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ARTICLE

Neurocognitive Functioning in Adult Survivors of Childhood Non-Central Nervous System Cancers

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Background We sought to measure self-reported neurocognitive functioning among survivors of non-central nervous system (CNS) childhood cancers, overall and compared with a sibling cohort, and to identify factors associated with worse functioning.

Methods In a retrospective cohort study, 5937 adult survivors of non-CNS cancers and 382 siblings completed a validated neuropsychological instrument with subscales in task efficiency, emotional regulation, organization, and memory. Scores were converted to *T* scores; scores in the worst 10% of siblings' scores (ie, *T* score ≥63) were defined as impaired. Non-CNS cancer survivors and siblings were compared with multivariable linear regression and log-binomial regression. Among survivors, log-binomial models assessed the association of patient and treatment factors with neurocognitive dysfunction. All statistical tests were two-sided.

Results Non-CNS cancer survivors had similar or slightly worse (<0.5 standard deviation) mean test scores for all four subscales than siblings. However, frequencies of impaired survivors were approximately 50% higher than siblings in task efficiency (13.0% of survivors vs 7.3% of siblings), memory (12.5% vs 7.6%), and emotional regulation (21.2% vs 14.4%). Impaired task efficiency was most often identified in patients with acute lymphoblastic leukemia who received cranial radiation therapy (18.1% with impairment), myeloid leukemia who received cranial radiation therapy (21.2%), and non-Hodgkin lymphoma (13.9%). In adjusted analysis, diagnosis age of younger than 6 years, female sex, cranial radiation therapy, and hearing impairment were associated with impairment.

Conclusion A statistically and clinically significantly higher percentage of self-reported neurocognitive impairment was found among survivors of non-CNS cancers than among siblings.

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Approximately 80% of children and adolescents diagnosed with cancer will achieve survival beyond 5 years (1). Neurocognitive impairment is a potential late effect in survivors that can limit quality of life and overall functioning in society (2). Previous studies (3) have shown an association between treatment with several chemotherapeutic agents and subsequently altered behavioral and emotional functioning. However, few studies permit examination of effects from multiple specific chemotherapeutic agents with and without cranial radiation therapy.

Early studies of neurocognitive functioning focused on the particularly high-risk group of children with central nervous system (CNS) tumors. Because of the presence of an intracranial mass and the frequent need for neurosurgery and high-dose cranial radiation therapy, survivors of CNS tumors often experience devastating cognitive declines of 20–40 IQ points (4). Additional studies (5) reported that children with non-CNS types of cancer have less severe, but still clinically significant, impairment in neurocognitive functioning, including executive function (ie, "the ability to organize, plan, hold information in mind and manipulate it and self-monitor behavior").

Most available studies (6,7) of neurocognitive functioning in non-CNS cancer patients, which were among children with acute lymphoblastic leukemia who received cranial radiation therapy at 18–24 Gy as prophylaxis against CNS leukemia, reported that these patients experienced diminished IQ and academic functioning. To reduce long-term neurocognitive toxicity, more intensive intrathecal or systemic chemotherapy was used as a strategy to reduce or eliminate cranial radiation therapy. However, some investigators (8–10) concluded that patients still developed neurocognitive impairment that appeared to have been caused by the intrathecal and/or high-dose systemic chemotherapy. Methotrexate is the most frequently implicated chemotherapy agent because of its well-characterized acute neurotoxicity (11) and because of the magnetic resonance imaging finding of parenchymal white matter changes in some patients with acute lymphoblastic leukemia (5). Waber et al. (12) suggested that corticosteroids, particularly dexamethasone, also cause neurocognitive changes.

Further studies are needed to understand how individual cancer therapies contribute to the risk of long-term neurocognitive impairment. Although provocative, past studies generally included small samples, focused on the immediate period after treatment,

CONTEXT AND CAVEATS

Prior knowledge

Neurocognitive impairment is a potential late effect in cancer survivors that can limit quality of life and overall functioning in society. Associations have been found between treatment with several chemotherapeutic agents and subsequently altered behavioral and emotional functioning. Few studies have permitted the study of multiple specific chemotherapeutic agents with and without cranial radiation therapy.

Study design

In a retrospective cohort study, adult survivors of non-central nervous system (CNS) cancers and siblings completed a validated neuropsychological instrument with subscales in task efficiency, emotional regulation, organization, and memory. Non-CNS cancer survivors and siblings were compared.

Contribution

Non-CNS cancer survivors had similar or slightly worse mean test scores for all four subscales than siblings. However, frequencies of impaired survivors were approximately 50% higher than siblings in task efficiency, memory, and emotional regulation. Impaired task efficiency was most often identified in patients with acute lymphoblastic leukemia or with myeloid leukemia who received cranial radiation therapy and in those with non-Hodgkin lymphoma. In adjusted analysis, diagnosis age of younger than 6 years, female sex, cranial radiation therapy, and hearing impairment were associated with impairment.

Implications

All non-CNS cancer survivors, particularly those with leukemia or lymphoma, should be monitored for difficulties in academic performance so that appropriate interventions and/or accommodations may be given during childhood. Monitoring is especially important for those who received any cranial radiation therapy, who are female, who are treated when aged younger than 6 years, and who have hearing deficits.

Limitations

The study design was retrospective. Some treatments may not be used in more modern regimens.

From the Editors

included only patients with acute lymphoblastic leukemia, or were based on experiences at a single institution. We used the heterogeneity and distribution of treatment exposures in the Childhood Cancer Survivor Study (CCSS) cohort to overcome many of the previous disadvantages in this investigation. We restricted this analysis to the non-CNS tumor patients so that the treatment effects could be isolated from those of intracranial tumors. The aims of this study were to describe neurocognitive functioning in survivors of non-CNS cancers of childhood, overall and compared with a sibling cohort, and to identify treatment and patient characteristics that are associated with neurocognitive impairment.

Subjects and Methods

Description of Subjects

The CCSS is a multisite retrospectively ascertained cohort that was designed to study the late effects of childhood cancer therapy. Inclusion criteria for the cancer survivors in this study included 1) diagnosis of leukemia, CNS malignancy, Hodgkin disease, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; 2) diagnosis and initial treatment at one of the 26 collaborating centers between January 1, 1970, and December 31, 1986; 3) aged younger than 21 years at diagnosis; and 4) survival for at least 5 years from the date of diagnosis (13).

Beginning in August 1994, participants completed an extensive baseline questionnaire about their demographic, medical, and psychosocial status. After obtaining a signed medical release from each patient, data were abstracted from the medical record regarding their initial cancer treatment, treatment for any relapse, and preparatory regimens for bone marrow transplantation. Cumulative data for oral methotrexate and glucocorticoids were not available; glucocorticoid history for non-oncology conditions was not abstracted. The study design and cohort characteristics have been described previously (14), and further details are available at http://ccss.stjude.org. All CCSS protocol and contact documents were reviewed and approved by the human subjects committee at each participating institution, and written informed consent was obtained for all participants.

The flowchart that describes characteristics of CCSS participants that were collected in surveys at baseline, the follow-up in 2000, and the follow-up in 2003 is described in Figure 1. A randomly selected subset of survivors was asked to identify all their living siblings, from which the sibling closest in age to the survivor was selected and asked to participate. Of the 4782 eligible siblings, 3845 (80.4%) participated on the initial baseline survey in this ongoing longitudinal follow-up study.

The 2003 follow-up survey contained a self-report standardized assessment of neurocognitive functioning. This survey was particularly time-consuming because of its length (>24 pages) and its emphasis on cognitive and psychological functioning. Therefore, it was sent to all eligible survivors, but only a selected subsample of 500 siblings received the full survey that included the cognitive and psychological questions. The remaining siblings and survivors received a shortened version of the survey that did not include the cognitive or psychological questions. The full survey was completed by 5937 (87%) of the 6824 participating CCSS survivors of non-CNS childhood cancers and 382 (76%) of the 500 participating CCSS siblings. The siblings included in this analysis were similar to the remaining siblings in terms of sex, age at evaluation, and ethnicity. Siblings included in this analysis were slightly more likely to have a high school diploma or college degree (97.6% in current analysis vs 94.6% of the remaining siblings, $P = .04$).

