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Psychological Outcomes in Long-Term Survivors of Childhood Brain Cancer: A Report From the Childhood Cancer Survivor Study

Brad J. Zebrack, James G. Gurney, Kevin Oeffinger, John Whitton, Roger J. Packer, Ann Mertens, Norman Turk, Robert Castleberry, ZoAnn Dreyer, Leslie L. Robison, and Lonnie K. Zeltzer

From the University of Southern California School of Social Work; the Department of Pediatrics, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA; the Department of Pediatrics, University of Minnesota, Minneapolis, MN; the University of Texas Southwestern Medical Center, Dallas; Texas Children's Hospital, Houston, TX; the University of Washington, Seattle, WA; the Departments of Neurology and Pediatrics, Children's National Medical Center; The George Washington University, Washington, DC; and the Department of Pediatrics, School of Medicine, University of Alabama, Birmingham, AL.

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Address reprint requests to Brad Zebrack, PhD, USC School of Social Work, 669 W 34th St, Los Angeles, CA 90089-0411; e-mail: zebrack@usc.edu.

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ABSTRACT

Purpose
To evaluate and compare psychological outcomes in long-term survivors of pediatric brain cancer and siblings of childhood cancer survivors, and to identify significant correlates of psychological distress.

Methods
One thousand one hundred one adult survivors of childhood brain cancer and 2,817 siblings completed a long-term follow-up questionnaire allowing assessment of symptoms associated with depression, somatization, and anxiety, as well as demographic, health, and medical information.

Results
A large majority of siblings and survivors report few, if any, symptoms of psychological distress. The prevalence of distress approximating clinically significant levels for both survivors (11%) and siblings (5%) reflects rates found in the general population. Yet when accounting for significant sociodemographic, socioeconomic, and health-status variables, survivors of childhood brain cancer, in the aggregate, appear to report significantly higher global distress and depression scores than do siblings. As in the general population, higher levels of distress among survivors and siblings were associated with female sex, low household income, lower educational attainment, being unmarried, not being employed in the past 12 months, and poor physical health status. No diagnostic or treatment-related variables were directly and significantly associated with increases in distress symptoms for survivors of childhood brain cancer.

Conclusion
Cancer treatment does not appear to contribute directly to increased psychological distress. Instead, distress appears to be associated with diminished social functioning that may be related to cancer type or treatment. Implementation and evaluation of supportive interventions that enhance survivors' social and vocational skills should be considered.

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INTRODUCTION

Malignant tumors of the brain and CNS (ie, brain cancer) account for approximately 17% of all cancers among persons aged 20 years and younger, and approximately 2,200 new cases are diagnosed in the United States annually [1]. Due in large part to advances in neurosurgery, radiation therapy, and chemotherapy, 5-year relative survival for children diagnosed with brain cancer in the United States improved from 54.8% between 1974 and 1976 to 69.9% between 1992 and 1998 [2]. As survival rates for pediatric cancer patients have improved, a greater recognition of the need to address the impact of cancer and its treatment on psychosocial outcomes and quality of life has emerged [3,4].

Children who survive malignancies to the brain are at high risk for a complex array of neurologic, psychosocial, and endocrinologic sequelae [5,6]. Yet despite these difficulties, this patient population remains understudied. Childhood brain cancer survivors are often excluded in studies evaluating school performance or health status

of childhood cancer survivors, in part because of concerns about the impact of cognitive limitations on validity of assessment or because of the concern that those with a history of a childhood brain tumor may not fairly represent the greater population of children with cancer [7,8]. Most existing follow-up reports of morbidity in pediatric brain cancer patients have focused primarily on neurocognitive, neurologic, behavioral, and endocrinologic deficits [5,9-17]. Study in the field of pediatric oncology has yet to identify critical variables that influence long-term brain cancer survivors' psychosocial status, including factors that may place them at risk for future health problems or impede their ability to successfully integrate into society. The extent to which demographic, medical, and socioeconomic variables relate to psychological distress in long-term survivors of childhood brain cancer has not been clearly delineated.

