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Psychological Outcomes in Long-Term Survivors of Childhood Leukemia, Hodgkin's Disease, and Non-Hodgkin's Lymphoma: A Report From the Childhood Cancer Survivor Study

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Psychological Outcomes in Long-Term Survivors of Childhood Leukemia, Hodgkin's Disease, and Non-Hodgkin's Lymphoma: A Report From the Childhood Cancer Survivor Study

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ABSTRACT. *Objective.* **To evaluate and compare psychological outcomes in long-term survivors of pediatric leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma and sibling controls.**

Methods. **Adult survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma (N = 5736) and sibling controls (N = 2565) were administered a long-term follow-up questionnaire allowing assessment of symptoms associated with depression and somatic distress.**

Results. **The majority of respondents in this study did not demonstrate symptomatology indicative of depression or somatic distress. Survivors, however, were significantly more likely than sibling controls to report symptoms of depression and somatic distress. Women were significantly more likely to indicate symptoms of depression and somatic distress than were men; however, this difference did not vary by survivor/sibling status. Similarly, socioeconomic (SES) variables predicted symptomatic levels of depression and somatic distress for both survivors and siblings, and these effects did not vary by survivor/sibling status. Among leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma survivors, in addition to gender and SES, the only treatment variable that predicted scores indicating depressive symptomatology was exposure to intensive chemotherapy. Exposure to intensive chemotherapy also predicted scores indicative of somatic distress symptoms. No other medical variables, including diagnostic category, age at diagnosis, time since diagnosis, and duration of treatment, predicted symptomatic scores for depression and somatic distress.**

Conclusions. **This large, sibling-controlled, multisite study of young adult survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma found that survivors had significant increased risk for reporting symptoms of depression and somatic distress and that intensive chemotherapy added to this risk. However, being a cancer survivor did not compound the effects of gender and SES variables on the 2 outcomes measured. The ability of SES, gender, and treatment-related variables to predict psychological symptoms in this cohort of childhood survivors and sibling controls calls for future research into varied biological and psychosocial pathways by which cancer influences future psychosocial functioning.** *Pediatrics* **2002;110:42–52;** ***childhood cancer, survivor, psychological distress, depression.***

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ABBREVIATIONS. SES, socioeconomic status; CCSS, Childhood Cancer Survivor Study; BSI, Brief Symptom Inventory; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; RR, relative risk; CI, confidence interval.

Psychosocial sequelae among childhood cancer survivors have been the subject of previous investigations, but the generalizability of these findings are often limited by small sample sizes, data derived from single institutions, and lack of a control group. Furthermore, these studies do not provide consistent results. Koocher and O'Malley[1] suggested that many survivors of childhood cancer were at increased risk for maladaptive psychosocial sequelae, and recent research by others has reported at least moderate emotional difficulty, including depression[2,3] and symptoms of posttraumatic stress.[4–7] Other investigations have demonstrated behavioral adjustment problems and preoccupation with somatic concerns,[3,8,9] lowered self-esteem and body image,[10,11] and other psychosocial adjustment problems.[3,12–21] In sharp contrast, some reports indicate that survivors of childhood cancer are psychologically normal and relatively well adjusted when compared with varied control groups or with standardized norms.[2,4,6,13,22–31] In addition, some investigators have reported that a significant portion of the childhood cancer survivor population seems to be better adjusted than their peers or better adjusted than they were themselves before their diagnosis.[30,31]

Various substantive but sometimes contradictory findings indicate key sociodemographic and medical variables that may predispose survivors to cope worse or to report negative psychosocial outcomes. For instance, more negative outcomes have been reported for survivors who are male,[19,32] who are female,[33] whose cancer was diagnosed at an earlier age,[23] whose cancer was diagnosed at an older age,[30] who are currently older,[3–5] who experienced more intense treatments,[34,35] who have more serious or visible after-effects,[3,36] and who are of lower family income or socioeconomic status (SES).[3,4,23,30,37]

Although most long-term survivors may be relatively normal in psychosocial terms and on most psychological measures, a small but significant minority may experience ongoing and extreme or serious psychological and/or social adjustment problems; how large a proportion and how substantial a set of problems are unclear. Furthermore, study in this field has yet to identify critical sociodemographic, medical, and treatment-related variables that influence long-term survivors' psychosocial status and perhaps place them at risk for future health problems.

In light of consistent findings regarding low levels of psychological distress in childhood cancer survivors, findings from this study of the largest cohort of childhood cancer survivors in existence have the potential to contribute relatively definitive conclusions about the prevalence of depressive symptoms and somatic distress in survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma. Using the Childhood Cancer Survivor Study (CCSS), a large, multi-institutional study of long-term survivors of childhood cancer and sibling controls, we report the results of an analysis to 1) identify childhood cancer survivors who are at risk for reporting symptoms of depression and somatic distress; 2) compare the likelihood of survivors and sibling controls to report symptoms of depression and somatic distress; and 3) investigate the relationship of key demographic, medical, and treatment variables with these psychological outcomes.

METHODS

Participants and Procedures

This study, referred to as the CCSS, was established in 1993 through funding from the National Cancer Institute and exists as a large research resource for studies of childhood cancer survivors. Coordinated through the Department of Pediatrics at the University of Minnesota, the CCSS represents the largest and most comprehensively characterized epidemiologic research cohort of childhood cancer survivors ever assembled in North America. The population presented in this report is derived from a group of 20 304 individuals who were treated for cancer during childhood or adolescence at 25 centers across the United States and Canada. These individuals fulfilled the following eligibility criteria: 1) diagnosis of leukemia, central nervous system malignancies (all histologies), Hodgkin's disease, non-Hodgkin's lymphoma, kidney cancer, neuroblastoma, soft tissue sarcoma, or malignant bone tumor; 2) diagnosis and initial treatment at 1 of the 25 collaborating CCSS institutions; 3) diagnosis date between January 1, 1970, and December 31, 1986; 4) younger than 21 years at the time of diagnosis; and 5) survival of at least 5 years from the time of diagnosis.