Instruments of Neurocognitive Functioning and Psychological Distress

To assess self-reported neurocognitive functioning in the CCSS population, an instrument was developed for the CCSS population that was based on the adult version of the Behavior Rating Inventory of Executive Functioning (BRIEF-A), a multidimensional standardized behavior rating inventory (15). Items that were representative of multiple scales from the BRIEF were selected and then combined with independently derived items that were designed to assess the neurocognitive domains of processing speed, memory, and academic functioning. The resulting 25 items generated reliable

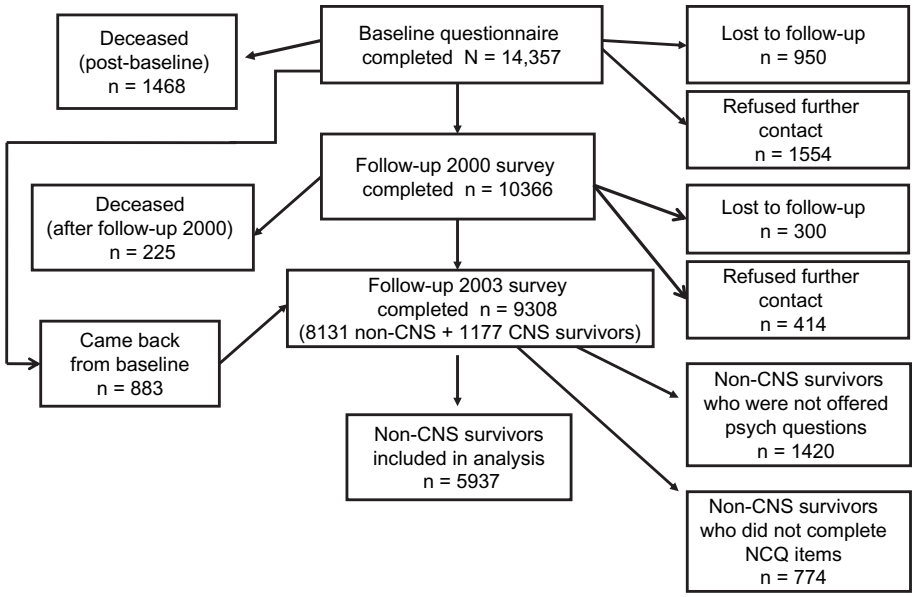

Figure 1. Flow diagram of study participation. Participants were from the Childhood Cancer Survivor Study. CNS = central nervous system; NCQ = Neurocognitive Questionnaire.

and valid factors in a group of siblings of CCSS survivors and in a group of healthy survivors with no history of CNS disease or treatment. Participants were asked to report the degree to which they experienced any of the 25 problems over the past 6 months with a Likert scale ranging from 1 to 3 (ie, 1 = "never a problem," 2 = "sometimes a problem," and 3 = "often a problem"). The factor structure for the CCSS–Neurocognitive Questionnaire (NCQ) was developed by using 382 siblings of cancer survivors and was validated in a restricted subset of 1671 cancer survivors from the entire CCSS cohort. However, 5249 (88.4%) of the 5937 non-CNS cancer survivors were not included in the validation process of the CCSS-NCQ. Further details regarding the validation process were reported previously (16).

The CCSS-NCQ instrument has the following four reliable factors that accurately discriminate survivors who are at "high risk" for neurocognitive dysfunction from healthy "low-risk" survivors and siblings: task efficiency (eg, "I am slower than others when completing my work" or "I have problems completing my work"), emotional regulation (eg, "I get upset easily" or "I get frustrated easily"), organization (eg, "I am disorganized" or "My desk/workspace is a mess"), and memory (eg, "I have trouble remembering things, even for a few minutes") (16,17). The sums of items endorsed on each factor were converted to *T* scores so that the sibling group had a mean score of 50 and a standard deviation of 10, with higher scores indicative of greater reported neurocognitive impairment.

Psychological distress was evaluated on the baseline and the 2003 follow-up survey with the Brief Symptom Inventory-18, an 18-item checklist that measures symptoms of anxiety, depression, and somatic distress (18). Responses were scored to generate a Global Severity Index score as well as anxiety and depression subscales (19). Subjects with standardized *T* scores of 63 or higher were classified as having psychological distress, consistent with guidelines in validation studies of the test manual (20).

Data Analysis

Demographic characteristics were compared between non-CNS cancer survivors and siblings by use of the *t* test and χ^2 test. CCSS-NCQ scores were summarized for non-CNS cancer survivors and siblings. Results for the four factors of CCSS-NCQ (ie, task efficiency, organization, memory, and emotional regulation) (16) were reported as 1) means and standard deviations of *T* scores and 2) percentages of individuals with scores in a low functioning range (ie, with impairment), which was calculated as percentages of patients with *T* score of 63 or higher, approximately corresponding to the worst 10% range of siblings' scores. Non-CNS cancer survivors and siblings were compared on each of the four CCSS-NCQ factor scores (16) by use of multiple linear regression and on each of the four impairment outcomes (yes or no) by use of multivariable log-binomial regression with adjustment for current age, sex, and race. When non-CNS cancer survivors and siblings were compared, we used a modification of linear regression by generalized estimating equations to account for potential within-family correlation (21). When variables with more than two levels were compared between survivors and siblings, bootstrap methods to account for potential within-family correlations by resampling families were used (22).

Among non-CNS cancer survivors, log-binomial models were used to assess the association of patient and treatment factors on neurocognitive dysfunction. Specifically, the proportion of subjects with a *T* score in the "impaired" range as defined above (ie, "prevalence" of the impairment) was compared across groups defined by the patient and treatment factors. Prevalence ratios (PRs), impairment in subgroups of survivors compared with the referent group, were reported with corresponding 95% confidence intervals (CIs), which were based on the standard large sample inference method for generalized linear models. When the log-binomial regression did not converge numerically, we used the COPY method (23).

We initially performed an unadjusted analysis for each patient and treatment factor, including sex, ethnicity (nonwhite or white), age at diagnosis (0–5 or ≥6 years), time since diagnosis (15–19, 20–24, 25–29, or 30–34 years), age at evaluation (17–24, 25–34, or ≥35 years), cranial radiation therapy (>18 Gy, 0.1–18 Gy, or none), corticosteroid therapy (dexamethasone with or without prednisone,

prednisone only, or none), methotrexate therapy (systemic + intrathecal, systemic without intrathecal, or none), cytarabine therapy (systemic + intrathecal, systemic without intrathecal, or none), anthracycline dose (none, ≤100, 101–400, or >400 mg/m^2), cyclophosphamide dose (none, ≤4480, 4481–9750, or >9751 mg/m^2), emotional distress (yes or no), depression (yes or no), anxiety (yes or no), sensory deficits (hearing with or without visual deficits, visual deficits only, or none), followed by multivariable log-binomial regression analysis, including factors that were marginally statistically significant in the unadjusted analysis (ie, $P < .2$). Consistent with previously published studies (24,25) of cognitive function outcomes that were similar to those observed in this study, we did not correct for multiple comparisons because our analysis assessed a priori hypothesized associations of multiple dimensions of neurocognitive functioning that have been established to be of scientific interest in our patient population. We tested a priori hypothesized interactions between age at diagnosis and sex, age at diagnosis and treatment exposures, and sex and treatment exposures in the following manner. Initially, a forward selection was used with an entry P value criterion of .05 for these hypothesized two-way interactions: This resulted in one statistically significant two-way interaction for the emotional regulation outcome. We considered treatment exposures within the first 5 years from the original diagnosis of cancer in defining treatment variables. All statistical analyses were conducted with SAS version 9.1 and R version 2.7.1. Two-sided statistical inferences were used throughout the analyses.