From a large, multi-institutional epidemiological study of long-term survivors of childhood cancer and a sibling comparison group, this study aims to (1) determine the prevalence of symptoms related to global and dimensional aspects of psychological distress (depression, somatization, and anxiety) reported by young adult survivors of pediatric brain cancer; (2) compare the prevalence of such reported symptoms to siblings and population norms; and (3) identify sociodemographic and medical or treatment variables that may increase the likelihood of survivors reporting these psychological symptoms.

METHODS

Participants and Procedures

The Childhood Cancer Survivor Study (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 epidemiological research cohort of childhood cancer survivors ever assembled in North America. The population presented in this report is derived from a group of 20,267 individuals 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, CNS malignancy (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 one of the 25 collaborating CCSS institutions; (3) diagnosis date between January 1, 1970, and December 31, 1986; (4) age younger than 21 years at the time of diagnosis; and (5) survival of at least 5 years from the time of diagnosis.

Of the 20,267 childhood cancer survivors identified by the collaborating institutions, 2,994 (14.8%) could not be located and were considered lost to follow-up. Among the 17,273 subjects located, 14,024 (81.2%) consented to participate and completed a self-report questionnaire. The CCSS also included a random sample of 3,701 siblings of survivors diagnosed with all forms of pediatric malignancies. Included among all CCSS respondents were 1,281 survivors of brain cancer and 2,916 siblings, all of whom were 18 years of age or older at the time they enrolled in CCSS. Of these, 1,101 brain cancer survivors and 2,817 siblings of the entire cohort completed enough information to be included in the analyses presented here. One hundred eighty respondents were eliminated from analyses because of incomplete data or because the questionnaire was completed by a surrogate.

The CCSS protocols and questionnaires were approved by the Institutional Review Boards of all collaborating institutions. All contacted patients were informed that participation in the study was voluntary and were asked to sign a medical release to be returned with the mailed survey, permitting abstraction of medical record data. Medical record abstraction, according to a structured protocol, was conducted at each CCSS center and included detailed clinical information about cancer type and treatments received. A 24-page baseline questionnaire, completed by all study participants (the survivors and the siblings), provided information on demographics, personal and family medical history, medical late effects, 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, including comparison of respondents and nonrespondents, is provided elsewhere [18]. In brief, participants and nonparticipants were very similar with regard to sex, cancer diagnosis, age at diagnosis, age at contact, and type of cancer treatment. The only major difference observed was with life status.

Measures

Psychological health status was evaluated via 18 five-point Likert scale items (0 = "not at all"; 4 = "extremely") exploring the degree to which particular problems had distressed or bothered the respondent during the last 7 days. These items constitute the Brief Symptom Inventory-18 (BSI-18), a standardized self-report symptom inventory designed to serve as a screen for depression, somatization, and anxiety in medical and community populations [19]. Responses to all 18 items are summed to determine a Global Severity Index (GSI), with scores ranging from 0 to 72. In addition, three six-item summated subscales (depression, somatization, and anxiety) with scores ranging from 0 to 24 are reported. A principal components analysis of these 18 psychological health status items in this sample confirmed the three-factor structure of the BSI-18. Cronbach's alpha as a measure of internal reliability for this sample was 0.88 for the depression subscale, 0.70 for somatization, and 0.79 for anxiety.

Medical risk factors for both survivors and siblings were self-reported health, which was dichotomized from a five-category scale to fair/poor and good/very good/excellent, and prevalence of late effects or serious health conditions. Prevalence of late effects or serious health conditions was approximated using an algorithm to determine whether respondents were currently experiencing or had experienced in the past a "major medical condition." Criteria for "major medical condition" were either a positive response to use of anticonvulsants, cardiovascular medications, or chemotherapy/immune suppressants within a prescribed 2-year period (posttreatment), or a positive response to the presence of any one of a series of acute or chronic conditions at some time during the last 2 years. (This list includes complete deafness, dialysis, congestive heart failure, myocardial infarction, stroke or cerebrovascular incident, current use of oxygen, cirrhosis, coronary artery bypass surgery, angioplasty, heart transplant, lung transplant, kidney transplant, repeated seizures, convulsions, or blackouts, diagnosis

of a second cancer [confirmed new malignancy, excluding basal cell carcinoma or recurrent/relapse], amputation, joint replacement.) Sociodemographic and socioeconomic (SES) risk factors included sex, race or ethnicity, marital status, age at interview, highest educational attainment, household income, and employment status.

