

Scarring, Disfigurement, and Quality of Life in Long-Term Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose

Childhood cancer survivors are at increased risk for adverse outcomes and chronic medical conditions. Treatment-related scarring, disfigurement, and persistent hair loss, in addition to their long-term impact on psychological distress or health-related quality of life (HRQOL), have received little attention.

Patients and Methods

Self-reported scarring/disfigurement and persistent hair loss were examined in 14,358 survivors and 4,023 siblings from the Childhood Cancer Survivor Study. Multivariable models were used to examine associations with demographic and cancer treatment. The impact of disfigurement and hair loss on HRQOL (ie, Medical Outcomes Short Form-36) and emotional distress (ie, Brief Symptom Inventory-18) was examined.

Results

Survivors reported a significantly higher rate of scarring/disfigurement compared with siblings for head/neck (25.1% v 8.4%), arms/legs (18.2% v 10.2%), and chest/abdomen (38.1% v 9.1%), as well as hair loss (14.0% v 6.3%). In age-, sex-, and race-adjusted models, cranial radiation exposure ≥ 36 Gy increased risk for head/neck disfigurement (relative risk [RR], 2.42; 95% CI, 2.22 to 2.65) and hair loss (RR, 4.24; 95% CI, 3.63 to 4.95). Adjusting for cranial radiation, age, sex, race, education, and marital status, survivor hair loss increased risk of anxiety (RR, 1.60; 95% CI, 1.23 to 2.07), whereas head/neck disfigurement increased risk of depression (RR, 1.19; 95% CI, 1.01 to 1.41). Limitations due to emotional symptoms were associated with head/neck disfigurement (RR, 1.24; 95% CI, 1.10 to 1.41), arm/leg disfigurement (RR, 1.19; 95% CI, 1.05 to 1.35), and hair loss (RR, 1.26; 95% CI, 1.09 to 1.47).

Conclusion

Survivors of childhood cancer are at increased risk for disfigurement and persistent hair loss, which is associated with future emotional distress and reduced quality of life. Future studies are needed to better identify and manage functional outcomes in these patients.

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INTRODUCTION

Advances in pediatric oncology have led to remarkable increases in overall survival into adulthood.¹ However, effects of cancer therapy on young, developing bodies continue to manifest years after therapy completion.² Potential late effects include obesity, thyroid dysfunction, cardiovascular abnormalities, and secondary neoplasms, among others.²⁻⁶ Little attention has been directed toward non-life-threatening consequences of childhood cancer such as scarring, disfigurement, or persistent hair loss that may adversely affect psychosocial functioning and quality of life.

Scarring and disfigurement in childhood cancer survivors occur secondary to tissue biopsies, high-dose radiation therapy (especially to the head and neck region, which can lead to cranial and spinal deformities), placement of catheters or central lines, and surgeries to resect tumors or amputate limbs.⁷⁻⁹ Hair loss results from cranial radiation or chemotherapy (ie, busulfan or cyclophosphamide).¹⁰ In addition, survivors treated with ionizing radiation are at increased risk for nonmelanoma skin cancers, leaving additional scarring or disfigurement.³

Available data on the prevalence of these outcomes among adult childhood cancer survivors are limited. A small single-site study of dermatologic

conditions and scarring conducted in a long-term follow-up clinic found 33% of 78 adult childhood cancer survivors reported treatment-related scarring compared with 1.5 to 4.5% in the general population.¹¹

Although scarring and disfigurement during childhood can negatively affect emotional functioning and quality of life,¹²⁻¹⁴ no data have been published examining this impact in long-term survivors or childhood cancer. The current report is the first to provide prevalence data related to scarring, disfigurement, and persistent hair loss in adult survivors of childhood cancer, as well as to examine the impact of these sequelae on emotional distress and quality of life.

PATIENTS AND METHODS

Participants

Participants included survivors and sibling controls from the Childhood Cancer Survivor Study (CCSS). The CCSS is a resource funded by the National Cancer Institute and consists of a retrospective cohort of survivors treated for childhood cancer at one of 26 collaborating institutions in North America. Human subjects committees at each institution approved the study protocol, and participants provided informed consent for questionnaires and medical record abstraction. Participants were diagnosed before age 21 years with leukemia, CNS cancers, Hodgkin's lymphoma, non-Hodgkin's lymphoma, kidney cancers, neuroblastoma, soft-tissue sarcomas, or bone tumors; started treatment between January 1, 1970, and December 31, 1986; and survived at least 5 years from diagnosis. Details of this cohort and the study design have been described elsewhere.¹⁵⁻¹⁸ The data used in this analysis reflect the CCSS database as of March 2010.