Results

Characteristics of the non-CNS cancer survivor group and the sibling comparison group are shown in Table 1. Cancer survivors were slightly younger than siblings (32.2 vs 34.1 years, $P < .001$) but were similar in terms of sex and education.

After adjusting for age, sex, and race, those in the non-CNS childhood cancer survivor group had statistically significantly worse self-reported neurocognitive functioning than those in the sibling comparison group in task efficiency, memory, and emotional regulation (Table 2). However, self-reported neurocognitive functioning varied among the diagnosis groups. Non-CNS cancer survivors with a history of acute lymphoblastic leukemia, myeloid leukemia, or non-Hodgkin lymphoma had the most impaired scores. Among the 1939 survivors with acute lymphoblastic leukemia, 314 (16.2%) reported impaired task efficiency ($P < .01$), which was largely accounted for by those who had received cranial radiation therapy.

Generally, survivors with soft tissue sarcoma, Ewings tumor, or Wilms tumor had self-reported neurocognitive functioning scores that were similar to or better than those in the sibling comparison group. Survivors with osteosarcoma had slightly poorer scores in

Table 1. Characteristics of non-central nervous system (CNS) cancer survivors and their siblings*

Characteristic	Non-CNS survivors (n = 5937)	Siblings (n = 382)	P†
Sex, No. (%)			
Male	2876 (48.4)	182 (47.6)	.78
Female	3061 (51.6)	200 (52.4)	
Age at evaluation, y ± SD (range)	32.2 ± 7.6 (17.0–54.1)	34.1 ± 8.4 (17.8–58.4)	<.001
Ethnicity, No. (%)			
White	5397 (91.2)	336 (93.9)	.08
Nonwhite	521 (8.8)	22 (6.1)	
Education, No. (%)			
Less than high school diploma	219 (3.7)	9 (2.4)	.36
High school diploma	2886 (48.6)	181 (47.5)	
College degree	2831 (47.7)	191 (50.1)	
Cancer diagnosis, No. (%)			
Acute lymphoblastic leukemia	1939 (32.7)	N/A	N/A
Myeloid leukemia (AML or CML)	292 (4.9)		
Hodgkin disease	908 (15.3)		
Non-Hodgkin lymphoma	509 (8.6)		
Neuroblastoma	433 (7.3)		
Soft tissue sarcoma	613 (10.3)		
Osteosarcoma	382 (6.4)		
Ewings and other bone tumors	212 (3.6)		
Wilms tumor	649 (10.9)		
Age at diagnosis, y ± SD (range)	8.5 ± 6.0 (0–20)	N/A	N/A
Years since diagnosis ± SD (range)	23.7 ± 4.5 (16.0–34.3)	N/A	N/A
Treatment, No. (%)			
Chemotherapy without RT	1663 (29.8)	N/A	N/A
RT without chemotherapy	452 (8.1)		
Chemotherapy and RT	3178 (57.0)		
No chemotherapy or RT	284 (5.1)		

* Percentages are based on the total with available data for each variable. AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; N/A = not applicable; RT = radiation therapy.

† Generalized estimating equations with binary response were used to account for the family effect when comparing with siblings. Bootstrap was used to account for the family effect when comparing with siblings. All statistical tests were two-sided.

Table 2. Comparison of overall self-reported neurocognitive functioning outcomes between non-central nervous system (CNS) cancer survivors and their siblings*

		Task efficiency				Organization				Memory				Emotional regulation			
Group	No.	Mean *T* score (SD)	*P*†	% Impaired‡	*P*	Mean *T* score (SD)	*P*	% Impaired	*P*	Mean *T* score (SD)	*P*	% Impaired	*P*	Mean *T* score (SD)	*P*	% Impaired	*P*
Siblings	382	50.0 (48.7–51.3)	Ref	7.3 (4.7–9.9)	Ref	50.0 (48.7–51.3)	Ref	12.0 (8.8–15.3)	Ref	50.0 (48.7–51.3)	Ref	7.6 (4.9–10.3)	Ref	50.0 (48.7–51.3)	Ref	14.4 (10.9–17.9)	Ref
Total non-CNS cancer survivors	5937	52.6 (52.2–53.1)	<.001	13.0 (12.1–13.8)	.005	49.9 (49.5–50.2)	.71	12.4 (11.6–13.3)	.991	51.5 (51.1–51.9)	.005	12.5 (11.7–13.4)	.01	51.8 (51.4–52.2)	.004	21.2 (20.1–22.2)	.003
Diagnosis group																	
Acute lymphoblastic leukemia	1939	54.7 (53.9–55.5)	<.001	16.3 (14.6–17.9)	<.001	49.5 (48.9–50.1)	.47	12.3 (10.8–13.7)	.95	52.9 (52.2–53.7)	<.001	14.3 (12.8–15.9)	.004	52.6 (51.9–53.2)	<.001	26.4 (24.4–28.4)	<.001
−CRT	624	51.7 (50.4–52.9)	.75	11.1 (8.6–13.5)	.16	49.1 (48.1–50.1)	.18	11.9 (9.3–14.4)	.70	50.7 (49.5–51.9)	.49	13.0 (10.3–15.6)	.21	51.8 (50.7–52.9)	.31	19.2 (16.1–22.3)	.37
+CRT	1168	56.3 (55.3–57.4)	<.001	18.1 (15.9–20.3)	<.001	49.7 (49.0–50.5)	.62	12.6 (10.7–14.5)	.95	53.9 (53.0–54.9)	<.001	14.8 (12.8–16.9)	.003	53.0 (52.2–53.8)	<.001	30.6 (27.9–33.2)	<.001
Myeloid leukemia (AML or CML)	292	54.5 (52.5–56.6)	<.001	14.7 (10.7–18.8)	.005	49.9 (48.3–51.4)	.84	12.3 (8.6–16.1)	.97	52.4 (50.5–54.2)	.006	13.4 (9.5–17.3)	.04	52.2 (50.5–53.8)	.03	27.1 (22.0–32.2)	<.001
−CRT	120	51.7 (48.7–54.8)	.60	7.5 (2.8–12.2)	.83	49.2 (46.8–51.5)	.41	11.7 (5.9–17.4)	.78	49.4 (46.8–52.0)	.46	15.0 (8.6–21.4)	.10	52.2 (49.6–54.8)	.26	20.0 (12.8–27.2)	.35
+CRT	156	57.5 (54.5–60.4)	<.001	21.2 (14.8–27.6)	<.001	50.5 (48.4–52.7)	.61	12.8 (7.6–18.1)	.86	55.1 (52.5–57.7)	<.001	12.8 (7.6–18.1)	.09	52.5 (50.3–54.8)	.02	34.0 (26.5–41.4)	<.001
Hodgkin disease	908	51.2 (50.2–52.2)	.03	12.1 (10.0–14.2)	.05	49.9 (49.1–50.8)	.52	12.0 (9.9–14.1)	.81	51.5 (50.6–52.5)	.07	11.9 (9.8–14.0)	.006	51.6 (50.6–52.5)	.003	15.8 (13.4–18.1)	.35
Non-Hodgkin lymphoma	509	51.8 (50.5–53.2)	.002	14.0 (10.9–17.0)	.002	50.1 (48.9–51.2)	.96	13.0 (10.1–15.9)	.73	51.8 (50.4–53.2)	.005	13.0 (10.1–15.9)	.001	51.8 (50.6–53.1)	<.001	20.4 (16.9–23.9)	.006
Neuroblastoma	433	52.3 (50.7–53.9)	.06	12.0 (9.0–15.1)	.04	49.8 (48.5–51.2)	.94	13.4 (10.2–16.6)	.76	50.0 (48.5–51.4)	.72	11.3 (8.3–14.3)	.51	51.3 (49.9–52.7)	.72	20.8 (17.0–24.6)	.07
Soft tissue sarcoma	613	51.4 (50.2–52.7)	.03	10.4 (8.0–12.9)	.16	50.1 (49.1–51.1)	.99	10.8 (8.3–13.2)	.46	50.3 (49.1–51.5)	.63	9.8 (7.4–12.1)	.21	50.8 (49.7–51.9)	.23	17.9 (14.9–21.0)	.11
Osteosarcoma	382	51.8 (50.2–53.4)	.01	10.0 (7.0–13.0)	.39	50.7 (49.4–52.0)	.53	15.2 (11.6–18.8)	.25	50.7 (49.2–52.2)	.69	10.7 (7.6–13.8)	.08	51.6 (50.2–52.9)	.02	19.4 (15.4–23.3)	.05
Ewings and other bone tumors	212	50.8 (48.9–52.8)	.25	8.5 (4.7–12.2)	.83	49.8 (48.2–51.5)	.68	10.9 (6.7–15.0)	.60	50.3 (48.4–52.2)	.88	9.0 (5.1–12.8)	.41	50.1 (48.2–52.0)	.84	16.0 (11.1–21.0)	.46
Wilms tumor	649	50.9 (49.7–52.1)	.78	9.2 (7.0–11.5)	.42	49.8 (48.8–50.9)	.93	12.8 (10.2–15.4)	.91	49.7 (48.6–50.8)	.87	12.9 (10.4–15.5)	.12	51.5 (50.3–52.6)	.50	17.0 (14.1–19.8)	.56