Of the 20 304 childhood cancer survivors included in the cohort, 2996 (14.8%) could not be located and were considered lost to follow-up. Among the 17 308 subjects located, 14 193 (82%) completed a baseline questionnaire. The CCSS also includes a random sample of 3316 siblings of survivors who were contacted and asked to participate. The data presented and analyzed here were collected via self-report questionnaires from a subset of the CCSS composed of 5736 survivors of leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma over the age of 18 at the time they enrolled in CCSS and 2565 sibling controls 18 years of age or older. We restricted the scope of this report to leukemia and lymphoma survivors because 1) the diagnostic groupings of acute leukemia and lymphoma represent a substantial proportion of the cancers diagnosed during the pediatric and adolescent ages; 2) the largest number of reports within the literature that address psychosocial factors in childhood cancer survivors are among leukemia patients, although most of these reports are based on a small number of study subjects; 3) the treatment strategies used in leukemia and lymphoma patients, although heterogeneous enough to allow for comparisons by treatment-specific groupings, also have common similarities; and 4) to have included all childhood cancer diagnoses would have resulted in such a diverse population that it would not have been feasible to present and discuss detailed results within the confines of a single article.

Medical record abstraction, according to a structured protocol, was conducted at each CCSS center and included detailed information about cancer type, treatments received, and clinical characteristics of the survivor. A 24-page baseline questionnaire, completed by the survivors and siblings, provided information on demographics, personal and family medical history, functional limitations, psychological outcomes, work history, and living circumstances. Study questionnaires can be viewed at www.cancer.umn.edu/ccss. A detailed description of the CCSS study design, methods, and cohort characteristics is provided elsewhere.[38] The CCSS was approved by the Institutional Review Boards of all participating institutions. All participants were informed that participation in the study was voluntary, and all respondents provided informed consent before completion and return of the mailed survey.

Measures

Psychological health status was evaluated via a series of 20 5-point Likert scale items (from 1 = "not at all," to 5 = "extremely") exploring the degree to which particular problems had distressed or bothered the respondent during the past 7 days. These items were selected from the Brief Symptom Inventory (BSI)[39] and other investigations of psychosocial health status in both ill and healthy populations. A principal components analysis of these 20 psychological health status items extracted 2 factors that accounted for 46% of the common variance. The following 9 items with factor loadings (following orthogonal varimax rotation) >0.56 (range: 0.56–0.81) and no more than 0.48 for any other factor composed a first factor labeled "depressive symptoms": thoughts of ending life, feeling lonely, feeling blue, feeling no interest in things, feeling hopeless about the future, feelings easily hurt, feelings of worthlessness, feeling fearful, and feeling tense or keyed-up. The second factor, labeled "somatic distress," was composed of the following 7 items with factor loadings >0.55 (range: 0.55–0.64) and no more than 0.51 for any other factor: faintness or dizziness, pains in heart or chest, nausea or upset stomach, trouble getting breath, hot or cold spells, numbness or tingling, and feeling weak in parts of body. The items that compose these 2 factors are the same as those that compose the depression and somatization factors of the BSI.[39] Cronbach's α, as a measure of internal reliability, was 0.89 for the 9 items of the "depressive symptoms" factor and 0.76 for the 7 items of the "somatic distress" factor.

Factor scores were then dichotomized into "symptomatic" and "nonsymptomatic" categories for each of the 2 factors. The rationale for dichotomizing the outcome variables here is based, first, on the frequency distributions for the 2 factor scores representing depressive and somatic symptoms (Fig 1). These distributions are highly skewed and suggest that most survivors and sibling controls reported few, if any, depressive or somatic symptoms, thereby presenting difficulties in analyzing the factor scores as continuous outcome measures. Second, given that the pediatric survivorship literature suggests that most survivors are psychologically healthy but that a subset continue to experience ongoing psychosocial sequelae, the analysis presented here focuses on the subgroups of survivors and sibling controls whose scores approximate clinical symptomatology.

The criteria for determining the threshold for symptomatic scores were as follows. For the depressive symptoms factor, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for Major Depressive Episode require that depressed mood or loss of interest or pleasure in things plus 3 additional indicators be present for a clinical diagnosis. Thus, respondents who indicated 1) that either "feeling blue" or "feeling no interest in things" had distressed or bothered them "quite a bit" or "extremely" in the past 7 days and 2) that at least 3 additional items ("thoughts about ending life," "feeling lonely," "feelings easily hurt," "feeling hopeless about the future," "feeling worthless") had been moderately distressing were regarded as reporting symptomatic depression. For somatic distress, a BSI score indicat-