Among the 20,691 eligible survivors treated at CCSS collaborating institutions, 17,633 were located, and 14,358 (81.4%) participated in the baseline survey. Fifty percent of participating survivors were randomly selected and asked to nominate their nearest-age sibling for the comparison group. Of the 4,775 eligible siblings sent a baseline questionnaire, 4,023 (84.3%) participated in the baseline survey. Baseline surveys were completed by parents for survivors and siblings who were younger than 18 years and for survivors who died \geq 5 years after diagnosis but before the survey. A follow-up survey was conducted starting in 2003 (2003 follow-up) that focused on health behaviors and psychosocial outcomes. The follow-up was sent to 11,570 survivors, and 9,307 (80.4%) completed it. To be included in the analyses of the distress and quality-of-life outcomes, the 2003 survey must have been completed by a survivor who was at least 18 years old at that time, resulting in an analytic sample of 7,178 survivors.

Medical Record Abstraction

Information related to cancer treatment was abstracted from the survivor's medical record. Surgery and chemotherapy were categorized into three groups: (1) surgery with chemotherapy, (2) surgery without chemotherapy, and (3) no surgery (chemotherapy alone). Radiation exposure variables were created for the following body regions: cranial, limbs, and trunk of body. Radiation to the limbs and radiation to the trunk were coded as dichotomous variables. Cranial radiation was grouped by dosage as follows: none, scatter exposure only, direct cranial less than 20 Gy, direct cranial 20 to 35 Gy, and direct cranial \geq 36 Gy.

In addition to the original cancer-related surgery abstracted from medical records, subsequent surgeries were reported through a series of questions in the baseline survey. These were grouped into three categories: surgery on limb(s), surgery on head or neck, and surgery on trunk of body. The body region-specific indicators were used when assessing risk for scarring or disfigurement. For the remaining analyses, the body region-specific surgeries were combined into a single dichotomous variable (ie, yes = yes on any region-specific indicator).

Outcome Variables

Information on the prevalence of scarring and disfigurement was obtained on the baseline survey, which included separate yes/no questions for

head/neck, arm/leg, and chest/abdomen areas and the presence of persistent hair loss.

Psychological distress and quality-of-life data were taken from the 2003 follow-up. Distress was evaluated using the Brief Symptom Inventory (BSI), an 18-item self-report measure of symptoms experienced over the prior 7 days. Scoring results in a global severity index and three subscale scores (ie, anxiety, depression, and somatization). Scores were dichotomized on the basis of whether performance was "impaired" or not, with impairment defined as a score \geq 90th percentile on standardized norms.¹⁹ Health-related quality of life (HRQOL) was evaluated using the Medical Outcomes Short Form, a 36-item self-report measure of general health over the past 4 weeks. Scoring results in two summary scales (ie, physical component summary and mental component summary) and eight individual subscales.²⁰ All scores were dichotomized with *t* scores at least one standard deviation below the population mean (\leq 40) classified as poor health outcomes.

Statistical Analysis

Comparisons between survivors and siblings were performed using generalized estimating equations with robust variance estimates to account for intrafamily correlation.²¹ For each outcome, relative risk (RR) estimates and accompanying CIs and *P* values were obtained via statistical modeling. Because outcomes were not rare, a modified Poisson regression approach with robust variance estimation was used to calculate relative risks.²² Sex, race, and age at time of questionnaire were included as adjustment factors in all multivariable models. With the exception of the models comparing cancer survivors versus sibling controls, all multivariable models were adjusted for the patient's age at cancer diagnosis, recurrence of the primary cancer, and diagnosis with a second (new) malignant neoplasm before the time the outcome variable was measured. In models for scarring and hair loss, the impact of proxy reporting was investigated. Analyses of psychological distress and quality-of-life outcomes were restricted to cases with self-reported data. Factors for education and marital status were included in models for psychological distress and quality of life. Factors relating to cancer treatments were first evaluated in univariable analyses and included in multivariable models if they showed a two-sided *P* value \leq .10. For psychological distress and quality of life, which each have multiple subscale scores, the multivariable model structure was determined for outcomes on the basis of the scale's overall summary score. For consistency and comparability, analyses of individual subscale component dimensions were done using the same structure as for the summary score. Potential interactions between demographic factors (sex, marital status at the time of the BSI/HRQOL assessment) and scarring/disfigurement or hair loss were investigated for the psychosocial and HRQOL outcomes. Interaction terms of interest were first added to the multivariable model as a set. Nonsignificant interactions were then removed, and the final model was estimated. In the multivariable modeling, a two-sided *P* value less than .05 was considered statistically significant, although we exercised caution in interpreting *P* values between .05 and .01 because of the number of variables considered. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and STATA 11 (STATA, College Station, TX) software.