Diagnostic and treatment variables for survivors included tumor type (astrocytoma or glial tumors, primitive neuroectodermal tumor or medulablastomas, and all others) and maximum radiation dose to the brain (0-29 Gy, 30-49 Gy, 50 Gy and greater). Year of diagnosis (1970 to 1973, 1974 to 1978, 1979 to 1986) is included to examine the potential effect of changes in treatment and supportive care over time. Chemotherapy exposure was coded as a dichotomous variable (yes or no). Age at diagnosis was examined as a continuous variable as well as categorized to represent three critical developmental stages (0 to 4 years, 5 to 11 years, and 12 years and older) [20].

Data Analysis

Bivariate and multivariate analyses were used to compare raw scores for survivors with siblings on the GSI and three subscale measures (depression, somatization, and anxiety) of the BSI-18. Respondents' raw scores also were converted to T-scores based on a linear transformation that standardizes scores for the BSI-18 while adjusting for sex differences observed in the normative population [20]. This procedure enabled a comparison of survivor and sibling scores to community norms. By definition, the standardized population distribution of T-scores for the GSI and three subscales have means of 50 and standard deviations of 10. Once T-scores were obtained for survivors and siblings, comparison with population norms entailed running a one-sample *t*-test with the null hypothesis that the sample mean would be 50. This process was conducted for the GSI and repeated for each of the three subscales. Finally, T-scores of 63 or greater for any two of the three subscales represent a criterion for identifying subjects considered to be a positive risk for psychological distress [19]. The proportions of survivors and siblings fitting this criterion for positive risk were identified.

Generalized linear mixed modeling (PROC MIXED, SAS Institute, Cary, NC) was used to examine the associations of sociodemographic, SES, and health status variables— age, sex, race or ethnicity, income, education, employment status, marital status, self-reported health, and existence of a major medical condition—with the global and subscale distress outcomes. Mixed modeling controls for the potential lack of independence between survivors and siblings who come from the same family and allows the estimation of least squared means for comparison of factor effects of correlated data. General linear models were used to examine BSI scores for brain cancer survivors only in multivariate modeling of key treatment-related variables (age at diagnosis, year of diagnosis, maximum cranial radiation dosage, tumor type, and chemotherapy exposure) in addition to sociodemographic, SES, and physical health-related variables.

For all multivariate analyses, a model building process involved the following steps. First, bivariate analyses were used with all independent variables to determine statistically significant associations with the GSI and the three subscales. For each outcome, all variables showing statistically significant associations were retained and examined in a saturated multivariate regression model; that is, one in which all independent variables were entered into the model, allowing for simultaneous significance testing. Determination of "best fit" mixed models that included both brain cancer survivors and siblings were determined through comparison of Akaike Information Criteria [21]. Final models that best fit the survivors-only data were identified by maximizing the amount of variance accounted for in the outcome measure when adjusting for the number of significant correlates from the model building process (the adjusted R^2).

RESULTS

The demographic and health-related characteristics of the 1,101 brain cancer survivors and 2,817 siblings are shown in Table 1. Additionally, Table 1 includes cancer-related variables for the survivor group. Compared with the sibling cohort, a significantly smaller proportion of survivors were female ($\chi^2 = 17.0$; $P < .001$), college graduates ($\chi^2 = 87.3$, $P < .001$), currently married ($\chi^2 = 307.9$; $P < .001$), currently employed ($\chi^2 = 233.1$; $P < .001$), and reported household incomes at least \$20,000 ($\chi^2 = 112.9$; $P < .001$). Survivors also were significantly younger than siblings ($t = 13.63$; $P > .001$). Furthermore, a significantly larger proportion of the survivor group reported their health as fair or poor ($\chi^2 = 91.0$; $P < .001$), and reported a major medical condition ($\chi^2 = 560.2$; $P < .001$).