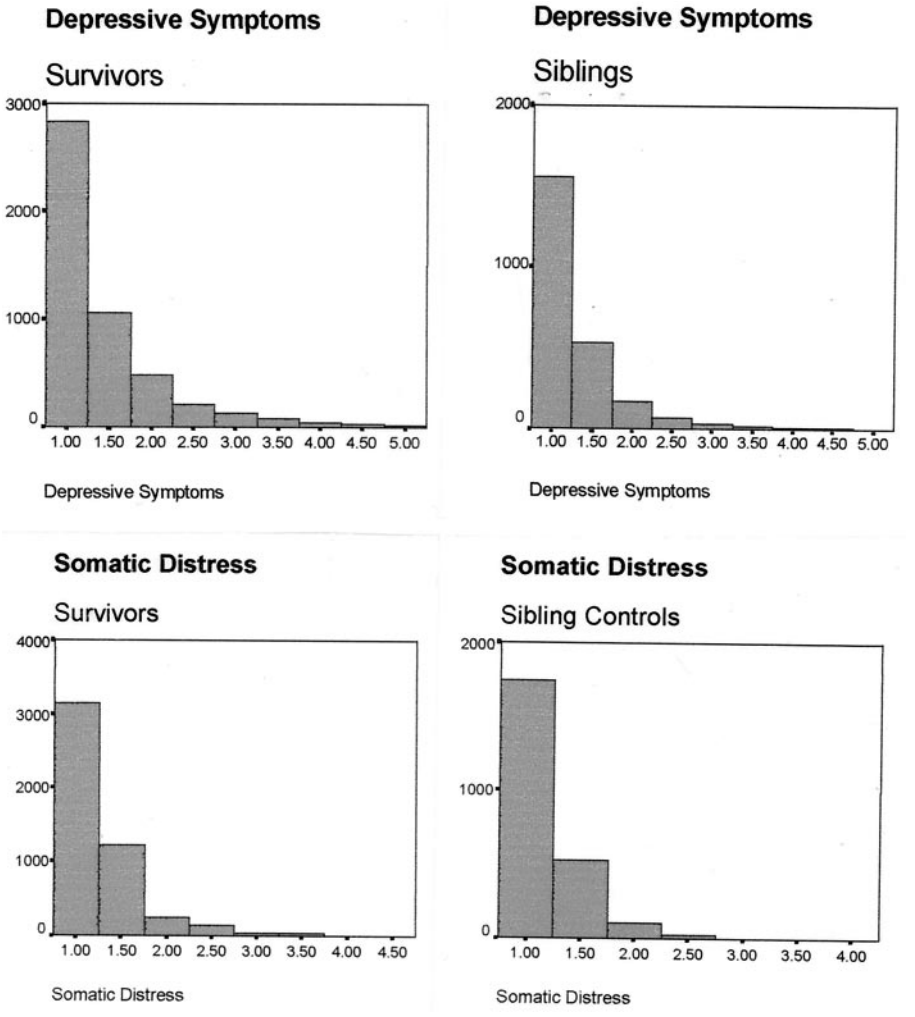

Fig 1. Bar graphs illustrating and comparing frequency of depressive symptom scores and somatic distress scores for survivors and sibling controls.

ing "caseness" for nonpatient norms occurs approximately at the 90th percentile.[39] A factor score of 12 on the somatic distress scale in this study population corresponds with the 90th percentile; thus, respondents who scored 12 or above were assigned a value indicating symptomatic for somatic distress.

Although the BSI is an appropriate screening tool for identifying symptoms associated with clinical depression or somatic distress, it is not in and of itself a method for diagnosing clinical levels of distress. *DSM-IV* criteria for diagnosing clinical depression has greater clinical specificity and relevance—not all individuals identified by the BSI as depressed would subsequently be diagnosed with Major Clinical Depression according to *DSM-IV* criteria. Therefore, we used *DSM-IV* criteria as a conservative and more clinically relevant approach for determining a cutoff score indicative of depressive symptomatology. Because no *DSM-IV* criteria exist for somatic distress, per se, the BSI scoring method for determining caseness was the next best clinically relevant criteria for determining a cutoff score for a symptomatic level of somatic distress in this epidemiologic cohort. This approach is consistent with our purpose of identifying respondents who demonstrate a significantly increased likelihood for reporting psychological symptoms.

Statistical Procedures

Two sets of analyses are reported here: 1 comparing survivor and sibling responses and 1 comparing only survivors' responses across 3 diagnostic categories of leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma. To estimate the effects of age, gender, SES (ie, household income, educational attainment, employment status), and survivor/sibling status on the occurrence of reporting symptomatic scores for survivors and sibling controls, we calculated odds ratios using logistic regression models to examine univariate and multivariate effects. To correct for the nonindependence of survivors and siblings (some are pairs from the same family), we used generalized estimating equation models.[40] Similar analyses examined the likelihood that leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma survivors would report symptomatic scores in multivariate models simultaneously controlling for gender, age, age at diagnosis, socioeconomic variables (household income, educational attainment, employment status), cranial radiation (irrespective of dose), duration of therapy ($<$4 years versus $\geq$4 years), and intensity of chemotherapy. For purpose of analyses, categorization of intensity of therapy within the 3 disease categories (ie, leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma) used a combination of regimen-defined criteria and the actual distributions of cumulative doses of specific chemotherapeutic agents to derive disease-specific criteria to classify a group of survivors as intensively treated. All survivors of acute myelogenous leukemia were considered to have received intensive chemotherapy, as were all survivors with cumulative exposure of $>$2000 mg/m^2 intravenous cyclophosphamide and $\geq$120 mg/m^2 anthracycline. Within Hodgkin's survivors, those who received both chemotherapy and non–central nervous system irradiation were considered intensively treated, whereas non-Hodgkin's lymphoma survivors who received cumulative doses of $\geq$6500 mg/m^2 intravenous cyclophosphamide plus $\geq$300 mg/m^2 anthracycline were classified in the intensive therapy category. Various multivariate models including all potentially significant variables and 2-way interactions were examined. The models presented here are those that best fit the data while adjusting for the number of terms in the model. Parameters were removed and added to the model in turn, and the Akaike Information Criterion was used to select the "best fit" model.[41]

RESULTS

The demographic, medical, and treatment characteristics of the 5736 childhood leukemia/lymphoma survivors and the demographic characteristics of 2565 sibling controls are listed in Table 1. The average age at study was 26.9 and 29.0 years for survivors and controls, respectively. Compared with the sibling cohort, a smaller proportion of survivors were female, college graduates, and currently married. Survivors also were less likely to have been employed in the last year and to report high household incomes.

Sociodemographic Risk Factors for Reporting Symptomatic Scores for Depression or Somatic Distress

A total of 4914 leukemia/lymphoma survivors and 2446 siblings answered all of the items used to derive the depression and somatic distress scores. The proportions of survivors and siblings who indicated symptomatic scores for depression are presented in Table 2. Compared with siblings, leukemia/lymphoma survivors are more likely to score symptomatic levels for depression (3.4% and 5.4%, respectively). The proportion of survivors who reported symptomatic scores for depression is approximately

TABLE 1. Descriptive Statistics of Leukemia, Hodgkin's Disease, and Non-Hodgkin's Lymphoma Survivors and Siblings Over Age 18 at Study