* Data are the mean raw score *T* score values. Comparisons were adjusted for age, sex, and race. AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; CRT = cranial radiation therapy.

† Survivors and siblings were compared using regressions with the modification by generalized estimating equations to account for potential within-family correlations, adjusted for age, sex, and race. All statistical tests were two-sided.

‡ Percentages of patients with scores in the worst 10% range of siblings' scores (ie, a *T* score of ≥63).

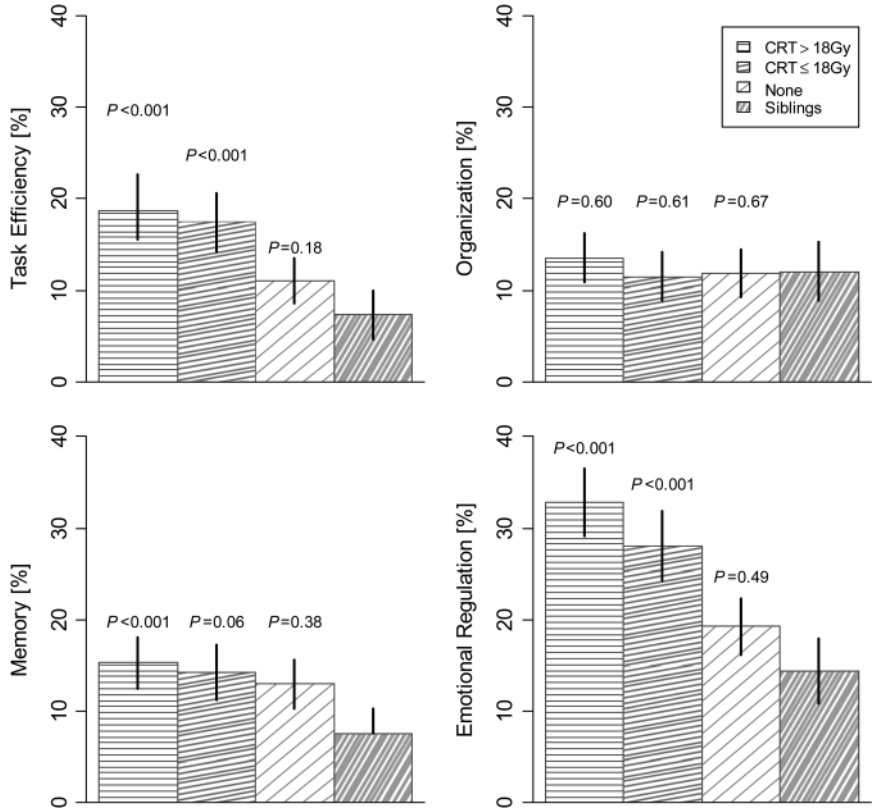

Figure 2. Percentages and 95% confidence intervals of impaired neurocognitive functioning among participants, stratified by receipt of cranial radiation therapy (CRT), compared with siblings (*P* values are for comparisons with siblings). Subgroups were non-central nervous system (CNS) survivors treated with a CRT dose of greater than 18 Gy, non-CNS survivors treated with CRT dose of 18 Gy or less, non-CNS survivors who did not receive CRT, and siblings. Impaired functioning was defined by *T* scores of 63 or higher on the Neurocognitive Questionnaire.

task efficiency (*T* score = 51.8, *P* = .01) and emotional regulation (*T* score = 51.6, *P* = .02) than siblings (*T* score = 50.0).

Percentages of scores in the impaired range were stratified by cranial radiation therapy (>18 Gy, 0.1–18 Gy, or none) and compared between survivors of acute lymphoblastic leukemia and siblings (Figure 2). Survivors had impairments that were approximately 50% higher than those among the siblings in task efficiency (13.0% of survivors vs 7.3% of siblings), memory (12.5% of survivors vs 7.6% of siblings), and emotional regulation (21.2% of survivors vs 14.4% of siblings). Impaired task efficiency was most often identified in patients with acute lymphoblastic leukemia who received cranial radiation therapy (18.1% with impairment), myeloid leukemia who received cranial radiation therapy (21.2% with impairment), non-Hodgkin lymphoma (13.9% with impairment), neuroblastoma (12.1% with impairment), or Hodgkin lymphoma (12.0% with impairment).

Associations Between Patient Characteristics and Self-Reported Neurocognitive Functioning Among Survivors

In unadjusted analysis, the patient characteristics of female sex (PR = 1.9, 95% CI = 1.7 to 2.2), age younger than 6 years at diagnosis (PR = 1.4, 95% CI = 1.2 to 1.6), and age of 17–24 years at evaluation (vs ≥35 years; PR = 1.6, 95% CI = 1.3 to 1.9) were statistically significantly associated with impaired memory (Table 3). Similar patterns were observed for emotional regulation. Weaker associations were observed for task efficiency.

In unadjusted analysis of concurrent conditions, survivors reporting emotional distress, including anxiety and depression, were at elevated risk for impaired task efficiency, organization, memory, and emotional regulation (Table 3). Survivors with hearing (PR = 1.8, 95% CI = 1.5 to 2.2) or isolated vision deficits (PR = 1.5, 95% CI = 1.3 to 1.8) were more likely to have impaired emotional regulation than those without sensory problems; hearing loss was also associated with worse organization (Table 3).

In unadjusted analysis of treatment factors (Table 3), cranial radiation therapy with a dose of greater than 18 Gy was associated with the greatest risk of impairments in task efficiency (PR = 1.8, 95% CI = 1.5 to 2.1), memory (PR = 1.3, 95% CI = 1.1 to 1.6), and emotional regulation (PR = 1.7, 95% CI = 1.5 to 2.0). Cranial radiation therapy at lower doses was associated with a similar or only slightly lower risk of impaired self-reported neurocognitive functioning.

Treatment with corticosteroid, methotrexate, or cytarabine was statistically significantly associated with worse task efficiency and emotional regulation (Table 3). Treatment with dexamethasone was not associated with additional risk compared with treatment with prednisone alone. Treatment with methotrexate that was administered intrathecally, compared with no methotrexate or systemic methotrexate only, was associated with greater risk of self-reported neurocognitive impairment. For task efficiency, treatment with intrathecal methotrexate was associated with a higher risk of dysfunction (PR = 1.4, 95% CI = 1.2 to 1.6) than treatment with systemic methotrexate only (PR = 0.9, 95% CI = 0.7 to 1.2). Neither treatment with anthracycline nor treatment with cyclophosphamide was associated with self-reported neurocognitive functioning.