RESULTS

Reported Scarring in Survivors Versus Siblings

Survivors were more likely to be younger, male, and nonminority than siblings (Table 1). Scarring and disfigurement were higher (all *P* < .001) for survivors compared with siblings across all sites: head or neck (25.1% v 8.4%), arms or legs (18.2% v 10.2%), chest or abdomen (38.1% v 9.1%), and persistent hair loss (14.0% v 6.3%). For hair loss, prevalence rates for survivors and siblings were also calculated and stratified by sex (males, 14.7% v 8.8%; female, 13.3% v 3.9%). In regression models adjusted for age at baseline, sex, and race, survivors were at higher risk than siblings to have scarring or disfigurement in the region of the head/neck (RR, 3.00; 95% CI, 2.69 to 3.34), arm/leg (RR, 1.89; 95% CI, 1.70 to 2.08), and chest/abdomen (RR, 4.26; 95%

Table 1. Demographic and Clinical Characteristics of Cancer Survivors and Siblings

Characteristic	Survivors (n = 14,358)*		Siblings (n = 4,023)*		P
	No.	%	No.	%	
Age at diagnosis, years					
0-4	5,753	40.1	NA		
5-9	3,201	22.3	NA		
10-14	2,913	20.3	NA		
15-21	2,491	17.3	NA		
Age at baseline, years					< .001
5-20	5,237	36.5	1,092	27.1	
20-29	5,884	41.0	1,418	35.2	
30-39	2,905	20.2	1,170	29.1	
40-49	332	2.3	343	8.5	
Elapsed time, years					
Diagnosis to baseline			NA		
Mean	16.1				
SD	4.9				
Baseline to follow-up 2003†			NA		
Mean	7.7				
SD	1.2				
Sex					< .001
Male	7,713	53.7	1,937	48.1	
Female	6,645	46.3	2,086	51.9	
Race					< .001
White	12,691	89.2	3,569	92.0	
Black	713	5.0	113	2.9	
Other/mixed	830	5.8	199	5.1	
Diagnosis					
Leukemia	4,830	33.6	NA		
CNS	1,876	13.1	NA		
Hodgkin's lymphoma	1,927	13.4	NA		
Non-Hodgkin's lymphoma	1,080	7.5	NA		
Kidney tumor	1,256	8.7	NA		
Neuroblastoma	954	6.6	NA		
Soft tissue sarcoma	1,246	8.7	NA		
Bone tumor	1,189	8.3	NA		
Surgery and chemotherapy (treatment for primary cancer diagnosis)					
No surgery (chemotherapy only)	2,307	18.4	NA		
Surgery, no chemotherapy	2,388	19.1	NA		
Surgery, with chemotherapy	7,825	62.5	NA		
Cranial radiation, Gy					
None	4,085	33.8	NA		
Scatter exposure only	3,751	31.1	NA		
Direct, ≤ 20	1,402	11.6	NA		
Direct, 20-36	1,465	12.1	NA		
Direct, ≥ 36	1,376	11.4	NA		
Nonmelanoma and melanoma skin cancer					
No	14,167	98.7	NA		
Yes	187	1.3	NA		
Surgeries reported on baseline questionnaire‡					
Surgery on limb(s)§	1,088	7.7	40	1.0	< .001
Surgery on head or neck	1,143	8.1	57	1.4	< .001
Surgery on trunk of body	2,325	16.6	120	3.0	< .001

(continued in next column)

Table 1. Demographic and Clinical Characteristics of Cancer Survivors and Siblings (continued)

Characteristic	Survivors (n = 14,358)*		Siblings (n = 4,023)*		P
	No.	%	No.	%	
Scarring/disfigurement and hair loss					
Head/neck scarring or disfigurement	3,557	25.1	335	8.4	< .001
Arm/leg scarring or disfigurement	2,576	18.2	408	10.2	< .001
Chest/abdomen scarring or disfigurement	5,405	38.1	366	9.1	< .001
Persistent hair loss					
All subjects	1,989	14.0	251	6.3	< .001
Male	1,115	14.7	169	8.8	< .001
Female	874	13.3	82	3.9	< .001
Person filling out the baseline questionnaire					< .001
Self	9,525	66.3	3,201	79.6	
Proxy for survivor	3,672	25.6	822	20.4	
Proxy for deceased patient	1,161	8.1	0	0.0	

Abbreviations: MRAF, Medical Record Abstract Form; NA, not applicable; SD, standard deviation.

*Sample sizes vary slightly because of a small amount of missing data, which accounts for minor variations in percentages.

†This mean was computed for the 7,178 survivors who met the eligibility requirement for inclusion in the analyses of Brief Symptom Inventory and health-related quality of life outcomes for this study. Follow-up 2003 data on siblings were not used in this study.

‡Surgery types in this section are not mutually exclusive. Statistics reported in these rows are number Yes and % Yes.

§A small number of subjects (n = 7) failed to report limb/digit amputations that were noted in their MRAF cancer treatment records on their baseline questionnaire. For these subjects, the amputation report from the MRAF supersedes the baseline questionnaire data.

CI, 3.85 to 4.71). For hair loss, sex-specific RR estimates for survivors versus siblings were 1.76 (95% CI, 1.51 to 2.05) for male survivors and 3.58 (95% CI, 2.87 to 4.47) for female survivors after adjusting for age and race.