	Diagnostic Category				
	All Survivors (n = 5736)	Leukemia (n = 2991)	Hodgkin's Disease (n = 1843)	Non-Hodgkin's Lymphoma (n = 902)	Siblings (n = 2565)
Gender					
Male	3175 (55.4%)	1549 (51.8%)	989 (53.7%)	637 (70.6%)	1207 (47.1%)
Female	2561 (44.6%)	1442 (48.2%)	854 (46.3%)	265 (29.4%)	1357 (52.9%)
Race/ethnicity					
Nonwhite	547 (10.0%)	314 (11.1%)	141 (8.0%)	92 (10.8%)	155 (6.3%)
White	4907 (90.0%)	2525 (88.9%)	1622 (92.0%)	760 (89.2%)	2315 (93.7%)
Household income					
<$20 000	1081 (21.6%)	614 (24.0%)	275 (16.7%)	192 (23.8%)	302 (12.8%)
$20 000–$60 000+	3925 (78.4%)	1943 (76.0%)	1367 (83.3%)	615 (76.2%)	2059 (87.2%)
Education					
High school graduate or less	589 (10.9%)	375 (13.4%)	124 (7.0%)	90 (10.5%)	146 (5.9%)
High school graduate to some college	3258 (60.1%)	1791 (63.9%)	962 (54.7%)	505 (58.9%)	1324 (53.9%)
College graduate/postgraduate	1572 (29.0%)	637 (22.7%)	673 (38.3%)	262 (30.6%)	987 (40.2%)
Employment status					
Not currently employed*	645 (12.0%)	381 (13.4%)	168 (10.1%)	96 (11.1)	192 (7.6%)
Employed in last year	4733 (88.0%)	2469 (86.6%)	1494 (89.9%)	770 (88.9%)	2351 (92.4%)
Marital status					
Not currently married†	3230 (58.9%)	2046 (70.6%)	701 (40.9%)	483 (55.2%)	1132 (44.9%)
Currently married	2258 (41.1%)	854 (29.4%)	1012 (59.1%)	392 (44.8%)	1390 (55.1%)
Chemotherapy intensive					
Yes	1685 (36.4%)	680 (27.9%)	913 (60.5%)	92 (13.4%)	
No	2946 (63.6%)	1755 (72.1%)	597 (39.5%)	594 (86.6%)	
Cranial radiation					
Yes	1725 (40.1%)	1598 (71.2%)	11 (0.8%)	116 (18.0%)	
No	2572 (59.9%)	646 (28.8%)	1396 (99.2%)	530 (82.0%)	
Duration of chemotherapy (y)					
Mean (SD)	2.5 (2.4)	3.7 (2.1)	1.0 (2.0)	1.7 (1.6)	
Median	2.3	3.1	0.5	1.5	
Range	0–20.9	0–20.9	0–18.1	0–18.1	
Age at study					
Mean (SD)	26.9 (6.2)	24.4 (5.0)	30.8 (6.1)	27.4 (6.0)	29.0 (7.3)
Median	26	24	31	27	28
Range	18–48	18–42	18–48	18–45	18–56
Years since diagnosis					
Mean (SD)	16.3 (4.8)	16.4 (4.6)	16.2 (5.1)	15.9 (4.6)	
Median	16	16	16	15	
Range	5–29	5–29	5–28	5–27	
Age at diagnosis					
Mean (SD)	10.1 (5.5)	7.5 (4.9)	14.1 (4.1)	11.0 (4.7)	
Median	10	6	15	11	
Range	0–20	0–20	2–20	0–20	
Life stage at diagnosis					
0–4 years old	1240 (21.6%)	1103 (36.9%)	45 (2.4%)	92 (10.2%)	
5–9 years old	1406 (24.5%)	919 (30.7%)	229 (12.4%)	258 (28.6%)	
10–14 years old	1618 (28.2%)	643 (21.5%)	646 (35.1%)	329 (36.5%)	
15–21 years old	1472 (25.7%)	326 (10.9%)	923 (50.1%)	223 (24.7%)	

SD indicates standard deviation.
* Not currently employed = never worked + not worked in last year.
† Not currently married = never married + widowed + divorced + separated + living together as married.

TABLE 2. Demographic Risk Factors for Scoring Symptomatic for Depression

	Sibling Controls		Leukemia Survivors		Hodgkin's Disease Survivors		Non-Hodgkin's Lymphoma Survivors	
	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*
Respondents								
Survivors			141 (5.6)		87 (5.5)		37 (4.7)	
Siblings	82 (3.4)							
Gender								
Female	60 (4.6)	2.44 (1.49, 4.00)	89 (7.2)	1.87 (1.32, 2.66)	55 (7.2)	1.96 (1.25, 3.06)	15 (6.6)	1.72 (0.87, 3.37)
Male	22 (1.9)	1.00	52 (4.0)	1.00	32 (3.8)	1.00	22 (3.9)	1.00
		<.001		<.001		.003		.11
Age at study entry								
18–24 y	27 (3.7)	1.71 (0.88, 3.35)	76 (5.7)	0.82 (0.38, 1.74)	9 (3.9)	0.74 (0.34, 1.61)	15 (5.7)	1.14 (0.40, 3.24)
25–34 y	42 (3.7)	1.74 (0.93, 3.27)	57 (5.3)	0.75 (0.35, 1.62)	53 (6.1)	1.19 (0.73, 1.94)	17 (4.0)	0.79 (0.28, 2.19)
>34 y	13 (2.2)	1.00	8 (6.9)	1.00	25 (5.1)	1.00	5 (5.0)	1.00
		.15		.97		.71		.55
Race/ethnicity								
Nonwhite	6 (4.1)	1.32 (0.56, 3.10)	14 (5.5)	0.97 (0.55, 1.72)	8 (6.6)	1.26 (0.59, 2.67)	2 (2.4)	0.46 (0.11, 1.96)
White	70 (3.2)	1.00	120 (5.6)	1.00	74 (5.3)	1.00	34 (5.1)	1.00
		.52		.93		.55		.30
Household income								
<$20 000	16 (5.6)	1.78 (1.01, 3.12)	55 (10.6)	2.67 (1.85, 3.85)	25 (11.0)	2.49 (1.52, 4.06)	9 (5.7)	1.23 (0.57, 2.69)
$20 000–$60 000+	63 (3.2)	1.00	71 (4.3)	1.00	59 (4.7)	1.00	26 (4.7)	1.00
		.04		<.001		<.001		.60
Education								
<High school graduate	9 (7.6)	3.37 (1.52, 7.46)	21 (8.5)	2.27 (1.24, 4.15)	10 (10.5)	2.56 (1.20, 5.43)	7 (11.1)	5.15 (1.67, 15.90)
High school graduate-some college	45 (3.6)	1.53 (0.92, 2.55)	89 (5.9)	1.51 (0.95, 2.39)	45 (5.8)	1.35 (0.83, 2.17)	22 (5.0)	2.19 (0.87, 5.47)
College graduate-postgraduate	23 (2.4)	1.00	24 (4.0)	1.00	29 (4.4)	1.00	6 (2.4)	1.00
		.005		.008		.024		.004
Employment status								
Not currently employed†	7 (4.0)	1.20 (0.54, 2.64)	30 (10.2)	2.16 (1.41, 3.29)	20 (13.9)	3.46 (2.03, 5.91)	7 (9.3)	2.41 (1.02, 5.72)
Currently employed	75 (3.3)	1.00	111 (5.0)	1.00	64 (4.5)	1.00	29 (4.1)	1.00
		.65		<.001		<.001		.05