Because many of these therapies are administered concurrently, additional stratified analyses were conducted (Table 4). Neck radiation without cranial radiation therapy was not associated with self-reported neurocognitive impairment. In the setting of cranial

Table 3. Patient and treatment factors that were associated with self-reported impaired neurocognitive functioning outcomes among non-central nervous system survivors: univariate analysis*

		Task efficiency			Organization			Memory			Emotional regulation		
Patient or treatment factor	**No.**	**%**	**PR (95% CI)**	***P*†**	**%**	**PR (95% CI)**	***P***	**%**	**PR (95% CI)**	***P***	**%**	**PR (95% CI)**	***P***
Sex													
Female	3061	14.8	1.3 (1.2 to 1.5)	<.001	12.5	1.0 (0.9 to 1.2)	.75	16.3	1.9 (1.7 to 2.2)	<.001	23.5	1.3 (1.1 to 1.4)	<.001
Male	2876	11.0	1.0 (ref.)		12.3	1.0 (ref.)		8.5	1.0 (ref.)		18.6	1.0 (ref.)	
Ethnicity													
Nonwhite	521	13.2	1.0 (0.8 to 1.3)	.85	12.1	1.0 (0.8 to 1.2)	.80	14.8	1.2 (1.0 to 1.5)	.11	24.0	1.1 (1.0 to 1.4)	.09
White	5397	13.0	1.0 (ref.)		12.5	1.0 (ref.)		12.3	1.0 (ref.)		20.9	1.0 (ref.)	
Age at diagnosis													
0–5 y	2680	13.5	1.1 (0.9 to 1.2)	.28	12.6	1.0 (0.9 to 1.2)	.73	14.9	1.4 (1.2 to 1.6)	<.001	24.9	1.4 (1.2 to 1.5)	<.001
≥6 y	3257	12.6	1.0 (ref.)		12.3	1.0 (ref.)		10.6	1.0 (ref.)		18.1	1.0 (ref.)	
Time since diagnosis													
15–19 y	1590	12.6	0.9 (0.7 to 1.2)	.54	12.9	1.2 (0.9 to 1.5)	.18	13.5	1.3 (1.0 to 1.7)	.03	21.4	1.1 (0.9 to 1.3)	.31
20–24 y	2125	12.5	0.9 (0.7 to 1.2)	.50	12.5	1.1 (0.9 to 1.5)	.27	13.5	1.3 (1.0 to 1.7)	.03	20.1	1.0 (0.9 to 1.2)	.73
25–29 y	1541	13.8	1.0 (0.8 to 1.3)	.84	12.5	1.2 (0.9 to 1.5)	.27	11.4	1.1 (0.9 to 1.5)	.40	23.0	1.2 (1.0 to 1.4)	.07
30–34 y	681	13.5	1.0 (ref.)		10.9	1.0 (ref.)		10.1	1.0 (ref.)		19.5	1.0 (ref.)	
Age at evaluation													
17–24 y	1221	12.8	0.9 (0.8 to 1.1)	.55	13.1	1.0 (0.9 to 1.2)	.68	16.4	1.6 (1.3 to 1.9)	<.001	25.8	1.4 (1.2 to 1.6)	<.001
25–34 y	2599	12.7	0.9 (0.8 to 1.1)	.39	11.9	0.9 (0.8 to 1.1)	.48	12.4	1.2 (1.0 to 1.4)	.05	20.9	1.1 (1.0 to 1.2)	.07
≥35 y	2117	13.5	1.0 (ref.)		12.6	1.0 (ref.)		10.5	1.0 (ref.)		18.8	1.0 (ref.)	
Cranial radiation therapy													
>18 Gy	908	19.1	1.8 (1.5 to 2.1)	<.001	13.5	1.1 (0.9 to 1.3)	.29	15.1	1.3 (1.1 to 1.5)	.006	31.3	1.7 (1.5 to 2.0)	<.001
>0 and ≤18 Gy	652	17.3	1.6 (1.4 to 2.0)	<.001	11.2	0.9 (0.7 to 1.2)	.45	14.0	1.2 (1.0 to 1.5)	.11	29.0	1.6 (1.4 to 1.9)	<.001
None	3910	10.6	1.0 (ref.)		12.3	1.0 (ref.)		11.8	1.0 (ref.)		18.0	1.0 (ref.)	
Corticosteroid therapy													
Dexamethasone ± prednisone	397	14.6	1.4 (1.1 to 1.8)	.009	10.1	0.8 (0.6 to 1.1)	.25	12.1	1.1 (0.8 to 1.5)	.56	21.4	1.2 (1.0 to 1.5)	.09
Prednisone only	2531	15.1	1.5 (1.3 to 1.7)	<.001	13.2	1.1 (0.9 to 1.3)	.22	14.3	1.3 (1.1 to 1.5)	<.001	25.0	1.4 (1.3 to 1.5)	<.001
None	2659	10.3	1.0 (ref.)		12.1	1.0 (ref.)		11.1	1.0 (ref.)		17.9	1.0 (ref.)	
Methotrexate therapy													
Systemic + IT	2247	15.4	1.4 (1.2 to 1.6)	<.001	12.6	1.0 (0.9 to 1.2)	.66	14.8	1.3 (1.1 to 1.5)	<.001	26.0	1.5 (1.3 to 1.6)	<.001
Systemic − IT	552	10.3	0.9 (0.7 to 1.2)	.60	12.7	1.0 (0.8 to 1.3)	.77	9.4	0.8 (0.6 to 1.1)	.16	20.5	1.1 (1.0 to 1.4)	.14
None	2788	11.1	1.0 (ref.)		12.2	1.0 (ref.)		11.5	1.0 (ref.)		17.8	1.0 (ref.)	
Cytarabine therapy													
Systemic + IT	777	15.6	1.3 (1.1 to 1.6)	.005	11.5	0.9 (0.7 to 1.1)	.37	14.8	1.2 (1.0 to 1.5)	.04	26.3	1.3 (1.2 to 1.5)	<.001
Systemic − IT	581	14.8	1.2 (1.0 to 1.5)	.05	12.6	1.0 (0.8 to 1.3)	.98	13.1	1.1 (0.9 to 1.4)	.51	26.2	1.3 (1.1 to 1.5)	<.001
None	4229	12.0	1.0 (ref.)		12.6	1.0 (ref.)		12.1	1.0 (ref.)		19.8	1.0 (ref.)	
Anthracycline dose (tertiles)													
None	3170	13.0	1.0 (ref.)		12.4	1.0 (ref.)		12.9	1.0 (ref.)		21.1	1.0 (ref.)	
Low (≤100 mg/m^2)	749	13.2	1.0 (0.8 to 1.2)	.87	9.9	0.8 (0.6 to 1.0)	.06	12.0	0.9 (0.8 to 1.2)	.50	22.4	1.1 (0.9 to 1.2)	.42
Moderate (101–400 mg/m^2)	765	12.2	0.9 (0.8 to 1.2)	.53	14.1	1.1 (0.9 to 1.4)	.19	13.5	1.0 (0.9 to 1.3)	.70	22.1	1.0 (0.9 to 1.2)	.55
High (>400 mg/m^2)	727	10.7	0.8 (0.7 to 1.0)	.10	12.1	1.0 (0.8 to 1.2)	.85	10.0	0.8 (0.6 to 1.0)	.04	19.7	0.9 (0.8 to 1.1)	.39
Cyclophosphamide dose (tertiles)													
None	2945	11.8	1.0 (ref.)		12.4	1.0 (ref.)		12.7	1.0 (ref.)		20.6	1.0 (ref.)	
Low (≤4480 mg/m^2)	808	13.2	1.1 (0.9 to 1.4)	.27	12.4	1.0 (0.8 to 1.2)	.99	11.6	0.9 (0.7 to 1.1)	.42	23.3	1.1 (1.0 to 1.3)	.09
Moderate (4481–9750 mg/m^2)	807	14.3	1.2 (1.0 to 1.5)	.06	12.3	1.0 (0.8 to 1.2)	.92	13.5	1.1 (0.9 to 1.3)	.54	22.6	1.1 (0.9 to 1.3)	.22
High (>9751 mg/m^2)	807	12.8	1.1 (0.9 to 1.3)	.46	11.6	0.9 (0.8 to 1.2)	.57	11.6	0.9 (0.7 to 1.1)	.42	19.8	1.0 (0.8 to 1.1)	.64

(Table continues)

Table 3 (continued).