Clinical Predictors of Scarring and Disfigurement in Survivors

Surgery as part of treatment for primary cancer, with or without chemotherapy, was associated with a two-fold increased risk of head/neck, arm/leg, and chest/abdomen scarring (Table 2). There was a dose-dependent effect of cranial radiation on risk for persistent hair loss (RR, 4.24 for ≥ 36Gy, 3.55 for 20 to < 36 Gy, 2.23 for < 20 Gy, and 1.49 for scatter v no radiation). Radiation targeting the limbs and trunk of body were associated with scarring (RR, 2.43, 95% CI, 2.19 to 2.69; and RR, 1.52, 95% CI, 1.44 to 1.60, respectively). Skin cancer was associated with head/neck scarring (RR, 1.40; 95% CI, 1.14 to 1.72). Recurrence and diagnosis with a second malignant neoplasm were associated with each of the scarring outcomes (all $P < .01$). Recurrence was also associated with persistent hair loss ($P < .001$).

Risk Factors for Increased Distress

Depressive symptoms increased for participants with head/neck (RR, 1.19; 95% CI, 1.01 to 1.41) or arm/leg (RR, 1.22; 95% CI, 1.02 to 1.45) scarring or disfigurement (Table 3). The association between persistent hair loss and depressive symptoms was significant only for

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Table 2. Multivariable RRs for Scarring or Disfigurement and Persistent Hair Loss

Characteristic	Type of Condition Reported on Baseline Questionnaire:											
	Head/Neck Scarring or Disfigurement			Arm/Leg Scarring or Disfigurement			Chest/Abdomen Scarring or Disfigurement			Persistent Hair Loss		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Age at diagnosis, years												
0-4 (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
5-9	1.08	0.99 to 1.18	.08	0.97	0.85 to 1.10	.59	0.83	0.77 to 0.88	<.001	1.28	1.13 to 1.46	<.001
10-21	1.09	0.99 to 1.20	.07	1.06	0.93 to 1.21	.37	0.80	0.74 to 0.86	<.001	1.66	1.44 to 1.91	<.001
Age at baseline, years												
5-20 (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
20-29	1.08	0.96 to 1.20	.20	1.26	1.07 to 1.49	<.01	0.98	0.89 to 1.07	.61	0.99	0.86 to 1.14	.91
30-49	0.98	0.85 to 1.13	.80	1.22	1.01 to 1.48	.04	0.88	0.79 to 0.89	.03	1.07	0.89 to 1.30	.45
Sex												
Male (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Female	0.99	0.93 to 1.05	.64	1.19	1.10 to 1.29	<.001	1.14	1.09 to 1.19	<.001	1.02	0.93 to 1.11	.74
Race												
White (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Black	0.88	0.75 to 1.05	.16	1.12	0.92 to 1.36	.26	0.89	0.78 to 1.01	.07	0.94	0.73 to 1.23	.67
Other/mixed	0.97	0.83 to 1.12	.65	1.10	0.93 to 1.31	.25	0.92	0.82 to 1.03	.14	1.38	1.16 to 1.64	<.001
Surgery and chemotherapy (treatment for primary cancer diagnosis)												
No surgery (chemotherapy only) (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Surgery, no chemotherapy	2.81	2.42 to 3.28	<.001	2.07	1.72 to 2.48	<.001	2.26	2.01 to 2.54	<.001	1.09	0.91 to 1.29	.34
Surgery, with chemotherapy	1.88	1.63 to 2.17	<.001	2.04	1.73 to 2.40	<.001	2.48	2.23 to 2.76	<.001	1.04	0.91 to 1.19	.53
Cranial radiation, Gy												
None (reference group)	1.00	—	—							1.00	—	—
Scatter exposure only	1.28	1.17 to 1.40	<.001							1.36	1.17 to 1.58	<.001
Direct, ≤ 20	1.13	0.98 to 1.31	.09							2.19	1.84 to 2.62	<.001
Direct, 20-36	1.12	0.97 to 1.28	.13							3.13	2.67 to 3.67	<.001
Direct, > 36	2.40	2.20 to 2.63	<.001							3.61	3.08 to 4.23	<.001
Radiation targeting limb(s)												
No (reference group)				1.00	—	—						
Yes				2.43	2.19 to 2.69	<.001						
Radiation targeting trunk of body												
No (reference group)							1.00	—	—			
Yes							1.52	1.44 to 1.60	<.001			
Skin cancer												
No (reference group)	1.00	—	—				1.00	—	—			
Yes	1.40	1.14 to 1.72	<.01				0.93	0.79 to 1.10	.39			
Surgery affecting head/neck area reported on baseline questionnaire												
No (reference group)	1.00	—	—							1.00	—	—
Yes	1.89	1.75 to 2.03	<.001							1.07	0.93 to 1.24	.35
Surgery affecting limb(s) reported on baseline questionnaire												
No (reference group)				1.00	—	—						
Yes				2.45	2.23 to 2.68	<.001						
Surgery affecting trunk of body reported on baseline questionnaire												
No (reference group)							1.00	—	—			
Yes							1.82	1.74 to 1.92	<.001			
Recurrence												
No	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	1.25	1.15 to 1.36	<.001	1.16	1.04 to 1.29	<.01	1.10	1.04 to 1.18	<.01	1.42	1.26 to 1.59	<.001
Diagnosed with a second malignant neoplasm												
No	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	1.48	1.30 to 1.70	<.001	1.33	1.11 to 1.60	<.01	1.29	1.18 to 1.40	<.001	1.15	0.93 to 1.41	.19
Proxy reporting												
Self-report (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Surrogate for survivor	1.05	0.93 to 1.18	.45	0.83	0.69 to 1.00	.05	1.25	1.14 to 1.36	<.001	0.54	0.44 to 0.66	<.001
Surrogate for deceased patient	1.12	1.00 to 1.26	.05	1.01	0.87 to 1.18	.866	1.11	1.01 to 1.21	.03	2.53	2.21 to 2.89	<.001