Psychological Distress: Comparing Survivors, Siblings, and Normative Data

Overall, a large majority of siblings and survivors reported few, if any, symptoms of psychological distress within the previous seven days. Eleven percent of survivors, compared with 5% of siblings, fit the criteria for "positive risk" for psychological distress. In contrast, 45% of survivors and 51% of siblings scored 2 or less for the GSI, a summated rating scale ranging from 0 to 72. For each of the three subscales, 65% to 77% of survivors and 76% to 85% of siblings scored 2 or less on scales ranging from 0 to 24.

A comparison of mean scores on the GSI and the three subscales for survivors and siblings is presented in Table 2. In the aggregate, brain cancer survivors reported significantly higher GSI scores and depression and somatization subscale scores when compared with siblings. Using T-scores to compare survivors and siblings with standardized norms on the BSI-18, both study groups reported significantly lower scores for the GSI and the three subscales than did community norms (standardized scores for community norms are mean of 50 and standard deviation [SD] of 10 for the GSI and three subscales).

Medical and Treatment-Related Factors Associated With Psychological Distress for Survivors Only

Raw mean scores for the GSI and the three subscales, stratified by medical and treatment-related variables, are summarized in Table 3. Mean score differences were not statistically significant for any diagnostic or treatment variable.

Table 1. Characteristics of Brain Cancer Survivors and the Sibling Comparison Group

	Brain Cancer Survivors (n = 1,101)		Siblings (n = 2,817)	
	No. of Patients	%	No. of Patients	%
Sex				
Female	507	46.0	1,503	53.4
Male	594	54.0	1,313	46.6
Ethnicity				
White	996	90.8	2,507	92.3
Non-white	101	9.2	210	7.7
Income, $US				
< 20,000	254	28.0	328	12.7
≥ 20,000	652	72.0	2,249	87.3
Education				
< HS graduate	111	11.0	147	5.5
HS graduate	644	63.5	1,462	54.2
College Graduate	259	25.5	1,086	40.3
Employment status				
Not employed in last 12 months	281	25.9	214	7.7
Currently employed	804	74.1	2577	92.3
Marital status				
Not married	803	74.4	1,187	42.9
Married or live as married	276	25.6	1,577	57.1
Self-rated health				
Poor or fair	151	13.9	138	4.9
Good, very good, excellent	934	86.1	2,651	95.1
Major medical condition				
Yes	361	35.4	146	5.5
No	656	64.6	2,525	94.5
Tumor type				
Astrocytoma or glial tumors	714	64.9		
PNET or medulloblastoma	202	18.3		
Other CNS	185	16.8		
Year of diagnosis				
1970-1973	177	16.1		
1974-1978	335	30.4		
1979-1986	589	53.5		
Chemotherapy				
Yes	205	21.1		
No	766	78.9		
Missing data	127			
Maximum brain radiation dosage				
0-29 Gy*	313	35.1		
30-49 Gy	112	12.6		
50 Gy and greater	467	52.3		
Brain Radiation (for recipients only)				
Localized	298	51.6		
Whole brain	280	48.4		
Missing data	314			
Age at diagnosis, years				
0-4	186	16.9		
5-11	508	46.1		
12 and older	407	37.0		
Mean SD	26.5		29.4	
SD	5.5		7.2	
Range	18-44		18-56	

Abbreviations: HS, high school; PNET, peripheral neuroectodermal tumor; SD, standard deviation.
*Three-hundred ten survivors received no radiation therapy; three received some but less than 30 Gy of brain radiation dosage.