Patient or treatment factor	No.	Task efficiency			Organization			Memory			Emotional regulation		
		%	PR (95% CI)	P†	%	PR (95% CI)	P	%	PR (95% CI)	P	%	PR (95% CI)	P
Emotional distress‡													
Yes	576	39.4	3.9 (3.4 to 4.4)	<.001	30.4	2.9 (2.5 to 3.4)	<.001	49.7	5.8 (5.2 to 6.6)	<.001	59.4	3.5 (3.2 to 3.8)	<.001
No	5345	10.1	1.0 (ref.)		10.5	1.0 (ref.)		8.5	1.0 (ref.)		17.0	1.0 (ref.)	
Depression§													
Yes	665	34.4	3.4 (2.9 to 3.8)	<.001	27.5	2.6 (2.3 to 3.0)	<.001	44.2	5.2 (4.6 to 5.9)	<.001	54.7	3.2 (3.0 to 3.5)	<.001
No	5259	10.3	1.0 (ref.)		10.5	1.0 (ref.)		8.5	1.0 (ref.)		16.9	1.0 (ref.)	
Anxiety§													
Yes	444	36.3	3.3 (2.8 to 3.8)	<.001	27.3	2.4 (2.1 to 2.9)	<.001	51.1	5.4 (4.8 to 6.1)	<.001	56.1	3.1 (2.8 to 3.4)	<.001
No	5479	11.1	1.0 (ref.)		11.2	1.0 (ref.)		9.4	1.0 (ref.)		18.3	1.0 (ref.)	
Sensory deficits													
Hearing ± visual	163	16.6	1.3 (0.9 to 1.9)	.12	17.8	1.5 (1.0 to 2.1)	.03	12.3	1.0 (0.7 to 1.5)	.95	36.2	1.8 (1.5 to 2.2)	<.001
Visual only	301	18.9	1.5 (1.2 to 1.9)	<.001	14.0	1.2 (0.9 to 1.5)	.34	14.3	1.1 (0.9 to 1.5)	.34	30.6	1.5 (1.3 to 1.8)	<.001
Neither	5400	12.5	1.0 (ref.)		12.1	1.0 (ref.)		12.4	1.0 (ref.)		20.1	1.0 (ref.)	

* Displayed are stratified percentages and prevalence ratios (PRs) of scores categorized as impaired (ie, in the worst 10% range of siblings' scores). CI = confidence interval; CRT = cranial radiation therapy; IT = intrathecal; ref. = referent.

† Two-sided statistical inference from log-binomial regression or COPY method was used.

‡ Global Severity Index of ≥63 from Brief Symptom Inventory-18 (BSI).

§ Subscale score ≥63 from BSI.

radiation therapy, systemic methotrexate and/or corticosteroid therapy did not increase the risk of neurocognitive impairment. Without concurrent cranial radiation therapy, neither systemic methotrexate nor corticosteroid therapy without the other was associated with self-reported neurocognitive dysfunction. However, systemic methotrexate and corticosteroids together resulted in slightly elevated risk of impaired memory (PR = 1.2 for task efficiency, 95% CI = 1.0 to 1.5). Without cranial radiation therapy, patients who receive cumulative methotrexate doses of more than 5000 mg/m^2 systemically (via an intravenous or intramuscular route) did not have higher risk of impaired neurocognitive functioning scores than those who receive 0.1–5000 mg/m^2.

Multivariable Regression Analyses

Variables that were marginally statistically significant in unadjusted analysis were examined in multivariable log-binomial regression analyses (Table 5). Emotional status was not included in the multiple regression models because of the overlap of elements of the Brief Symptom Inventory-18 and CCSS-NCQ instruments. For task efficiency, younger age at evaluation (ie, 17–24 years), age younger than 6 years at diagnosis, female sex, cranial radiation therapy, and sensory deficits were associated with increased risk of impairment. There was no additional risk of impairment at doses of cranial radiation therapy that were greater than 24 Gy compared with those that were 18–24 Gy (data not shown).

Female sex was statistically significantly associated with emotional regulation dysfunction, with higher risk observed among women who received cranial radiation therapy (PR = 2.1, 95% CI = 1.7 to 2.5). Younger age at diagnosis and female sex were associated with memory impairment. Sensory deficits were associated with organizational dysfunction, organization, and emotional regulation.

Association With Adult Life Outcomes

Table 6 displays proportions (ie, percentages) and prevalence ratios of neurocognitive functioning scores stratified by work status, education, and independence of living. Two-sided statistical inference from log-binomial regression or COPY method was used to compare prevalence ratios within the different adult life outcomes. Impaired task efficiency, organization, memory, and behavioral regulation were all statistically significantly associated with lack of employment, lower educational attainment, and not living independently. Non-CNS cancer survivors who never worked and did not live independently were 1.9 times (95% CI = 1.4 to 2.6) and 1.4 times (95% CI = 1.5 to 1.8) more likely to have impaired memory than those who had ever worked and who lived dependently, respectively.

Discussion

Overall, we found that 13%–21% of survivors of non-CNS cancers in this study had impairment in task efficiency, organization, memory, or emotional regulation, as determined by self-report on a standardized instrument. This rate of impairment was approximately 50% higher than that in the sibling comparison group. However, mean test scores of non-CNS cancer survivors varied only slightly (<0.5 SD) or not at all from those of the comparison

Table 4. Association of selected treatments with self-reported impaired neurocognitive functioning outcomes among non-central nervous system cancer survivors: univariate analysis*

Treatment	No.	Task efficiency			Organization			Memory			Emotional regulation		
		%	PR (95% CI)	P†	%	PR (95% CI)	P	%	PR (95% CI)	P	%	PR (95% CI)	P
CRT ± NRT combinations													
CRT ± NRT	1559	18.3	1.8 (1.5 to 2.1)	<.001	12.6	1.0 (0.9 to 1.2)	.84	14.6	1.2 (1.1 to 1.4)	.010	30.2	1.6 (1.5 to 1.8)	<.001
NRT only	878	11.6	1.1 (0.9 to 1.4)	.24	11.8	1.0 (0.8 to 1.2)	.68	11.6	1.0 (0.8 to 1.2)	.84	15.3	0.8 (0.7 to 1.0)	.02
No CRT or NRT	3025	10.2	1.0 (ref.)		12.4	1.0 (ref.)		11.9	1.0 (ref.)		18.7	1.0 (ref.)	
CRT, methotrexate, and/or steroid combinations‡													
CRT − methotrexate or steroid	111	18.0	1.8 (1.2 to 2.7)	.007	12.6	1.1 (0.6 to 1.8)	.82	18.0	1.6 (1.1 to 2.5)	.02	27.0	1.6 (1.1 to 2.2)	.006
CRT + methotrexate ± steroid	1452	18.3	1.8 (1.5 to 2.1)	<.001	12.5	1.1 (0.9 to 1.3)	.56	14.3	1.3 (1.1 to 1.5)	.003	30.5	1.8 (1.6 to 2.0)	<.001
Steroid − CRT or methotrexate	474	13.3	1.3 (1.0 to 1.7)	.05	13.1	1.1 (0.8 to 1.4)	.47	12.4	1.1 (0.9 to 1.5)	.38	18.6	1.1 (0.9 to 1.3)	.49
Methotrexate − CRT or steroid	305	6.9	0.7 (0.4 to 1.0)	.07	13.8	1.2 (0.9 to 1.6)	.34	9.8	0.9 (0.6 to 1.3)	.53	18.7	1.1 (0.8 to 1.4)	.53
Methotrexate + steroid − CRT	1009	11.3	1.1 (0.9 to 1.4)	.35	12.2	1.0 (0.8 to 1.3)	.81	13.7	1.2 (1.0 to 1.5)	.03	19.0	1.1 (0.9 to 1.3)	.22
No methotrexate, steroid, or CRT	2119	10.2	1.0 (ref.)		11.9	1.0 (ref.)		11.0	1.0 (ref.)		17.2	1.0 (ref.)	
Cumulative IV ± IM methotrexate among survivors with no CRT													
>5000 mg/m^2	317	10.7	1.0 (0.7 to 1.4)	.99	12.6	1.0 (0.8 to 1.4)	.85	11.4	1.0 (0.7 to 1.3)	.84	17.7	1.0 (0.8 to 1.3)	.99
0.1–5000 mg/m^2	445	10.1	0.9 (0.7 to 1.3)	.70	11.2	0.9 (0.7 to 1.2)	.54	12.6	1.1 (0.8 to 1.4)	.61	18.4	1.0 (0.8 to 1.3)	.71
None	3091	10.7	1.0 (ref.)		12.3	1.0 (ref.)		11.7	1.0 (ref.)		17.7	1.0 (ref.)	