Abbreviation: RR, relative risk.

Table 3. Multivariable RRs for Depression, Anxiety, and Somatization

Characteristic	BSI Depression Subscale			BSI Anxiety Subscale			BSI Somatization Subscale			BSI Global Status Index		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Head/neck scarring or disfigurement												
No (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	1.19	1.01 to 1.41	.03	1.19	0.95 to 1.48	.12	(male) 1.51*	1.19 to 1.91	< .001	1.19	1.00 to 1.43	.05
							(female) 1.07*	0.89 to 1.29	.46			
Arm/leg scarring or disfigurement												
No (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	1.22	1.02 to 1.45	.03	1.11	0.88 to 1.40	.38	1.23	1.05 to 1.43	.01	1.25	1.04 to 1.51	.02
Chest/abdomen scarring or disfigurement												
No (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	(married) 1.24†	0.96 to 1.62	.10	(married) 1.08†	0.79 to 1.47	.64	1.18	1.02 to 1.36	.02	1.07	0.90 to 1.27	.44
	(div/sep) 1.27†	0.87 to 1.84	.22	(div/sep) 1.94†	1.21 to 3.10	.01						
	(never married) 0.80†	0.65 to 0.98	.03	(never married) 1.03†	0.78 to 1.35	.85						
Persistent hair loss												
No (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	(male) 1.15*	0.86 to 1.54	.34	1.60	1.23 to 2.07	< .001	1.42	1.18 to 1.71	< .001	1.44	1.15 to 1.80	< .01
	(female) 1.60*	1.22 to 2.11	.001									
Age at diagnosis, years												
0-4 (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
5-9	1.02	0.84 to 1.23	.87	0.96	0.74 to 1.23	.73	1.12	0.93 to 1.34	.23	0.98	0.79 to 1.22	.86
10-21	1.02	0.81 to 1.29	.86	1.08	0.81 to 1.45	.60	1.11	0.90 to 1.39	.33	1.05	0.81 to 1.36	.73
Age at time of BSI Assessment, years												
< 30 (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
30-39	1.00	0.81 to 1.22	.98	1.01	0.78 to 1.30	.96	0.95	0.78 to 1.15	.60	1.00	0.80 to 1.26	.99
≥ 40	1.23	0.92 to 1.66	.16	0.88	0.60 to 1.27	.49	1.03	0.79 to 1.34	.85	1.15	0.84 to 1.58	.39
Sex												
Male (reference group)				1.00	—	—				1.00	—	—
Female	‡			0.98	0.82 to 1.17	.84	‡			1.16	1.00 to 1.34	.06
Race												
White (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Black	0.86	0.55 to 1.34	.50	1.04	0.61 to 1.77	.88	1.09	0.75 to 1.57	.66	1.03	0.67 to 1.60	.88
Other/mixed	1.10	0.80 to 1.51	.57	1.02	0.67 to 1.57	.91	0.86	0.61 to 1.20	.36	1.01	0.69 to 1.46	.98
College graduate												
No	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	0.79	0.68 to 0.92	< .01	0.71	0.59 to 0.86	< .001	0.63	0.55 to 0.73	< .001	0.64	0.54 to 0.75	< .001
Marital status												
Married/living as married							1.00	—	—	1.00	—	—
Divorced, separated, widowed, or no longer living as married	‡			‡			1.48	1.23 to 1.79	< .001	1.95	1.54 to 2.47	< .001
Never married or lived as married	‡			‡			1.10	0.94 to 1.30	.24	1.88	1.55 to 2.29	< .001
Cranial radiation, Gy												
None (reference group)	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Scatter exposure only	0.82	0.68 to 0.99	.04	0.73	0.58 to 0.92	.01	1.11	0.94 to 1.31	.23	0.88	0.73 to 1.07	.21
Direct, ≤ 20 Gy	1.00	0.79 to 1.26	.99	0.69	0.50 to 0.95	.02	1.21	0.96 to 1.52	.10	0.77	0.58 to 1.02	.07
Direct, 20-36 Gy	1.01	0.80 to 1.27	.93	0.76	0.56 to 1.05	.09	1.18	0.94 to 1.49	.14	1.01	0.78 to 1.30	.93
Direct, ≥ 36 Gy	0.88	0.68 to 1.15	.35	0.79	0.56 to 1.11	.17	1.03	0.80 to 1.34	.82	0.77	0.57 to 1.05	.09

