≥ 20,000 *v* < 20,000*							3.25	1.30 to 8.14	.012				3.32	1.26 to 8.77	.016						
Ethnicity																					
Other *v* non-Hispanic white*																0.06	0.004 to 0.85	.037			
Major medical condition																					
Yes *v* no*	0.20	0.06 to 0.65	.008	0.32	0.14 to 0.73	.006	0.48	0.23 to 1.00	.049	0.32	0.15 to 0.68	.003	0.44	0.19 to 1.00	.049				0.19	0.08 to 0.43	<.001

NOTE. Only results for significant factors are shown. SF-36 mental summary and social functioning subscales had no significant relationship with any factor: age at onset of OF, age at follow-up, age at cancer diagnosis, marital status, education, income, ethnicity/race, currently receiving OCP/HRT, cranial irradiation, and major medical condition.

Abbreviations: HRT, hormone replacement therapy; OCP, oral contraceptive pill; OF, ovarian failure; SF-36, Medical Outcomes Study Short Form-36.

*Referent.

that survivors of childhood cancer may be at greater risk compared with survivors of adult-onset cancers.

Survivors in our study were also less likely to have a sexual partner and were more likely to have never been sexually active compared with the sibling group. This finding is consistent with studies among survivors that demonstrate delays in psychosexual development and in achieving developmental milestones such as dating and age at first sexual intercourse.[5,10,15]

Our survivors also reported significantly higher rates of somatic symptoms, memory difficulties, and anxiety compared with siblings. One clinically significant finding was that one half to two thirds of survivors as well as siblings indicated problems with sleep, menstruation, and attractiveness. Our findings also indicated that although survivors did not report significantly impaired emotional QOL, they did endorse difficulties in physical functioning, which affected their ability to fulfill their roles and responsibilities. This finding is similar to the data of van Dijk[4] in which 20% of childhood cancer survivors reported limitations in their sexual life as a result of their illness and reported less positive QOL, compared with a normative sample.

In addition, among our survivors, OF was a risk factor for poorer sexual functioning and was related to survivors' sleep and vasomotor problems. However, survivors with OF did not endorse higher rates of psychological problems (eg, depression, somatization, and/or anxiety) suggesting that overall, outside the realm of sexual functioning, they were functioning quite well. Survivors' sexual dysfunction seems to be related to physiologic damage from cancer treatment rather than being related to sexual self-perception.

Only 40% of women with OF were taking OCP/HRT; however, it did not seem to improve psychological or sexual functioning. Although this finding may seem surprising, it is similar to what has been reported by others.[15] These results highlight a need for greater attention to treating OF and raises questions about whether OCP/HRT are truly ineffective in ameliorating sexual dysfunction or whether there are other relevant factors, such as type/dose of estrogen and compliance.

There are several limitations to note with regard to our study. First, survivor participants and nonparticipants differed in a variety of ways, potentially limiting our ability to generalize our findings and possibly leading to both underestimates and overestimates of dysfunction. In addition, we had only moderate response rates to our questionnaire, which may increase the potential for bias. Although response rates for siblings were lower, nonparticipant siblings only differed from participants on educational status. Nonetheless, our response rates are similar to other self-reported research of this topic[10] and do not seem to reflect a systematic response bias as reflected by our participants having similar characteristics as the overall CCSS survivor and sibling cohorts. Our respondents were likely older, better-educated women with fewer disabilities. In addition, our analyses excluded those who were not sexually active, and some participants who were not sexually active may have been less likely to have participated. Thus, our rates of sexual problems are probably underestimates. Last, we recognize the potential limitations introduced by the specific measures chosen for this study. Although the psychosexual measures used were rigorously validated and psychometrically sound, they may not have measured all aspects of the multifaceted construct of psychosexual functioning. Despite these limitations, this study has major strengths, including the large sample size, inclusion of participants with diverse cancer diagnoses, detailed sociodemographic and treatment data, and the inclusion of a large comparison group.

On the basis of our study, it is clear that adult female survivors of childhood cancer experience greater psychosexual dysfunction compared with siblings. OF is a significant risk factor among survivors, which does not seem to be moderated by use of OCP/HRT. Those at high risk are in need of targeted and tailored psychosexual interventions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jennifer S. Ford, Wendy Leisenring, Leslie L. Robison, Charles A. Sklar
Financial support: Leslie L. Robison
Administrative support: Leslie L. Robison
Provision of study materials or patients: Leslie L. Robison
Collection and assembly of data: Jennifer S. Ford, Wendy Leisenring, Marilyn Stovall, Lonnie Zeltzer, Leslie L. Robison, Charles A. Sklar
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Table A1. CCSS Institutions and Investigators