* Displayed are stratified proportions (%) and prevalence ratios (PRs) of scores categorized as impaired, that is, in the worst 10% range of siblings' scores. CI = confidence interval; CRT = cranial radiation therapy; IM = intramuscular; IV = intravenous; NRT = neck radiation therapy; ref. = referent.

† Two-sided statistical inference from log-binomial regression or COPY method was used.

‡ In this stratified analysis, "methotrexate" refers to any methotrexate (oral, IV, IM, or intrathecal).

group, indicating that there are vulnerable subgroups. Patient groups at highest risk were those with acute lymphoblastic leukemia and myeloid leukemia but only if they also received cranial radiation therapy. Hodgkin lymphoma, neuroblastoma, and non-Hodgkin lymphoma survivors were impaired compared with siblings, but less so. On the basis of these results, we recommend that patients in these cancer diagnosis groups should receive neuropsychological screening as part of cancer survivorship follow-up care, especially if cranial radiation therapy was given at ages younger than 6 years. Emotional distress was associated with all aspects of measured self-reported neurocognitive functioning but not with cancer diagnosis or exposure to cranial radiation therapy. This distress may stem from the impact that the neurocognitive problems have on daily living skills, employment, and educational attainment. Alternatively, depression and anxiety may manifest as cognitive disturbances or the self-perception of dysfunction, as has been found in the general population (26). Another compelling finding from this study is that hearing difficulty was associated with an increased risk in self-reported neurocognitive dysfunction (for task efficiency, PR = 1.7, 95% CI = 1.3 to 2.0; for organization, PR = 1.6, 95% CI = 1.1 to 2.3; and for emotional regulation, PR = 1.6, 95% CI = 1.3 to 2.0). Chemotherapy exposures, including treatment with methotrexate and prednisone, were not statistically significantly associated with self-reported neurocognitive functioning after adjusting for age, sex, and cranial radiation therapy.

To gain a better understanding of the external validity of our findings, we examined the association between cognitive functioning in participants and key adult life outcomes by use of log-binomial regression in a univariate analysis. We found that impaired task efficiency, organization, memory, and behavioral regulation were associated with unemployed status, lower educational attainment, and not living independently. Similarly, we recently reported (27) that the likelihood of never marrying was higher in CCSS survivors with impaired cognitive functioning. The cognitive, emotional, and physical factors associated with living independently will be examined more closely in the CCSS cohort in a future analysis.

We found that higher doses of cranial radiation therapy were associated with worse self-reported neurocognitive functioning but that even doses of 18 Gy or less were detrimental. This association was also apparent when the analysis was restricted to patients with acute lymphoblastic leukemia. Previous studies (28–33) have, however, reported conflicting data on the role of radiation. Waber et al. (28) concluded that children with acute lymphoblastic leukemia who were randomly assigned to receive 18 Gy of cranial radiation therapy performed similarly on neuropsychological testing to those who were randomly assigned to receive intrathecal chemotherapy. Likewise, Mulhern et al. (29) reported no differences in Verbal, Performance, or Full-Scale IQ among patients who received cranial radiation therapy at 18 or 24 Gy or no irradiation. However, conclusions of more previous studies (30–33) are consistent with that of this study, in that prophylaxis with cranial radiation therapy for patients with acute lymphoblastic leukemia was associated with greater dysfunction.

Younger age at diagnosis and female sex have been identified previously as risk factors for worse neurocognitive impairment among cancer patients who did (30,34) or did not (33–36) receive

Table 5. Multivariable model of all patient, treatment, and medical factors associated with self-reported impaired neurocognitive functioning among non-central nervous system cancer survivors*

	Task efficiency		Organization		Memory		Emotional regulation	
Variables	**PR (95% CI)**	***P*†**	**PR (95% CI)**	***P***	**PR (95% CI)**	***P***	**PR (95% CI)**	***P***
Age at evaluation								
17–24 y	1.1 (0.9 to 1.3)	.38	1.1 (0.8 to 1.5)	.52	1.3 (1.0 to 1.7)	.09	1.1 (0.9 to 1.3)	.36
25–34 y	0.9 (0.8 to 1.1)	.26	1.0 (0.8 to 1.2)	.78	1.1 (0.9 to 1.3)	.61	0.9 (0.8 to 1.1)	.23
≥35 y	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Age at diagnosis								
0–5 y	1.3 (1.1 to 1.5)	<.001	1.1 (0.9 to 1.3)	.63	1.3 (1.0 to 1.6)	.02	1.3 (1.1 to 1.5)	<.001
≥6 y	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Sex								
Female	1.3 (1.1 to 1.4)	<.001	1.0 (0.8 to 1.1)	.77	2.0 (1.7 to 2.3)	<.001		
Male	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)			
CRT								
>18 Gy	1.7 (1.4 to 1.9)	<.001	1.0 (0.8 to 1.3)	.91	1.2 (0.9 to 1.5)	.16		
>0 and ≤18 Gy	1.6 (1.3 to 1.9)	<.001	0.9 (0.7 to 1.2)	.62	1.0 (0.8 to 1.3)	.75		
None			1.0 (ref.)		1.0 (ref.)			
CRT stratified by sex								
Female								
>18 Gy							2.1 (1.7 to 2.5)	<.001
>0 and ≤18 Gy							2.0 (1.6 to 2.4)	<.001
No CRT							1.1 (1.0 to 1.3)	.21
Male								
≤18 Gy							1.4 (1.1 to 1.7)	.007
>0 and ≤18 Gy							1.3 (1.0 to 1.7)	.04
No CRT							1.0 (ref.)	
Corticosteroid								
Dexamethasone ± prednisone	1.0 (0.7 to 1.2)	.71	0.8 (0.6 to 1.2)	.36	1.1 (0.8 to 1.6)	.55	1.0 (0.7 to 1.2)	.77
Prednisone only	1.1 (0.9 to 1.3)	.22	1.2 (0.9 to 1.4)	.22	1.2 (1.0 to 1.5)	.08	1.1 (0.9 to 1.3)	.24
None	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Methotrexate IT therapy								
Yes	1.0 (0.8 to 1.1)	.64	0.9 (0.7 to 1.2)	.67	1.0 (0.8 to 1.3)	.83	1.0 (0.8 to 1.1)	.71
No	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Methotrexate IV + IM dose								
None	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
0.1–5000 mg/m^2	1.2 (1.0 to 1.4)	.04	1.1 (0.9 to 1.4)	.36	0.9 (0.7 to 1.2)	.63	1.2 (1.0 to 1.4)	.05
>5000 mg/m^2	1.1 (0.9 to 1.3)	.42	0.9 (0.7 to 1.2)	.33	1.0 (0.8 to 1.3)	.76	1.1 (0.9 to 1.3)	.40
Anthracycline dose (tertiles)								
None	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Low (≤100 mg/m^2)	0.9 (0.7 to 1.0)	.07	0.7 (0.6 to 1.0)	.03	0.8 (0.7 to 1.1)	.16	0.9 (0.7 to 1.0)	.07
Moderate (101–400 mg/m^2)	1.0 (0.9 to 1.2)	.88	1.2 (0.9 to 1.5)	.14	1.0 (0.8 to 1.3)	.93	1.0 (0.9 to 1.2)	.90
High (>400 mg/m^2)	0.9 (0.7 to 1.0)	.13	1.0 (0.8 to 1.3)	.85	0.8 (0.6 to 1.0)	.09	0.9 (0.7 to 1.0)	.13
Cyclophosphamide dose (tertiles)								
None (referent)	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
Low (≤4480 mg/m^2)	1.1 (0.9 to 1.3)	.21	1.1 (0.9 to 1.4)	.53	0.9 (0.7 to 1.1)	.34	1.1 (0.9 to 1.3)	.21
Moderate (4481–9750 mg/m^2)	1.1 (1.0 to 1.3)	.15	1.0 (0.8 to 1.3)	1.00	1.1 (0.9 to 1.4)	.29	1.1 (1.0 to 1.3)	.17
High (>9751 mg/m^2)	1.0 (0.8 to 1.1)	.69	0.9 (0.7 to 1.2)	.47	1.1 (0.8 to 1.3)	.68	1.0 (0.8 to 1.1)	.67
Sensory deficits								
Hearing ± visual	1.7 (1.3 to 2.0)	<.001	1.6 (1.1 to 2.3)	.009	1.1 (0.7 to 1.6)	.78	1.6 (1.3 to 2.0)	<.001
Visual only	1.1 (0.9 to 1.4)	.22	1.0 (0.7 to 1.5)	.91	1.1 (0.8 to 1.6)	.40	1.1 (0.9 to 1.4)	.23
Neither	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	