(continued on following page)

Table 3. Multivariable RRs for Depression, Anxiety, and Somatization (continued)

Characteristic	BSI Depression Subscale			BSI Anxiety Subscale			BSI Somatization Subscale			BSI Global Status Index		
	RR	95% CI	<i>P</i>	RR	95% CI	<i>P</i>	RR	95% CI	<i>P</i>	RR	95% CI	<i>P</i>
Surgery on baseline questionnaire												
No	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	1.24	1.06 to 1.45	.01	1.18	0.97 to 1.44	.10	1.34	1.16 to 1.55	< .001	1.35	1.14 to 1.60	< .001
Recurrence												
No	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	1.19	0.99 to 1.44	.07	0.98	0.75 to 1.29	.91	1.09	0.91 to 1.32	.35	1.10	0.88 to 1.37	.41
Diagnosed with a second malignant neoplasm												
No	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Yes	1.09	0.79 to 1.50	.61	0.85	0.54 to 1.36	.50	1.24	0.97 to 1.57	.08	0.95	0.67 to 1.35	.78

Abbreviations: BSI, Brief Symptom Inventory; div/sep, divorced/separated; RR, relative risk.

*This model included a significant two-way interaction term between the risk factor in this row (head/neck scarring or persistent hair loss) and the subject's sex. The result shown in the cell is the RR of impairment on the BSI outcome for the scarring or hair loss variable (yes v no) among the male or among the female subjects only, as noted in the cell's top margin.

†This model included a significant two-way interaction term between chest/abdomen scarring and marital status. The result shown in the cell is the RR of impairment on the BSI outcome for the chest/abdomen scarring variable (yes v no) among subjects in the marital status category noted in the cell's top margin.

‡An overall RR estimate is not shown for this demographic factor as a result of the presence of significant interactions with other variables in the model.

females (RR, 1.60; 95% CI, 1.22 to 2.11). There was also a significant interaction between marital status and chest/abdomen scarring, resulting in lower risk for symptoms of depression in survivors who were never married (RR, 0.80; 95% CI, 0.65 to 0.98). Anxiety symptoms were associated with persistent hair loss (RR, 1.60; 95% CI, 1.23 to 2.07). There was a significant interaction between chest/abdomen scarring and marital status, resulting in higher symptoms of anxiety in survivors who were divorced, separated, or widowed (RR, 1.94; 95% CI, 1.21 to 3.10). Somatization was associated with arm/leg (RR, 1.23; 95% CI, 1.05 to 1.43) and chest/abdomen (RR, 1.18; 95% CI, 1.02 to 1.36) scarring or disfigurement and with persistent hair loss (RR, 1.42; 95% CI, 1.18 to 1.71). The impact of head/neck scarring on somatization was significant only for male survivors (RR, 1.51; 95% CI, 1.19 to 1.91). Survivors with a history of surgery had increased somatization (RR, 1.34; 95% CI, 1.16 to 1.55). Persistent hair loss was found to be a strong predictor of impairment on the Global Severity Index (RR, 1.44; 95% CI, 1.15 to 1.80). Being a college graduate was associated with a lower risk of depression (RR, 0.79; 95% CI, 0.68 to 0.92), anxiety (RR, 0.71; 95% CI, 0.59 to 0.86), and somatization (RR, 0.63; 95% CI, 0.55 to 0.73), and it is notable that scarring and disfigurement remained important even after adjusting for education.

Risk Factors for Decreased HRQOL

Relative risks for HRQOL outcomes associated with scarring/disfigurement and hair loss variables are shown in Table 4. All models are adjusted for the subject's age at cancer diagnosis, age at the time of assessment, sex, race, education, marital status, treatments received for cancer diagnosis, self-reported surgery, recurrence of primary cancer, and diagnosis with a second malignant neoplasm. Interactions between sex and scarring/disfigurement and hair loss were examined, found not to be significant, and were dropped from the final model. Interactions between marital status and scarring/disfigurement and hair loss were also examined. Two significant interactions were identified, for the arm/leg scarring ($P = .03$) and hair loss variables ($P = .04$) in the Physical Component Summary Score

model. Stratum-specific RRs are provided for the factors involved in the significant interactions.