* Logistic regression analyses (generalized estimating equation models for respondents and gender); Cochran-Armitage trend test/*P* value reported for variables with >2 categories.
† Not currently employed = never worked + no work in last year.
Note: $N = 2412$ for siblings for whom a depressive symptoms score could be calculated; $N = 4907$ for survivors for whom a depressive symptoms score could be calculated.

equal for the 3 diagnostic groups. Age at study entry is not related to reporting a symptomatic score for depression; however, the relative risk of women who reported symptomatic scores for depression is significantly greater than that of men for leukemia and Hodgkin's survivors as well as sibling controls. In addition, SES seems to be significantly related to reporting a symptomatic score for all respondents. The relative risks for reporting a symptomatic depression score are greater among respondents with lower household incomes and lower levels of education. Also, survivors who had not been employed during the previous year are at significantly greater risk of reporting symptomatic scores for depression as compared with survivors who had been employed.

The proportions of siblings and survivors who reported a symptomatic score for somatic distress are presented in Table 3. Overall, 622 (12.7%) leukemia/lymphoma survivors are found to have a symptomatic score for somatic distress as are 195 (8.0%) of siblings. Across diagnostic categories, more Hodgkin's disease survivors (15.0%) report symptomatic somatic distress scores than leukemia (11.6%) or non-Hodgkin's lymphoma survivors (11.4%). Similar to the depressive symptoms outcome, female respondents are significantly more likely to score a symptomatic level for somatic distress. Unlike depressive symptoms, however, age at study entry is significantly related to somatic distress for Hodgkin's disease survivors, with younger respondents being significantly less likely (relative risk [RR] = 0.59; 95% confidence interval [CI]: 0.36–0.94) than respondents over the age of 34 years to indicate symptomatic somatic distress (test for trend, $P = .012$). As for socioeconomic factors, the relative risks for reporting a symptomatic score are significantly greater among respondents with lower household incomes and lower levels of education and among respondents who had not been employed during the previous year.

Medical and Treatment-Related Risk Factors for Reporting Symptomatic Scores for Depression and Somatic Distress

Among the medical and treatment-related factors, only exposure to intensive chemotherapy seems to be related to depressive symptoms, and only for leukemia survivors (Table 4). The relative risk of a symptomatic score among leukemia survivors who received intensive chemotherapy is 1.62 (95% CI: 1.11–2.36) when compared with survivors who did not receive similar therapies. Neither age at diagnosis nor years since diagnosis seems to be a significant

TABLE 3. Demographic Risk Factors for Scoring Symptomatic for Somatic Distress

	Sibling Controls		Leukemia Survivors		Hodgkin's Disease Survivors		Non-Hodgkin's Lymphoma Survivors	
	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*
Respondents								
Survivors			293 (11.6)		239 (15.0)		90 (11.4)	
Siblings	195 (8.0)							
Gender								
Female	139 (10.6)	2.30 (1.66, 3.16)	206 (16.8)	2.81 (2.16, 3.66)	140 (18.4)	1.68 (1.27, 2.22)	39 (17.0)	2.05 (1.31, 3.22)
Male	56 (4.9)	1.00	87 (6.7)	1.00	99 (11.9)	1.00	51 (9.1)	1.00
		<.001		<.001		<.001		.002
Age at study entry								
18–24 y	66 (9.0)	1.37 (0.91, 2.07)	155 (11.6)	1.40 (0.71, 2.73)	26 (11.2)	0.59 (0.37, 0.95)	29 (11.0)	0.70 (0.36, 1.37)
25–34 y	89 (7.9)	1.19 (0.81, 1.76)	128 (11.8)	1.42 (0.73, 2.79)	128 (14.6)	0.81 (0.60, 1.09)	46 (10.8)	0.69 (0.37, 1.29)
>34 y	40 (6.7)	1.00	10 (8.6)	1.00	85 (17.5)	1.00	15 (15.0)	1.00
		.12		.66		.023		.42
Race/ethnicity								
Nonwhite	15 (10.3)	1.33 (0.76, 2.31)	38 (14.8)	1.39 (0.96, 2.02)	17 (13.9)	0.93 (0.54, 1.58)	9 (11.0)	0.98 (0.47, 2.05)
White	177 (8.0)	1.00	238 (11.1)	1.00	208 (14.9)	1.00	74 (11.1)	1.00
		.32		.08		0.78		.96
Household income								
<$20 000	37 (12.8)	1.79 (1.22, 2.62)	103 (19.8)	2.40 (1.83, 3.15)	57 (25.0)	2.15 (1.53, 3.02)	33 (20.9)	2.68 (1.65, 4.33)
$20 000–$60 000+	150 (7.6)	1.00	156 (9.4)	1.00	168 (13.4)	1.00	50 (9.0)	1.00
		.003		<.001		<.001		<.001
Education								
<High school graduate	14 (11.8)	2.45 (1.31, 4.59)	51 (20.7)	2.73 (1.80, 4.15)	26 (27.4)	3.33 (1.99, 5.58)	14 (22.2)	3.73 (1.74, 8.00)
High school graduate-some college	112 (8.9)	1.80 (1.28, 2.55)	164 (10.8)	1.26 (0.91, 1.75)	133 (17.3)	1.84 (1.35, 2.52)	50 (11.5)	1.69 (0.96, 2.97)
College graduate-postgraduate	50 (5.2)	1.00	53 (8.7)	1.00	67 (10.2)	1.00	18 (7.1)	1.00
		.001		.001		.001		.001
Employment status								
Not currently employed†	23 (13.1)	1.83 (1.15, 2.91)	70 (23.9)	2.81 (2.08, 3.80)	42 (29.2)	2.62 (1.78, 3.88)	17 (22.7)	2.59 (1.43, 4.69)
Currently employed	171 (7.6)	1.00	222 (10.0)	1.00	195 (13.6)	1.00	72 (10.2)	1.00
		.01		<.001		<.001		.002

* Logistic regression analyses (generalized estimating equation models for respondents and gender); Cochran-Armitage trend test/*P* value reported for variables with more than 2 categories.
† Not currently employed = never worked + no work in last year.

risk factor for reporting a score indicative of a symptomatic level of depression.