Multivariate Analyses of Risk Factors Associated With Psychological Distress for Survivors and Siblings

Once accounting for statistically significant sociodemographic, SES, and health status variables, GSI scores for survivors and siblings appeared to differ significantly at the $P < .05$ level, with survivors reporting significantly higher symptom levels (Table 4). Survivors also scored significantly higher symptoms for depression when compared with siblings; however, the differences in somatic distress and anxiety subscales scores were not statistically significant (Table 4). The statistically significant difference in GSI scores for survivors and siblings thus appears to be a function of the mean difference in depression subscale scores. Sociodemographic, SES, and health status variables also appeared to have independent associations with psychological distress symptoms for survivors and siblings (Table 4). Female respondents reported significantly higher levels of symptoms across all three distress categories, and thus a significantly higher GSI score. Unmarried respondents reported significantly higher depression and anxiety scores as well as a higher GSI score. Somatic distress symptoms appeared to increase with age. Respondents living in households with income less than $20,000 reported significantly greater symptom levels across the board, and not being employed in the past 12 months was significantly associated with greater somatic distress. Low educational attainment appeared associated with higher levels of depression. With regard to physical health, respondents who perceived their health to be fair or poor reported significantly higher levels of distress. Those reporting a major medical condition reported significantly higher levels of somatic distress and anxiety, but not depression.

For childhood brain tumor survivors alone, multivariate results were similar to those for the combined survivor-sibling cohort. Demographic, SES, and physical health variables appeared significantly associated with distress (Table 5). One notable difference is that sex did not appear associated with depression; however, female survivors were more likely to report greater somatic distress and thus a significantly higher GSI. In addition, a significant interaction effect for the GSI and the anxiety subscale is noted, with low-income survivors who perceived their health as fair or poor reporting significantly higher levels of distress than all others. Finally, nonwhite survivors reported greater anxiety symptoms than did white survivors and nonwhite survivors living in households with income less than $20,000 reported greater anxiety than all others.

When controlling for key sociodemographic, SES, and physical health variables, no treatment-related variables (brain tumor type, year of diagnosis, cranial radiation exposure, chemotherapy exposure) appeared significantly associated with any distress outcome.

Table 2. Comparison of Brain Cancer Survivors, Siblings, and Standardized Norms on the BSI-18 Global Severity Index (GSI) and Three Subscale Scores

	Brain Cancer Survivors (n = 1,101)			Siblings (n = 2,817)				
	Raw Score		Standardized T-Score*	Raw Score		Standardized T-Score*	*t* test† Score	*P*
	Mean	SD		Mean	SD			
GSI‡	6.38	8.56	46.9	4.61	6.34	44.8	6.33	< .001
Depression§	2.85	4.26	49.1	1.81	3.18	46.5	8.69	< .001
Somatic distress§	1.60	2.66	47.8	1.09	1.92	46.2	6.09	< .001
Anxiety§	1.95	3.14	45.9	1.70	2.57	45.4	1.73	.09

Abbreviations: BSI-18, Brief Symptom Inventory-18; SD, standard deviation.
*Standardized T-scores are used to compare survivors and siblings to standardized norms. The standardized mean T-scores and standard deviations for community norms on the GSI and 3 subscales are 50 and 10 respectively.
†One-tailed *t*-test used to compare means for survivors and siblings.
‡Raw mean score ranges from 0-72.
§Raw mean scores range from 0-24.

DISCUSSION

Overall, the majority of long-term survivors of childhood brain cancer and a comparison group of siblings are psychologically well and do not report symptoms of psychological distress. The prevalence of distress at levels approximating clinical significance among both survivors (11%) and siblings (5%) is consistent with that in the general population [22,23]. However, after accounting for variables that appear as risk factors for psychological distress in the general population, brain cancer survivors appear more likely than a comparison group of siblings to report symptoms of distress, particularly depression.