All eight HRQOL subscales were adversely affected by one or more of the scarring, disfigurement, or hair loss variables. Impaired general health was associated with scarring or disfigurement and persistent hair loss (head/neck RR, 1.17, 95% CI, 1.04 to 1.32; arm/leg RR, 1.21, 95% CI, 1.07 to 1.36; chest/abdomen RR, 1.16, 95% CI, 1.04 to 1.30; hair loss RR, 1.39, 95% CI, 1.21 to 1.60). Impairment in physical function was associated with arm/leg scarring or disfigurement (RR, 2.18; 95% CI, 1.86 to 2.54) and with hair loss (RR, 1.30; 95% CI, 1.06 to 1.60). Increased bodily pain was associated with arm/leg scarring or disfigurement (RR, 1.72; 95% CI, 1.50 to 1.96) and with hair loss (RR, 1.30; 95% CI, 1.10 to 1.55). Reduced mental health was associated with persistent hair loss (RR, 1.42; 95% CI, 1.10 to 1.82) and with head/neck scarring or disfigurement (RR, 1.26; 95% CI, 1.02 to 1.55). Role limitation due to emotional functioning was associated with head/neck (RR, 1.24; 95% CI, 1.10 to 1.41) and arm/leg (RR, 1.19; 95% CI, 1.05 to 1.35) scarring or disfigurement and persistent hair loss (RR, 1.26; 95% CI, 1.09 to 1.47). Scarring/disfigurement and hair loss also negatively impacted vitality and social functions.

DISCUSSION

To our knowledge, this is the largest study to examine scarring, disfigurement, and persistent hair loss within survivors of childhood cancer. As would be expected, a higher rate was found among survivors compared with siblings, with survivors four times more likely to report chest/abdomen scarring or disfigurement, three times more likely to report head/neck scarring or disfigurement, more than twice as likely to report persistent hair loss, and nearly twice as likely to report arm/leg scarring or disfigurement. Furthermore, among survivors, the presence of persistent hair loss was associated with depressive symptoms, anxiety, and increased somatization, controlling for treatment

Table 4. Multivariable Relative Risks for Impairment in Health-Related Quality of Life

Characteristic	SF-36 Subscales*											
	Physical Function			Role Physical			Bodily Pain			General Health		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Head/neck scarring or disfigurement, yes v no	0.86	0.72 to 1.03	.10	1.18	1.05 to 1.33	<.01	1.08	0.93 to 1.25	.31	1.17	1.04 to 1.32	<.01
Arm/leg scarring or disfigurement, yes v no	2.18	1.86 to 2.54	<.001	1.50	1.34 to 1.68	<.001	1.72	1.50 to 1.96	<.001	1.21	1.07 to 1.36	<.01
Chest/abdomen scarring or disfigurement, yes v no	0.91	0.77 to 1.06	.21	1.10	0.99 to 1.23	.09	1.15	1.01 to 1.32	.04	1.16	1.04 to 1.30	<.01
Persistent hair loss, yes v no	1.30	1.06 to 1.60	.01	1.25	1.09 to 1.44	<.01	1.30	1.10 to 1.55	<.01	1.39	1.21 to 1.60	<.001
Characteristic	SF-36 Subscales*											
	Vitality			Social Function			Role Emotional			Mental Health		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
Head/neck scarring or disfigurement, yes v no	1.09	1.00 to 1.18	.04	1.07	0.97 to 1.18	.20	1.24	1.10 to 1.41	<.001	1.26	1.02 to 1.55	.03
Arm/leg scarring or disfigurement, yes v no	1.14	1.05 to 1.23	<.01	1.15	1.04 to 1.27	<.01	1.19	1.05 to 1.35	<.01	1.11	0.89 to 1.38	.34
Chest/abdomen scarring or disfigurement, yes v no	1.02	0.95 to 1.10	.59	1.07	0.98 to 1.17	.12	1.10	0.98 to 1.23	.10	1.07	0.88 to 1.30	.49
Persistent hair loss, yes v no	1.17	1.06 to 1.29	<.01	1.17	1.04 to 1.32	.01	1.26	1.09 to 1.47	<.01	1.42	1.10 to 1.82	<.01
Characteristic	SF-36 Summary Scores*											
	Physical Component Summary Score			Mental Component Summary Score								
	RR	95% CI	P	RR	95% CI	P						
Head/neck scarring or disfigurement, yes v no	1.00	0.86 to 1.16	.99	1.29	1.14 to 1.47	<.001						
Arm/leg scarring or disfigurement, yes v no	(married) 1.64†	1.38 to 1.95	<.001	1.14	1.00 to 1.30	.05						
	(div/sep) 1.92†	1.39 to 2.64	<.001									
	(never married) 2.22†	1.76 to 2.79	<.001									
Chest/abdomen scarring or disfigurement, yes v no	1.00	0.87 to 1.14	.95	1.00	0.89 to 1.13	.96						
Persistent hair loss, yes v no	(married) 1.20†	0.94 to 1.52	.14	1.22	1.03 to 1.44	.02						
	(div/sep) 1.29†	0.86 to 1.94	.23									
	(never married) 1.72†	1.30 to 2.26	<.001									

Abbreviations: div/sep, divorced/separated; RR, risk ratio; SF-36, Medical Outcomes Short Form.

*All models included adjustment for age at cancer diagnosis, age at the time of assessment, sex, race, education, marital status, treatments received for primary cancer diagnosis (surgery/chemotherapy and cranial radiation categories), self-reported surgery from the baseline questionnaire, recurrence of primary cancer, and diagnosis with a second malignant neoplasm.