Among all survivors combined, exposure to intensive chemotherapy seems to be significantly related to a symptomatic somatic distress score (RR = 1.24; 95% CI: 1.03–1.50), and exposure to cranial radiation is associated with a reduced risk of symptomatic somatic distress (RR = 0.77; 95% CI: 0.62–0.94; Table 5). Younger age at diagnosis is significantly associated with a lower risk of reporting symptomatic scores for somatic distress. Also, survivors (particularly Hodgkin's disease survivors) seem to be at higher risk of scoring a symptomatic level of somatic distress if >20 years postdiagnosis.

Multivariate Analyses of Risk Factors for Symptomatic Scores

To calculate RR estimates associated with respondent status (survivor or sibling) while controlling for the effects of sociodemographic variables, we constructed multivariate models for symptomatic depression and somatic distress as outcomes. The final model for symptomatic depression included respondent status, gender, household income, education, and employment status. When these variables are considered simultaneously, risk of a symptomatic depression score is significantly higher among leukemia/lymphoma survivors (RR = 1.58; 95% CI: 1.21–2.06). The best model for symptomatic somatic distress consisted of the same variables included in the final depression score model, plus age. Within this model, leukemia/lymphoma survivors are also found to have a statistically significant increased risk of a symptomatic somatic distress score (RR = 1.69; 95% CI: 1.40–2.04).

Multivariate models were constructed to identify demographic, socioeconomic, medical, and treatment-related factors most predictive of a symptomatic score for the outcomes of depression symptoms and somatic distress among survivors (Table 6). The best model for predicting a symptomatic score for depression consisted of female gender, exposure to intensive chemotherapy, low household income, and lower educational attainment. When considering risk for a symptomatic somatic distress score, the following risk factors are statistically significant: female gender, exposure to intensive chemotherapy, low household income, lower educational attainment, increasing age, and currently being unemployed.

DISCUSSION

This article presents findings on the largest investigation of psychological outcomes among young adult survivors of pediatric leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma ascertained from a retrospective cohort and using a cross-sec-

TABLE 4. Medical and Treatment-Related Risk Factors for Respondents Who Scored Symptomatic for Depression

	All Survivors		Leukemia		Hodgkin's Disease		Non-Hodgkin's Lymphoma	
	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*
Intensive chemotherapy								
Yes	97 (6.8)	1.41 (1.07, 1.85)	47 (8.1)	1.62 (1.11, 2.36)	49 (6.4)	1.59 (0.96, 2.64)	1 (1.4)	0.26 (0.03, 1.91)
No	127 (4.9)	1.00	77 (5.2)	1.00	23 (4.1)	1.00	27 (5.2)	1.00
		.01		.01		.07		.18
Cranial radiation								
Yes	77 (5.2)	0.92 (0.69, 1.23)	76 (5.5)	0.91 (0.64, 1.32)	0 (0.0)	0.00	1 (1.1)	0.18 (0.02, 1.37)
No	125 (5.6)	1.00	34 (6.4)	1.00	65 (5.3)	1.00	26 (5.5)	1.00
		.59		0.63		NA		.10
Duration of therapy								
>4 y	27 (4.6)	0.80 (0.53, 1.22)	28 (4.8)	0.76 (0.48, 1.20)	2 (4.8)	0.86 (0.20, 3.63)	0 (0.0)	0.00
<4 y	188 (5.7)	1.00	92 (6.2)	1.00	69 (5.5)	1.00	27 (4.7)	1.00
		.30		0.24		.84		NA
Age at diagnosis								
0–10 y	118 (5.2)	0.95 (0.74, 1.21)	93 (5.4)	0.91 (0.64, 1.31)	13 (5.5)	1.02 (0.55, 1.87)	12 (4.0)	0.77 (0.38, 1.56)
11 y and up	147 (5.5)	1.00	48 (5.9)	1.00	74 (5.4)	1.00	25 (5.1)	1.00
		.67		0.63		.95		.47
Years since diagnosis								
5–10 y	28 (6.0)	1.14 (0.72, 1.81)	14 (6.8)	1.40 (0.72, 2.71)	9 (4.8)	0.82 (0.37, 1.80)	5 (6.4)	1.35 (0.41, 4.40)
11–20 y	177 (5.4)	1.02 (0.76, 1.38)	98 (5.6)	1.15 (0.75, 1.76)	54 (5.4)	0.92 (0.56, 1.51)	25 (4.4)	0.91 (0.39, 2.15)
>20 y	60 (5.3)	1.00	29 (4.9)	1.00	24 (5.8)	1.00	7 (4.8)	1.00
		.63		0.32		.61		.72

NA indicates not applicable.
* Logistic regression analyses; Cochran-Armitage trend test/*P* value reported for variables with more than 2 categories.