Factors found to be related to survivors' reports of psychological distress symptoms are the same as important variables associated with distress in the general population—namely, socioeconomic status indicators, physical health status, and sex [24,25]. As in the general population, we found being female and having low socioeconomic status (as measured by income, educational attainment, and employment status) to be risk factors for distress among brain cancer survivors. However, when comparing survivors with siblings on measures of psychosocial and physical health variables (Table 1), childhood brain cancer survivors appear more likely to experience physical health problems and limited opportunities with

Table 3. Standardized T-Scores on the BSI by Select Medical and Treatment Variables for Brain Cancer Survivors

		GSI		Depression		Somatic Distress		Anxiety	
	No. of Patients	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Tumor type									
Astrocytoma or glial	714	47.17	10.46	49.32	9.88	47.93	8.31	46.31	9.16
PNET or medulloblastoma	202	46.27	10.46	48.65	10.24	47.35	7.70	45.64	9.21
Other	185	46.38	9.86	48.72	9.68	47.52	8.26	44.83	8.72
Chemotherapy									
Yes	205	47.20	9.96	49.49	10.11	47.52	7.82	45.76	8.59
No	766	47.06	10.52	49.30	10.02	47.89	8.28	46.14	9.29
Maximum brain radiation dosage									
0-29 Gy	313	47.28	10.77	49.39	10.24	47.96	8.36	46.74	9.62
30-49 Gy	112	46.12	10.11	48.19	9.38	47.01	7.93	45.64	9.04
50 Gy and greater	467	47.22	10.40	49.71	10.20	48.00	8.26	47.72	8.90
Age at diagnosis, years									
0-4	186	46.65	9.86	48.91	9.53	47.51	7.63	45.85	8.72
5-11	508	47.48	10.67	49.57	10.34	48.11	8.60	46.58	9.56
12 and older	407	46.22	10.17	48.60	9.52	47.42	7.92	45.18	8.65
Year of diagnosis									
1970-1973	177	46.86	10.40	49.21	9.87	47.72	8.36	46.12	9.00
1974-1978	335	46.93	10.24	49.10	9.96	47.61	7.79	46.07	9.07
1979-1986	589	46.85	10.43	49.07	9.90	47.85	8.37	45.81	9.18

NOTE. No significant differences at $P < .05$.
Abbreviations: BSI, Brief Symptom Inventory; GSI, Global Severity Index; SD, standard deviation; PNET, primitive neuroectodermal tumor.

Table 4. Multivariate Models Predicting Raw Mean BSI Scores for Brain Cancer Survivors and Siblings

	GSI				Depression				Somatic Distress				Anxiety			
	LS Mean	SE	F	*P*	LS Mean	SE	F	*P*	LS Mean	SE	F	*P*	LS Mean	SE	F	*P*
Respondent status																
Survivor	9.20	0.32	4.41	.038	4.05	0.16	14.88	<.001	2.57	0.09	0.91	.342	2.65	0.12	0.51	.478
Sibling	8.56	0.32			3.49	0.15		2.48	0.10		2.74	0.12				
Sex																
Female	9.72	0.30	50.00	< .001	4.01	0.15	15.78	< .001	2.80	0.09	57.75	< .001	2.99	0.11	39.68	< .001
Male	8.04	0.31			3.53	0.15			2.24	0.09			2.40	0.11		
Income, $US																
< 20,000	9.49	0.36	13.12	.001	3.99	0.18	7.05	.012	2.69	0.11	10.78	.002	2.95	0.14	15.93	< .001
≥ 20,000	8.28	0.29			3.55	0.14			2.36	0.09			2.44	0.10		
Education																
< HS graduate	9.55	0.49	2.02	.142	4.32	0.25	5.67	.005								
HS graduate or some college	8.58	0.28			3.47	0.14										
College graduate	8.52	0.33			3.52	0.16										
Employment status																
Not employed in last year									2.66	0.12	4.76	.036				
Currently employed									2.39	0.09						
Marital status																
Not currently married	9.71	0.29	43.30	< .001	4.39	0.14	96.14	< .001					2.83	0.11	7.61	.007
Married or living as married	8.06	0.32			3.15	0.16							2.56	0.12		
Self-rated health																
Poor or fair	11.93	0.46	162.94	< .001	5.10	0.23	123.26	< .001	3.41	0.14	148.97	< .001	3.49	0.18	74.06	< .001
Good, very good, or excellent	5.84	0.24			2.44	0.11			1.63	0.07			1.91	0.08		
Major medical condition																
Yes	9.49	0.39	9.77	.003					2.91	0.11	41.70	< .001	2.86	0.14	5.02	.029
No	8.27	0.29							2.13	0.09			2.53	0.11		
Age											9.17	.003				