Institution	Investigators
St Jude Children's Research Hospital, Memphis, TN	Greg T. Armstrong, MD, MSCE,*† Melissa Hudson, MD,†‡§ Leslie L. Robison, PhD,† Daniel M. Green, MD,† Kevin R. Krull, PhD,† Kiri Ness, PhD†
Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL	Jennifer Reichek, MD, MSW‡
Children's Healthcare of Atlanta/Emory University, Atlanta, GA	Lillian Meacham, MD,‡ Ann Mertens, PhD†
Children's Hospitals and Clinics of Minnesota Minneapolis, St Paul, MN	Joanna Perkins, MD, MS‡
Children's Hospital Colorado, Aurora, CO	Brian Greffe, MD‡
Children's Hospital, Los Angeles, CA	Kathy Ruccione, RN, MPH‡
Children's Hospital, Oklahoma City, OK	John Mulvihill, MD†
Children's Hospital of Orange County, Orange, CA	Leonard Sender, MD‡
Children's Hospital of Philadelphia, Philadelphia, PA	Jill Ginsberg, MD‡
Children's Hospital of Pittsburgh, Pittsburgh, PA	Jean Tersak, MD‡
Children's National Medical Center, Washington, DC	Sadhna Shankar, MD,‡ Roger Packer, MD†
Cincinnati Children's Hospital Medical Center, Cincinnati, OH	Stella Davies, MD, PhD†‡
City of Hope Medical Center, Los Angeles, CA	Smita Bhatia, MD†‡
Cook Children's Medical Center, Ft Worth, TX	Paul Bowman, MD, MPH‡
Dana-Farber Cancer Institute/Children's Hospital, Boston, MA	Lisa Diller, MD†‡
Fred Hutchinson Cancer Research Center, Seattle, WA	Wendy Leisenring, ScD†‡
Hospital for Sick Children, Toronto, Ontario, Canada	Mark Greenberg, MBChB,‡ Paul C. Nathan, MD, MSc†‡
International Epidemiology Institute, Rockville, MD	John Boice, ScD†
Mayo Clinic, Rochester, MN	Vilmarie Rodriguez, MD‡
Memorial Sloan-Kettering Cancer Center, New York, NY	Charles Sklar, MD,†‡ Kevin Oeffinger, MD†
Miller Children's Hospital, Long Beach, CA	Jerry Finklestein, MD‡
National Cancer Institute, Bethesda, MD	Roy Wu, PhD,† Nita Seibel, MD,† Peter Inskip, ScD,† Julia Rowland, PhD†
Nationwide Children's Hospital, Columbus, Ohio	Randy Olshefski, MD,‡ Sue Hammond, MD†
Riley Hospital for Children, Indianapolis, IN	Terry A. Vik, MD‡
Roswell Park Cancer Institute, Buffalo, NY	Denise Rokitka, MD, MPH‡
St Louis Children's Hospital, St Louis, MO	Robert Hayashi, MD‡
Seattle Children's Hospital, Seattle, WA	Scott Baker, MD,‡ Eric Chow, MD, MPH†
Stanford University School of Medicine, Stanford, CA	Neyssa Marina, MD, MS,‡ Sarah S. Donaldson, MD†
Texas Children's Hospital, Houston, TX	Zoann Dreyer, MD‡
University of Alabama, Birmingham, AL	Kimberly Whelan, MD, MSPH‡
University of Alberta, Edmonton, Alberta, Canada	Yutaka Yasui, PhD†‡
University of California at Los Angeles, Los Angeles, CA	Jacqueline Casillas, MD, MSHS,‡ Lonnie Zeltzer, MD†
University of California at San Francisco, San Francisco, CA	Robert Goldsby, MD‡
University of Chicago, Chicago, IL	Tara Henderson, MD, MPH‡
University of Michigan, Ann Arbor, MI	Raymond Hutchinson, MD‡
University of Minnesota, Minneapolis, MN	Joseph Neglia, MD, MPH†‡
University of Southern California, Los Angeles, CA	Dennis Deapen, DrPH†
University of Texas Southwestern Medical Center, Dallas, TX	Daniel C. Bowers, MD‡
University of Texas MD Anderson Cancer Center, Houston, TX	Louise Strong, MD,†‡ Marilyn Stovall, MPH, PhD†

NOTE. CCSS is collaborative, multi-institutional project, funded as resource by National Cancer Institute, of individuals who survived ≥ 5 years after diagnosis of childhood cancer. CCSS involves retrospectively ascertained cohort of 20,346 childhood cancer survivors diagnosed before age 21 years between 1970 and 1986 and approximately 4,000 siblings of survivors, who serve as control group. Cohort was assembled through efforts of 26 participating clinical research centers in United States and Canada. Currently, we are expanding cohort to include additional 14,000 childhood cancer survivors diagnosed before age 21 years between 1987 and 1999. For information on how to access and use CCSS resource, visit www.stjude.org/ccss.