TABLE 5. Medical and Treatment-Related Risk Factors for Respondents Who Scored Symptomatic for Somatic Distress

	All Survivors		Leukemia		Hodgkin's Disease		Non-Hodgkin's Lymphoma	
	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*	No. (%)	RR (CI) *P* Value*
Intensive chemotherapy								
Yes	205 (14.4)	1.24 (1.03, 1.51)	79 (13.6)	1.29 (0.97, 1.73)	120 (15.6)	1.16 (0.85, 1.58)	6 (8.2)	0.60 (0.25, 1.43)
No	307 (11.9)	1.00	162 (10.9)	1.00	77 (13.8)	1.00	68 (13.0)	1.00
		.02		.08		.35		.25
Cranial radiation								
Yes	162 (10.9)	0.77 (0.62, 0.94)	153 (11.1)	0.91 (0.67, 1.25)	0 (0.0)	0.00	9 (9.6)	0.69 (0.31, 1.37)
No	308 (13.8)	1.00	64 (12.1)	1.00	181 (14.8)	1.00	63 (13.4)	1.00
		.01		.55		NA		.32
Duration of treatment								
>4 y	65 (11.1)	0.84 (0.64, 1.11)	56 (10.8)	0.91 (0.66, 1.25)	8 (19.0)	1.35 (0.62, 2.96)	1 (4.5)	0.35 (0.05, 2.61)
<4 y	429 (13.0)	1.00	173 (11.7)	1.00	186 (14.8)	1.00	70 (12.1)	1.00
		.23		.56		.45		.30
Age at diagnosis								
0–10 y	257 (11.4)	0.81 (0.68, 0.96)	199 (11.6)	1.01 (0.77, 1.31)	28 (11.9)	0.74 (0.48, 1.12)	30 (10.0)	0.79 (0.50, 1.26)
11 y and up	365 (13.7)	1.00	94 (11.5)	1.00	211 (15.5)	1.00	60 (12.3)	1.00
		.02		.97		.15		.32
Years since diagnosis								
5–10 y	69 (14.7)	1.04 (0.77, 1.41)	29 (14.1)	1.27 (0.79, 2.03)	29 (15.6)	0.78 (0.49, 1.24)	11 (14.1)	1.32 (0.58, 3.01)
11–20 y	391 (11.8)	0.81 (0.67, 0.99)	197 (11.3)	0.99 (0.74, 1.33)	131 (13.1)	0.63 (0.47, 0.86)	63 (11.1)	1.01 (0.56, 1.80)
>20 y	162 (14.2)	1.00	67 (11.4)	1.00	79 (19.2)	1.00	16 (11.0)	1.00
		.54		.49		.055		.57

* Logistic regression analyses; Cochran-Armitage trend test/*P* value reported for variables with more than 2 categories.

tional design. Although the findings here indicate survivors to be approximately 1.6 to 1.7 times more likely to report symptomatic levels of depressive symptoms and somatic distress than a comparison group of siblings, the results also support the assertion that the majority of childhood cancer survivors are psychologically healthy.

The prevalence rates and risk factors for depression and distress reported here reflect rates and risk factors in the general population. Cross-sectional epidemiologic surveys in the general population have identified symptoms of major clinical depression or distress in 3% to 10% of young adults between the ages of 18 and 44.[42–45] The rates for depression found here fall within that range. As in the general population, we also found being female[46] and having low SES[47] to be risk factors for distress among both leukemia/lymphoma survivors and siblings, yet the effects of gender and SES on the outcomes measured here did not vary between survivors and siblings. Thus, being a cancer survivor does not compound the risks for depression and distress associated with these demographic characteristics. Female cancer survivors and survivors with low household in-

TABLE 6. Multivariate Models That Predict Symptomatic Depression and Somatic Distress Scores*

Outcome	Characteristic	RR (95% CI)	*P* Value
Depression	Gender		
	Female	2.06 (1.53, 2.76)	<.0001
	Male	1.00	
	Intensive chemotherapy		
	Yes	1.46 (1.09, 1.96)	.01
	No	1.00	
	Household income		
	<$20 000	2.21 (1.64, 2.99)	<.0001
	$20 000–$60 000 and over	1.00	
	Education		
	<High school graduate	2.27 (1.39, 3.70)	.001
	High school graduate-some college	1.41 (1.01, 1.97)	.04
	College graduate-postgraduate	1.00	
Somatic distress	Gender		
	Female	2.13 (1.72, 2.63)	<.0001
	Male	1.00	
	Age (y)	1.04 (1.02, 1.05)	<.0001
	Intensive chemotherapy		
	Yes	1.30 (1.06, 1.61)	.01
	No	1.00	
	Household income		
	<$20 000	1.92 (1.52, 2.44)	<.0001
	$20 000–$60 000 and over	1.00	
	Education		
	<High school graduate	2.63 (1.80, 3.85)	<.0001
	High school graduate-some college	1.55 (1.21, 1.97)	<.001
	College graduate-postgraduate	1.00	
	Employment status		
	Not currently employed†	1.59 (1.16, 2.17)	.004
	Currently employed	1.00	

* See text for variables considered in constructing the above multivariate models.
† Not currently employed = never worked + no work in last year.

comes, low levels of educational attainment, and recent histories of unemployment are no more likely than siblings with the same risk factors to report depression or somatic distress symptoms.

Among the leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma survivors evaluated in this study, the only treatment variable that predicts survivors' reporting symptomatic levels of depression or somatic distress is being exposed to intensive chemotherapy. Neither exposure to cranial irradiation or duration of treatment nor other medical variables, such as diagnostic category, age at diagnosis, or years since diagnosis, increase survivors' risks for reporting symptomatic levels of depression or somatic distress. This finding of the salience of exposure to chemotherapy as the single treatment and medical risk variable might relate to the seriousness of personal illness experiences related to intensive chemotherapy. For example, reduced absolute neutrophil counts can increase risk for sepsis or typhlitis, which in turn would necessitate hospitalizations, possibly even in the intensive care unit. Similarly, high-dose steroids can increase risk for aseptic vascular necrosis of the hip, associated with pain and requiring hospitalization. Thus, intensive chemotherapy tends to be more potentially life-threatening than the experience with radiotherapy, and the possibility that long-term physical effects attributable to chemotherapy create distress increases with age.

Alternatively, this subset of survivors may have experienced more social disruptions, such as missed school or restrictions in social activities, that resulted, years later, in reduced employment or career opportunities. Such experiences also might set up a subgroup of survivors to experience posttraumatic stress symptoms, such as hypervigilance, physiologic response to reminders about having had cancer, or avoidance of reminders of having had cancer.[4,48] Even if these symptoms of posttraumatic stress regress over time, new pains or somatic experiences might reactivate earlier memories and fears related to events during intensive chemotherapy. Such survivors might then tend to monitor their body for early "warning signs" of impending crisis and become more distraught if symptoms arise. This theory might explain the additional finding of increasing age as another risk factor for somatic distress. As people age, they naturally tend to have more "aches and pains." However, if a subgroup of survivors are already hypervigilant about scanning their body for "early warning signs of a somatic disaster," then the increase in normal symptoms of aging might create even more distress. Although exposure to intensive chemotherapy might place a subgroup of survivors at increased psychological vulnerability because of psychologically stressful events taking place during treatment, another potential explanation is that these individuals in fact have more chronic health problems. These possibilities need to be investigated to develop appropriate prevention and intervention strategies.