Abbreviations: BSI, Brief Symptom Inventory; GSI, Global Severity Index; LS, least-squared.

regard to work, school, and marriage. Thus, in the aggregate, brain cancer survivors' risks for experiencing distress may be compounded by a greater likelihood of experiencing physical and psychosocial limitations.

It is notable that treatment intensity was not directly and significantly related to psychological outcomes in this large sample. Any significant associations between treatment variables and psychological distress at the bivariate level were attenuated when simultaneously accounting for sociodemographic, SES, and physical health variables. If treatment does in fact influence psychological well-being, its effect may be indirect by limiting social opportunities (eg, employment, educational attainment, income attainment, marriage) that appear directly related to well-being. We also recognize the potential bidirectional relationship of social functioning and psychological distress, which suggests that distress may be an antecedent to diminished social functioning.

Several limitations should be considered when interpreting these findings. Because these participants represent a volunteer study population, self-selection bias is a possibility. It may be that some eligible survivors did not complete and return questionnaires because of high levels of anxiety, depression or distress, or possibly because cognitive limitations prevented them from doing so. For example, survivors of brain tumors may have impaired cognitive function as a result of their therapy and thus, the potential exists that some may have encountered difficulty in understanding the content of the baseline questionnaire. To minimize the possible effect of cognitive impairment and/or reading ability, we offered participants the option of completing the questionnaire over the telephone with a trained interviewer. In situations where the survivor was deemed to be sufficiently impaired, thus calling into question their ability to accurately respond to the questions, surrogate respondents were used for the baseline questionnaire. Because of the topic of the current analysis, we did not include information on any subjects for whom a surrogate was required.

Also, we cannot rule out the possibility that some degree of under-representation of brain cancer survivors may have occurred despite rigorous procedures uniformly implemented to maximize case ascertainment at all participating CCSS institutions. However, given that the 5-year survival rate during the cohort period of 1970 to 1986 was lower for brain tumor patients than for the majority of

Table 5. Multivariate Models Predicting BSI Scores for Brain Cancer Survivors Only