* Displayed are prevalence ratios (PRs) of scores categorized as impaired (ie, in the worst 10% range of siblings scores). CI = confidence interval; CRT = cranial radiation therapy; IM = intramuscular; IT = intrathecal; IV = intravenous; ref. = referent.

† Two-sided statistical inference from log-binomial regression or COPY method was used.

cranial radiation therapy. We also found this association among our study subjects. For emotional regulation, there was a statistically significant interaction between age and sex, with girls diagnosed at age younger than 6 years having the worst outcome.

Recently, there has been concern about the association between nonradiation treatments and neurocognitive impairment among cancer patients. Among prospective longitudinal studies, some investigators (9,10) have found that nonirradiated patients with acute lymphoblastic leukemia are neurocognitively impaired, whereas others (37–39) have found that they are within the average range. Methotrexate treatment has been implicated because the drug crosses the blood–brain barrier (40), causes leukoencephaly on

Table 6. Self-reported neurocognitive functioning outcomes among non-central nervous system survivors, stratified by key adult life outcomes: univariate analysis*

		Task efficiency			Organization			Memory	
Outcome	**No.**	**%**	**PR (95% CI)**	***P*†**	**%**	**PR (95% CI)**	***P***	**%**	**PR (95% CI)**
Ever worked									
No	162	20.4	1.6 (1.2 to 2.2)	.003	18.5	1.5 (1.1 to 2.1)	.01	23.5	1.9 (1.4 to 2.6)
Yes	5775	12.8	1.0 (ref.)		12.2	1.0 (ref.)		12.2	1.0 (ref.)
Education									
Not high school graduate	219	24.2	2.4 (1.9 to 3.2)	<.001	20.5	1.8 (1.4 to 2.4)	<.001	23.7	2.5 (1.9 to 3.2)
High school graduate	2886	15.1	1.5 (1.3 to 1.8)	<.001	12.8	1.1 (1.0 to 1.3)	.11	14.6	1.5 (1.3 to 1.8)
College graduate	2831	9.9	1.0 (ref.)		11.4	1.0 (ref.)		9.5	1.0 (ref.)
Living independently‡									
No	1402	15.9	1.3 (1.1 to 1.5)	<.001	15.3	1.3 (1.1 to 1.5)	<.001	16.0	1.4 (1.2 to 1.6)
Yes	4508	12.0	1.0 (ref.)		11.5	1.0 (ref.)		11.4	1.0 (ref.)

* Displayed are stratified proportions (%) and prevalence ratios (PRs) of scores categorized as impaired (ie, in the worst 10% range of siblings scores). CI = confidence interval; ref. = referent.

† Two-sided statistical inference from log-binomial regression or COPY method was used.

‡ Patients who live alone, with spouse or partner, with roommate, in a dormitory, with children, in the military, or with friends were classified as living independently.

neuroimaging (10), and has been associated with worse impairment at higher doses (41). Treatment with corticosteroids (12,42) and intrathecal chemotherapy (33) is also potentially associated with increased risk because of their higher concentrations in the CNS. Adult survivors of breast cancer who had undergone hematopoietic stem cell transplantation have been documented to have decreased neurocognitive functioning (42). In their recent review of non-CNS cancer and cancer therapy, Wefel et al. (42) speculated that chemotherapy may cause neurocognitive dysfunction through metabolic changes, anemia and central hypoxia, hormonal changes from gonadotoxic therapy, and proinflammatory cytokine activation.

We did not find that treatment with methotrexate, corticosteroids, anthracyclines, or alkylators was associated with worse self-reported neurocognitive functioning, independent of cranial radiation therapy. Among non-CNS cancer survivors who received cranial radiation therapy, treatment with methotrexate and corticosteroid was not associated with increased impairment. Even without cranial radiation therapy, increased systemic methotrexate treatment was not associated with increased impairment. Although no specific chemotherapy was associated with cognitive functioning, it should be noted that Hodgkin lymphoma, neuroblastoma, non-Hodgkin lymphoma, and osteosarcoma were associated with impairment in task efficiency, even though these cancers are not treated with cranial radiation therapy. It is not clear whether it is an aspect of chemotherapy or other part of the treatment experience that is responsible for these associations.

The association between hearing and academic performance has been established in otherwise healthy children but is only starting to gain recognition among childhood cancer survivors. Gurney et al. (43) studied 137 survivors of neuroblastoma and found that hearing loss was associated with learning problems and worse school functioning. In our study of survivors of many different cancers, hearing deficits were associated with impairment in task efficiency, organization, memory, and emotional regulation.

Our study had several limitations. The study design was retrospective, not prospective. Therefore, precancer neurocognitive status was not available. Neurocognitive functioning was assessed with a self-report instrument rather than performance testing. There is evidence in the literature that self-reported neurocognitive functioning predicts both performance-based assessments of dysfunction and neuroimaging abnormalities (44,45). A study of 1049 participants by de Groot et al. (44) found that self-reported change of neurocognitive function on rating scales preceded measured dysfunction and dementia as measured by neurocognitive performance. Mahone et al. (45) recently concluded that report of working memory on the BRIEF is associated with frontal gray matter volume but not with temporal, parietal, or occipital gray matter volume or white matter volume; these results support the specificity of self-reported working memory ratings. Although patients in our cohort generally received the same range of chemotherapeutic agents that are currently used, some treatments may not be applicable to the experience of children treated with more modern regimens. For example, contemporary patients with acute lymphoblastic leukemia are less likely to receive cranial radiation therapy and more likely to receive dexamethasone treatment.

From this multisite study, we conclude that there is a statistically and clinically significantly higher percentage of impairment in self-reported neurocognitive functioning among survivors of non-CNS cancers than among their siblings. Self-reported neurocognitive impairment was associated with important life outcomes in adults, such as unemployment, marriage status, and lack of independent living. Thus, we recommend that parents, medical providers, and educators should monitor all non-CNS cancer survivors, particularly those with leukemia, lymphoma, and neuroblastoma, for difficulties in learning and academic performance so that the appropriate intervention and/or accommodation may be given during childhood. Focused screening is especially important for children who received any cranial radiation therapy, who are female, who are treated in the preschool age range, and who have hearing deficits. There are ongoing studies (46) of potential interventions for affected individuals, including stimulant use and cognitive behavioral therapy. Future studies are warranted to elucidate the mechanism through which neurocognitive processing problems arise in nonirradiated patients, including investigation into possible inherited susceptibility.

Supplementary Data

Supplementary data can be found at http://www.jnci.oxfordjournals.org/.

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Notes

The authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript. N. S. Kadan-Lottick had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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