The gender differences demonstrated here are a particularly important area for future investigations. Are male and female survivors truly experiencing

significantly different levels of depression and/or somatic distress or are the differences a function of differences in how men and women express themselves? Or, are the differences a function of measures that are more sensitive to the ways in which women express their psychological status? Women in the general population are more likely than men to be identified as depressed,[46,49,50] and thus it is no surprise that women in the CCSS cohort are at higher risk for reporting depressive symptomatology and somatic distress. However, although the risk of reporting depression and somatic distress in female survivors is not significantly higher than for female siblings, being female may compound the RR for survivors when added to other risk factors, such as SES. Conversely, in the general population, men are more likely than women to engage in risky health behaviors such as substance abuse[51] and successful suicide.[52] Future research must also focus on health risk behaviors in cancer survivors to determine whether male survivors are at an increased risk for deleterious behavioral outcomes when compared with female survivors.

Having low SES is a risk factor for reporting the psychological symptoms measured in this study for both survivors and siblings. Like gender, having a low SES adds to other risk factors for the survivors. However, in this study, the findings could not distinguish between the effects of the SES of the survivors' families from the survivors' own achieved socioeconomic achievements in the years after cancer as a contributory factor to psychological outcome. Future analyses of the interrelationships of socioeconomic variables and psychological outcomes in cancer survivors must compare personal educational and income attainment of individual survivors to their own siblings to estimate risks for outcome after controlling for family SES variables. Such case-control comparisons will identify survivors' family SES and/or survivors' posttreatment abilities to achieve education, income, and employment as potential targets for intervention. Furthermore, the directionality of the relationship between psychological distress and SES has yet to be established. Educational and income attainment may just as well be influenced by psychological status as contribute to it. Finally, future studies of depression and psychological distress in long-term survivors need to control for non–cancer-related childhood adversities (eg, death of a parent, parental divorce, family mental illness) that have been demonstrated to be significant predictors of adult depression.[53]

The frequency distributions of both depression and somatic distress scores for both survivors and siblings were highly skewed, suggesting that survivors and siblings share the tendency, for whatever reasons, to report few, if any, depressive and somatic symptoms. Some investigators have attributed the tendency of cancer survivors to report fewer negative outcomes to "adaptive repression" or denial[24,54] or to "response shift–changed conceptualizations of quality of life resulting from changes in health."[55,56] These investigators suggest that these cognitive adaptive processes bias self-reported outcomes and thus must be "controlled for." An alternative explanation is that these findings represent true cognitive changes based on these individuals' experiences, as may be the case for both survivors and siblings in this study. Although this study found a subgroup of survivors whose scores approximated clinical indications of depression and somatic distress, the majority of survivors did not report these outcomes. Thus, studies need to explore reasons for this positive response in the larger subset of survivors to determine whether this is a cognitive process unique to survivors of life-threatening traumas or a universal phenomenon used by survivors and nonsurvivors alike.

The main limitation of this study is the use of nonstandardized measures of depression and somatic distress. We recognize the arbitrariness of selecting a cutoff score on a diagnostic screening tool to distinguish symptomatic respondents from others; however, given the absence of diagnostic measures for psychological symptoms in this data set, any other theoretical or statistical approach to determine a cutoff score also would be arbitrary. For the purposes of approximating a subset of respondents who experienced clinical symptomatology in this epidemiologic cohort, we relied on existing scoring methods and objective criteria from the *DSM-IV*. We selected *DSM-IV* criteria to assist us in determining a conservative selection that decreased the possibility of assigning false positives, ie, assigning an individual score to the symptomatic category when it truly may not have been indicative of psychological distress. We expected that this approach would provide more value for the clinical implications of our findings than a purely statistical cutoff score, such as using a median split. Providing strength and salience to our categorization of scores as clinically relevant, the proportions of respondents who scored symptomatic levels for depression and distress are consistent with rates of depression and general mental distress identified in the general population, including the common risk factors of gender and SES.

Another limitation is the possibility that using siblings as a control group may in fact result in an underreporting of the level of depression and somatic distress in survivors. As studies of sibling adaptation to childhood cancer have shown, siblings of children with cancer may report more symptoms than healthy controls who do not have a sibling with cancer.[57–60] Thus, siblings may not be an optimal control group for representing the psychological health status of young people without a cancer history.

Identifying key variables associated with psychological distress outcomes in childhood cancer survivors is critical for the development of appropriate and efficacious health promotion and psychosocial support interventions initiated throughout a continuum of care, from diagnosis through long-term follow-up. Using the largest data set of long-term survivors of childhood cancer to date, we demonstrated that although most survivors of childhood cancer do not have major psychological sequelae, there is a subgroup that is at increased risk for experiencing

and reporting psychological distress. Furthermore, low SES and female gender, as well as exposure to intensive chemotherapy, add risk to the development of these psychological problems, yet as survivors of childhood cancer grow into adulthood, move further in time from their cancer experience, and transition into adult health care settings, the potential exists for symptoms of distress to go unrecognized or to be assumedly best treated pharmacologically. Thus, appropriate long-term follow-up must include assessments of both potential physiologic and psychosocial factors that may be contributing to distress. Clinics attuned to the specific needs and experiences of childhood cancer survivors and the education of primary care physicians who may come into contact with this growing population are necessary for ensuring that these young people receive appropriate attention and care over the long term. These findings also call for additional research that 1) examines the interactive biological and psychosocial pathways by which cancer and its treatment influence future psychosocial functioning and 2) teases out biological factors, such as late health effects from chemotherapy or irradiation, from socioeconomic influences, including the potential fallout that arises from missed school, limited career opportunities, and/or poor medical monitoring and access to health care that may merge to result in adverse psychological sequelae.

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"The belief that youth is the happiest time of life is founded upon a fallacy. The happiest person is the person who thinks the most interesting thoughts, and we grow happier as we grow older."

—William Lyon Phelps

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