Abbreviation: CCSS, Childhood Cancer Survivor Study.

*Project principal investigator.

†Member of CCSS Steering Committee.

‡Institutional principal investigator.

§Project co-principal investigator.

Table A2. Psychosexual Functioning Among Survivors With OF by OCP/HRT Status: SFQ (n = 235)

Subscale	OCP/HRT (n = 94)			No OCP/HRT (n = 141)			Mean Difference*	*P*
	No.†	Mean	95% CI	No.†	Mean	95% CI		
Interest	91	1.85	1.42 to 2.28	139	1.59	1.22 to 1.97	0.25	.2
Desire	89	2.06	1.54 to 2.57	133	1.99	1.54 to 2.44	0.07	.78
Arousal	86	1.53	1.11 to 1.95	131	1.44	1.07 to 1.80	0.09	.63
Satisfaction	86	3.04	2.28 to 3.79	128	2.69	2.01 to 3.37	0.35	.29
Masturbation	70	0.61	0.23 to 0.98	110	0.65	0.33 to 0.97	−0.04	.82
Relationship	87	2.92	2.56 to 3.27	129	3.01	2.69 to 3.34	−0.1	.53
Activity	63	2.25	1.78 to 2.73	104	2.2	1.76 to 2.63	0.06	.78
Problems	61	5.35	1.27 to 9.43	102	3.53	−0.19 to 7.25	1.82	.31
Vaginal dryness	59	2.09	1.40 to 2.78	98	2.31	1.68 to 2.93	−0.21	.48
Vaginal tightness	60	2.4	1.72 to 3.08	95	2.54	1.92 to 3.16	−0.13	.65
Painful penetration	60	2.38	1.76 to 3.01	100	2.17	1.60 to 2.74	0.21	.44
Vaginal bleeding	60	1.53	1.01 to 2.06	99	1.58	1.10 to 2.07	−0.05	.82
Sharp pain	60	1.64	1.23 to 2.05	98	1.71	1.33 to 2.08	−0.06	.72
Increased sensitivity	60	1.61	1.08 to 2.14	97	1.84	1.35 to 2.32	−0.23	.33
Overall SFQ score	61	2.98	1.86 to 4.11	105	2.51	1.49 to 3.54	0.47	.34

NOTE. Adjusted for age at study, age at primary diagnosis, marital status, education level, income, ethnicity/race, cranial irradiation, and major medical condition.
Abbreviations: HRT, hormone replacement therapy; OCP, oral contraceptive pill; OF, ovarian failure; SFQ, Sexual Functioning Questionnaire.
*Mean difference from beta coefficient in adjusted models for OF compared with no OF.
†Missing No. for row not shown.

Table A3. Psychosexual Functioning Among Survivors With OF by OCP/HRT Status: WHQ (n = 235)

Subscale	OCP/HRT (n = 94)		No OCP/HRT (n = 141)		OR*	*P*
	N	%	N	%		
Depressed mood					0.6	.2
> 0 to 1	66	70.2	86	61.0		
0	28	29.8	55	39.0		
Somatic symptoms					0.72	.57
> 0 to 1	83	88.3	125	88.7		
0	11	11.7	16	11.3		
Memory/concentration					0.82	.62
> 0 to 1	57	60.6	84	60.0		
0	37	39.4	56	40.0		
Vasomotor symptoms					0.63	.25
> 0 to 1	38	40.4	65	46.1		
0	56	59.6	76	53.9		
Anxiety/fears					0.84	.66
> 0 to 1	56	59.6	82	58.2		
0	38	40.4	59	41.8		
Sexual behavior					1.42	.44
> 0 to 1	49	61.3	81	70.4		
0	31	38.8	34	29.6		
Sleep problems					0.37	.026
> 0 to 1	74	78.7	95	67.4		
0	20	21.3	46	32.6		
Menstrual problems					0.62	.22
> 0 to 1	67	71.3	82	58.2		
0	27	28.7	59	41.8		
Attractiveness					0.84	.65
> 0 to 1	48	51.1	82	58.2		
0	46	48.9	59	41.8		

NOTE. Adjusted for age at study, age at primary diagnosis, marital status, education level, income, ethnicity/race, cranial irradiation, and major medical condition.
Abbreviations: HRT, hormone replacement therapy; OCP, oral contraceptive pill; OF, ovarian failure; WHQ, Women's Health Questionnaire.
OF as referent.