†This model included a significant two-way interaction term between the risk factor in this row (arm/leg scarring or persistent hair loss) and marital status. The result shown in the cell is the relative risk of impairment on the Physical Component Summary for the scarring or hair loss variable (yes v no) among subjects in the marital status category noted in the cell's top margin.

with cranial radiation. This finding is noteworthy considering previous reports linking cranial radiation to increased psychosocial distress, and decreased HRQOL did not control for persistent hair loss.^{23,24} The moderating effect of persistent hair loss in the impact of cranial radiation on psychosocial outcomes and quality of life should be considered in future research.

The associations between increased distress and scarring or disfigurement are consistent with existing research; however, the effects of scarring or disfigurement on childhood cancer survivor's quality of life have received less attention in the published literature.^{25,26} A study on adverse effects of surgical interventions in 22 long-term survivors of cancer in neonates and infants indicated that more than 50% reported psychological problems resulting from scar formation.²⁷ Within our study, surgical scarring was associated with increased distress. Moreover, our results suggest that head/neck scarring and persistent hair loss were two of the strongest predictors, suggesting that outward physical appearance played a prominent role in emotional adjustment. This theory is supported by research in facial trauma victims, who demonstrate lower satisfaction with life, more

negative perception of body image, higher incidence of posttraumatic stress disorder, and increase in depression compared with control population.²⁸ Also, patients with melanoma have been reported to experience more distress associated with visible scarring, particularly among females.²⁹ Interestingly, a study of 49 pediatric burn patients evaluated 1 to 7 years after their burn reported that for male patients, as the number of visible scars on the patient's face, head, neck, and hands increased, the scores for physical appearance and happiness and satisfaction decreased ($P < .001$).³⁰

Although body image was not assessed in the present study, scarring, disfigurement and persistent hair loss are known to result in body image disturbances among cancer survivors.^{31,32} In the childhood cancer literature, survivors assessed during adolescent years (ages 14 to 17 years) and diagnosed within the previous 12 months report changes in their body image that left them feeling vulnerable and exposed.³³ Our results show that survivors with head/neck scarring disfigurement and persistent hair loss are more likely to identify role limitations owing to emotional problems, which may suggest an impact from negative self-esteem or self-image. The diagnostic groups

with the highest proportion of survivors reporting head/neck scarring in our study were patients treated for CNS tumors (64.3%) or Hodgkin's disease (38.0%). The proportion reporting head/neck scarring was highest among survivors who were between 10 and 14 years old at diagnosis (28.8%), a critical time for development of one's self-esteem.

Several limitations must be considered when interpreting results of the current study. First, although cancer treatment information was based on chart reviews, the data on scarring, disfigurement, and persistent hair loss were obtained via questionnaire. Furthermore, of the 14,358 survivors and 4,023 siblings for whom a baseline questionnaire was returned, self-report was done by 9,525 survivors (66.3%) and 3,201 siblings (79.6%), and surrogates completed the questionnaire for the remaining participants who had either cognitive limitation, were deceased, or were younger than 18 years of age. Baseline surrogate report for deceased participants was associated with increased risk of hair loss, likely because of more intensive medical interventions before death. Surrogate report among survivors was associated with decreased hair loss, but increased chest/abdomen scarring. Although surrogate report may not be ideal, without it, rates of scarring in deceased and younger survivors would not have been captured. There was no surrogate reporting for BSI and Medical Outcomes Short Form outcomes. The data reported were collected at two different times. Specifically, scarring, disfigurement, and hair loss data were collected first at baseline, and the psychosocial and HRQOL data were assessed approximately 8 years later (mean, 7.1; standard deviation, 1.2). Given the breadth of issues experienced by survivors, comprehensive report at each time point was not feasible as a result of patient burden. We acknowledge that other life events may have taken place in the 8-year interval between surveys. These could include additional treatments received for cancer recurrence and second primary cancers, on which unfortunately, we do not have complete data. Nonetheless, it is highly likely that the scarring, disfigurement, and persistent hair loss reported at baseline were present at the 2003 follow-up.

Despite these limitations, it is clear that scarring, disfigurement, and persistent hair loss are prevalent sequelae of cancer treatment that

persist into adulthood. More importantly, they can adversely affect psychological function and quality of life in survivors of childhood cancer. This information is important for practitioners in the field of childhood cancer care to be more aware of so that interventions facilitating coping skills, emotional adjustment, and management strategies can be implemented for patients at highest risk.

Future prospective, longitudinal studies are needed to more clearly understand the impact of scarring, disfigurement, and persistent hair loss on body image, emotional health, and the quality of life of childhood cancer survivors. Implementing more in-depth approaches for data collection with survivors affected by these sequelae will broaden our knowledge of this area of long-term follow-up survivor care, with the ultimate goal of promoting survivor's HRQOL. Furthermore, efforts toward the minimization of scarring, disfigurement, and persistent hair loss during pediatric cancer diagnosis and treatment represent a natural next step toward the optimization of care and survivors' well-being.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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