	GSI (Adjusted R^2 = 0.140)				Depression (Adjusted R^2 = 0.089)				Somatic Distress (Adjusted R^2 = 0.096)				Anxiety (Adjusted R^2 = 0.097)			
	LS Mean	SE	F	*P*	LS Mean	SE	F	*P*	LS Mean	SE	F	*P*	LS Mean	SE	F	*P*
Sex																
Female	11.00	0.62	5.23	.023	3.98	0.26	1.54	.215	2.60	0.14	14.54	< .001				
Male	9.53	0.62			3.66	0.26			1.99	0.14						
Ethnicity																
Non-white													4.04	0.44	7.43	.007
White													2.85	0.20		
Income, $US																
< 20,000	12.31	0.79	16.91	< .001									4.50	0.39	28.97	< .001
≥ 20,000+	8.23	0.65											2.10	0.33		
Education																
< HS graduate					4.55	0.41	3.54	.030								
HS graduate or some college					3.42	0.23										
College graduate					3.49	0.41										
Marital Status																
Not currently married					4.46	0.22	17.41	< .001								
Married/living as married					3.18	0.31										
Employment status																
Not employed in last year									2.49	0.17	3.95	.047	3.69	0.31	2.98	.085
Currently employed									2.11	0.14			3.20	0.28		
Self-rated health																
Poor or fair	14.15	0.92	59.77	< .001	5.21	0.37	52.28	< .001	3.03	.021	39.05	< .001	4.38	0.38	25.84	< .001
Good, very good, excellent	6.38	0.46			2.46	0.37			1.56	0.10			2.52	0.25		
Major medical condition																
Yes	11.24	0.64	7.45	.007					2.64	0.15	15.92	< .001				
No	9.30	0.63							1.95	0.14						
Brain radiation dosage																
0-29 Gy	11.03	0.68	1.20	.302									3.74	0.31	2.19	.112
30-49 Gy	9.57	0.96											3.37	0.39		
50 Gy and greater	10.20	0.58											3.23	0.27		
Age	−.114	0.06	3.62	.057					−.029	0.04	4.13	.042				
Income $US and ethnicity																
< 20K, non-white													5.93	0.67	6.02	.014
< 20K, white													3.67	0.30		
≥ 20K, non-white													2.16	0.56		
≥ 20K, white													2.04	0.24		
Income $US, and health																
< $20K, poor or fair	17.51	1.38	7.04	.008									6.39	0.57	13.95	< .001
< $20K, good or better	7.10	0.73											3.20	0.37		
$20K, poor or fair	10.79	1.20											2.36	0.49		
$20K, good or better	5.67	0.48											1.83	0.30		

Abbreviations: BSI, Brief Symptom Inventory; GSI, Global Severity Index; LS, least-squared; HS, high school.

other eligible diagnoses, fewer brain cancer patients would be expected to survive and be eligible for entry in this cohort. Thus, the fact that brain tumor patients represent 14% of the survivors eligible for the CCSS cohort is not dramatically different from population-based data presented in the SEER Pediatric Monograph showing that CNS malignancies represent 16.7% of all cancers younger than 20 years.

Use of the BSI-18 criterion for determining "positive risk" for distress is somewhat limiting, in that the age group from which community norms on the BSI-18 were derived is significantly older than our study group, with only 10.5% of the normative population younger than 30 years. Thus, drawing definitive conclusions from any comparison of siblings and survivors to standardized norms for the BSI-18 is tenuous. We also acknowledge caution in comparing survivors with siblings who were exposed to the same stresses on the family as the survivor, thereby perhaps making siblings more susceptible to distress than their peers. However, we note that the percentage of siblings whose GSI scores approximated clinical distress levels fell well within the range found in the general population, making them

more like the general population than different. Finally, the survey questions only asked about psychological symptoms that were experienced within the previous 7 days. Such a cross-sectional evaluation may not be sensitive to other temporal patterns of psychological distress, nor can it be assured that the symptomatology described did not originate before the onset of the brain cancer.

The important strengths of this study include the large, population–based nature of the participant sample, and the inclusion of a relevant comparison group. Most studies of cancer patient populations are limited to a small, homogeneous clinical sample that is subject to referral biases and does not include subjects for comparison purposes. This study recruited a diverse patient base with a full spectrum of brain cancer subtypes and treatment approaches, thus allowing much greater generalizability of the findings. Additional follow-up and assessment of this subgroup of CCSS participants would be helpful to evaluate changes over time, with increasing duration from cessation of cancer treatment.

An important clinical implication of the findings reported here is that the mental health status of brain cancer survivors who report symptoms of distress may be improved by psychosocial support interventions that enhance social and vocational skills. This skill building, as well as social and community supports to assist those survivors with cognitive deficits, may enhance survivors' abilities to enter intimate relationships or to obtain and maintain gainful employment opportunities. Legal and advocacy support also may ensure that appropriate workplace accommodations are made for cancer survivors, as mandated in the United States by the Americans with Disabilities Act. Medical treatment and long-term follow-up that addresses and alleviates cognitive and physical sequelae to the extent possible also may enhance these survivors' psychosocial functioning and reduce distress. The implementation and evaluation of the efficacy of individual and community-based interventions are warranted.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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